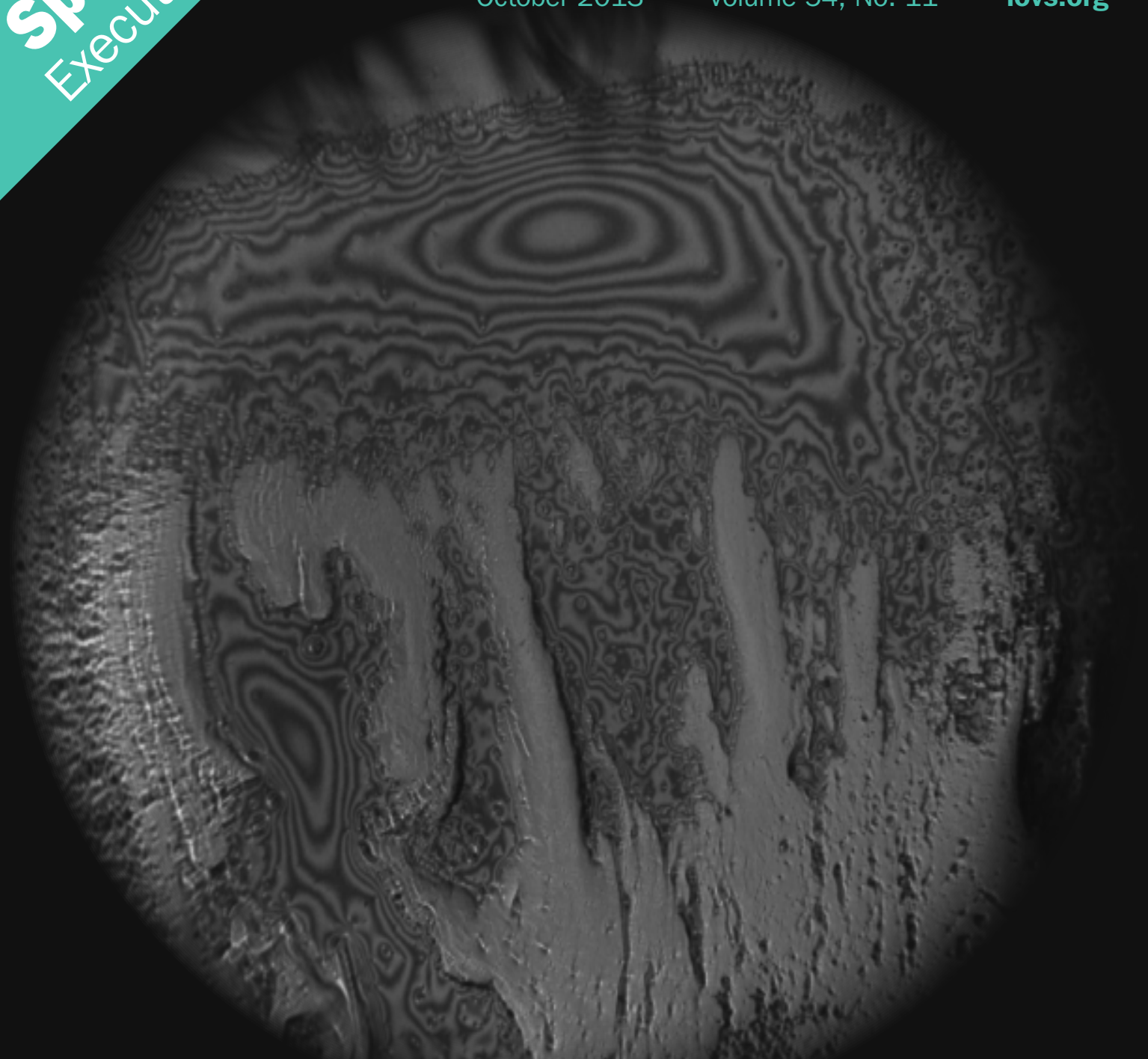


Special Issue
Executive Summary

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The TFOS International Workshop on
Contact Lens Discomfort



A significant, international research effort is being directed towards understanding the composition and regulation of the precorneal tear film. This effort is motivated by the recognition that the tear film plays a critical role in maintaining corneal and conjunctival integrity, protecting against microbial challenge and preserving visual acuity. In addition, research is stimulated by the knowledge that tear film deficiency, which occurs in countless individuals throughout the world, may lead to ocular surface desiccation, corneal ulceration, an increased incidence of infectious disease, and potentially pronounced visual disability.

To promote further progress in this field of vision research, the Tear Film & Ocular Surface Society (TFOS; www.tearfilm.org) was created and incorporated as a non-profit organization in 2000. The purpose of this Society is to advance the research, literacy, and educational aspects of the scientific field of the tear film and ocular surface.

Since its incorporation, TFOS has launched numerous initiatives, including:

- organization of International Conferences on the Tear Film and Ocular Surface in Maui in November 2000 (310 participants, 233 presentations), Puerto Rico in 2004 (400 participants, 270 presentations), Taormina, Italy, in 2007 (500 participants and 261 presentations), Florence, Italy, in 2010 (600 participants and almost 300 presentations), and Taormina, Italy in 2013 (500 participants and 256 presentations)
- organization and sponsorship of the TFOS International Dry Eye Workshop (DEWS), and publication of the TFOS DEWS report in *The Ocular Surface*
- organization and sponsorship of the TFOS International Workshop on Meibomian Gland Dysfunction (MGD), and publication of this TFOS MGD Workshop report in *Investigative Ophthalmology & Visual Science*
- organization and sponsorship of the TFOS International Workshop on Contact Lens Discomfort (CLD), and publication of this TFOS CLD Workshop report in *Investigative Ophthalmology & Visual Science*
- publication of a 1,385-page book (Adv Exp Med Biol 2002, vol 506A & B) about the tear film and ocular surface in health and disease
- sponsorship of the peer-reviewed journal, *The Ocular Surface*, and facilitation of its growth into one of the highest ranked ophthalmic journals in the world
- awarding of more than 200 Young Investigator Travel Awards

In addition, TFOS activities have helped to promote increased international awareness of external eye diseases, enhance governmental funding for tear film and ocular surface research, stimulate the development of therapeutic drugs and diagnostic devices, and influence the design and conduct of clinical trials of novel treatments for ocular surface disorders.

At present, TFOS has a distribution to ~ 5,000 basic scientists, clinical researchers and industry representatives in more than 80 countries. On behalf of TFOS, I hope that you enjoy this TFOS CLD Workshop report.

Sincerely,

David A. Sullivan, Ph.D.
Founder, Tear Film & Ocular Surface Society

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- TFOS7** **The TFOS International Workshop on Contact Lens Discomfort: Executive Summary** *Jason J. Nichols, Mark D. P. Willcox, Anthony J. Bron, Carlos Belmonte, Joseph B. Ciolino, Jennifer P. Craig, Murat Dogru, Gary N. Foulks, Lyndon Jones, J. Daniel Nelson, Kelly K. Nichols, Christine Purslow, Debra A. Schaumberg, Fiona Stapleton, David A. Sullivan, and the members of the TFOS International Workshop on Contact Lens Discomfort*
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All articles in this Special Issue were peer reviewed prior to being scientifically accepted for publication.

Cover: This image is taken from a custom-built interferometer and represents the pre-lens tear film in a soft contact lens-wearing patient. As observed in the image, there is significant tear film instability and breakup revealing dry spots and exposure of the contact lens surface, which is noted to be observed with contact lens discomfort.

The TFOS International Workshop on Contact Lens Discomfort: Introduction

Jason J. Nichols,¹ Lyndon Jones,² J. Daniel Nelson,³ Fiona Stapleton,⁴ David A. Sullivan,⁵ Mark D. P. Willcox,⁴ and the members of the TFOS International Workshop on Contact Lens Discomfort

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See the tables for the members of the TFOS International Workshop on Contact Lens Discomfort.

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Keywords: contact lenses, dry eye, discomfort, discontinuation

For many years, the contact lens field had focused on safety associated with contact lens wear—and for good reason, given the lack of understanding of the risk factors and etiology of serious complications such as microbial keratitis. However, as knowledge came to light on these complications through the 1980s and 1990s, it allowed for practitioners to become more comfortable managing these complications, along with the introduction of products that helped reduce or prevent some of these problems. It was during this time, beginning in the mid-1980s, that the field itself became cognizant of the issues associated with comfort, or discomfort, during contact lens wear.

Since that time, we have witnessed the field (and industry) shift its attention toward understanding the issue of contact lens discomfort (CLD). Contact lens discomfort is a substantial and burdensome problem experienced frequently by contact lens wearers. It is well established that most contact lens wearers experience CLD, at least occasionally, although many experience CLD to such a severity that they feel compelled to alter their wearing habits. Common, although palliative at best, treatments include the periodic use of rewetting drops, contact lens removal, contact lens refitting (using different lens designs or materials or replacement schedules), and changes in the contact lens care solutions or regimens, in addition to other less commonly used approaches including topical or systemic medications, alterations in diet, and punctal plugs. Ultimately, CLD is the primary factor associated with permanent discontinuation from contact lens wear.

Given the importance of the issue of CLD to both patients and practitioners alike, the time was right to move the field forward by taking steps to bring global consensus to our current understanding of this condition.

PURPOSE AND OBJECTIVES

In recognition of this need, and after discussions with international experts (i.e., Jennifer Craig, Gary Foulks, Lyndon Jones, Eric Papas, Jason Nichols, Kelly Nichols, Fiona Stapleton, and Mark Willcox) in January 2012, David Sullivan, president of the Tear Film & Ocular Surface Society (TFOS), recommended to the TFOS governing board that TFOS sponsor a workshop on CLD. The goal would be to build a global consensus concerning CLD using an evidence-based approach. The TFOS governing board agreed. TFOS raised funds from industry to support this initiative, invited individuals to serve on a steering committee, and asked this committee to establish detailed objectives, project a timeline, and select additional workshop participants. TFOS also selected *Investigative Ophthalmology and Visual Science (IOVS)* to publish the CLD Workshop report after consultation with members of the governing board and steering committee.

PROCESS

Organization

A steering committee was formed in February 2012 and met in June 2012 in San Diego, California. The membership of the steering committee can be found in Table 1.

The steering committee was charged with several tasks, and the CLD Workshop was modeled after two prior workshops, both sponsored by TFOS: the Dry Eye Workshop (DEWS; provided in the public domain by TFOS at <http://www.tearfilm.org/tearfilm-reports-dews-report.php>) and the Meibomian Gland Dysfunction (MGD; provided in the public domain by TFOS at <http://www.tearfilm.org/tearfilm-reports-mgdreport>).

TABLE 1. TFOS CLD Workshop Steering Committee Organization

Chair: Jason J. Nichols (United States)
 Vice chair: Mark Willcox (Australia)
 Organizer: David A. Sullivan (United States)
 Members: Joseph Ciolino (United States), Jennifer Craig (New Zealand), Gary Foulks (United States), Lyndon Jones (Canada), Kelly K. Nichols (United States), Christine Purslow (United Kingdom), Fiona Stapleton (Australia)
 Consultants: Anthony Bron (United Kingdom), Carlos Belmonte (Spain), Murat Dogru (Japan), James F. Saviola (United States), Debra A. Schaumberg (United States)
 Operations manager: Rose M. Sullivan (United States)

php) Workshop. The first charge of the steering committee was to develop the CLD Workshop's mission, including a series of critical content areas and aims and objectives for workshop focus. These were developed by the steering committee as they were seen as key areas that would serve as the thematic foundation for the workshop in terms of their importance in characterizing CLD. The mission of the CLD Workshop was as follows:

1. Conduct an evidence-based evaluation of CLD in health and disease;
2. Develop a contemporary understanding of the definition, classification, epidemiology, and neurobiology of CLD;
3. Examine the role of lens materials, design, and care in the etiology of CLD;
4. Assess the biocompatibility of contact lenses with the tear film and ocular surface;
5. Develop appropriate norms of trial design, including outcome measures for CLD;
6. Develop recommendations for the management and therapy of CLD; and
7. Develop recommendations for future innovative research in CLD.

Following the creation of the CLD Workshop's mission, a second charge of the steering committee was the formation of nine specific subcommittees, including their membership. In total, 79 international experts were assembled to develop and achieve consensus on CLD using an evidence-based approach. The steering committee also appointed subcommittee chairs and steering committee liaisons to each subcommittee. The subcommittees and their membership can be found in Table 2.

Workshop Process

The CLD Workshop spanned an approximate 18-month period from beginning to end, and included a series of meetings and open presentations of the various subcommittees on the approach and content. Once each subcommittee was formed and members accepted their invitation for involvement, each of the eight subcommittees (Table 2) met for a one- to one- and a half-day in-person meeting in September and October 2012 in various locations across the world in order to develop draft subcommittee report outlines. The subcommittee outlines were intended to document the scope and aims of each subcommittee and were to be developed in draft form by each subcommittee. Following the subcommittee meetings, each subcommittee submitted a draft outline to the entire workshop for review and content by mid-October 2012. Following an open period of comment, the steering committee reviewed and edited each outline, followed by approval of each outline and return of a final outline to the various subcommittees. The steering committee was charged with oversight of all

TABLE 2. Subcommittees and Membership

Subcommittee Name	Membership
Definition and Classification	Kelly K. Nichols, chair and subcommittee (SC) liaison (United States) Desmond Fonn (Canada) Lance Forstot (United States) Brien Holden (Australia) Jing-Feng Huang (United States) Jean Jacob (United States) J. Daniel Nelson (United States) Rachel Redfern (United States)
Epidemiology	Kathy Dumbleton, chair (Canada) Christine Purslow, SC liaison (United Kingdom) Murat Dogru, consultant (Japan) Barbara Caffery (Canada) Sheila Hickson-Curran (United States) Jami Kern (United States) Takashi Kojima (Japan) Philip Morgan (United Kingdom) Danielle Robertson (United States)
Contact Lens Materials, Design & Care	Lyndon Jones, chair and SC liaison (Canada) Noel Brennan (United States) Jose Manuel Gonzalez-Meijome (Portugal) John Lally (United States) Carole Moldonada-Codina (United Kingdom) Tannin Schmidt (Canada) Lakshman Subbaraman (Canada) Graeme Young (United Kingdom)
Neurobiology of Discomfort and Pain	Fiona Stapleton, co-chair and SC liaison (Australia) Mark Rosenblatt, co-chair (United States) Carlos Belmonte, consultant (Spain) Carolyn Begley (United States) David Bereiter (United States) Darlene Dartt (United States) Juana Gallar (Spain) Blanka Golebiowski (Australia) Pedram Hamrah (United States) Carl Marfurt (United States)
Contact Lens Interactions with the Ocular Surface & Adnexa	Nathan Efron, chair (Australia) Jason J. Nichols, co-SC liaison (United States) Mark Willcox, co-SC liaison (Australia) Anthony Bron, consultant (United Kingdom) Reiko Arita (Japan) Stefano Barabino (Italy) Erich Knop (Germany) Maria Markoulli (Australia) Alison McDermott (United States) Edoardo Villani (Italy)
Contact Lens Interactions with the Tear Film	Jennifer Craig, chair and SC liaison (New Zealand) Pablo Argüeso (United States) Cecile Maissa (United Kingdom) Ulrike Stahl (Canada) Alan Tomlinson (United Kingdom) Jay Wang (United States) Mark Willcox (Australia) Norihiko Yokoi (Japan)

TABLE 2. Continued

Subcommittee Name	Membership
Trial Design & Outcomes	Gary Foulks, chair and SC liaison (United States) James F. Saviola, consultant (United States) Debra A. Schaumberg, consultant (United States) Robin Chalmers (United States) William Gleason (United States) Isabelle Jalbert (Australia) Nancy Keir (Canada) Richard E. Lippman (United States) Trefford Simpson (Canada) Craig Woods (Australia)
Management & Therapy	Eric Papas, chair (Australia) Joseph Ciolino, SC liaison (United States) Deborah Jacobs (United States) William Miller (United States) Heiko Pult (Germany) Afsun Sahin (Turkey) Sruthi Srinivasan (Canada) Joseph Tauber (United States) James Wolffsohn (United Kingdom)
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subcommittee outlines to ensure that the outlines were broad in scope yet not overly redundant with one another.

Following steering committee approval of the final outlines, the subcommittees were charged with developing a draft version of the subcommittee report (based on the content outline). Again, these reports were intended to be evidence based, using the American Academy of Ophthalmology's Preferred Practice Pattern guidelines for levels of evidence. By steering committee directive, the subcommittees were primarily asked to focus on peer-reviewed literature, but could include non-peer-reviewed literature in their reports when needed (e.g., when there was no peer-reviewed literature).

Subcommittee representatives reviewed their progress at a meeting of the Industry Liaison Subcommittee (ILS) in Houston, Texas, in January 2013. The role of the ILS was to provide proactive and reactive comments about the goals of, and draft reports from, all other subcommittees. Toward that end, ILS members forwarded their constructive critiques to specific subcommittees for their consideration. In this way the workshop process was able to benefit from the collective experience and knowledge of all industry sponsors.

Subcommittee draft reports were due to the steering committee by April 1, 2013, in anticipation of a post-Association for Research in Vision and Ophthalmology (ARVO) TFOS CLD Workshop plenary session (May 10–11, 2013, Seattle, WA). All subcommittee report drafts were openly circulated prior to the post-ARVO meeting to the entire CLD Workshop for review.

At the post-ARVO plenary session, the eight subcommittee chairs presented the draft version of their subcommittee

TABLE 3. TFOS CLD Workshop Harmonization Subcommittee

Chair: Jason J. Nichols (United States)
Vice chair: Mark Willcox (Australia)
Members: Lyndon Jones (Canada), J. Daniel Nelson (United States), Fiona Stapleton (Australia)

reports to all members of the CLD Workshop in attendance (the entire CLD Workshop membership). This was an open period for further comments, suggestions, dialogue, development, and refinement of the draft reports. Each subcommittee was then tasked with refining their draft reports and submitting them to the steering committee by June 1, 2013.

Following submission of the draft reports to the steering committee, the reports were assigned to the Harmonization Subcommittee appointed by the steering committee, the membership of which can be found in Table 3. The goals of the Harmonization Subcommittee were to review, edit, and develop the subcommittee draft reports to ensure that all content included was evidence based and that the content was expansive and broad in scope. Further, the Harmonization Subcommittee was tasked by review of all of the eight subcommittee reports to have a global overview of the content of each, also ensuring that each report was focused on its outlines and on removing redundancies.

The subcommittee report harmonization period lasted through September 2013, and once each report was taken through the harmonization process and finalized, the final version was returned to the subcommittee for their review. Lastly, the reports were submitted to *IOVS* prior to the TFOS Seventh International Conference on the Tear Film & Ocular Surface: Basic Science and Clinical Relevance (Taormina, Sicily, September 18–21, 2013). During this conference, the CLD Workshop reports were presented to the public for the very first time.

FUTURE DIRECTIONS

While the details of the subcommittee reports and findings are found within the pages of this journal, it is important to recognize that it became apparent to many involved in the workshop process that “we just don't know as much as we thought we knew” about CLD. While there are hundreds, even perhaps thousands, of scientific papers that may relate to CLD in some way, it is clear that there are still significant gaps in our knowledge about this condition.

While it is obvious that CLD is a condition associated with the wearing of contact lenses, the condition remains equivocal in many senses. Below are key areas that need further study, delineation, and characterization, broken down by subcommittee.

Definition and Classification

1. Relative to classifying CLD, is it appropriate to differentiate CLD as distinct from dry eye disease, given the significant overlap of phenotypic characteristics of the two conditions?
2. Are there better ways to classify CLD, rather than focusing on contact lens and patient attributes?

Epidemiology

1. What is the natural history of CLD? What is the average age of onset, and how long do patients live with CLD prior to dropping out of contact lenses?

2. What are the risk factors for CLD?
3. Should CLD be considered distinct from other forms of dry eye disease (e.g., MGD) when the epidemiology of dry eye disease is evaluated?

Materials, Design, and Care

1. What contact lens material attributes have the most influence on CLD?
2. Are there advanced technologies in lens design that could reduce CLD?
3. What specific components in contact lens care systems matter most in improving comfort during CL wear? Are there specific steps in the regimen that matter more than others in terms of comfort?
4. How significant is replacement frequency in improving CLD? Are there substantially meaningful differences between lenses replaced daily, every two weeks, and monthly in preventing patients from reducing or discontinuing contact lens wear?

Neurobiology of Discomfort

1. What models can be used to determine the exact sensory pathways in CLD? Do sensory changes to the conjunctiva occur as a result of neural adaptation due to the continued stimulus of a contact lens, and how do those sensory changes mediate discomfort?
2. Does neural sensitization due to hyperosmolarity or inflammatory mediators in the tears contribute to CLD?
3. What corneal mediators, or neuropeptides, are altered during contact lens wear that interplay with the neurobiological system?
4. Is the key interaction related to CLD the upper lid (lid wiper zone) with the contact lens, and what role does sensing cooling effects have in CLD?

Ocular Surface and Adnexa

1. Is meibomian gland loss or atrophy in contact lens wearers the initial cascade that leads to other tissue changes provoking symptoms of discomfort?
2. How can contact lenses and care solutions be better improved to increase biocompatibility during lens wear?
3. Are changes to the ocular surface, such as corneal and conjunctival staining or changes in goblet cell density, more important in CLD than we presently realize?

Tear Film

1. Relative to the altered lipid layer and increased evaporation during contact lens wear, can the actual class, or species, of lipid that is associated with these changes be determined?
2. Are proteins from the ocular surface released into the tear film that change the stabilization of the tears during contact lens wear, leading to structural alterations of the tear film?

3. What role is there for mucin degradation during contact lens wear in CLD?
4. Is it possible to better elucidate how the “compartments” of the pre- and postlens tear film found during contact lens wear impact on CLD in a relative sense, if at all?

Trial Design and Outcomes

1. How will the definition of CLD as determined in this workshop report be adopted in clinical trial research?
2. Can trial design be better standardized and can validated endpoints be agreed upon?
3. Is it possible to determine specific objective outcomes, or even biomarkers, that predict symptoms reported by patients with CLD?

Management and Therapy

1. It is well recognized that most management strategies and therapies used in managing CLD are not entirely effective. What investments are needed to move the field forward to advance clinical care of these patients?
2. How can future knowledge of the impact of various contact lens materials and care solution attributes be harnessed into improving the care of the patient with CLD?
3. Are pharmaceutical agents or devices alone, or in combination with contact lenses, able to improve CLD in order to prolong safe and comfortable wear of contact lenses?

CONCLUSIONS

The TFOS International Workshop on Contact Lens Discomfort was an 18-month process of open communication, dialogue, and transparency among workshop participants that culminated in a series of evidence-based reports. These eight reports are the work and dedication of 79 global experts, and are the consensus-based efforts that define the current state of CLD, a condition characterized by episodic or persistent adverse ocular sensations that can ultimately lead to decreased wearing time or discontinuation of contact lens wear. It is the aspiration of those involved in the CLD Workshop that these reports serve as a blueprint for future research and clinical activity such that CLD can be reduced or eliminated, leading to successful long-term wear of contact lenses for millions of people across the world.

Acknowledgments

The CLD Workshop participants thank Amy Gallant Sullivan (United States, TFOS executive director) and Rose Sullivan (United States, TFOS operations manager) for their help in the fundraising for and organization of this workshop.

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APPENDIX**Disclosures**

The Tear Film & Ocular Surface Society (TFOS) supported authors with travel funds to subcommittee meetings.

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The TFOS International Workshop on Contact Lens Discomfort: Executive Summary

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See the tables in the Introduction for the members of the TFOS International Workshop on Contact Lens Discomfort.

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Contact lens discomfort (CLD) is a frequently experienced problem, with most estimates suggesting that up to half of contact lens wearers experience this problem with some frequency or magnitude. This condition impacts millions of contact lens wearers worldwide. Yet, there is a paucity of consensus and standardization in the scientific and clinical communities on the characterization of the condition, including the definition, classification, epidemiology, pathophysiology, diagnosis, management, influence of contact lens materials, designs and care, and the proper design of clinical trials.

The Tear Film & Ocular Surface Society (TFOS), which is a nonprofit organization, has conducted two prior international, consensus building workshops, including the Dry Eye WorkShop (DEWS; available in the public domain at <http://www.tearfilm.org/tearfilm-reports-dews-report.php>) and the Meibomian Gland Dysfunction Workshop (MGD; available in the public domain at <http://www.tearfilm.org/tearfilm-reports-mgdreport.php>). To that end, TFOS initiated the process of conducting a similar workshop in January 2012—a process that took approximately 18 months to complete and included 79 experts in the field. These experts participated in one or more topical subcommit-

tees, and were assigned with taking an evidence-based approach at evaluating CLD. Eight topical subcommittees were formed, with each generating a related report, all of which were circulated for presentation, review, and input of the entire workshop membership.

The entire workshop originally is being published in this issue of IOVS, in English, with subsequent translations into numerous other languages. All of this information is intended to be available and accessible online, free of charge. This article is intended to serve as an Executive Summary of the eight subcommittee reports, and all information contained here was abstracted from the full reports.

DEFINITION AND CLASSIFICATION OF CLD

While clinicians practicing in the area of contact lenses all are familiar with CLD, a variety of terms and verbiage have been used to describe this problem. Typically these patients present with symptoms of ocular discomfort of some sort (e.g., dryness, irritation, discomfort, fatigue, and so forth), and it is common

that these symptoms usually increase over the day while the patient is wearing the contact lenses. However, beyond this, no standard definition has been agreed upon globally with consensus as to what this problem is. As such, the definition of “CLD” is the following:

Contact lens discomfort is a condition characterized by episodic or persistent adverse ocular sensations related to lens wear, either with or without visual disturbance, resulting from reduced compatibility between the contact lens and the ocular environment, which can lead to decreased wearing time and discontinuation of contact lens wear.

The CLD Workshop membership characterized each of the terms in the definition, considering many other concepts in the development of the final definition. The rationale for the specific terminology included in the definition, and related terminology, can be found detailed in this subcommittee report. However, it is important to note that the CLD Workshop recognizes that CLD occurs while a contact lens is worn, and that the removal of contact lenses mitigates the condition (in particular the adverse ocular sensations). However, CLD is a condition that occurs after the initial “adaptation” period a neophyte goes through when first adjusting to contact lens wear. Physical signs may, or may not, be present in accompanying the adverse ocular sensations. Moving forward, the condition should be recognized as noted above, and the terms “contact lens dry eye” or “contact lens-related dry eye” should not be used when talking about contact lens discomfort. These terms should be reserved for an individual who has a preexisting dry eye condition, which may or may not be exaggerated when contact lenses are worn. Contact lens dropout refers to discontinuation of contact lens wear for a sustained period of time.

Classification of CLD was challenging, as classifying a disease relates to the ability to categorize it based on knowledge of the etiology. In addition, to our knowledge there has not been a previous classification scheme, and an understanding of etiologic factors has been identified in the other subcommittee reports as significantly lacking for CLD. The CLD Workshop felt that the two major categories of CLD were the contact lens and the environment (Fig. 1). The contact lens category was divided further into four subcategories: material, design, fit and wear, and lens care. The environment category also was broken down further into four subcategories: inherent patient factors, modifiable patient factors, ocular environment, and external environment. Details of each of these subcategories can be found within the Definition and Classification Report.

Lastly, very little is agreed upon regarding the temporal progression of CLD, as this relates to contact lens dropout (or permanent cessation of contact lens wear). As such, the modes of progression also are presented in Figure 1, showing the temporal progression of CLD as patients begin to struggle, which is followed by the adoption of management strategies (e.g., reducing wearing time), and ultimately by contact lens dropout.

EPIDEMIOLOGY OF CLD

The epidemiologic assessment of CLD faces many challenges, not least of which is the accurate assessment of the frequency of the condition. Since the first publication in 1960 linking hygienic contact lens care and comfortable lens wear, the issue of CLD remains a major reason for discontinuation of contact lens wear. It is estimated that there currently are more than 140 million contact lens wearers worldwide. It is much more

difficult to estimate the number of individuals who previously have worn contact lenses and then abandoned lens wear as a result of CLD. Studies report that between 12% and 51% of lens wearers “drop out” of contact lens wear, with CLD the primary reason for discontinuation.

While there have been tremendous developments in lens polymers, designs, replacement modalities, and care regimens over the last 50 years, the challenge of preventing or managing CLD still is a problem in clinical practice. A major deficiency in the literature is the lack of information derived from contact lenses that differ in only one parameter.

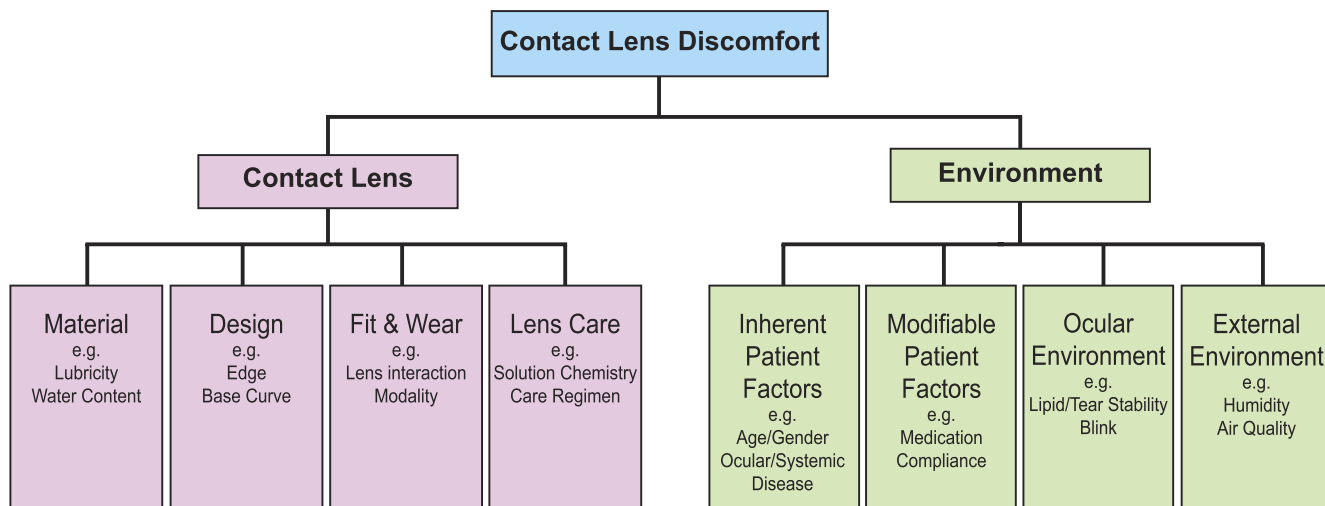
Our limited understanding of the etiology and correlation between signs and symptoms makes it all the more difficult to diagnose and manage CLD. The tools used to diagnose CLD and the expectations of contact lens wearers continually change, making it difficult to draw conclusions over time and to compare results from multiple studies. There are few validated instruments for assessing comfort in contact lens populations, and these tend to produce data that are highly variable, as most rely on a patient’s recall. In addition, the lack of postmarket surveillance studies, which would address many of the issues related to CLD in a longitudinal fashion, prevent drawing meaningful conclusions regarding the impact of technological advances on CLD. Future epidemiologic work designed to clarify the natural occurrence and evolution of CLD in rural and urban population settings, and in various countries and races are very much needed to enrich our understanding of CLD and associated risk factors.

As CLD is reported primarily by symptomatology as opposed to the observation of signs, and while the precise etiology of CLD is yet to be determined, the use of symptoms as an outcome measure is appropriate, because it relates directly to the patients’ experience with contact lenses, and the motivation to seek and use treatment, regardless of the presence of observable signs. The frequency and intensity with which these symptoms are reported can be assessed with the use of questionnaires. Further research and agreement of a universal adoption of a single measure of CLD is needed. The Contact Lens Dry Eye Questionnaire has been well received and, perhaps, is the most likely candidate for widespread CLD assessment.

CONTACT LENS MATERIALS, DESIGN, AND CARE

The influence of contact lens materials and designs, including rigid and soft contact lenses in these aforementioned areas, has been of significant controversy in terms of their association or etiologic influence in CLD. Further, there also has been great interest in the role of contact lens care solutions, regimen practices in caring for contact lenses, and wearing schedule differences in terms of their influence on CLD.

The vast majority of today’s market is made up of soft contact lenses (~90%), while rigid lenses make up the remainder of the market. Of soft lenses used, silicone hydrogel lenses now make up the majority of the market share within most major worldwide markets. Through the years, there has been a question about the role of materials and designs on the problem of CLD. This issue was first recognized in the peer reviewed literature in the early 1970s for rigid lens materials and in the 1980s for soft lens materials. Since that time, practitioners and scientists have questioned the influence of polymer chemistry, and various other material attributes that can be measured and quantified. The attributes considered have included the bulk (e.g., water content, dehydration, ionicity, oxygen transmissibility, modulus, and mechanical factors) and the surface (e.g., friction, wettability, surface modification) of contact lens materials. To date, almost none of



Progression of CLD



FIGURE 1. Classification of CLD.

these attributes, with the possible exception of friction based on early evidence, appears to be associated directly with CLD. Studies evaluating these factors, however, can be difficult to draw conclusions from in that they are confounded with differing designs, lack of rigor, lack of consistent definitions (e.g., of discomfort), and an inability to hold the design constant when testing the influence of a material or its attribute. Lastly, contact lens material chemistry also is known to influence tear film component deposition (proteins and lipid primarily), but the role of deposition in general is equivocal, perhaps again due to difficulties and inconsistencies in measurement and quantification of deposition.

Contact lenses vary in terms of their designs, and there has been some notion that the design of a lens influences the on-eye comfort during wearing. There is no question that the design of contact lenses influences their ability to fit the ocular surface properly, and this is influential in terms of overall performance. For instance, for soft contact lenses, moderate on-eye movement (with tear exchange) and corneal coverage are recognized as being important, but its overall association with CLD is not entirely clear. Likewise, in rigid lens fitting, the influence of the eyelid-edge interaction is recognized as being important in terms of patient comfort, but this relation again is not entirely clear in terms of its overall association with CLD. However, there is even less consensus when considering the influence of various design attributes on CLD. That said, the size, shape, and contour of lens edges appear to be some of the most influential determinants of contact lens comfort for soft and rigid contact lenses.

Lastly, contact lens care solutions, contact lens care practices, and contact lens wear schedules certainly are of

interest in terms of understanding their role(s) in CLD. To date, the peer-reviewed literature does not give a clear indication of specific formulations or components that may be associated either with increasing CLD or with improving contact lens comfort. However, most practitioners agree that regular contact lens care by contact lens wearers, including rub, rinse, and adequate soaking (disinfection and cleaning) are important in the success of lens wear. Further, most agree that increasing the frequency of replacement of soft contact lenses is ideal for ocular health and potentially improving comfort, although it is difficult to define the ideal replacement schedule. To our knowledge, large-scale, well-controlled studies using contemporary devices have not been conducted to provide insight into these issues.

NEUROBIOLOGY OF DISCOMFORT AND PAIN

Contact lenses interact with some of the most richly innervated areas of the body, such as the cornea, lid margin, and to a lesser extent the conjunctiva, and so it perhaps is not surprising that the eye can detect and sometimes react to the presence of the contact lens. The sensory (afferent) nerves (i.e., those that react to “pain” stimuli), which are derived from the ophthalmic and maxillary regions of the trigeminal ganglion, give rise to numerous intraepithelial terminals, some of which may extend to within a few micrometers of the ocular surface. The sensory nerves of the cornea consist of polymodal receptors (which can react to near-noxious or noxious mechanical energy, heat, cooling, chemical irritants, and by a large variety of inflammatory mediators), mechano-nociceptors

(which respond to mechanical forces of a magnitude close to that required to damage corneal epithelial cells), and cold-sensitive thermoreceptors (which react to temperature drops produced by evaporation of tears at the corneal surface, or application of cold and hyperosmolar solutions). Activation of these nociceptors is via specific ion channels; however, there appears to be no linear relationship between channel activation and contact lens discomfort.

Postreceptor propagation of the sensory nerve signal travels from the source through trigeminal ganglion to terminate in multiple spatially discrete zones along the rostrocaudal axis of the trigeminal brainstem sensory complex (TBSC) of the central nervous system. In this region, sensory nerves terminate mainly in the ventral aspect of the transition region between caudal interpolaris of the spinal trigeminal nucleus and caudalis of the same region (Vi/Vc) or at the spinomedullary junction (Vc/C1). Evidence suggests that ocular sensory neurons at Vi/Vc or Vc/C1 serve different functions in ocular homeostasis and sensation. Drying or detection of cold at the ocular surface stimulates the Vi/Vc region only. Transection of the spinal trigeminal tract at Vi/Vc eliminates pain sensation upon corneal stimulation, but a sense of corneal touch remains. Pharmacologic blockade of only Vi/Vc prevents reflex lacrimation evoked by chemical stimulation of the ocular surface. The ascending projections from second-order ocular neurons in the TBSC to higher brain centers are not well known and no systematic mapping study has been reported, even though the complex nature of many ocular perceptions, such as dryness, grittiness, itch, irritation, and fatigue, suggests interactions across multiple psychophysical channels that require integration at higher brain centers.

Contact lens wear may, or may not, alter nerve fiber density, tortuosity, branching, beading, thickness, or reflectivity. The large changes in morphology of the subbasal nerve plexus in the cornea during orthokeratology (OK) lens wear increase the threshold to sensation. Changes in corneal sensitivity with contact lens wear have been reported widely, but the underlying mechanism is not known, and the outcomes of studies may be very dependent on the type of instrument used to test sensitivity. The fact that tactile/pneumatic stimulus of the cornea after soft contact lens wear is reduced, but no associated change occurs in symptoms of discomfort during lens wear, suggests that the touch response in the cornea, and, hence, propagation of the stimulus through Vc/C1, is not associated with CLD. This then may implicate the cooling, osmolality differences detected through the Vi/Vc region. An alternate hypothesis, but not necessarily mutually exclusive, is the possibility of mechanical stimulation of the nociceptors in the lid wiper region of the eyelids. Stimulation of subacute inflammation of the ocular surface during lens wear may occur, and nerves can respond to the production of a variety of inflammatory mediators, including cytokines and arachidonic acid metabolites. The key neurotransmitters involved in the transmission of ocular sensations in human cornea and conjunctiva have been identified as substance P and calcitonin gene-related peptide (CGRP). No change in tear levels of substance P was found in a group of contact lens wearers compared to nonwearers, which may indicate no role for substance P in CLD. No reports on changes to CGRP were found. Conversely, the neurotrophin nerve growth factor (NGF) appears to be upregulated in CLD. As NGF is involved in survival and maintenance of sympathetic and sensory neurons, its upregulation suggests that nerves either are being damaged (and so need extra NGF for repair) or being altered in other ways during CLD.

Much more research needs to be performed to enable a comprehensive outline of the neurobiology of CLD. Better integration of the research from the peripheral and central

nervous system, with observations of nerve morphology/structural changes, and the biochemistry of the system could only be beneficial to our understanding of CLD. An important first step would be to design experiments to determine which tissue (e.g., corneal or lid margin) is the primary sensory location of CLD.

CONTACT LENS INTERACTIONS WITH THE OCULAR SURFACE AND ADNEXA

It would appear obvious that the interactions of a contact lens with the ocular surface and tear film are critical in the successful wear of the lens and the development of CLD. This subcommittee investigated the impact of contact lenses on the ocular surface and attempted to link these interactions to the development of CLD. A thorough review of the literature identified many dozens of ocular surface tissue alterations that may occur as a result of lens wear. While many of these result in frank pain (e.g., microbial keratitis), it was determined that such obvious pathologic complications were not the remit of this exercise and that the subcommittee would consider only potential tissue alterations that were associated with CLD (as defined above), and not pain that remained upon removal of the lens.

The cornea serves as the major surface on which the lens sits and could be a significant factor in CLD, particularly as it relates to its neurobiology. However, morphologic and apoptotic changes within the corneal epithelium have not been linked to CLD, nor have any changes in corneal epithelial barrier function. Despite many publications examining corneal staining associated with CL wear, overall, there appears to be, at best, a weak link between CLD and corneal staining, and it is not a major factor for most CL wearers. No stromal (keratocyte density, stromal opacities, stromal infiltrates, and stromal neovascularization), endothelial, or limbal (redness or stem cell deficiency) changes induced by lens wear were proven to be associated with CLD. While hypoxia can be a complication with many lens types or designs, no specific association with any hypoxic changes or marker of hypoxia could be linked directly to CLD.

The conjunctiva proved to be a tissue more closely linked to the development of CLD. Bulbar conjunctival staining, typically viewed using lissamine green, was found in some studies to be associated with CLD, particularly soft lens edge-related staining, and this may be related to lens edge design. While edge design and modulus may be linked to the development of conjunctival epithelial flaps, there appears to be no association between this tissue change and CLD. Bulbar hyperemia was not linked to CLD. Cytologic changes in the bulbar conjunctiva do occur in some wearers with CLD, but the many months it takes to reverse these changes obviously argues against a strong association with CLD, as CLD is relieved rapidly by removal of the lens from the eye.

The palpebral conjunctiva has an important role in controlling the interaction with the ocular surface and lens. Two specific issues potentially linked to CLD include alterations to the meibomian glands and to the leading edge of the palpebral conjunctiva as it moves across the lens surface (the so-called "lid-wiper" zone). Contact lens wear does appear to impact the function of the meibomian glands and reduced meibomian gland function has been associated with contact lens wear, but further studies are required for confirmation. Alterations to the lid-wiper area are more common in contact lens wearers who are symptomatic, and some studies have related these tissue changes to CLD. However, further work is necessary to investigate whether lid wiper epitheliopathy (LWE) is caused by specific properties of the lens material,

whether upper LWE is more or less relevant than lower LWE, whether making changes to contact lens properties, rewetting drops, or solutions can influence positively the degree of LWE, and to what extent modification of LWE will alleviate CLD. Finally, the lid margin is colonized more frequently with microbes than the conjunctiva, but the frequency of isolation varies between wearers. The role of lid microbiota has been studied only superficially during CLD and this also is an area worthy of future study, given that microbial toxins can impact ocular comfort.

In conclusion, some evidence is available to suggest a link between conjunctival and lid changes with CLD, with the strongest evidence being that related to meibomian gland and LWE changes. No convincing evidence of a link to CLD was unearthed with respect to any of the other forms of CL-associated tissue changes. Future studies would benefit from longitudinal designs that attempt to understand what pathophysiological changes occur in new wearers over time, and whether changes to lens materials, design, fit, or other factors impact these tissue changes. Studies also should examine whether the magnitude or timing of such changes can be related to the magnitude and timing of CLD.

CONTACT LENS INTERACTIONS WITH THE TEAR FILM

In evaluating contact lens interactions with the tear film and how those interactions might result in discomfort, the workshop considered the biophysical and the biochemical effects of contact lens wear on the tear film and their influence on discomfort.

The physical presence of a contact lens in situ divides the tear film into a pre- and postlens tear film, creating new interfaces with the ocular environment. Tear film changes occur upon lens application and during subsequent wear. In addition, biochemical differences are likely to exist between the pre- and postlens tear film layers. Partitioning of the tear film upon contact lens application and wear causes a series of compositional changes that result in a less stable tear film on the front surface of the lens and less well-defined changes to the postlens tear film layer. The resulting prelens tear film has reduced lipid layer thickness, reduced tear volume, and increased evaporation rate compared to the normal tear film. While the direct impact of these tear properties on discomfort has not been elucidated fully, the evidence to date specifically suggests that decreased tear film stability, increased tear evaporation, reduced tear film turnover, and tear ferning are associated with CLD. Further evidence is needed to support the associations between tear volume, surface tension, osmolarity, pH, and ocular surface temperature and CLD.

With respect to biochemical changes in tear film composition associated with contact lens wear, there appears to be no relationship between total protein, lactoferrin, and lysozyme with CLD. Current evidence suggests that levels of tear lipocalin-1, levels and activity of sPLA2, and levels of degraded lipids may be increased, and phospholipids decreased in CLD, which may be consistent with biochemical and functional changes in the tear lipid layer. Certain polar lipids, specifically the (O-acetyl)-omega-hydroxy fatty acids and their esters, have been associated with symptom reporting and may be important in CLD. Further evidence is needed to establish links between MUC5AC and other changes in the tear proteome with CLD. Given the potential evidence for frictional wear and lid wiper epitheliopathy in the pathophysiology of CLD, it may be expected that tissue and tear proteases, and inflammatory mediators would be increased in the tear film; however, such changes have not yet been demonstrated consistently.

There are significant gaps in our understanding of the extent to which tear film changes in contact lens wear are responsible for CLD. There is good evidence for associations between changes in tear lipids likely in the prelens tear film and CLD, although it is not clear if these changes are causal, or that they are present before contact lens wear. To understand these relationships better, it is important to use the definition of CLD as defined herein in future research and to study relevant subject groups using an appropriate study design. The lack of evidence for the postlens tear film in CLD likely relates to the current difficulties in evaluating this layer, in addition to the fact that this layer is relatively stagnant, as it largely is trapped and stagnant behind the contact lens.

Evidence also suggests that the parameters of the prelens tear film are interrelated and, therefore, it is difficult to identify a single component as being responsible for CLD. Tear film stability (via evaporation), however, is recognized as a key factor in CLD, and it appears to be a consequence of multiple tear film characteristics and their interactions. Given the relevance of prelens tear film stability in CLD, future research should focus on the development of novel materials or surface treatments to resist tear evaporation during wear, and on the development of wetting agents in care products to promote long-term contact lens wettability.

TRIAL DESIGN AND OUTCOMES

Design of clinical trials to determine the possible causes of CLD, for the most part, have not been optimal and numbers of participants in the trials generally small. Surprisingly, given the strong association of CLD with discontinuation of contact lens wear, the design of clinical trials has tended to focus on performance of certain contact lenses or lens care solutions, rather than the specific nature and etiology of contact lens discomfort. This may be due to the majority being industry-sponsored clinical trials.

Most clinical trials have evaluated the role of lens type (material differences), use of care systems, and effect of lens fitting, but they have been limited in their ability to isolate one factor from others. A significant limitation has been the lack of a consensus-based definition of CLD to date. Other limitations include lack of control of confounding variables or use of proper controls. An example of this is the problem often found when reports have been published on the results of changing wearers from their habitual lens of choice to a new (sometimes experimental) lens. Without appropriate masking and controls (for example, not only changing to the new lens type, but refitting a portion of subjects with or crossing over the subjects into their habitual lenses once masked), results tend to suffer from inherent bias.

This subcommittee report details many types of bias that should be considered in future work in this area. Further, prospective trial designs with randomization of subjects and double masking is optimal. Consideration of run-in and wash-out periods are important to avoid memory bias or changes that may occur to physiology during wear of lenses. Appropriate entry criteria and adequate sample size determinations a priori are critical.

Finally, it was determined that certain factors from clinical trials, at least potentially, had been associated with CLD. These included lid wiper epitheliopathy, tear film stability/volume, and lid parallel conjunctival folds. It was recommended that further appropriately designed clinical trials be performed to assess these factors (and others). Although no single outcome parameter of contact lenses was found to be validated fully, it was concluded that the Contact Lens Dry Eye Questionnaire currently was the most appropriate subjective outcome for

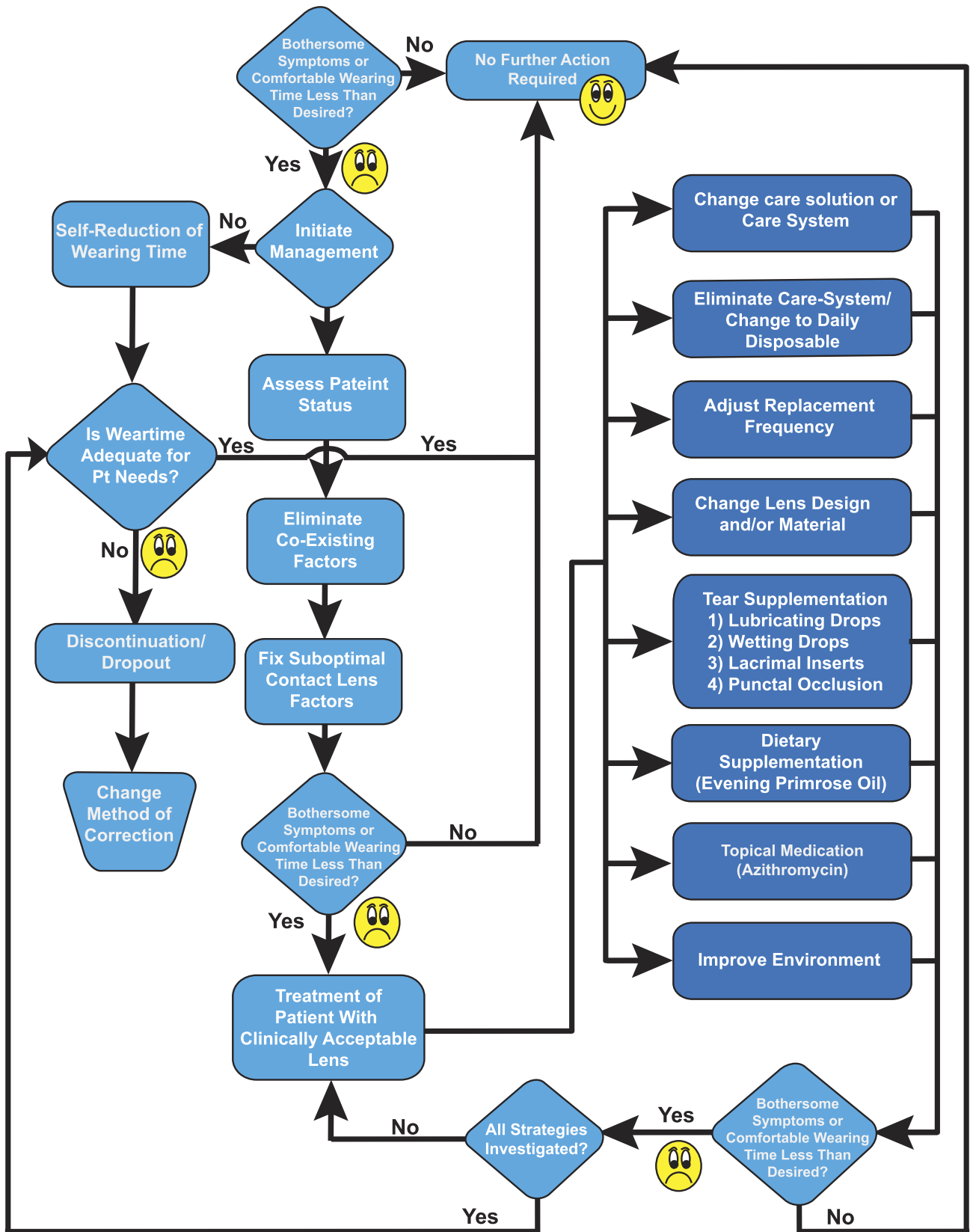


FIGURE 2. Summary of the management strategies for CLD.

CLD. An even more reliable and sensitive outcome parameter is needed for future work in this area.

MANAGEMENT AND THERAPY OF CLD

The condition of CLD is a considerable management and therapy challenge in clinical practice. While the causes of the short-term discomfort following difficulty with lens insertion generally are understood and appropriate remedies are straightforward, symptoms of discomfort and dryness that persist and increase toward the end of the day pose a more intractable problem. Managing wearers in these circumstances requires careful, individual assessment to eliminate concurrent conditions that may confuse the clinical picture, followed by a determination of the most likely cause or causes, and identification of corresponding treatment strategies (Fig. 2). The aim is to ensure that the contact lens is in a clinically acceptable ocular environment without obvious lens deficits of either a physical or behavioral nature.

A careful history of the presenting problem and the general status of the patient is a critical first step in the management process for CLD. Key elements in the evaluation include the age and sex of the wearer, timing and onset of symptoms, type of lens and lens material, care systems, lens replacement schedules, use of additional wetting agents, wear times and patterns, compliance and adherence to instructions, the occupational environment, coexisting disease, and current medications.

It is important to recognize that the symptom “discomfort” is relatively nonspecific, as discomfort can result from many sources other than the contact lens. Coexisting pathologies that may be responsible for the patient’s symptoms, such as ocular medicamentosa, systemic disease (autoimmune diseases and atopic disease), eyelid disease (blepharitis and anatomic abnormalities), tear film abnormalities, and conjunctival and corneal diseases, are important to identify and treat before focusing on the contact lens as the source of discomfort.

After noncontact lens causes of CLD have been identified and treated, the focus is on the contact lens and care system. Contact lens defects, such as edge chips and tears, deposits, and nonwetting surfaces, are typical causes of contact lens-related problems. Contact lens design properties (such as edge design), material properties, and on-eye fit, also are issues that must be considered. Care solutions and their components or improper care regimens also may at times contribute to CLD, and the benefits of daily disposable lenses may, in part, be due to elimination of these factors. However, the solution in the blister pack of disposable lenses also can be a source of CLD, particularly on application of contact lenses.

Frequent and appropriately-timed replacement of contact lenses may reduce or eliminate deposit formation. Switching to a different care system may have some effect on deposit formation. Although changing lens material may be helpful, it is difficult to separate material from design and surface effects as sources of CLD.

Fitting with steeper base curves, using larger diameter lenses, alternating the back lens surface shape, and using lenses with a thinner center thickness may improve CLD. However, it is difficult to manipulate lens parameters in isolation from each other, as altering one parameter may influence the other parameters.

The use of topical artificial tears and wetting agents, oral essential fatty acids (FA), punctal occlusion, and topical medications (e.g., azithromycin, cyclosporine A), along with avoiding adverse environments (e.g., aircraft cabins) and altering blinking behavior, all have been used in treatment of patients with dry eye and may be useful adjuncts in reducing CLD, although these require more substantial evidence in the future relative to their use (or lack thereof).

All these tactics may have limited effect on CLD and incremental improvements in CLD may be all that can be expected reasonably from any single intervention. The addition of treatments in a stepwise manner may be required to provide the maximum possible relief. Unfortunately, given the current state of knowledge of CLD, some patients will have residual levels of CLD that are sufficiently bothersome that it causes them to discontinue contact lens wear.

CONCLUSIONS

The TFOS International Workshop on CLD has addressed many areas of interest within the contact lens community as they relate to characterizing the ever-persistent problem of CLD. As noted, this international group of experts provided a framework that future studies and clinical activities can build upon when working in this area. It is critically important that the definition of CLD (as noted above) be applied in trials and studies that address CLD, including validated outcomes, such that there is consistency across research activities. Likewise, prospective natural history studies, which have not been performed to date, will help us better determine the incidence and risk factors for this condition, including factors that may relate to the patient or contact lenses in some way (e.g., material characteristics, designs, care system characteristics, care regimens). Etiologic considerations, including interactions with the ocular surface and tear film, need better models that will allow improved preclinical insight, and ultimately bench to the clinic translation in the development of novel products. Lastly, clinicians must be diligent in working with patients with CLD. It is important that the process of prevention and management of CLD starts early, perhaps even before the onset of symptoms, to improve the long-term prognosis of successful, safe, and comfortable contact lens wear.

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The TFOS International Workshop on Contact Lens Discomfort: Report of the Definition and Classification Subcommittee

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See the tables in the Introduction for the members of the TFOS International Workshop on Contact Lens Discomfort.

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INTRODUCTION AND GOALS OF THE DEFINITION AND CLASSIFICATION SUBCOMMITTEE

Current scientific understanding of contact lens discomfort (CLD) has been limited by a lack of consensus regarding terminology, as well as gaps in knowledge of the steps with which discomfort leads to discontinuation of lens wear. The goals of this subcommittee were to develop a comprehensive definition and an evidence-based classification scheme of CLD, as well as to clarify associated terminology.

In the clinical context, end of day discomfort is an important factor and one of the most common complaints associated with contact lens wear discontinuation.¹⁻⁸ The condition of CLD can occur with any lens material type or design, and wearing modality; however, it is reported most often in conjunction with soft contact lenses (conventional and silicone hydrogel), as they make up the bulk of the contact lens market. While descriptions of CLD have been used widely in the literature, no uniform definition of CLD has been agreed upon or reported previously to our knowledge. Previously, the term CLD has been used to generally describe symptoms, while failing to delineate underlying mechanisms or outcomes.

Discomfort is considered “a mental or bodily distress, or something that disturbs one’s comfort,”⁹ and comfort is considered “a condition or feeling of pleasurable ease, well-being, and contentment.”⁹ When contact lens wearers are queried, comfort often is equated with the feeling of “non-lens

wear” or what the lens feels like soon after insertion, which often is considered clinically as comfortable lens wear. Attributes of comfortable lens wear include the ability to wear the lens without sensation (lack of lens awareness), to maintain visual clarity, and to have complete tolerance, including the ability to wear lenses as long as desired without problem. When assessing contact lenses, clinicians and scientists sometimes use contact lens comfort or discomfort to determine if the lens is compatible with the eye. It is expected that successful wear can be achieved when a patient has normal ocular surface and lid function, and when the contact lens is compatible with the lids and ocular surface, and minimally disrupts the tear film.¹⁰

In developing a definition, this subcommittee addressed the following four questions: (1) What is CLD? (2) How is CLD characterized? (3) What factors are associated or causative with CLD to classify it? (4) What are the resultant outcomes of CLD? Existing terminology also was reviewed to augment the definition and describe the clinical condition further.

DEFINITION OF CLD

Contact lens discomfort is a condition characterized by episodic or persistent adverse ocular sensations related to lens wear, either with or without visual disturbance, resulting from reduced compatibility between the contact lens and the ocular environment, which can lead to decreased wearing time and discontinuation of contact lens wear.

TERMINOLOGY RELATED TO THE NEW DEFINITION AND OTHER CONSIDERATIONS

Previously, CLD was considered to be a definable clinical condition. The term condition, considered as “a defective state of health”¹¹ or “a state of health,”¹² accurately describes the collection of abnormal signs and symptoms associated with the discomfort experienced by contact lens wearers as a result of the impact of lens wear on the ocular environment. An additional definition of the term condition is “a certain response elicited by a specifiable stimulus,” which also is appropriate for describing CLD.¹³

Many chronic conditions are experienced as episodic events in the early or emerging stages. Episodic is defined as having symptom-free periods that alternate with the presence of symptoms.¹⁴ Conditions that are persistent are those existing or continuing for a long time; those that continue to exist despite treatment.¹⁵ There is no question that CLD can be episodic and persistent.

Adverse ocular sensations are the increased perception, awareness, and feeling of the contact lens on the ocular surface, which can include symptoms of dryness and irritation, among others.

Visual disturbance is the perception, after initial contact lens adaptation, of transient visual symptoms and/or measurable visual disruption related to the wearing of the contact lens. In the case of CLD, visual disturbance can be a primary or secondary complaint, or it may not be present.

Compatibility of a contact lens with the eye, and its associated anterior structures and glands is a fundamental goal in the development of contact lenses. The ultimate contact lens would not elicit undesirable local/systemic effects. Compatibility is defined as the ability to exist in harmony¹⁶; therefore, contact lens compatibility can be defined as a state of the lens being able to exist in harmony with the ocular environment.

For the purpose of the definition, the ocular environment includes structures of the eye and adnexa, including the cornea, conjunctiva, eyelids, tear film, and main and accessory lacrimal glands, as well as the meibomian glands.

Wearing time encompasses any aspect of the time that the contact lens is worn, and includes comfortable wearing time, and the total wearing time during the day and/or overnight (during sleep). The total wearing time is the number of contact lens wearing hours with a specific modality; for instance, the total daily wearing time for a daily lens wearer is the overall time the patient reports between contact lens insertion and removal. The comfortable wearing time is the number of wearing hours that the patient characterizes the lens as being comfortable (without adverse ocular sensations) for a specific modality; for instance, the comfortable daily wearing time for a daily lens wearer is the number of comfortable wearing hours between contact lens insertion and removal, usually less than the total wearing time. Comfortable wearing time and total wearing time can be used clinically, as well as in research settings, to characterize successful or unsuccessful wear, as well as to characterize the quality of the wearing period.

The CLD occurs while wearing a contact lens; removal of the contact lens diminishes or eliminates the condition, and, in particular, the adverse ocular sensations. It should be noted that CLD, as defined here, is a condition that occurs after initial adaptation to contact lens wear and generally is not related to insertion of or adaptation to a contact lens. Discomfort may be accompanied by physical signs, including but not limited to conjunctival hyperemia, changes to the meibomian glands, or corneal or conjunctival staining (refer to the Tear Film & Ocular Surface Society [TFOS] CLD Workshop Report of the Contact Lens Interactions with the Ocular Surface and Adnexa

Subcommittee). The full range of severity can occur with CLD, from mild discomfort to ocular sensations requiring immediate lens removal. Clinically, CLD is reported to impact a patient's quality of life, although the association with severity and chronicity has yet to be delineated (refer to the TFOS CLD Workshop Report of the Epidemiology Subcommittee for more information on prognostic factors).

EXISTING TERMINOLOGY RELATED TO CLD

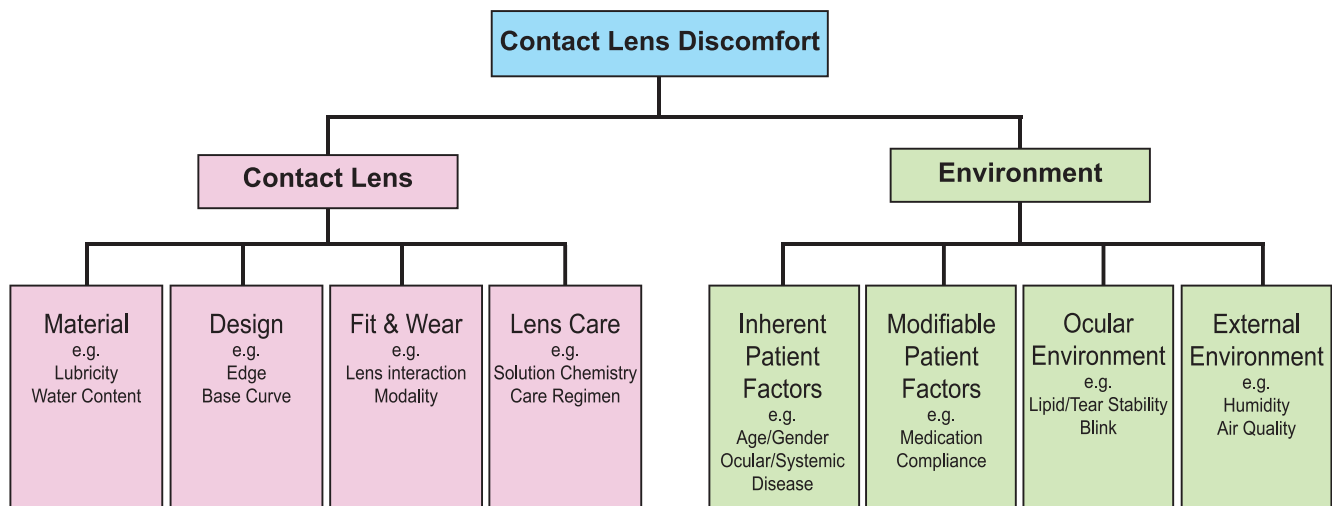
A number of other terms currently are used in the scientific literature that relate to CLD. Contact lens dryness often is used by patients to describe the adverse ocular sensations experienced while wearing contact lenses. However, in reality it likely is not the dryness of the contact lens, as the term implies, but rather adverse ocular sensations reported by patients. Contact lens dryness, therefore, should not be used to describe this condition, except to describe a specific symptom associated with CLD. Terms that describe the symptoms of dry eye experienced by contact lens wearers include contact lens dry eye, contact lens-related dry eye, or contact lens-induced dry eye (CLIDE), but to our knowledge there is no evidence in the literature to define or to provide an associated definitive pathophysiology.

The 2007 TFOS Dry Eye Workshop (DEWS) report lists discomfort as the one of the main symptoms of patients with dry eye, and defines dry eye as “. . . a multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance, and tear film instability, with potential damage to the ocular surface. It is accompanied by increased osmolarity of the tear film and inflammation of the ocular surface.”¹⁷ This definition suggests an association between discomfort and dry eye, although the direct mechanisms are not delineated. Similar pathophysiological changes that occur in dry eye can be observed in contact lens wearers; alternatively, contact lens wear can be a precipitating factor in dry eye disease and/or meibomian gland dysfunction.¹⁷⁻¹⁹ Thus, the terms contact lens dry eye or contact lens-induced dry eye (CLIDE) should be used to describe the pathophysiology of preexisting dry eye in a contact lens wearer.

Some features of subclinical dry eye may become clinically apparent once a contact lens is placed on the eye. In this case, the contact lens can amplify a preexisting dry eye state leading to increased symptoms of dryness. The use of the term contact lens dry eye is appropriate to describe the clinical scenario of increased tear film evaporation in patients with preexisting meibomian gland dysfunction²⁰ or other types of dry eye. Contact lens wear has been associated with an increase in meibomian gland atrophy measured with meibography, which also can be associated with an increase in tear evaporation.^{21,22}

Throughout the literature, the terms contact lens dry eye, contact lens-related dry eye, and contact lens-induced dry eye often are used to describe a symptomatic condition during lens wear that mimics the symptoms of dry eye. However, when the lenses are removed and symptoms no longer persist, this scenario is not a dry eye condition. Therefore, these terms should not be used interchangeably with CLD.

A number of terms in the literature have been used to describe the cessation of lens wear, including discontinuation, dropout, intolerance, abandonment, and lapse, and they often are used synonymously with each other.^{1-3,6,23} It is recommended, henceforth, that discontinuation of contact lens wear should describe the process of temporary or permanent cessation of lens wear. Further, contact lens dropout should refer to an individual who has discontinued wear for a sustained period of time. Thus, discontinuation of lens wear has the end-result of contact lens dropout. Time references can be used to clarify



Progression of CLD

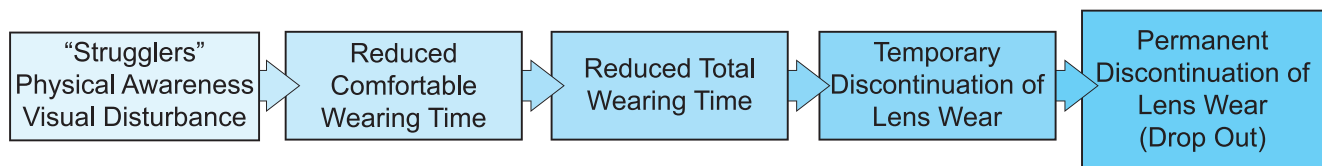


FIGURE. Classification of CLD. Examples of each subcategory are provided, but not intended to list all potentially related factors within each subcategory.

discontinuation and dropout; for example, discontinuation of lens wear for a sustained period of time (e.g., one year) could be considered permanent dropout.

The word tolerance in medicine is a general term that refers to “the ability to endure continued exposure with a lack of or low levels of immune response,” or “the capacity to endure pain.”^{24,25} Intolerance, the “quality or state of being intolerant,” then would be the lack of ability to tolerate a stimulus. Thus, contact lens intolerance is the state of being unable to tolerate contact lenses. The condition of CLD may well be a predisposition to intolerance with lenses and leads to, but is not synonymous with, discontinuation. The community often synonymously applies the terms intolerance and discontinuation, but intolerance should be considered, henceforth, as the physiological process by which a patient moves toward permanent discontinuation, and should not be used to describe an individual who has dropped out of lens wear.

CLASSIFICATION OF CLD

As yet to our knowledge, no definitive classification systems for CLD have been reported in the literature, although descriptions of groupings and etiologic approaches have been suggested. A prior attempt to standardize successful contact lens wear included considerations of wearing time, comfort, vision, and ocular physiology.²⁶ Additional efforts to characterize successful contact lens wear have included contact lens factors,²⁷ clinical evaluation of the fit and contact lens interactions,²⁸ and tear film considerations.²⁹ However, most approaches evaluating CLD discuss the various factors or

clinical findings associated with symptoms, such as patient, contact lens, and environmental factors. Additional factors associated with CLD are discussed in detail in the TFOS CLD Workshop Report of the Epidemiology Subcommittee.

The CLD classification scheme in the Figure categorizes discomfort into two major subclasses: the contact lens and the environment. These major subclasses are subdivided further into their potentially contributing elements; the contact lens subclassification is categorized further into material, design, fit and wear, and lens care. The environment subclassification is subdivided further into patient (inherent and modifiable factors) and environment (ocular and external) subcategories.

Material, design, and fit and wear, and lens care subcategories may impact CLD, and are discussed in detail in the TFOS CLD Workshop Report of the Contact Lens Materials, Design and Care Subcommittee. The contact lens material subcategory relates to the inherent polymeric composition of the lens material, and may include, but are not limited to, lubricity, water content, and wettability.³⁰ Lubricity, a promising material characteristic, may have a significant role in reducing wear and tear associated with interacting surfaces (e.g., material and lid).^{31,32} Water content, ionicity, and dehydration have been widely studied relative to the impact on contact lens wear. Dehydration characteristics have been shown to be difficult to measure on-eye as well as in regards to CLD, yet it is presumed that dehydration would be expected to impact the fit of the lens.^{33–35} While material oxygen transmissibility is a requirement for corneal health and the prevention of corneal edema,³⁶ it does not appear to be substantiated as of yet in terms of its relation to CLD (refer to the TFOS CLD Workshop

Report of the Contact Lens Materials, Design and Care Subcommittee for more information).

Contact lens materials and designs are important for movement and fit of the lens on the cornea and ocular surface. While different, the effects of material, design, and fit are challenging to separate as each impact the other. Design effects, such as the sharpness, thickness, contour, or slope of the lens edge, have been reported to have corneal, conjunctival, and lid effects.³⁷⁻⁴³ The thickness of the lens, and thickness variation across the lens, also can trigger adverse corneal and lid responses.^{36,44} In addition, the pressure exerted by the contact lens, or by regions of the contact lens based on design, can affect the corneal epithelial cells and parasympathetic nerves, in addition to tear exchange.⁴⁵⁻⁵⁰ Tear effects represent the elements of patients actually using their contact lenses following the fitting; for example, wear may represent whether the patient wears lenses on a daily or overnight basis, or whether the patient wears and replaces their lenses on a daily, 2-week, or monthly schedule. Deposition on or within the contact lens material is the result of tear film component interactions with the chemical moieties and/or pores within the material,⁵¹⁻⁵⁶ and is associated with material, and fit and wear, as well as lens care. More in depth discussions on the effects of contact lens care, including solution chemistry and the impact of the care regimen, can be found in the TFOS CLD Workshop Report of the Contact Lens Materials, Design, and Care Subcommittee.

The influence of the environment on CLD is based on patient and environment factors. Patient factors can be described as inherent, or existing as a permanent characteristic or attribute,⁵⁷ or patient factors can be modifiable. Inherent patient factors include demographic factors, such as age, sex, and race, as well as ocular and systemic disease. It is possible to modulate, although perhaps not eliminate, a patient's disease through treatment. Modifiable patient factors include, but are not limited to, medication use and contact lens wear, and/or care compliance. Medications can affect tear film production and precorneal tissue health,⁵⁸ and ocular and systemic diseases have been shown to impact the health and function of the tissues, and nerves of the cornea, conjunctiva, eyelids, and glands associated with tear film production.⁵⁹⁻⁶⁴

External environment factors include climate, allergens/pollutants, and visual demand. The climate the eye is exposed to, in terms of relative humidity, temperature, and air currents, can affect the tear film integrity and the contact lens material hydration, and, therefore, is a potential factor associated with CLD.⁶⁵⁻⁷⁰ For example, allergens and pollutants introduced to the ocular surface by the air or touch can produce adverse reactions in the tear film, cornea, conjunctiva, and eyelids that are associated with CLD.^{22,71-74} Visual demand and use of computers, as well as adverse lighting, can produce ocular strain due to unnatural blink rates.⁷⁵⁻⁷⁹ Patient and environment factors are discussed further in the TFOS CLD Workshop Report of the Epidemiology Subcommittee.

By definition, CLD occurs when there is reduced compatibility between the contact lens and the ocular environment. The lids, glands, ocular tissues, tear film, and blinking all may have a role in this process. The lipid layer, and the role of the lipid layer in tear stability and reducing evaporation, are examples of factors related to the ocular environment. Tear film deficiencies in production or exchange can impact the health of the entire ocular surface. The completeness and rate of the eyelid blink also has been shown to be associated with contact lens wear, and possibly CLD.⁷⁹⁻⁸¹ Further detailed discussion of the interaction of the contact lens with the tear film and ocular environment can be found in the TFOS CLD Workshop Report of the Contact Lens Interactions with the Tear Film Subcommittee and the TFOS CLD Workshop Report

of the Contact Lens Interactions with the Ocular Surface and Adnexa Subcommittee.

The modes of progression of CLD are presented in the Figure. The five steps show the progression from struggling and lens awareness, to reduced wearing time, to temporary and permanent discontinuation (drop out) of contact lens wear.

SUMMARY

The condition of CLD is a major concern for patients and clinicians alike, in that the end result of this condition is permanent contact lens discontinuation, or drop out. Successful contact lens wear can be described best as harmonious coexistence of the contact lens on the eye without any adverse effects. Ultimately, the ideal contact lens has material, design, and care characteristics allowing for optimal fit and wear, vision, and comfort, with minimal patient and environment effects, thereby preventing discontinuation, promoting ocular health, and improving quality of life.

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The TFOS International Workshop on Contact Lens Discomfort: Report of the Subcommittee on Epidemiology

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See the tables in the Introduction for the members of the TFOS International Workshop on Contact Lens Discomfort.

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The first citation in PubMed referencing the issue of comfort with contact lenses is a paper from 1960 linking hygienic contact lens care and comfortable lens wear.¹ Unfortunately, not all contact lens wearers are able to achieve acceptable comfort; and while tremendous developments in lens polymers, designs, replacement modalities, and care regimens have occurred over the past 50 years, the challenge of preventing or managing contact lens discomfort (CLD) is still common in clinical practice. Our limited understanding of the etiology and the correlation between signs and symptoms makes it more difficult for eye care practitioners (ECPs) to diagnose and manage CLD.

It has been estimated that there are currently more than 140 million contact lens wearers worldwide (Nichols JJ, written communication, 2013). It is much more difficult to estimate the number of individuals who have previously worn contact lenses and then abandoned lens wear as a result of CLD. Studies have reported that between 12% and 51% of lens wearers “drop out” of contact lens wear,²⁻⁶ with CLD remaining the primary reason for discontinuation.^{2,4}

EPIDEMIOLOGY

The World Health Organization defines epidemiology as “The study of the distribution and determinants of health-

related states or events (including disease), and the application of this study to the control of diseases and other health problems.”⁷ While CLD is not considered a disease, it cannot be denied that it is a health-related state, which can have profound consequences for contact lens wearers, ECPs, and the ophthalmic industry. Contact lens wearers who persistently experience discomfort with their lenses may initially reduce their daily wearing time to cope with the condition; this could be followed by wearing lenses less frequently and ultimately discontinuing lens wear altogether.^{2,4}

HISTORICAL CONTEXT

There has been increased interest in and reporting of CLD in the literature. A PubMed search for “contact lens” in the title or abstract fields elicited 7024 responses. When “comfort” or “discomfort” was added to the search terms, 406 reports resulted. If these data are broken down by decade, 2.6% of contact lens papers in the 1970s referred to comfort/discomfort in the title or the abstract (a similar percentage for the 1980s), rising to approximately 7.5% of the relevant literature since 2000.

Review of the literature suggests that there have been discrete periods of research interest in CLD. Since lens types,

modalities, and care regimens have changed radically over the past 25 years, it is important to reference the era in which data were collected when discussing the epidemiology of CLD. Much of the work reported in the 1980s and 1990s sought to describe the frequency and related symptomatology in CLD (Vajdic CM, et al. *IOVS* 1996;37:ARVO Abstract 5178).⁸⁻¹³ With perhaps one notable exception,¹⁴ work focusing on the determinants of CLD has been largely conducted over the last 15 years,¹⁵⁻²⁴ although few fully controlled studies have been undertaken. Around the turn of the millennium, the relevance of contact lens hydration and dehydration to CLD was reported by a number of authors.²⁵⁻²⁹ Although silicone hydrogel lenses were introduced into the market in 1999, information on the effects of these materials (and directly or indirectly, their enhanced oxygen transmission characteristics) on CLD was reported only beginning in 2005.³⁰⁻³⁶

Even though lens storage systems have been a longstanding and fundamental part of contact lens wear, their impact on CLD and related phenomena has been primarily reported in the last 10 years,³⁷⁻⁴⁵ with only a few earlier reports. More recently, studies investigating the possible benefits of “sustained-release” comfort-enhancing agents from daily disposable lenses have been reported.⁴⁶⁻⁴⁸

SCOPE OF REPORT

The goals of the Epidemiology Subcommittee of the CLD Workshop were to (1) provide a clinical context of CLD and to differentiate this condition from dry eye that can occur in both contact lens and non-contact lens wearers; (2) report on the frequency of CLD; (3) investigate the factors that are associated with CLD; (4) examine the impact of CLD from both a quality of life and economic perspective; and (5) consider future research directions for evaluating the epidemiology of CLD. The emphasis of this report is on CLD as a symptom, not as a sign, and on CLD that is not due to a specific pathophysiology to which it could otherwise be attributed.

The objective was to focus on associations that have been reported from clinical and epidemiological studies. The report was not intended to expound on the mechanistic or etiological considerations of CLD that are described in detail in the other workshop subcommittee reports. The epidemiology of CLD with disposable soft lenses was primarily considered within a historical context with respect to other lens types where relevant.

CLINICAL CONTEXT: THE CLINICAL PICTURE OF CLD

Eye care practitioners are all too familiar with patients presenting with the symptoms and sometimes the associated signs of CLD. However, the clinical picture of CLD is not as well represented in the literature as are the subjective and objective attributes of dry eye.

SYMPTOMS OF CLD

While the generic symptom “discomfort” may be the most frequently cited reason for discontinuing contact lens wear, what the term “discomfort” actually means to individuals is more complex. Reporting of CLD symptoms may be influenced by personal factors such as the motivation to wear contact lenses and personal economics. For example, patients who dislike wearing spectacles are less likely to complain about their contact lenses and may be more tolerant of their lenses. Creative approaches to this potential bias include subjective

assessment of symptoms in real time via text messaging and e-mail prompts on handheld Web-enabled devices.^{49,50}

Dryness

In 1986, McMonnies and Ho⁵¹ identified contact lens wear as a provocative factor in what was termed “marginal dry eye.” Since then the frequent clinical use of the terms “contact lens induced dry eye” and “contact lens induced dryness” suggests that a sensation of “dryness” is the common interpretation of such discomfort. Dryness appears to diminish when lenses are removed⁵² and to change during the wearing period, with increased symptoms observed in the afternoon and evening.⁵²⁻⁵⁵

Other Symptoms in CLD

Receptors on the ocular surface do not respond to dryness *per se*. The perception of symptoms of contact lens-related discomfort is complex and likely results from interactions across multiple psychophysical channels. The neurobiological mechanisms underlying perception of symptoms are discussed in the report from the Neurobiology of Discomfort and Pain Subcommittee. Other than dryness, “scratchy” and “watery” sensations have been reported 52% and 30% of the time, respectively, in daily hydroxyethyl methacrylate (HEMA) contact lens wearers.⁵⁶ Other symptoms have also been reported. Among a sample of 83 adapted contact lens wearers, blurry vision was a frequent symptom. Scratchiness and irritation were infrequent symptoms, and light sensitivity and eye soreness were seldom experienced.⁵⁴ In a large population-based study of dry eye (2500 subjects including some contact lens wearers), blurred vision was found to be the most commonly reported symptom.⁵⁷

In a cross-sectional study examining the differences between spectacle wearers and those wearing rigid gas-permeable contact lenses (RGPCl) and soft contact lenses (SCL), there were no significant differences in the frequency of ocular symptoms between the SCL and RGPCl wearers, and the most common symptom was tired eyes. Symptoms of tiredness, itchiness, watering, pain, aching, excessive blinking, and burning had similar rates of occurrence for all three groups. However, symptoms of dryness and self-reported redness were reported more frequently in contact lens wearers compared to spectacle wearers.¹³

CLINICAL SIGNS IN CLD

The published literature contains many references to traditional clinical tests that may be helpful in the diagnosis of CLD. These include assessment of the pre-lens tear film,^{16,58-60} meibomian glands,⁶¹ bulbar and limbal hyperemia,⁶² and corneal and conjunctival staining.⁶³⁻⁶⁵ A recent multicenter study conducted by Young and colleagues⁶⁶ in the United States and Canada specifically investigated which tests commonly undertaken in ECP offices are helpful in the diagnosis of contact lens dryness. The symptomatic participants exhibited a wide range of clinical signs accompanying their CLD, but there was not one single common sign that was present in all participants. However, poor lens wetting was reported in 40%, and 39% of participants had rapid pre-lens noninvasive tear breakup times (NITBUT) and precorneal fluorescein breakup times (FBUT). Further detailed discussion of the clinical signs reported to be associated with CLD can be found in the reports by the Contact Lens Interactions with the Ocular Surface and Adnexa and the Clinical Trial Design and Outcomes Subcommittees.

THE RELATIONSHIP BETWEEN SYMPTOMS AND SIGNS IN CLD

In populations with dry eye disease, the lack of association between clinical signs and symptoms is frequently reported.^{67,68} The most common clinical signs have also been demonstrated to be poorly correlated with symptoms in CLD,⁶⁸ but this may be a reflection of the tests employed. Investigating symptoms in SCL wearers is likely to have more diagnostic value than conducting clinical tests. This is supported by Young and colleagues,⁶⁶ who reported that 23% of the symptomatic participants did not exhibit typical clinical signs of dryness. A set of tests combining both subjective and objective assessments may be more predictive for CLD or dryness than a single diagnostic test.^{60,69}

DEFINITIONS FOR DRY EYE AND CLD

Dry eye disease is a common clinical presentation in eye care offices. The Tear Film & Ocular Surface Society (TFOS) Dry Eye Workshop (DEWS) report of 2007 established the working definition: “Dry eye is a multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance, and tear film instability with potential damage to the ocular surface. It is accompanied by increased osmolarity of the tear film and inflammation of the ocular surface.”⁷⁰ The prevalence of dry eye disease varies with populations and the working definitions of dry eye and runs as high as 33%.^{57,71–74}

Contact lens discomfort is also a common clinical presentation in contact lens practice and is found in greater numbers than dry eye itself.^{75–77} The definition of CLD as set out by the Definition and Classification Committee is as follows: “Contact Lens Discomfort (CLD) is a condition characterized by episodic or persistent adverse ocular sensations related to lens wear either with or without visual disturbance, resulting from reduced compatibility between the lens and ocular environment, which can lead to decreased wearing time and discontinuation from lens wear.”

HOW DO CLD AND DRY EYE INTERACT?

Clearly, the entities of dry eye and CLD can intertwine. Clinical wisdom suggests that those patients who have traditional signs and symptoms of dry eye disease are more likely to have CLD when fitted with contact lenses.⁵³ In addition, as the presence of dry eye disease increases with age,⁷⁸ it is likely that in some individuals not diagnosed with dry eye at the time of fitting, their CLD may instead be a manifestation of acquired dry eye disease.

HOW ARE CLD AND DRY EYE DIFFERENT?

There are many individuals without signs or symptoms of dry eye who suffer irritation when wearing their contact lenses and note relief with lens removal.⁵² As reported in the recent study by Young and colleagues,⁶⁶ 23% of the subjects with CLD had no signs of dry eye. Conversely, practitioners often have patients with significant signs of dry eye who report being able to wear their contact lenses comfortably. The insertion of a contact lens introduces numerous factors that may be related to CLD, including surface deposits and wettability, disturbance of the tear film, stimulation of eyelids, oxygen availability, the trapping of debris under lenses, the loss of tear film under lenses, interaction of the lens material and design with the ocular tissues, interference with the blink, and the use of care

solutions and lubricating drops. A single factor or a combination of these entities may contribute to CLD.

DIFFERENCES IN SYMPTOMS BETWEEN CLD AND DRY EYE

It is interesting to note the differences in the symptoms between dry eye and CLD. The ocular surface sensations that individuals experience are related to the innervation of the cornea, conjunctiva, and lids^{79–81} and are discussed with respect to CLD in the report by the Neurobiology of Discomfort and Pain Subcommittee. Many questionnaires have been used to document the specific symptoms reported by individuals with dry eye and CLD. Using the McMonnies questionnaire, patients with dry eye most commonly reported symptoms of “dryness,” “grittiness,” and “burning.”⁸² Holly⁸³ related that in dry eye, “sandy” and “gritty” feelings were most common along with “burning” and a “foreign body sensation.” In contrast, “dryness” is reported as the most common symptom in contact lens wearers, followed by “scratchiness” and “watery eyes.”^{54,56} There can be distinct differences between the symptoms reported by dry eye sufferers and those of contact lens wearers experiencing CLD.⁵² Contact lens wearers report symptoms more frequently and with increased intensity late in the day.⁷⁶ Surprisingly, older contact lens wearers have been shown to experience fewer symptoms as they age compared to dry eye patients.^{73,84,85}

DIFFERENCES IN SIGNS BETWEEN CLD AND DRY EYE

Dry eye patients can present with no observable signs of dry eye; however, most have some combination of low Schirmer scores, ocular surface staining, low tear breakup times, low tear meniscus heights, high tear osmolarity, and meibomian gland dysfunction (MGD).⁷⁰ Contact lens discomfort patients may have some of these characteristics, but they are often absent. Objective findings specific to CLD may relate to lid changes including lid wiper epitheliopathy (LWE).⁸⁶ Corneal staining has been associated with the use of some care systems and contact lenses,³⁸ although some amount of corneal staining is considered normal in contact lens wearers.⁸⁷

In summary, patients with dry eye are more likely to have contact lens-related symptoms of discomfort. However, a significant number of contact lens wearers who suffer from CLD show no signs of dry eye disease. Clinicians have a difficult job in determining which factors have caused CLD and establishing if they are patient or contact lens related.

THE SPECTRUM OF CLD

As with many diseases and conditions, CLD is reported with varying levels of intensity, which may or may not impact the patient’s contact lens wearing patterns. A representation of this “spectrum” of CLD is presented in Figure 1 in the report of the Definition and Classification Committee. However, it is important to recognize that some individuals may not progress from one “stage” to the next in a sequential manner. A large proportion of individuals may report symptoms of CLD and could be considered to be “strugglers.” These individuals may continue to wear their lenses despite their discomfort, possibly with the use of contact lens rewetting drops or artificial tears.⁵³ Some wearers who are struggling with CLD may choose to decrease their daily wearing time, particularly if they experience increasing discomfort as the day progresses. Simply removing lenses has been anecdotally reported to greatly relieve CLD for many individuals. Decreased wearing time may

be followed by a decrease in the number of days each week that lenses are worn (the wearing frequency), and both of these behaviors have been reported by dissatisfied lens wearers.⁴ A natural progression is from less frequent lens wear to extended periods when lenses are not worn at all. Temporary discontinuation of lens wear has been reported in the literature by several authors.^{2,3,5,6} Unfortunately, the most dissatisfied contact lens wearers will eventually become former lens wearers with permanent discontinuation from lens wear, often called “dropout.”^{2,3}

FREQUENCY OF CLD

In order to gain a better understanding of CLD, it is important to recognize how often the condition occurs in the population. Clarification of the terminology that is used to report this problem is necessary. In some studies, “counts” are used to report the number of individuals who experience symptoms associated with CLD. “Incidence” is generally used to report the number of new cases of a condition that develop in a population within a specified period of time, and may not be the most appropriate term to use when referring to how often contact lens wearers experience discomfort. “Prevalence” is the term usually used in the contact lens literature and in this case represents the number of people who experience CLD in a defined population. “Frequency” is an overarching term that is used to describe counts, prevalence, and incidence.

ASSESSMENT METHODS AND EVALUATION OF CLD

As discussed earlier, CLD is primarily reported according to symptomatology as opposed to the observation of signs. While the precise etiology of CLD is yet to be determined, the use of symptoms as outcome measures is appropriate because it relates directly to the patients’ experience with contact lenses and the motivation to seek and use treatment, regardless of the presence of observable signs. The frequency and intensity with which these symptoms are reported can be assessed with the use of questionnaires. McMonnies⁸² and McMonnies and Ho⁸⁸ developed a questionnaire to evaluate, in part, ocular discomfort symptoms and reported its use in individuals wearing and not wearing lenses. A number of questionnaires have been developed to assess dry eye symptoms in non-lens wearers^{89–91}; however, the first questionnaire developed specifically to assess symptoms in contact lens wearers was the Contact Lens Dry Eye Questionnaire (CLDEQ).^{53,54} Both the McMonnies and CLDEQ questionnaires have been used as assessment tools in studies of CLD.^{55,82} A short version of the CLDEQ has been reported to be more accurate in predicting CLD and better at discriminating a contact lens-related dry eye diagnosis than McMonnies’ questionnaire. Using the full model parameters for the CLDEQ there appears to be a predictive efficiency of 1.50, with a sensitivity of 83% and specificity of 67%.⁵⁵ More recently, a revised version of the CLDEQ has been developed, the CLDEQ-8.⁹² The scores from the CLDEQ-8 have been shown to correlate well with baseline CLD status and to be capable of measuring changes in CLD scores associated with refitting with different contact lens materials.⁹²

POPULATION-BASED CLD STUDIES

Contact lens discomfort is commonly encountered in clinical practice and frequently reported in the literature. However, few studies have addressed the frequency of CLD in a natural population setting, as most studies investigate its occurrence in clinical practices or hospital settings. A PubMed search

employing the keywords “contact lens discomfort,” “population study,” and “epidemiological study” revealed no prospectively designed epidemiological studies investigating the natural occurrence and evolution of CLD, dryness, or related symptomatology associated with contact lens wear in a population-based setting for adapted contact lens wearers or in individuals who started wearing contact lenses for the first time. Most of our knowledge of the magnitude of CLD in population-based investigations comes from epidemiological studies designed specifically for the investigation of the prevalence of dry eye disease. However, the majority of these studies were conducted in older populations, and contact lens wear was infrequently reported.

The first population-based dry eye study to investigate dry eye symptoms in contact lens wear was conducted in Canada in the mid-1990s.⁷¹ The purpose of the Canadian Dry Eye Epidemiology Study (CANDEES) was to determine the overall prevalence and severity of dry eye symptoms in a population ranging in age from younger than 10 years to older than 80 years and to obtain details regarding possible associated factors. In total, 13,517 questionnaires were returned, with 24.3% of these (3285) from contact lens wearers. Overall, 50.1% of the contact lens wearers had dry eye symptoms compared to 21.7% of the respondents who did not wear contact lenses.

More recently in the Japanese Koumi study, 2791 residents completed a dry eye questionnaire; 105 were contact lens wearers.⁹³ Contact lens use was found to be associated with a composite outcome of clinically diagnosed dry eye disease or severe symptoms of dry eye disease. The prevalence of severe dryness symptoms in contact lens wearers was found to be 28% in males and 35% in females. In another epidemiological study investigating the prevalence of dry eye disease among 3433 high school students, contact lens wear was reported by 1298 of the respondents; and, compared to findings in non-contact lens wearers, contact lens wear was associated with a significantly higher prevalence of severe dry eye symptoms (37% in both boys (odds ratio [OR], 4.14; 95% confidence interval [CI], 3.42–5.00) and girls (OR, 4.68; 95% CI, 3.02–7.26).⁹⁴ A recent, similarly designed study from Shandong Province, China, reported a prevalence of dryness symptoms in 8.4% of the 1885 high school students evaluated and 32.8% of the 122 contact lens wearers.⁹⁵ In another study designed to estimate the prevalence of dry eye disease among 3549 Japanese office workers using visual display terminals (1349 contact lens wearers), contact lens wearers were more likely to report severe symptoms of dry eye (prevalence, 50.4%).⁹⁶

It is important to recognize that there may be significant differences in the prevalence of CLD according to geographical location. The only population-based studies reported in the literature were conducted in Canada, Japan, and China; the results from these studies are summarized in Table 1.

CLINICAL PRACTICE/HOSPITAL–BASED CLD STUDIES

Although population-based studies are preferred in epidemiological research, more studies of CLD are performed in clinical practice, office, or hospital settings. Studies in these settings do not require the resources and complex sampling techniques that are required for population-based studies yet are still able to provide insight into symptoms of discomfort and dryness, which continue to be the most commonly cited reasons for discontinuation of contact lens wear.^{2–6} Table 2 summarizes the prevalence of CLD that has been reported in clinical and research-based studies in the preceding quarter of a century. The results of such studies in limited populations may not be generalizable, and there may be issues of sampling, appropri-

TABLE 1. Prevalence of CLD From Population-Based Studies

Study	Location	Number of Contact Lens Wearers	Age	Sex	Symptom Assessment	Prevalence	References
CANDEES study	Canada	3285	10–80 y	Not reported for contact lens wearers	Presence or absence of dryness and severity rating	Overall: 50.1%	Doughty et al., 1997 ⁷¹
Koumi study	Japan	105	≥40 y	Male 24%, female 76%	Severe symptoms of both ocular dryness and irritation	Male 28%, female 35.0%	Uchino et al., 2011 ⁹³
Japanese VDT users study	Japan	1390	≥22 y	Male 60%, female 40%	Severe symptoms of both ocular dryness and irritation	Overall: 50.4%	Uchino et al., 2008 ⁹⁶
Japanese high school students study	Japan	1298	15–18 y	Male 77%, female 23%	Severe symptoms of both ocular dryness and irritation	Male 36.8%, female 37.4%	Uchino et al., 2008 ⁹⁴
Chinese senior high school students study	China	122	Not mentioned	Not mentioned	Severe symptoms of both ocular dryness and irritation	Overall: 32.8%	Zhang et al., 2012 ⁹⁵

ateness of controls, and other biases, which need to be considered in their interpretation.

In 1986, McMonnies and Ho⁵¹ were the first to report that soft lens wearers had more frequent symptoms of dryness than both non-lens wearers and hard contact lens wearers. Brennan and Efron⁵⁶ conducted the first study to specifically investigate the extent of symptoms of discomfort associated with wearing soft HEMA lenses and to correlate patient and lens factors with these symptoms. A total of 104 SCL wearers in the contact lens clinic at the University of Melbourne, Australia, reported how frequently they experienced symptoms during contact lens wear. Dryness was the most frequently reported symptom; 75% of the patients surveyed reported experiencing this symptom to some extent.

Almost a decade passed before the next publication appeared in the literature reporting the prevalence of symptoms of discomfort during contact lens wear. In a study designed to investigate the preocular tear film characteristics of SCL wearers, Guillon and colleagues⁹⁷ in the United Kingdom assessed symptomatology with the McMonnies questionnaire and reported that 44% of the 184 SCL wearers in their study were symptomatic for CLD. Another study was conducted in Australia at a similar time involving 171 SCL wearers and 48 RGPCL wearers.¹⁴ Once again, the lens wearers were asked to report the frequency of ocular symptoms: 13% of SCL wearers and 23% of RGPCL wearers experienced dryness either often or constantly.

With the exception of the dry eye study conducted by Doughty and colleagues⁷¹ in 1997, the first studies to specifically report on the prevalence of CLD in North America started to appear in the literature in the year 2000. Begley and colleagues⁵⁴ reported a prevalence of dryness of 37% and evening discomfort during contact lens wear of 37% in a population of 83 patients in a private optometry office in Toronto, Canada. The questionnaire used in this study was the precursor to the CLDEQ. A larger study soon followed, conducted in optometric practices in Canada and the United States, the results of which were published in 2001 and 2006.^{52,53} In this study 367 contact lens wearers (83% SCL, 17% RGPCL) completed the original CLDEQ. Ocular discomfort was reported by 79% of respondents and dryness by 77%. A

study conducted during a similar time frame at the University of Waterloo in Canada used the Dry Eye Questionnaire (DEQ) to evaluate symptoms in presbyopes wearing SCLs and reported dryness in 68% of the study participants.⁹⁸

Guillon and Maissa⁷⁵ conducted an additional larger study to evaluate dry eye symptomatology of lens wearers in the United Kingdom and reported their findings in 2005. In their study, 502 SCL wearers completed the McMonnies questionnaire; and overall, 43% reported dryness, with 28% reporting these symptoms to be moderate to severe compared to 15% in the age-matched nonwearers. About the same time, Nichols and colleagues⁷⁶ used a survey to evaluate self-reported dry eye disease and dryness symptoms across refractive modalities. They reported that 53% of the 393 contact lens wearers responded that they thought they had dry eye, and 68% reported symptoms of dryness while wearing their lenses.⁷⁶ After controlling for age and sex, the authors reported that contact lens wearers were 12 times more likely than emmetropes and five times more likely than spectacle wearers to report dry eye. This survey was followed by the Contact Lens and Dry Eye Study (CLADES). In this study Nichols and Sinnott⁶⁰ employed the CLDEQ and reported a prevalence of dry eye of 55.3% in a cohort of 360 contact lens wearers (91% SCL, 9% RGPCL).

The first study in the literature that investigated the prevalence of ocular surface symptoms in a sample of more than 1000 SCL wearers was reported in the literature in 2006.⁹⁹ This study was conducted across the United States and Canada in 82 optometry and two ophthalmology offices. Overall, 28% of respondents reported symptoms of dryness, 17% discomfort, and 31% reduced comfortable wearing time.

In a study conducted by Richdale and colleagues⁴ that was designed to determine the frequency and factors associated with contact lens dissatisfaction and discontinuation, 453 current and lapsed SCL and RGPCL lens wearers completed a self-administered survey in which they reported the presence or absence of a series of symptoms while wearing contact lenses. Overall, 73% reported at least one symptom, with 76% of the reported symptoms being dryness and 67% discomfort. Thirty-five percent of the current wearers also reported dissatisfaction with their lens wear. In a smaller study

TABLE 2. Prevalence of CLD From Clinical Practice/Hospital-Based Studies

Study	Location	Number and Type of CL Wearers	Age	Sex	Symptom Assessment	Prevalence	References
Marginal dry eye diagnosis: history versus biomicroscopy	Australia	177 non-CL 163 SCL 160 rigid	Not reported	Not reported	Dryness, grittiness, burning, soreness, scratchiness (McMonnies questionnaire)	CL wearers reported symptoms more frequent than non-CL; SCL > rigid	McMonnies and Ho, 1986 ⁵¹
Symptomatology of HEMA CL wear	Australia	104 SCL	24 ± 9 y	Male 48% female 52%	Self-reported often or seldom	Dryness 75%	Brennan and Efron, 1989 ⁵⁶
Preocular tear film characteristics	United Kingdom	184 SCL	31 ± 7 y	Male 46% female 54%	McMonnies questionnaire	44% symptomatic	Guillon et al., 1997 ⁹⁷
Frequency of ocular symptoms	Australia	171 SCL 48 RGP	17–67 y	Male 33% female 67%	Self-reported often or constantly	Dryness 13%–23% (SCL–RGP)	Vajdic et al., 1999 ¹³
Responses of CL wearers to a dry eye survey	Canada	68 SCL 15 RGP	18–78 Average 41 ± 13 y	Male 31% female 69%	Questionnaire (preliminary version of CLDEQ)	Dryness 37% evening discomfort 37%	Begley et al., 2000 ⁵⁴
Optometric practices in North America	United States and Canada	305 SCL 62 RGP	18–94 Average 39 y	Male 36% female 64%	CLDEQ	Ocular discomfort 79% dryness 77%	Begley et al., 2001 ⁵⁵ ; Chalmers and Begley, 2006 ⁵²
Symptoms in presbyopes following 6 mo lens wear	Canada	141 SCL	40–71 Average 51.5 ± 6.3 y	Male 21% female 79%	Dryness Visual changes DEQ	Dryness 68%	du Toit et al., 2001 ⁹⁸
Dry eye symptomatology of SCL wearers	United Kingdom	502 SCL	17–69 Average 34 ± 10 y	Male 33% female 67%	McMonnies questionnaire	43% (28% moderate to severe symptoms)	Guillon and Maissa, 2005 ⁷⁵
Self-reported dry eye disease across refractive modalities	United States	393 (type not reported)	Average 30.3 ± 10.7 y	Male 33.9% female 66.1%	Self-reported dry eye Dryness (occasionally to constantly)	Dry eye 52.7% dryness (occasionally, frequently, or constantly) 68.1%	Nichols et al., 2005 ⁷⁶
CLADES	United States	327 SCL 33 RGP	Average 31.1 ± 11.5 y	Male 32% female 68%	CLDEQ	55.3%	Nichols and Sinnott, 2006 ⁶⁰
Prevalence of ocular surface symptoms in CL wearers	United States and Canada	1092 SCL	18–42 Average 28 y	Male 30% female 70%	CLDEQ	Dryness 28% discomfort 17% reduced comfortable WT 31%	Riley et al., 2006 ⁹⁹
Frequency and factors associated with CL dissatisfaction and discontinuation	United States	453 (current and lapsed SCL and RGP wearers)	Average 32.1 ± 11.0 y	Male 36% female 64%	Self-administered survey presence/absence of symptoms	73% reported one or more symptoms (76% dryness, 67% discomfort) 35% of current wearers reported dissatisfaction Symptoms often 24%	Richdale et al., 2007 ⁴
Symptoms of CL wearers using VDTs, Portugal	Portugal	71 SCL	19–38 Average 24.9 ± 5.5 y	Male 31% female 69%	Presence/absence of symptoms		Gonzalez-Mejome et al., 2007 ¹⁰⁰
CL dryness symptoms in UK wearers	United Kingdom	932 SCL	<20 to >61 y	Male 30% female 70%	CLDEQ (modified scoring)	Dryness 31% (plus marginal 13%)	Young et al., 2011 ¹⁰¹

CL, contact lens; WT, wearing time.

conducted in Portugal, the prevalence of CLD was investigated among 71 SCL wearers who were using visual display terminals (VDTs). Symptoms were reported to occur “often” by 24% of the study participants.¹⁰⁰

The majority of studies investigating the prevalence of CLD were conducted prior to the widespread use of contemporary contact lens materials. However in 2011, Young and colleagues¹⁰¹ reported on the prevalence and factors associated with contact lens-related dryness in a large cohort of contact lens wearers in the United Kingdom. The CLDEQ was self-administered to 932 SCL wearers at 12 clinical sites; 37% were wearing silicone hydrogel lenses and 30% daily disposable lenses. Both frequency and late-day intensity of dryness were considered in the analysis of the results. Overall, 31% of the wearers reported dryness consistent with contact lens-related dry eye (CL-DE) with a modified scoring technique, and 13% reported marginal CL-DE. The class of lens materials was not significantly related to CL-DE status. Further discussion of the possible role of lens material and replacement frequency on the prevalence of CLD is provided in the section on lens-related factors and the TFOS Subcommittee report on materials, design, and care.

In those who continue to wear contact lenses, the prevalence of CLD and dryness symptoms in the literature has been remarkably consistent, with rates averaging around 50% (Table 2). This is significantly greater than the rates that have been reported in non-lens wearers.^{13,55,71,75,102}

FACTORS ASSOCIATED WITH CLD

In contrast to dry eye and other ocular diseases, relatively little is known regarding the factors that may be associated with CLD. This section discusses the literature evidence for factors relating to the patient, the contact lenses, and the environment in which they are worn.

Patient-Related Factors

Nonmodifiable Factors Associated With CLD. *Sex.* The evidence supporting a strong association for sex effects in CLD is mixed. Chalmers and colleagues⁵² evaluated 1054 patients with a mean age of 39 years for symptoms of CLD. Using the CLDEQ, they found no difference in either the frequency or intensity of dryness associated with contact lens between males and females. Young and colleagues¹⁰¹ also reported on dryness symptoms in 932 SCL wearers across the United Kingdom (ages ranging from younger than 20 to older than 61 years). In agreement with Chalmers and colleagues, sex was not associated with dry eye status in contact lens wearers. In contrast, du Toit and colleagues⁹⁸ reported a sex effect in their study of 150 neophyte and established presbyopic contact lens wearers aged 40 and older. Using the DEQ to assess dryness symptoms, they reported that females had higher overall dryness ratings and experienced more frequent symptoms than males. In addition, Nichols and Sinnott⁶¹ showed, in the 360 lens wearers in CLADES, that female sex was associated with contact lens dry eye status, even after controlling for confounding factors. Similarly, González-Mejome and colleagues¹⁰⁰ evaluated 71 contact lens wearers within an academic population and concluded that females were more likely to report symptoms of scratchiness compared to males. Riley and coworkers⁹⁹ also reported on 1092 established soft lens wearers, from two ophthalmology and 82 optometric practices in North America, ranging from 18 to 39 years of age. In their study, patients were separated into one of two groups using the CLDEQ, “problem patients” and “problem-free patients.” In the problem patients group, there was a

statistically significant increase in the proportion of women compared to the problem-free group. Lastly, in CLADES, Nichols and Sinnott⁶⁰ showed that female sex was predictive of contact lens dry eye, after controlling for multivariate factors.

While studies indicate that women may be more likely to report symptoms of contact lens dryness and discomfort, female sex does not appear to be a consistent factor relating to lens dropout. Pritchard and colleagues⁵ reported on 1444 surveys completed by established and lapsed lens wearers in Canada and found no association between male or female sex and lens discontinuation. More recently, Dumbleton and colleagues² surveyed 4207 patients across Canada and again found no difference in sex distribution between current and lapsed wearers. In contrast to these reports, Richdale and colleagues⁴ surveyed 730 subjects from a university-based population and identified male sex as a significant factor associated with lens discontinuation. The findings from this latter study may reflect differences in motivation to continue lens wear as opposed to sex differences leading to discomfort.

Age. Age has been shown occasionally to be associated with CLD. The strongest piece of evidence supporting an association between age and symptomatic contact lens wear stems from a study by Chalmers and colleagues,¹⁰³ who reported that dryness associated with contact lens wear was inversely correlated with age, with more symptoms reported by younger wearers.⁵² In contrast to non-contact lens wearers with dry eye, dryness was greatest in patients 20 to 40 years old and reported less often in the older age groups. Similarly, in the presbyopic study by du Toit and colleagues,⁹⁸ the authors reported that younger wearers (40–51 years old) experienced dryness 1.4 times more frequently than older wearers (52–71 years old). In 882 young adults recruited from various clinical sites in North America, Chalmers and colleagues¹⁰³ reported that hydrogel lens wearers had more frequent dry eye symptoms, increasing as a function of age up to 35 years old. However, this age effect was not evident for silicone hydrogel lens wearers. Since more silicone hydrogel wearers in this study reported a previous dry eye diagnosis than hydrogel wearers, the authors speculated that the silicone hydrogel lens cohort likely included unsuccessful hydrogel patients who had been refitted with silicone lenses, potentially confounding the relationship between lens dryness and age in this latter group. Lastly, Nichols and Sinnott⁶⁰ did not show age to be related to contact lens dryness in CLADES when controlling for multiple other factors.

Ethnicity. In contrast to dry eye, where there is an increased incidence of disease in Hispanic and Asian populations,⁸⁴ a clear association between ethnicity and CLD has not been identified.⁶⁰ A steeper corneal curvature in Chinese subjects has been shown to adversely affect lens fit for SCL.¹⁰⁴ Differences in tears, including a reduced tear volume and changes in rheological properties, have also been reported for Asians compared to non-Asians (Lin M, Svitova T. *IOVS* 2010;51:ARVO E-Abstract 4155).¹⁰⁵ While these differences may impact lens comfort and dryness symptoms, there are no definitive studies that establish a linkage between them.

Poor Tear Film Quality/Quantity. Expert clinicians argue that, in a prefitting examination, reduced tear volume, shortened breakup time, and reduced tear production, as measured by Schirmer tests, are predictors for symptomatic contact lens wear. Evidence provided by Glasson and colleagues⁵⁹ support that the tear film of contact lens wearers is important in understanding CLD and achieving success with lens wear. In their early study, they evaluated 10 soft lens wearers, split equally into tolerant and nontolerant groups. Comfort was assessed using the McMonnies questionnaire. The

results of this pilot study indicated that tolerance was associated with tear breakup time and tear flow rate, with tolerant wearers demonstrating greater tear stability and faster tear flow. In a subsequent study to further examine these findings, 38 tolerant and intolerant lens wearers were assessed for clinical changes in tear film before and after lens wear.¹⁶ For the purposes of this study, the authors defined patients as intolerant if they were able to wear lenses for only 6 hours or less; comfort symptoms were once again assessed using the McMonnies questionnaire. Baseline patient characteristics that were correlated with tolerance to lens wear included the maximum blink interval, NITBUT, pattern of tear film breakup, phenol red thread test, and tear meniscus area and height. The authors concluded that the tear film of tolerant and intolerant wearers is different in the absence of a contact lens.

Blink Rate and Completeness of Blinking. Little evidence exists to support an association between changes in blink rate and comfort with lens wear. It has been proposed that longer blink intervals and incomplete blinking may lead to drying of and deposits on the front surface of the lens during wear.¹⁰⁶ However, wear of noncontemporary lens materials has been reported to increase blink rate when compared to that of non-lens wearers.¹⁰⁷ It is theorized that an increased blink rate occurs as a result of irritation of the eyelid and/or ocular surface during lens wear. A recent study by Ishak and colleagues¹⁰⁸ confirmed a lens-induced increase in blink rate in subjects wearing contemporary silicone hydrogel and hydrogel lens materials. Using video recordings, blink rate was measured at baseline and after 1 and 2 months of lens wear. After 2 months, the mean blink rate was found to be 20 and 22 blinks per minute for silicone hydrogel and hydrogel lens wearers, respectively, which was significantly increased compared to 15 blinks per minute for the non-lens-wearing controls. There was no difference in the completeness of the blink between groups.

The impact of blink rate on CLD becomes important during near tasks in which concentration can negatively influence blink rate. Jansen and coworkers¹⁰⁹ reported on 15 established soft lens wearers and determined the interblink interval with and without lenses during listening to music compared to playing a video game. Only non-lens wearers demonstrated the expected increase in the interblink interval associated with a near task, while the interblink interval in lens wearers was not significantly altered. Contact lens wearers did, however, show greater tear breakup than non-lens wearers, which correlated with lens discomfort. These findings suggest that changes in tear film stability during the blink may be a more important parameter influencing lens wear than blink rate. In support of this view, Bitton and colleagues¹¹⁰ further evaluated tear film changes that occur in the interblink interval during lens wear. Using optical coherence tomography, the authors investigated changes in tear meniscus height in 25 soft lens wearers and 25 non-lens wearers. After approximately 9 hours of lens wear, a reduction in tear meniscus height and volume during the interblink interval was moderately associated with grittiness. No correlation was evident for dryness. While this is suggestive of a relationship between tear film changes during the interblink interval and CLD, these findings should be interpreted with caution, as the lenses were removed prior to performance of tear meniscus measurements.

Systemic Disease. There is very little evidence in the literature to indicate that systemic disease impacts comfort or dryness symptoms during contact lens wear. One study evaluated a potential relationship between systemic factors (including thyroid conditions, diabetes, hypertension, cancer, heart disease, osteoporosis, and arthritis) and contact lens dry eye, but failed to detect any significant associations.⁶⁰ However, a subsequent study did report an association

between polycystic ovary syndrome and contact lens intolerance.¹¹¹

Seasonal Allergies. Patients with seasonal allergic conjunctivitis have been shown to have alterations in the tear film and ocular surface.¹¹² In a study by Chalmers and Begley,⁵² symptoms of dryness were investigated in 367 current contact lens wearers using the CLDEQ. In this cohort, 42.6% of wearers reported a positive history for seasonal allergies. However, this was not a factor associated with dryness during lens wear. In contrast to this, Nichols and Sinnott⁶⁰ reported on 360 patients who completed the CLDEQ. In their univariate analysis, they reported that dryness was statistically associated with seasonal allergies, but this was not significant in the final multivariate model. Two other reports investigated the use of topical antiallergy agents in enhancing comfort in patients with seasonal allergies. The first evaluated the use of olopatadine hydrochloride 0.1% ophthalmic solution in 20 SCL wearers who had a history of allergic conjunctivitis without any current signs or symptoms.¹¹³ Patients were treated with a single drop of the study medication or a placebo control prior to lens insertion and then underwent allergen challenge. There was a significant improvement in comfort for patients undergoing treatment at all time points, and reported wearing time was longer. In a second study, the effects of epinastine 0.05% ophthalmic solution on contact lens comfort in patients with current seasonal allergies was evaluated in daily SCL wearers over a 7-day period.¹¹⁴ For this study, 76 patients received the test agent, and 71 received the placebo control. Similar to what occurred in the prior study, use of the test agent resulted in enhanced comfort and a 1.33 hours per day increase in comfortable wearing time. Collectively, these findings indicate that, at least for a subset of allergy sufferers, the ocular response to seasonal allergies may be associated with reduced lens comfort.

Modifiable Factors Associated With CDL. Medication. There are several early reports in the literature of contact lens intolerance in women using oral contraceptives.¹¹⁵⁻¹¹⁷ However, Brennan and Efron⁵⁶ were the first to report a relationship between the use of systemic medication and CLD in SCL wearers. In their study of 104 soft lens wearers, use of oral contraceptives was shown to be statistically associated with symptoms of scratchiness and dryness. In support of this work, Chen and colleagues¹¹⁸ investigated symptoms of dry eye in 97 women using the Symptom Assessment in Dry Eye (SANDE) and Ocular Surface Disease Index (OSDI) questionnaires. Of the 48 contact lens wearers evaluated, the authors found that there was a significant increase in dry eye symptoms in patients who reported using oral contraceptives. In contrast to this study, in a sample of 360 contact lens wearers, Nichols and Sinnott⁶⁰ reported that use of over-the-counter pain medication was associated with contact lens dry eye status. However, there was no statistical association with any other systemic medication, including oral contraceptives, hormone replacement therapy, and antihistamines.⁶⁰ Fraunfelder and coworkers¹¹⁹ evaluated 2379 possible adverse events relating to the use of isotretinoin. All reports received prior to March 1999 were compiled and sent to the National Registry of Drug-Induced Ocular Side Effects for review. The likelihood of adverse events arising from the use of isotretinoin was determined using the World Health Organization definitions for causality assessment of suspected adverse reactions. In total, the authors found 38 documented cases of intolerance to contact lens wear after initiation of drug use. From this study, decreased tolerance to contact lens wear was classified as a "certain" clinical event. While dry eye was also classified as "certain," a small percentage of dry eye cases were determined to be permanent. The long-term effects of isotretinoin use on CDL have not been established.

Diet, Hydration, and Alcohol Intake. Factors such as diet, hydration status, and alcohol intake have been shown to be associated with dry eye, but few studies have begun to investigate the relationship between these factors and CLD. Kokke and colleagues¹²⁰ evaluated the effects of omega-6 fatty acids taken orally for the treatment of contact lens-associated dry eye. Evening primrose oil containing gamma-linolenic acid and linoleic acid was given six times a day to 76 females wearing frequent-replacement soft lenses over a 6-month period. Participants were classified as symptomatic for contact lens-induced dry eye using the McMonnies questionnaire. After 6 months of treatment, dryness during lens wear had improved. Lazon de la Jara and colleagues¹²¹ also investigated the effects of oral omega-3 supplements on comfort during contact lens wear in a non-placebo-controlled study. In this study, 45 patients were assessed for ocular comfort during lens wear over a 6-week treatment period. While the authors found a significant improvement in end-of-day comfort in non-lens wearers, this effect was not evident while wearing lenses.¹²¹ Ramamoorthy and colleagues²² evaluated the effects of alcohol consumption on CL-DE as part of a larger, cross-sectional survey involving 360 patients. While the percentage of patients reporting dry eye the day after alcohol consumption was increased, this finding was not statistically significant. There are no available data on the effects of adequate hydration on CLD.

Smoking. Ward and colleagues¹²² investigated the effects of passive cigarette smoke exposure on the ocular surface and tear film in SCL wearers. The authors observed that even brief passive cigarette smoke exposure significantly destabilized the tear film and resulted in an increase in the vital staining scores in both contact lens wearers and nonwearers. While acute smoke exposure caused only an insignificant increase in symptom visual analogue scale scores in contact lens wearers, the authors concluded that repeated and/or chronic smoke exposure would likely be associated with significant symptomatology. This is an issue that needs to be addressed in future studies.

Cosmetics. Expert clinical evidence suggests that use of specific soaps, lotions, and cosmetics may contribute to CLD. While practitioners frequently express concern with respect to the use of these products by contact lens wearers, there is little scientific evidence available to support their role in CLD. A recent study by Luensmann and colleagues¹²³ assessed the effects of commonly used cosmetics (including mascara, hand lotion, and eye makeup remover) on the physical parameters of silicone hydrogel lenses in vitro, but assessment of CLD was not part of the study design.

Compliance. Dumbleton and colleagues¹²⁴ reported on the effects of patient compliance with the manufacturers' recommended replacement frequency on lens comfort. This observational study consisted of 1344 patients from 158 ECPs in the United States. All patients were established silicone hydrogel lens wearers and replaced lenses at either 2-week or 1-month intervals. Patients were asked to complete an anonymous survey regarding both their replacement frequency and comfort with current lenses. Patients were considered noncompliant if lenses were worn for more than 17 days for 2-week replacement lenses and more than 31 days for 1-month replacement lenses, irrespective of whether or not the lenses had been prescribed based on the manufacturer's recommended replacement schedule. The authors found that patients who reported poor compliance with replacement frequency had both reduced comfort and vision ratings at the end of the day and when lenses needed to be replaced compared with compliant patients.

Psychological/Fatigue. Psychological factors, including end-of-day fatigue, have been suggested as causative factors for CLD. In a recent article by Santadomingo-Rubido and colleagues,⁴⁹ the authors evaluated ocular surface comfort in 88 subjects including contact lens and non-contact lens wearers. The study findings indicated that end-of-day comfort was reduced in all subjects, regardless of lens status. While they provided no definitive evidence to support it, the authors speculated that ocular and/or physical fatigue might contribute to end-of-day symptomatology. In CLADES, Nichols and colleagues¹²⁵ also evaluated mood or affect as it relates to contact lens dry eye—including both positive and negative scales of affect using the Positive and Negative Affect Schedule (PANAS). In this study, they showed neither dimension of affect to be related to contact lens dry eye. Other psychological factors may contribute to CLD, such as a potential for a poor initial fitting experience. However, there is not sufficient evidence to support this theory.

Summary of Patient-Related Factors. The evidence from the literature supports some occasional but not entirely consistent patient-related factors as associated with CLD, including female sex, younger age, poor tear film quantity and quality, seasonal allergies, and the use of some systemic medications. However, there is little evidence to support that ethnicity, blink rate and blinking patterns, systemic disease, diet, alcohol, smoking, cosmetic use, or psychological factors play a role in CLD.

Factors Secondary to Lens Wear. Contact lens wear has been shown to be associated with a decrease in pre-lens tear film thickness^{60,126} and stability,^{17,26,66,127,128} increased tear osmolality,²⁴ loss or shortening of the meibomian glands,^{61,129} alterations in corneal sensitivity,^{130,131} and cellular changes in the corneal and conjunctival epithelia.¹³²⁻¹³⁵ These changes and their potential impact on CLD are described in detail in the reports from the Contact Lens Interactions with the Ocular Surface and Adnexa Subcommittee and the Contact Lens Interactions with the Tear Film Subcommittee. In a recent publication, Young and colleagues⁶⁶ reported that approximately one-quarter of symptomatic wearers do not have any clinical signs. This suggests that etiologies other than changes to the ocular surface and tear film are responsible.⁶⁶ A subsequent study by Spyridon and colleagues¹³⁶ investigated 2154 established contact lens wearers who were grouped into either a sensitive eye or a nonsensitive eye category. The authors found that patients with sensitive eyes were more likely to report symptoms of dryness without any accompanying clinical signs than nonsensitive eye patients. The intermixing of different patient groups such as those classified as "sensitive" or patients with undiagnosed or subclinical dry eye etiologies may mask the identification of true clinical factors associated with CLD.

Environmental Factors. Although clinical experience may suggest that many environmental factors can impact the comfort of contact lenses, the literature is mostly devoid of good evidence to support this. There are a number of observational studies and larger surveys, but only a few small well-controlled trials. Often, multiple environmental factors are changing at the same time, making conclusions about specific effects more difficult.

To characterize the problems facing contact lens wearers, Young and colleagues¹³⁷ surveyed 496 hydrogel contact lens wearers in the United States, and reported their comfort ratings in challenging environments such as high altitude, airplanes, dusty or polluted or smoky environments, low humidity, windy conditions, and air-conditioned or heated cars. A high percentage of survey participants (varying between approximately 40% and 70%) self-reported comfort challenges while wearing their contact lenses in such environments. These data

represent the perceptions of the patients surveyed, as they were acquired from the patient's memory rather than during the actual challenging activity or environment. These data represent a snapshot of the issue at hand, but do not clearly make a definitive link between the specific environmental condition and CLD.

Low Humidity. A few well-controlled experiments that studied the effect of humidity, specifically low-humidity environments (defined in most studies as relative humidity [RH] lower than 30%), have contributed to a body of evidence that supports this factor as clearly connected to CLD. Observational studies first suggested this relationship with increased CLD, deposits, and tear breakup time when the RH in the subject's workplace was lower than 31%.¹² This original study suggested lens deposition as a major factor and was conducted prior to the advent of frequent-replacement and daily disposable lenses. Although lens deposition has not been eliminated in contemporary disposable lenses, it is much reduced compared to that with conventional (nonreplaced) lens wear.

Environmental effects have been studied more recently in controlled environmental chambers where humidity, temperature, and, in some cases, wind speed can be well controlled and varied.^{100,138-140} Maruyama and colleagues¹³⁹ compared tear meniscus height and tear interferometry patterns, NITBUT, and symptoms in subjects who wore hydrogel contact lenses and those who did not wear lenses. A controlled adverse environment, where temperature and RH were well controlled and recorded, was used for the study. As air temperature and RH were concurrently decreased, there was no change in meniscus height (as a measure of tear volume), but the pre-lens tear film thinned, NITBUT decreased, and subjective dryness scores increased. The results suggested that the symptoms of CLD are related to pre-lens tear film thinning (rather than a reduction in tear volume), and that temperature and RH together can contribute to the effect.

In another controlled environmental chamber experiment, González-García and colleagues¹³⁸ studied subjects with minimally symptomatic dry eye, defined as subjects who reported only dry eye with contact lenses and who were otherwise healthy. The researchers exposed their subjects to controlled temperature and reduced humidity (20°C, 20% RH) for 2 hours with and without hydrogel contact lenses and then exposed them to a more "normal environment" with similar temperature and higher humidity (24°C, 34% RH). Subjects were instructed to perform a standardized task (reading) during the experiment (wind was not introduced into the environment). Symptoms and signs were exacerbated by the low-humidity environment with and without contact lens wear, providing perhaps the most compelling evidence that low RH is a key environmental factor that influences CLD. The authors of this experiment also concluded that in normal humidity, contact lenses can act as a stressor and can induce symptoms not noted in non-contact lens wearers.

These findings are supported by the work of Guillon and Maissa,¹⁴¹ who studied tear evaporation using a closed environment (goggle-type apparatus) around the eyes, where temperature and RH were well controlled. Their experiment, which involved 379 subjects in total, evaluated tear film evaporation of contact lens wearers 1 day after lens removal compared to non-contact lens wearers. The authors defined normal RH as 40% (range, 35%–45%) and low RH as 30% (range, 25%–35%). The tear evaporation rate with contact lenses at higher RH was similar to the precorneal tear film evaporation of nonwearers at low RH. The authors concluded that contact lenses stress the tear film system and that their experiment supported increased tear evaporation as a mechanism for CLD. Other authors have studied lens dehydration in

controlled adverse environment (CAE) conditions, and have not found bulk water loss from hydrogel lenses to be impacted by extremes of low RH and temperature, supporting surface evaporation and tear thinning as potential mechanisms for CLD.^{29,139}

More recently, the effects of controlled simulated wind, along with temperature and low RH, on contact lens wearers' symptoms and measurable ocular signs (tear evaporation, osmolarity, and breakup time) were studied in hydrogel and silicone hydrogel daily disposable lens wearers.¹⁴⁰ Thirty-one subjects participated in the experiment, which involved just 20 minutes in a CAE at 18°C with a very low RH of 18%. Wind flow, controlled with fans blowing at the research subjects at wind speeds of 1.2 m/s, was an added environmental factor mimicking the conditions of a dry, windy day. Subjects wearing the hydrogel contact lenses showed more worsening of both subjective symptoms and clinical signs in the CAE conditions than those wearing silicone hydrogel lenses. Blink rate increased significantly with hydrogel lens wear but not with silicone hydrogel lens wear, suggesting that the subjects were reacting to induced environmental stresses. These authors measured a reduction in tear meniscus height with the hydrogel lens wearers, acknowledging that this finding differed from the results of Maruyama and colleagues.¹³⁹ The introduction of wind to this specific experiment was suggested as a probable reason for the difference and further suggested wind and airflow as additional factors that exacerbate evaporation from the ocular surface.

Temperature. Although it is hypothesized that increased temperature would increase tear evaporation and lead to increased CLD,¹⁴² there does not appear to be a well-controlled study that has looked at varying only temperature while keeping RH constant.

Climate. The connection between CLD and climate is well known clinically, with discomfort symptoms increasing in desert (hot and dry) or arctic (cold and dry) conditions compared to tropical climates. However, it is likely that low humidity is the main factor in such situations, perhaps aggravated by the addition of wind flow; but there are no well-designed or controlled studies conducted outdoors to substantiate the clinical experience.

Pollution and Air Quality. Although approximately 70% of hydrogel contact lens wearers in the survey conducted by Young and colleagues¹³⁷ in 2007 reported that they were "always or frequently" uncomfortable in contact lenses in smoky environments, there is little additional evidence that connects smoky environments with CLD. Eng⁹ cited smoky aircraft cabins as an occupational hazard for flight attendants who wore contact lenses. In these circumstances, low-humidity cabin air was almost certainly also a factor; and this study, published in 1979 when smoking was still common in aircraft cabins, does not represent the contemporary challenge of contact lens wearers.⁹ In a later study, Vajdic and colleagues¹³ surveyed contact lens wearers and spectacle wearers. They did not find that smoking (as opposed to a smoky environment) had a significant effect on the reporting of ocular symptoms. They also did not find a difference in the frequency of reporting symptoms between wearers of rigid gas-permeable and soft lenses, suggesting low sensitivity of the data collection methods used.

Occupational Factors. Airline crew members unquestionably work in an environment with low humidity and sealed air circulation. In 1982, Eng and colleagues¹⁰ set up a laboratory on a McDonnell Douglas DC-10 flying between Oakland, California, and Honolulu, Hawaii. They recorded a decline in humidity from 47% to 11% within 30 minutes of takeoff and

concluded that low cabin humidity is likely the most significant factor in discomfort for contact lens wearers during flight.

The majority of today's office workers use computers; the use of VDTs with contact lens wear has been shown to increase symptoms of "scratchiness."¹⁰⁰ The number of hours of VDT use has also been associated with an increase in "burning sensations" in contact lens wearers.¹⁰⁰ These findings have been supported by additional studies in which office workers who wore contact lenses and spent more than 4 hours engaged in VDT work had a lower tear meniscus volume with significant dry eye and visual symptoms.¹⁴³ Other researchers have reported more than 4 hours per day of VDT use to be a risk factor in dry eye disease, and contact lens wear to be an additional risk factor.⁹⁶ The mechanism involved is believed to be related to the reduced blink rate that occurs during VDT work, which reduces tear spreading, and the longer interblink interval that allows contact lens surface drying, leading to increased lid sensation and symptoms.¹⁴⁴

Air Conditioning and Heating/Internal Environments. One study has reported that symptoms associated with discomfort increase in contact lens wearers in environments that are air conditioned or heated.¹⁰⁰ It is thought that this may be due to variations in humidity or airflow rather than temperature alone. Others have surveyed occupants of office buildings and reported that 29% complained of ocular discomfort, although this survey was not specifically conducted in contact lens wearers.¹⁴⁵ In this study, the investigators measured various aspects of indoor air quality including carbon dioxide, formaldehyde, temperature, and humidity. The same authors also evaluated air quality in aircraft and recommended optimal conditions for RH and temperature of cabin air of 40% to 60% and 20°C to 24°C, respectively.¹⁴⁶

Altitude/Atmospheric Pressure. Experiments to evaluate the effect of low atmospheric pressure and simulated high altitudes were conducted by Castren¹⁴⁷ and Castren et al.¹⁴⁸ in 1984 and 1985 (these studies were specifically interested in aviation). In a first experiment, Castren¹⁴⁷ used a decompression chamber with 560 millibars of pressure (similar to that expected at an altitude of 4000 meters above sea level). Contact lens comfort was negatively impacted, although there was no control of RH in this experiment and it was conducted in a very low RH environment (20%–22%). The same author conducted an additional experiment ($n = 7$ subjects) in which only atmospheric pressure changed.¹⁴⁸ The subjects spent 4 hours in a decompression chamber where atmospheric pressure was lowered from the normal value of 1000 millibars (750 mm Hg) to 560 millibars (420 mm Hg). Keeping other key factors constant, such as humidity and temperature, subjects were tested with and without contact lenses. All subjects wearing contact lenses suffered subjective ocular discomfort, and some developed objective signs. The control group without contact lenses did not develop any symptoms during the test. The authors concluded that the effects were caused by hypoxia.

Summary of Environmental Factors. It is evident from the literature that CLD symptoms can occur due to an increased tear evaporation rate from the lens surface brought about by a reduction in RH. In addition to RH, variables such as air movement (wind) and blink rate-altering visual activities, such as VDT use, may exacerbate signs and symptoms of CLD. There is little solid evidence to support or dispel the connection between other environmental factors such as temperature, altitude, smoky environments, air conditioning or indoor heating, and CLD, although clinically, many of these factors are reported as stressors to contact lens wearer comfort. Any variation in the prevalence of CLD in different geographical regions due to climate or seasonality is not supported by solid

evidence, and is likely secondary to the effects of humidity and wind.

Impact or Morbidity of CLD

Contact lens discomfort can have profound effects for the patient, the ECP, and ophthalmic industry. The impact on each of these constituents is considered in turn.

The Patient. As described earlier, contact lens wearers who experience CLD may respond in a number of different ways depending on the frequency and severity of their symptoms. Initially they may simply report CLD as an occasional inconvenience, but do not adjust their wearing habits as a consequence of it. With greater severity or frequency, however, individuals may start to struggle with their lens wear and reduce the number of hours each day and days each week during which they wear lenses.^{2,4} Ultimately, periods of time may pass when these "strugglers" temporarily discontinue lens wear; a proportion of these may permanently drop out of lens wear and either wear spectacles or undergo refractive surgery.

There is good evidence that discontinuation from contact lens wear is more complex than the situation in which a lens wearer uses lenses for a period of time and then ceases wear permanently. In the most detailed assessment of the "natural history" of lens wear reported in the literature, Pritchard and colleagues³ described their survey of over 1400 contact lens wearers who had used lenses for an average of 5 years. One-third of their sample reported ceasing lens wear on at least one occasion, but 77% of this discontinuing group started using contact lenses for a second time. Approximately half of this resuming-wear group then stopped using contact lenses for a second time, but again, most commenced lens wear for a third time. Dumbleton and colleagues² report a similar pattern in 4207 current and lapsed lens wearers, with 40% reporting lapsing for a period of at least 4 months. However, although 62% resumed lens wear, 32% eventually discontinued lens wear. These findings demonstrate that many contact lens wearers enter and exit the market repeatedly over a few years. This suggests that these wearers have periods during which lens wear is successful, meeting their daily requirements, but eventually they may discontinue wear, often due to CLD.

Quality of Life. Contact lens discomfort can interfere with a patient's everyday life, whether this is during daily activities or work. Clinical assessments and measurements are often unable to evaluate these important aspects relating to CLD and the ultimate success of patients with contact lenses. Therefore alternative methods of evaluating patient-reported outcomes might be extremely important. Research investigating patient-centered outcomes is widespread in health care and can be used both to identify patients needing particular attention and to assess the results of interventions.¹⁴⁹ These quality of life (QOL) assessments have been mainly used in ophthalmic research to compare different types of vision correction.^{150–154} Pesudovs and colleagues¹⁵⁵ specifically developed a QOL questionnaire for contact lens wearers. Quality of life assessments have also been used to investigate the impact of dry eye,^{89,156} but have not been widely used to assess the impact of CLD. One study was conducted by Jutai and colleagues,¹⁵⁷ in which a psychosocial assistive devices scale was reported to be able to predict retention and discontinuation of contact lens wearers, although the specific reasons for discontinuation were not evaluated.

Economic Impacts. In discussions of the economic impact of CLD and discontinuation from contact lens wear, the consequences for the ECP and the industry are always considered, while little attention is given to the contact lens wearer. Contact lens wearers who experience CLD may initially try to alleviate their symptoms by simply purchasing

over-the-counter lubricating drops. When this approach does not provide sufficient relief, they may visit their ECP for advice and possible refitting with alternative lens types. There are no reports in the literature on the actual costs to the patient; these cannot be ignored and could be substantial when the patient's time is also taken into account.

The Eye Care Practitioner

Contact lens discomfort is a regular and ongoing problem in eye care practices. Somewhere between 50% and 94% of contact lens-wearing patients present with problems related to their contact lenses.^{53,71,75,76} Of equal importance are those patients who no longer return to the office because of dissatisfaction or silently discontinue lens wear. In the United States, it has been estimated that 3 million contact lens wearers drop out of lens wear each year.¹⁵ While there is very little evidence of the effects of CLD on patient retention at ECP offices, chair time, and overall economic impact to the ECP, there is value in discussing the possible influence of CLD on these factors.

Patient Retention. The problem of patient retention is critical to the ECP. Practitioners see themselves as problem solvers and pride themselves in providing their patients with contact lenses that afford good visual acuity and comfort. A significant amount of time is spent fitting lenses, teaching patients to handle and care for lenses, and optimizing lens and solution choices. When patients subsequently present with CLD, the complexity of this clinical entity requires much time and effort on the part of both patients and practitioners. The differential diagnosis of the etiology of symptoms includes dry eye disease,⁵³ lens fit and movement,¹⁵⁸ lens dehydration,^{26,159} protein and lipid deposits,^{127,160} solutions used in cleaning and storing,^{161,162} tear osmolarity,²⁴ and wearing time and replacement schedules.⁴⁶ To understand the cause in each particular individual requires a full analysis of the ocular surface and the contact lens/solution interactions. Ideally one change at a time should be made to determine the cause of the patient's CLD, but this can require multiple visits with expensive and time-consuming refits. Patients may become discouraged and simply drop out of lens wear.

Patient Evaluation. In order to process the presenting problem of CLD, a thorough history must be undertaken that includes details of wear time, care and handling, replacement schedules, work habits, and the patient's environment. This should be followed by a careful evaluation of the contact lenses on the eye: movement, centration, lens condition, and pre-lens tear breakup time. Removal of the lenses will then allow for a full tear film and ocular surface assessment that ideally includes tear flow testing with Schirmer or phenol red thread tests, fluorescein staining of the cornea, tear film breakup time, lissamine green staining of the conjunctiva, and an investigation of the superior tarsal conjunctiva, along with any other dry eye tests that the practitioner feels appropriate, including tear osmolarity, tear meniscus height, and looking for conjunctivochalasis. There are two important issues to consider concerning the validity of these tests and observations: the fact that the patient has just removed his or her contact lenses and the poor association between CLD and ocular signs.⁶⁶ Ideally the dry eye workup should be conducted after the patient has stopped lens wear for some days. However, this adds further chair time, requiring several hours or days in the quest to determine the cause and solve the problem of CLD.

Economic. Practitioners often find that the time and expense of trying to solve CLD are a detriment to their income. The dropout rate of patients whose CLD is not solved is also an economic burden to the practitioner. There is not much evidence in the literature concerning the magnitude of the

economic impact of CLD on the ECP. Rumpakis¹⁶³ estimated that a single patient dropping out of lens wear could result in a lifetime loss of income of almost \$20,000. Another study has reported that contact lens patients are 60% more profitable for the ECP than patients who wear only spectacles.¹⁶⁴ Further research into CLD should help to reduce the prevalence and economic burden of CLD for patients and practitioners.

The Contact Lens Industry

Contact lens discomfort can also have a significant impact on the investment in research and development and product development within the contact lens industry.

Impact of Product Technology Advances. Over the last several decades, the contact lens industry has seen continuous improvement in contact lens technology. The introduction of soft and frequent-replacement contact lenses, the advancement of silicone hydrogel lenses, and the development of improved care regimens raised the expectations that these novel products would address issues related to contact lens wear and improve the overall lens wearing experience. While there is certainly evidence to suggest improvement, it remains unclear if these enhancements have impacted the prevalence of CLD, the primary complaint associated with contact lens discontinuation.²⁻⁵

Several factors impede the ability to show significant improvements when one compares newer lens technologies. First, lenses of any unique material have exclusive properties with respect to dehydration, oxygen transmission, deposition profile, fit, modulus, and surface qualities. Any clinical trial utilizing available lenses is constrained by the fact that these features are predetermined by the lens material and cannot be studied in isolation.¹³⁸ Consequently, multiple factors change with each product introduction, making it difficult to isolate the factors that may be responsible for improvement. An additional potential confounding factor, the lens care regimen, is rarely controlled for in lens studies and often ignored in the analyses. In a survey conducted in Canada and the United States, 47% of contact lens wearers reported that removing their lenses provided a complete resolution of their CLD.⁵³ Therefore, for approximately half of those surveyed, there appeared to be other confounding factors contributing to CLD.

Impact on the Contact Lens Market. Despite technological advances in lens designs, materials, and lens care solutions, approximately 25% of contact lens wearers eventually discontinue lens wear, primarily as a result of CLD.^{2,4,49} Nichols¹⁶⁵ has recently reported that growth in the actual number of contact lens wearers in the United States has been consistently flat for the past several years, with as many people discontinuing contact lens wear as people entering the market. The same report indicated that several of the larger contact lens markets have shown little growth over the last 10 years, although in the United States there was a trend toward modest growth in 2012, with new technologies in silicone hydrogel, daily disposable, and multifocal lenses believed to be responsible.

Understanding that the impact that CLD has a significant effect on the industry, it is not surprising that contact lens and contact lens solution companies fund a great deal of the research in this area. Of the papers referenced in this section, nearly 80% were sponsored by industry.

FUTURE RESEARCH DIRECTIONS

As reviewed above, CLD is a major issue for contact lens wearers, practitioners, and industry alike. A major deficiency in the literature is the lack of information derived from contact lenses that differ in only one parameter. While it remains

impossible to conduct prospective studies of this form with marketed products, the community would greatly benefit from an analysis of custom-made lenses that would allow for the generation of such a dataset. This would require significant input (and financial investment) from one or more lens manufacturers, but would represent a major advance in our understanding.

An alternative approach that can be used is to collect data from *noninterventional* or *registration* trials. Rather than using a very careful a priori clinical study design, such approaches derive their power from the large number of data points that they can accrue. Assuming that the key clinical data are collected in a consistent manner (which may or may not be the case), appropriate statistical modeling could be employed to determine the relationship between various lens-related factors and CLD. Noninterventional trials do require a wide mixing of all lens parameters such that each combination is represented within the collected dataset. In fact, this remains a significant problem within the contact lens area because any single manufacturer tends to offer only a small range of parameters, often with great similarity, so achieving the desired range across all lens types is likely to be difficult.

SUMMARY AND CONCLUSIONS

The epidemiological assessment of CLD faces many challenges, not least of which is the accurate assessment of the prevalence of the condition. The tools used to diagnose CLD and the expectations of contact lens wearers themselves continually change, making it difficult to draw conclusions over time and to compare results from multiple studies. There are few validated instruments for assessing comfort in contact lens populations, and these tend to produce data that are highly variable, as most rely on a patient's recall. In addition, the lack of postmarket surveillance studies, which would address many of the issues related to CLD, prevents us from drawing meaningful conclusions regarding the impact of technological advances on this issue. Future epidemiological work designed to clarify the natural occurrence and evolution of CLD in rural or urban population-based settings in various countries and races appears to be very much needed to enrich our understanding of CLD, since it is such a common clinical complaint.

Unfortunately, CLD remains a demanding problem affecting short- or long-term success with contact lens wear. Lens wearers address the problem mostly by removing their lenses—a relatively inconvenient measure that may suggest ineffective use of current treatments. In the near term, clinicians and researchers in the clinical field should continue to manage contact lens-related dryness through thoughtful choice of lens material, lens care, and rewetting systems, along with assessment of patient-related risk factors, management of environmental triggers, and other associated factors that may contribute to dryness symptoms.

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The TFOS International Workshop on Contact Lens Discomfort: Report of the Contact Lens Materials, Design, and Care Subcommittee

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See tables in the Introduction for the members of the TFOS International Workshop on Contact Lens Discomfort.

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INTRODUCTION AND GOALS OF THE MATERIALS, DESIGN, AND CARE SUBCOMMITTEE

Examining the role of the contact lens material, design, and the care system is fundamental to understanding contact lens discomfort (CLD). However, a systematic review that tries to determine the governing factors is fraught with difficulties. A lack of a validated “instrument” (or single validated questionnaire) for measuring discomfort makes it impossible to compare between studies because reported levels of comfort (or discomfort) are inconsistent. Subject classifications can vary widely, from studies that include only neophytes or asymptomatic contact lens (CL) wearers to studies including only those contact lens-wearing subjects who experience marked dryness or symptoms of discomfort. Also, it is difficult to measure issues of importance in isolation because changing one factor in a contact lens or care solution can invariably affect another. An illustration of this relates to a change in hydrogel water content, which also affects oxygen permeability, oxygen transmissibility, modulus, and possibly lens thickness. Finally, various confounding factors between studies also make true comparisons problematic. Typical examples would include differences between brands of lenses made from the same material (which may have differing geometric designs, edge configuration, or production methods); wearing modality (lenses may be worn on a daily wear [DW] basis, overnight occasionally, or for up to

30 nights on a continuous wear [CW] basis); duration of use prior to replacement, wearing time during the day (from just a few hours to most of the day); and care product differences or exposures (which could range from no exposure in the case of daily disposable [DD] materials to a preserved system that has extensive uptake and release from the contact lens material being examined).

The purpose of this report is to summarize evidence-linking associations, mechanistic and etiological factors between contact lens materials, designs, and care solutions with CLD. The potential factors associated with this are many and varied, and graphically display the complexity of this issue.

Contact Lens Materials

Given the fact that approximately 90% of the world's contact lens wearers are wearing soft lenses with no recent change in this figure,¹ this report primarily concerns itself with the role of soft lens materials and designs and care solutions in CLD, with some discussion of rigid gas permeable lens (RGP) materials or designs where appropriate.

Conventional Hydrogel Materials

The pioneering work of Wichterle and colleagues^{2,3} is well known as a basis for the development of hydrogel polymers for soft contact lenses, including lightly cross-linked polymers of 2-

hydroxyethyl methacrylate (polyHEMA, 38% equilibrium water content [EWC]). Subsequent versions of polyHEMA-based materials with increased EWCs were made by copolymerizing it with both hydrophobic monomers (e.g., methyl methacrylate [MMA]) or other monomers of varying hydrophilicities (e.g., *N*-vinyl pyrrolidone [NVP]; methacrylic acid [MAA]).⁴ Appendix A provides an overview of the characteristics of some commonly prescribed hydrogel materials. It was believed that a higher EWC would lead to a more wettable and comfortable lens (and increased oxygen transmissibility). However, it soon became apparent that dehydration is more pronounced with higher water hydrogels, particularly those with higher amounts of free water.^{5,6} This was sometimes associated with corneal desiccation staining^{5,7} and ultimately reduced end-of-day comfort.⁸

In an attempt to enhance the biocompatibility of soft lenses, a novel material combining polyHEMA with a synthetic analogue of phosphorylcholine (PC) with water content of approximately 60% (omafilcon A) was developed in the early 1990s.⁹ The introduction of hioxifilcon A in the late 1990s, where a nonionic copolymer of polyHEMA and glycerol methacrylate (GMA) were combined, was claimed to achieve excellent biomimicry by imitating the wetting properties of mucin. These approaches were designed in part to resist on-eye dehydration and deposition, although improvements in comfort were varied.¹⁰⁻¹⁸

Silicone Hydrogel Materials

Despite many attempts to harness the oxygen permeability of silicone rubber in contact lens materials, it was not until the late 1990s that two low-water content silicone hydrogel (SiHy) contact materials, lotrafilcon A (24% water) and balafilcon A (36% water), were released. The original intent for silicone hydrogels (due to their very high oxygen permeability) was for use as extended wear (EW) materials,¹⁹ but their use for daily wear has since become dominant (including their use as daily disposables).¹ Silicone hydrogel development typically focused on compositions or macromers based on silicone-containing monomers (TRIS, siloxy macromer) that are sufficiently compatible with a range of hydrophilic monomers (including *N,N*-dimethyl acrylamide, NVP, polyHEMA).^{4,20-29} Although the siloxane groups confer high oxygen permeability, they also give rise to inherent wettability issues, so several strategies have been employed to render SiHy surfaces more hydrophilic. Appendix B provides an overview of the characteristics of some SiHy materials.

Bulk Properties of Soft Lens Materials

Water Content and Ionicity. Equilibrium water content and ionicity are used to classify lens materials by the Food and Drug Administration (FDA) and International Organization for Standardization, because of their impact on clinical performance.^{30,31} Although the relevance of such a grouping has been confirmed for such factors as dehydration and deposition, the relation with wearing comfort is less clear.

Nichols and Sinnott⁸ reported higher odds (odds ratio [OR]: 2.25) for CL-related dry eye in patients wearing high EWC lenses, but ionicity was not related with dryness symptoms. In a follow-up analysis, Nichols and colleagues³² showed that when compared with FDA Group I materials (the referent material), both FDA Groups II and IV were associated with a 2 to 3 times increased odds of contact lens dry eye. Further, in a small study with 10 subjects, Wilson and colleagues³³ reported better comfort for patients fitted randomly with an FDA Group II lens (nelfilcon A, non-ionic high EWC) compared with an FDA Group IV (etafilcon A, ionic high EWC) lens. Similar

results were found by Guillon and colleagues³⁴ when comparing the same materials in 22 patients in a crossover study wearing the lenses for 1 week in a random order. However, these studies ignore the effect of lens design, and the differences cannot be exclusively attributed to the different material properties.

Efron and colleagues compared the *initial* comfort of low (38%), medium (55%), and high (70%) EWC lenses and concluded that lower water content materials were more comfortable than higher EWC lenses in a nondispensing study where comfort was rated after 5 minutes of wear.³⁵ This study excluded potential confounding factors such as edge design or surface finishing, as all lenses were lathe-cut in an identical design by the same manufacturer. Young³⁶ also evaluated comfort in a study aiming to predict the success of fitting low (38%), medium (54%–58%), and high EWC (69%–74%) contact lenses. The results suggested improved comfort for low EWC lenses: First, the average comfort score was higher (8.4 for low, 8.2 for medium, and 8.2 for high EWC lenses). Second, low EWC flat-fitting lenses were significantly more comfortable than medium and high EWC lenses.³⁶

Silicone hydrogel materials have an additional confounding factor to the understanding of the potential role of EWC on CLD. The majority of these lenses have a low EWC, but they have substantially differing oxygen transmissibilities, modulus values, and surface wetting properties from traditional hydrogel materials. Dumbleton and colleagues³⁷ conducted a study to evaluate the comfort of five different SiHy materials randomly fitted for 1-month periods, using a crossover design. All lenses generally performed similarly at the end of each period, although there was a slight difference for the ionic lens material to be associated with lower comfort at dispensing. Thus, the potential influence of material properties other than EWC or ionicity prevent any solid conclusions being drawn regarding the potential influence of these factors in SiHy material comfort.

In summary, several studies point to the increased comfort of low EWC lenses, with no direct impact of ionicity for conventional hydrogel materials. To date, no studies have been able to adequately draw any conclusions on the direct impact of these two factors for silicone hydrogels.

Oxygen Transmissibility. There has been a temptation to presume that oxygen transmissibility (Dk/t) is a key factor in contact lens comfort, and some of the circumstantial evidence and clinical dogma hints in this direction. Studies to determine the impact of oxygen transmissibility may be conducted either using lens materials of varying Dk/t or using sealed goggles in which the oxygen tension is varied. Millodot found reduced corneal sensitivity after exposing the cornea to hypoxic gaseous environments for up to 10 hours, following short-term wear of impermeable PMMA contact lenses and low Dk/t hydrogel lenses, and also cumulatively over years of wear of PMMA lenses.³⁸⁻⁴¹ Contrary to the position that a greater supply of oxygen to the cornea might improve comfort, Millodot suggested that “a diminution of sensation with the wear of contact lenses is obviously beneficial as it helps the subject adapt more easily to the lenses.”⁴² To further this argument, the use of a topical anesthetic has been suggested as a means to assist adaptation to rigid contact lenses.⁴³

Measurement of comfort while exposing the cornea to gaseous environments would be the obvious method of choice to discern the impact of hypoxia on comfort, but none of the studies in which this method has been employed has done so. It should be appreciated that many of the studies listed as evidence for or against an influence of Dk/t on comfort were not necessarily designed with that specific purpose in mind (Table 1). Highlighting the shortfalls in such study designs to meet this end does not necessarily mean that they do not

TABLE 1. Studies of Comfort With Lenses of Different Dk/t Values

First Author	Year	Lenses		Modality	Study Type	n	Sites	Duration	Rand	Masked	Cont/Comp	Dk/t Effect*
		Test	Control									
Brennan ⁴⁴	2002	SiHy	Hyd	CW/EW	Pros	212	Multi	1 y	✓		✓	✓
Morgan ⁴⁶	2002	SiHy	SiHy	CW	Pros	30	Single	2 mo	✓	S	Xover	N
Malet ⁴⁵	2003	SiHy	Hyd	CW/EW	Pros	134	Multi	3 mo/1 mo	✓		Xover	✓
Fonn ⁴⁷	2003	SiHy	Hyd	Open	Pros	39	Single	7 h	✓	I, S	Xover	N
Chalmers ⁴⁸	2005	SiHy	Hyd	CW and EW/EW	Pros	117	Multi	1 y/†				✓
		SiHy	Hyd	CW and EW/DW	Pros	120	Multi	1 y/†				✓
Riley ⁴⁹	2006	SiHy	Hyd	DW	Pros	112	Multi	2 wk/†		S‡		✓
Santodomingo ⁵⁰	2006	SiHy	SiHy	DW and EW	Pros	21/24	Single	1.5 y	✓		✓	N
Dumbleton ⁵¹	2006	SiHy	Hyd	DW	Pros	87	Single	2 mo		S‡		✓
Young ⁵²	2007	SiHy	Hyd	DW	Pros	496	Multi	2 wk				✓
Dillehay ⁵³	2007	SiHy	Hyd	DW	Pros	779	Multi	2 wk		S‡		✓
Cheung ⁵⁴	2007	SiHy	Hyd	DW	Pros	30	Single	1 mo	✓	I, S‡	✓	N
Bergenske ⁵⁵	2007	SiHy	Hyd	EW/DW	Pros	398	Multi	3 y/†				✓
Brennan ⁵⁶	2007	SiHy	SiHy	EW	Pros	45	Single	1 y	✓		✓	N
Schafer ⁵⁷	2007	SiHy	Hyd	CW	Pros	278	Multi	3 y/†				✓
Ousler ⁵⁸	2008	SiHy	Habit	DW	Pros	11	Single	75 min	✓	I, S	Xover	✓
Dumbleton ³⁷	2008	SiHy	Hyd	DW	Pros	55	Single	1 mo				✓
Ozkan ⁵⁹	2008	SiHy	Hyd	DW	Pros	15	Single	6 h	✓	S	✓	X
Chalmers ⁶⁰	2009	SiHy	Hyd	†	Retro	183/699	Multi	†			✓	✓
Long ⁶¹	2009	SiHy	Hyd	DW	Pros	128	Multi	1 mo				✓
Santodomingo ⁶²	2010	SiHy	Hyd	†	Pros	24/22	Single	3 d			✓	N
Young ⁶³	2011	SiHy	Hyd	DW	Retro	363/454	Multi	†			✓	✓
Maissa ⁶⁴	2012	SiHy	Hyd	DW	Pros	30	Single	10 d	✓	I, S‡	Xover	X
Young ⁶⁵	2012	SiHy	Hyd	†	Retro	226/48	Multi	†			✓	N

Features of studies in which comfort between lenses with different oxygen transmissibility values can be at least in part compared. The primary purpose of the studies was not necessarily comparison of the lens types. All papers shown were published in peer-reviewed journals. Checkmark indicates feature is present. Slash mark is used to separate test and control group data where different. Cont/Comp, control or comparator lens run contemporaneously; Habit, habitual; Hyd, hydrogel; I, investigator masked; N, effect not shown; Pros, prospective; Rand, randomized study; Retro, retrospective; S, subject masked; SiHy, silicone-hydrogel; X, reverse effect shown; Xover, crossover study.

* Indicates whether lenses with higher Dk/t were more comfortable.

† Details not explicitly provided in the paper.

‡ Partially subject masked (assumes subjects would notice some differences in handling between SiHy and hydrogel lenses).

contain valuable information, but rather that using these studies to infer comfort is linked to oxygen supply is fraught with difficulties. For example, Brennan and colleagues⁴⁴ and Malet and colleagues⁴⁵ conducted open-label, multicenter, prospective, randomized studies with balafilcon A ($n = 212$) and lotrafilcon A ($n = 134$) SiHy lenses, respectively, worn in continuous wear (up to 29 nights without removal) with etafilcon A lenses as controls worn in extended wear (up to 6 nights). The Brennan study⁴⁴ was contralateral eye and the Malet study⁴⁵ was crossover. In both studies, the SiHy lenses were reported to perform better with respect to comfort than the control hydrogel lens. These are the only two peer-reviewed studies that have used such designs and found these outcomes. However, both of these studies were open-label so the treatment arm was masked to neither subject nor investigator.

A multitude of studies have reported switching of existing hydrogel wearers out of their habitual lenses and into silicone hydrogels.^{37,48,49,51-53,55,57,61} Consistently, these studies have reported improvements in subjective response with the SiHy lenses compared with the hydrogels. However, the other common feature of these studies is the omission of a concurrent randomized, masked, control (e.g., "switching" back into a hydrogel lens) that would enable confirmation of a claimed improvement in comfort.

Six investigations that were randomized, partially controlled studies and were at least subject-masked have considered comfort differences between hydrogels and silicone hydrogels. Fonn and Dumbleton⁴⁷ conducted a double-masked, contralat-

eral, 7-hour, open-eye, nondispensing trial on 39 symptomatic and asymptomatic subjects. They found no difference between the hydrogel and SiHy lenses in comfort and dryness ratings. Cheung and colleagues⁵⁴ conducted a prospective, double-masked, contralateral eye study in which they compared the comfort of two weekly replacement SiHy and hydrogel lenses in 33 subjects over 1 month of daily wear. They were unable to detect a significant difference in subjective comfort scores between lens material types. In the only extended wear trial of this group, Martin and colleagues⁶⁶ measured comfort after 7 days of contralateral eye contact lens wear of a SiHy and hydrogel in 20 subjects. They found that the SiHy lens was more comfortable and led to less dryness than the hydrogel lenses. In a single-center, double-masked, randomized, crossover, pilot clinical trial, Ousler and colleagues exposed 11 masked subjects to a controlled adverse environment for 75 minutes while wearing SiHy and habitual soft lenses.⁵⁸ They found greater relief of subjective ocular discomfort associated with lens wear in adverse environmental conditions whilst wearing the SiHy. Ozkan and Papas,⁵⁹ in a prospective, contralateral eye trial, compared comfort of a SiHy and hydrogel lens on 15 experienced lens wearers over 6 hours. Overall comfort was slightly (but significantly) higher for the low Dk hydrogel compared with the SiHy over this short time frame. Recently, Maissa and colleagues⁶⁴ compared the comfort of four silicone hydrogels and one hydrogel in a prospective, crossover, double-masked, 10 day, daily wear trial. In rank order of comfort, the hydrogel was scored highest by

the subjects and was statistically superior in comfort to one of the SiHy lenses at both the beginning and end of day.

The controls in each of these six prospective, randomized, subject-masked studies are inadequate to test whether Dk/t alone is linked to lens comfort, as properties other than Dk/t that may affect comfort, such as lens material surface properties and edge design, vary between the SiHy and hydrogel lenses under test. Nonetheless, the experimental designs are “more robust” than those other studies listed above, where subjects were swapped out of their habitual lenses to test lenses alone or where masking was inadequate. Interestingly, and in contrast to those studies, four of these better-executed studies did not find that SiHy lenses were superior in comfort to hydrogel lenses and indeed, in two of these studies, the hydrogel was more comfortable. Study design differences should be kept in mind when reconciling this apparent discrepancy. Overall, hydrogels seem to produce a more favorable comfort response in daily wear and shorter-term studies. During open eye wear, hydrogel lenses have sufficient Dk/t to provide near normal oxygen supply, at least to the central cornea.⁶⁷ The impact of the lower Dk/t of hydrogels will be exaggerated during eye closure, or extended or continuous wear. Importantly, the study by Martin and colleagues⁶⁶ was under extended wear conditions and this may partially explain the difference in results between that and the other “more robust” designs. A further confounding factor is study duration. The longest time of follow-up for the randomized, subject-masked studies was 30 days, where the “inferior” study designs saw patients followed, in some cases, for 3 years.

In recent years, four large cross-sectional studies have compared comfort between SiHy and hydrogel lenses. As noted above, Ramamoorthy and colleagues³² presented detailed statistical analysis of a cross-sectional and nested case-control study of 360 participants. The authors found FDA material classification to be a strong predictor of contact lens-related dry eye classification. Silicone hydrogel lens wear was found to be significantly protective from dryness symptoms in a univariate regression, but dropped out in the final multivariate model with FDA Group. The authors suggested that this could be because silicone hydrogels are low in EWC and correlate with FDA grouping. This finding may be highly relevant in discussions on the influence of Dk/t on comfort, as it points to the confounding effects of other material and lens properties. Chalmers and colleagues⁶⁰ report on the analysis of a baseline self-administered questionnaire completed by 882 contact lens wearers comprised of 699 wearing hydrogel and 183 SiHy lenses at 84 clinical sites. Diagnosis of dry eye increased with age in the hydrogel wearers from 10.6% (at 18–24 years) to 21.1% (at 30–35 years), while it remained steady at 19% in the SiHy wearers. While not precluding selection or survival bias, this study suggests that wearers of hydrogel materials find their lenses at least the equal of silicone hydrogels (with regard to symptoms of dryness) up to 30 years of age. Young and colleagues were involved in two prospective, multicenter, nonrandomized, cross-sectional, observational studies of soft contact lens-related dryness that were partially controlled for Dk/t and where subjects responded to a questionnaire based on the Contact Lens Dry Eye Questionnaire (CLDEQ), from which they were classified as either having dry eye or not. In the first study of 932 daily wearers of soft contact lenses, the proportion of subjects scoring positive for contact lens dry eye did not differ by lens material (hydrogel versus SiHy).⁶⁵ There were, however, differences in specific questions of typical and end-of-day comfort where the hydrogel performed less favorably. In their follow-up paper, they identified 226 soft contact lens wearers with self-reported contact lens-related dryness as classified by a questionnaire and 48 asymptomatic

control subjects.⁶⁵ This study showed that participants with and without symptoms of CL-related dryness did not differ by SiHy lens use. Interpretation of these cross-sectional studies must be made in the context of aforementioned limitations, but overall, the studies provide somewhat equivocal results.

Collectively, the above studies cast doubt on the suggestion that the higher Dk/t is associated with greater comfort. Therefore, it is not surprising that studies in which different brands of SiHy lenses are compared have been unable to discern a greater comfort response for those lenses with higher Dk/t. Morgan and Efron conducted a single-center, randomized, subject-masked, crossover study on 30 subjects wearing two brands of SiHy lenses each for 8 weeks.⁶⁸ The brand with the higher Dk/t did not show superior comfort to the brand with the lower Dk/t. Santodomingo and colleagues considered the same two brands used in both daily wear and continuous wear in a total of 45 subjects for 18 months.⁵⁰ Again, they found no superiority of comfort in the lens with higher Dk/t. Brennan and colleagues followed 45 subjects in a prospective, partially controlled randomized, partially masked contralateral eye study of three different SiHy lens brands for a period of 12 months.⁵⁶ Again, the lens with the highest Dk/t was not found to provide superior comfort.

While it may be appealing to attribute measured comfort benefits to the higher oxygen transmissibility of the SiHy lenses, a host of other confounding factors will drive the comfort response. Inadequacies of the control lens in experimental studies, including lens design, modulus, surface characteristics, and the modality of wear (daily disposable, reusable frequent replacement, flexible wear, extended wear, continuous wear) rather than Dk/t per se, may be responsible for the outcomes achieved. Duration of wear, where adaptation to the higher modulus lenses takes place, might interact with the lens material effect. Other experimental biases in the form of selection, novelty, halo, Hawthorne, survival, or similar effects resulting from study designs that are inadequate to randomize or mask the control product may also influence the outcome.

In summary, there have been no Level I evidence studies that can provide an answer to the question of whether oxygen levels influence comfort. What can be said is the following:

1. Where lenses of higher Dk/t are found to be more comfortable than lenses of lower Dk/t, there are deficiencies in experimental design or inadequacies in the control lenses that prevent definite attribution of such differences to oxygen.
2. There are circumstances where lenses of lower Dk/t have been found to be more comfortable than lenses with higher Dk/t; therefore, any effect that oxygen may be having on comfort is being overshadowed by other factors or there simply may be no or a converse relation.
3. Where comfort differences between higher and lower Dk/t lenses are found to be statistically insignificant, the method used to measure comfort may not be sufficiently sensitive to detect differences.

Modulus and Mechanical Factors. The two most important quantifiable mechanical properties are tear strength (elongation at break) and modulus, which can be measured in stretching (tensile or elastic) or compression (rigidity) mode. While modulus is a specific material parameter, the effective “stiffness” of a contact lens will also be influenced by its specific geometry (lens thickness profile) as a thick lens made from a low modulus material may still be considered relatively inflexible or stiff. A thinner lens made from a low modulus material will drape over the cornea, distributing itself evenly on the ocular surface with minimum lid interaction. In some

instances, an increase in stiffness will help mask corneal astigmatism but possibly at the expense of initial comfort.⁶⁹ Although the rigidity modulus has historically been useful for RGP materials, it is the tensile modulus that has primarily been most often quoted for soft lens materials.^{22,23,70-72}

The first generation silicone hydrogels (lotrafilcon A, balafilcon A) had tensile moduli that were significantly greater than most conventional hydrogels,^{22,23,71} such that for some wearers a comfort or wearer adaptation period was needed and there was an increased potential for mechanically induced ocular complications.^{19,21,73-75} Subsequent SiHy development has progressed to lower modulus materials through chemical structure modification and/or increased EWC.^{4,19,21-23,25,73,74}

The higher modulus of SiHy materials was initially seen as an issue when refitting hydrogel wearers into these more oxygen permeable materials. However, when Riley and colleagues⁴⁹ refitted 257 patients wearing hydrogel materials with a SiHy with a relatively low modulus (senofilcon A), they reported that 50% of subjects reported no contact lens-related discomfort. Most of the studies reporting refitting hydrogel wearers into silicone hydrogels report similar or higher levels of success, even when materials with a high modulus are employed.⁵¹ However, as noted recently by Guillon,⁷⁶ the study design may partly explain these findings, as most refitting studies lack a concurrent control group or adequate masking. When comparing the ability of material to predict contact lens dry eye, Ramamoorthy and colleagues³² were unable to show any difference between the 11 (or more) individual materials being compared, including at least two SiHy materials. In the few studies reported where study bias was minimized by using a control group using low modulus hydrogel lenses, no differences in comfort between hydrogel and silicone hydrogels could be identified or attributed to modulus.^{47,54}

Dehydration. Subjective reports of “dryness” and “discomfort” are well recognized as the main factors for contact lens discontinuation^{77,78}; and this has remained unchanged over the last decade, regardless of the new lens materials introduced.⁷⁹ This has led to an intuitive relationship being proposed between soft lens dehydration and discomfort, particularly at the end of the day. A connection between dehydration and discomfort seems plausible given: (1) the potential correlation between lens thickness and desiccation staining^{7,80}; (2) the potential correlation between corneal staining and discomfort^{81,82}; and (3) the increased friction presumably induced by dehydrated, dry lens surfaces.⁸³ However, a proven relationship between dehydration and discomfort has been supported by relatively few studies.^{13,84,85} This is perhaps not surprising, given the difficulties in evaluating material dehydration and types of dehydration (e.g., initial temperature-induced dehydration followed by evaporative dehydration).⁸⁶⁻⁸⁸ It is this latter dehydration that is potentially problematic, as it produces a water gradient^{89,90} that draws water through the lens and, ultimately, results in corneal desiccation staining.^{7,91,92} Evaporative dehydration tends to be localized and therefore may result in only a small change in a given lens' overall water content. Likewise, evaporative dehydration may be less apparent with higher power lenses and, therefore, may be even more difficult to monitor in a subject group of varying prescription.

In addition to patient and environmental factors, differences in dehydration do exist between materials. A number of in vitro studies have shown that bulk water loss is closely related to initial EWC, with low EWC lenses (including silicone hydrogels) dehydrating less than higher EWC hydrogels.^{6,93-96} In studies that have evaluated lens dehydration^{10,11,13,15,84,89,97-106} and also recorded comfort ratings, a significant relationship between the two has not been consistently shown.

Hall and colleagues¹³ fitted four contact lens materials to 10 subjects and recorded dehydration and comfort after 4, 8, and 12 hours. At the 12-hour time-point there was a moderate negative correlation between comfort and dehydration for etafilcon A lenses ($r = -0.64$, $P = 0.04$), but no correlation for the remaining three materials.¹³ In a study in which omafilcon A was shown to dehydrate significantly less than other lenses of similar EWC (etafilcon A), Lemp and colleagues¹⁰³ concluded from their 76-subject crossover study that the increased comfort found with the omafilcon A lenses was related to decreased on-eye dehydration.

In contrast with the work by Hall and Lemp, Fonn and colleagues¹⁰² found no correlation, either in symptomatic ($r = 0.33$, $P > 0.05$) or asymptomatic subjects, between the change in lens water content for omafilcon A and etafilcon A and change in comfort over 7 hours of lens wear in a contralateral, double-masked, nondispersing study. Maldonado-Codina and Efron¹⁰⁷ conducted a crossover study with 34 subjects to evaluate the impact of manufacturing technology and material composition on the clinical performance of five hydrogel lenses worn for 1 month each. Despite a significantly higher dehydration of the ionic (FDA Group IV) material after 6 hours and after 1 month of lens wear, there was no significant difference in overall comfort between lens types. Lastly, in perhaps the largest analyses of the relationship between material dehydration and comfort, Nichols and Sinnott⁸ and Ramamoorthy and colleagues¹⁰⁶ showed that while indeed higher EWC hydrogel lenses tend to dehydrate to a greater degree than lower water lenses, the degree of dehydration was not associated with contact lens dry eye classification of the subjects.

In conclusion, considering the body of literature available, including several well-designed studies that attempted to address this topic, it is not likely that a causative or associative relation exists between on-eye bulk dehydration of materials and discomfort using the current methods used to capture either dehydration or subjective comfort.

Surface Properties of Soft Lens Materials

Friction and Lubricity. Lubrication, which can be defined as any means capable of controlling friction and wear of interacting surfaces in relative motion, provides defense against wear (the loss of material from interacting surfaces in relative motion usually related to friction). Materials with low friction and low wear are thought of as being well lubricated, or having good lubricity.

Friction coefficient measurements are most often made as an indicator of the quality of lubrication or lubricity, since wear measurements of biological surfaces are challenging. A friction coefficient is the ratio of the frictional force between two contacting surfaces in relative motion to the normal force between those surfaces. A variety of in vitro test setups with different test characteristics (scale, geometry, counter surface) and parameters (protocol, environment, lubricant, lens condition) have been used to assess friction coefficients of contact lenses. While each in vitro test setup has advantages and disadvantages, it remains unclear which, if any, is representative of in vivo function and/or friction and there are no standards on the techniques as such.

Several contact lens friction studies exist in the peer-reviewed literature.^{83,108-115} Collectively, these studies demonstrate that friction associated with contact lenses is a challenging field of study, and support the notion that reported friction coefficients must always be considered in the context of the experimental parameters in which they were measured, which is outside the scope of this report. It is also important to note that while this is an expanding area of scientific interest,

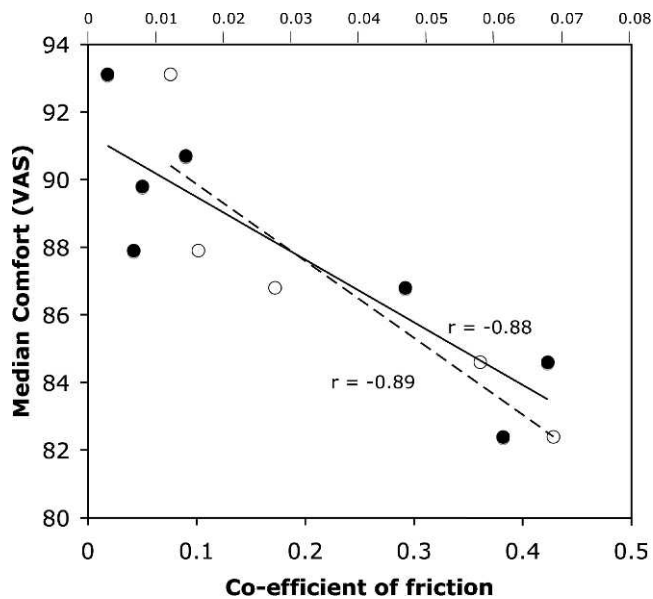


FIGURE. Plot of median end-of-day comfort from Brennan and Coles^{116,117} versus coefficient of friction reported by Ross and colleagues¹¹⁸ (open circles, dashed line, scale above plot area) and Roba and colleagues¹¹⁵ (closed circles, unbroken line, scale below plot area).

the aforementioned studies did not relate friction to comfort in contact lens wear.

Some recent evidence, albeit preliminary, does exist for an association between contact lens friction and comfort.^{116,117} Initially, coefficient of friction values from Ross and colleagues¹¹⁸ were compared with end-of-day comfort values from over 700 separate 1-month wearing trials and demonstrated a significant correlation ($r^2 = 0.79$, $P < 0.01$).¹¹⁶ More recently, peer-reviewed coefficient of friction data¹¹⁵ were used for the same analysis, and once again demonstrated significant correlations ($r^2 > 0.83$; $P < 0.01$).¹¹⁷ Additionally, these coefficient of friction data were shown to be highly correlated ($r^2 = 0.91$, $P < 0.0002$) with 2-hour mean comfort data from work conducted by Andrasko investigating corneal staining¹¹⁹ (Figure).

Tucker and colleagues (Tucker R, et al. *IOVS* 2012;53:ARVO E-Abstract 6093) developed an inclined plane method to determine friction coefficients of a variety of soft contact lens materials. This data was then compared with subjective data for insertion comfort, overall comfort, and end-of-day comfort from a database of clinical trials in a more recent analysis (Kern J, et al. *IOVS* 2013;54:ARVO E-Abstract 494). A statistically significant relationship was demonstrated between lens coefficient of friction and subjective comfort, suggested to be clinically relevant given the range of friction coefficients measured, and an approximate 0.025 reduction in the friction coefficient (obtained from the inclined plane method) was associated with a 1-unit improvement in comfort on a 10-point scale.

Data from these two recent frictional studies (Kern J, et al. *IOVS* 2013;54:ARVO E-Abstract 494)¹¹⁷ provides the strongest evidence to date that contact lens lubricity may be associated with comfort, although again, there is no Level I evidence as such. A caveat on this interpretation is that the coefficient of friction and comfort data tend to cluster together by lens manufacturer; thus, a manufacturer might tend to have higher comfort scores and lower coefficient of friction for two or more lenses in their portfolio. It is conceivable that characteristics other than low coefficient of friction—for example, edge

design—is common to the various lenses of that manufacturer and that one of these is the defining determinant of comfort.

Wettability. The term “wettability” is traditionally used to describe the tendency for a liquid to spread over a solid surface¹²⁰ and consequently has been widely adopted by the contact lens industry to describe the ability of the tear film to spread and remain on the surface of a contact lens. When a lens is applied to the eye, it fundamentally disrupts the normal tear film structure and physiology in a number of ways, including increasing the evaporation rate^{121–123} and decreasing tear film stability.^{121,124–126} The quality of the tear film over a lens is thought to play a key role in the lubrication of the lens/ocular surface system and will ultimately influence how much friction and “wear and tear” will result.

Despite widespread use of the term, no physical measurement exists that can completely quantify wetting. Notwithstanding this limitation, a number of different laboratory (in vitro) and clinical (in vivo) techniques have been adopted to investigate the wetting properties of contact lens surfaces, details of which are outside the scope of this report. Wettability is thought to be important for all types of contact lenses, but in particular for silicone hydrogels, which tend to be more hydrophobic compared with their conventional hydrogel counterparts, at least in the laboratory.

In Vitro Wettability. In vitro investigations of wettability have provided us with a wealth of information about lens surfaces and what factors affect them in the laboratory. Overwhelmingly, reports in the literature document the investigation of soft lenses, particularly in recent years. Those that do investigate rigid lenses have shown that the contact angles obtained are significantly affected by the methodology^{127,128} and since no recent reports exist that have used more current automated techniques, it is difficult to make any kind of meaningful comparisons with soft lenses. Studies have reported contact angles for unworn lenses in water or saline or other components^{129–134} and have shown that angles obtained for the same lenses can vary due to the differences in methodology or experimental conditions.¹³⁵ Despite all of these data, none has been able to show any relationship between in vitro measurements and on-eye clinical wetting and, further, whether these laboratory measurements are in any way related to comfort. For example, both Nichols and colleagues¹³⁶ and Thai and colleagues¹³⁴ investigated the effect of adding hydroxypropyl methylcellulose (HPMC) to a multipurpose contact lens solution and, despite differences in in vitro or in vivo wettability and tear film thickness, there was no overwhelming preference for either care solution.

Ex Vivo Wettability. In an attempt to make in vitro measures of contact angle more relevant, researchers have attempted to perform contact angle analysis on lenses postremoval, but there are surprisingly few publications that have measured the wettability of ex vivo contact lenses and related it to comfort. Tonge and colleagues¹³⁷ measured dynamic contact angles of etafilcon A lenses after various periods of wear in lenses that had been presoaked in either saline or a surfactant; the surfactant-exposed lenses showed significantly lower-advancing contact angles than the saline-treated lenses (however, there was no statistically significant difference for the receding contact angle between the two treatments). Of particular note in the work was that comfort was reported as being better for the surfactant-soaked lenses compared with the saline-soaked lenses at all time points measured, although only six subjects were included. There appear to be no other studies that have related ex vivo wettability to comfort associated with contact lens wear.

In Vivo Wettability. In vivo wettability has been investigated using a range of relatively simple slit lamp-based procedures

and grading scales,^{138,139} in addition to more indirect techniques such as the prelens noninvasive tear break-up time (NITBUT),^{102,140-143} tear thinning time,^{54,124,125,134,144} investigating the rate of evaporation from the lens surface,^{122,145} wavefront sensing,¹⁴⁶ high-speed videokeratometry,¹⁴⁷ and techniques based around specular reflection.¹⁴⁸

One investigation compared comfort and NITBUT in nelfilcon A and nelfilcon A AquaRelease lenses.¹⁴⁹ The authors reported that subjective ratings of comfort over a 16-hour period were consistently higher for the eye wearing the AquaRelease compared with the eye wearing the conventional nelfilcon A lens. NITBUT was greater with the AquaRelease than the conventional nelfilcon A lenses. In multivariate modeling, Nichols and Sinnott⁸ showed that prelens tear film thinning time was highly predictive of contact lens dry eye status, even when including EWC, osmolality, and lipid layer thickness (both significant themselves) in the multivariate statistical model.

Conclusive evidence that laboratory measures of contact angle can predict the wetting performance of a contact lens on-eye is lacking. Furthermore, the link between clinical measures of wettability and contact lens comfort remains not understood, with some evidence that surrogate measures do show a relation. It is likely that the assessment of wettability provides us with an indirect method of investigating the lubrication present in the lens/eye “system” and conclusive results across numerous studies have eluded us because the techniques we have employed to probe the tear film do not accurately reflect its complex and dynamic nature.¹⁵⁰

Wetting Agent Incorporation

The wetting agents discussed in this section of the review are limited to agents that are releasable and incorporated into contact lenses. Wetting agents in multipurpose solutions or contact lens packaging solutions will be addressed in another section. Wetting agents may be firmly embedded and provide enhanced wettability due to the materials being exposed at the lens interface or may be progressively released from the material over the course of the day.

Polyvinyl Alcohol. The nelfilcon A material is a polyvinyl alcohol (PVA)-based hydrogel specifically developed for use in a daily disposable lens. Maissa and colleagues¹⁵¹ suggested that the comfort level achieved with this lens “may result from a slow release of some residual entangled PVA” from the cross-linked PVA lens matrix. Using an *in vitro* release model, Tighe and colleagues¹⁵² suggested that the mechanical effect of the eyelid greatly accelerates soluble PVA release from the lens surface, which implies that the release is mechanically triggered or “blink activated” when placed on the eye. The next iteration of this material exploited this effect by intentionally adding nonfunctionalized PVA of appropriate molecular weight to enhance the elution of PVA, thereby increasing the comfort of these lenses.¹⁵³ It was demonstrated in a contralateral eye study that adding this nonfunctionalized PVA enhanced tear stability and subjective comfort over a 16-hour wearing period relative to the original nelfilcon A product.¹⁴⁹ A further enhancement incorporated an optimized blend of nonfunctional PVA in the lens matrix coupled with hydroxypropyl methylcellulose (HPMC) and polyethylene glycol in the packaging saline. Tear film stability was significantly greater with DACP than with its predecessor and was comparable to tear film stability without lenses.¹⁵⁴ However, comfort data were not reported in this study, which brings into question whether there was any subjective improvement in reported in-eye comfort.

Hyaluronic Acid. Hyaluronic acid (HA), a hydrophilic glycosaminoglycan found throughout the human body, has

been used in contact lens rewetting drops and in a range of artificial tear products to treat mild, moderate, and severe dry eye,^{155,156} and has been used as a novel internal wetting agent for contact lens materials.¹⁵⁷⁻¹⁶² However, to our knowledge, HA has not been shown in any clinical studies to directly improve comfort associated with contact lens wear.

Comparison Between Rigid and Soft Lens Materials

At first glance, there is a considerable difference between the comfort associated with rigid and soft lenses. However, while this is true in the short term, there is little evidence that medium and long-term comfort is substantially different between them. Fonn and colleagues¹⁶³ found no significant differences in ratings of comfort after 6 months between eyes of 27 patients fitted contralaterally with a soft and a rigid lens. However, average comfort was significantly lower for the eye wearing the rigid lens over the initial 3-month period. For the 16 patients who remained in the study for an additional period of 3 months, comfort between both eyes was reduced but remained only marginally lower for the rigid lens-wearing eye.

Morgan and colleagues¹⁶⁴ were unable to find a difference in comfort between a group of adapted rigid lens wearers and soft lens wearers using lenses on a continuous wear basis. Maldonado-Codina and colleagues¹⁶⁵ compared the comfort scores reported by subjects successfully wearing rigid or soft lenses on a daily wear basis with comfort reported by neophytes fitted with high oxygen transmission rigid lenses and silicone hydrogels on a daily wear basis for 2 weeks, followed by 11.5 months of continuous wear. Their results showed that, while neophytes in the SiHy group presented with a high comfort score from the very beginning, the rigid lens group reported significantly improved comfort scores over the first 2 weeks, remaining at the same level as the silicone hydrogels over the 12 months in continuous wear.¹⁶⁵ Subjects who were experienced rigid lens wearers actually reported the highest comfort levels of all wearers, suggesting that long-term rigid lens wearers may ultimately be the “most comfortable” of all lens wearers.

Finally, Nichols and Sinnott⁸ and Ramamoorthy and colleagues³² used a variety of statistical modeling approaches in a cross-sectional sample of 360 contact lens-wearing subjects to evaluate rigid lenses, compared with soft lens wearers, in predicting contact lens dry eye. Similar to other studies, rigid lens wear was not associated with a difference in predicting classification of subjects with or without contact lens dry eye.

In summary, there is little published evidence of a significant difference in the reported comfort between soft and rigid lenses in the long term, once the initial adaptation phase is complete. However, clinicians are aware of the fact that many RGP-wearing patients report increased comfort when they are switched into a soft lens, so this lack of evidence may relate more to the fact that such a study has not been conducted.

Lens Design and Fit

Soft Lens Design and Fit. The fact that soft contact lens fit can affect contact lens wearing comfort is supported by the practical experience of every contact lens practitioner. Moreover, it seems logical that a soft lens showing excessive movement or failing to cover the cornea will cause irritation through interaction between the cornea and edge of the lens. Nevertheless, few clinical studies have shed light on correlations between the subtleties of soft lens fit and comfort responses. The reasons for this are probably 2-fold: first,

although many clinical trials have identified differences in comfort between lens types, only a few have systematically varied design parameters. Many clinical studies compare lenses of differing material as well as design. However, those studies that have sought to systematically evaluate lens design have tended to involve old, relatively thick designs in low EWC materials.¹⁶⁶⁻¹⁶⁹ Second, since so many factors affect contact lens-wearing comfort, it is difficult to control for all potentially confounding factors (e.g., modulus, thickness, and edge profile).

Corneal Coverage and Lens Diameter. An essential requirement of successful rigid contact lens fit is for the edge to stay clear of the cornea in all positions. Due to their inherent flexibility, the reverse is true with soft lenses. Since the lens edge rests against the eye and, due to stretching, exerts pressure, it has to overlap the relatively sensitive cornea to avoid discomfort. In order to allow for blink-induced movement, an overlap of at least 0.5 mm is assumed to be necessary. However, there appears to have been no work to confirm the optimum amount of overlap. A potential source of confusion is the fact that the true cornea is >1 mm larger than the visible iris diameter (“white-to-white diameter”).^{170,171} Furthermore, the limbal transition zone varies between individuals and, thus, visible iris diameter is a poor predictor of corneal diameter.¹⁷²

The pioneers of soft lens design assumed that the smallest acceptable lens diameter was optimal. But this was soon reassessed and early 12.5- and 13.5-mm designs were replaced by larger lenses.^{173,174} One early study found that 13.5-mm diameter lenses showed full corneal coverage in approximately 50% of eyes, while 12.5-mm lenses gave total coverage in less than one-third of eyes.¹⁷⁵ One study of tear replacement found an interrelation between lens diameter, comfort, lens movement, and “tear replenishment,” with smaller diameter lenses giving reduced comfort, greater movement, and faster tear replenishment.¹⁷⁶ However, these apparent interrelations are confounded by the fact that the lens diameters were relatively small (12.0–13.5 mm) and that their closeness to the typical corneal diameter is likely to have impacted comfort.

Most current soft contact lenses fall within the diameter range 13.8 to 14.2 mm. However, since all lenses shrink when raised from room temperature to eye temperature,^{87,177} the diameter on-eye is quite different, being 13.54 to 14.16 mm in one study.⁸⁷ It is possible, therefore, that some lenses are uncomfortable due to them being smaller than expected when placed on the eye.

Lens Movement and Base Curve. It is assumed that some lens movement is necessary in order to encourage postlens lubrication and, in turn, avoid mechanical irritation and corneal desiccation. However, there has been little or no research to examine the consequences of zero soft lens movement. Of perhaps greater interest to lens wearing comfort is the opposite situation of excessive movement. The conventional belief is that excessive movement causes discomfort through encroachment of the lens edge onto the cornea. However, an alternative explanation might be irritation through excessive interaction between the lens and the lids. It is difficult to quantify the true amount of lens movement as some movement takes place when the lids are closed.¹⁷⁸

An extensive evaluation of soft lens fit reviewed more than 2000 contact lens fittings that had been classified as loose, tight, or optimal.³⁶ Unacceptable fittings categorized as “loose” tended to show more movement and poorer comfort, with the mean comfort score for loose fittings being 7.4 compared with 8.5 for optimal fittings (on a 10-point scale). A relatively large proportion (63%) of loose fittings were found to be less than comfortable (<9 on 0-10 scale). Only one study has noted a significant correlation between lens movement and comfort, with less mobile lenses being rated more comfortable.¹⁷⁹

Conventional contact lens practice assumes that the greatest influence on tightness of fit is back surface radius of curvature (base curve; BC). Most soft lens designs incorporate a single spherical curve on the back surface, although some soft lenses have utilized bicurve and aspheric designs. One of the most systematic evaluations of the effect of BC variation was undertaken with relatively thick, low EWC lenses; therefore, the findings have to be treated with some caution.¹⁸⁰ Lowther and Tomlinson¹⁶⁷ attempted to determine the minimum change in BC required to effect a significant change in various clinical outcomes such as vision, corneal edema, lens movement, and comfort. A change in BC of 0.95 mm was required to have a significant effect on comfort. A later study of midwater lenses found that a 0.6 mm flattening of BC resulted in significantly poorer comfort.¹⁸¹ A study with first generation SiHy lenses found improved comfort with 24% of patients by switching from an 8.60- to an 8.40-mm BC.¹⁸² However, the clinical picture is clouded by a proportion of the flatter lens fittings showing edge stand-off due to the relatively stiff material characteristics. Other studies of individual lens designs available in two BCs have found no significant difference in comfort when subjects were fitted with both BCs.^{183,184} However, this might be explained by the relatively small differences in BC in the products used in these studies (0.3 and 0.4 mm).

Lens Centration and the Lens-Eye Relationship. It is assumed that soft lenses decenter in order to reach an equilibrium state that balances the various forces from the lids as well as the lens-ocular surface interaction. It seems unlikely that small amounts of decentration (e.g., <0.3 mm) are likely to affect comfort as this does not significantly alter the interaction of the lens with the cornea or the lids. However, in some cases there may be confounding factors, with centration being influenced by a factor that also affects comfort (e.g., looseness of fit). To our knowledge, no studies have examined the effect of minor changes in lens centration on comfort during lens wear.

Edge Alignment and Lens Edge Profile. The design parameters related to lens edge profile are less easy to specify as they encompass the thickness at various points near the edge and the actual shape of the edge profile. A study of lathe-cut low EWC lenses found no significant difference in comfort when the edge thickness was systematically varied between 0.08 and 0.16 mm.¹⁶⁸ Similarly, no significant difference was found in a study of high-water lenses varying in edge thickness from 0.12 to 0.24 mm.¹⁶⁹ However, these edge thicknesses are relatively thick compared with molded designs and it is possible that the range was not wide enough to detect differences.

Modern molded designs generally taper to a thinner edge than lathe-cut and older molded designs. Several edge shapes have been identified in the literature, including so-called “rounded,” “knife,” and “chisel” edges.^{64,185} In a study by Maissa and colleagues,⁶⁴ the lens with the thickest edge shape (rounded) gave poorer comfort than one of the chisel edge designs and two of the knife edge designs. This rounded edge profile was also slightly less comfortable in the work by Hubner and colleagues.¹⁸⁵ It is plausible that the thinner designs sit closer to the bulbar conjunctiva and have less interaction with the lids than the rounded design. Alternatively, since the lens types were of varying materials, it is possible that the relatively high modulus of the rounded design may also have been a factor influencing comfort. Evidence for the reduced lid interaction theory is provided by ocular coherence tomography (OCT) imaging.¹⁸⁶⁻¹⁸⁸ These show that thin, tapered edge designs show a smoother transition between the conjunctiva and the lens surface and produce less disruption (“buildup”) of conjunctival tissue at the lens

edge.¹⁸⁷ Sharper, pointed edge designs also show less movement than thicker, rounded edges and induce more pronounced conjunctival staining.¹⁸⁵

Another finding that may relate to edge fit comes from one study that found better comfort with a bicurve back surface design compared with a moncurve design, even though all other parameters were held constant, including sagittal depth and edge thickness.¹⁶⁹ It is possible that the bicurve design afforded better alignment with the eye at the periphery of the lens, reducing localised pressure at this point.

Toric and Multifocal Designs. More sophisticated lens designs such as those incorporating prescriptions to correct astigmatism and presbyopia are thicker than spherical designs and this may affect comfort during wear.

Toric Contact Lenses. A study of contact lens dropouts found a disproportionately high number of astigmatic lapsed wearers.⁷⁷ When, as part of the same study, these lapsed wearers were refitted with contact lenses, there was a higher failure rate with toric soft lenses than spherical lenses. In a recent survey of soft lens wearers, symptoms of dryness were more frequent among toric soft lens wearers (43% vs. 30%, $P = 0.04$).⁶³ This mirrored the findings of a 1989 study that also found more symptoms of dryness in toric than spherical soft lens wearers (40% vs. 13%, $P < 0.01$).¹⁸⁹ There is evidence that CLD from a variety of sources is often misinterpreted as dryness.⁶⁵ The interaction of the lid margin with front surface irregularities may be difficult to distinguish from the interaction with a dry lens surface.

An early study of toric soft contact lenses systematically evaluated the clinical performance of toric designs of varying prism and truncation.¹⁹⁰ Although comfort was assessed and contributed to the outcome variable of “overall acceptance,” the comfort results were not reported separately. Not surprisingly, there was a tendency for the designs with thicker prism and more truncation to be less acceptable. Using a more recent prism ballasted, but non-truncated, design, Cho and colleagues found no significant difference in comfort between this and its spherical equivalent.¹⁹¹

Multifocal Soft Lenses. Clinical trials that evaluate multifocals in comparison with spherical soft lenses give some insight into possible effects on comfort from multifocal optical designs. However, there are few such studies. One study from 1990 found no significant difference in comfort, even though the lens was a diffractive multifocal incorporating optic zone on the back surface.¹⁹² A more recent study of a low EWC aspheric multifocal found no significant difference in symptoms compared with a single vision lens used for monovision.¹⁹³

Rigid Lens Design and Fit

Rigid lenses are undoubtedly less comfortable initially than soft lenses.^{163,165,194} The discomfort arises from the interaction between the rigid edge of the lens and the eyelids, particularly the upper lid margin, as evidenced by the various strategies adopted to minimize the discomfort.¹⁹⁵ Some rigid lens wearers reduce their blink rate or adjust their head posture to minimize the lid interaction. When fitting rigid lenses, practitioners often raise the patient's eyelids to alleviate the initial discomfort. The possibility that the cornea is an additional center of discomfort is suggested by piggyback soft-rigid lens combinations, which tend to be more comfortable than rigid lenses alone.^{196,197} However, this may be due to a cushioning effect that reduces the edge clearance of the rigid lens. The fact that the discomfort reduces when the eyes are held closed would also tend to refute this.

Three important factors relating to the edge of rigid lenses govern comfort; these are the thickness and shape of the edge

and the amount of clearance from the cornea. The greater the edge clearance, the greater the interaction with the eyelids and, in turn, poorer comfort.¹⁹⁸ Cornish and Sulaiman¹⁹⁹ evaluated the effect of rigid lenses of varying center thickness ([CT], 0.10–0.21 mm) on comfort and found that the thinnest design was actually the least comfortable, which was attributed to greater on-eye lens flexure. Mandell²⁰⁰ attempted to characterize edge shape by specifying the location of the edge apex and lens thickness at various distances from the edge, and found less comfortable edges tended to incorporate an apex close to the lens front surface. Shanks evaluated 13 edge shapes and noted differences in comfort between lenses, but came to no overall conclusion on the optimum shape.²⁰¹ Korb and Exford²⁰² proposed an alternative strategy for maximizing comfort. Rather than finishing the peripheral contour of the lens so as to allow the upper lid to slide easily over the lens, they modified the edge and periphery to encourage “lid attachment.” The most systematic clinical evaluation of rigid lens edges was by La Hood,²⁰³ who assessed the comfort of four representative edge designs in four subjects: round, square, rounded anterior with square posterior, and square anterior with round posterior. The two designs with rounded anterior edges were significantly more comfortable than the other two. There was no significant difference in comfort between the lenses with square and rounded posterior edge profiles. The results confirm that the interaction of the lens edge with the eyelid is the most important factor in determining comfort in rigid lens wear.

Large Diameter Lenses. Large diameter RGP lenses might improve comfort by reducing lens movement and reducing the interaction of the lid with the edge of the lens. One potential classification for rigid lenses according to their overall diameter is “corneal” (<12.5 mm), “corneoscleral” (12.5–15.0 mm), and “scleral” lenses (>15.0 mm).²⁰⁴

While there is clinical evidence of the short-term improved comfort with corneoscleral and scleral lenses compared with corneal RGP lenses, few well-controlled studies have addressed this point. Sorbara and Mueller²⁰⁵ compared the comfort of RGP lenses with different overall diameters in a nondispensing study in patients with keratoconus. The authors concluded that smaller diameter lenses (8.7 and 9.0 mm) were initially more comfortable in central cones, while larger lenses (10.1 and 10.4 mm) were preferred in oval cones. According to their results, lens movement was not directly related to comfort.

To date, there is no solid evidence of the benefits of corneoscleral and scleral lenses compared with corneal RGP lenses in terms of comfort, beyond clinical intuition. The average comfort ratings reported by some authors for scleral lenses (with diameters from 18.0–25.0 mm) fitted to patients with several ocular surface diseases²⁰⁶ are in the same range as comfort values already reported for corneal lenses in healthy subjects.^{163,165} Nevertheless, a direct comparison cannot be drawn, as most of the corneoscleral lenses were prescribed for eyes with serious eye disease.

In conclusion, considering the growing interest in the use of corneoscleral and scleral rigid lenses for eyes that do not exhibit disease or abnormal surface profiles, it is clearly necessary to conduct well-controlled, randomized studies where the potential for enhanced comfort of these lenses over standard diameter rigid lenses is investigated.

Tear Exchange. Placement of a contact lens on the eye leads to disruption of the tear film and to stagnation of the postlens tear layer during soft contact lens wear.^{207,208} Liberal exchange of this layer is generally considered preferable because it more closely represents the natural free flow of tears when no contact lens is in place and because buildup of debris behind the lens has been anecdotally associated with increased likelihood of corneal inflammatory events.^{209–214}

Measurement of tear exchange is almost exclusively conducted by determining the expulsion of a “marker” of some sort from behind the lens, which is typically sodium fluorescein, using a technique called fluorophotometry.

McNamara and colleagues¹⁷⁶ used fluorophotometry to measure tear exchange in 23 subjects while they wore lenses of four different diameters in separate 30-minute wearing trials. Increased tear exchange was accompanied by decreased comfort, although intuitively the effects are linked and both are the result of decreasing lens diameter. Paugh and colleagues²¹⁵ found fluorescence decay over 30 minutes to be greater with a prototype lotrafilcon A contact lens than thinner, less mobile etafilcon lenses in 11 subjects, but found no significant correlation between lens comfort and tear exchange rate.

Lin and colleagues²¹⁶ investigated the effect of scalloped microchannels on the posterior surface of contact lenses on tear exchange over a 30-minute period, measuring comfort concurrently. They theorized that the channels might lead to increased tear exchange and were able to show this in Asian, but not in non-Asian, subjects. The microchannels do not induce any discernible change in comfort during the relatively short wearing times for which this design has been studied.^{216,217} One further method that may increase tear exchange is to fenestrate lenses, which would increase the flow of tears from the back surface of the lens to the front surface. To date, no studies appear to have investigated tear exchange with fenestrated soft lenses, but one paper²¹⁸ was able to demonstrate that such a procedure does result in markedly reduced comfort due to interactions between the palpebral conjunctiva and the fenestrations.

The above methods of achieving increased tear exchange all involved increased lens movement, which is the likely associated factor. Unfortunately, increased lens movement is also associated with decreased comfort. The conventional view and some evidence is that tightly fitting lenses are comfortable and that loose-fitting lenses are likely to be less comfortable than well-fitting lenses.^{36,77}

In summary, there is little evidence that increasing tear exchange will have a positive effect on lens comfort and, to the contrary, changes to lens parameters that may bring about increased tear exchange are likely to have a simultaneous negative impact on lens comfort.

Miscellaneous Factors

Tinted Lenses. The tints on soft contact lenses can be translucent or opaque and in general, three types of tint are commonly used: visibility (or “handling”) tints, enhancement tints, and those with an opaque (or semiopaque) tint. Opaque tints can be applied using dot matrix printing on the lens surface,²¹⁹ which can result in a relatively rough surface,^{220,221} and one study comparing these lenses with their clear equivalent found increased discomfort with the colored lenses.²²¹

Manufacturers have tried to overcome this problem by either housing the tint within the lens itself in the form of a laminate or applying a hydrophilic “coating” layer.²²⁰ The laminate construction has the advantage of encapsulating the printed matrix, but leads to increased lens thickness,²²² which in turn may have a detrimental effect on comfort. Opaque lenses also have a fixed pupillary aperture that may lead to the wearer being more aware of these lenses due to constrictions of the visual field,^{223,224} peripheral vision blur,²²⁵ and so-called “annular tinted contact lens syndrome” where subtle distortions of the cornea and induced astigmatism have been observed, with a subsequent reduction in vision.^{222,226} These visual problems may have an impact on the perceived comfort

of the contact lenses, since problems with vision appear to affect comfort (Papas E, et al. *IOVS* 2003;44:ARVO E-Abstract 3694). In contrast, Gauthier and colleagues²²⁵ compared opaque colored lenses with their clear equivalents and observed no difference in overall comfort. Thus, evidence remains contradictory in terms of impact of lens tinting on comfort in contact lens wear.

Indicator Markings. Since most soft lenses are cast-molded, indicator markings on these lenses are placed onto the metal mold inserts by techniques such as electric discharge, diamond point engraving, and laser etching. The importance of the form of these markings to comfort have been the subject of various patents, with some placing much importance on these markings being composed of individual dots no greater than 90 μm in diameter being recessed into the lens front surface by a depth of 2 to 10 μm .^{227,228} There is no published literature to date relating lens markings to in eye comfort, but anecdotal reports have occurred of lens wearers reporting increased lens awareness when lens markings have been added to or changed for existing products. In addition, anecdotal reports exist of these markings becoming filled with tear film components,²²⁹ and these deposits could act as a source of irritation.

Contact Lens Deposition

Since the commercialization of soft lenses in the early 1970s, clinicians have realized that contact lens materials rapidly attract tear film contaminants and that this deposition impacts lens performance.^{230,231} While intuitively it would appear obvious that there would be a link between comfort and contact lens deposits, proving such a link is somewhat more challenging, as many studies rely on visible deposition rather than biochemically measuring the actual degree of deposition. Visible measures of deposition are usually done either on-eye at the slit lamp biomicroscope or off-eye using various versions of the RUDKO scale, first reported by Allergan in the mid-1970s.²³² This is problematic, as it is known that visible and measured deposition show a poor correlation.^{233,234}

Visible Deposits and Comfort. Roughly half of the studies conducted to date investigating comfort and its link with deposition have used visible deposition rather than biochemical analysis of deposits (Table 2).

The earliest of these studies by Nilsson and colleagues^{235,236} showed that lenses with the greatest level of deposition were generally less comfortable²³⁵ and that the use of a weekly enzyme cleaner resulted in increased comfort.²³⁶ While no direct correlation between comfort and deposition was reported in either paper, each surmised that increasing deposition was an important factor in reducing lens comfort. However, one study conducted at around the same time²³⁷ and two later studies^{238,239} were unable to demonstrate any correlation between visible deposition and comfort.

A larger multicenter study²⁴⁰ investigated lenses that were replaced every day versus those worn for up to 1 year. The daily disposable lenses, not surprisingly, exhibited reduced deposits over the course of the study and exhibited higher levels of comfort. The investigators linked these two factors, but many other factors (e.g., surface wettability; care solution effects) could have been the major reason for the improved comfort. Two other studies^{241,242} conducted at a similar point in time looking at the impact of frequent replacement of lenses on subjective performance were also able to link reduced levels of visible deposits with improved comfort. Of these, only one study²⁴¹ actually reported a correlation between subjective responses and deposition, and while the correlation was weak ($r = -0.33$), it was statistically significant. The remaining five studies (Truong TN, et al. *IOVS* 2008;49:ARVO E-Abstract 4833)^{44,54,243,244} all included SiHy materials that were replaced

in 4 weeks or less. Of these, four reported no correlation between visible deposits and comfort^{44,54,243,244} and the only piece of work to suggest such a link exists is a conference abstract (Truong TN, et al. *IOVS* 2008;49:ARVO E-Abstract 4833) using a retrospective analysis of short-term wear of various lenses.

In summary, studies conducted using visible methods to determine lens deposition have provided poor evidence that comfort and deposits are linked, particularly over the 1 month or less that lenses are now typically worn. Future studies would be ill advised to rely on visible assessment of deposition to relate to contact lens comfort.

Quantified Protein Deposits and Comfort. To date, a dozen studies have used various biochemical analyses to quantify protein deposition and attempt to link it with contact lens comfort, and these are summarized in Table 3.

Of the nine studies looking at hydrogel materials alone (investigating all FDA categories), eight were not able to show any correlation between the quantity of protein deposited and comfort.^{11,245–251} The only exception to this was a study by Lebow and Christensen²⁵² that investigated the impact of two care systems (one using a daily cleaner) on protein deposits and comfort in 76 subjects wearing ionic, high EWC lenses. They found that the subjects using the daily cleaner reported improved comfort and that the lenses collected from these subjects showed reduced protein (lysozyme) deposition. No actual correlation analysis was reported, but the authors surmised that the reduced deposition and comfort were linked. Subbaraman and colleagues²⁵¹ examined the correlation between symptoms and protein deposition over an 8-hour period in 30 subjects using an FDA Group IV material; while they were unable to report any significant correlation between total protein and symptoms, they were able to show a correlation ($r \geq 0.64$; $P < 0.001$) between reported comfort and the amount of denatured lysozyme. They concluded that while comfort cannot be linked with quantity of protein deposited, it might be related to the amount of denatured protein on the contact lens.

Of the three studies investigating protein deposition and comfort when subjects wore SiHy materials, the results were equivocal. One study²⁵³ showed no relevant correlation, while another²⁵⁴ showed that a rewetting drop resulted in increased comfort and reduced total protein, total lysozyme, and increased protein activity and thus a relationship was surmised. The most recent study on a large sample of SiHy lenses was able to show a weak correlation ($r = -0.13$) with comfort on insertion.²⁵⁵ To date, no study has investigated the link between denatured protein and comfort for SiHy materials, but one in vitro study²⁵⁶ has reported that lysozyme activity does reduce over time following its deposition on both hydrogels and silicone hydrogels.

In summary, the main conclusion is that the amount of deposited protein appears unrelated to contact lens comfort, but protein activity may be correlated. However, further work in this area—particularly with regard to the degree of activity of proteins other than lysozyme—is required to confirm any such relation.

Quantified Lipid and Mucin Deposits and Comfort. The final area linking contact lens deposition and comfort are those quantifying the amount of lipid or mucin deposition, and these five studies are summarized in Table 4.

The two studies reporting on mucin deposition (one looking at hydrogel materials only²⁵⁷ and the other including silicone hydrogels²⁵⁸) were both unable to link the amount of mucin deposition with comfort. This lack of association was also reported for lipids in two studies looking at hydrogel materials.^{11,247} A more recent study investigating lipid deposition on a variety of SiHy materials was able to show weak (but

significant) correlations for both overall comfort ($r = -0.13$; $P = 0.03$) and comfort on insertion ($r = -0.16$; $P = 0.008$).²⁵⁵

In summary, the evidence-linking lipid or mucin deposition with contact lens comfort is either nonexistent or weak and future work should, perhaps, be directed at investigating mucin or lipid breakdown products rather than total lipid or mucin, if such a link is to be established.

Wearing Modality

Lens Wearing Schedule (Daily, Flexible, Extended, or Continuous Wear). Comparison of comfort differences between daily wear; flexible wear (occasional overnight wear); extended wear (regular overnight wear for up to 6 sequential nights); and continuous wear (regular overnight wear for over 6 sequential nights) of contact lenses is difficult because of numerous confounding factors. By virtue of the known average difference in comfort between contact lens wearers and nonwearers, a greater degree of discomfort on awakening is to be expected in those who sleep in lenses. Differences between daily wear comfort and comfort after sleep may be a function of hypoxia or tear disturbances rather than the wear schedule. Further, those who sleep in their lenses may self-select or survive in that modality on the basis of comfort, and prolonged wear such as extended wear means a longer wearing period and comfort differences may be related to the exposure time rather than the modality.

A number of studies have compared comfort between daily wear and extended wear of hydrogel lenses. Poggio and Abelson²⁵⁹ conducted a historical cohort study of 2433 cosmetic contact lens wearers. They reported that users of disposable extended wear lenses reported symptoms less frequently at routine visits than users of nonreplaced hydrogel daily wear lenses. It is important to note that the lens materials and designs and replacement frequencies were different in the two groups, meaning that the comfort difference can be not attributed to the wearing schedule in isolation.

Nichols and colleagues²⁶⁰ conducted a randomized, cross-over, dispensing clinical trial specifically for the purpose of comparing daily disposable and disposable extended-wear modalities, using commercially available etafilcon brands. There was no significant difference between DD and EW in terms of lens comfort and awareness. However, a significant number of patients reported increased levels of ocular discomfort and irritation in the morning while in the extended-wear modality. Despite this, the subjects preferred the extended wear option overall, on the basis of convenience. The study by Aakre and colleagues²⁶¹ followed 49 successful DD wearers, with 19 continuing to wear DD hydrogel lenses and 30 refitted with SiHy lenses on a 30-day/night schedule over 6 months. They were unable to demonstrate differences between the two modalities in terms of comfort and dryness.

Chalmers and colleagues⁴⁸ looked at previous daily and EW of hydrogel lenses and its impact on symptoms with wear of lotrafilcon A SiHy lenses. The study feature of interest here, in terms of comparing wearing schedules, is that at baseline there was more than double the number of subjects who had previously worn hydrogel lenses in daily mode that experienced end-of-day dryness often or every day and who experienced moderate or severe end-of-day dryness compared with those who had worn hydrogel lenses in EW. This may be the result of a difference in the material and design of lenses prescribed for daily and EW, a direct protective effect of EW brought about by, for example, corneal hypoxia, or a bias phenomenon brought about by self-selection or survival. Santodomingo and colleagues compared DW and CW of each of two SiHy lenses over 18 months and found little evidence of major difference in symptoms of comfort and dryness between

TABLE 2. Studies Comparing Comfort With Visible Deposits

Author	Study Design	Study Period/ Age of Lens at Analysis	SCL Materials	Number of Subjects	Visible Deposits Recorded or Graded	Correlation With Comfort Scores	Level of Evidence
Hydrogel materials only							
Nilsson and Andersson ²³⁵	Prospective, observational, daily wear, nonmasked, single site	Single visit (lens age not controlled)	Variety of hydrogel materials	34 existing wearers	Graded 0–3 on-eye at the slit lamp	Subjects with greatest amount of discomfort displayed the greatest level of deposition: Correlation surmised	III
Nilsson and Lindh ²⁵⁶	Prospective, randomized (use of an enzyme tablet), contralateral eye, daily wear, investigator-masked, single- site	6 mo	FDA group I (polyHEMA) and group II (75% water content)	66 existing wearers	Graded 0–3 on-eye at the slit lamp; grades 2 and 3 subsequently graded off-eye using a modified RUDKO system	Lens exposed to weekly enzyme cleaner exhibited reduced visible deposits and increased comfort: correlation surmised	II
Gellatly et al. ²⁵⁷	Prospective, observational, daily wear, nonmasked, single site	Single visit (lens age not controlled)	PolyHEMA	51 existing wearers	Graded off-eye using a modified RUDKO system	No correlation	II
Nason et al. ²³⁸	Prospective, nonrandomized, daily wear, nonmasked, multicenter	2 wk	Etafilcon A	48 existing wearers of crofilcon A	Graded 0–3 on-eye at the slit lamp	No correlation	II
Nason et al. ²⁴⁰	Prospective, randomized (frequency of replacement), daily wear, nonmasked, multicenter	Periods from 1 d to 1 y	Etafilcon A; polyHEMA	177 existing wearers	Graded 0–3 on-eye at the slit lamp	Reduced visible deposits and better comfort with shorter frequency of replacement: Correlation surmised	II
Bruce et al. ²³⁹	Prospective, observational, daily wear, nonmasked, single-site	Single visit (lens age not controlled)	Etafilcon A; polyHEMA; vifilcon A	50 existing wearers (26 ranked “comfortable”; 24 “uncomfortable”)	Graded off-eye using a modified RUDKO system	No correlation	II
Pritchard et al. ²⁴¹	Prospective, randomized (frequency of replacement), daily wear, investigator- masked, single-site	1 mo, 3 mo, or up to 2 y	polyHEMA	119 neophytes	Graded off-eye using a modified RUDKO system	Longest replacement period had reduced comfort and increased visible deposition: Correlation weak but present	I
Solomon et al. ²⁴²	Prospective, randomized (lens material/frequency of replacement), daily wear, nonmasked, multicenter	Periods from 1 day to 3 months	Etafilcon A; polyHEMA; tetrafilcon A; vifilcon A	229 existing wearers	Graded 0–3 on-eye at the slit lamp	Longest replacement period had lowest comfort and greatest visible deposition: Correlation surmised	I

TABLE 2. Continued

Author	Study Design	Study Period/ Age of Lens at Analysis	SCL Materials	Number of Subjects	Visible Deposits Recorded or Graded	Correlation With Comfort Scores	Level of Evidence
SiHy materials included							
Brennan et al. ⁴⁴	Prospective, randomized (material), contralateral eye, extended wear, nonmasked, multicenter	1 y	Balafilcon A; Etafilcon A	123 (completed 1 y); existing wearers or neophytes	Graded 0–4 on-eye at the slit lamp	Comfort > for balafilcon A; visible deposits > for balafilcon A; No correlation	I
Stern et al. ²⁴³	Prospective, partially randomized (overnight wearing period), extended wear, nonmasked, single-site	Wearing periods close to 1 mo	Lotrafilcon A	39 neophytes and 115 existing wearers	Graded 0–4 on-eye at the slit lamp	No significant differences in comfort or visible deposits between the 2 periods of overnight wear (6 vs. 30 nights); No correlation	I
Nichols ²⁴⁴	Prospective, nonrandomized, 2-phase (cleaning without and then with a rub step), daily wear, nonmasked, multicenter (phase I) and single-site (phase II)	2 wk	Galyfilcon A	Phase I: 118 existing wearers; Phase II: 33 “heavy depositors” from Phase I	Graded 0–4 on-eye at the slit lamp and off-eye using a digitized modified RUDKO system	Digital rub reduced visible deposition; No correlation	II
Cheung et al. ⁵⁴	Prospective, randomized (material), contralateral eye, daily wear, double-masked, single-site	2 wk	Etafilcon A; galyfilcon A	30 asymptomatic existing wearers	Graded off-eye using a modified RUDKO system	Galyfilcon A exhibited greater deposition; similar comfort between lenses; No correlation	I
Truong TN, et al. <i>IOVS</i> 2008; 49:ARVO E-Abstract 4833	Retrospective, analysis of data from database of 60 single studies, single site	Lens age not reported; appear to be short-term fitting studies (6 h)	Various SiHy materials	275 existing wearers	Not described	Visible deposition correlated with comfort scores	III

TABLE 3. Studies Comparing Comfort With Quantified Protein Deposits

Author	Study Design	Study Period/ Age of Lens at Analysis	SCL Materials	Number of Subjects	Visible Deposits Recorded or Graded	Laboratory Analytical Methods Used	Correlation With Comfort Scores	Level of Evidence
Hydrogel material(s) only								
Lin et al. ²⁴⁵	Prospective, randomized (lens material), daily wear and extended wear, nonmasked, single-site	Various periods from 1 min to 7 d	Etafilcon A; polyHEMA	4 neophytes and 11 existing wearers	Graded on-eye at the slit lamp using a modified RUDKO system	SDS-PAGE	Increased protein with etafilcon A material: No correlation	I
Lever et al. ²⁴⁶	Prospective, nonrandomized, observational, daily wear, nonmasked, multicenter	Single visit (lens age not controlled; lens replacement) 1 mo and 3 mo	FDA groups I, II, III, and IV	977 lenses from 890 existing wearers	Graded off-eye using a modified RUDKO system	Ninhydrin assay	No correlation	I
Jones et al. ²⁴⁷	Prospective, randomized (wearing period), daily wear, investigator masked, single site	1 mo and 3 mo	Vasurfilcon A	12 existing wearers	Graded 0–3 on-eye at the slit lamp	UV spectroscopy	Protein deposits increased with wearing period; comfort no difference: No correlation	I
Lebow and Christensen ²⁵²	Prospective, randomized (solution system), daily wear, investigator masked, multicenter	3 mo	3× FDA group IV materials	76 existing wearers	Graded off-eye using a modified RUDKO system	HPLC	OPTIFREE solution resulted in reduced visible and protein deposition and increased comfort: Correlation surmised	I
Young et al. ¹¹	Prospective, randomized (material), contralateral eye (material), daily wear, double-masked, single-site	1 mo	Etafilcon A; etafilcon A; omafilcon A; polyHEMA; Weicon CE	30 (mix of neophyte and existing wearers)	None	Spectrophotofluorimetry	No correlation	I
Bruinsma et al. ²⁴⁸	Prospective, nonrandomized (wearing period), daily wear, nonmasked, single-site	10 d and 50 d	Etafilcon A	10 neophytes	None	SDS-PAGE	Comfort worse with lenses worn for longer period of time: No correlation	II
Michaud and Giasson ²⁴⁹	Prospective, randomized (replacement period), daily wear, investigator-masked, single-site	1 d up to 26 d	Etafilcon A	17 existing wearers	None	Total protein by UV-colorimetric assay	No correlation	I
Caron et al. ²⁵⁰	Prospective, randomized (rewetting drop), daily wear, double-masked, single-site	2 wk	Etafilcon A	22 asymptomatic existing wearers (18 analyzed)	None	Modified Lowry	Reduced protein with Clens 100 drops: No correlation	I

TABLE 3. Continued

Author	Study Design	Study Period/ Age of Lens at Analysis	SCL Materials	Number of Subjects	Visible Deposits Recorded or Graded	Laboratory Analytical Methods Used	Correlation With Comfort Scores	Level of Evidence
Subbaraman et al. ²⁵¹	Prospective, randomized (wearing time), crossover, daily wear, investigator-masked, single-site	2, 4, 6, or 8 h	Etafilcon A	30 existing wearers (16 symptomatic of dryness)	None	SDS-PAGE; Western blot; micro-BCA; lysozyme activity assay	No correlation between comfort and total protein or total lysozyme, but strong correlation with denatured lysozyme ($R \geq 0.64$)	I
SiHy material(s) included								
Subbaraman et al. ²⁵⁴	Prospective, randomized (drop use—surfactant-based rewetting drop vs. saline drop), crossover, extended wear, investigator-masked, single-site	1 mo	Lotrafilcon A	24 existing wearers	None	SDS-PAGE; Western blot; dot blot; lysozyme activity assay	Use of a surfactant-containing rewetting drop resulted in increased comfort on insertion, reduced total protein, reduced lysozyme and increased protein activity; Correlation surmised	I
Santos et al. ²⁵³	Prospective, randomized (material), contralateral eye (material), daily wear, subject-masked, single-site	15 d (etafilcon A); 30 d (all other materials)	Balafilcon A; etafilcon A; galyfilcon A; tetrafilcon A; lotrafilcon B	31 neophytes	None	SDS-PAGE; fluorescence microscopy	No correlation	II
Zhao et al. ²⁵⁵	Prospective, nonrandomized, parallel group, daily wear, double-masked, single-site	2 or 4 wk	Balafilcon A; galyfilcon A; lotrafilcon B; senofilcon A	583 lenses	None	Bicinchoninic acid or NanoOrange	Weak association with comfort on insertion ($R = -0.13$)	II

TABLE 4. Studies Comparing Comfort With Lipid and Mucin Deposits

Author	Study Design	Study Period/ Age of Lens at Analysis	SCL Materials	Number of Subjects	Visible Deposits Recorded or Graded	Laboratory Analytical Methods Used	Correlation With Comfort Scores	Level of Evidence
Hydrogel material(s) only								
Jones et al. ²⁴⁷	Prospective, randomized (wearing period), crossover, daily wear, investigator-masked, single-site	1 and 3 mo	Vasurfilcon A	12 existing wearers	Graded 0–3 on-eye at the slit lamp	Fluorescence spectrophotofluorimetry	Lipid deposits increased with wearing period; comfort no difference; no correlation	I
Young et al. ¹¹	Prospective, randomized (material), contralateral eye (material), daily wear, double-masked, single-site	1 mo	Atafilcon A; etafilcon A; omafilcon A; polyHEMA; Weicon CE	30 (mix of neophyte and existing wearers)	None	Spectrophotofluorimetry	No correlation	I
Berry et al. ²⁵⁷	Prospective, observational, daily wear, nonmasked, single-site	Single visit (lens age not controlled; min of 3 wk old)	Variety of hydrogel materials	50 existing wearers (19 graded as being symptomatic)	None	Dot and Western blots	Mucin deposition similar between symptomatic and asymptomatic subjects; no correlation	II
Silly material(s) included								
Zhao et al. ²⁵⁵	Prospective, nonrandomized, parallel group, daily wear, double-masked, single-site	2 or 4 wk	Balaafilcon A; galyfilcon A; lotrafilcon B; senofilcon A	583 lenses	None	Thin-layer chromatography	Weak association with comfort on insertion ($R = -0.16$) and comfort overall ($R = -0.13$)	II
Berry et al. ²⁵⁸	Prospective, nonrandomized, daily wear, double-masked, single-site	2 wk	Senofilcon A; vifilcon A	33 neophytes	None	Dot and Western blots	Materials can modulate mucin adherence; no correlation	I

the two wearing schedules.⁵⁰ Bergenske and colleagues⁵⁵ reported on 317 subjects wearing SiHy lenses in CW and compared them with 81 neophytes introduced to hydrogel lens DW in a prospective, 3-year, open-label, nonrandomized study. They found that wearers of the hydrogel lenses reported during-the-day and end-of-day dryness more frequently. Ramamoorthy and colleagues¹⁰⁶ considered a range of factors that might be associated with contact lens-related dry eye in a cross-sectional study. This study considered both SiHy and hydrogel lens wearers combined. Those who wore their lenses overnight were almost one-third as likely to be classified as having “dry eye” as those who did not, in a univariate model. However, a model that controlled potential confounding factors (age, sex, recent contact lens refitting, and number of weekly applications of artificial tears/rewetting drops) did not show overnight wear to be a significant factor.

As noted earlier, the wearing modality may interact with the effect of oxygen on comfort, if such an effect exists. Perhaps surprisingly, a tentative conclusion can be drawn that, apart from relatively minor dryness upon awakening, individuals who sleep in lenses are not at a disadvantage and indeed may benefit in terms of comfort and dryness compared with those who do not sleep in lenses and wear them on a daily wear basis. There have been no studies reporting superior comfort in DW, save for comfort on awakening. To date, inadequacies of study designs prevent more definitive conclusions from being drawn.

Duration of Wear. The comfort and dryness response to contact lens wear may not be static. Certainly, practitioners and patients are familiar with comfort adaptation to gas-permeable lenses. Fonn and colleagues¹⁶³ and Morgan and colleagues¹⁶⁴ have both tracked the dramatic change in comfort that occurs during the initial few weeks of wear. SiHy lenses are generally stiffer than hydrogel lenses and may also have surfaces with higher coefficient of friction, as discussed earlier. It is reasonable to propose that a similar, albeit lesser, adaptation may occur during wear of these lenses as takes place during the initial wear of gas-permeable lenses. Certainly, while the first week of wear may show the largest adaptation to comfort, the study of Chalmers and colleagues⁴⁸ suggested that there is a gradual decrease in the percentage of subjects with more severe dryness frequency and also with moderate or severe dryness over 6 to 12 months while wearing SiHy lenses in CW mode.

The impact of duration of wear may also explain in part the differences observed between studies when comparing hydrogels and silicone hydrogels. In short-term studies (up to 30 days) particularly for DW, hydrogels would generally seem to provide equal or superior comfort.^{47,54,59,64,116} In longer-term studies, silicone hydrogels would appear to provide better comfort.^{44,45,48,55}

A confounding and possible competing factor in considering the impact of duration of wear on comfort is the effect of lens replacement frequency. There does not appear to be any Level I evidence to support the contention that duration of wear is important in determining contact lens comfort.

Lens Age and Replacement Frequency. Lens age is an obvious candidate for influencing CLD, as lenses begin to attract tear film components immediately upon application to the eye.^{245,262-264} Complexing and denaturation of this material can then lead to potentially problematic deposits on and within the lens.^{265,266}

In an early cross-sectional study, Brennan and Efron¹⁸⁹ found that increasing lens age led to increased frequency of dryness, but they were only able to separate differences between lenses younger and older than 6 months that had been worn on a conventional (nonplanned replacement) basis. The move toward disposable lenses in the late 1980s was an

initiative to limit the amount of deposition, in the hope of diminishing complications.^{267,268} Frequency of replacement of contact lenses thus becomes highly relevant as a factor affecting contact lens wearing comfort and also offers a framework to examine the effect of lens age on comfort.

A series of studies discussed below identified improved comfort with disposable or frequent replacement reusable lenses and, furthermore, with increasing frequency of lens replacement. However, it is important to remember that the lenses used for this purpose are not necessarily made from the same lens material or with the same design as the comparator lenses or cared for with the same system. The imperfect control in such instances leaves open the possibility that it is not the lens replacement frequency as much as these other factors that are responsible for the observed improvements in comfort. A further challenge faced by researchers is achieving appropriate masking with respect to the replacement frequency in dispensing studies. Table 5 lists studies that allow the effect of lens age or different replacement frequencies on comfort to be compared, along with an indication of the quality of the studies in conforming with the evidence-based principles adopted within this report.

Boswall and colleagues conducted a retrospective chart review at a single contact lens practice from extended wear patients, of whom 65 wore disposable (7- to 14-day replacement) contact lenses and 61 wore nonplanned replacement lenses.²⁷⁰ They found severe symptoms (itching, burning/drying, and foreign body sensation) to be reduced in the disposable group, implying that increasing lens age is a factor in producing such symptoms. However, the average wearing time each day for the nonreplaced lenses was longer, presenting a possible confounding factor. Poggio and Abelson's²⁵⁹ historical cohort study compared disposable extended wear with nonreplaced daily and extended wear lenses. They found that disposable extended wear contact lens users reported symptoms less frequently at scheduled visits than both conventional daily wear and conventional extended wear users and that they had a lower rate of unscheduled visits for symptoms.

Poggio and Abelson's²⁷¹ historical cohort study of 1954 daily wearers of soft contact lenses found that those using reusable, frequently replaced lenses had a significantly lower reported frequency for symptoms (particularly grittiness, scratchiness, irritation, and pain) compared with nonplanned replacement conventional wearers. In 1996, Pritchard and colleagues²⁴¹ randomly assigned 119 neophytes to either a 1- or 3-month replacement schedule or nonreplacement group while wearing thin 38% EWC polyHEMA contact lenses. While there were reduced complications with the more frequently replaced lenses, ratings of comfort and overall satisfaction were not found to be different between the groups. Potential reasons for there being no difference include the possibilities that replacement frequency does not influence comfort, replacement frequency is less important in thin low EWC lenses, their technique lacked sensitivity to measure such a difference in this population, or subject bias induced by their knowledge of how often they replaced their lenses.

Relatively few studies have compared the comfort advantage of 2-week versus 1-month replacement and there are certainly no Level I evidence that make this comparison. Malet and Schneider²⁷⁵ reported a prospective study of 3066 daily wearers of monthly replacement lenses who were refitted at over 300 individual practices into a 2-week replacement regime. This observational study concluded that subjective comfort was improved by reducing replacement intervals to 2 weeks. The study made a particular point in identifying that the improved subjective comfort was also dependent on a compatible lens cleaning regimen.²⁷⁵

TABLE 5. Studies Comparing Comfort of Lenses of Different Age

First Author	Year	Lens Age			Material	Modality	Study Type	n	Sites	Duration	Rand	Masked	Cont/Comp	Peer Review	Lens Age Effect*
		Test	Control	Control											
Brennan ¹⁸⁹	1989	<6 mo	>6 mo	Hyd	DW	Retro	71/33	Single	$\mu = 22$ mo			✓	✓	✓	
Boswall ²⁷⁰	1993	1-2 wk	Conv	Hyd	EW	Retro	65/61	Single	$\mu = 23/26$ mo			✓	✓	✓	
Poggio ²⁷¹	1993a	2 wk	Conv	Hyd	DW	Retro	1258/696	Multi	8-27 mo			✓	✓	✓	
Poggio ²⁵⁹	1993b	2 wk	Conv	Hyd	EW	Retro	905/473	Multi	8-34 mo			✓	✓	✓	
		2 wk	Conv	Hyd	EW/DW	Retro	905/1055	Multi	8-34 mo			✓	✓	✓	
Nason ²⁴⁰	1994	1 d	Conv	Hyd	DW	Pros	70/125	Multi	1 y			✓	✓	✓	
Snyder ²⁷²	1995	1 d	2 wk	Hyd	DW	Pros	18	Single	2 wk	✓	I, S	✓	✓	✓	
Nilsson ²⁷³	1995	1 d	Conv	Hyd	DW	Pros	20	Single	3 mo			✓	✓	✓	
Solomon ²⁴²	1996	1 d	Conv	Hyd	DW	Pros	73/136	Multi	3 y	✓		✓	✓	✓	
		1 d	2 wk	Hyd	DW	Pros	73/112	Multi	3 y	✓		✓	✓	✓	
		1 d	1-3 mo	Hyd	DW	Pros	73/20	Multi	3 y	✓		✓	✓	✓	
Pritchard ²⁴¹	1996	1 mo	3 mo	Hyd	DW	Pros	37/41	Single	2 y	✓		✓	✓	N	
		1 mo	Conv	Hyd	DW	Pros	37/41	Single	2 y	✓		✓	✓	N	
Nichols ²⁶⁰	2000	1 d	2 wk	Hyd	DW/EW	Pros	50	Single	1 mo	✓		Xover	✓	N	
Sulley ²⁷⁴	2001	2 wk	1 mo	Hyd	DW	Pros	525	Multi	1 mo				✓	✓	
Malet ²⁷⁵	2002	2 wk	1 mo	Hyd	DW	Pros	3066	Multi	1 mo				✓	✓	
Aakre ²⁶¹	2004	1 d	1 mo	Hyd/SiHy	DW/CW	Pros	19/30	Single	6 mo	✓		✓	✓	N	
Frangie ²⁶⁹	2008	2 wk	1 mo	Both	DW	Retro	434	Survey	†				✓	✓	
Ramamoorthy ³²	2008	2 wk	1 d	†	†	Retro	176/22	Single	†			✓	✓	N	
		2 wk	1 mo	†	†	Retro	176/109	Single	†			✓	✓	N	
		2 wk	1 q	†	†	Retro	176/19	Single	†			✓	✓	N	
Dumbleton ²⁷⁶	2010	2 wk	1 mo	SiHy	†	Retro	717/617	Survey	†			✓	✓	X	
Lazon de la Jara ²⁷⁷	2013	1 d	2-4 wk	SiHy	DW	Pros	39/213	Single	3 mo			✓	✓	✓	

Studies listed enable comparison of comfort versus age of contact lenses. The major experimental paradigm that allows such comparisons are investigations in which different lens replacement frequencies are used (Brennan and Eifron¹⁸⁹ and Frangie et al.²⁶⁹ are the exceptions). Note that prior lens usage varies between experiments. Both, both hydrogel and silicone hydrogels were worn; Conv, nonplanned replacement; q, quarter. See Table 1 for other abbreviations.

* Indicates that increasing lens age is associated with decreasing comfort.

† Details not explicitly provided in the paper.

Sulley and Meyler's study²⁷⁴—with a similar design—yielded similar results. In both studies, the lens materials and designs were different between the replacement frequency groups, subjects were not masked, and there was not a concurrent control lens run alongside the 2-week replacement lenses.

In a conference abstract, Jones and colleagues²⁷⁸ reported that subjects replacing their lenses on a daily disposable or 2-week schedule were less likely than monthly wearers to report dryness. Frangie and colleagues²⁶⁹ surveyed 271 and 163 patients wearing a variety of monthly replacement hydrogel and SiHy lens brands, respectively. A total of 68% of the hydrogel wearers and 71% of the SiHy wearers noticed a decrease in comfort during the month. Less than 10% of both groups noticed that this occurred within the first 2 weeks of the wearing period, with the remaining 90% finding that the discomfort developed in the third and fourth weeks of the month. While they did not provide statistical analysis, Long and colleagues⁶¹ showed data that supports the concept that lenses after a month of wear are less comfortable than after 2 weeks of wear.

One study stands in contradiction to the general trend of reports that have found shorter replacement schedules lead to better comfort. Dumbleton and colleagues²⁷⁶ conducted a survey of 1344 wearers of SiHy contact lenses through practitioners in the United States, with approximately half wearing lenses with a manufacturer's recommended 2-week replacement schedule and the other half on a monthly schedule. Noncompliance was found to lead to lower comfort, perhaps expectedly. After adjusting for compliance, the authors reported modest but statistically significantly better comfort with the monthly replacement lenses compared with the lenses recommended for a 2-week modality. The study surveyed existing wearers and so selection and survival bias cannot be ruled out in addition to differences in lens materials and design.

Most of the remaining studies considering the impact of replacement frequency have looked at the effect of daily disposables on lens comfort. Early hydrogel lens studies considered the 1-day replacement modality against conventional lens replacement.^{240,242,273} Daily replacement led to a number of benefits, including improvements on a range of comfort measures. Daily disposability also led to a range of comfort benefits against lenses planned to be replaced on a 1- to 3-month basis.²⁴² Solomon and colleagues²⁴² also found benefits of a daily versus a 2-week replacement schedule. It is interesting to note that the single study investigating the impact of replacement frequency on comfort, which conforms to the gold standard principles of a controlled, randomized, masked study did not find a difference between daily and two weekly replacements.²⁷² However, it is not clear in this study whether the method for measuring comfort was adequate to detect differences, whether the sample size ($n = 18$) was sufficiently powered to detect a difference, whether lens care influenced comfort, and whether the lens type used was not resistant to the effects of aging.

The potential comfort advantage of daily disposal of SiHy lenses versus other replacement schedules has not been widely studied. In the one available study to-date, Lazon de la Jara and colleagues²⁷⁷ reported that end-of-day comfort and dryness ratings were significantly better for daily disposable wear than when the same material and design was used in a reusable manner with either hydrogen peroxide or multi-purpose care systems.

Two studies have compared daily disposable lenses with extended or continuous wear. In the first, daily disposable hydrogel lenses were compared with a 2-week replacement hydrogel.²⁶⁰ There was no difference between the daily

disposable and extended wear modalities with respect to subjective responses, except that those sleeping in their lenses found comfort on awakening to be inferior. In the second study, daily disposable hydrogel lenses were compared with monthly replacement silicone hydrogels in continuous wear.²⁶¹ There were no differences of note between the two groups.

A final study looking at the effect of a variety of replacement intervals on lens comfort was conducted by Ramamoorthy and colleagues.³² Individuals ($n = 360$) were surveyed with the CLDEQ and categorized as either having or not having dry eye. Daily, 2-week, monthly, and quarterly replacement schedules were all represented in the sample, as were both hydrogel and SiHy lenses. Replacement schedule was not found to be predictive of how the subjects were classified. However, it is not clear that the study was powered to make determinations with respect to the different schedules and to what extent selection and survival bias were influential.

In summary, there is almost a complete absence of masked, randomized, controlled studies that consider the impact of replacement schedule on comfort and dryness, preventing a definitive statement being made on the topic. Nonetheless, there is a tendency for the studies that provide circumstantial evidence regarding replacement schedules to suggest that replacement that is more frequent is conducive to greater comfort.

Time of Day. End-of-day dryness and discomfort arguably represent the most challenging issue for the contact lens industry today. While discomfort is the major reason cited for contact lens discontinuation,^{77,78} a breakdown by the exact nature of discomfort is illuminating. Chalmers and Begley²⁷⁹ studied responses to a questionnaire of 1054 patients who presented for eye care in a multicenter cross-sectional study. The leading causes of discontinuation among the 167 former contact lens wearers in their sample were dryness and end-of-day discomfort, which were cited by 41.9% and 38.3%, respectively.

Begley and colleagues²⁸⁰ surveyed 367 unselected contact lens wearers in their 2001 cross-sectional study of North American optometric clinical practices, finding that the percentage reporting moderate to intense ocular discomfort increased from 19% in the morning to 56% in the evening. The frequency of dryness among the 367 contact lens wearers in the group was significantly higher late in the wearing day compared with earlier in the day, with an increase from 12.7% who reported moderate to intense dryness in the first 2 hours of wear to 28.5% late in the day.²⁷⁹ In an analysis of questionnaire responses from 84 clinical sites in North America, Chalmers and colleagues⁶⁰ found that between 3% and 15% of subjects, depending on age and type of lens material worn, reported end-of-day discomfort ("extreme" or "very") and between 7% and 24% report end-of-day dryness. Young and colleagues⁶³ reported severity of end-of-day dryness to be of sufficient significance to categorize subjects as having "contact lens-associated dry eye" in 31% of wearers.

While noticed even in nonwearers and spectacles wearers, all symptoms—but particularly end-of-day dryness—are more pronounced in contact lens wearers.^{279–281} Further, contact lens wearers report markedly fewer symptoms without the lenses in place: for example, only 1.5% report moderate to intense late-day dryness according to Chalmers and Begley.²⁷⁹

Evidence in support of decreased comfort toward the end of the day necessarily cannot arise from Level I studies, as it is virtually impossible to conduct a controlled, masked, randomized study where time of day is the key independent variable. Nonetheless, a large volume and variety of experiments, often investigating other phenomena or as part of multivariable analyses, provide undeviating data to support the hypothesis

that comfort decreases during the day and is exacerbated by contact lens wear.

The original empirical demonstration of decreasing comfort toward the end of the day appears to have been by Pritchard and Fonn.⁸⁴ In their 1995 study, which sought to link lens dehydration with symptoms, 19 subjects rated dryness on visual analog scales during 7 hours' wear of three different hydrogel lenses. Dryness ratings rose consistently for all three lens types at 1, 3, and 7 hours after lens insertion. In a follow-up study, Fonn and colleagues sought to determine whether lens dehydration correlated with discomfort and dryness in two different lens types in 40 subjects, but this time they separated subjects into symptomatic and asymptomatic groups.¹⁰² They replicated the findings of increased dryness and decreased comfort over a 7-hour period of hydrogel lens wear in the asymptomatic group, but interestingly there was no significant variation over time in the symptomatic group. Others have confirmed the finding among hydrogel lens wearers.^{46,282,283}

Fonn and Dumbleton⁴⁷ published the first paper reporting reduced end-of-day comfort with SiHy lenses in a 7-hour nondispensing study of 20 asymptomatic and 19 asymptomatic wearers. Again, like the 1999 study from the same group, the reduced end-of-day comfort was isolated to the symptomatic group. The paper suggested that the degree to which comfort diminishes and dryness increases is very similar to that observed with hydrogel lenses. Many others have reported decreased comfort over the course of the day among SiHy wearers.^{61-65,276,284-291}

Wear of daily disposable contact lenses is not protective from the effect of time of day on comfort and dryness. Walker and colleagues measured a drop in mean comfort across the day when comparing two different hydrogel daily disposable lenses in a 20-site study of 282 subjects.²⁹² Diec and colleagues²⁹⁰ tracked decreasing comfort across the day for a series of hydrogel and SiHy lenses worn on a daily disposable basis. They found no difference between lenses but noticed decreased comfort across the course of the day.

While there may be differing degrees of discomfort between daily wearers and those who sleep in their contact lenses, extended or continuous wear also does not seem to prevent the phenomenon of decreased comfort and increased dryness toward the end of the day. In their 2005 study looking at wearers switched out of hydrogels and into silicone hydrogels, Chalmers and colleagues⁴⁸ observed among the baseline data for those using hydrogel lenses on an extended basis, more than 50% greater frequency and severity of end-of-day dryness. Subbaraman and colleagues²⁵⁴ and Schafer and colleagues⁵⁷ have made supporting observations with extended wear of silicone hydrogels. These consistent findings also seem to hold up across different ethnicities. Long and McNally²⁸⁶ studied symptoms in 88 Asian subjects that were switched from hydrogel lens wear to SiHy lens wear. Decreased comfort and increased dryness toward the end of day was evident both before and after switching lens type. Indeed, 84% of subjects reported end-of-day dryness either occasionally, frequently, or all the time with their habitual lenses.

Investigators have used variables based around wearing time both to demonstrate the consequence of end-of-day dryness and also as a measure of comfort for testing experimental hypotheses.^{32,49,63,65,285,292-294} As an example, Young and colleagues found mean comfortable wearing time in a group of UK subjects classified as having contact lens associated dry eye to be 9.1 hours compared with 12.4 hours in those without dry eye and, in a sample of North American wearers, 9.4 hours in the dry eye group compared with 12.1 hours in those without dry eye.^{63,65}

The interaction between the lens and the lid wiper appears to play a significant role in end-of-day dryness and discomfort.²⁹⁵ Lens surface coefficient of friction appears to be correlated to overall lens comfort and in particular to end-of-day comfort (see previous section on friction and lubricity).¹¹⁶ Certainly the simple addition of lubricants yields immediate, if short-term, benefits in comfort.⁵⁹ However, the mechanism by which coefficient of friction might be linked to end-of-day comfort is uncertain. Daily accumulation of lens surface buildup, or diminution of tear quality during the course of the day, may lead to higher lens surface friction later in the day. Alternatively, lens surface friction may remain relatively stable, although at a raised level during wear compared with the bare cornea, but the lid-wiper region becomes irritated or damaged with erosion of cells during the course of a day's wear as a result of the rubbing between the lid and the front surface of the lens and so becomes uncomfortable. Overnight, the affected epithelium repairs and, on awakening and reapplication of the contact lens, the cycle begins again.

To date, there are no records of measurement of lens surface friction changes over the course of a day. The more modest changes of comfort across days and weeks of wear as evidenced by the data on replacement schedules above compared with the dramatic change over the course of a day would argue more strongly for the latter hypothesis of "wear and tear and then repair" to explain end-of-day discomfort. One further piece of evidence relates to the fact that replacement of a lens during the middle of the day appears to have minimal impact on end-of-day comfort,²⁹⁶ suggesting that a fatigue-like response in one or more ocular tissues or stimulation of ocular surface nociceptors induced by the presence of the contact lens occurs. Without doubt, further research is needed to ascertain the true origin of end-of-day dryness with contact lens wear.

From a scientific standpoint, the hypothesis that contact lens comfort decreases toward the end of the day can never be tested in a controlled, randomized, masked study because normal subjects will always have awareness of the duration for which they have worn the lenses and naturally the sequence of such measures. Thus, while the various studies reported here may be controlled, randomized, and masked with respect to lenses, care systems, or some other independent variable, they are not with respect to time of day and daily duration of wear. Nonetheless, the wealth of reporting on the matter and the overwhelming consistency of the data lead us to identify this problem as one of the major, if not the leading, issue with contact lens wear today.

Care Products and Packaging Solutions

Compositions of Care Solutions. A contact lens care solution is composed of several important components, including preservatives (or biocides), surfactants, chelating agents, and buffering agents. All these components have different functions and are incorporated into a lens care system to provide adequate disinfection efficacy and enhanced comfort. The difference in clinical performance observed between various lens care solutions may be due to the differing components and concentrations in the care products and the manner in which these components interact with the lens material. An essential point to consider is that the care system can result in reduced comfort or enhanced comfort—two very different outcomes; one is likely caused by uptake and subsequent release of the components of the care system and the other by the adsorption of a comfort "additive" to the lens material from the care system.

Biocides. Various biocides are incorporated into lens care regimens at different concentrations and the effect of these

biocides on subjective comfort and how these biocides interact with different lens materials has attracted significant interest.

Peroxide-Based Systems. Hydrogen peroxide-based solutions are used at a concentration of 3% (30,000 ppm). The subjective sensitivity threshold for peroxide ranges between 50 and 300 ppm, and it is recommended that the solutions be neutralized to a concentration of less than 100 ppm. When present in high concentrations, residual peroxide can be toxic to the cornea and can cause discomfort/pain.²⁹⁷⁻³⁰⁰

Few studies have compared the effect of peroxide-based systems on subjective symptoms in a comparison with other care systems that are preserved with a different biocide. A randomized, single-masked, crossover design study evaluated the degree and frequency of corneal fluorescein staining and subjective responses in 85 hydrogel lens wearers following the use of PHMB-based (ReNu) and peroxide-based (AO Sept) systems for 1 month.³⁰¹ It was found that the overall comfort and comfort in the evening were significantly better when the subjects used the peroxide-based system ($P = 0.02$ for both occasions). Another study investigated the clinical and subjective performance of a peroxide-based lens care system (ClearCare) in comparison to a Polyquad/Aldox-based multipurpose solution (MPS; OPTI-FREE RepleniSH) when used with lotrafilcon B and senofilcon A SiHy lenses.²⁸⁵ This randomized, contralateral (lens type) and crossover (care system) study involved 24 participants and they found that the peroxide-based system resulted in longer reported comfortable wearing times than the MPS (10.93 vs. 9.84 hours; $P < 0.01$). However, no significant difference was found between solutions in overall ratings of subjective comfort, or dryness. While these two studies taken in isolation would appear to suggest that peroxide-based systems are superior to preserved systems, there are multiple other components that differ between the products and this makes it impossible to support the fact that it is merely the biocide alone that resulted in the reported comfort differences.

PHMB-Based Versus Polyquad-Based Systems. Several studies have compared the effect of using a PHMB-based system when compared with a polyquaternium-based MPS. A multisite, 231-subject, double-masked, crossover study was performed to evaluate the subjective comfort and satisfaction and clinical signs with two MPSs used with alphafilcon A and etafilcon A lenses.³⁰² Subjects used each of the two MPSs, Polyquad/Aldox-based (OPTI-FREE Express) and PHMB-based (ReNu MultiPlus), for 28 days and found that subjective ratings of comfort and satisfaction were in favor of the polyquad-based MPS. Epstein found that the users of the PHMB-preserved product reported decreased comfort over the course of the day.³⁰³ Interestingly, it was also reported that the PHMB-based system was also associated with a reduction in relative corneal sensitivity ($P = 0.004$). However, a subsequent letter to the editor questioned this latter finding.³⁰⁴ A randomized, controlled, and investigator-masked clinical study compared the clinical performance of a PHMB-based (MeniCare Soft) and Polyquad/Aldox-based (OPTI-FREE Express) MPS with two SiHy lenses (lotrafilcon A and galyfilcon A),³⁰⁵ and found no significant difference between the two solutions.

In another study, subjective symptoms and clinical signs of tolerability and comfort were compared in silicone and hydrogel lens wearers using a Polyquad/Aldox-based system (OPTI-FREE Express) and a PHMB-based system (ReNu MultiPlus).³⁰⁶ The participants who used the Polyquad/Aldox-based system reported greater comfort than the PHMB-based system. These results should be interpreted with caution because 65% of the subjects in this study used the Polyquad/Aldox-based system while only 28% used PHMB-based MPS prior to enrollment, and this could potentially create a bias toward their habitual care system.

Another study was conducted as a prospective, bilateral, clinical trial with a single-masked investigator, and randomized crossover design with four phases to assess the compatibility of a SiHy lens material with four different MPS (one based on Polyquad/Aldox: OPTI-FREE RepleniSH, and three based on PHMB: ReNu MultiPlus, Solo-Care Aqua, and MeniCare Soft).³⁰⁷ No difference was found in comfort between the four care systems. A recent study investigated the performance of two new MPSs (polyquaternium/alexidine-based Complete RevitaLens and polyquaternium/PHMB-based Biotrue) during a month of SiHy lens wear in neophyte volunteers.²⁹¹ The investigators did not find statistically significant differences between the two systems.

Finally, a randomized, investigator-masked, crossover clinical trial including 31 subjects compared a Polyquad/Aldox (OPTI-FREE Express) solution to a PHMB-based solution (Complete Moisture Plus) in subjects wearing etafilcon A lenses. Each participant used the assigned care solution for 7 days, with a 1-day washout period, followed by subsequent use of the alternative solution. While interferometric differences in the prelens tear film thickness were observed (likely based on viscosity differences between the solutions), there was no overall difference in subject preference for a care solution, but “comfort” was the primary reason for a preference selection when asked their reason for preference.¹³⁶

Long-Term Use of PHMB-Based Versus Polyquad-Based Systems. Long-term users of two different preservative systems were studied to investigate whether prolonged use of these systems was associated with an increase in the frequency of dry eye.³⁰⁸ Subjects were required to have consistently used a PHMB-based or polyquad-based solution for 2 years. This investigator-masked study, involving 89 FDA Group IV hydrogel or SiHy lens wearers, found that PHMB users reported significantly more grittiness or scratchiness (67% vs. 44%; $P = 0.02$). However, no significant differences between the two preservative system groups were noted for the range of other dry eye evaluations or the remaining clinical assessments.³⁰⁸

Studies Investigating Consumer Acceptance of MPS. One study evaluated comfort when switching to Polyquad/Aldox based MPS (OPTI-FREE RepleniSH) when compared with two different PHMB-preserved MPS.³⁰⁹ This multicenter, open-label study enrolled 109 contact lens wearers who were dispensed with the test solution in place of their habitual solution. Subjects assessed their experience with their habitual solution (baseline) and the test solution (day 30) using Likert-style questions. They reported that the Polyquad/Aldox MPS was associated with a statistically significant improvement in instillation comfort, end-of-day comfort, clear vision, and overall satisfaction.³⁰⁹ It is difficult to determine if a natural bias is introduced in studies such as these, as subjects given new solutions or lenses will often rate “new” products as being superior due to the mere fact that they are new, therefore, “they must be better.”

In summary, although a few studies have shown that lens wearers using a care solution that is preserved with a specific biocide show better comfort than another product, it is important to note that a lens care solution is composed of many ingredients that may also impact subjective symptoms. Therefore, it cannot be concluded that a specific biocide alone will provide improved comfort.

Surfactants and Wetting Agents. In contact lens solutions, surfactants are used as detergents or cleaners, removing loose debris, microorganisms, and deposits by combining with these substances to form micelles, which are then removed during the rinsing procedure. Surfactants also play a role in enhancing the wettability of contact lenses,^{132,137,310} especially

SiHy lenses, which are generally more hydrophobic than conventional hydrogel lens materials.³¹¹⁻³¹³

The most common surfactants found in MPS are poloxamers (Pluronic F87, Pluronic F127, Pluronic 17R4) and poloxamines (Tetronic 1304, Tetronic 1107).^{314,315} HPMC, which has been used for many years in rigid gas-permeable care products for its lubricating, conditioning, and cushioning functions, has also been used in soft lens solutions as a wetting agent.³¹⁶ It has been shown to be effective in controlling both symptoms and signs in patients with dry eye³¹⁷ and to enhance tear film stability in lens wearers.¹³⁴ A block copolymer (EO-BO) containing poly(ethylene oxide) and poly(butylene oxide) has also been recently introduced and its ability to adsorb to SiHy materials has been confirmed using x-ray photoelectron spectroscopy and ultra-performance liquid chromatography.³¹⁰

A randomized, controlled, double-masked, multicenter study involving 362 subjects at 19 investigational sites in the United States investigated the performance of two MPSs (tetronic-containing MPS [OPTI-FREE RepleniSH] and poloxamine-containing MPS [ReNu MultiPlus]) with habitual lenses.²⁹³ They found that the comfort and dryness mean scores were significantly better for the tetronic-containing MPS compared with the poloxamine-containing MPS at day 28 and the mean scores for scratchiness and burning were significantly lower at day 14. The improved performance of the MPS was attributed to the presence of wetting agents, including C9-ED3A and propylene glycol in the tetronic-containing MPS. It was speculated that the presence of these novel wetting agents aids in cleaning, chelation, wetting, and lowering biocide lens uptake, especially in combination with Tetronic 1304.²⁹³

The wetting effect of three different lens care solutions (two care solutions with wetting agents [OPTI-FREE RepleniSH and ReNu MultiPlus] and one solution without any wetting agent [ClearCare]) on blink rate, dryness symptoms, and vision performance on 65 habitual lens wearers was studied.³¹⁸ They found that solutions with wetting agents led to significantly fewer eye blinks and better ocular comfort for contact lens wearers. Moreover, the presence of wetting agents in lens care solutions also resulted in better visual performance when compared with wearing daily disposable contact lenses.

The effect of an EO-BO containing MPS (OPTI-FREE PureMoist) was compared with a MPS containing a conventional surfactant-containing MPS (ReNu Fresh) with SiHy and HEMA-based lenses.³¹⁹ It was a multicenter (30-site) study involving 573 participants over several visits. The patients found that their “lenses felt moist” at day 90 when using the MPS containing the novel surfactant ($P \leq 0.02$) and the “lens acceptability at day 90” was better when the MPS with the novel surfactant was used ($P \leq 0.03$).³¹⁹ Another study that recruited over 3000 patients from 313 ophthalmologic practices in France to participate in a 1-month prospective observational clinical study found that replacing etafilcon A lenses once every 2 weeks combined with an MPS incorporating ingredients designed for lens conditioning contributed to significant improvements in lens wearing comfort.²⁷⁵ Another study showed that HPMC incorporated in an MPS could form a thicker, longer-lasting layer of fluid on the hydrogel lens, leading to improvements in tear function in contact lens wearers.¹³⁴

In summary, based on these studies, it appears that many wetting agents and/or surfactants that can remain on the lens material can improve subjective symptoms in contact lens wearers, possibly by improving the lens hydrophilicity and also by making the lenses feel “moist.” However, the long-term efficacy of these surfactant-containing solutions in patients who are dry-eyed and need contact lenses warrants further investigation.

Chelating Agents. Chelating agents are added to lens care regimens to act synergistically with other agents to improve disinfection efficacy and to aid in removal of tear film components.³¹⁴ The common chelating agents found in lens care regimens include EDTA, citrate, and hydroxyalkylphosphonate.³¹⁵ Studies published to date have compared the clinical performance of a specific care regimen in comparison with only citrate-containing regimens.^{252,320,321} A multicenter, investigator-masked, randomized study investigated the effect of two citrate-containing regimens on subjective comfort and deposition on a FDA Group IV lens material and compared that with a noncitrate containing MPS.³²⁰ Significant differences favoring the citrate-based regimens were observed in ocular awareness, lens awareness, visual clarity, end-of-day comfort, and end-of-day dryness.³²⁰ These findings were consistent with that of another study, where it was found that the use of a dedicated daily cleaner in conjunction with a citrate-containing system can provide patients with more comfortable and cleaner lenses.²⁵² Another study that compared comfort when using a citrate-containing MPS versus an MPS containing HPMC found no significant difference in comfort between the two solutions.³²¹

In summary, all the above-mentioned studies compared a few lens care solutions and attributed any increased performance to the presence of a specific component. However, this is not possible to prove, as other formulation differences between the products may also have contributed to the perceived differences in comfort. In order to specifically determine the association between lens care solution and discomfort and dryness, two studies have conducted extensive regression analysis. In the first study,³² the relationship between contact lens characteristics, hydrogel lens materials, care solutions, and patient-related factors and dry eye status in contact lens wearers was assessed retrospectively in 360 contact lens wearers. Interestingly, there was no significant association between contact lens-related dry eye and contact lens care solutions, when grouped either by preservative type or by product brand (both $P = 0.99$).³² Another more recent study examined the factors associated with contact lens-related dryness symptoms in soft contact lens patients.⁶³ Soft contact lens wearers ($n = 932$) from 12 clinical sites were examined and they found that neither the lens material nor the lens care systems were specifically related to contact lens-related dry eye status.

These two studies suggest that contact lens-related dryness is associated with a diverse range of underlying causes and that lens care product is not a significant factor. It should be noted that both these studies derived data from retrospective studies by pooling data from multiple studies and/or sites and conducted advanced statistical analysis to determine the association between dry eye symptoms and the lens care regimen. Nevertheless, it is important to identify how different components in a lens care solution interact with contact lens materials and if this could have an impact on the physiological and subjective performance of contact lenses.

Interaction of Contact Lenses With MPS. Silicone hydrogel materials are hydrophobic and these materials may exhibit higher attraction for certain hydrophobic/lipophilic entities, such as tear lipids³²² and nonpolar active agents found in certain MPS products.^{323,324} When a MPS interacts with a contact lens, any of the components found in the solution can be adsorbed onto the surface or absorbed into the bulk of the lens material.^{310,323,325,326} Preservative uptake from lens care solutions to soft lens materials is influenced by several properties of the lens, including EWC, ionicity, and hydrophobicity.^{323,324,327} These adsorbed components may potentially cause discomfort to contact lens wearers.

The biocide uptake into and onto various contact lenses and its subsequent influence on clinical signs and symptoms were investigated in several studies.^{326,328-331} The physiological and subjective responses of subjects wearing balafilcon A silicone hydrogels and the ocular response to use of a lens care product containing Polyquad/Aldox and another containing PHMB was reported by Jones and colleagues.³²⁸ The PHMB-based lens care product was associated with increased corneal and conjunctival staining and more stinging or burning on lens insertion compared with the product containing Polyquad/Aldox.³²⁸ However, the investigators were not able to relate the degree of staining with the reported symptoms. This is in contrast to two more recent publications, in which increased amounts of corneal staining led to reduced subjective comfort.^{329,332}

A series of pilot studies was conducted over 11 months to assess combinations of three different hydrogel lenses (FDA Group II [alphafilcon A], Group IV [etafilcon A] and one SiHy [lotrafilcon A]) and four MPSs.³³¹ New lenses were soaked overnight in one of four MPSs and were fitted on subjects who rated comfort and ocular symptoms. Corneal staining was evaluated at baseline and after lens removal. The investigators found corneal staining to be most frequent when PHMB-preserved solutions were used with Group II lenses. Instead, with the polyquad-based system, the extent of staining was low with all the lenses tested. They also found that when PHMB-based products were used with the FDA Group II material, corneal staining was evident after 1 to 4 hours of wear. However, they did not see any association between significant symptoms and the extent of staining.³³¹

Another study investigated the physiological and subjective responses of the short-term use of various lens care products with two SiHy contact lenses (lotrafilcon B or galyfilcon A) and examined whether changes to the surface of lenses was correlated with the responses.³²⁶ Both these lens types were presoaked for 1 week in Polyquad/Aldox-based (OPTI-FREE Express) or PHMB-based (Aquify) solution and participants wore them for 6 hours. It was found that lotrafilcon B lenses soaked in PHMB caused a decrease in comfort, an increase in burning/stinging after 1 hour of wear, and an increase in lens awareness on lens insertion. When lotrafilcon B lenses were soaked in Polyquad/Aldox, they found an increase in burning/stinging after 1 and 6 hours.³²⁶ The investigators concluded that release of various components of MPS from contact lenses can have a significant influence on corneal staining and comfort responses during wear.

In summary, the results from these studies show that contact lenses interact differently with MPS depending upon their polymeric makeup. These results also show that the uptake and subsequent release of components by soft contact lenses can affect corneal staining and subjective comfort.

In conclusion, while retrospective studies suggest that the lens care product is not associated with the contact lens-related dryness and discomfort, the importance of contact lens care solutions in overall lens wear cannot be discounted and a recent publication has shown that subjective satisfaction, particularly in symptomatic wearers, can be influenced by the combination of lens and solution prescribed.³³³ It is critical to note that a lens care solution is composed of several components. Therefore, it would be erroneous to conclude that any individual component in a care solution will have a direct impact on subjective symptoms. Based on the evidence to date, it appears that incorporation of surfactants or wetting agents into lens care products may improve subjective comfort, possibly by improving the hydrophilicity of the lens material. However, it is difficult to isolate a specific component in a lens care product and correlate that factor with improved subjective symptom.

There is adequate evidence that suggests different lens care solutions interact differently with various contact lens materials and this depends on the properties of both the contact lens material and lens care solution. Thus, the mechanisms contributing to symptomatology during lens wear may vary based on how the components in a lens care solution interact with the lens material.

Physical Properties of Care Solutions

Soft contact lens care solutions are made of a wide range of components, as described in the previous section. The combination and concentration of these agents will have a significant impact on the physical properties of the solution and this could potentially influence patient comfort. The following section provides a brief overview of various physical properties of contact lens care solutions and whether these properties may have an impact on contact lens comfort.

pH. The pH of human tears ranges between 6.6 and 7.8,³³⁴ and the human eye is capable of tolerating pH values in the range of 6.2 to 9.0 at 0.2 M strength.³³⁵ When the pH of the contact lens solution falls outside this range, patients complain of ocular discomfort and stinging.³³⁶⁻³³⁸ Buffering agents used in soft contact lens solutions directly affect their pH, and it is possible that the type of buffer used in a particular solution could also affect subsequent patient comfort.

A study that investigated the pH of 10 different contact lens care solutions showed that most solutions (except nonneutralized peroxide systems) had pH values that were close to neutral and fell within the reported tolerable pH range for the ocular surface.³³⁹ The large difference in the pH of peroxide-based solutions before neutralization is the principal reason for burning, stinging, and epithelial cell damage seen in patients who mistakenly insert the nonneutralized solutions directly onto the ocular surface.²⁹⁹

Viscosity. Viscosity of a solution has the potential to influence patient comfort upon lens insertion or at the end of the day, through interactions between the solution, the lens, and the patient's tear film. Viscosity of water is 1.0 cP and that of the tear film ranges between approximately 5.0 and 1.5 cP at 25°C for normal patients.^{340,341}

A study that investigated the viscosity of various lens care solutions found that all the solutions had viscosity values that ranged between 0.96 and 1.26 cP, but some go as high as 3 cP.³³⁹ Several studies have determined the impact of HPMC-containing solutions on patient comfort.^{134,136,342} One study investigated the physical properties of multipurpose contact lens solutions with and without the addition of HPMC, and also determined if there are significant differences in the tear physiology of two groups of patients wearing soft contact lenses soaked in HPMC and non-HPMC solutions.¹³⁴ This study showed that the prelens tear thinning time was longer and the prelens tear film structure was improved with use of the HPMC-containing solution.¹³⁴ Another clinical trial that compared the prelens tear film thickness of etafilcon lens wearers showed that the patients who used the HPMC-containing solution showed a greater prelens tear film thickness ($3.02 \pm 1.07 \mu\text{m}$) when compared with those that used a non-HPMC containing solution ($2.72 \pm 0.86 \mu\text{m}$).¹²⁴ This study also showed no statistical difference in study subjects' preference for either solution, but nearly every subject (90.3%) suggested "comfort" as their reason for preference.¹²⁴ In summary, it appears that lens care solutions that incorporate viscosity-enhancing agents can create a thicker and longer-lasting layer of fluid on hydrogel lens and this can potentially lead to improvements in tear function in contact lens wearers. However, if the viscosity is too high, then potential blurring effects may mitigate these comfort advantages.

Osmolality. Osmolality of contact lens solutions could play a role in patient comfort, as studies have demonstrated that tear film osmolality plays a significant role in the discomfort reported by dry eye patients.³⁴³⁻³⁴⁶ A study that investigated the osmolality of 10 different contact lens care solutions showed that the osmolality values fell between 275 and 310 mOsm/kg,³³⁹ indicating that the majority of soft contact lens solutions are hypo-osmotic compared with human tears. To our knowledge, no published studies have been conducted to investigate the relationship between solution osmolality and contact lens comfort.

Surface Tension. The surface tension of pure water is approximately 72 mN/m and human tears have a surface tension value in the range of 40 to 46 mN/m.^{340,347} In a contact lens care solution, the presence/absence and type/number of surfactants will have a substantial impact on the surface tension of the solution. A study that investigated the surface tension of various care solutions showed that most multipurpose solutions have surface tension values that ranged between 29 and 40 mN/m.³³⁹ Among all the care solutions, the ones that did not incorporate surfactants (for example, peroxide-based systems and saline) had surface tension values that were close to that of water, whereas the solutions that had one or more surfactants had surface tension values that were closer to that of human tears. To our knowledge, no published studies have been specifically conducted to investigate the relationship between surface tension and comfort.

In summary, contact lens care solutions differ in certain physical properties and, by design, most care solutions fall within acceptable limits of ocular physiological tolerance. When properties of these solutions do not fall within the acceptable limits, clinically, this could result in burning, stinging, and epithelial cell damage. Minor shifts in the values may have the potential to influence patient comfort initially and/or at the end of the day. To date, very little has been published directly investigating the relationship between physical properties of lens care solutions with contact lens symptoms and this warrants further investigation.

Rewetting Drops

Contact lens wearers use rewetting drops for many reasons, including managing contact lens dry eye, lens dehydration and its associated dryness, general ocular lubrication, acting as a mechanical buffer between the lens and cornea, and lens surface rewetting and cleaning. Numerous formulations of lubricating eye drops exist and contain a wide variety of ingredients including cellulose derivatives, oil-based emulsions, paraffin, polyvinyl alcohol, polyacrylic acid, Polyvinylpyrrolidone, glycerin, HA, hydroxypropyl guar, polyethylene glycol, and propylene glycol.

It has been reported that 47% of contact lens wearers use rewetting drops, but that they only provide moderate and nonsustained relief from symptoms of discomfort, in addition to inconvenience with the need for repeat instillation.²⁸⁰ There is the suggestion that a regimen of more than one type of lubricating eye drop may be needed for symptomatic contact lens wearers due to the multifactorial nature of CLD.³⁴⁸ If used in a proactive manner, the same eye drop has been shown to produce greater symptom relief than its use in a reactive manner.³⁴⁹ While there are a number of studies that demonstrate some level of symptom relief for contact lens wearers, there appears to be relatively little advantage with the use of rewetting drops or ocular lubricants compared to the use of saline.^{59,254,350-353}

One study has shown that the use of a lubricant eye drop containing hydroxypropyl guar, propylene glycol, and polyethylene glycol (Systane) twice daily (pre- and post-contact

lens wear) resulted in an increase in comfortable wear time and improved other subjective assessments of lens wear acceptability in symptomatic hydrogel lens wearers, compared with the use of a saline control drop (Feng Y, et al. *IOVS* 2006;47:ARVO E-Abstract 2381).

Composition of Packaging Solutions

In an attempt to alleviate symptoms of dryness and discomfort, a number of manufacturers incorporate a variety of agents into both the lens material and also, more recently, the packaging solutions that are used to ship contact lenses. These so-called “blister-pack solutions (BPS)” now commonly include incorporation of water-soluble polymers, surfactants, and often unnamed “wetting agents” that have been previously described in this report.^{153,354-359} The alterations made to the BPS are to aid in preventing the lenses from sticking to the blister pack, enhance lens wettability, and improve initial comfort of the lenses after application to the eye.³⁵⁴

One of the earliest published studies to suggest that adhering surfactants to lens materials may enhance in-eye comfort was that by Tonge and colleagues,^{137,354} who showed that soaking etafilcon A lenses in a solution containing poloxamine 1107 improved in-eye comfort and that the surfactant was retained for several hours after wear. To date, while several studies have examined comfort between lens materials with and without wetting agents (as previously described in this review) and studies have shown that contact angle wettability is raised in some materials once the BPS is removed,^{312,356} no published study has systematically examined whether the modified BPS has a direct impact on contact lens comfort. However, given the growth in the number of lens materials that are shipped in BPS that contain surface-active agents³⁵⁷ it would seem likely that manufacturers have determined their positive impact in in-house unpublished studies.

Future Directions

Careful review of this report points toward several areas for future research that would enhance our understanding of CLD and the key factors associated with materials, design, and care systems.

One area that continues to be a frustration is the lack of association between in vitro data and their ability to predict in vivo performance. The industry would be well served by the development of in vitro methodologies that help to predict on-eye performance. An area that appears to show the most promise relates to the results from coefficient of friction evaluations. However, this field is in its relative infancy for contact lens materials and the development of methods that are more meaningful to on-eye comfort require substantial work. Current assessment methods vary widely, resulting in wide variation in the data obtained. International standardization of laboratory measurements such as frictional testing of hydrogels, as well as those for others such as contact angle and dehydration, would be a welcome addition to the industry. For frictional measurements, the relative importance of methodology, type of friction, and how these values relate to clinical observations such as lid wiper epitheliopathy, lid-parallel conjunctival folds, corneal and conjunctival staining, and in-eye wettability, are all areas worthy of future investigation. Other related areas that need substantial development relate to improved methods for determining in-eye wettability and investigation of the tear film in the vicinity of the lid wiper area and how these factors relate to comfort.

There is no doubt that contact lens materials change their hydration after being placed onto the ocular surface. It would

be expected that a change in bulk surface hydration will impact wettability and friction. However, bulk dehydration shows only a tenuous relationship with comfort for most materials, but the development of improved methods to investigate surface dehydration (and impact on comfort) are more important than ever due to new materials that exhibit differing bulk and surface characteristics. When undertaking dehydration studies, factors such as the time intervals for assessment, standard procedures for sample handling, and eventual reinsertion in the ocular surface for subsequent measures, and control of environmental conditions and time of day all need standardization and agreement.

Much of the published clinical work in relation to soft lens material, design or solution properties has been poorly conducted, with inappropriate or missing controls, making conclusions regarding their impact on discomfort difficult. Future work investigating the impact of various characteristics must be conducted using well-controlled, randomized, cross-over studies in which all variables (replacement period, solution system, wearing time, etc.) are considered. This area requires some fundamental studies in which the isolation of a single change in a material, design, or solution characteristic is investigated. This work can only be conducted with the close cooperation of industry since this cannot be undertaken using only commercially available products. Areas of investigation of particular note relate to comparisons of some of the newer hydrogel-based materials against modern silicone hydrogels, comparisons between materials that “release” components into the tear film versus the base material without the release agent, and silicone hydrogels with standard or base surface wettability versus those with enhanced hydrogel-type coatings.

When it comes to bulk material properties, the trend thus far has been toward a modulus low enough to maximize on-eye comfort while balancing handling, durability, and rightness of fit. However, the conventional tensile modulus test involves unidirectional static loading; therefore, dynamic mechanical testing may be more appropriate, given the cyclic dynamic motion of eyelid movement coupled with the elastic and viscous flow characteristics of hydrogel materials (the cornea is also viscoelastic). For example, dynamic mechanical testing of silicone hydrogels demonstrates a characteristic rise in elastic modulus or shear-dependent elastic response that is typically not present in conventional hydrogels with similar EWC. There is the suggestion that, in order to improve comfort of current SiHy lenses, this elastic component should be similar to that for conventional hydrogels. However, this work has not been conducted in a systematic manner.

With regard to rigid lenses, increased interest in the use of RGP scleral lenses points toward a substantial number of potential studies in this area, with specific data being needed on comfort changes over the course of the day and comparative studies against corneal rigid lenses in nonpathological corneas. Large diameter RGP lenses offer an opportunity to provide a test platform with no bulk hydration changes, slower deposition, limited lens movement and minimal lid-lens edge interaction. Thus, studies comparing RGP scleral designs against both corneal rigid lenses and soft lenses may be of value. Of specific interest in the area of both rigid and soft lens design, methods to assess the impact of lens “edge” design on-eye must be developed, such that differing designs in identical materials can be compared. Methods to investigate tear replenishment and expulsion from beneath lenses must also be developed to aid us in understanding their impact on factors such as end-of-day comfort and inflammatory responses.

Further work to better understand the reasons behind the success of frequent replacement lenses is also needed, particularly with new materials. What is the optimal period of replacement for certain materials, and what are the methods

used to determine this? How widely does this differ for different patients? What are the factors associated with the optimal replacement period? Is it due to changes in the material itself, the accumulation of certain tear film components, or those from the care system? What changes occur over time (over the day and over the lifetime of the lens) to both the ocular tissues in contact with the lens and the material itself? On a related note, studies to better understand the accumulation of tear film components remain to be undertaken. In particular, a better understanding of the impact of denatured proteins (other than lysozyme), lipid breakdown products and the deposition of many other tear film components are required.

There also remain large gaps in our knowledge of the role of care systems, packaging solutions and “comfort” drops on CLD. As with material-based studies, potentially valuable investigations in which systematic changes in various components are evaluated have yet to be undertaken. The short- and long-term impact of the uptake and release of lens care components and how they affect comfort are areas of future interest. Should care systems remove all tear film constituents that are deposited onto materials, or should they be designed to leave in place certain components that may help “biocompatibility”? If some components should be left in place, which ones and how much is “enough”? Finally, how effective is the delivery of wetting agents from the materials in reducing CLD and which agents are the most efficacious—and for how long?

Summary

In summary, a thorough review of the literature shows that there are surprisingly few proven links between CLD and factors related to the contact lens material, design, and care system. However, clinical acumen (in addition to recent studies^{277,333}) demonstrates that, in contact lens wearers who exhibit unacceptable comfort, making changes to the lens material, design, care system, and replacement schedule can improve comfort. It is also pertinent to consider, as pointed out in this review, the limitations of laboratory and academic studies, which might miss relevant variables present in the “real world.” Conclusions derived from well-conducted, well-controlled groups of subjects in a formal clinical trial might not be transferable to the thousands of patients that ultimately use the products, subjected to issues such as noncompliance, that may directly impact evaluation of comfort.

Much work remains to unravel the complexities of CLD. It is clear that a number of fundamental studies must be undertaken if an increased understanding of the role of materials, design and care regime in contact lens dryness is to occur. This will require substantial intellectual input and funding from both industry and academia alike.

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APPENDIX A. Examples of Some Commonly Prescribed Hydrogel Contact Lens Materials

Commercial Name	Manufacturer	Water Content	CT	Dk/t
SofLens 38 (polymacon)	Bausch + Lomb	38	0.035	22
Biomedics 55 (ocufilcon D)	CooperVision	55	0.07	21
Acuvue 2 (etafilcon A)	Johnson & Johnson	58	0.084	20
SofLens daily disposable (hilafilcon B)	Bausch + Lomb	59	0.09	19
PROCLEAR (omafilcon A)	CooperVision	62	0.065	30
Focus Dailies (nelfilcon A)	CIBA Vision	69	0.10	26

APPENDIX B. Examples of Some Commonly Prescribed Silicone Hydrogel Contact Lens Materials

Commercial Name	Manufacturer	Water Content	CT	Dk/t	Modulus, MPa	Surface Treatment
Air Optix Night & Day Aqua (Iotrafilcon A)	Alcon	24	0.08	175	1.4	25-nm plasma coating
Air Optix Aqua (Iotrafilcon B)	Alcon	33	0.08	138	1.0	25-nm plasma coating
DAILIES TOTAL1 (delefilcon A)	Alcon	33	0.09	156	0.7	Soft surface gel with >80% water content
PureVision (balafilcon A)	Bausch + Lomb	36	0.09	101	1.1	Plasma oxidation process
Acuvue OASYS (senofilcon A)	Johnson & Johnson	38	0.07	147	0.72	None; internal wetting agent (PVP)
Acuvue Advance (galyfilcon A)	Johnson & Johnson	47	0.07	86	0.40	None; internal wetting agent (PVP)
1 Day Acuvue TruEye (narafilecon A)	Johnson & Johnson	46	0.085	118	0.66	None; internal wetting agent (PVP)
BIOFINITY (comfilcon A)	CooperVision	48	0.08	160	0.75	None
AVAIRA (enfilcon A)	CooperVision	46	0.08	125	0.50	None
Menicon PremiO (asmofilcon A)	Menicon	40	0.08	161	0.90	Plasma oxidation
Clariti (Filcon II 3)	Sauflon	58	0.07	86	0.50	Nondisclosed
Definitive (efrofilcon A)	Contamac	75	0.08*	76	0.35	None

PVP, polyvinyl pyrrolidone; USAN, United States Adopted Name.

* Estimated as lathe-cut lens designed to practitioner specification.

The TFOS International Workshop on Contact Lens Discomfort: Report of the Subcommittee on Neurobiology

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See the tables in the Introduction for the members of the TFOS International Workshop on Contact Lens Discomfort.

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This report characterizes the neurobiology of the ocular surface and highlights relevant mechanisms that may underpin contact lens-related discomfort. While there is limited evidence for the mechanisms involved in contact lens-related discomfort, neurobiological mechanisms in dry eye disease, the inflammatory pathway, the effect of hyperosmolarity on ocular surface nociceptors, and subsequent sensory processing of ocular pain and discomfort have been at least partly elucidated and are presented herein to provide insight in this new arena. The stimulus to the ocular surface from a contact lens is likely to be complex and multifactorial, including components of osmolarity, solution effects, desiccation, thermal effects, inflammation, friction, and mechanical stimulation. Sensory input will arise from stimulation of the lid margin, palpebral and bulbar conjunctiva, and the cornea.

Keywords: contact lens, dry eye, discomfort, neurobiology

OCULAR SURFACE NEUROBIOLOGY

Anatomy and Morphology

Contact lenses interact directly with the ocular surface and contiguous areas of the upper and lower eyelids during lens wear. All of these areas are densely innervated by sensory fibers of the trigeminal nerve. Of these, the cornea is the most richly innervated of all ocular structures and the most densely innervated surface epithelium in the human body, while the conjunctiva and eyelid margins receive more modest innervations.

Origins of Corneal Sensory Nerves. Corneal sensory nerves originate from relatively modest numbers of neurons, numbering no more than several hundred, in the ophthalmic and maxillary regions of the trigeminal ganglion (TG).¹ The nerves to the cornea and adjacent areas of the bulbar conjunctiva reach the eye by traveling first in the nasociliary branch of the ophthalmic nerve, then via two long ciliary

nerves and a communicating branch to the ciliary ganglion. While in transit, the fibers branch and anastomose repeatedly to give rise to multiple nerve bundles that approach the anterior segment at equidistant intervals around the limbal circumference. Sensory fibers exit the anterior portion of the plexus to supply the cornea and limbal conjunctiva, while additional fibers exit the posterior part of the plexus to supply the iris and ciliary body. The inferior cornea in a small number of individuals may also receive minor sensory inputs from branches of the maxillary division of the trigeminal nerve.^{2,3}

Corneal Innervation: Stromal Nerves. Nerve fibers (Fig. 1) enter the human cornea from the limbus in 60 to 80 prominent, evenly spaced, radially directed, midstromal nerve bundles.^{4–7} A variable number of smaller fascicles enter and ramify within the peripheral cornea in a more superficial plane. At their point of entry, approximately 70% to 80% of the nerves are unmyelinated (C fibers); the remainder are finely myelinated (A- δ) fibers that shed their myelin sheaths within a millimeter or so after entering the cornea.^{8,9} Some nerves terminate in the

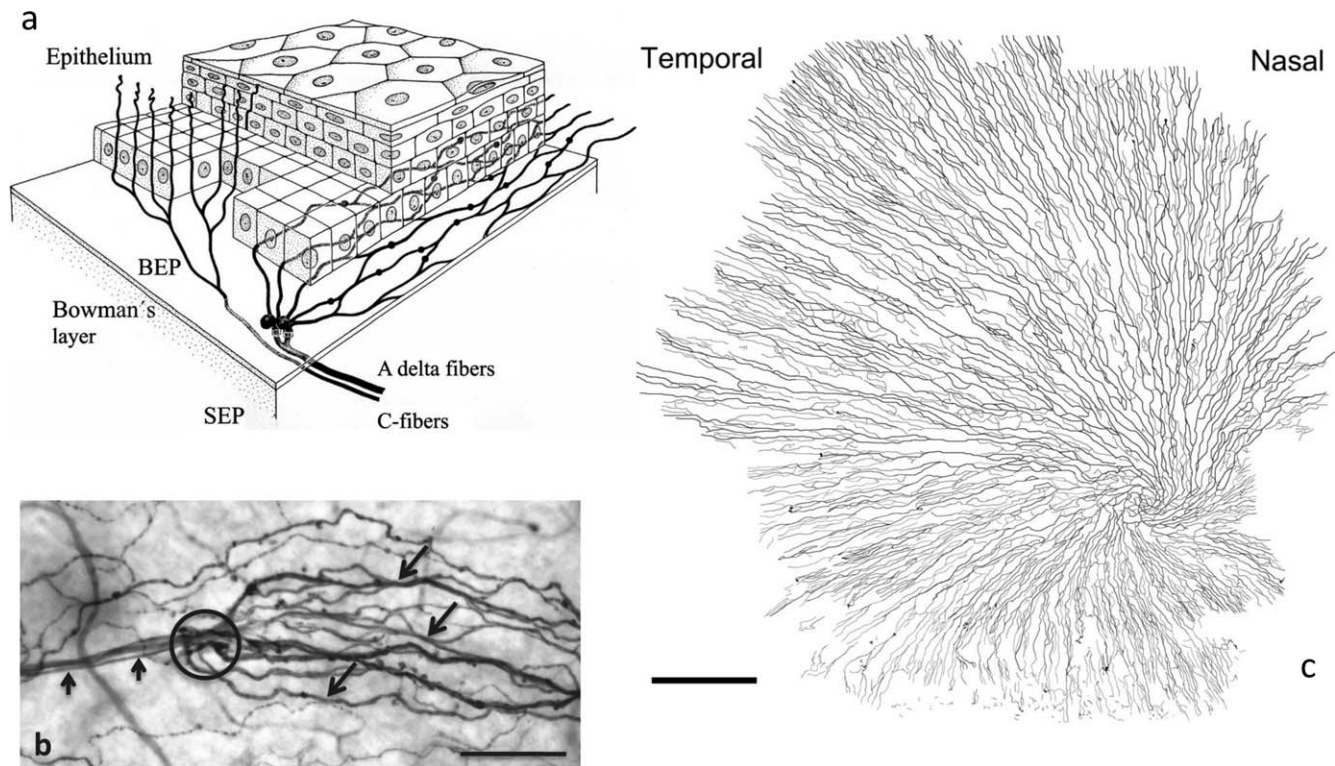


FIGURE 1. Subbasal nerve fibers. **(a)** Schematic representation of the human corneal epithelial innervation. Three-dimensional reconstruction from digital sections was obtained with confocal laser scanning microscopy of excised corneas. Stromal nerve bundles in the subepithelial plexus penetrate the epithelial basal lamina, turn abruptly at acute angles, and divide into multiple daughter fibers called subbasal nerves. The subbasal nerves run horizontally within the deepest part of the basal epithelial cell layer and give rise to numerous, superficially directed intraepithelial terminals. Reproduced with permission from figure 2 in Guthoff RE, Wiens H, Hahnel C, Wree A. Epithelial innervation of human cornea: a three-dimensional study using confocal laser scanning fluorescence microscopy. *Cornea*. 2005;24:608-613. Copyright 2005 Lippincott Williams & Wilkins. BEP, basal epithelial plexus; SEP, subepithelial plexus. **(b)** A subepithelial nerve fiber (*short arrows*) in a human cornea penetrates (*circle*) Bowman's layer and the epithelial basal lamina to form an "epithelial leash formation" composed of multiple radially directed subbasal nerves (*long arrows*) of varying diameters. The nerves in this figure (and in Figs. 2a, 3) have been stained immunohistochemically with primary antiserum against the pan-neuronal marker neurotubulin. *Scale bar:* 100 μ m. **(c)** The central portion of the human subbasal nerve plexus. Nerve tracings are constructed from a montage of 575 *in vivo* confocal microscopy images. The SNFs radiate toward the periapical cornea, where they form a gentle whorl-like complex. *Scale bar:* 1 mm. Reproduced with permission from figure 3a in Lum E, Golebiowski B, Swarbrick HA. Mapping the corneal sub-basal nerve plexus in orthokeratology lens wear using *in vivo* laser scanning confocal microscopy. *Invest Ophthalmol Vis Sci*. 2012;53:1803-1809. Copyright 2012 Association for Research in Vision and Ophthalmology.

stroma as free nerve endings,⁷ while others form intimate anatomical relationships with stromal keratocytes that suggest possible reciprocal functional interactions.¹⁰

Corneal Innervation: Epithelial Nerves. Approximately 200 to 500 stromal nerve fibers penetrate Bowman's layer, mainly in the peripheral and intermediate cornea, to supply the human corneal epithelium^{7,10,11}; the peripheral epithelium also receives additional input from nerves that enter the corneal epithelium directly from the limbal plexus (Fig. 1). Subbasal nerve fibers (SNFs) (Fig. 2) appear by confocal microscopy and transmitted light microscopy as single nerve fibers of variable diameter; however, in reality each SNF consists, at the electron microscopic level, of up to 40 individual unmyelinated axons (Fig. 2b).¹¹ After entering the epithelium, the axons shed their Schwann cell investments and continue as naked axon cylinders. Individual SNFs in human corneas course horizontally, roughly parallel to one another and to the ocular surface, for distances of up to 6 to 8 mm.⁷

Subbasal nerves in adjacent leashes, especially in the central and intermediate corneal zones, anastomose with one another extensively via short connecting axons to produce a dense, mesh-like subbasal nerve plexus (Fig. 1c). The human subbasal nerve plexus has a highly distinctive appearance and a measurable density; thus, alterations in SNF density or

morphology, such as occurs in dry eye, diabetes, keratoconus, herpes simplex virus infection, normal aging, and following refractive surgeries, can be monitored quantitatively and qualitatively by *in vivo* confocal microscopy (discussed in more detail below) to assess temporal changes in innervation status.^{12,13}

Each SNF gives rise to numerous intraepithelial terminals. The terminals distribute throughout all layers of the corneal epithelium and are most dense in the basal and wing cell layers; however, occasional terminals may extend to within a few micrometers of the ocular surface¹⁴ (Fig. 2c).

The terminus of each intraepithelial fiber is tipped by a slightly bulbous free nerve ending. At the ultrastructural level, these expansions resemble nociceptor nerve endings described in other tissues.¹⁵ The anatomical associations formed between nerve terminals and surrounding epithelial cells do not constitute true synapses; however, the intimate nature of these contacts may permit bidirectional, receptor-mediated interactions.¹⁶

The innervation density of the human central corneal epithelium is difficult to calculate but has been estimated at approximately 7000 nerve terminals per square millimeter.¹⁷ Corneal sensitivity¹⁸ and nerve terminal density¹⁹ are highest in the central cornea and decrease progressively when moving

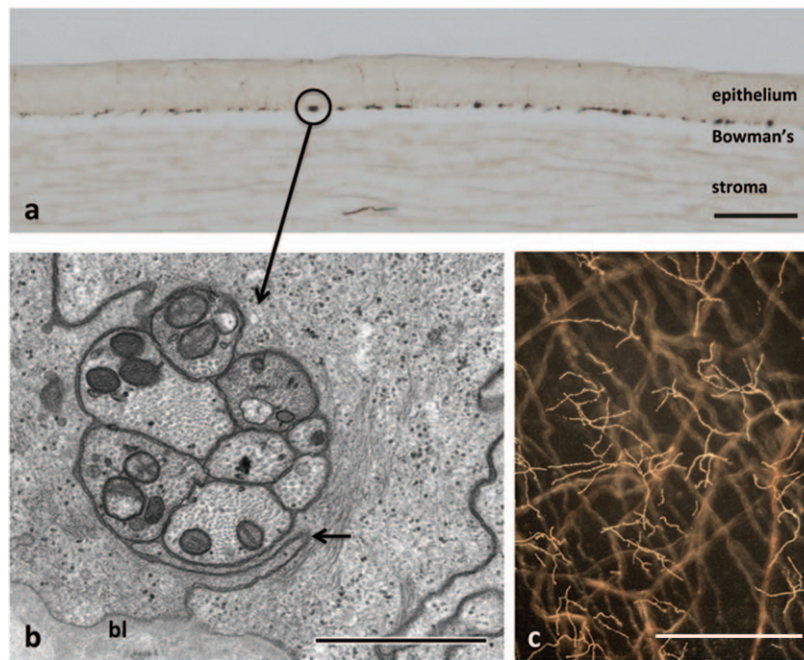


FIGURE 2. Ultrastructure of human SNFs and intraepithelial terminals. (a) Perpendicular section (30 μm thick) of a human cornea. The SNFs (e.g., circle) have been sectioned perpendicular to their long axes and are located in the basal epithelium immediately superficial to the epithelial basal lamina and Bowman's layer. Scale bar: 100 μm . (b) Electron micrograph of a cross-section through a human SNF. The SNF consists at the ultrastructural level of eight individual unmyelinated axons. The axons are located within a focal widening of the intercellular cleft (arrows) between two adjacent basal epithelial cells. bl, Basal lamina. Scale bar: 1 μm . Reproduced with permission from Figure 5c in Müller IJ, Marfurt CF, Kruse F, Tervo TM. Corneal nerves: structure, contents and function. *Exp Eye Res.* 2003;76:521–542. Copyright 2003 Elsevier. (c) Nerve terminals in the superficial layers of the dog corneal epithelium. Subbasal nerve fibers are seen in a deeper plane of focus. Calibration bar is 50 μm .

peripherally. The richness of this innervation, coupled with the absence of a keratinized surface epithelium and the proximity of the nerve terminals to the ocular surface, provides a nociceptive detection system of unparalleled sensitivity. It has been hypothesized that injuries to single epithelial cells may be sufficient to trigger pain perceptions.⁹

Corneal Nerve Neurochemistry. Corneal sensory nerves are phenotypically diverse and express one or more of six different neuropeptides (see the reviews by Marfurt^{20,21} and by Müller and colleagues¹⁷). Calcitonin gene-related peptide (CGRP) and substance P (SP) are expressed in approximately 40% to 60% and 10% to 20%, respectively, of mammalian corneal sensory nerves and are the only sensory neuropeptides identified to date in human corneas. Other neuropeptides expressed in more limited numbers of corneal sensory nerves include neurokinin A (a member of the tachykinin family) secretoneurin (a member of the chromogranin/secretogranin family), pituitary adenylate cyclase-activating peptide (a member of the vasoactive intestinal peptide-glucagon-secretin superfamily), and galanin. The extent to which these peptides coexist with CGRP and/or SP, or represent phenotypically distinct populations of corneal sensory nerves, remains unknown. Still other corneal sensory nerves are apparently “nonpeptidergic” and may utilize excitatory amino acids such as glutamate.^{22,23} Substance P, and perhaps CGRP, promotes corneal epithelial maintenance and physiological renewal by activating cellular pathways that stimulate epithelial cell proliferation, migration, adhesion, and differentiation. Topical application of insulin-like growth factor 1 and SP²⁴ or SP and epidermal growth factor²⁵ accelerates corneal epithelial wound healing in experimental animal models and in clinical patients with persistent corneal epithelial defects.²⁶ In marked contrast, little or nothing is known of the physiological effects of other corneal neuropeptides.

Innervation of the Conjunctiva and Eyelid Margin.

Compared with corneal sensory nerves, less is known of the morphology and neurochemistry of the conjunctival sensory nerves. Much of what is known is derived from work performed in animal models, including primates. Anatomically, the conjunctiva is divided into three major divisions. The bulbar conjunctiva covers the sclera of the anterior globe, the fornical conjunctiva lines the fornices, and the palpebral or tarsal conjunctiva lines the eyelids. Sensory innervation of the bulbar conjunctiva, palpebral conjunctiva, and eyelid margin is supplied by branches of the supratrochlear, supraorbital, infratrochlear, and lacrimal nerves (all branches of the ophthalmic nerve) and the infraorbital nerve (a branch of the maxillary nerve).^{27,28} The conjunctival sensory innervation consists mainly of unmyelinated, but also some finely myelinated, axons that terminate as unencapsulated free nerve endings in the stroma, along the surfaces of blood vessels and in the epithelium.^{29–31} Many of the sensory nerves contain CGRP or SP.^{32–34} Small numbers of bulbar conjunctival fibers in humans originate from large-diameter, heavily myelinated axons that terminate as Krause corpuscles or other complex encapsulated nerve endings. Krause corpuscles are found in all areas of the human bulbar conjunctiva but are most dense in a 1.0-mm-wide annular zone located just outside the limbus.³⁵ The function of the latter corpuscles remains debated, but they are probably rapidly adapting touch receptors. The extent to which conjunctival and corneal sensory nerves represent separate or collateral branches of the same ocular neuron is uncertain.

In contrast to work in the cornea, morphological estimates of conjunctival nerve density are not readily available; alternatively, conjunctival sensitivity has been measured by using a Cochet-Bonnet or Belmonte esthesiometer. The results of several studies^{36–41} have shown that touch sensitivity of the

conjunctiva is considerably less than that of the cornea, although this difference is apparently less pronounced when tested with a cooling stimulus compared with a tactile stimulus.^{42,43} Mechanical sensitivity is much higher in the limbal conjunctiva than in the tarsal and bulbar conjunctiva.^{37,44,45} Sensitivity of the tarsal conjunctiva has been especially difficult to evaluate due to technical issues but is estimated to be about half as sensitive as the lid margin.⁴⁵ The sensitivities of the inferior and temporal bulbar conjunctiva to tactile and chemical stimulation have been estimated to be about 1.6 to 1.7 times lower than that of the corneal apex.^{40,43} Regional differences (i.e., temporal versus inferior) in bulbar conjunctival sensitivity to mechanical stimulation have been reported by several investigators.^{36,37,44,46} Conjunctival sensitivity,^{37,40,46} similar to corneal sensitivity,^{18,47} decreases progressively as a function of age, although an increase in sensitivity with age has also been reported when a pneumatic stimulus is used.⁴¹

Innervation of the Eyelid. The eyelid margin, in addition to the cornea, is a key contact zone between the contact lens and the ocular surface. A relationship between ocular discomfort due to contact lens wear and lid margin sensitivity has been known since the early days of contact lens practice.⁴⁸ Tactile sensitivity at the eyelid margin is surprisingly high^{37,45,49,50}; although lower than that of the central cornea, it is distinctly higher than that of the conjunctiva. Differences among studies may reflect interindividual variations in eyelid sensitivity,⁴⁵ technical challenges associated with careful sampling of these areas,⁵¹ and disparities in the exact regions of the “lid margin” that were investigated. Recent histological investigations have divided the human eyelid margin into three subzones⁵² that were insufficiently defined and unknown to earlier researchers. Systematic studies of eyelid touch sensitivity that take into consideration these zonal distinctions remain to be performed; however, McGowan and colleagues⁴⁵ in a study of upper and lower human eyelid sensitivity in 30 subjects observed that the “marginal angle,” which represents exactly the anterior part of the zone now known as the lid wiper, had a significantly higher sensitivity than the occlusal surface of the free lid margin. Several investigators have reported that sensitivity in the lower lid margin is significantly greater than that in the upper lid.^{45,51} However, it should be cautioned that the necessity of everting the upper lid margin before testing with an esthesiometer may adversely affect sensitivity measurements of this structure. The issue warrants additional investigation because it has been speculated that symptoms of contact lens discomfort (CLD) may originate, in part, from movement of the sensitive lid wiper area of the upper and lower eyelid across the contact lens.^{53,54}

The robust literature on ocular surface innervation contains, surprisingly, only a single morphological investigation of the sensory innervation of the human eyelid margin.²⁹ This study revealed by combined light and electron microscopy an impressive array of sensory nerve terminals, including abundant Meissner corpuscles, other simple corpuscular endings, Merkel disc endings, and dermal and intraepithelial free nerve endings.²⁹ In addition, complex arrays of lanceolate, circular Ruffini, Merkel, and free nerve endings envelop the eyelashes.²⁹ The remarkable density of sensory terminals revealed by this histological investigation is consistent with the clinical observations of high tactile sensitivity of the human eyelid margin.

Neurophysiology and Sensation

Peripheral Nervous System Mechanisms. The present knowledge of the functional types of sensory nerve fibers

innervating ocular and periocular structures is incomplete. Considerable effort has been devoted in the last decades to analyzing the electrophysiological properties of nerve fibers innervating the cornea and, to a lesser degree, the bulbar conjunctiva (see the reviews by Belmonte and colleagues^{9,55}). In contrast, detailed functional studies of the sensory afferents supplying the palpebral conjunctiva, lid borders, and extraocular muscles (in particular those conveying nociceptive signals from these tissues) are scarce, and their functional characteristics are mentioned only incidentally in some of the studies devoted to the trigeminal innervation of the face.

There is experimental evidence that subtle molecular and genetic differences exist within the traditional subclasses of TG neurons.⁵⁶ The specificity of the molecular signature of the various subtypes of primary sensory neurons appears to correlate functionally with their individual short-term and long-term impulse responses to inflammation and physical or chemical trauma.

Functional Types of Sensory Neurons Innervating the Ocular Surface. Most of the corneal neurons with myelinated (A- δ) axons have conduction velocities between 2 and 15 m/s, whereas neurons with unmyelinated axons, the C-type neurons, conduct at less than 2 m/s.⁵⁷⁻⁶⁰ The lid margins also possess morphologically specific terminals (Meissner and Merkel corpuscles and Ruffini and other corpuscular endings) whose functional identification as thick myelinated, fast-conducting low-threshold mechanoreceptors is well established.⁶¹

Most (about 70%) of the sensory nerve fibers innervating the cornea and the bulbar conjunctiva are polymodal nociceptors, with the majority being C-type neurons. They are activated by near-noxious or noxious mechanical energy, heat, and chemical irritants and by a large variety of endogenous chemical mediators released by damaged corneal tissue and resident and migrating inflammatory cells, or by leakage from limbal vessels.⁵⁷⁻⁶⁰ A proportion (<50%) of polymodal fibers also increase their firing rate when the corneal temperature is reduced below 29°C.⁶² Many chemical agents (cytokines, prostaglandins, bradykinin, capsaicin, and mustard oil) known to excite polymodal nociceptors in other tissues also activate ocular nociceptors; acidic solutions (pH 5.0-6.5) evoke their impulse discharges at corneal polymodal nociceptors.^{58-60,62,63}

Polymodal nociceptors often undergo inactivation (i.e., progressive reduction or suppression of the impulse response to repeated stimulation) at intensities around or over noxious levels after stimulation.⁶⁴ However, when the stimulus causes some level of tissue injury (which triggers local inflammation), they develop an ongoing, irregular impulse firing; their threshold for activation by mechanical, thermal, and chemical stimuli decreases, and the impulse discharge evoked by suprathreshold stimulation increases. Collectively, these phenomena are termed *sensitization*.⁶⁵⁻⁶⁷ Polymodal nociceptor neurons are connected centrally with higher-order relay neurons of the pain pathways. Hence, the psychophysical correlate of their immediate activation is acute pain.⁶⁸ When sensitization is developed, the psychophysical correlates are allodynia (pain evoked by innocuous stimulation), hyperalgesia (enhanced pain in response to noxious stimuli), and spontaneous pain, due respectively to the lowered threshold, enhanced responsiveness, and spontaneous discharge of polymodal nociceptors.^{64,66,69}

About 15% to 20% of the nerves innervating the cornea, all thinly myelinated (A- δ), are mechano-nociceptor fibers that respond only to mechanical forces in an order of magnitude close to that required to damage corneal epithelial cells. They are phasic sensory receptors that signal the presence of the

stimulus and, to a very limited degree, its intensity and duration. The threshold force required to activate mechanoreceptors is relatively low (about 0.6 mN) but slightly over the mechanical threshold of polymodal nociceptors.⁷⁰ Mechanoreceptors in the cornea are probably responsible for the immediate, sharp sensation of pain produced by touching or scratching of the corneal surface. There is experimental evidence for a transient reduction of their mechanical threshold during allergic keratoconjunctivitis,⁷¹ and it is possible that repeated stimulation of mechanoreceptors is a feature of contact lens wear.

Another category of corneal nerve fibers that represents 10% to 15% of the total population are cold-sensitive thermoreceptors. These are A- δ and C fibers that discharge spontaneously at rest and increase their firing rate when the normal temperature of the corneal surface (around 33–34°C) is reduced (they are transiently silenced upon warming).^{59,72–74} Accordingly, cold thermoreceptor activity increases with temperature drops produced by evaporation of tears at the corneal surface, blowing of cold air onto the cornea, or application of cold and hyperosmolar solutions.^{59,75–77} However, while the pre-lens tear film temperature is cooler than the non-contact lens wearing eye, underneath the lens the temperature is higher.⁷⁸ Conceivably, cold receptors on the lid margin may be implicated in CLD. Such receptors are able to detect and encode the intensity of a stimulus by their impulse frequency within very small temperature ranges of 0.5°C or less,^{59,75,76} thus explaining the perception of corneal temperature reductions of such magnitude as a conscious sensation of cooling⁷⁹ and/or dryness.⁸⁰ Although most of the corneal cold thermoreceptors have a very low thermal threshold (i.e., they increase their background firing with a temperature reduction of <2.0°C), there is a subpopulation with a higher thermal threshold (detecting a temperature reduction of >5°C).^{81,82}

There is increasing evidence that corneal cold thermoreceptors respond to other stimuli. They are activated not only by temperature reductions (as those occurring during interblink tear evaporation) but also by an increase in tear osmolarity, as well as about 50% of them by heat (>45°C) and capsaicin.⁵⁵ Their activity is modulated by inflammation, which reduces their ongoing and stimulus-evoked impulse activity⁷¹ and by peripheral injury that increases both parameters. They stimulate basal tearing and blinking.⁷⁶ The information they provide to the brain is used not only to evoke temperature sensations but also to evoke unpleasant sensations when the ocular surface dries, possibly through the recruitment of higher-threshold cold thermoreceptors.^{81,83} Under inflammatory conditions, cold thermoreceptors become less sensitive, so that the firing frequency of their continuous background activity at normal temperature, and the magnitude of the impulse response to cooling, are both reduced.⁷¹ Counterintuitively, injury appears to enhance the background activity of cold thermoreceptor terminals, a consequence of the enhancement of sodium currents and the reduction of potassium currents after axonal injury.⁷¹

Molecular and Cellular Mechanisms for Transduction and Coding of Physical and Chemical Stimuli. The molecular transduction mechanisms used by the various functional classes of TG sensory receptor neurons innervating ocular and periocular tissues are different. This is also true for the sodium, potassium, and calcium voltage-sensitive channels involved in the generation of propagated nerve impulses. Moreover, each class of neuron is provided with different membrane receptor proteins to interact with diffusible chemicals and proinflammatory substances and with various downstream effectors. This enables each receptor neuron type

to react differently to the various forms of stimulus energy, thereby modifying their impulse response.⁸⁴

Various ion channels have been associated with nociceptor and thermosensitive neurons of the TG innervating the tissues of the face and head. While some are present in ocular neurons, detailed evidence on the functional expression of specific transducing channels in identified ocular TG neurons is lacking to date.

Transient Receptor Protein Channels. Transient receptor protein (TRP) channels constitute a superfamily of cation-permeable ion channels that are classified based on their sequence homology into the following six subfamilies: TRPC, TRPV, TRPM, TRPA, TRPP, and TRPML.⁸⁵ A distinct feature of most TRP channels is their polymodal activation by physical stimuli (e.g., temperature and mechanical forces) and exogenous and endogenous chemical substances. This characteristic makes them effective detectors of environmental stimuli, acting as a molecular interface between the external world and the nervous system.

TRPV1 channels are key receptors for detecting noxious stimuli such as acidic pH,⁸⁶ heat (>43°C),⁸⁷ and chemicals, including capsaicin⁸⁷ and anandamide.⁸⁸ TRPV1 is expressed within a major class of nociceptive neurons⁸⁹ with A- δ and C axons. Some receptors for inflammatory mediators, including prostaglandin E₂ (PGE₂) receptors,⁹⁰ β -adrenergic type 1 through 3 receptors,⁹¹ serotonin type 7 receptors,⁹² and H₂ receptors, possibly exert their sensitizing effect through modulation of TRPV1 activity. Thus, TRPV1 behaves as the final integrator of a large variety of noxious stimuli. Almost all dorsal root ganglion neurons expressing TRPV1 coexpress the ionotropic purine receptor P2X₃.⁹³

TRPA1 channels are expressed in a subpopulation of unmyelinated nociceptors that also express the capsaicin receptor TRPV1, suggesting an important role in nociception. Consistent with this hypothesis,⁹⁴ TRPA1 is activated by a diverse assortment of pungent or irritating reactive chemical compounds, including those found in mustard oil (allyl isothiocyanate), cinnamon oil (cinnamaldehyde), gas exhaust (acrolein), raw garlic and onions (allicin), and formalin (formaldehyde); all of these elicit a painful burning or pricking sensation.^{95–100} Hence, TRPA1 signals the presence of a plethora of noxious stimuli in the environment and endogenous molecules released in inflamed tissues. Compounds activating TRPA1 have in common their reactivity with amino acid residues in the N-terminal cytoplasmic domain.^{101,102} Moreover, TRPA1 has been suggested as a putative transducer of natural physical stimuli, including both cold and mechanical forces.^{95,103} Thus, like TRPV1, TRPA1 is a molecular “switchboard” integrator for a range of diverse noxious stimuli. In addition to the contribution of this channel to the detection of direct chemical and physical stimuli, recent genetic and pharmacological evidence suggests that TRPA1 also has a major role in inflammatory pain, as well as in the mechanical and cold hyperalgesia that is associated with peripheral inflammation.⁹⁹ TRPA1 is sensitized by both bradykinin and Protease activated receptor 2, thus reinforcing its role in inflammatory pain.⁹⁶

Transient Receptor Potential Melastatin 8 Channels. Transient receptor potential melastatin 8 (TRPM8) is a cold-activated cation channel.¹⁰⁴ TRPM8 channels are expressed mainly in a small subpopulation of peripheral sensory neurons with A- δ or C axons that detect small temperature decreases, thus corresponding to low-threshold cold thermoreceptor neurons but also in other neurons that respond to stronger temperature decreases and express the phenotype of nociceptive neurons.¹⁰⁵ Inflammatory mediators decrease TRPM8-dependent nerve activity.¹⁰⁵

Other TRP Channels. Additional classes of TRP channels have been identified in primary sensory neurons associated

with mechanotransduction, osmolarity detection, thermal detection, and other functions. TRPV2, TRPV4, TRPC5, and TRPM3 are examples.¹⁰⁴

Acid-Sensing Ion Channels. The acid-sensing ion channels (ASICs) are members of the epithelial sodium channel/degenerin superfamily, and several are expressed in TG neurons. ASICs may have a significant role in pain and inflammation. For instance, ASIC3 responds synergistically to slight acidification (pH 7.0), hypertonicity, and arachidonic acid (AA).¹⁰⁶ ASIC isoforms are expressed in Merkel cell-neurite complexes, periodontal Ruffini endings, and specialized nerve terminals of skin and muscle spindles.¹⁰⁷

Potassium Channels. Background potassium channels TREK-1, TREK-2, and TRAAK are mechanostimulated and temperature gated.¹⁰⁸⁻¹¹¹ These channels are expressed in primary sensory neurons.^{111,112} Both TRAAK and TREK-1 are likely candidates to regulate sensory neuron excitability in response to temperature and mechanical stimuli.

Correlation Between Molecular and Cellular Mechanisms and Quality of Sensation. As indicated by Viana and Belmonte,⁸⁴ there is growing evidence that the relationship between the various ion channels described above and proposed as specific transducer molecules for stimuli of different quality is not as neatly associated with the distinct functional types of sensory receptors (mechanoreceptors, thermal receptors, and polymodal nociceptors) as originally proposed. First, many ion channel molecules initially associated with the transduction of only one particular form of energy are also activated by stimuli of different quality, implying a limited degree of specificity in their transducing capacities. Second, molecular sensors associated with a stimulus quality and hence with a sensory receptor type and ultimately with a sensory modality may be concomitantly expressed in sensory receptor neurons functionally defined as specific for another stimulus quality. Third, activation of voltage-gated channels involved primarily in nerve impulse generation can also influence the gating of transducing channels, dramatically modifying their activation profile.

Thus, the capacity of different functional types of somatosensory receptor neurons to preferentially detect and encode specific stimuli into a discharge of nerve impulses appears to result from a characteristic combinatorial expression of different ion channels in each neuronal type that finally determines their transduction and impulse firing properties. Transduction channels do not operate in isolation, and their cellular context should also be taken into consideration to fully understand their function. Moreover, the inhomogeneous distribution of transduction and voltage-gated channels at soma, axonal branches, and peripheral endings of primary sensory neurons influences the characteristics of the propagated impulse discharge that encodes the properties of the stimulus. Alteration of this concerted operation of ion channels in pathological conditions may underlie the changes in excitability accompanying the abnormal peripheral signaling taking place after persistent stimulation and/or inflammation as may occur during CLD.

Central Nervous System Mechanisms. The concept of the lacrimal functional unit has served as a useful framework to assess the organization of a multicomponent system that links the ocular surface, through sensory nerves and central nervous system (CNS) integrative circuits, to critical efferent processes such as tear secretion that maintain ocular surface integrity and underlie ocular sensations.¹¹³⁻¹¹⁵ Peripheral mechanisms in dry eye disease (DED) have received considerable attention^{70,116,117}; however, far less is known regarding CNS mechanisms. Several lines of evidence support the hypothesis that altered CNS processing has a critical role in abnormal ocular sensations, potentially including CLD. Brainstem circuits

necessary for ocular homeostatic reflexes are well connected with brain regions that influence the sensory, affective, and autonomic aspects of pain.¹¹⁸⁻¹²⁰ Many ocular sensations such as wetness, dryness, grittiness, itch, and irritation are complex and likely result from interactions across multiple psychophysical channels.¹²¹ Interactions across modalities and that demonstrate spatial and/or temporal summation likely cannot be explained on the basis of peripheral afferent nerve activity alone.¹²² Most critically, symptoms of CLD often do not correlate well with signs of ocular surface dysfunction.

Central Neural Pathways for Ocular Sensation and Homeostasis. The ophthalmic branch of the trigeminal nerve supplies the ocular surface, periocular tissues, and nearly all tissues within the eye.²⁷ The cell bodies for ocular sensory nerves lie along the medial border of the TG and represent only 2% to 5% of the total TG population in rodents^{123,124} and primates¹²⁵ despite evidence that the ocular surface is the most densely innervated structure in the body.¹⁸

Ocular TG neurons project centrally to terminate in multiple spatially discrete zones along the rostrocaudal axis of the trigeminal brainstem sensory complex (TBSC). The TBSC is composed of a principal trigeminal nucleus (Vp) in the pons and the spinal trigeminal nucleus (Vsp) in the medulla. The Vsp is further subdivided into subnucleus oralis (Vo), interpolaris (Vi), and caudalis (Vc) based on anatomical and functional properties (see the study by Bereiter et al.¹²⁶). Anatomical tracing studies in primates,¹²⁵ cats,^{127,128} and rodents^{123,129,130} indicate that corneal and conjunctival afferent fibers terminate mainly in the ventral aspect of the transition region between caudal Vi and Vc (Vi/Vc transition) and at the spinomedullary junction (Vc/C1). Middle portions of Vc and more rostral regions of the TBSC receive sparse input from corneal afferent fibers, although conjunctival afferents also terminate in rostral TBSC.¹³⁰ A restricted projection pattern as seen for corneal afferents is also seen for TG neurons that supply the eyelids,^{131,132} lacrimal gland,^{133,134} and meibomian gland.^{128,135} The significance of multiple zones of termination for corneal afferents in the TBSC is not known and may simply reflect the need for redundancy in a system critical to preserve retinal function. Alternatively, although not mutually exclusive, discrete groups of second-order ocular neurons may serve different functions.¹³⁶

Converging lines of evidence from anatomical and neurophysiological studies support the hypothesis that ocular surface-responsive neurons at the Vi/Vc transition and caudal Vc/C1 region serve different functions in ocular homeostasis and sensation. First, the immediate early gene product, Fos protein, induced after noxious stimulation of the ocular surface, is expressed in a bimodal distribution at the Vi/Vc transition and Vc/C1 junction regions.¹³⁷⁻¹³⁹ However, administration of morphine¹⁴⁰ or neurokinin (e.g., SP) receptor antagonists¹⁴¹ before stimulation markedly reduces Fos at the Vc/C1 junction, with lesser effects at the Vi/Vc transition. Second, cold¹³⁹ or drying the ocular surface¹⁴² selectively produces Fos at the Vi/Vc transition, suggesting modality-specific input to each region. Third, neural recording indicates that neurons at both regions encode the intensity of mechanical and chemical stimulation of the ocular surface^{143,144}; however, dryness¹⁴² or cold¹⁴⁵ preferentially activates neurons at the Vi/Vc transition. Fourth, the receptive field (RF) properties of ocular cells at the Vc/C1 region are consistent with a role in nociception because all are excited by pinch of periorbital skin, whereas many neurons at the Vi/Vc transition are activated only by ocular surface stimulation.¹⁴⁴ Fifth, morphine inhibits ocular surface input to all neurons at the Vc/C1 junction, whereas nearly 40% of those at the Vi/Vc transition become more responsive to ocular surface stimulation.¹⁴⁶ This unexpected finding

suggests that ocular neurons at the Vi/Vc transition may contribute to ocular itch sensations that often accompany intrathecal or epidural morphine administration for spinal pain.^{147,148} Sixth, diffuse noxious inhibitory controls, a form of stimulus-induced analgesia that requires CNS integration, reduces corneal input to most Vc/C1 neurons, while fewer Vi/Vc transition neurons are inhibited.¹⁴⁴ Seventh, sensitization following corneal nerve injury or inflammation is thought to underlie the discomfort and irritation in most forms of DED.¹¹⁶ In animal models of uveitis¹⁴⁹ or photokeratitis¹⁵⁰ that cause anterior segment inflammation, enhanced responsiveness to corneal input is seen only by neurons at the Vc/C1 junction, whereas cells at the Vi/Vc transition often display reduced responsiveness. Early neurosurgical treatments to reduce trigeminal neuralgic pain by transection of the spinal trigeminal tract at the level of the Vi/Vc transition eliminated pain sensation to corneal stimulation; however, a sense of corneal touch remained.¹⁵¹ Collectively, these results suggest that the caudal Vc/C1 junction region mediates irritation and pain sensations in DED, while the Vi/Vc transition region is more likely involved in other ocular sensations such as dryness, coolness, and itch, as well as homeostatic reflexes. Based on a resistance to morphine and stimulus-evoked analgesia, ocular neurons at the Vi/Vc transition region also may form the ascending limb of the pathway that recruits endogenous pain controls from higher brain regions.¹³⁶ Indeed, the ventral Vi/Vc transition region projects heavily to the thalamic nucleus submedius,¹⁵² a midline nucleus involved in pain modulation.¹⁵³ Last, pharmacological blockade of the Vi/Vc transition region, but not the Vc/C1 junction region, prevents reflex lacrimation evoked by chemical stimulation of the ocular surface¹⁴² or by exposure to bright light.¹⁵⁴ Similarly, the Vi/Vc transition region also is necessary for corneal stimulation-evoked eyeblink, while the Vc/C1 junction region serves mainly a modulatory role.¹⁵⁵

The ascending projections from second-order ocular neurons in the TBSC to higher brain centers are not well known, and no systematic mapping study has been reported to date. Many corneal neurons in Vc project to the parabrachial area (PBA) in the midbrain rather than the thalamic ventral posteromedial nucleus,¹⁵⁶ consistent with earlier neural recording studies.^{144,157} The PBA receives convergent input from cranial, spinal, and visceral sensory nerves and projects heavily to limbic brain areas, consistent with a role in affective and/or autonomic aspects of pain.¹⁵⁸ Corneal stimulation activates neurons in the amygdala,¹⁵⁹ as well as neurons in the PBA that project to the amygdala.¹⁶⁰ Corneal neurons at the Vi/Vc transition also project preferentially to the superior salivatory nucleus, the major source of parasympathetic preganglionic neurons to the eye and lacrimal gland, and to the facial motor nucleus for control of eyeblink,¹⁶¹ while neurons at the Vc/C1 junction region project preferentially to the posterior thalamic nucleus (PO).¹⁶² Nociceptive neurons in the PO project to the amygdala and insular cortex rather than primary somatosensory cortex (S1).¹⁶³ Thus, two of the major projection targets of second-order corneal neurons in the TBSC are the PBA and PO, brain regions with weak direct connections to S1. Indeed, the ocular surface is poorly represented in S1 and S2 cortex. In their 1937 study, Penfield and Boldrey¹⁶⁴ could elicit no ocular sensations by electrical stimulation of S1. More recently, mapping studies of S1 in monkey,^{165,166} squirrel,¹⁶⁷ or rat¹⁶⁸ demonstrated no cortical neurons driven by ocular surface stimuli. By contrast, stimulation of insular cortex readily evokes sensations of tingling and pain in the face and eye.¹⁶⁹ Interestingly, selective stimulation of low-threshold unmyelinated C fibers in skin contributes to tactile sensitivity and causes increased activity in insular cortex but not in S1 or S2.¹⁷⁰ It is not known if low-threshold unmyelinated corneal afferents share this unique

projection pathway. In summary, the anatomical organization of ascending corneal pain pathways, at least under naive conditions, appears different from cutaneous pain pathways and projects heavily to brain regions associated with affective, emotional, or autonomic aspects of pain rather than sensory discrimination. Figure 3 summarizes the major ascending brain pathways described for trigeminal sensory fibers that supply the eye.

Ocular Sensations and CNS Integration. Corneal nerve endings express numerous receptor subtypes associated with encoding mechanical, thermal, and chemical stimulus modalities^{79,171}; however, the complex nature of many ocular perceptions such as dryness, grittiness, itch, irritation, and fatigue suggests interactions across multiple psychophysical channels^{121,172} that require integration at higher brain centers. Psychophysical channels are not independent as supported by evidence that ocular mechanical and chemical thresholds are altered by varying the effective intensity of each modality.¹²¹ The perception of itch and pain may be integrated by different brain regions because itch increases activity in insular cortex in an intensity-dependent manner, while pain causes greater increases in the sensory thalamus.¹⁷³ It is not known if the same brain areas integrate ocular itch and pain.

When presented alone, mechanical stimulation of the conjunctiva and cornea produces similar estimates of intensity, although lower scores for irritation are reported for conjunctiva stimulation.⁷⁹ However, after coincident mechanical stimulation of the cornea and conjunctiva, the magnitude of discomfort is reduced significantly compared with conjunctiva stimulation alone¹⁷⁴ and suggests an interaction between two sources of coincident input, resulting in altered ocular perception. In animal models of ocular inflammation, the convergent cutaneous RF area of ocular neurons at the Vc/C1 junction region is significantly enlarged after inflammation, consistent with spatial summation, whereas neurons at the Vi/Vc transition region are not affected.^{149,150} It is not yet known if RF areas of ocular neurons in TBSC are modified in animal models specific for dry eye.

Neural Control of the Ocular Response. The dense innervation of the ocular surface has a number of critical functional consequences. Stimulation of nerves on the ocular surface is responsible for a number of ocular sensations (pain, itch, dryness, and others) as described in detail above. The type and intensity of stimulation to the ocular surface will influence the ocular responses to the stimulation. Given the need to maintain an intact and clear cornea, the responses to intense noxious stimuli appear to be primarily protective in nature. Protective reflexes, including blink and lacrimation, can be rapid and profound.

Nerve impulses carried by trigeminal nerves synapse within the CNS, when a suitable threshold is reached, cause firing of facial nerve central nerve VII (CNVII) and through the temporal and zygomatic branches of CNVII actuate firing of the orbicularis oculi muscles to cause eyelid closure. While using the same efferent mechanism, the blink reflex seems to differ from baseline initiation of involuntary blink used for ocular surface maintenance.

Reflex lacrimation similarly results from stimulation of CNV fibers, which can lead to firing of parasympathetic CNVII fibers that innervate the lacrimal gland and lead to tearing.¹⁷⁵ The requirement for CNV function is not absolute for basal tearing because some lacrimal function remains after disruption of CNV function. More recent data suggest that a portion of tearing required for normal ocular surface homeostasis may require intact corneal innervation because TRPM8-containing nerves have a role in both the sensation and development of dry eye syndrome (see above).⁷⁶ The

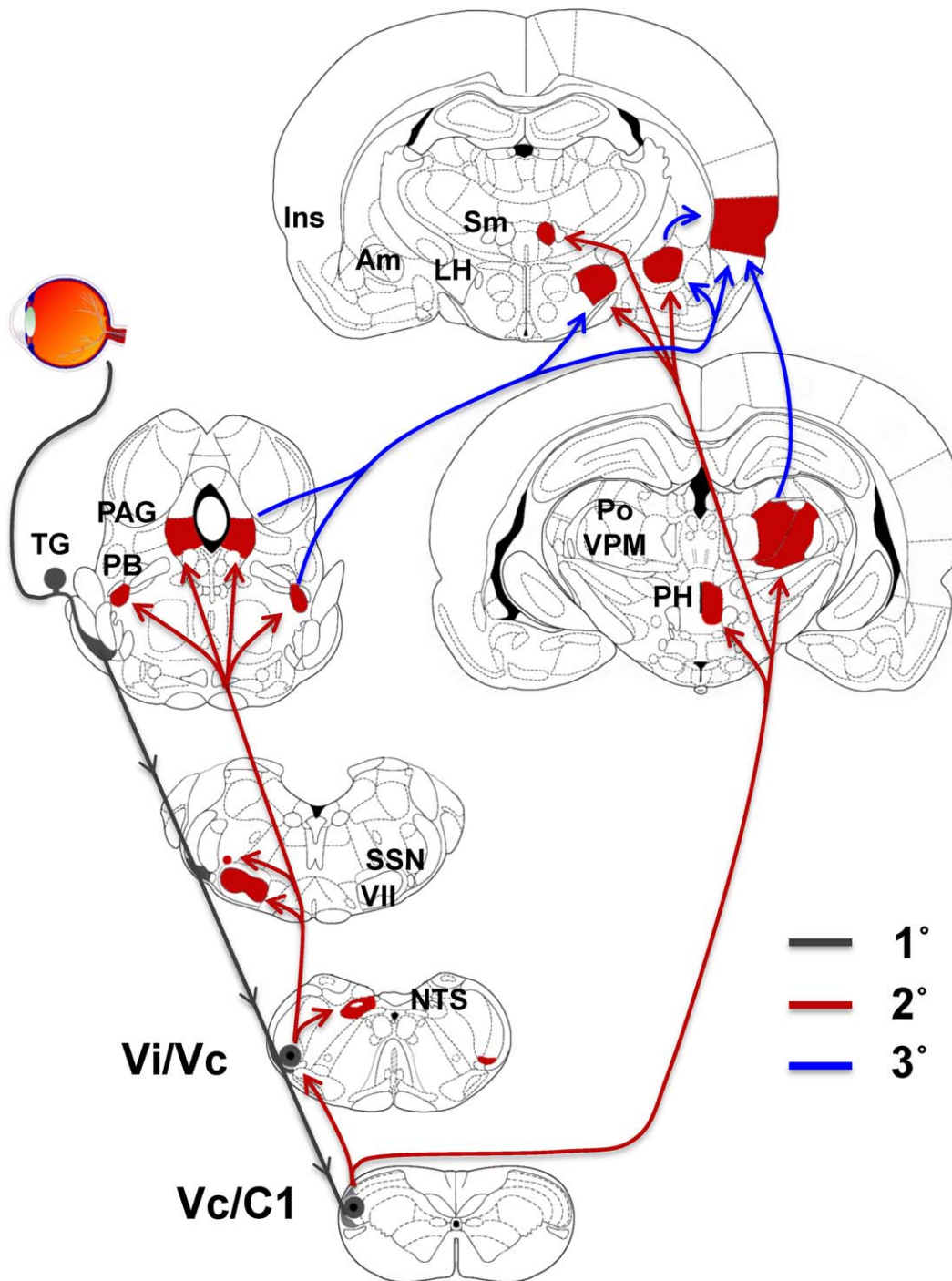


FIGURE 3. Major ascending brain pathways for trigeminal sensory fibers that supply the eye. The cell somata of sensory fibers are found within the TG and project centrally to terminate in two spatially discrete regions of the trigeminal brainstem complex, the trigeminal subnucleus interpolaris/caudalis transition region (Vi/Vc) and the caudalis/upper cervical cord junction (Vc/C1). Second-order ocular neurons in Vi/Vc and Vc/C1 project to brain regions that mediate eyeblink (facial motor nucleus, VII), lacrimation (superior salivatory nucleus, SSN), and cardiovascular reflexes (nucleus tractus solitarius, NTS). Projections to higher centers such as the periaqueductal gray (PAG), PBA (PB), lateral hypothalamus (LH), posterior hypothalamus (PH), and amygdala (Am) contribute to the affective and modulatory aspects of ocular pain, while projections to posterior thalamus (posterior nuclear group, Po; ventral posteromedial nucleus, VPM) and insular cortex (Ins) mediate sensory-discriminative aspects. Note that a small group of ocular responsive neurons also are found in the contralateral Vi/Vc. The source of input to this group is not well defined. 1°, Primary afferent fibers (*gray*); 2°, second-order projections (*red*); 3°, third-order projections (*blue*).

more profound volumes of tears needed for protection of the ocular surface in the face of noxious stimuli depend on the CNV. The on-demand production of tears in the face of noxious stimuli can serve to wash away particulate matter or dilute chemical irritants.

Neural Regulation of Tear Production. Each of the tissues involved in tear production is innervated by sensory afferent and parasympathetic and sympathetic efferent nerves. The innervation of the corneal epithelium and the sensory innervation of the conjunctival epithelium are described

above. The meibomian gland receives sensory, parasympathetic, and sympathetic innervation.¹⁷⁶ The parasympathetic innervation predominates with VIP-containing parasympathetic nerves surrounding the acini. The sympathetic nerves that contain tyrosine hydroxylase and the sensory nerves that contain CGRP and SP are more sparsely located. Parasympathetic nerves that contain acetylcholine and VIP predominate in the main and accessory lacrimal glands and surround the acini and ducts within these glands, while sympathetic nerves are present around acinar cells and blood vessels. Within the lacrimal gland, few CGRP-containing and SP-containing sensory nerves are detectable. Parasympathetic nerves containing VIP and acetylcholine, as well as sympathetic nerves containing tyrosine hydroxylase and dopamine β -hydroxylase, surround the conjunctival goblet cells,³² but the sensory nerves appear to have no direct interactions with the goblet cells.³²

Although the meibomian gland is extensively innervated, little is known about the role of nerves in stimulating lipid production. There is no published research to date on the role of nerves and their neurotransmitters in the holocrine secretion of the meibomian gland. However, immortalized human meibomian gland cells possess acetylcholine and VIP receptors, which upon activation increase intracellular calcium concentration and stimulate cell proliferation.¹⁷⁷

Parasympathetic nerves of the lacrimal gland, using their neurotransmitters acetylcholine and VIP, stimulate both protein and fluid secretion in animal models and humans. This mechanism is the primary driver of tear secretion and in particular accounts for overflow tears. Acetylcholine and VIP use different cellular mechanisms to stimulate secretion. Sympathetic nerves can alter blood flow, with vasodilation increasing electrolyte and water secretion and vasoconstriction decreasing it, or these sympathetic neurotransmitters can directly induce protein, electrolyte, and water secretion. The sympathetic regulation of lacrimal gland secretion is less pronounced than parasympathetic regulation. Adenosine triphosphatase released from both parasympathetic and sympathetic neurons, as well as by other mechanisms, can activate purinergic receptors of the P2X₇ and P2X₃ subtypes. Activation of these receptors stimulates protein secretion. In addition, P2X₇ receptors interact in a complex way with muscarinic and α_1 -adrenergic stimulation of protein secretion. Sensory neurotransmitters (CGRP and SP) do not significantly stimulate lacrimal gland secretion.

Conjunctival goblet cells utilize apocrine secretion to release granules containing the gel-forming mucin MUC5AC, electrolytes, and water from their apical surfaces. Although both parasympathetic and sympathetic nerves surround conjunctival goblet cells, evidence to date shows that only the parasympathetic neurotransmitters acetylcholine and VIP stimulate conjunctival goblet cell mucin secretion.^{178,179} Sympathetic neurotransmitter receptors are present on goblet cells, but whether sympathetic neurotransmitters stimulate mucin secretion remains to be investigated. However, ATP that can be released from sympathetic nerves, as well as by other mechanisms, can stimulate purinergic receptors of the P2Y₂ subtype. Activation of these purinergic receptors stimulates goblet cell mucin secretion. Sensory nerves do not contact conjunctival goblet cells and have not been implicated in the regulation of goblet cell secretion.¹⁷⁸

Although the mechanisms of electrolyte and water secretion by lacrimal gland, conjunctival, and corneal epithelial cells are very similar, no published experiments to date have shown whether the activation of nerves stimulates conjunctival epithelial fluid secretion. However, sympathetic and sensory neurotransmitters, as well as ATP, cause electrolyte and water secretion. Sympathetic neurotransmitters interact with β_2 -adrenergic receptors to elevate cAMP and stimulate secretion,

while ATP that can be released by sympathetic nerves and by other mechanisms activates P2Y₂ receptors to increase intracellular calcium concentration and stimulate secretion. Because of its large surface area compared with the cornea, the conjunctiva can supply the precorneal, nonoverflow tear film.

The corneal epithelium can also secrete electrolytes and water into the tear film, but its contribution to the tear volume is limited. Stimulation of β -adrenergic receptors by norepinephrine released from sympathetic nerves elevates cellular cAMP levels to cause secretion driven by chloride secretion.¹⁷⁹

OCULAR SURFACE NEUROBIOLOGY METRICS

In Vivo Confocal Microscopy of Corneal Nerves

The foundations of understanding of the architecture of corneal innervation have been established by light and electron microscopy. However, observation using these methods is limited by the rapid degeneration of corneal nerves after death (Müller and colleagues¹⁷ have shown this to occur within 13.5 hours). In vivo confocal microscopy has proven to be a useful tool in the examination of the organization of the subbasal plexus (SBP) in humans, enabling the observation of various parameters of nerve morphology, including nerve fiber density, width, tortuosity, branching, and beading frequency.

Confocal examination has enabled visualization of alterations in subbasal epithelial nerve morphology. Such changes occur in ocular¹⁸⁰⁻¹⁸² and systemic¹⁸³ disease and following refractive surgery.

Reduced nerve fiber density has been shown in both Sjögren's and non-Sjögren's dry eye, as well as increases in nerve fiber beading, branching, reflectivity, tortuosity, bead-like formation, and nerve sprouting.¹⁸⁴⁻¹⁹² However, other studies have demonstrated no difference^{188,191} or even increased nerve fiber density in patients with dry eye.¹⁸⁵ These variable results may be attributed to different stages and severity of dry eye in patients enrolled in these studies.¹⁹³ Nerve fiber density and tortuosity have been associated with corneal sensitivity,^{190,192,196} implying that nerve coverage of the cornea is important in its sensory response.

Only a few studies have examined the effects of soft contact lens wear on SBP morphology, with just one report of a reduction in nerve fiber density with silicone hydrogel lens wear of longer than 1 year.¹⁹⁷ Other investigators have not found changes in nerve fiber density, tortuosity, branching, beading, thickness, or reflectivity with hydrogel or silicone hydrogel lens wear¹⁹⁸⁻²⁰⁰ (Golebiowski B, et al. *IOVS* 2006;47:ARVO E-Abstract 86; Lum E, et al. *IOVS* 2012;53:ARVO E-Abstract 6108). However, marked alterations to the SBP have been demonstrated in a recent series of studies investigating the effects of orthokeratology (OK) lens wear²⁰¹ (Lum E, et al. *IOVS* 2012;53:ARVO E-Abstract 6108). The nerve redistribution shown in OK wear appears to reflect topographic changes resulting from the mechanical pressure applied by the reverse geometry rigid lens designed specifically for this purpose. These changes in topography are also associated with increases in threshold to sensation using the Cochet-Bonnet esthesiometer, but no evidence was presented regarding comfort of the lenses or changes in comfort.²⁰¹

The lack of effect on corneal nerve morphology observed in the wear of soft lenses suggests that these conventional lens types do not cause sufficient insult to the SBP so as to necessitate overt structural changes such as those seen in recovery from other more injurious conditions (e.g., refractive surgery or corneal or systemic disease). However, it is possible that structural alterations that do occur as a result of contact lens wear may be below the resolution of the confocal

microscope or not able to be detected with current sampling techniques. Ultrastructural alterations within nerve fiber terminals or changes to individual nerve fibers cannot currently be observed by confocal microscopy.

The changes in nerve morphology observed in dry eye^{190,192,196,202} and following LASIK²⁰³⁻²⁰⁷ have been shown to be associated with changes in sensitivity, suggesting that subbasal nerve structure may be related to neural function. However, the evidence in contact lens wear is equivocal (Table 1).

Ocular Surface Sensitivity and Sensations in Contact Lens Wear

Whereas electrophysiological data for corneal and conjunctival sensory function are available for animals, such experiments cannot be performed in living humans. Consequently, sensory information pertaining to the human ocular surface *in vivo* has been gathered by evaluating subjective responses to carefully controlled stimulation of the cornea and the conjunctiva. Specific application of mechanical, chemical, or thermal stimuli has been enabled by various esthesiometer designs. However, measurement of ocular surface sensitivity is affected by the psychophysical technique utilized,²⁰⁸ as well as the type of instrument used. Measurement of threshold of detection of mechanical, chemical, and thermal stimuli is the most common method. Some investigators have also utilized subjective grading of suprathreshold stimuli to determine the relationship between the magnitude of the stimulus presented and its perceived intensity,^{63,79,209-211} and some have made observations of the quality and attributes of the evoked sensations.^{43,63,79,212,213}

Measurement Techniques. The instrument most commonly used to measure ocular surface sensitivity, both experimentally and clinically, has been the Cochet-Bonnet esthesiometer. Due to its portability and relative ease of use, this instrument has been traditionally considered the gold standard for ocular surface sensitivity measurement. The Cochet-Bonnet esthesiometer is based on the concept by Von Frey and uses a fine nylon filament, 0.08 or 0.12 mm in diameter, which can be varied in length from 0.5 to 6.0 cm to produce different intensities of stimulus.²¹⁴ Measurements are made in length of filament (in centimeters) and converted to pressure. This instrument has a number of key limitations, however, including poor stimulus reproducibility and most critically a truncated stimulus range, meaning that it is not suitable for sensitivity measurement in up to half of healthy subjects.^{215,216}

A number of esthesiometers have been developed to overcome some of the limitations of the Cochet-Bonnet instrument; these include the electromagnetic Drager esthesiometer,³⁸ the temperature-controlled saline jet esthesiometer,²¹⁷ the carbon dioxide laser esthesiometer (Brennan NA, Maurice DM. *IOVS* 1989;30:ARVO Abstract S148), and the noncontact esthesiometer. The noncontact instruments utilize a jet of gas as the method of stimulation and include the noncontact corneal esthesiometer,²¹² the Belmonte esthesiometer,²¹⁰ and its modified version, the Cooperative Research Centre for Eye Research and Technology (CRCERT)-Belmonte esthesiometer.²¹⁸ The noncontact instruments have a greater range of stimulus intensity than the Cochet Bonnet instrument and are thus able to detect more subtle changes in corneal sensitivity. In addition, the Belmonte instruments have the capacity to stimulate the ocular surface with chemical, thermal, and mechanical stimuli and subsequently to affect all of the various nociceptor subpopulations. The CRCERT-Belmonte esthesiometer enables a more precise application of such mechanical, chemical, and cooling stimuli.²¹⁸

Recent work has demonstrated differing effects on corneal and conjunctival sensitivity with different types of esthesiometers. The newer, noncontact instruments differ markedly from the Cochet-Bonnet esthesiometer in their stimulus characteristics, and this should be taken into account when comparing findings between studies. The air jet, which is dynamic and dispersed, clearly differs from the discrete punctate stimulus of the Cochet-Bonnet filament, and its exact mode of action is to some degree uncertain. The mode of stimulation of these newer instruments is likely to be a combination of a localized reduction in ocular surface temperature in addition to deformation of the epithelial surface.^{215,216,219} The two types of instruments may therefore measure different aspects of the sensory response of the ocular surface.

Contact Lens Wear and Ocular Surface Sensitivity. A change in corneal sensitivity with contact lens wear has been widely reported,^{200,218,220-230} although the mechanism of this change is not known. Several investigators suggest that sensitivity is altered due to decreased levels of oxygen available to the cornea during lens wear, which may interfere with corneal metabolism.²²³ Others, however, have put forward a mechanical etiology.^{228,230} Another possibility is sensory adaptation of peripheral neuroreceptors (Chen J, Simpson T. *IOVS* 2008;49:ARVO E-Abstract 2562). Numerous studies have demonstrated a reduction in corneal sensitivity with polymethyl methacrylate (PMMA),^{220-222,229} rigid gas permeable (RGP),^{200,220,222,224,225} OK,^{228,231} and conventional hydrogel^{225,226} contact lenses. More recently, however, studies^{227,228,232} investigating silicone hydrogel and disposable hydrogel lens materials have not shown changes in corneal sensitivity with these lenses in short-term or long-term wear.

Corneal sensitivity changes as a result of contact lens wear have been shown to occur within a few hours of PMMA and RGP lens wear²²² and after one night's wear of OK lenses.²²⁸ In PMMA wear, the magnitude of reduction is shown to be relative to the length of wear in years,²²¹ but investigations of hydrogel lens wear have not shown such an effect.^{225,232} Recovery of sensitivity upon stopping lens wear is likewise likely to be prompt; Millodot^{233,232} reported an almost complete recovery of sensitivity within the first hour after lens removal following 8 hours of PMMA and hydrogel lens wear, although recovery following long-term PMMA wear took a number of months.²²¹ Other investigators, also using the Cochet-Bonnet esthesiometer, showed recovery of sensitivity 1 week after transfer from PMMA to RGP lens wear²²⁴ and within 4 hours of stopping long-term hydrogel lens wear.²³⁵ Interestingly, a decrease in corneal sensitivity has also been reported upon ceasing long-term extended wear of hydrogel lenses.²³²

The mechanism of sensitivity change of the ocular surface as a result of contact lens wear is not completely understood. The mechanical effect of the lens has been proposed to alter sensory function, and the availability of oxygen to the cornea may also have a role. Hypoxia was proposed as a mechanism in reduction of corneal sensitivity in older-style lens materials with no or low permeability to oxygen.²²³ However, this does not explain contact lens wear-induced sensitivity change in the conjunctiva or changes in corneal sensitivity with lens materials highly transmissible to oxygen.^{220,227,228} It is more plausible that sensory changes occur as a result of neural adaptation to the presence of the continuous stimulus of a lens^{72,211,230} or neural sensitization in response to the presence of hyperosmolarity or inflammatory mediators induced by lens wear. In addition, morphological change to corneal nerve fibers such as that seen as a consequence of corneal disease or surgery or ultrastructural changes to the terminal neurons cannot be ruled out. It is probable that reduced neural transmission resulting in decreased corneal sensitivity occurs as a combination of all or some of these factors.

TABLE 1. Nerve Morphology Changes Described During Contact Lens Wear

Source	Subjects	Control	Nerve Morphology Parameters				Association With Sensitivity	
			Density/ <i>n</i>	Tortuosity	Branching	Beading		Other
Patel et al., ²⁰⁰ 2002	Mixed CL wearers (<i>n</i> = 20)	Nonwearers (<i>n</i> = 20)	No Δ	No morphological differences	No association (COBO)
Oliveira-Soto and Efron, ¹⁹⁷ 2003	SCL wearers (<i>n</i> = 38)	Nonwearers (<i>n</i> = 14)	No Δ	No Δ	No Δ	No Δ	No Δ in thickness, orientation, reflectivity	...
Liu et al., ¹⁹⁷ 2009	SiHy wearers (<i>n</i> = 18)	Nonwearers (<i>n</i> = 6)	↓	...	No Δ	Sensitivity associated with density (COBO)
Golebiowski et al. <i>IOVS</i> 2006;47:ARVO E-Abstract 86	SiHy wearers (<i>n</i> = 27)	Hydrogel wearers (<i>n</i> = 27)	No Δ	No Δ	No Δ	...	No Δ in thickness, orientation	No association (modified Belmonte)
Dogru et al., ¹⁹⁸ 2011	2-wk SiHy wearers (<i>n</i> = 17)	Nonwearers (<i>n</i> = 17)	No Δ	No Δ in sensitivity at end (COBO)
Jalbert et al. <i>Optom Vis Sci</i> 2012;89:AAO Abstract	SCL wearers (<i>n</i> = 22)	Nonwearers (<i>n</i> = 20)	No Δ	Sensitivity associated with density (COBO)
Lum et al., ²⁰¹ 2012	OK wearer	Nonwearer	Corneal map showed marked alterations in subbasal plexus appearance
Lum et al. <i>IOVS</i> 2012;53:ARVO E-Abstract 6108	OK wearers (<i>n</i> = 16)	Nonwearers (<i>n</i> = 16)	↓ Central (OK only), no Δ midperiphery
Lum et al. <i>Optom Vis Sci</i> 2012;89:AAO Abstract	SCL wearers (<i>n</i> = 16)	Nonwearers (<i>n</i> = 18)	↓ Central, no Δ midperiphery	↓ Central sensitivity in OK wearers (COBO)

Belmonte, Belmonte esthesiometer; CL, contact lens; COBO, Cochet-Bonnet esthesiometer; SCL, soft contact lens; SiHy, silicone hydrogel contact lens; Δ, change; ↓, decreasing; ellipsis, not applicable.

Comparatively little information is available on the effects of contact lens wear on the conjunctiva. A reduction of lid margin and tarsal conjunctival sensitivity in response to PMMA, RGP, and low oxygen transmissibility soft contact lens wear has previously been noted (Abelson MB, *IOVS* 1993;34:ARVO Abstract s1006).⁵⁰ However, increased bulbar conjunctival sensitivity has also been shown with silicone hydrogel lens wear^{218,227} and in discontinued lens wearers (Tan ME, et al. *IOVS* 1997;38:ARVO Abstract S1336). Such discrepancies may be related to the different instruments used to measure sensitivity.

Neuropeptides in Tears

The key neurotransmitters involved in the transmission of ocular sensations in human cornea and conjunctiva have been identified as SP and CGRP. Substance P and probably CGRP are important in corneal wound healing. In animal models, SP released by sensory nerve fibers has been shown to stimulate corneal epithelial cell growth^{236,237} and, together with insulin-like growth factor 1, to promote corneal cell migration.^{25,238} Other metabolites of SP induce neurogenic inflammation in the cornea and conjunctiva upon exposure to pathogens, allergens, or irritants or following injury²³⁹ (see the reviews by Beuerman and Stern²⁴⁰ and by McDermott and colleagues²⁴¹). In humans, SP has been successfully used to heal the corneal epithelium in neurotrophic keratopathy.^{242,243} Less evidence exists for the role of CGRP, but it may have a role in epithelial cell renewal and wound repair,^{234,244} possibly by modulating epithelial cell differentiation.²³⁷

Neurotrophic factors derived from ocular surface epithelia such as nerve growth factor (NGF) are known to promote intraepithelial nerve growth during development but also support corneal nerve regeneration after injury. Nerve growth factor stimulates epithelial cell proliferation and differentiation in the human cornea and conjunctiva²⁴⁵⁻²⁴⁷ and may modulate ocular surface inflammation. Topical treatment with NGF has been shown to accelerate corneal healing in neurotrophic keratitis^{245,248} and recovery of corneal sensitivity after LASIK.²⁴⁹

All three neuropeptides, SP, CGRP, and NGF, have been found in normal human tears,²⁵⁰⁻²⁵⁴ and alterations in tear neuropeptides could be a useful indicator of corneal health and nerve function. To date, only a few studies have attempted to measure tear neuropeptide levels in dry eye or contact lens wear. Reduced levels of CGRP²⁵⁰ and increased NGF^{250,255} have been found in the tears of patients with dry eye, and these changes are associated with severity of dry eye signs; no difference has been shown in SP. Nerve growth factor has likewise been shown to be upregulated in contact lens wearers with dry eye, but not in lens wearers without dry eye.¹⁹⁷ Calcitonin gene-related peptide has not previously been measured in contact lens wear. A relationship between tear neuropeptide levels and ocular symptoms or ocular surface sensitivity has not as yet been elucidated in dry eye. However, higher postoperative tear NGF levels appear to be associated with improved corneal sensitivity and tear function following LASIK and PRK.²⁵⁴

Symptoms of Pain and Discomfort

In addition to more complex central and peripheral processes, it is possible that a mechanism of ocular discomfort in contact lens wear is the direct effect of contact lenses on the sensitivity response of the neural terminals in the cornea and/or conjunctiva. Changes in tear film composition of symptomatic lens wearers or dry eye sufferers could be expected to have an

effect on neuroreceptors sensitive to chemical stimuli, increased interaction between the lid and the ocular surface or the lens and the ocular surface is likely to affect mechanoreceptors in these patients, and changes in local temperature caused by inflammatory processes or the lens itself may stimulate thermoreceptive neurons.

In contact lens wear, as in dry eye, symptoms of ocular discomfort have not consistently been shown to be correlated with objectively measured clinical signs. However, due to the marginal nature of symptoms experienced, eliciting meaningful symptoms of ocular discomfort experienced by contact lens wearers has itself been fraught with difficulty. Hence, the lack of association between symptoms reported by lens wearers and clinically observed signs may in part be due to poor sensitivity of the symptomatology instruments applied.

There are few reports in the current literature exploring the relationship between ocular discomfort symptoms during contact lens wear and corneal or conjunctival sensitivity. One study has reported increased conjunctival sensitivity in symptomatic soft contact lens wearers (Tan ME, et al. *IOVS* 1997;38:ARVO Abstract S1336). Another reports a reduction in corneal sensitivity upon hydrogel lens wear discontinuation to be associated with a simultaneous reduction in the symptom of dryness (Golebiowski B, et al. *Proceedings of the Fifth International Conference on the Tear Film and Ocular Surface: Basic Science and Clinical Relevance* 2007;68). A study comparing symptomatic and asymptomatic lens wearers found higher corneal responses to suprathreshold stimuli in the symptomatic subjects, but no difference was observed between the two groups in threshold responses.²¹¹ All three studies utilized the modified Belmonte esthesiometer with an air jet at corneal temperature as the stimulus.²¹⁸ These findings in contact lens wearers are supported by studies showing a positive association between sensitivity and symptoms in patients with dry eye when this instrument is used. De Paiva and Pflugfelder²⁵⁶ and Situ and colleagues²⁵⁷ showed higher corneal sensitivity in symptomatic patients with dry eye than in healthy subjects. Tuisku and colleagues¹⁹³ likewise reported a correlation between higher sensitivity and symptoms in a group of patients with Sjögren's syndrome.¹⁹³

In contrast, previous studies²⁵⁸⁻²⁶¹ using the traditional Cochet-Bonnet esthesiometer report that sensitivity to a nylon filament stimulus is reduced with increased symptoms of dry eye and in Sjögren's syndrome. Reports using the Belmonte esthesiometer, which utilizes an air jet at room temperature as its stimulus, likewise show a negative correlation between reduced sensitivity and increased symptoms in dry eye and Sjögren's syndrome.^{196,262} Interestingly, one study²⁶³ investigating the occurrence of evening symptoms showed greater symptoms to be associated with higher sensitivity measured with the Cochet-Bonnet instrument.

These discrepancies in relation to stimulus type are of interest when viewed alongside studies examining the relationship between symptoms and sensitivity after refractive surgery. The relationship between discomfort symptoms and sensitivity in LASIK studies²⁶⁴⁻²⁶⁹ is consistently a negative one, irrespective of the instrument used. This hints further that the etiology of ocular discomfort in dry eye or contact lens wear is distinct from that which occurs as a result of nerve injury after LASIK.

It has been proposed that reduced sensitivity interferes with the blinking mechanism²⁷⁰ and with the feedback loop to the lacrimal gland²⁷¹ and results in increased tear evaporation and reduced tear secretion, leading to increased symptoms of dry eye. Conversely, it is also possible that higher symptom levels lead to reduced sensitivity; Xu and colleagues²⁵⁸ postulated that reduced sensitivity may occur due to a lessened perception of pain, which results from an adaptive response

of the corneal nerves to increased stimulation in patients with dry eye.

It must also be considered that it may be the gradient of the subjects' response to suprathreshold stimulation that is responsible for increased perception of discomfort, rather than their response at threshold. Hence, it is possible that the key to differences in symptomatology between subjects lies in their altered response to suprathreshold stimuli, and such differences warrant further exploration.

PHYSIOLOGY AND MECHANISMS OF PAIN/DISCOMFORT IN CONTACT LENS WEARERS

While different mechanisms of pain (neuropathic or inflammatory) have been well described for certain chronic conditions, the mechanisms involved in contact lens-related discomfort are not easily classified. Some mechanisms that have been proposed and to some degree researched include mechanical, chemical, dehydration (including cooling and changes to osmolality of tears), and inflammation.

Mechanical

Contact lenses interact directly with the ocular surface, including the cornea, conjunctiva, and eyelid tissues during lens wear. These tissues are highly innervated by sensory branches of the trigeminal nerve, and the touch sensitivity has been reported to be higher in the cornea, limbal conjunctiva, and lid margins compared with that of bulbar conjunctiva.^{18,37,45} With the advance in optical coherence tomography imaging techniques, studies^{272,273} have revealed high-resolution details of the contact region between the lens and the eye and lens edge fitting. A recent study²⁷⁴ has shown small but significant changes in the morphology of the limbal/scleral region with soft contact lens wear. In addition to frictional wear, the peripheral corneal topography, lid anatomical features, lens design and rigidity, and surface characteristics are also contributing factors to this mechanical related complication. Lid wiper epitheliopathy and lid-parallel conjunctival folds are two clinical signs potentially related to frictional wear in contact lens-induced dry eye.^{54,275}

Additionally, contact lens wear affects the functioning of the sensory nerves as assessed by their sensitivity, which may have an important role in contact lens-related discomfort.²³⁴ Studies have shown a reduction in corneal sensitivity to tactile^{226,234} and pneumatic²⁷⁶ stimuli after soft contact lens wear, although no associated change in symptoms was reported.^{229,232,277} It has been suggested that decrease of corneal sensitivity with contact lens wear could be due to sensory adaptation to mechanical stimulation.^{50,230} The close interaction between the lens and the ocular surface may repeatedly stimulate mechano-nociceptor and polymodal nociceptors, which may lead to neural adaptation for the purpose of efficiently encoding the dynamic range of stimuli in the sensory system²⁷⁸ and sensitization⁹ to protect the ocular surface from potential damage.

A recent study²¹¹ suggested that corneal mechanical adaptation may have a role in contact lens discomfort because a symptomatic group of contact lens wearers showed no adaptation to suprathreshold mechanical stimuli. Conversely, increased bulbar conjunctival sensitivity to pneumatic stimuli has been noted in unadapted lens wearers and adapted lens wearers refitted with silicone hydrogel lenses after a short period of no lens wear,^{218,227} suggesting that transient sensitization to mechanical stimuli may occur during lens wear. It remains unclear what role sensitization has in contact lens-related discomfort.

Although the mechanical interaction between the lens and the eye could be a stimulus to the ocular surface-induced discomfort or pain, in certain situations contact lenses could be used to temper pain by limiting possible stimulation of the exposed corneal nerve endings by movements of the lid over the cornea. For example, bandage contact lenses have been used after refractive surgery to relieve pain and promote epithelial wound healing.²⁷⁹⁻²⁸¹ In contact lens wear in the absence of overt pathology, direct mechanical stimulation of the corneal nociceptors may be partly abrogated, but a discomfort sensation may result from other stimuli to corneal nociceptors, including osmolarity or thermal changes in addition to mechanical and other effects on the conjunctiva and eyelids.

Solutions

Care systems for use with contact lenses have been associated with a range of adverse effects, including delayed hypersensitivity responses, corneal and conjunctival "toxicity," limbal stem cell damage, papillary conjunctivitis, and corneal staining.^{282,283} Discomfort from and discontinuation of lens wear may be a consequence of these chronic low-grade effects. Contemporary multipurpose solutions have reduced the frequency of certain complications of lens wear; however, discomfort seems to be reported irrespective of the preservative used, and formulation of care systems and discomfort are not consistently associated with overt signs such as corneal staining.^{284,285}

Several cross-sectional, cohort, and crossover studies²⁸⁶⁻²⁹² of varying quality have evaluated the effect of care systems on discomfort. In two large-scale studies^{286,292} that included 1500 community-based lens wearers, symptoms of dryness and discomfort were evaluated, and while the dry eye score or self-report of dry eye predicted overall lens comfort, there was no relationship in multivariable analysis between lens material or lens care system and dry eye score. Similarly, in a small cohort study²⁸⁷ of wearers, a polyhexamethylene biguanide (PHMB)-preserved care system was not associated with sensations of dryness but was associated with higher symptom reporting of grittiness and scratchiness. Corneal chemical sensitivity is increased with a PHMB-preserved care system compared with polyquaternium 1/myristamidopropyl dimethylamine (Polyquad/Aldox; Alcon Laboratories, Fort Worth, TX).²²⁷ Studies of lens comfort with multipurpose solutions have been confounded in some instances by the presence of corneal staining, which may be associated both with discomfort²⁹³ and inflammation.²⁹⁴

In contrast, a lower frequency of discomfort has been reported in individuals using multipurpose solutions containing wetting agents,²⁹⁵ although there are conflicting reports of the effect of formulation, specific preservatives, or excipients in care systems in eye lubricants or packaging solutions on comfort (see the Report of the Contact Lens Materials, Design & Care Subcommittee). Contact lenses may act as a slow-release vehicle for such adsorbed components to the ocular surface, which can influence comfort.²⁹⁶ In symptomatic subjects, there is evidence for improved comfort with changing to an alternative combination of lens and care solution.²⁹⁷ A recent study²⁹⁸ comparing the comfort of a single type of silicone hydrogel contact lens (Senofilcon A; Johnson & Johnson Vision Care, Jacksonville, FL) worn on a daily-wear schedule with multipurpose disinfecting solution containing PHMB, polyquaternium 1/myristamidopropyl dimethylamine, or hydrogen peroxide (which contained a surfactant) compared with comfort during daily disposable lens wear found that all lens care products reduced comfort relative to the daily disposable modality and that PHMB and polyquater-

nium 1/myristamidopropyl dimethylamine only increased the incidence of corneal infiltrative events and solution-induced corneal staining.

There are limited data on the effect of solutions on the neurobiology of the ocular surface; however, any discomfort response to care or packaging solutions is likely to be initially modulated by polymodal nociceptors on the ocular surface. Symptoms of grittiness and burning, perhaps analogous to those reported with certain care systems, have been reported in nonwearers in association with reduced corneal mechanical and chemical sensitivity thresholds (increased sensitivity to stimuli).²⁹⁹ However, the lack of difference in corneal mechanical sensitivity between symptomatic and asymptomatic contact lens wearers²¹¹ and between nonwearers and wearers²³⁰ would suggest that mechanical sensitivity is preserved and that this occurs despite exposure to care solutions. In short-term lens wear investigations, however, corneal and conjunctival chemical sensitivity was increased (lower threshold) with a PHMB-preserved solution, and this was associated with increased ocular surface staining.²²⁷

In summary, the effects of care solution on lens-related comfort are equivocal. Corneal mechanical sensitivity to pneumatic stimuli does not appear to be associated with comfort or changed with care system use or type. Solution use may affect chemical sensitivity of the conjunctiva, and solution effects upon the lids have not been studied to date.

Desiccation

Contact lens wear disrupts the tear lipid layer, causing increased tear evaporation and a lower tear breakup time (see the review by Rohit and colleagues³⁰⁰), supporting the Dry Eye WorkShop³⁰¹ classification of contact lens dry eye as due to evaporative causes. Increased tear evaporation from the front surface of the lens is not necessarily accompanied or followed by overt corneal damage under the contact lens; however, thin high-water content lenses do reportedly cause pervaporation from the post-contact lens tear film and subsequent corneal staining.³⁰² There is evidence also that increased tear evaporation persists following removal of the contact lens, which has been hypothesized to be due to changes to the conjunctiva,³⁰³ related either to mechanical or desiccation effects occurring at the edge of the contact lens. The effect of this chronic irritant is unclear, but it is conceivable that sensitization of conjunctival polymodal receptors may occur from this increase in sensory input.

The implications of the change in ocular surface temperature due to contact lens wear are unclear. On the one hand, the contact lens may act as an insulator, evidenced as increased ocular surface temperature by 2°C on lens removal.³⁰⁴ Conversely, an increased tear evaporation rate is likely to be the cause of cooling of the pre-contact lens tear film during wear.³⁰⁵ Given the increasing evidence for stimulation of cold-sensitive receptors and a sensation of dryness, it may be reasonable to hypothesize a link between a contact lens-induced temperature change and discomfort or dryness; however, no clear link has been demonstrated between absolute corneal temperature or temperature change and CLD.

Hyperosmolarity

Some studies,³⁰⁶⁻³¹⁰ with one exception,¹⁷⁷ have found that contact lens wear results in increased osmolarity of the tear film or soft contact lenses, although there may not be an association with increased dry eye symptoms.³¹¹ Either way, the sensory effect of tear film hyperosmolarity with contact

lens wear may be difficult to measure because the soft contact lens is likely to represent a complex stimulus for the surface neural system. A hyperosmolar tear film that does not penetrate the contact lens is likely to stimulate only conjunctival neurons, which are relatively less sensitive to chemical stimuli compared with the cornea.^{40,43,227} If hyperosmolarity penetrates the posterior surface of the contact lens when on the eye, it may result in relatively constant hyperosmolar conditions over the cornea. Thus, the contact lens could essentially act to either block or exacerbate the effects of tear film hyperosmolarity. An interesting concept is that of contact lens osmolality,³¹² which has been shown to effect comfort during lens wear.

Inflammation

Lipid Autacoid Production and AA Metabolism. Arachidonic acid is an essential polyunsaturated fatty acid of the omega-6 classification. Metabolism of AA produces a large family of eicosanoids that are proinflammatory or anti-inflammatory (see the review by Licican and Gronert³¹²). Activation of cytosolic phospholipase A2 by exogenous threats such as contact lens wear releases AA that can be metabolized by the following three families of enzymes to form lipid autacoids³¹³: cyclooxygenases (COXs), lipoxygenases (LOXs), and cytochrome p450s (CYP450s). All three enzymes are found in the cornea.³¹⁴⁻³¹⁶ Activation of COX-1 and COX-2 produces prostaglandins, including PGD₂, PGF_{2α}, PGE₂, and 15-deoxy-deltaPGJ₂. Some prostaglandins are proinflammatory (PGE₂), whereas others are anti-inflammatory (PGE₁ and PGE₃). The prostaglandins along with the other lipid autacoids discussed exert their effects through specific G protein-linked receptors that have been identified.

The LOX enzymes (5-LOX, 12-LOX, and 15-LOX) form 5(S)-hydroxyeicosatetraenoic acid (HETE), 12(S)-HETE, and 15(S)-HETE, respectively. These compounds can be further metabolized to leukotrienes (LTB₄, LTC₄, LTD₄, and LTE₄) and lipoxins (LXA₄). Leukotrienes exacerbate inflammation, whereas lipoxins resolve and terminate it. Corneas express 12/15-LOX and produce 15(S)-HETE and hence LXA₄.^{317,318}

The CYP450 enzymes produce epoxide-eicosanoids and hydroxyeicosanoids. These enzymes are ubiquitously expressed in all tissues, including the cornea.³¹⁹ In the cornea, CYP4B1 produces 12(R)-HETE, which is metabolized to 12(R)-HETRe.³²⁰ The latter compound is implicated in corneal inflammation. Platelet-activating factor (PAF) is another autacoid with proinflammatory effects in the cornea. The PAF is upregulated in the cornea following injury.³²¹

In addition to the omega-6 fatty acid AA, omega-3 fatty acids are released by cells. Two important omega-3 fatty acids are eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). During the inflammatory response, these fatty acids are metabolized to proresolution mediators that actively terminate inflammation. Activation of COX-2 produces the resolvin (Rv) RvE1 from EPA.³²² Activation of 12/15-LOX produces protectins and neuroprotectins (NPD1) from DHA.^{322,323} The NPD1 is specifically produced in nerves and aids in their regeneration.³²⁴ Further activation of 5-LOX generates RvD1 from DHA.³²⁵ Without dietary supplementation, EPA concentrations are very low. In contrast, DHA is found in all human tissues.

Unlike many anti-inflammatory agents such as corticosteroids that block resolution of inflammation, aspirin jump-starts it. Aspirin works by producing novel compounds that alter the biosynthesis of lipoxins, Rvs, and protectins to produce aspirin-triggered lipid mediators that are epimers (see the review by Serhan et al.³²⁶). In the presence of aspirin, a novel family of bioactive, proresolution mediators is produced.³²⁷

TABLE 2. Summary of the Neurophysiology of Sensations That May Be Responsible for CLD

Factors	Stimulus Modality	Transduction Channels	Sensory Neurons	CNS Second-Order Neurons	Sensations
CL-associated factors					
Fit, movement, edge	Mechanical	SA, TRPV1, TRPA1, ASICs 1, 3	Polymodal nociceptor, LT and HT mechanoreceptor	WDR, HT mechanoreceptor	Irritation, foreign body, grittiness
Drying (evaporation of tears)	Osmolarity	TRPV1-4, TRPA1, TRPC5, TRPM3, ASIC3	Polymodal nociceptor	LT mechanoreceptor	Dryness, irritation, stinging, burning
	Cooling	TRPM8, TRPA1, K2P	Cold thermoreceptor	WDR	Coolness
	Shrinking (mechanical)	SA, TRPV1, TRPA1, ASIC1-3	Polymodal nociceptor	HT mechanoreceptor	Irritation, grittiness
Eyelid over CL surface	Mechanical	SA, TRPA1, TRPV1, ASICs 1, 3	Polymodal nociceptor, LT and HT mechanoreceptor	WDR, HT mechanoreceptor	Irritation, foreign body, grittiness
Solution-associated factors	Chemical	TRPV1, TRPA1, ASICs	Polymodal nociceptor	WDR, HT mechanoreceptor	Irritation, burning
Inflammation	Chemical	TRPV1, TRPA1, ASIC3, P2X, K ⁺ TRPM8, GPCR	Polymodal nociceptor MIA Cold thermoreceptor MIA	WDR, HT mechanoreceptor WDR, HT mechanoreceptor	Irritation, burning, stinging, Coolness, cold pain, itch

CL, contact lens; GPCR, G protein-coupled receptor; HT, high threshold; K2P, two-pore potassium channels; LT, low threshold; MIA, mechanically insensitive afferent; P2X, purinergic channels; SA, stretch-activated channels; TRP, transient receptor potential; WDR, wide dynamic range.

Aspirin acetylates COX-2 and produces R-containing instead of S-containing precursors of the 17-R-hydroxy series that produces aspirin-triggered lipoxins, RvDs, and RvEs. Macrophages and neutrophils work in concert with epithelial cells to produce proinflammatory and proresolution mediators. Corneal injury induces influx of polymorphonuclear leukocytes (PMNs) into the tears and cornea.^{328,329}

AA Metabolite Production in Contact Lens Wear. Contact lens wear can increase production of several lipid autacoids. Contact lens wear in the setting of giant papillary conjunctivitis (now known as contact lens-related papillary conjunctivitis) caused an increase in tear LTC₄ in patients.³³⁰ The production of cytokines and LTB₄ was examined in tears during overnight eye closure in contact lens-wearing individuals under a variety of situations.³³¹⁻³³³ In all individuals, PMNs were increased in the tears during closed-eye conditions (overnight), during adverse events related to contact lens wear such as contact lens-associated red eye and contact lens-induced peripheral ulcer, and in nonadapted contact lens-wearing individuals compared with adapted contact lens-wearing individuals and individuals not wearing contact lenses. The increase in PMNs was found along with an increase in tear LTB₄. During adverse events, PAF was also increased. Despite these findings, there have been limited published associations between CLD and lipid mediators.

Other Inflammatory Mediators and Ocular Pain and Discomfort. Other inflammatory mediators have been shown to be present in tears, some of which are upregulated during contact lens wear (see the Report of the Subcommittee on Contact Lens Interactions With the Tear Film). Of particular interest is the upregulation of IL-6, IL-8, and TNF α during contact lens wear. It has been shown that IL-6 can be both a stimulator for nerve regeneration and a mediator of pain,^{334,335} and IL-8 and TNF α can induce hyperalgesia.^{335,336} Furthermore, the possibility of release of the potent pain mediator bradykinin³³⁵ as the result of activation of the kinin-kallikrein cascade during contact lens wear³³⁸ may also result in CLD.

Effect of Proinflammatory and Proresolution Mediators on Neuropathic Pain. There is an extensive literature demonstrating that the proinflammatory lipid mediators PGE₂ and PAF and the leukotrienes LTA₄ and LTC₄ can induce neuropathic pain and affect peripheral nociceptors such as are found on corneal sensory nerves (see the reviews by Petho and Reeh,³³⁹ Kawabata,³⁴⁰ Noguchi and Okubo,³⁴¹ and Tsuda and colleagues³⁴²). The evidence is especially strong for PGE₂.

Table 2 summarizes the underlying neurobiology of sensations that may underlie CLD. The contribution of these potential mechanisms to the sensation of discomfort may vary with the characteristics of the contact lens (material characteristics such as friction coefficient, charge, water content, and roughness and edge characteristics such as shape, thickness; care or packing solution; fitting relationship, and movement) and the ocular tissue affected.

TREATMENTS (NEUROBIOLOGICAL TARGETS)

A number of solutions have been proposed including changing the fit, design, or lubrication of contact lenses to address mechanical stimulation of the cornea, conjunctiva, and lids. Some silicone hydrogel lenses have a high coefficient of friction, which could create frictional wear^{343,344} and may stimulate surface mechanoreceptors, but the modulus of this lens type has decreased over time, so that lenses are more pliable. Reducing mechanical insult to the conjunctiva, as manifested by the development of conjunctival flaps and

increased conjunctival staining,³⁴⁴⁻³⁴⁶ may help improve comfort. The Contact Lens Materials, Design and Care Subcommittee (see this edition) reports that evidence to date suggests thin edges that minimize the transition between the conjunctiva and lens may be optimal in this regard. It is likely that future contact lens designs or rewetting drops will improve lubrication^{347,348} to minimize friction and stimulation of surface mechanoreceptors.

While the effects of care solution on lens-related comfort are equivocal in large-scale epidemiological studies, some basic principles would apply in limiting the potential for interactions between excipients or other features of the care system and polymodal nociceptors on the ocular surface. Certain combinations of lens and care systems have been associated with increased ocular symptoms,^{288,297} and switching symptomatic wearers to alternative combinations may be associated with symptomatic improvement.²⁹⁸ Avoidance of in-eye solutions or carryover of care systems with high osmolarity or low pH may reduce stinging and discomfort. Consistent with this finding, hypo-osmolar drops show some benefit in lens comfort.³⁴⁹ The use of daily disposable contact lenses avoids chronic exposure of the ocular surface to care solutions,²⁹⁹ although there is daily exposure to the effects of the packing solution, which may include exposure to hyperosmolar solutions or to wetting agents.

Desiccation or dehydration remains an unproven but plausible cause of discomfort. Increasing the stability of the pre-contact lens tear film and limiting desiccation and tear breakup at the edge of the contact lens would appear to be rational strategies. Such approaches may involve lens material changes (e.g., incorporation of wetting agents into material polymers to prolong tear breakup time³⁵⁰ and retard the tear evaporation rate³⁰⁴).

A number of pharmacological agents have been used to control neuropathic pain.³⁵¹⁻³⁵³ These agents were initially developed for the treatment of epilepsy, and the mechanism of action of these agents is thought to be the alteration of neuronal excitability.³⁵⁴ Altered excitability of corneal nerves seems to have a role in chronic corneal pain and may be a mediator of discomfort felt by contact lens wearers. Thus, agents that treat corneal neuropathic pain may have a role in treating CLD.

The γ -aminobutyric acid analogues gabapentin and penguinin have been used to limit abnormal ocular sensations, but at present only to reduce conditions that cause significant eye pain.³⁵⁵⁻³⁵⁸ While these antiepileptics may also have benefit for patients with more moderate forms of ocular discomfort, no data have yet been generated. Given that these agents are administered systemically and have significant potential adverse effects, the establishment of treatment guidelines for conditions such as CLD will need to be developed.

Nerve growth factor is a potent stimulator of axonal growth and regeneration.^{359,360} In the setting of neurotrophic keratitis, NGF has been shown to aid in the healing of persistent epithelial defects.^{248,361-370} During nerve injury, release of NGF appears to increase neuronal excitability and lower pain threshold.^{26,371} In a number of pain models, anti-NGF antibodies have been demonstrated to effectively decrease neuropathic pain in the setting of inflammation.³⁷² As described above, alterations in corneal innervation are seen in DED and possibly in contact lens wear. Whether treatment with NGF to normalize nerve architecture would be of benefit to these patients is unclear. Alternatively, in patients with significant discomfort, anti-NGF therapy could treat the symptoms. Further studies will be needed to determine whether modulation of NGF signaling at the ocular surface could be a useful tool to treat CLD.

FUTURE DIRECTIONS FOR RESEARCH

Pain/Discomfort Questionnaires

A number of questionnaires have been used to assess symptoms of dry eye and ocular discomfort among contact lens wearers.^{177,288,373-381} Most were developed from a clinical perspective, listing common symptoms of ocular irritation associated with contact lens wear. Because the symptoms are ultimately derived from stimulation of a combination of corneal, conjunctival, and eyelid margin neurons, it may be helpful to design future questionnaires that take into account the neurobiological underpinnings of the symptoms. However, designing such a questionnaire to give meaningful information about the basic stimuli causing dry eye symptoms could be fraught with complications.

One potential problem is that it can be difficult to distinguish the nature of stimuli to the ocular surface. There are three basic groups of sensations (mechanical, chemical, and thermal) detected by ocular surface neurons.⁹ However, a chemical stimulus can be interpreted as mechanical in origin, and mechanical and thermal stimuli may be confused with each other or identified as chemical. All three types can have an irritative component,^{40,43} so that it may be difficult to parse the typical symptoms of CLD into these categories.

In addition, most of the symptoms associated with contact lens dry eye, including discomfort, dryness, soreness, irritation, grittiness, and scratchiness,^{379,382} are not easily related to categories of mechanical, chemical, or thermal stimulation. These are often considered symptoms of ocular irritation and may arise from inflammation and/or chronic stimulation of surface nociceptors, resulting in hyperalgesia or alterations or damage to neurons over time.⁵⁵ Thus, future studies are needed to better understand the relationship between patient symptoms and sensations resulting from stimulation of various categories of neurons in contact lens wear.

Morphological and Functional Studies

There is likely relevance of the conjunctiva and lid margin in contact lens-related discomfort, with a relative paucity of morphological estimates of conjunctival and lid margin nerve density. This would appear to be an important area of future study whether attempted by classic histological staining methods and/or in vivo confocal microscopy.

Animal Models

Contact Lenses for Animal Models. The effective development of animal models of dry eye has been critical in our understanding of the disease, as well as the identification and testing of possible dry eye therapeutics.³⁸³ Contact lens-wearing animal models have been developed for the study of contact lens keratitis,^{384,385} cataract formation,^{386,387} and hypoxia,³⁸⁸ with specific lens parameter requirements for rat^{384,389} and mouse³⁸⁶ lenses, whereas some rabbit^{387,390} and guinea pig³⁸⁵ studies have used human lenses. Manufacture of animal lenses is challenging, and some investigations have required tarsorrhaphy to aid lens retention. For studies of corneal neurobiology and CLD, the design and fitting characteristics of the lens will be important. Given the array of transgenic mouse models, as well as the panoply of methods to assess the ocular surface in murine models, the development of suitable contact lenses will be a major benefit to the contact lens research community.

Pain Models. The assessment of ocular pain in animal models is fraught with difficulty. Existing pain models have characterized the behavioral responses in murine and rabbit

models when noxious stimuli are presented. These stimuli are often very intense and include chemical stimuli or mechanical trauma. The number of blinks in response to the stimulus or the wiping of the eye with a paw can be measured.³⁹¹⁻³⁹⁷ Responses to more modest challenges with ostensibly less intense stimuli are often difficult to reliably quantify. Additionally, most current pain models are for acute stimuli, although these may also be able to assess the effect of chronic stimuli.¹⁵⁰ Thus, most of the currently available models do not carefully examine discomfort or low-intensity pain, as would be common for contact lens wear. Moreover, the discomfort in contact lens wear is frequently chronic and develops over time.

The development of behavioral and electrophysiological measurements of more modest abnormal corneal sensations that are more chronic will be needed. Standardized and careful behavioral models using contact lenses (as described above) can allow for the elucidation of mechanisms of CLD, as well as a platform for testing treatments. Electrophysiology performed in contact lens models will help identify peripheral and central mechanisms responsible for CLD. Differences (if any) between CLD and dry eye can be examined, and treatments with potential benefit can be more rationally selected and tested.

Natural History or Chronicity of Discomfort

Discomfort in contact lens wear leading to temporary or permanent discontinuation of wear occurs over a time frame of many months or years. The limited information on disease onset and progression, as well as the lack of prospective clinical studies in contact lens wear, suggests that understanding of the basis for transition from acute to chronic ocular discomfort will require a greater emphasis on longitudinal studies at the clinical and preclinical levels.

The past decade has seen marked advances in elucidating the dynamic nature of pain and the mechanisms involved in its transition from an acute physiological and protective state to a persistent and often deleterious state (see the studies by Woolf and Salter³⁹⁸ and by Basbaum and colleagues⁶⁸). Neurons at all levels of the neuroaxis involved in pain processing are subject to positive and negative modulatory influences, from the ion channels on sensory neurons that transduce peripheral signals to synaptic plasticity by higher-order neurons at cortical levels. To better define the mechanisms for the transition from acute to chronic sensory dysfunction in DED and in CLD, several issues need to be addressed.

Greater focus should be directed at understanding the mechanisms for the most frequently reported symptoms of discomfort such as dryness, grittiness, and itch,^{382,399} as well as to extend these observations for longer times and to couple these measurements with behavioral correlates of ocular sensation in future studies. Given the importance of tear or contact lens hyperosmolarity, it will be necessary to determine the properties of putative osmoreceptive channels and to understand how chronic exposure to hyperosmolarity and inflammation influences channel activity and alters ocular sensation. Interaction between TRPV1 and NGF, for example, is likely to have a significant role in initiating and/or maintaining sensitization of peripheral and central corneal nociceptive neurons to chemical and mechanical stimuli relevant in CLD. Activation of satellite glia in sensory ganglia^{400,401} and both microglia and astrocytes in the CNS⁴⁰² are critical in the mediation of persistent pain following nerve injury; however, it is not known if glial activation has a significant role in ocular surface discomfort. Future studies should consider glial activation as a possible mediator of the transition from acute

to persistent symptoms in the development of different forms of ocular surface discomfort.

SUMMARY

The morphology of corneal nerves has been well studied, especially with the recent advent of *in vivo* techniques. However, less is known about the innervation of the conjunctival and eyelid tissues, which probably have a primary role in CLD. Current understanding of ocular surface sensation is likewise incomplete and especially so for these tissues. It is evident from the review presented above that learnings gained from research into dry eye inform much of the current knowledge of the neurobiology of CLD. This is particularly so with regard to postreceptor and central processing, which modulates ocular surface sensation and its relationship with subjectively experienced symptoms.

Aspects of the contact lens that generate CLD via neurobiological mechanisms include its physical interaction with the ocular surface, induction of hyperosmolarity, and the presence of chemical mediators in lens solutions and possibly those resulting from inflammation. Development of future treatments should target all of these facets with specifically designed contact lenses and solutions and treatments aimed at modulating peripheral and CNS response, in addition to classic and novel dry eye treatment.

The more subtle response of CLD compared with dry eye requires further development of sophisticated and sensitive measurement and analytical techniques at all stages along the discomfort pathway. These should include examination of physical and functional aspects of ocular surface nerves and neuroreceptors, changes in tear film biochemistry (e.g., assessment of concentration of neuropeptides), and development of improved questionnaires.

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The TFOS International Workshop on Contact Lens Discomfort: Report of the Contact Lens Interactions With the Ocular Surface and Adnexa Subcommittee

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See the tables in the Introduction for the members of the TFOS International Workshop on Contact Lens Discomfort.

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The report of this subcommittee concerns the impact of contact lenses (CLs) on the ocular surface, with a particular emphasis on CL discomfort (CLD). We define the ocular surface, its regional anatomy, and the physiological responses of each region to CL wear.

DEFINITION OF THE OCULAR SURFACE

The ocular surface consists of the continuous mucosal surface that begins with the cornea centrally and extends, via the limbus, to the bulbar and fornical conjunctiva to end with the tarsal conjunctiva.^{1,2} Classically, the tarsal conjunctiva is further subdivided into proximal and distal parts by the presence of a subtarsal fold,³ which runs parallel to the lid margin at approximately 2 mm from its posterior border. The distal part, termed the marginal conjunctiva, is of particular importance to lid function during blinking and extends from the fold to the mucocutaneous junction on the occlusal surface of the lid margin. That part that is apposed to the globe is the site of the so-called "lid wiper" zone of the lid, which has an important role in distributing the tear film across the ocular surface. Many aspects of the ocular surface are covered in several excellent reviews, including the functional anatomy and immunology,⁴⁻⁶ ocular allergy,^{7,8} and ocular surface reconstruction.⁹⁻¹⁵

THE TEARS AND TEAR FILM

The exposed ocular surface is at all times covered by the tear film. When the eyes are closed, the tear-filled space so formed is termed the conjunctival sac. Aqueous tears, secreted by the main and accessory lacrimal glands, enter the upper and outer parts of the sac, replenishing the tears. As the eyes open, in the upstroke of the blink, the tears exposed by the widening palpebral fissure form the preocular tear film and the tear menisci.¹⁶⁻¹⁸ The precorneal tear film is estimated to be approximately 3 μm in thickness.¹⁹

The menisci, lying at the interface between the lid margins and the surface of the globe, provide the route by which the tears reach the lacrimal puncta and canaliculi and thence enter the nasolacrimal system. In the steady state, tears lost from the exposed ocular surface by evaporation during the blink interval and those lost by tear drainage, balance that produced by tear secretion. Meibomian lipid (meibum), derived from the tarsal meibomian glands, is delivered to the lid margin skin just anterior to the mucocutaneous junction and is spread onto the surface of the tear film in the upstroke of the blink.^{20,21} The tear film lipid layer retards evaporative water loss from the eye, playing a critical role in protecting the ocular surface from desiccating stress.

Integrated Lacrimal Functional Unit

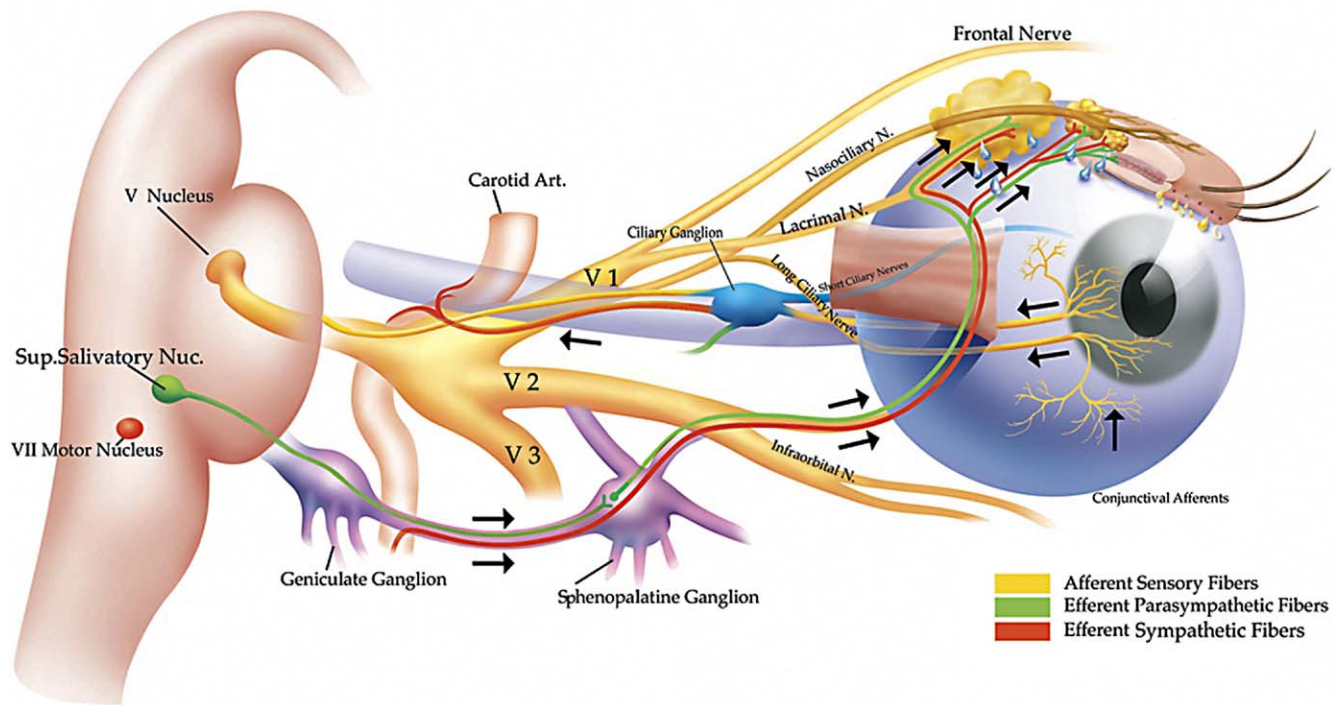


FIGURE 1. The Lacrimal Functional Unit is an integrated system comprising the lacrimal glands, ocular surface (cornea, conjunctiva, meibomian glands, goblet cells, and lids), and the sensory and motor nerves that connect them. Trigeminal sensory fibers arising from the ocular surface, particularly the cornea, run to the superior salivatory nucleus in the pons, from where efferent fibers pass, in the nervus intermedius, to the sphenopalatine ganglion. Here, postganglionic fibers arise that terminate in the lacrimal gland, nasopharynx, and vessels of the orbit. Another neural pathway controls the blink reflex, via trigeminal afferents and the somatic efferent fibers of the seventh cranial nerve. Higher centers feed into the brainstem nuclei and there is a rich sympathetic supply to the epithelia and vasculature of the glands and ocular surface.²³ Figure courtesy of Michael Stern.

OCULAR SURFACE AND THE LACRIMAL-FUNCTIONAL UNIT

The ocular surface may be thought of as an integrated functional unit,^{5,22,23} protected from environmental stress by homeostatic processes that control tear flow and tear film formation.²⁴ In addition to the cornea and conjunctiva,⁴ its component parts include the main²⁵⁻²⁷ and accessory lacrimal glands,²⁸ the meibomian glands²⁹ and mucin-producing epithelial cells and goblet cells,³⁰ the blink mechanism,³¹ and events accompanying the closed eye condition.³² Homeostasis involves, in particular, a reflex arc between the ocular surface and the brain stem,^{33,34} and in addition, immunologic,³⁵ inflammatory,³⁵ and endocrine regulation.³⁶

The ocular surface is richly innervated by trigeminal afferents and the lacrimal and meibomian glands each receive a parasympathetic and a sympathetic nerve supply. Inputs and outputs from these nerves form the basis of a reflex arc between the ocular surface, brainstem, and lacrimal glands, which adjusts tear secretion to meet daily demands. This is referred to as the *lacrimal functional unit*.^{33,34,37} The sensory innervation of the cornea is particularly rich,³⁸ while that of the lid margin mucosa is similar to that of the central cornea.³⁹ These afferents cooperate to stimulate reflex tear production and spontaneous blinking, in addition to mediating sensation. Additional inputs to the lacrimal gland from higher centers of the brain are involved in emotional tears. Sensory inputs from the nasolacrimal system may suppress tear production.⁴⁰ Figure 1 graphically portrays this integrated system.

A loss of sensory drive to the brain stem salivary or blink centers can inhibit tear secretion⁴¹⁻⁴⁴ and reduce the rate of spontaneous blinking,^{45,46} compounding the effect of desiccating stresses to the eye. Impairment of feedback by either injury or inflammatory cytokines acting on the ocular surface may be an important contributor to ocular surface inflammation in dry eye disease.^{4,33,34,47-54}

CL INTERACTIONS WITH THE OCULAR SURFACE

Contact lens discomfort must relate to the interactions between the CL and the ocular surface and alterations to its tissues during lens wear. These changes are described below on a regional basis.

IMPACT OF CLS ON THE CORNEA

Corneal Structure and Function

The cornea is the transparent, anterior, avascular part of the corneoscleral envelope, separated from the sclera by the limbus. It has a rich sensory nerve supply from the trigeminal nerve,^{55,56} details of which are discussed in the subcommittee report on the neurobiology of discomfort and pain.

The cornea is covered by a stratified squamous, nonkeratinized epithelium whose surface cells are connected by tight junctions that seal the intercellular space. These cells exhibit microvillae, which increase the surface area and facilitate interactions with the tear film. The apical membranes of these

cells express a glycocalyx composed chiefly of transmembrane mucins,³⁰ which confers wettability to the corneal surface.⁵⁷ A similar arrangement occurs in the conjunctiva. The glycocalyx, together with the tight junctions, creates a relatively impervious barrier to the passage of small, water-soluble molecules, such as the dyes used in clinical practice to stain the cornea (e.g., fluorescein and lissamine green).^{58,59} This is the basis for the very limited degree of punctate staining of the cornea and conjunctiva seen in the normal eye.

Deeper cells are highly interdigitated and connected by desmosomes. The deepest layer consists of columnar, basal cells, which are approximately 10 μm in diameter. The intercellular space, narrow in the normal epithelium, is expanded in the presence of epithelial edema and the separation of these regularly arranged cells, acting as a diffraction grating, is responsible for the “rainbows around lights” reported in the presence of early epithelial edema.⁶⁰ Specialized adhesion complexes, consisting of hemidesmosomes, anchoring fibrils, and anchoring plaques attach these cells firmly to the underlying anterior limiting layer, which is composed of fine, tightly woven collagen fibrils.⁶¹ These form a smooth, rigid base for the epithelium.

The transparent stroma is one of the most highly organized tissues of the body, composed of collagen fibrils arranged as flat lamellae, lying within a matrix of proteoglycans. The lamellae show greater interweave anteriorly, where a proportion are inserted into Bowman's layer.^{62,63} The narrow and highly uniform width and spacing of the fibrils within the lamellae is the basis of stromal transparency.⁶⁴ Peripherally, as the lamellae pass through the limbus to combine with the sclera, this order is lost and the marked variation in fibril diameter and spacing results in the opacity of the sclera. Sandwiched between the lamellae are the keratocytes, which form an interconnecting network coupled by gap junctions.^{65,66} These cells are responsible for production and maintenance of the stromal collagen and the proteoglycans, which maintain spacing between the collagen fibrils. Keratocytes, transforming to myofibroblasts, are also the source of the fibrotic response to corneal stromal injury,^{67,68} which can lead to permanent scarring.

Descemet's membrane is the basal lamina of the endothelium and forms a scaffold over which endothelial cells may spread to maintain continuity following cell loss or injury. Contiguous cells are joined by macula occludens junctions, which form a more leaky barrier than that found in the epithelium. They permit the movement of water and nutrients from the aqueous humor into the cornea. The energy-dependent activity of the corneal endothelium, driving Na^+ / K^+ -activated ion pumps, and the movement of sodium (Na^+) and bicarbonate (HCO_3^-) ions out of the cornea, leads to a steady, osmotically driven, outward movement of water into the anterior chamber.⁶⁹ This generates a negative hydrostatic pressure within the stroma, reduces its water content (corneal deturgescence), and preserves the regular order of the collagen fibrils necessary for its transparency. This negative pressure, transmitted to the intercellular spaces of the epithelium, ensures that it is normally edema-free.

When endothelial function fails and the hydrostatic pressure in the stroma becomes less negative, the stroma swells, fibril order is lost, and the cornea thickens and becomes progressively less transparent. Stromal swelling is more limited anteriorly where the lamellar interweave is greatest.^{70,71} In the presence of a normal ocular pressure, when the hydrostatic pressure becomes positive, epithelial corneal edema also occurs^{72,73} and there is a further and more marked loss of transparency, due to irregular, surface astigmatism. Epithelial, and to some extent stromal edema, may also result from breaches in the corneal epithelium.

In humans, mature corneal endothelial cells do not divide significantly and their density decreases with age,⁷⁴ and cells spread and enlarge to maintain a functional monolayer. Excessive cell loss due to injury can disturb the functional integrity of the endothelium, leading to corneal decompensation, stromal swelling, and loss of transparency.⁷⁵

The nutrition of the cornea relies almost entirely on materials supplied by the aqueous humor. The oxygen supply is provided by the tear film for the anterior cornea and from the anterior chamber for the posterior cornea. Carbon dioxide, the product of cellular metabolism, is readily lost to the atmosphere.

Epithelium

Many different effects of CL wear on the corneal epithelium have been reported. The epithelial cells of the cornea secrete a range of active soluble molecules into the tear film. This is discussed more fully in the subcommittee report on the CL interactions with the tear film.

Morphological Changes. CL wear has a number of effects on corneal morphology and ultrastructure, including epithelial thinning and increased cell size.⁷⁶⁻⁷⁸ Using specular microscopy, Mathers and colleagues⁷⁹ reported that extended wear (EW) soft contact lenses (SCL) and daily wear (DW) rigid lenses resulted in larger epithelial cells than controls, whereas the epithelial cells of DW SCL subjects were not different from controls. Similarly, other studies show that while mean cell area is not affected by DW, lenses worn on an EW modality induce a gradual increase in cell area.⁸⁰⁻⁸⁴

Epithelial cells harvested by corneal impression cytology from SCL wearers were also found to be larger than those from non-lens wearers.^{85,86} Overall, for hydrogel and silicone hydrogel (SiHy) DW lenses, effects on cell size are minor but become more obvious with EW.⁷⁷ For rigid lenses, cells increase in size by 10% to 30% during DW.⁸⁷ One hypothesis for this increase in cell size is that it is associated with slowing of epithelial renewal, such that cells are retained on the surface for a longer period of time, allowing more time for them to flatten and enlarge,⁸⁴ but other factors, such as mechanical compression, particularly with rigid lenses, may be involved.⁷⁷ Holden and colleagues⁸⁸ reported that long-term EW of SCL caused a 5.6% decrease in epithelial thickness. Several other studies have used in vivo laser scanning confocal microscopy (LSCM) to study lens effects on the epithelium. Ladage and colleagues⁸⁷ did not see an effect on epithelial thickness after 4 weeks of DW SCL, whereas an almost 10% decrease in thickness was observed with rigid lens wear. They also noted that epithelial cell surface area increased 3% to 10%, depending on lens type. Patel and colleagues⁸⁹ showed that temporal but not central epithelial thickness was reduced in corneas of long-term (>10 years) CL wearers. Corneal epithelial basal cells were found to be less regular in low oxygen transmissibility (Dk/t) lens wearers than high Dk/t and non-lens wearers, and both types of lens wear were associated with epithelial thinning, compared with non-lens wearers.⁹⁰ Yagmur and colleagues⁹¹ studied the eyes of hydrogel CL wearers (average wear duration of approximately 3.5 years) and controls. They observed that corneal epithelial cells were enlarged in eyes wearing lenses with a mean Dk/t ratio of approximately 27. They attributed this and other corneal changes, such as reduced keratocyte density, to both mechanical and hypoxic effects. A recent review by Robertson⁷⁶ summarizes epithelial thickness and size changes with various materials as a function of wear modality and the author suggests partial dependence on oxygen transmission for thinning associated with overnight hydrogel wear, but a mechanical cause for that seen with first-generation SiHy lenses.

Alonso-Caneiro and colleagues⁹² recently reported on the use of optical coherence tomography to assess the effects of 6 hours of SCL wear on morphology. Subtle, but significant, changes were observed and these were most apparent at the limbus, presumably due to greater pressure in this area. Epithelial thinning of $2.84 \pm 0.84 \mu\text{m}$ was observed for the cornea versus $5.47 \pm 1.71 \mu\text{m}$ for the limbus, with the SiHy lens causing the least surface changes.

A scanning electron microscopic study on samples of epithelium harvested prior to photorefractive keratectomy showed that there was no difference in the number of surface microvilli among CL wearers and non-lens wearers, but that epithelial mucin was reduced in the lens-wearing group.⁹³ Morphological studies in orthokeratology models have revealed an expected central epithelial thinning and peripheral thickening for myopic correction, and the reverse for hyperopic corrections.⁹⁴⁻⁹⁷ Nieto-Bona and colleagues⁹⁷ used LSCM to study epithelial morphological changes induced by 1 month use of orthokeratology lenses. Basal epithelial cell density was reduced and wing and superficial cells showed enhanced visibility. Superficial cells also were increased in height and width.

To date, no direct correlation between any of these morphological changes with CLD has been reported.

Epithelial Homeostasis. Studies have shown that the normal process of sloughing of corneal epithelial cells is impeded by CL wear. This occurs with all lens types and wear modalities and tends to recover over time, suggesting that an adaptation to lens wear occurs.^{87,98,99} Normal exfoliation is an apoptotic process driven by factors such as eyelid shear forces and centripetal pressure and involves loss of superficial cell expression of the antiapoptotic protein Bcl-2 prior to sloughing. Yamamoto and colleagues¹⁰⁰ observed a reduction in the total number of Bcl-2-negative and TUNEL- (marker for apoptosis) staining cells, suggesting that rigid lens wear blocks necessary changes in Bcl-2 expression that must occur before exfoliation is possible. Lens-induced effects on desquamation do not appear to be related to lens Dk/t.^{77,101}

More than a decade of studies indicate that lens wear inhibits basal epithelial cell proliferation in the central cornea, causes delay in vertical migration as cells move toward the surface, and reduces apoptotic desquamation of superficial cells. As normal corneal epithelial homeostasis helps maintain a smooth surface for refraction of light and barrier function, compromise to this process could contribute to ocular surface changes that lead to CLD. However, to date, no direct correlation has been demonstrated.

Barrier Function. The corneal epithelium forms a formidable barrier to the external environment and disruption of the barrier may result in edema and permit entry of microbes. Thus, compromise of the barrier by CL wear is an important issue. Although an early study by Boets and colleagues¹⁰² did not show any difference in corneal epithelial permeability in CL wear using a peroxide or biguanide care solution, hypoxia associated with lens wear has been implicated in reducing corneal barrier function.

Clinical studies using fluorometry to quantify fluorescein penetration from the tear film to the stroma, indicate that hypoxia and also tear stagnation play a significant role in reducing epithelial barrier function with various modalities of lens wear.¹⁰³⁻¹⁰⁷ However, other factors are also involved. Two studies using SiHy lenses, which eliminate concerns associated with hypoxia, confirm this. Lin and colleagues¹⁰⁸ demonstrated changes in epithelial permeability under a 30-day continuous wear modality. Notably, Asian eyes appeared to be more susceptible to permeability changes than non-Asian eyes. Duench and colleagues¹⁰⁹ demonstrated an increase in epithelial permeability with DW of a SiHy lens, which they

proposed was due to mechanical effects from the stiffer SiHy material. They were also able to show increases associated with the use of solutions. No direct link between CLD and epithelial permeability has been shown.

Corneal Erosions. CL wear has been associated with corneal erosions, in which a full-thickness detachment of epithelium in a localized, well-circumscribed area of the cornea occurs.¹¹⁰⁻¹¹² As reviewed by Markoulli and colleagues,¹¹¹ several mechanisms may be involved, including lens adhesion, mechanical damage from exacerbated thinning due to lens dehydration, bacterial proteases, and reduced epithelial density leading to reduced hemidesmosomes. Hypoxia-related decreased carbon dioxide efflux and epithelial cell acidification may contribute to altered cell appearance and metabolism during wearing of lenses with low Dk/t.^{113,114} This complication is typically symptomatic, especially following lens removal.

Corneal Staining. "Corneal staining" is a general term that refers usually, to the punctate uptake of a dye, such as fluorescein, rose Bengal, or lissamine green, into the corneal epithelium.¹¹⁵

Corneal staining is an ubiquitous feature of CL wear; however, it is important to note that it is also frequently observed in non-lens wearers.^{116,117} The frequency of corneal staining of any severity in a population of CL wearers may be as high as 60%,¹¹⁶ but often staining is of a low level and generally clinically insignificant. Brautaset and colleagues¹¹⁸ reported an incidence of 19.5% corneal staining among 338 adapted hydrogel lens wearers, with no subjects displaying staining greater than grade 2 (on a 0-4 scale).

Corneal staining can be caused by a number of factors, which can be grouped into various categories, including mechanical, inflammatory, exposure, metabolic, toxic, allergic, and infectious. Sources of mechanical staining include lens defects, poor lens quality (e.g., rough edge),¹¹⁹ lens binding (which may occur with overnight EW rigid lenses),¹²⁰ excessive lens bearing due to poor fit, foreign bodies beneath the lens, or abrasion occurring during lens insertion or removal.

In SCL wearers, exposure keratitis manifests typically as a band of inferior arcuate staining.^{121,122} This is due to epithelial disruption as a result of drying of the corneal surface¹²¹⁻¹²³ and is often associated with incomplete blinking. Desiccation staining with SCL can be categorized as a form of exposure keratitis.^{124,125} This condition appears as a central punctate stain and most often occurs when high water content lenses are made too thin, causing water to be drawn out of the cornea when the lens dehydrates.¹²⁶ The classic pattern of 3 and 9 o'clock staining in rigid lens wearers is also primarily thought to represent a form of exposure keratitis, whereby the eyelids are bridged away from the corneal surface at the lens edge at the 3 and 9 o'clock corneal locations.¹²⁷

All CLs are known to induce various levels of epithelial hypoxia and hypercapnia,¹²⁸ resulting in the production of various metabolites (e.g., lactic and carbonic acid). Evidence that such changes can adversely affect comfort is lacking.

In a case-control study of 413 CL wearers, Nichols and Sinnott¹²⁹ examined a variety of lens- and subject-related factors, to determine their potential association with sodium fluorescein corneal staining. Several factors were shown to be related to increased corneal staining, including increased daily wearing times ($P = 0.0006$), lower income ($P = 0.0008$), lissamine green conjunctival staining ($P = 0.002$), CL deposition ($P = 0.007$), increased tear meniscus height ($P = 0.007$), and decreased hydrogel nominal water content ($P = 0.02$). The wearing of SiHy lenses (as opposed to hydrogel lenses) was protective against corneal staining ($P = 0.0004$). Notably, these

authors reported that neither CL care solutions nor disinfectants were associated with increased corneal staining.

Relatively little information is available relating corneal staining to discomfort. A paradox of the corneal staining response is that there appears to be no clear relationship between the severity of staining and the degree of ocular discomfort. For example, an exposure keratitis in the form of an extensive inferior arcuate diffuse staining pattern can be virtually asymptomatic, whereas a small tracking stain caused by a foreign body trapped beneath a rigid lens can be excruciatingly painful.

Studies examining various corneal staining associated with the combination of different CL materials and solutions have produced equivocal results, with some studies showing no correlation between CLD and staining¹³⁰⁻¹³² and others indicating that increased staining is associated with a reduction in lens comfort.¹³³⁻¹³⁵ A recent study, comparing dryness and corneal staining in a group of Asian and non-Asian wearers,¹³⁶ demonstrated that the Asian subjects exhibited a greater amount of staining and reported a higher level of CLD. Among Asians, CLD and staining were not related, whereas they were among non-Asians.

Despite many publications examining corneal staining associated with CL wear, overall, there appears to be, at best, a weak link between CLD and corneal staining and it is not a major factor for most CL wearers.

Stroma

Keratocyte Density. Using LSCM, various authors have reported the normal keratocyte density in the anterior stroma to be approximately 993 cells/mm², or 29,917 cells/mm³, decreasing toward the posterior stroma to approximately 621 cells/mm², or 18,733 cells/mm³, an approximate 60% decrease in cells per area or volume.¹³⁷ Also, keratocytes in the posterior stroma are less densely packed and overall their nuclei appear to be slightly larger and flatter than those in the anterior stroma.¹³⁷ Keratocyte density does not differ between males and females or between right and left eyes of a subject.¹³⁸ There is a decline in the density of keratocytes throughout the stroma with age,^{138,139} as well as an increase in the spacing of collagen fibers throughout life (by approximately 14% by age 90 years).¹⁴⁰ The stroma also contains nerve fibers and microdots, which are small highly reflective dots found throughout this tissue layer. The composition of these microdots is unknown, but it has been hypothesized that they represent dysgenic or apoptotic cellular remnants lying dormant in the stroma.¹³⁷

CL wear has an effect on keratocytes. Several studies have demonstrated an apparent loss of keratocyte density of approximately 18% to 30% in the anterior stroma and 7% to 18% in the posterior stroma, when wearing various lens types on either DW or EW schedules.^{91,141-143} The decrease in density was maintained when accounting for possible edema.¹⁴¹ However, not all studies have found this decrease.^{89,144} When a reduction has been noted, the density change was not affected by the Dk/t of the lens material.^{141,145} In a study examining the differences between no lens wear, SiHy lens wear, and high Dk/t rigid lens wear, Kallinikos and colleagues¹⁴⁶ found some reduction in keratocyte density in the anterior stroma with rigid lens wear, and in the posterior stroma with SiHy lenses compared with no lens wear.¹⁴⁶ These authors suggested that this was due to the physical presence of the lens and perhaps mechanical stimulation of the release of epidermal growth factor and IL-8 from corneal epithelial cells. Loss of keratocytes may be more profound for SCL wearers compared with rigid gas permeable wearers.¹⁴⁵ No reports

have studied whether any change in keratocyte density is related to CLD.

Stromal Opacities. Apparently benign posterior stromal opacities or white dots have been reported in the corneas of CL wearers.^{137,147-150} These stromal opacities seen using slit lamp biomicroscopy may be related to the stromal microdots seen using LSCM. The microdots have a size of 1 to 4 μm .^{151,152} The initial contention that the appearance of the microdots was associated only with CL wear has been tempered by the finding that these can also be seen in the corneas of non-lens wearers, albeit to a lesser extent.¹³⁷ The pathology and etiology of these formations is unknown. Although Brooks and colleagues¹⁴⁸ and Hsu and colleagues¹⁵³ noted that the development of deep stromal opacities was associated with ocular discomfort and photophobia, none of the other reports of deep stromal opacification or stromal microdots have reported any associated discomfort.

Stromal Infiltrates. CL wear may result in recruitment of cells into the cornea. These cells or "infiltrates" are presumed to be polymorphonuclear leukocytes (neutrophils) from the limbal vasculature, and this has been confirmed from corneal biopsies of CL wearers, with the adverse event named CL peripheral ulcer.¹⁵⁴ While a review of adverse events with CL wear is beyond the scope of this article, infiltrates of the cornea can occur without symptoms and may occur even in the absence of lens wear.¹⁵⁵ The rate of asymptomatic infiltrates in the cornea of CL wearers appears to be influenced by wearing different combinations of SiHy lenses and multipurpose disinfecting solutions,¹⁵⁶ although these results are equivocal.¹⁵⁷

While infiltration of the cornea during overt adverse responses is associated with ocular symptoms, they may also be present in asymptomatic patients, indicating that there is not a straightforward relationship between low levels of corneal infiltration and comfort during CL wear.

Stromal Neovascularization. Wear of low Dk/t CLs may be associated with the ingrowth of blood vessels into the normally transparent cornea.¹⁵⁸ This process of neovascularization is generally categorized as superficial or deep stromal. CL-induced neovascularization is asymptomatic and thus not related to CLD.

Endothelium

Endothelial Blebs. A phenomenon referred to as "endothelial blebs" can be observed in the endothelium of CL wearers.¹⁵⁹ The appearance is of black, nonreflecting areas in the endothelial mosaic that correspond with the position of individual cells or groups of cells. Inagaki and colleagues¹⁶⁰ compared the time course of endothelial bleb formation and disappearance between lenses of varying Dk/t in 20 subjects. Lenses of higher Dk/t induced the lowest bleb response and no difference was observed between rigid and soft lenses of similar Dk/t values.

Histological studies of this response were conducted by Vannas and colleagues.¹⁶¹ The "blebbed" endothelium displayed edema of the nuclear area of cells, intracellular fluid vacuoles, and fluid spaces between cells. Thus, endothelial blebs appear to be the result of a local edema phenomenon, whereby the posterior surface of the endothelial cell bulges toward the aqueous. The endothelial cell bulges in this direction because this represents the path of least resistance, as Descemet's membrane provides much greater resistance to cell swelling than the aqueous humor. Light from the blebbed cell is reflected away from the observer, which explains why they appear dark or absent.

The etiology of endothelial blebs has been explained by Holden and colleagues.¹⁶² These authors attempted to induce

blebs using a variety of stimulus conditions, and concluded that one physiological factor common to all successful attempts to form blebs was a local acidic pH change at the endothelium. Two separate factors induce an acidic shift in the cornea during CL wear¹²⁸: an increase in carbonic acid due to retardation of carbon dioxide efflux and increased levels of lactic acid as a result of lens-induced hypoxia and the consequent increase in anaerobic metabolism. When silicone elastomer lenses are worn, such metabolic changes do not take place because of their extremely high Dk/t. The time course of the appearance of blebs following lens insertion, and resolution following lens removal, is consistent with the time course of corneal pH change.¹⁶³

Endothelial Cell Density. Numerous studies have demonstrated a decrease in corneal endothelial cell density in the central corneas of rigid¹⁶⁴⁻¹⁶⁷ and soft^{166,168-170} lens wearers. One possible explanation for the apparent CL-induced endothelial cell loss has been provided by Wiffen and colleagues,¹⁷¹ who compared central and peripheral corneal endothelial cell densities in non-lens wearing subjects and long-term CL wearers. Central cell density (2723 ± 366 cells/mm²) was found to be significantly higher than peripheral cell density (2646 ± 394 cells/mm²) for the non-lens wearing group, but not for the CL-wearing group (2855 ± 428 cells/mm² central; 2844 ± 494 cells/mm² peripheral). Based on their results, Wiffen and colleagues¹⁷¹ suggested that CL wear causes a mild redistribution of endothelial cells from the central to the peripheral cornea. Thus, while there is no actual endothelial cell loss, there is a reduction in endothelial cell density in the central region of the cornea, which is counterbalanced by a commensurate increase in cell density in the corneal mid-periphery. The overall endothelial cell population of the cornea is therefore likely to be unaffected by CL wear and no reports exist of a correlation in cell density with CLD.

Endothelial Polymegethism. Polymegethism describes changes in endothelial cell size that occur such that the endothelial cells have a greater variation in cell size than normal, and is closely related to chronic hypoxia.^{172,173} Increases in corneal endothelial polymegethism are associated with the wear of polymethyl methacrylate (PMMA),^{144,164-167,174-178} rigid gas permeable,^{144,171,179,180} and conventional hydrogel^{188,166,169,171,177,178,181-185} lenses. However, SiHy^{168,186} and silicone elastomer¹⁸⁷ lenses do not induce significant levels of polymegethism. It is likely that the etiology of endothelial polymegethism is the same as that for endothelial blebs, in which lens-induced hypoxia and hypercapnia causes an acidic shift at the endothelium,¹⁶² resulting in altered cell morphology. Thus, endothelial polymegethism represents a chronic response and endothelial blebs represent an acute response to the same stimuli.

The morphological changes that constitute polymegethism have been explained by Bergmanson,¹⁸⁸ who conducted an ultrastructural study of the corneas of six long-term CL wearers. In normal circumstances, the lateral cell walls are extremely interdigitated. Bergmanson¹⁸⁸ noted that CL wear causes the cell walls to reorient so that, rather than remaining normal to the endothelial surface, they straighten out and align obliquely. The interpretation of this observation in terms of the three-dimensional structure of the endothelium is that endothelial cells have changed shape but the volume of each cell remains constant. By observing only the apical surface of the endothelium on specular reflection, it appears that a disparity in cell size has developed, whereas, in reality, the cells have merely become reoriented in three-dimensional space.

A further observation of Bergmanson¹⁸⁸ is that, although the endothelium of CL wearers showed some inter- and intracellular edema, the cells were otherwise of a healthy

appearance, containing normal organelles. This raises the possibility that, rather than representing an adverse effect, endothelial polymegethism is a nonproblematic adaptation to chronic metabolic stress induced by CLs.

Sweeney¹⁷⁷ has drawn an anecdotal association between endothelial polymegethism and a condition that she termed "corneal exhaustion syndrome." This is a condition in which patients who have worn hydrogel CLs for many years suddenly develop a severe intolerance to lens wear, characterized by CLD, reduced vision, photophobia, and an excessive edema response. These patients also displayed a distorted endothelial mosaic and moderate to severe polymegethism. Although the link between endothelial polymegethism and corneal exhaustion syndrome is not proven, it does appear that certain wearers can develop an intolerance of lenses over time as a response to chronic and severe lens-induced hypoxia. However, this is unlikely with modern CL materials and the link between hypoxia and CLD remains tenuous.

Endothelial Permeability. There is disagreement in the literature as to whether CL wear alters endothelial permeability. Dutt and colleagues¹⁸⁹ reported a significant increase in mean endothelial permeability, measured using corneal fluorophotometry, among CL wearers, indicating a defect in their endothelial barrier function. A significant increase in the mean endothelial pump rate was also noted among CL wearers. Using similar techniques, Chang and colleagues¹⁸⁴ reported decreased endothelial permeability among CL wearers. In contrast, Bourne¹⁹⁰ reported that the relative endothelial pump rate of 20 long-term CL wearers did not differ significantly from that of control subjects.

Despite these many alterations to the endothelium, to date there have been no reports of CLD associated with nonsevere endothelial cell changes.

Limbus

Limbal Structure. The limbus is a ring of tissue approximately 1.5 mm wide that marks the transition between the clear cornea and the sclera.¹⁹¹ The epithelium thickens on passing from the cornea to limbus and the number of cell layers increases to approximately 10^{192,193} and become arranged into a parallel series of radially disposed bars, separated by a vascular connective tissue.¹⁹⁴ These are the palisades of Vogt.¹⁹⁵ Visibility of the palisades at the slit-lamp is greatly enhanced in pigmented eyes, where the epithelial bars are outlined by pigmented basal cells. The vessels of the palisades arise from an episcleral vascular "circle," which also gives rise to the anterior conjunctival arteries and to the subepithelial marginal arcades of the cornea.^{196,197} The latter vessels form a series of vascular loops that surround the corneal periphery, their central tips providing a useful surface landmark for the periphery of Bowman's layer. They can be the source of superficial new vessels, arising as a pathological response to CL wear or to corneal injury, inflammation, or infection.

Basal, niche-like regions of the epithelial palisades house the stem cells of the cornea, whose division maintains the corneal epithelium.^{198,199} These cells divide infrequently in the normal cornea but give rise to daughter, transient amplifying cells,²⁰⁰ which migrate centripetally from the limbus to the cornea. Their further progeny migrate to the surface and undergo apoptosis prior to shedding.

Limbal Redness. The limbus can respond to CL wear by engorging the limbal vasculature, which is usually referred to as "limbal redness." During wear of low Dk/t SCL, the number of vessels filled with blood and the extent of filling increases, but this does not happen during wear of PMMA lenses,²⁰¹ suggesting that the response is local and not affected by hypoxia occurring at the central cornea. Papas²⁰² demonstrat-

ed that when eyes were exposed to anoxic conditions (100% nitrogen in goggles), the limbal vasculature responded by increasing blood flow, resulting in increased redness. Sustained increases in limbal redness during wear of low Dk/t lenses may lead to growth of limbal vessels into the cornea, which is considered to be an adverse response to lens wear. Wear of low Dk/t soft lenses for 9 months on an EW schedule results in a significant increase in neovascularization.²⁰³

With the advent of SiHy lenses, the number of studies examining limbal redness increased, with studies demonstrating no difference in limbal redness during wear of high Dk/t SiHy lenses compared with no lens wear.²⁰⁴ Use of low Dk/t soft lenses on a daily disposable basis resulted in higher levels of limbal redness than that determined when wearing two types of high Dk/t silicone hydrogel lenses.²⁰⁵ During EW, low Dk/t hydrogel lens wearers showed significantly higher levels of limbal redness than high Dk/t SiHy lens wearers.²⁰³ Refitting subjects from low Dk/t hydrogel lenses to high Dk/t SiHy lenses in either DW or EW schedules results in a significant decrease in limbal redness after just a few weeks.²⁰⁶⁻²⁰⁹ Refitting subjects with high Dk/t lenses also results in reduced signs of corneal neovascularization.²¹⁰⁻²¹² High Dk/t lenses do not induce changes to limbal redness even after 3 years of EW.²¹³

There is little evidence that limbal redness is related to CLD. While one study showed an improvement in comfort during lens wear after refitting with high Dk/t SiHy lenses and a corresponding decrease in limbal redness,²¹² another study demonstrated a similar improvement in comfort (but not limbal redness) even after refitting high Dk/t lens wearers into low Dk/t daily disposable hydrogel lenses.²¹⁴ The type of SiHy lens worn makes a difference to comfort, even though there may be no difference in clinical scores of limbal redness,²¹⁵ and while wearing a low Dk/t lens on a daily disposable basis resulted in increased limbal redness compared with wearing high Dk/t lenses on the same schedule, there was no relationship to comfort,²⁰⁵ suggesting that factors other than oxygen permeability (and, thus, limbal redness) are more important in the factors that drive the comfort response.

Limbal Stem Cell Deficiency. Limbal stem cells serve as the source for corneal epithelial cells, thus stem cell deficiency leads to an abnormal corneal surface, which exhibits fluorescein staining and a dull irregular reflex, often accompanied by decreased vision.²¹⁶ Other complications include photophobia, inflammation, hyperemia, recurrent or persistent epithelial defects, conjunctivalization, scarring, and ulceration.²¹⁶ Several studies show that SCL wear may result in stem cell deficiency.²¹⁶⁻²²⁹ The condition may be focal, affecting a small area, or, more rarely, occur as a severe, almost total stem cell loss.^{216,229} It has been suggested that the more severe form is the result of additional pathology to a cell population already stressed by years of lens wear that finally “exhausts” the stem cells.²²⁹ The true cause of the stem cell deficiency remains unknown, but it has been proposed that it may result from hypoxia and/or mechanical friction on the limbal tissue.^{216,220,228}

In a retrospective study of almost 600 SCL wearers, 2.4% of subjects were found to have focal limbal stem cell deficiency,²²¹ with approximately one-third being symptomatic, suggesting that the condition is more common than one would expect and often goes undetected.²¹⁶ Notably, the preponderance of subjects were female.^{216,221,229} Prolonged wear (both hours per day and numbers of years of wear) may also be a contributing factor.^{216,229} At least two studies show that the epitheliopathy resulting from this deficiency was primarily present in the superior cornea.^{216,221} Rigid gas permeable and scleral lenses do not cause limbal stem cell deficiency; indeed, these lenses have been reported as having beneficial effects in the management of corneal conjunctivalization and in the

reversal of stem cell deficiency.^{230,231} As yet there is no evidence for changes in limbal stem cells being related to CLD, and it seems unlikely that this could account for the acute form of CLD that occurs toward the end of the day, after as little as 1 day of wear in a neophyte wearer.

Corneal Edema

All CLs induce some level of edema, including silicone elastomer lenses, which have extremely high Dk/t values.²³² CLs restrict corneal oxygen availability,^{128,233,234} creating a hypoxic environment at the anterior corneal surface. To conserve energy, the corneal epithelium begins to respire anaerobically. Lactate, a by-product of anaerobic metabolism, increases in concentration and moves posteriorly into the corneal stroma. This creates an osmotic load that is balanced by an increased movement of water into the stroma. The sudden influx of water cannot be matched by the removal of water from the stroma by the endothelial pump, resulting in corneal edema and corneal thickening.^{235,236} A number of other possible mechanisms have been suggested as playing a role in lens-induced corneal edema, including retardation of carbon dioxide efflux (leading to tissue acidosis),¹²⁸ mechanical effects,²³⁷ temperature changes,²³⁸ hypotonicity,²³⁹ and inflammation.²⁴⁰ Nguyen and colleagues²⁴¹ have shown that the variability in CL-induced corneal swelling is associated with both corneal metabolic activity and endothelial function. This suggests that individuals with larger levels of corneal metabolic activity produce more lactic acid and thus more swelling.

The amount of edema is related primarily to the extent of corneal hypoxia that is induced by the lens. With low Dk/t hydrogel and rigid lenses, daytime central corneal edema typically varies between 1% and 6%,²⁴² and the level of overnight central edema measured on awakening generally falls in the range 10% to 15%.²⁴³ SiHy lenses induce less than 3% overnight central corneal edema,²⁴⁴ which is similar to the level of overnight edema without lenses.

While corneal swelling represents both a chronic and acute response to hypoxia, epithelial microcysts are considered to be an important indicator of chronic metabolic stress in the corneal epithelium in response to wearing low Dk/t lenses. Bergmanson²⁴⁵ postulated that microcysts represent an extracellular accumulation of broken down cellular material trapped in the basal epithelial layers. In a process similar to that which occurs in Cogan's microcystic dystrophy,²⁴⁶ the epithelial basement membrane reduplicates and folds, forming intraepithelial sheets that eventually detach from the basement membrane and encapsulate the cellular debris. There is no proven association of epithelial microcysts with CLD.

Dillehay²⁴⁷ argued that increasing levels of available oxygen during CL wear lead to improved comfort. However, these arguments were based largely on anecdotal information. No concrete evidence exists linking oxygen availability or the level of corneal edema during CL wear with CLD, and a recent review supports this.²⁴⁸

Shape Changes

Videokeratographic corneal mapping techniques reveal that all forms of CL wear are capable of inducing small, but statistically significant, changes in corneal topography.²⁴⁹⁻²⁵² Ruiz-Montenegro and colleagues²⁴⁹ reported the prevalence of abnormalities in corneal shape to be 8% in a control group of non-CL wearers, versus 75% in PMMA lens wearers, 57% in DW rigid lens wearers, 31% in DW hydrogel lens wearers, and 23% in EW hydrogel lens wearers.

The results of studies investigating corneal shape changes with SiHy lenses are equivocal. Various authors failed to observe

corneal curvature changes in subjects wearing low-²⁵³⁻²⁵⁵ and high-modulus^{253,254} SiHy lenses, during observation periods ranging from 1 to 18 months. However, Dumbleton and colleagues²⁵⁶ observed a small degree of central corneal flattening in both major meridians of 0.35 diopters (D) in subjects wearing high-modulus SiHy lenses over a 9-month period. Gonzalez-Mejome and colleagues²⁵⁰ noted a similar phenomenon in SiHy lens wearers over a 12-month wearing period. Maldonado-Codina and colleagues²⁵⁷ noted that, over a 12-month period of continuous wear, corneal curvature of subjects wearing high-Dk/t rigid lenses became flatter by 0.13 mm, compared with 0.04 mm for subjects wearing high-Dk/t SiHy lenses ($P = 0.0003$). The refractive findings in subjects wearing these lenses mirrored the corneal curvature changes.

Shape changes may also be induced by lens “binding,” in which the lens becomes immobile, which may occur with DW and EW of rigid lenses. Based on subject reports, lens binding occurs in 29% of DW²⁵⁸ and 50% of EW²⁵⁹ rigid lens subjects. Most other forms of lens-induced corneal shape change are either rare or are known to be associated with specific types of poorly designed or ill-fitting lenses.²⁶⁰

Corneal curvature changes in orthokeratology are deliberately induced to obtain a refractive effect, and appear to result from a combination of short-term corneal molding and a longer-term redistribution of anterior corneal tissue.^{261,262} It has also been suggested that the tear reservoir generated by the steeper secondary curves leads to pressure changes that are responsible for the corneal tissue redistribution.^{262,263}

To date, there are no reports linking CL-induced corneal shape change to CLD.

Temperature Change

Purslow and colleagues²⁶⁴ used a noncontact infrared camera to record the ocular surface temperature (OST) in subjects wearing hydrogel and SiHy CLs on a DW and EW basis. They found that OST immediately following CL wear was significantly greater compared to non-lens wearers ($37.1 \pm 1.7^\circ\text{C}$ vs. $35.0 \pm 1.1^\circ\text{C}$; $P < 0.005$). Lens surface temperature was highly correlated to, but lower than, OST (by $-0.62 \pm 0.3^\circ\text{C}$). There was no difference with modality of wear, but significant differences were found between the hydrogel and SiHy lens materials ($35.3 \pm 1.1^\circ\text{C}$ vs. $37.5 \pm 1.5^\circ\text{C}$; $P < 0.0005$). The authors concluded that OST is greater with hydrogel and greater still with SiHy CLs in situ, regardless of modality of wear, and concluded that the effect is likely due to the thermal transmission properties of the CL material.

Whereas Purslow and colleagues²⁶⁴ assessed OST immediately following CL wear, Ooi and colleagues²⁶⁵ developed a two-dimensional simulation of heat propagation in the human eye using finite element analysis to estimate OST during CL wear. In contrast to Purslow and colleagues,²⁶⁴ they calculated that the corneal surface temperature during CL wear decreased by an average of $0.52 \pm 0.05^\circ\text{C}$ compared with a bare cornea, for all lens types. The authors suggested that an increase in evaporation rate when a CL is worn increases the cooling effect on the ocular surface, resulting in a lower corneal surface temperature during lens wear. Neither of the above groups who examined OST changes with CL wear examined any link to CLD.

IMPACT OF CLS ON THE CONJUNCTIVA

Bulbar Conjunctiva

Conjunctival Staining. Dyes that have been used to assess conjunctival staining include sodium fluorescein, rose Bengal, and lissamine green. In SCL wearers, conjunctival staining is

often observed approximately 2 mm from the limbus, coinciding with the SCL edge.²⁶⁶ This is thought to be due to CL movement or changes in tear film characteristics at the lens edge.²⁶⁷

Several studies have shown greater conjunctival staining with CL wear compared with no CL wear. Lakkis and colleagues²⁶⁸ showed a significantly higher level of conjunctival staining in hydrogel wear compared to non-lens wearers, and found this to correlate with dryness and itchiness. Maldonado-Codina and colleagues²⁶⁷ showed greater conjunctival staining with two SiHy lenses compared with no lens wear or hydrogel lens wear. In a retrospective analysis of 338 experienced lens wearers, Brautaset¹¹⁸ found conjunctival staining in one-third of subjects. Morgan and colleagues²⁶⁹ found significantly greater conjunctival staining in a group of 35 neophytes fitted with SiHy daily disposable lenses compared with non-lens wearers, and this was the only clinical parameter measured to change significantly with lens wear. Guillon and Maissa²⁷⁰ assessed conjunctival staining and comfort in CL wearers using lissamine green. They found greater conjunctival staining in symptomatic subjects both with and without lens wear. These authors suggest that the pattern of staining indicates that the CL causes changes to the conjunctiva in areas not only confined to the lens edge, which they attributed to evaporation due to destabilization of the tear film by the CL.²⁷⁰

Various hypotheses have been postulated regarding CL-induced conjunctival staining, including changes to lens parameters with lens wear (Meadows DL, et al. *IOVS* 2009;50:ARVO E-Abstract 5652), CL modulus (Meadows DL, et al. *IOVS* 2009;50:ARVO E-Abstract 5652), poor lens fit (Meadows DL, et al. *IOVS* 2009;50:ARVO E-Abstract 5652),²⁷¹ or poor edge design.²⁶⁶ Meadows and colleagues (Meadows DL, et al. *IOVS* 2009;50:ARVO E-Abstract 5652) found that changing the lens material and fit impacted the level of conjunctival staining, whereas changing solution did not make a difference. Ozkan and colleagues²⁷² correlated changes to lens parameters with conjunctival staining. They showed a decrease in diameter with lens wear and increasing temperature, both in vivo and ex vivo, which did not correlate with comfort or conjunctival staining.²⁷² They were able to show that lenses with a “knife” or “chisel” edge-form caused more staining than a lens with a relatively “round” edge design. However, no significant difference in comfort was found between edge types after 1 week of wear and there was no correlation between conjunctival staining and comfort, or conjunctival staining and bulbar or limbal redness.²⁷² This is in agreement with Maissa and colleagues,²⁶⁶ who showed that conjunctival staining is most severe nasally and least severe superiorly, a factor they attribute to the flatter conjunctival topography in the nasal quadrant.

In rigid CL wearers, 3 and 9 o'clock corneal staining is visualized with the instillation of fluorescein, and is often accompanied by bulbar and limbal hyperemia and conjunctival staining. Greater inferior conjunctival staining in rigid CL wearers has been reported in a retrospective study by Swarbrick and Holden.¹²⁰ Van der Worp and colleagues²⁷³ showed that eyes with conjunctival staining demonstrated more corneal staining, compared with those with no conjunctival staining. Symptoms were more frequently reported in those with conjunctival staining, compared with those without.²⁷³

Conjunctival Flaps. The incorporation of silicone components into SCL materials, which increases the lens Dk/t, results in materials with higher modulus values.²⁷⁴ As a result, mechanical complications with SiHy materials are greater than those encountered with lower modulus hydrogel materials.^{110,112,275} One of these complications has been termed “conjunctival flaps.”^{112,276-280} These have been described as

“irregular free ends of the conjunctival tissue which move with blinking or other digital manipulation.”²⁷⁸

Conjunctival flaps are typically found 1.5 mm from the limbus in CL wearers and have been reported to resolve with lens discontinuation (Markoulli M, et al. *IOVS* 2007;43:ARVO E-Abstract 5391). Graham and colleagues²⁷⁹ found a 39% occurrence of conjunctival flaps in EW with SiHy lenses, whereas Santodomingo and colleagues²⁸⁰ reported a higher incidence with lotrafilcon A compared with balafilcon A and more events when lenses were worn overnight. Bergmanson and colleagues²⁷⁷ performed conjunctival impression cytology (CIC) on three non-CL wearers, three CL wearers with conjunctival flaps, and three CL wearers without conjunctival flaps. All CL wearers were fitted with lotrafilcon A in the 8.4-mm base curve. These authors found the samples taken over the conjunctival flap to consist of multilayers of epithelial cells and goblet cells and to be devoid of inflammatory cells. In contrast, the nonflap groups had only a single layer of epithelial cells. The authors conclude that conjunctival flaps consist of essentially healthy tissue that has been displaced by the CL edge.²⁷⁷ A biopsy study of the conjunctival tissue in the region of the conjunctival flap, compared with nonflap tissue in the same eye, supports the findings of the CIC study, that indeed there is no sign of inflammation.²⁷⁸ While the exact etiology of conjunctival flaps remains unknown, one compelling hypothesis put forward by Bergmanson and colleagues²⁷⁷ is that the mechanical effect of the lens edge results in a “snow plough” effect, where the CL “shovels” piles of epithelial cells aside. These cells form new desmosomal junctions to each other, but lose their connection to the underlying tissue, except to the side that they remain adherent.

The clinical impact of conjunctival flaps is currently unclear and it is not known whether their detection requires lens wear discontinuation until resolution. From the literature available to date it would appear not, although flaps may be an indication of a poor-fitting CL,²⁷⁷ which could require a change of lens modulus, edge design, base curve, or wear schedule. There appears to be no correlation between CLD and conjunctival flaps.

Lid Parallel Conjunctival Folds. Lid parallel conjunctival folds (LPCOFs) are subclinical parallel folds of the lower bulbar conjunctiva, parallel to the lower lid margin and have been found to be present in dry eye, but are not age-related.²⁸¹ Pult and colleagues²⁸² showed that lid wiper epitheliopathy (LWE) and LPCOF correlated with dryness in CL wearers, but other clinical factors, such as corneal staining, bulbar redness, or tear break-up time, did not correlate. The authors suggest that this could be due to a similar etiology of friction. The correlation among LPCOF, reduced tear film stability, and LWE could be suggestive of a mechanical etiology.²⁸² LWE also correlated positively with bulbar redness, suggesting that irritation from lens fit or other factors may be related to their development.²⁸²

Conjunctivochalasis. Conjunctivochalasis has been defined as the redundant, loose, nonedematous conjunctival tissue found at the lower eyelid, typically in older people. Because of its location at the position of the tear prism, it is thought that the presence of conjunctivochalasis can disturb the distribution of the tear film. Increased matrix metalloproteinase expression has been reported in the fibroblasts of conjunctivochalasis, suggesting that this is a result of collagen degradation.²⁸³ In support of this hypothesis, Zhang and colleagues²⁸⁴ using optical coherence tomography, found reduced conjunctival thickness in those with conjunctivochalasis and in older subjects. Mimura and colleagues²⁸⁵ reported an increase in conjunctivochalasis with increasing duration of CL wear. No reports linking CLD and conjunctivochalasis exist.

Hyperemia. Increased bulbar hyperemia has been reported in asymptomatic CL wear, in wearers of both rigid and

SCLs.²⁶⁷ Both subjective and objective assessment of bulbar conjunctival vasculature did not show a significant progressive change with SCL wear over a 10-month period.²⁸⁶ A significant difference was found in the rigid wearers in the temporal bulbar conjunctiva after 4 months of wear, a factor that was attributed to adaptation to rigid lens wear.²⁸⁶ Cheung and colleagues²⁸⁷ hypothesized that CL use causes damage to the conjunctival microvasculature by direct vaso-occlusion, due to damage to the conjunctival vessels or to the conjunctiva itself. These investigators compared the abnormalities in the conjunctival microvasculature of CL wearers with at least 2 years of experience with non-CL wearers. They found significantly higher abnormalities in CL users as opposed to non-CL wearers, and reported increased vessel diameter and changes to vessel contour in the region of the CL edge.²⁸⁷

Conjunctival Squamous Metaplasia. CL wear can induce distinct changes to the conjunctiva around the limbus, characterized by conjunctival squamous metaplasia (i.e., flattening of epithelial cell shape and enlarged cell diameter with loss of goblet cells)²⁸⁸ and alterations to the nuclei of cells that has been termed “snake-like chromatin”²⁸⁹ (Figs. 2, 3). This was observed in all CL wearers in the first systematic and prospective studies on conjunctival cytology in CL wearers by Knop and Brewitt.^{290,291} These changes are believed to occur as a result of mechanical friction on the epithelial cell surface, and may be reversed by cessation of lens wear.²⁸⁸

Studies by Adar and colleagues²⁹² and Sengor and colleagues²⁹³ confirmed that almost all CL wearers have varying degrees of squamous metaplasia. Simon and colleagues²⁹⁴ investigated the correlation between severity of cytological alterations and symptoms in wearers of SCLs and rigid gas permeable CLs. They found that 60% of symptomatic CL wearers had cytological alterations after 6 months of CL wear, which increased in severity with duration of CL wear and occurred at a higher prevalence and severity in symptomatic compared with asymptomatic CL wearers. This supports similar findings from Adar and colleagues,²⁹² who observed in a population of soft and rigid CL wearers that 60% of CL wearers had minor complaints and that the presence of complaints was related to a higher prevalence and severity of cytologic changes in such subjects.

These two studies support a potential causative link between cytological alterations in CL wear and CLD. In asymptomatic subjects, none of the rigid gas permeable wearers and one-third of the SCL wearers had abnormal CIC samples, possibly due to differences in fit between these lens types. In a prospective study,²⁸⁸ it was observed that conjunctival squamous metaplasia was evident after only 2 weeks of CL wear. The extent of alterations appeared to reach a plateau within 6 months of CL wear, as later confirmed by another study,²⁹⁴ although a longer study time would be necessary to verify this. After CL wear ceased, the cytological conjunctival changes proved to be reversible, although this took much longer (up to 2 years) than their induction in the first case.²⁸⁸ This finding obviously argues against a strong association with CLD, as CLD is rapidly relieved by removal of the lens from the eye.

Goblet Cell Density. Goblet cell density (GCD) is potentially an important morphological factor in CL wear because the mucin they secrete,^{30,295,296} along with lubricating proteins,²⁹⁷ is conceivably important for their ability to reduce friction on the ocular surface, which could be linked to CLD.

CL-induced changes in GCD, as identified by CIC, have been summarized by Doughty.²⁹⁸ This review indicated that most published studies concluded that CL wear results in a decrease in goblet cells in the conjunctiva, but the data are equivocal, with several studies showing no change or indeed an increase.

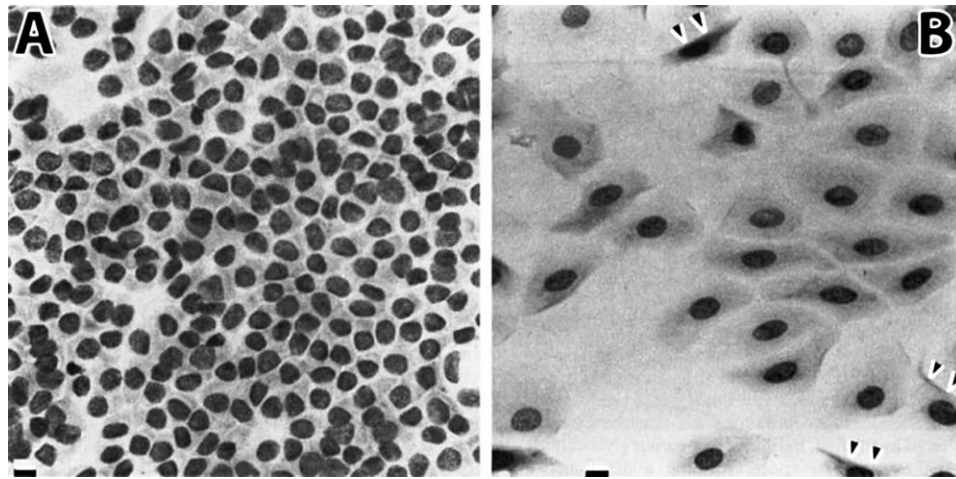


FIGURE 2. Conjunctival epithelial changes (squamous metaplasia) in CL wearers. After start of CL wear, a rapid change of the normal small cuboidal cell shape ([A] nucleo/cytoplasmic [n/c] ratio of approximately 1:1) into flat cells with enlarged diameter ([B] n/c ratio of approximately 1:5–1:8 or more) occurs in the bulbar conjunctiva, within the excursion zone of the lens. *Double arrowheads* in ([B]) indicate folding of flattened cell margins. Light microscopy; *scale bars*: 10 μ m. Reprinted with permission from Knop E, Brewitt H. Morphology of the conjunctival epithelium in spectacle and contact lens wearers—a light and electron microscopic study. *Contactologia*. 1992;14E:108–120. Copyright 1992 Georg Thieme Verlag.

This work highlighted the need for more objective and repeatable means by which to assess GCD by CIC.^{298–299}

Potential reasons for variations in GCD when assessed by CIC have been well described.^{288,301,302} Variations in results are related to a number of factors, including differences in sampling location, methodology to collect the sample, grading scale used to assess the collected tissue for squamous metaplasia, and field of view used to examine the tissue collected.^{288,299,300,302–304} One major issue when attempting to differentiate changes in GCD over time relates to the fact that in the perilimbal 12 o'clock position, which is the location used in many studies to conduct CIC, GCD changes

dramatically within just a few millimeters.^{288,305} Thus, even a small alteration in the location at which the CIC is conducted could produce very different results, without being related to true changes in GCD.

One other method that shows some promise for evaluating conjunctival changes is LSCM. Efron and colleagues³⁰⁶ performed *in vivo* LSCM on the bulbar conjunctiva of 11 healthy non-CL wearers and 11 asymptomatic CL wearers. The authors found greater conjunctival epithelial cell density in CL wearers in all cardinal positions compared with the non-lens wearing counterparts, but a reduced conjunctival epithelial thickness in lens wearers. The authors attribute this thinning to

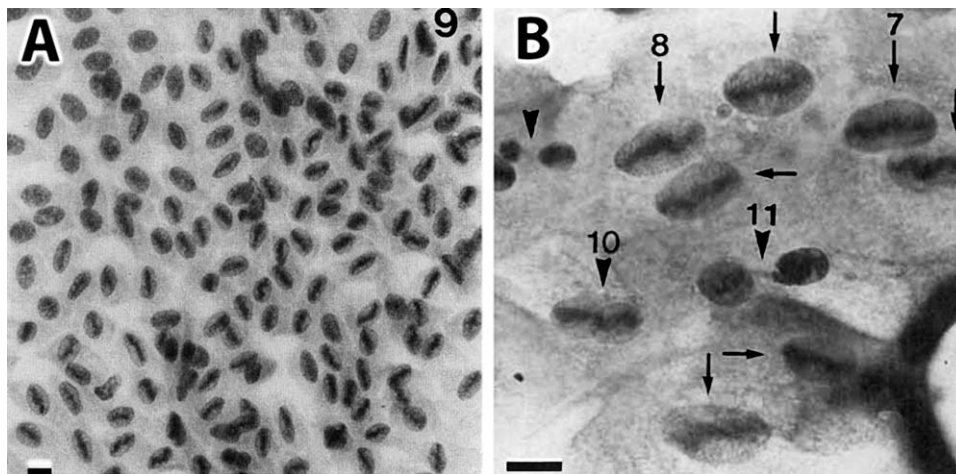


FIGURE 3. Conjunctival epithelial changes in CL wearers show a peculiar rearrangement of the nuclear chromatin (“snake-like chromatin”). Light microscopy overview (A) shows a group of such cells that are arranged similar to a fish “swarm,” here in a 7 to 1 o'clock direction. Increased magnification (B) shows individual flattened cells and nuclei with different stages of snake-like chromatin. Chromatin material, detached from the nuclear periphery, forms a central elongated structure that is first bar-shaped (nucleus “7” in [B]) and later undulated (nucleus “8” in [B]). Advanced stages develop a central segmentation (nuclei “10,” “11” in [B]). The accumulation of chromatin in the long axis of the nucleus together with later segmentation of the nucleus by cytoplasmic filaments that are rolled around it indicate the presence of chronic mechanical friction at the ocular surface of lens wearers that is conceivably related to CLD. Light microscopy; *scale bars*: 10 μ m. (A) Reprinted with permission from Knop E, Brewitt H. Morphology of the conjunctival epithelium in spectacle and contact lens wearers—a light and electron microscopic study. *Contactologia*. 1992;14E:108–120. (B) Reprinted from Knop E, Reale E. Fine structure and significance of snakelike chromatin in conjunctival epithelial cells. *Invest Ophthalmol Vis Sci*. 1994;35:711–719.³⁷⁵

a similar mechanism to that seen in corneal thinning in CL wear, as a result of mechanical and metabolic effects. The increased density was attributed to the delayed desquamation as a result of lens wear. GCD was not found to differ between the two groups.

To date, data linking GCD to CLD are lacking, but potentially worthy of future evaluation, particularly around the lid wiper region. Studies should examine the time course of GCD, and whether this links to CLD, or if the magnitude of GCD is linked to the severity of CLD.

Palpebral Conjunctiva

The palpebral conjunctiva plays an important role in controlling the interaction with the ocular surface and the CL. Slit-lamp examination of the upper tarsal conjunctiva reveals a pink mucous membrane with a satin-like, or a fine, uniform papillary appearance. Allansmith³⁰⁷ reported that 14% of non-CL wearers had a satin-smooth conjunctival appearance of the upper tarsal plate, 85% had small uniform papillae, and 1% had nonuniform papillae. Korb and colleagues³⁰⁸ reported that 0.6% of healthy subjects showed conjunctival papillae of more than 0.3 mm on the upper tarsal conjunctiva.

CL wear is known to induce CL papillary conjunctivitis (CLPC) in some wearers, which was first noted by Spring.³⁰⁹ It is a papillary reaction on the upper tarsal conjunctiva accompanied by discomfort and mucous production. The condition has been described in detail by Allansmith and colleagues,³¹⁰⁻³¹² and has been associated with both soft and rigid CL wear and can lead to CL intolerance and discontinuation of wear. The term “giant papillary conjunctivitis” is more general and indicates a noninfectious inflammatory disorder involving the superior tarsal conjunctiva with the presence of papillae measuring 0.3 mm or larger.

While subjects with overt CLPC will be symptomatic, there have been no direct reports linking CLD with general, nonpathological changes to the palpebral conjunctiva. However, the use of sensitive grading scales^{313,314} may be useful in detecting subtle changes to the palpebral conjunctiva, and may be useful in linking palpebral conjunctival changes with CLD. In one study that examined differences in comfort response and slit-lamp findings between two groups of CL wearers using different multipurpose disinfecting solutions, there was a possible effect of palpebral roughness on the symptoms of grittiness and scratchiness during CL wear.³¹⁵

IMPACT OF CLS ON MEIBOMIAN GLANDS

The meibomian glands are large sebaceous glands that are located in the tarsal plates of the eyelids^{316,317} and produce the lipids that serve, as the outermost layer of the precorneal tear film, to retard evaporation of the aqueous phase of the tears.³¹⁸ Meibomian gland dysfunction (MGD) is a chronic, diffuse abnormality of the meibomian glands, commonly characterized by terminal duct obstruction and/or qualitative/quantitative changes in the glandular secretion. This may result in alteration of the tear film, symptoms of eye irritation, clinically apparent inflammation, and ocular surface disease.³¹⁹

There is a long-standing clinical impression that CL wear increases the risk of MGD. Korb and Henriquez^{320,321} investigated the meibomian glands of individuals with a primary complaint of CL intolerance. They described clinical and cytological evidence indicating that the syndrome is due to obstruction of the meibomian gland orifices by desquamated epithelial cells that tend to aggregate in keratotic

clusters, resulting in changes in the meibomian gland contribution to the precorneal tear film.

Several studies have reported the prevalence of MGD in CL and non-CL wearers.^{320,322-324} A meta-analysis of such studies³²⁵ revealed that the prevalence did not differ significantly between the two groups, thus suggesting that CL wear may not increase the risk for MGD. This could be because many of these studies employed small sample sizes and used a wide variety of methods to confirm MGD.

In contrast, Arita and colleagues³²⁶ provided direct evidence that CL wear may affect the morphology of meibomian glands. Morphological observation of the meibomian glands revealed that the frequency of meibomian gland loss was significantly higher in CL wearers compared with non-lens wearers. These results strongly suggest that CL wear is a potential cause of alteration in meibomian glands, and may result in MGD.

Meibomian Gland Orifice Changes

Foaming of the lower tear meniscus, especially toward the outer canthus, is sometimes observed in individuals with CL-associated MGD.^{320,322} Korb and Henriquez³²⁰ found that foaming on the lower lid margins was apparent in 66.2% of symptomatic CL wearers but in only 3.7% of asymptomatic CL wearers ($P < 0.0001$). Hypersecretory CL-associated MGD is characterized by the release of a large volume of meibomian lipid (meibum) at the lid margin (foaming) in response to pressure on the tarsus. It remains unclear, however, whether the increased amount of lipid is the result of true hypersecretion, or the damming back of mildly obstructed secretions.³¹⁹ Long-standing cases of CL-associated MGD may be linked to lid margin abnormalities, such as vascularization, morphological irregularity of the lid margin, blockage (plugging) of orifices, and damage to the mucocutaneous junction.³²⁷ In severe cases, in which the meibomian gland orifices are blocked, there is an absence of glandular secretion. Symptomatic CL wearers in whom lid margin abnormalities are not apparent may have a condition referred to as “nonobvious MGD.”³²⁸

Morphological Changes of Meibomian Glands

Some studies have found no relation between meibomian gland dropout and CL wear.^{329,330} However, these studies examined only the glands in the central area of the lower eyelid, which may not necessarily reflect meibomian gland changes across the full width of the lid margin. Arita and colleagues³³¹ use a noninvasive meibography system that allows observation of the meibomian glands in both upper and lower eyelids (Fig. 4). They found that CL wear likely affects the morphology of meibomian glands, with the effects being greater on meibomian glands throughout the upper eyelid than on those in the lower eyelid.³²⁶ Partial or complete loss of the meibomian glands in each eyelid was significantly higher for CL wearers than for control individuals. The length of the affected meibomian glands was less than half that observed for normal glands. These patterns of meibomian gland changes were rarely detected in non-lens wearers, and suggest that CL wear is a potential cause of MGD.

The results of Arita and colleagues³²⁶ also suggested that CL wear produces different effects on the upper and lower eyelids. Wearers of rigid lenses showed a tendency for meibomian gland dropout in the upper eyelid, whereas wearers of SCLs showed a tendency for shortening of the glands in the lower eyelid. Their data suggested that lens material does not play a key role in CL-associated MGD.

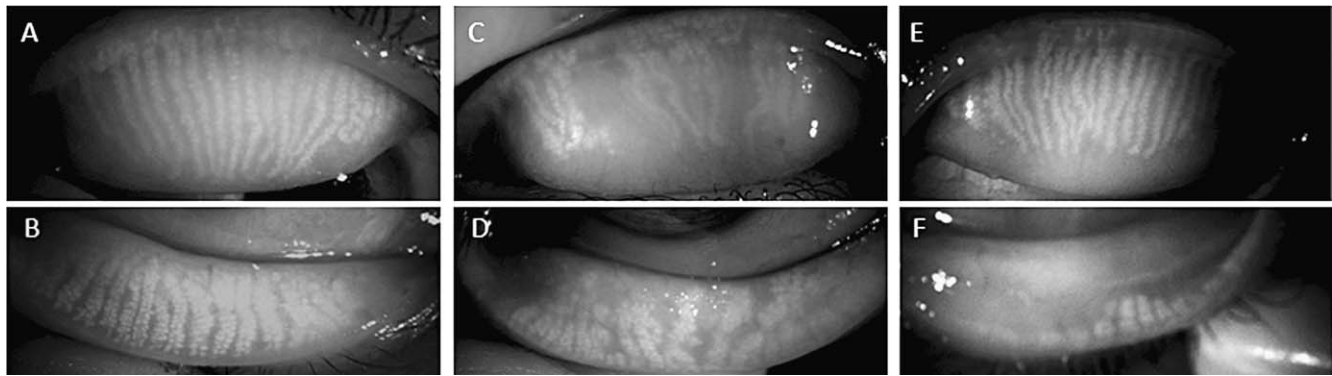


FIGURE 4. Representative noninvasive meibography images in a control subject (A, B) and in two CL wearers (C–F). Noninvasive meibography views of the meibomian glands from the conjunctival side, with the lids everted. The meibomian glands appear white. (A, B) A 31-year-old female, non-CL user. Meibomian glands in the upper (A) and lower (B) eye lids were observed. Shortening or dropout of meibomian glands was not observed. (C, D) A 37-year-old male who had used rigid CLs for 17 years. Those regions of the upper lid where meibomian glands were absent, appear black (dropout) (C). Shortening and distortion of meibomian glands were observed in the lower eye lid (D). (E, F) In a 32-year-old female who had used hydrogel CLs for 13 years, most meibomian glands in both the upper and lower eyelids were shortened. The shortening of the meibomian glands began not at the free border of the lid (in the region of the orifices), but proximally (in the fixed border of the tarsal plate).

Acinar Density and Size

Villani and colleagues³³² examined morphological changes in meibomian glands and the status of periglandular inflammation in CL wearers by LSCM (Fig. 5) and then investigated the relation between clinical and confocal findings. LSCM was applied to determine the cell density of the mucocutaneous junction epithelium, acinar unit density and diameter, glandular orifice diameter, meibum secretion reflectivity, and the appearance of the glandular interstice and acinar wall. The duration of CL wear was found to be correlated with acinar unit diameter ($P < 0.05$). Morphological changes in the meibomian glands revealed by LSCM were indicative of signs of meibomian gland dropout, duct obstruction, and periglandular inflammation. A comprehensive LSCM evaluation of the ocular surface in CL wearers should better clarify the role of

meibomian gland dropout and eyelid margin inflammation in the pathogenesis of CL-induced dry eye.

Meibum Composition

It remains unclear whether CL wear affects meibum composition or whether meibum composition affects the comfort of CL wear. Robin and colleagues³³³ found that all 15 subjects who wore EW SCLs and had lipid deposition on the lens showed abnormalities of meibomian gland morphology. Only 2 of the 13 subjects without lipid deposition on the lens had meibomian gland abnormalities. These results suggest that MGD may be associated with the development of SCL deposits, which can impact lens wettability and ultimately lead to CLD.

It is possible that CL wear affects not only the lipid layer of the tear film but also meibum composition itself. However, there is still a dearth of information regarding the exact nature of

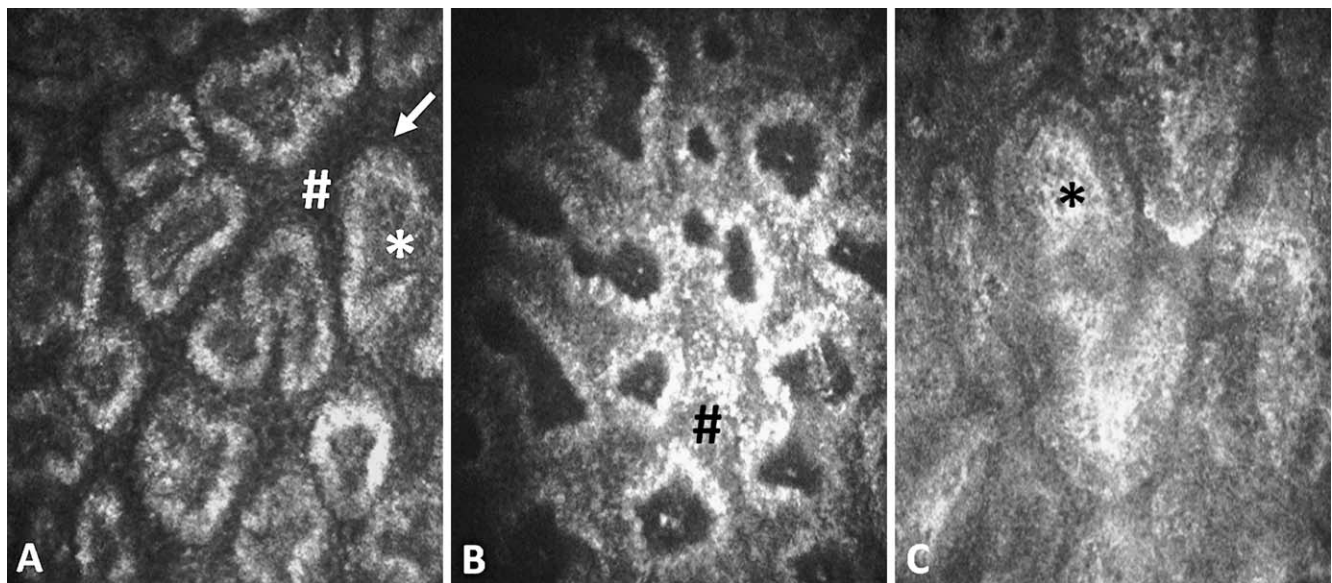


FIGURE 5. Meibomian gland changes in CL wearers, illustrated by in vivo confocal microscopy, performed at the lid margin. (A) Meibomian glands of a 35-year-old male, showing no obvious changes in acinar lumina (*), wall thickness (arrow), or interstitial space (#). (B) A 32-year-old male: The acinar unit density and size are slightly reduced and there is apparent periglandular infiltration (#), presumably by inflammatory cells. (C) A 39-year-old female: The acinar units appear greatly enlarged and hyper-reflective (*).

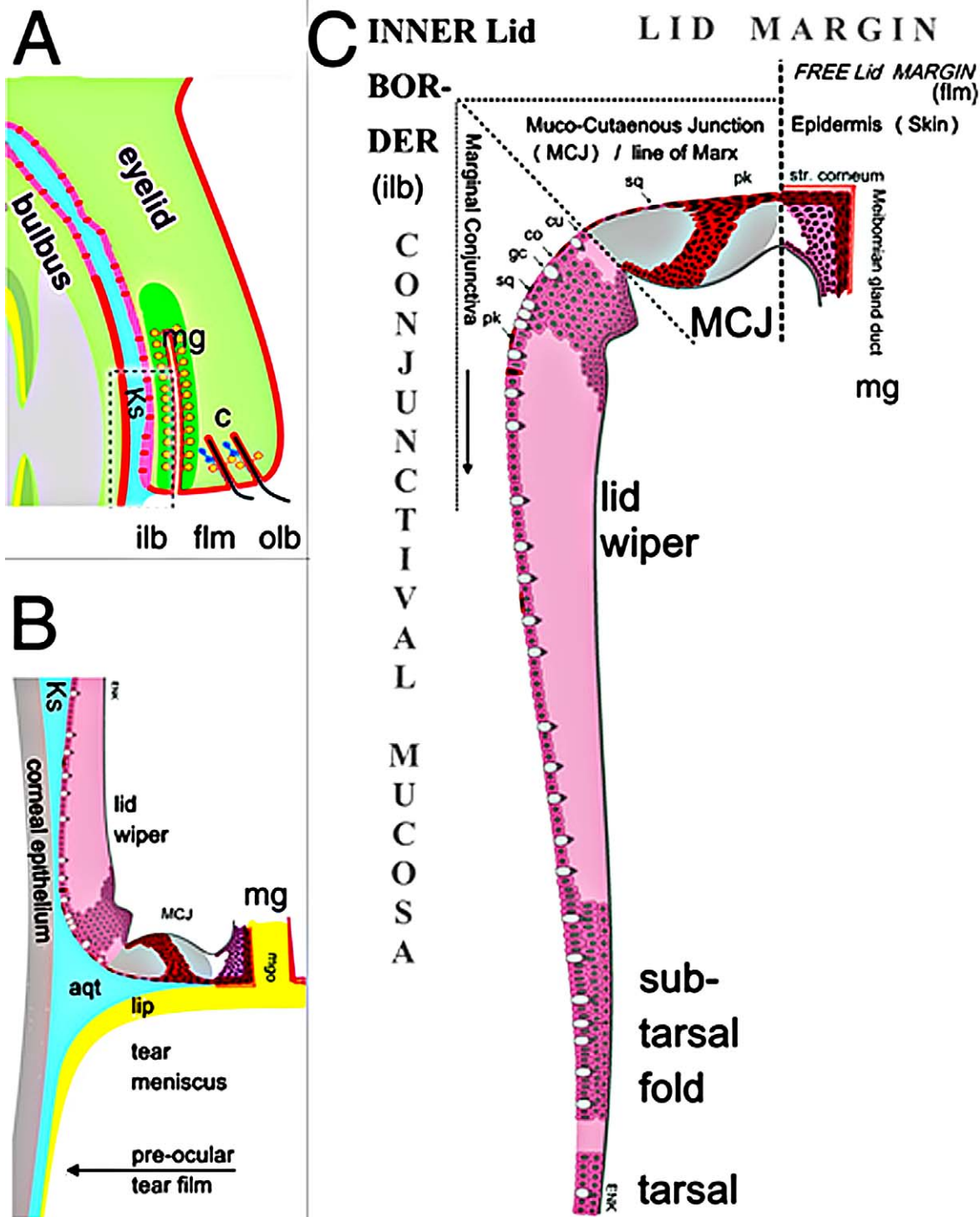


FIGURE 6. Tissue zones at the posterior eye lid margin. **(A)** Complete upper eye lid with meibomian gland (mg) and cilia (c); the area marked by a *dotted rectangle* represents the inner lid border. The rounded outer lid border (olb) can be differentiated from the sharp inner one (ilb) and the free lid margin (flm) extends from the cilia (c) to the meibom orifice. **(B)** The inner lid border is seen with the aqueous tear meniscus (aqt) overlying the line of Marx, and the tear film lipid layer (lip, not to size). The lid wiper is the only point of the lid margin that is apposed to and in touch with the globe; the upper tarsal conjunctiva is separated from the globe by Kessing's space (Ks in [A, B]). The marginal conjunctiva constitutes a thickened epithelial lip that represents the device for distribution of the tear film during a blink. **(C)** The lid wiper has goblet cells (*white dots* in [B, C]) for a rich mucin-water gel at the surface for lubrication and reduction of friction. Further zones of the posterior lid border are the mucocutaneous junction (mcj), the surface of which is the line of Marx) located between the crest of the inner lid border and the meibom orifice. The cornified epidermis extends from the free lid margin around the posterior rim of the meibom orifices where the meibomian oil is delivered onto the precorneal tearfilm. In most parts only the surface cells are shown. **(A)** Reprinted with permission from Knop N, Korb DR, Blackie CA, Knop E. The lid wiper contains goblet cells and goblet cell crypts for ocular surface lubrication during the blink. *Cornea*. 2012;31:668-679. **(B, C)** Modified from Knop E, Knop N, Zhivov A, et al. The lid wiper and mucocutaneous junction anatomy of the human eyelid margins: an in vivo confocal and histological study. *J Anat*. 2011;218:449-461.

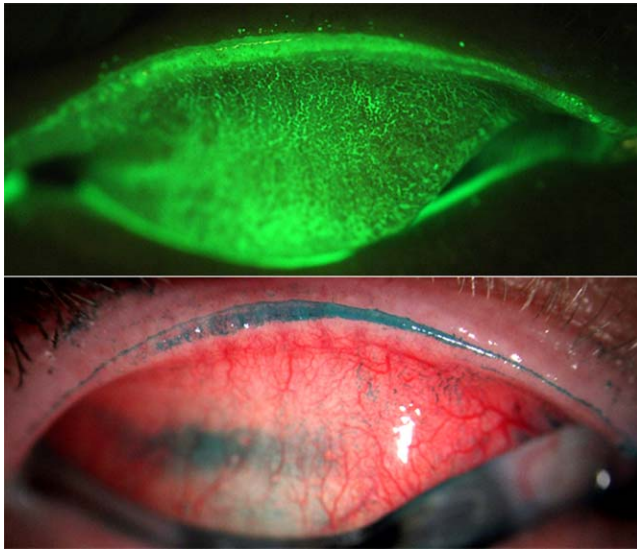


FIGURE 7. Lid wiper epitheliopathy. Horizontal band of lid margin staining extending horizontally from the medial canthus to the lateral canthus, and from the Marx line (*sharp green line* or border of superior staining) to the tarsal sulcus fold. Lid wiper epitheliopathy stained with fluorescein (*top*) and lissamine green (*bottom*). Photo courtesy of Sruthi Srinivasan.

meibum, as a result of the small sample quantities available. Recent advances in analytical techniques have provided some insight into meibum composition,^{334,335} but further work is necessary to determine the extent of interindividual variability in normal meibum, its effect on the comfort of CL wear, and the effect of lens wear on meibum composition.

IMPACT OF CLS ON THE LID MARGINS

Lid Margin Anatomy

The lid margin can be structurally and functionally differentiated into three distinct zones: the anterior and posterior lid border, and the free lid margin that is located between these.² The posterior border has at least three zones (Fig. 6)³³⁶; the posterior extension of the free lid margin skin epidermis (that encircles the meibomian orifices), the transition between the epidermis and conjunctival mucosa (mucocutaneous junction with its surface being the line of Marx), and the lid wiper zone (or the marginal conjunctiva).

The lid-wiper region is a thickened epithelial “lip” that has a conjunctival mucosal morphology that extends from the tarsal conjunctiva up to the crest of the posterior lid border, is apposed to the globe, and helps to distribute the precorneal tear film. The lid wiper contains goblet cells that produce mucin, which is likely used for lubrication and reduces the frictional force between the globe and lid margin during blinking.²⁹⁶ The lid wiper, because it is conceivably the only part of the lid margin that is in direct contact with the globe,³³⁷ will be in contact with the CL surface and is thus subjected to mechanical friction during the blink. The lid wiper zone has the highest neural sensitivity of all the conjunctival and lid regions, and is similar in this respect to the central cornea.^{39,338} Thus, it is of obvious importance during lens wear.

The line of Marx extends from the crest of the posterior lid border and is seen at the bottom of the tear meniscus.³³⁹ A thin band of stainable epithelial cells directly behind the mucocutaneous junction is the basis for Marx’s line. Previously, the line of Marx was assumed to be the zone in touch with the globe and to

represent the wiping surface of the lid border.^{340,341} However, this theory is not supported by its geometrical orientation to the globe, by the fact that it is visible in the upper eye lid without lid eversion,³⁴² and because it lacks specific lubrication.²⁹⁶

The conjunctiva extending proximally from the posterior lid margin to the subtarsal fold, corresponds to the lid-wiper region of the lid margin,^{343,344} which is directly apposed to the surface of the globe and is important in tear distribution during blinking and eye movements.³⁵⁶ Riolan’s muscle, the most central part of the orbicularis muscle at the lid margin, probably plays a role in this, as does the lubricative function of the goblet cells present in this region.²⁹⁶

Lid Wiper Epitheliopathy

A thickened epithelium at the posterior lid margin was observed as long ago as 1877 by Sattler³⁴⁵ and later by Virchow and Saemisch.³⁴⁶ However, its immediate functional implication was not recognized until the mid-1960s by Ehlers.³⁴⁷ He noticed that this “bead gliding over the cornea” must be assumed to be a perfect “windscreen wiper.” More recently, this region has received increased attention because of an observation by Korb and colleagues^{343,344,348} linking changes in this region of the lid in subjects who are symptomatic of dryness. The authors postulate that when the tear film is thinned or becomes unstable, or a lens surface is not stable and wettable, there is an increased mechanical/frictional effect on the lid-wiper region, as the lid travels across the ocular or lens surface during blinking. This process may lead to lid-wiper trauma and epitheliopathy, which can be viewed clinically by staining the marginal conjunctiva with commonly used ophthalmic dyes^{343,344,349} (Fig. 7).

LWE is found in 67% to 80% of symptomatic CL wearers, but in only 13% to 32% of asymptomatic subjects.^{343,350} This condition is also observed in the lower eyelid,³⁵¹ but significantly different LWE scores between symptomatic and asymptomatic subjects were found only in the upper eyelid.³⁵² By histology it has been verified in selected cases that cells with atypical keratinization (para-keratinization) increase in number and extend from the natural stainable line of Marx, where they physiologically occur, over the surface of the lid wiper epithelium.³³⁶

LWE may be one of the few clinical signs truly associated with dryness in lens wearers and nonwearers and much work is currently under way to determine its value in providing a better understanding of CLD.

Changes in Normal Microbiota

The lid margin is more frequently colonized with microbes than the conjunctiva and CLs,³⁵³ but the frequency of isolation varies. The number of colony-forming units that can be grown from swabs of the lid range from zero in some subjects up to 465.³⁵⁴⁻³⁵⁷

As shown in the Table, the most frequently isolated microbes are the coagulase-negative staphylococci, in both non-lens wear³⁵⁸⁻³⁶¹ and during lens wear.^{353,354,356,357,360,362,363} Other commonly isolated bacteria from both lens wearers and non-lens wearers include *Micrococcus* sp., viridans streptococci and other *Streptococcus* sp., *Corynebacterium* sp., *Propionibacterium* sp., and *Bacillus* sp. Gram-negative bacteria are not commonly isolated from the lid margins of CL or non-CL wearers. Stapleton and colleagues³⁵³ found that the frequency of isolation of microbes from lids increased significantly with time for experienced wearers of DW lenses, but for experienced wearers of EW lenses the frequency of isolation of microbes from lids reduced with time, but there was a greater frequency of isolation of potentially pathogenic microbes during EW. Other

TABLE. Frequency of Microbes Isolated From Lids of Non-Lens Wearers and Lens Wearers^{353,354,356-361,363}

Microbial Type	Non-CL Wearers, % Subjects	CL Wearers, % Subjects
Gram-positive bacteria: Firmicutes, Firmibacteria, Bacillales		
Coagulase-negative staphylococci	84-100	28-97
<i>capitis/warneri/cobnii/saprophyticus</i>	<1	2-43
<i>epidermidis/hominis</i>	28	25-62
<i>haemolyticus</i>		2-8
<i>lugdunensis</i>		<1-3
<i>hyicus</i>		5
<i>intermedius</i>		<1-2
<i>schleiferi</i>	<1	1-3
<i>Staphylococcus aureus</i>	3	<1-21
<i>Planococcus</i> sp.		<1-1
<i>Bacillus</i> sp.	22-26	<1-5
Gram-positive bacteria: Firmicutes, Firmibacteria, Lactobacillales		
<i>Streptococcus pneumoniae</i>		<1
<i>S. pneumoniae</i> and viridans streptococci	6	<1-3
Viridans streptococci	<1-41	1-15
<i>Streptococcus</i> sp.	4	1-6
<i>Lactobacillus</i> sp.		<1-1
Gram-positive bacteria: Actinobacteria, Actinobacteridae, Actinomycetales		
<i>Micrococcus</i> sp.	6-14	0-26
<i>Stomatococcus</i> sp.		1-2
<i>Corynebacterium</i> sp.	43	<1-32
<i>Propionibacterium</i> sp.	4-18	<1-61
Gram-negative bacteria: Proteobacteria, Gamma proteobacteria, Pseudomonadales		
<i>Acinetobacter baumannii</i>	4	
<i>Acinetobacter</i> sp.	<1	<1-9
<i>Moraxella</i> sp.	<1	1-3
<i>Moraxella catarrhalis</i>		<1
<i>Neisseria</i> sp.	5-6	<1-6
<i>Pseudomonas</i> sp.	<1	1-3
<i>Pseudomonas aeruginosa</i>		<1-1
Gram-negative bacteria: Proteobacteria, Gamma proteobacteria, Enterobacteriales		
<i>Escherichia coli</i>	<1-3	
<i>Escherichia vulneris</i>	<1	<1-1
<i>Enterobacter</i> sp.		<1-1
<i>Enterobacter cloacae</i>		<1
<i>Proteus</i> sp.	3	
<i>Serratia marcescens</i>	<1-6	<1-3
<i>Serratia ficaria</i>	6	<1-1
<i>Serratia liquefaciens</i>		3
Gram-negative bacteria: Proteobacteria, Gamma proteobacteria, Pasteurellales		
<i>Haemophilus influenzae</i>	<1	<1-5
<i>Haemophilus parainfluenzae</i>		<1
Gram-negative bacteria: Proteobacteria, Beta proteobacteria, Burkholderiales		
<i>Achromobacter</i> sp.		<1-1
<i>Achromobacter xylosoxidans</i>		<1
Gram-negative bacteria: Bacteroidetes, Flavobacteriaceae, Flavobacteriales		
<i>Chryseobacterium meningosepticum</i>		<1
Unidentified gram-negative rods	<1-2	2-5
Fungi (molds or yeasts)		2-4

microbes, such as fungi or protozoa, are not usually isolated. There are no reports of viral colonization of lids in healthy asymptomatic subjects.

There have been no studies to date examining the lid microbiota during CLD. One study³⁵⁹ examined the lid microbiota of dry-eye subjects (including those with MGD or

Sjögren's syndrome) and found that all dry-eye subjects had increased numbers of colonies of bacteria isolated compared with healthy non-dry eye subjects (106 ± 82 vs. 12 ± 18 colony-forming units per lid, respectively). There also tended to be more frequent lid colonization by *Corynebacterium* sp., *Staphylococcus aureus*, and coliform bacteria in the dry-eye

subjects compared with the non-dry eye control group. Given these findings, and the changes that occur to the lid microbiota during lens wear, there is the possibility that the ocular microbiota might have some role in CLD.

IMPACT OF CLS ON BLINKING

Blink patterns impact lens movement and the degree to which the lens and ocular surface may dry between blinks, both of which can affect the interaction of the lens with the ocular surface. In addition, a lens that is too mobile will interact with the lid during the blink and can influence lens comfort. Thus, consideration of blinking in CL wearers is warranted.

The manner in which a CL interacts with the ocular surface during eye movement and blinking is distinctly different for soft, rigid, or scleral lenses, due to differences in size, material, modulus, form, and fitting philosophy for these lens types. Rigid corneal lenses require a greater period of adaptation and often modify blink patterns during this adaptation phase. Although soft lenses are intrinsically tolerable,³⁶⁴ acceptance is greatly influenced by a variety of material properties, including water content, modulus, oxygen transmission, and wettability. Lens surface drying and feelings of discomfort will potentially impact blink frequency.

Blinking and Its Role in CLD

Blink rate is strongly influenced by the surrounding environment, attention, eye exposure, personal activity, and mental state and may vary with age and sex. Wide variations in normal blink rate are reported, likely due to the influence of different environmental conditions or measurement techniques. Blink rate is increased in dry eye disease and is further amplified by increasing airflow over the eye, in both healthy individuals and subjects with dry eye complaints.^{365,366} The increased blink rate appears to serve two functions, in that it refreshes the tear film more frequently and also increases the period of tear film coverage over the ocular surface, as both blink frequency and blink time are increased. In contrast, a reduction in blink rate increases the blink interval, thereby increasing evaporative loss from the eye for a given palpebral aperture size. This has obvious consequences for lens behavior, particularly related to tear film break-up and surface drying over the lens. Finally, blink completeness is reduced in CL wearers compared with healthy individuals.⁴⁶

CL Movement During Blinking

In the CL wearer, physical stresses are generated between the lens and the ocular surface, which vary according to lens type and fit, the nature and extent of the lid and eye movements, and how the lens sits on the surface of the eye.

The points of contact with the cornea and conjunctiva in the primary position of gaze differ significantly among the major lens subtypes. In the blink interval, rigid corneal lenses sit on the cornea, within the palpebral aperture, either making no contact with the lids, or, with a lid-attached fit, engaging with the upper tarsus. Occasionally, the lower lens edge may be supported on the lower lid margin.³⁶⁷ In comparison, soft and scleral lenses tuck beneath the upper and lower lid margins, straddling the cornea and perilimbal conjunctiva, and, with scleral lenses, extend onto the bulbar conjunctiva. Although soft lenses are flexible and modify their shape over the corneal and limbal area, scleral lenses are not, and conform very differently to either rigid corneal or soft lenses. There is only a very thin film of fluid between a soft lens and the cornea and minimal tear exchange occurs. The tear film is more

substantial in the case of corneal and scleral lenses, resulting in greater mobility for rigid corneal lenses. For the scleral lens, mobility and tear exchange is restricted by size and peripheral interactions with the bulbar conjunctiva. A key function of the blink is to replenish the tear film in front of and behind the lens. In some circumstances, lens fit may interfere with spreading of the tear film and this, along with the presence of the lens-edge-related meniscus, may encourage drying outside the edge of the lens (resulting in 3 and 9 o'clock staining), which can influence rigid lens comfort.^{368,369}

Blinking exerts both a backward, squeeze pressure on the lens and a shearing force, parallel to its anterior surface.³⁷⁰⁻³⁷² As the lens moves or fluid is exchanged behind the lens, these forces are transmitted to the cornea, limbus, and bulbar conjunctiva to varying degrees, according to lens type and fitting characteristics. Although there is limited tear exchange under a soft lens during the blink, the volume and distribution of fluid behind the lens is a major determinant of mobility.^{121,373} The post-lens tear fluid provides lubrication between the lens and the corneal surface and cushions the effects of blinking. It also facilitates tear exchange with the body of the tears and, thus, is important for the removal of cells and debris from behind the lens.³⁷⁴ For the relatively mobile, rigid corneal lens, the relationship between the lens and the ocular surface is dynamic. The lens moves with the eye during a large eye movement. By contrast, eye movement when wearing a well-fitted, relatively immobile soft lens will draw the lens surface across the upper and lower tarsal conjunctiva during horizontal versions, the locus of contact changing when the eye is elevated or depressed. These differences in physical interaction between lens subtypes and the ocular surface are relevant to the development of a variety of well-described complications that can result in CLD, including lid-wiper epitheliopathy.³⁴³ However, detailed studies of the relationship between the blink during wear of different CL types and CLD have yet to be undertaken.

CONCLUSIONS AND FUTURE DIRECTIONS

This report has reviewed CL-associated changes to the ocular surface and adnexa, and has considered which of these changes are associated with CLD. We have concentrated on physiological changes that may be associated with CL wear, but not necessarily identified or designated as an adverse response.

In this context, some evidence is available to suggest a link among LIPCOF, conjunctival metaplasia, GCD, MGD, and LWL with CLD, with the strongest evidence being that related to MGD and LWL. No convincing evidence of a link to CLD was unearthed with respect to any of the other forms of CL-associated tissue changes considered in this report.

When investigating the source of CLD, a full examination of all the anterior ocular structures that can be impacted by CL must be undertaken. This report draws particular attention to the importance of undertaking a careful assessment of the meibomian glands and lid margins, so as to establish the role that changes to these tissue structures may play in the cause of CLD.

Potential future areas of study could include closer inspection of the role of corneal staining in CLD, the development of more repeatable methods to ascertain GCD, and extensive work characterizing changes to the meibomian glands during CL wear and the role of LWL in CLD. Such studies would benefit from longitudinal designs that attempt to understand what pathophysiological changes occur in new wearers over time and whether changes to CL materials, design, fit, or other changes impact MGD and LWL. Studies

should also examine whether the magnitude or timing of changes can be linked to the magnitude and timing of CLD.

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The TFOS International Workshop on Contact Lens Discomfort: Report of the Contact Lens Interactions With the Tear Film Subcommittee

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See the tables in the Introduction for the members of the TFOS International Workshop on Contact Lens Discomfort.

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The aim of the subcommittee report was to review published evidence describing tear film changes secondary to contact lens wear and to examine the evidence for associations between tear film changes and contact lens-related discomfort (CLD) in order to identify potential etiologies for CLD and strategies for the optimization of comfort.

The report comprises two main sections; the first describes biophysical interactions between the contact lens and the tear film, and the second deals with biochemical changes to the tear film associated with contact lens wear.

In first considering the tear film structure, recent tomographic, interferometric, and reflectance spectral techniques indicate central corneal tear film thickness values around 3 μm ,¹⁻³ aligning closely with earlier measurements.^{4,5}

The thin outermost lipid layer of the tear film, on the order of 50 to 100 nm in thickness,^{6,7} forms the barrier between the environment and the eye. The lipid secretions arise mainly from the meibomian glands through orifices located at the mucocutaneous lid margin junctions, and are combined with a lesser lipid contribution from the eyelid glands of Moll and Zeiss.⁸ Spread over the tear film surface by blinking, the lipid layer comprises a thin inner polar layer, overlaid by a thicker outer nonpolar layer.^{9,10} In addition to preventing overspill of tear fluid onto the eyelids and contamination of the tear film by skin lipids,^{9,11} the most significant role of the lipid envelope is considered to be in retarding evaporation from the ocular surface.^{12,13}

The aqueous phase of the tear film forms the bulk of the tear film thickness.⁸ It arises primarily from the main lacrimal gland and accessory lacrimal glands of Krause and Wolfring,¹⁴ with additional fluid and electrolytes secreted by the ocular surface epithelial cells. The tear flow rate varies according to the level of sensory stimulation, in response to the demands of the external environment. The overnight tear production rate is significantly lower than that during the day.¹⁵

The role of the aqueous phase is to nurture and protect the epithelia by providing a medium for the transfer of oxygen and nutrients to the avascular corneal tissue; conveying signals between the structures bathed in aqueous; and flushing away epithelial debris, toxins, and foreign bodies.¹⁶ The electrolytes within the aqueous phase dictate the osmolarity of the tear fluid, as well as playing a role in regulating pH and maintaining epithelial integrity.¹⁶ Hyperosmolarity, which reflects an increased electrolyte concentration, is recognized to damage the ocular surface.¹⁷ Aqueous layer proteins contribute to ocular surface defense¹⁸ and maintenance of tear film stability.⁹ The proportions of plasma-derived and conjunctiva-derived proteins relative to lacrimal gland proteins within the tear film are dependent upon the tear flow rate and the level of ocular surface stimulation. As well as electrolytes and proteins, the tear film contains antioxidants to scavenge free radicals and growth factors important in epithelial regeneration and wound healing.¹⁹ Inflammation causes changes in the tear film constituents with release of inflammatory markers precipitating an escalating cycle of inflammation with ocular surface

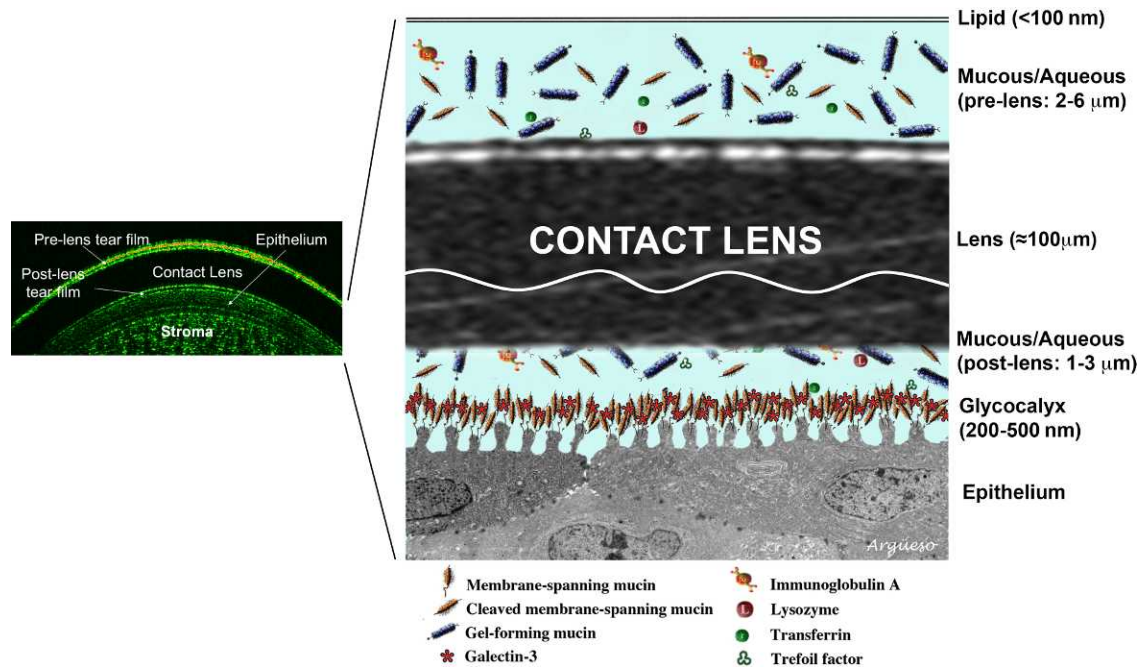


FIGURE 1. Tear film structure with a contact lens in situ (P. Argüeso).

irritation, tear film instability, epithelial cell dysfunction, and apoptosis, which ultimately affects corneal epithelial barrier function.¹⁷

The aqueous phase of the tear film contains soluble, gel-forming mucins, produced by the conjunctival goblet cells.^{20,21} These mucins are important for removing pathogens and debris from the ocular surface, smoothing the ocular surface, and for protecting the surface, through lubrication, from the blink and from environmental insult.¹⁶ Anchored to the apical plasma membrane of the corneal and conjunctival epithelial cells are the transmembrane mucins, which contribute to forming the glycocalyx. These molecules can interact with multiple proteins through both the extracellular and intracellular domains. Carbohydrate structures present on the highly glycosylated extracellular region allow interaction with carbohydrate-binding proteins, such as galectin-3, to promote barrier function on the most apical epithelial cell layer.²⁰

In situ, contact lenses (CLs) divide the tear film into pre- and postlens films (Fig. 1). This compartmentalization impacts the tear film in a number of ways, affecting both the biophysical and biochemical properties of the tear film. Contact lens wearers are recognized to exhibit significantly more ocular symptoms than nonwearers.²²⁻²⁴ In an attempt to determine the relevance of tear film changes to CLD, each of the tear film parameters is described for the non-CL-wearing eye and CL-wearing eye. Wherever possible, associations between the tear film changes and reported discomfort in CL wearers are discussed.

CHANGES IN THE BIOPHYSICAL PROPERTIES OF THE TEARS WITH CONTACT LENS WEAR AND THEIR EFFECT ON COMFORT

Blink Impact on Precorneal and Pre-Lens Tear Film Spread and Volume

The integrity of the tear film and of the superficial layer of ocular surface epithelium is codependent. Therefore, if

abnormalities are present in either one, a cycle of damage may be triggered at the ocular surface. For example, abnormalities in the tear film (presenting as an unstable tear film) can induce abnormalities in the ocular surface epithelium (presenting as decreased wettability and decreased barrier function) and vice versa, such that a suboptimal interaction between the tear film and the ocular surface epithelium ensues and is maintained in a cyclical fashion. Such possible interrelated vicious cycle mechanisms are presented here in the context of the tear film-CL interactions.

To help maintain clear vision and ocular surface health, eye blinks occur to distribute natural tears over the ocular surface, especially the corneal surface. Two major types of blink can be distinguished, complete and incomplete (partial), in which the eyelid covers more or less than 67% of the cornea, respectively.²⁵

It is reported that in healthy subjects, the proportion of incomplete blinking, for an unspecified vision task, can reach up to 20% of the total blinks.²⁶ The insertion of a CL onto the ocular surface might not modify the overall blinking frequency immediately; however, the following findings are repeatedly reported:

1. There is a higher percentage of incomplete blinks in rigid CL wearers.^{27,28}
2. Although no clear difference is observed in the frequency of incomplete blinks between soft CL wearers and control subjects, the correlation between the percentage of incomplete blinks and the grade of corneal fluorescein staining is much stronger in the eyes of subjects who wear soft CLs.^{25,29,30} Moreover, subjects with incomplete blinks reportedly suffer more from discomfort and dryness, and more lens deposits.^{25,31}

The ratio between the tear film breakup time (TBUT) and the interblink interval (IBI) defines the Ocular Protection Index (OPI). The ocular surface is considered to be protected when the TBUT matches or exceeds the IBI ($\text{OPI} \geq 1$). In the case of a blink rate of 12 per minute (mean IBI, 5 seconds) and a TBUT

of 4 seconds, an incomplete blink creates an approximate 10-second IBI, thus resulting in exposure of the corneal, conjunctival, and/or CL surface areas due to the lack of tear film integrity.

When the blink rate is reduced to 8 per minute during reading,³² the mean IBI is 7.5 seconds, and an incomplete blink increases the IBI of the exposed cornea, conjunctiva, or CL surface to approximately 15 seconds. However, when the blink rate is only 4 per minute, as is commonly observed during computer use,³³ the mean IBI is 15 seconds, and an incomplete blink creates an IBI of approximately 30 seconds for the exposed cornea, conjunctiva, or CL surface. Thus, incomplete blinks lead to a prolonged IBI, which in turn might result in increased evaporation and impaired tear film lipid layer (TFLL) spread over the ocular surface.

Studies have shown that in patients with dry eye and in subjects with CL (soft or rigid)-related dry eye symptoms, the blinking frequency is increased from 15.5 blinks/minute to more than 20.3 blinks/minute in order to compensate for the tear film instability.^{34,35} In the case of rigid CLs, the increased blinking frequency might also be the result of continuous increased frictional wear between the CL, palpebral conjunctiva, and the cornea.

Thus, serious attention must be paid to the reports^{36,37} that a CL care solution containing wetting agents might restore the normal blinking frequency (an indication of restored ocular comfort and tear film stability), while rewetting drops^{38,39} have just a temporary (up to 10 minutes) effect. The difference in the time scale of the beneficial effect of CL care solutions compared to the rewetting formulations indicates the possibility that the polymeric agents adsorbed to the CL surface gain much longer residence time at the ocular surface in comparison to compositions instilled as eye drops.

Lipid Layer Interferometry

The multilayer TFLL located adjacent to the mucoaqueous tear layer comprises nonpolar meibomian lipids (primarily wax and sterol esters) spread on top of a polar lipid surface.⁹ Two major functions of the lipid layer are to lower the tear surface tension, thus allowing the tear film to maintain its high area-to-volume ratio, and to inhibit the aqueous tear evaporation.¹⁰ Various instruments (and associated techniques) have been developed to visualize the tear film compartments and lipid layer, including the Doane interferometer,⁴⁰ King-Smith interferometer,² the Keeler Tearscope⁴¹ (Keeler Ltd., London, UK), and the DR-1 specular microscope.⁴² On the basis of these microscopy observations, six- and five-grade scales for visually assessing the TFLL have been proposed, which consider the thickness and uniformity of the lipid layer.^{43,44}

Over a CL surface, the grade of the lipid layer frequently deteriorates, indicating a thinning lipid layer,⁴³ due to lack of a sufficiently thick aqueous layer (a necessary prerequisite for TFLL spread), and/or forms patches with poor wettability.⁴⁴ Although soft CLs with high water content maintain a thicker aqueous layer immediately after insertion of the lens (and thus a high-grade lipid layer), they do not provide a long-term resolution.⁴⁵ Experiments evaluating the effect of low air temperature and low relative humidity on the tear film on the surface of soft CLs with different water content revealed that CLs with higher water content were more vulnerable to drying and after prolonged wear, these lenses resulted in thinner tear films with shorter noninvasive breakup time (NIBUT).⁴⁶ If the aqueous tear layer becomes too thin, direct interaction between tear film lipids and the CL surface becomes possible, and the formation of lipid deposits takes place.⁴⁷ The lipid deposition is especially problematic for silicone hydrogel CLs where, after continuous wear, hydrophobic lipid-attractive

patches readily appear over the CL surface. Once formed, lipid deposits result in impaired optical quality and nonwettability of the lens surface (with the latter resulting in instantaneous breakup of the film).⁴⁸

The quality of the TFLL and of the tear film in general can be evaluated by measurement of lipid layer spread with its subsequent fitting to exponential kinetics, for example, the Voigt model of viscoelasticity.⁴⁴ It has been found that a thicker lipid layer in eyes with sufficient aqueous tear shows significant elastic contribution in spreading, while in aqueous tear-deficient dry eye induced due to CL wear or other reasons, the extent of lipid layer spread decreases and the viscous contribution to its spread becomes dominant. Indeed, lipid layer spread becomes much slower after 8 hours of soft CL wear (measured as a >4-fold increase of the exponential time constant describing the spread kinetics).⁴⁹ The impaired lipid spread is thought to correlate with the thinner aqueous layer formed over the soft CL surface, particularly over the surface of silicone hydrogel CLs, in which the nonwettable hydrophobic silicone moieties might reorient themselves toward the lens surface after an initial breakup event.⁴⁷ This dramatic delay of lipid layer spread⁴⁹ is somewhat indicative of the deterioration of the CL surface experienced in the course of daily use, and reflects the decreased aqueous tear volume observed during daily CL wear.⁵⁰

Tear Film Stability

Qualitative changes in the lipid layer appearance manifest clinically as alterations in the tear film integrity, described as the stability of the preocular tear film, a clinical index of which is the tear breakup time. In the non-CL-wearing eye, thinner lipid layers have been associated with shorter tear breakup time measurements, and thicker layers with increased breakup times.^{12,51-55}

Tear film stability does not remain constant throughout the day. Decreases in TBUT have been observed in non-CL wearers immediately after awakening⁵⁶ and also toward the end of the day,⁵⁷ with the latter observation proposed to contribute toward increased end-of-day discomfort reported by office workers and CL wearers. Over the longer term, TBUT has been shown by a number of investigators to reduce with age⁵⁸⁻⁶⁰ while others have observed no difference with age.⁶¹ Sex also appears to have an effect on tear film stability, with females reported to exhibit reduced TBUTs relative to age-matched males.^{24,60,61} Conflicting effects of low ambient relative humidity on noninvasive tear film breakup in the non-lens-wearing eye have been reported.^{46,62}

Contact lenses disrupt the TFLL^{53,63} and reduce tear film thickness.^{3,64} The disruption is most marked with rigid lens wear, where typically no pre-lens lipid layer is visible clinically,⁶⁵ and tear breakup occurs within 2 to 3 seconds in contrast to values around 5 to 6 seconds over a soft CL.^{41,66} Larger, less mobile soft CLs have greater potential to support a pre-lens TFLL, but this lipid layer tends to be thinner and consequently susceptible to more rapid breakup than the non-CL tear film,⁶⁷⁻⁶⁹ irrespective of lens material.^{70,71} Overall tear film thinning has been shown to be significantly faster on the surface of a CL than on the corneal surface,⁷² This instability may be related to a thinner pre-lens film, but it has been proposed that even where the pre-lens and preocular tear films are similar in thickness, the pre-lens tear film is still considerably less stable.² The location of tear film breakup is also influenced by the presence of a CL, with the locus of tear film breakup of the pre-lens film most often being central, while that of the non-lens-wearing eye is more frequently parameniscal.⁷³ Although CL dehydration has been implicated as a major factor in the development of CL-related dry eye in

high water content soft lens wearers,⁷⁴ more recent evidence suggests that dehydration plays a less significant role⁷⁵; and the mechanism involved in the thinned lipid layer and reduced stability is related more to alterations in the lipid layer structure, possibly due to the affinity of the polar components of the lipid layer to the CL surface, resulting in increased tear evaporation and lens surface dewetting.⁵⁵

Comparison of the preocular tear film before and after CL wear highlights significant decreases in breakup time initially^{70,76,77}; but, over the longer term, preocular tear film breakup (without a CL in situ) appears to be largely unaffected by CL wear, irrespective of the material or wear regimen, with similar effects observed for continuous and daily wear.^{53,77,78}

In CL wearers, reduced pre-lens breakup times have been associated with increased symptoms of discomfort, both in hydrogel and silicone hydrogel lens wearers.^{70,75,78-86} Based on the differences in pre-lens breakup time between symptomatic and asymptomatic individuals, Hom and Bruce⁸⁷ suggested a cutoff TBUT value of 3 seconds as a suitable criterion for identifying tear film dysfunction likely to cause dryness symptoms in CL wearers.

With respect to tear film stability, consistent comfort differences relating to lens material have not been established, but environmental conditions have been described as further affecting symptoms of dryness and stability of the pre-lens tear film. Maruyama and colleagues⁴⁶ found reduced tear film thickness and breakup times in conditions of low relative humidity (20%), suggesting that increased evaporation plays a role in this process. In the presence of a soft CL, this was associated with increased symptoms of discomfort. Higher lens water content was found to correlate with increasing dryness symptoms, but not to tear film breakup.⁴⁶

Significant differences in NIBUT have been reported between CL wearers described as either tolerant or intolerant on the basis of their ability to tolerate lens wear for a period of at least 6 hours.⁷⁶ Tolerant wearers averaged a NIBUT of around 20 seconds in comparison to 13 seconds for intolerant wearers. Interestingly, the pattern of pre-lens tear film drying⁸⁸ on the CL surface was shown to vary with tolerance to CL wear, with all intolerant CL wearers exhibiting a streak pattern of breakup in comparison to tolerant wearers, in whom more spot breakup patterns were observed. Stepwise discriminant function analysis, used to predict tolerance or otherwise to ≥ 6 hours of lens wear, indicated that, of the broad range of tests performed, tear film stability indices (NIBUT and drying pattern) were the most highly predictive measures of tolerance.⁷⁶ Others, too, have conceded from a range of tests that NIBUT, combined with lid parallel conjunctival folds (LIPCOP) and Ocular Surface Disease Index (OSDI) score, provided the best predictive power (positive predictive value 87%, accuracy 91%) for symptom development in new CL wearers.⁸⁹

In a subsequent study by the same group, the effect of 6 hours of soft CL wear on a similarly large range of tear parameters was compared in tolerant and intolerant wearers.⁹⁰ At baseline, NIBUT was confirmed to be significantly shorter in the intolerant group than in the tolerant group. However, it was found, with CLs in situ, that NIBUT significantly declined over the 6-hour wear period in the tolerant group only, such that their mean NIBUT postwear was reduced to a level not significantly different from that of the intolerant wearers, with or without CL wear. It was postulated that reduced tear flow rates and phenol red thread test results in the intolerant group compared to the tolerant group after CL wear could be attributed perhaps to tear film instability.⁹⁰ The predictive nature of NIBUT in this study is consistent with that in the non-lens-wearing eye, where stepwise multiple regression analysis has shown that, along with ocular surface sensitivity, NIBUT is a significant predictor of symptoms as measured by

the OSDI.⁹¹ Chui and colleagues,⁷⁷ conversely, were unable to confirm NIBUT as a predictor of CL success (defined as ≥ 12 hours of wear without signs or symptoms), either alone or in combination with the phenol red thread test, as a measure of tear secretion.

As the tear film breaks up on the CL surface, a further consequence is degradation in visual performance.⁹²⁻⁹⁴ Changes in the CL hydration or changes in the quality of the tear film may also result in variations in visual performance.^{93,95} Given a shorter NIBUT associated with CLD and intolerance to CLs, there may be greater visual compromise associated with discomfort, and possibly blurring of the vision may provide one of the stimuli to blink in those patients in whom the pre-lens NIBUT is shorter than the interblink period.

Tear Film Evaporation

The normal tear film is lost from the ocular surface by evaporation, absorption, and drainage. Tear film evaporation is believed to be the main determinant of tear film thinning,^{96,97} and is acknowledged as a key component in tear dynamics and the development of dry eye.⁹⁸ Excessive evaporation of the tear film is recognized to cause tear hyperosmolarity triggering a cycle of ocular surface inflammation.¹⁷

With few exceptions,⁹⁹ the published literature reports that tear evaporation rates increase in dry eye,¹⁰⁰⁻¹⁰⁵ typically in association with a loss of integrity of the tear lipid layer.¹² The lipid layer has long been recognized to play an important role in inhibiting tear film evaporation^{13,106} on the basis of animal studies, and this has been confirmed in human studies where a 4-fold increase in tear evaporation is observed in the absence of a clinically visible or continuous lipid layer.¹² Reduced lipid layer integrity in the non-CL-wearing eye most commonly results from posterior blepharitis (most commonly meibomian gland dysfunction [MGD]) and anterior blepharitis^{17,107,108}; and associations of these conditions with symptoms of dry eye, tear film instability, age, and sex have been reported.^{102,109,110} Environmental conditions can also affect the rate of tear film evaporation, with increased rates apparent in healthy eyes, under conditions of low relative humidity.⁶²

It is generally accepted that tear evaporation increases with age, particularly in females.¹¹¹⁻¹¹³ Although other studies also reported higher evaporation rates in females than in males, the relationship with age was not confirmed.^{61,114}

Paradoxically, the application of artificial aqueous supplements has been shown to cause an immediate increase in the rate of tear film evaporation,¹¹⁵ a phenomenon attributed to tear film disruption upon instillation, most specifically disruption of the superficial lipid layer. Supporting this hypothesis are the more recent counter observations that the rate of tear evaporation can be decreased following supplementation with natural or artificial lipids.^{116,117}

Inconsistencies in evaporation rates described in the literature have been attributed to subject selection, measurement techniques, and instrumentation.¹¹⁸ Published studies reporting evaporation rates in the non-CL-wearing eye are summarized in Table 1.

The rate of tear film evaporation has been demonstrated to increase with a CL in situ.^{98,120,126,129} It is generally accepted that the physical presence of a CL disrupts the normal tear film structure, and in particular the lipid layer, facilitating a more rapid loss of tear fluid by evaporation. This is supported by research describing decreased tear film stability in the presence of a CL.^{70,71} Under constant environmental conditions, researchers have failed to demonstrate consistent differences in the tear evaporation rate with different lens materials, even between rigid and soft lenses.¹²⁰ As with non-CL-wearing eyes, there is significant variation in tear evapora-

TABLE 1. Evaporation Rates Reported for the Non-Contact Lens-Wearing Eye

Authors	TER ± SD, ×10 ⁻⁷ g/cm ² /s	TER Measurement Technique
Hamano and colleagues (1980) ¹¹⁹	26.9	Pressure gradient, open chamber (in contact with tears)
Tomlinson and Cedarstaff (1982) ¹²⁰	109.2 ± 49.3, at 70%	Resistance hygrometry
Cedarstaff and Tomlinson (1983) ¹²¹	119.8 ± 39.9, at 50% RH	Resistance hygrometry
Rolando and Refojo (1983) ¹²²	4.1 ± 0.4, at 29.5% RH	Change in relative humidity measured within closed chamber filled with dry air
Herold (1987) ¹²³	68.9 ± 18.9	Vapor pressure
Tomlinson and colleagues (1991) ¹²⁴	12.5 ± 6.9	Vapor pressure
Tomlinson and Cedarstaff (1992) ¹²⁵	166.7 ± 5.0, at 70%	Resistance hygrometry
Tsubota and Yamada (1992) ⁹⁹	15.6 ± 3.8, at 40% RH	Vapor pressure
Tomlinson and Giesbrecht (1994) ¹¹⁴	10.6 ± 6.6	Vapor pressure
Mathers and colleagues (1993) ¹⁰³	14.7 ± 6.4, at 30% RH 12.1 ± 5.5, at 40% RH	Change in relative humidity measured within closed chamber filled with dry air
Craig and Tomlinson (1997) ¹²	0.39 ± 0.37, at 48% RH	Vapor pressure
Goto and colleagues (2003) ¹⁰⁹	4.1 ± 1.4	Change in relative humidity measured in ventilated chamber system with air flow
Thai and colleagues (2004) ¹²⁶	10.8 ± 5.3	Vapor pressure
Guillon and Maissa (2010) ¹¹¹	16.6, median 15.9, at 30% RH 13.7, median 11.4, at 40% RH	Change in relative humidity measured within closed chamber filled with dry air
Khanal and colleagues (2009) ¹⁰¹	5.8 ± 2.8	Vapor pressure
Dogru and colleagues (2011) ⁸²	4.1 ± 0.3, at 30%-50% RH	Quartz crystal humidity sensor
Arciniega and colleagues (2011) ¹²⁷	5.5 ± 2.0, at 30% RH 3.8 ± 1.3, at 40% RH	Change in relative humidity measured within closed chamber filled with dry air
Kimball and colleagues (2010) ⁹⁶	53.9 ± 71.5	Extrapolated from spectral interferometry*
Petznick and colleagues (2013) ¹²⁸	26.8 ± 2.4	Extrapolated from infrared thermography

TER, tear evaporation rate.
* Includes four dry eye patients.

tion rate values between research groups for CL wearers; however, overall, the literature shows that CLs typically result in a 1.2× to 2.6× increase in the rate of tear evaporation relative to the non-lens-wearing eye, with no clear pattern relating to either lens form or water content (Table 2).^{120,126,129} It does, however, appear possible to differentiate lens types under adverse environmental conditions. Kojima and colleagues¹³⁰ found significant increases in evaporation rate in wearers of hydrogel lenses but not silicone hydrogel lens wearers¹³⁰ following exposure to a controlled adverse environment chamber that was significantly drier at 18%

relative humidity (RH) than the ambient environment (30%-40% RH).

Increased tear evaporation rates lead to dryness and discomfort symptoms in CL wearers. Kojima and colleagues¹³⁰ noted a relationship between increased tear evaporation and ocular discomfort in nonadapted CL wearers fitted with hydrogel lenses (etafilcon A) and exposed to a controlled adverse chamber environment with RH of 18%. Interestingly, however, no differences in either symptoms or evaporation rate were observed for neophytes fitted with silicone hydrogel lenses (narafilecon A) under the same conditions.¹³⁰

TABLE 2. Summary of Studies Reporting Tear Evaporation Rates in Contact Lens Wearers

Authors	% Increase in TER During Lens Wear		Lens Type	Lens WC, %	RH, %
Tomlinson and Cedarstaff (1982) ¹²⁰	216	PMMA			
	216	Paragon-18 (PMMA)			
	191	Silicone elastomer: Silsoft (Bausch and Lomb, Rochester, NY)			70
	187	Hydrogel Sauflon (Sauflon Pharmaceuticals Ltd., Twickenham, UK)		70	
Cedarstaff and Tomlinson (1983) ¹²¹	258	Hydrogel Cibasoft (Alcon, Fort Worth, TX)		38	
	135	Hydrogel 70%		70	
	138	Hydrogel 55%		55	70
	155	Hydrogel 38%		38	
Thai and colleagues (2004) ¹²⁶	127	Hydrogel: polymacon		38	
	123	Hydrogel: omafilcon A		62	
	142	Hydrogel: phemfilcon A		38	
	138	Silicone hydrogel: balafilcon A		36	NS
	140	Hydrogel: etafilcon A		58	
Guillon and Maissa (2008) ⁹⁸	156	Hydrogel		NS	30
	167	Hydrogel		NS	40

NS, not stated; PMMA, Polymethyl methacrylate; WC, water content.

Tear Film Temperature

The temperature of the normal ocular surface, and thus the adjacent tear film, is lower than core body temperature on account of its exposed location, somewhere on the order of 32°C to 36°C.¹³¹ Mean ocular surface temperature in dry eyes is reported to be similar to^{132,133} or slightly higher than that in normal eyes.^{134,135} Increased ocular surface temperatures measured in uveitis¹³⁶ suggest that the increased temperature in dry eye is likely attributable to ocular surface inflammation, a key element in dry eye.^{17,134}

Technological advances, resulting in the advent of noncontact infrared thermography, have enabled measurement of ocular temperature with significantly improved sensitivity as well as spatial and temporal resolution.^{133,134,137,138} This has led to the observation by most researchers that the ocular surface temperature varies across the exposed surface, with the normal cornea being warmest at the limbus and coolest centrally.^{134,139} With the exception of one study,¹³³ this temperature differential between the limbus and corneal center has been shown to be greater in dry eye, such that the central cornea is significantly cooler, relative to the limbus, in dry eyes than in normal eyes.^{100,134,135,140} The faster rate of cooling observed postblink in dry eyes has been attributed to a more rapid rate of tear film evaporation.¹³⁵

The relationship recognized to exist between tear film stability and ocular surface temperature^{46,100,141} suggests that ocular surface thermography is an indirect measure of tear film stability.¹⁴² More recently, thermography has also become recognized as a surrogate for evaporation rate measurement.^{113,128}

Variations in participant characteristics, study design, and methodology between published studies evaluating the effect of CLs on tear film temperature preclude direct comparison of their results. Participant age and health status, as well as the environmental conditions and the precise measurement site on the eye, can affect the results. The invasive nature of some earlier techniques, in contrast to the noncontact techniques reported more recently, further compounds this issue.

In one of the earliest reports, with thermistors embedded in scleral lenses, Hill and Leighton¹⁴³ observed insignificant temperature differences in the presence of the CLs, although temperatures increased significantly during eye closure. Hamano,¹⁴⁴ too, observed only small differences (<0.5°C) between eyes with and without rigid CLs using a noncontact radiometer. Conversely, Fatt and Chaston,¹⁴⁵ with a noncontact bolometer, recorded a more significant difference in ocular surface temperature, of 0.5 to 1.5°C, between hard CL wearers and non-lens-wearing eyes. They found the ocular surface temperature in soft CL wearers to differ no more than 0.5°C from the naked eye temperature. Also evaluating soft CLs, Martin and Fatt¹⁴⁶ detected insignificant differences in temperature beneath hydrogel lenses, using a technique with thermistors sandwiched between thin hydrogel CLs, although again they were able to observe significant temperature increases during eye closure. Montoro and colleagues,¹⁴⁷ as one of the first groups to use the current standard technique of infrared thermography with customized analysis software, identified irregular thermal patterns in a group of 19 CL wearers.

More sensitive current techniques indicate that the temperature of the pre-lens tear film in soft lens wearers is cooler than that of the non-CL-wearing eye,¹⁴⁸ while the temperature of the postlens tear film beneath the CL is higher.¹³¹ Lens materials with high water content and a correspondingly rapid rate of water loss show lower lens surface temperatures in situ than those with low water content.¹⁴⁸ This difference between lens materials is reflected

in ocular surface temperatures (postlens tear film), which increase beneath all CL materials,¹⁴⁶ but more so with silicone hydrogel lenses than with hydrogel lenses.¹³¹ This is attributed to the higher bound-to-free water ratio, which results in a lower rate of water loss from silicone hydrogel lenses.¹³¹

Few studies have directly evaluated comfort and ocular surface temperature in CL wearers. Hill and Leighton¹⁴⁹ experienced some success in correlating temperature-related sensations described by subjects to corneal temperatures assessed by thermistor units embedded in scleral CLs. Some predictive value could be assigned to specific descriptors, and it was concluded that tear film temperature could reflect the neural contributions that influence subjective experience.¹⁴⁹ However, such a study has not been performed with the high-resolution thermographic technology available now. Lowering the ocular surface temperature with cooled (4°C) artificial tears reduces ocular surface sensitivity and improves comfort.¹⁵⁰ This might suggest that, if ocular surface temperature is raised in CL wear, the concept of reducing ocular surface temperature could be advantageous. However, this should be viewed in conjunction with the hypothesis put forward that cold neuroreceptors in the corneal and lid margin may be partly responsible for CLD (see Report by the Subcommittee on Neurobiology).

Tear Film Thickness

The precorneal tear film (PCTF) is regarded as an important layer in keeping ocular surface wet and smooth so that epithelial integrity and sharp vision can be maintained. The thickness of the PCTF is a key parameter that relates to tear secretion, spreading, evaporation, and drainage. Previously no consensus could be reached on tear film thickness, mainly on account of the difficulty in measuring a fluid layer that is highly dynamic in nature.¹⁵¹ However, it is generally accepted that the total tear film thickness is around 3 µm.¹⁻⁴

Each blink alters the tear distribution, resulting in variation of the tear film thickness.^{151,152} During each blinking cycle, the tear film thickness varies within a couple of microns.¹⁵¹ If the blinking is delayed (by the subject's consciously refraining from blinking),¹⁵¹ the tear film thickness increases to approximately 7 µm due to reflex tearing. Recently, ultra-high-resolution optical coherence tomography (OCT) has been used to corroborate these measurements.¹⁵³⁻¹⁵⁵ The tear film begins to thin during the open-eye period due to redistribution and evaporation.^{1,72,151}

Nichols and King-Smith⁶⁴ found that the pre-lens tear film (PLTF) was approximately 2 µm with interferometry, which was about the same as measured at 3 minutes after lens insertion using ultrahigh-resolution OCT.¹⁵³ When the measurement was taken at the time of lens insertion, the PLTF was higher, at around 6 µm, due to reflex tearing or surplus lens wetting solution.¹⁵³ The PLTF thickness can be altered by adding drops onto the lens; however, the increase of the PLTF is transient (approximately 10 minutes) (Fig. 2).¹⁵³ Interferometry measurements reveal that PLTF thickness might be approximately 1 µm thinner compared to the 3.5-µm-thick PCTF and that the PLTF thinning rate is higher compared to that of PCTF (which in turn leads to a shorter TBUT of the PLTF).^{2,64,72,156}

The postlens tear film (PoLTF) may play an important role in the interactions with the ocular surface and may impact lens movement and ocular comfort.¹⁵⁷⁻¹⁵⁹ Depletion of the PoLTF may also cause lens adherence¹⁶⁰ and surface staining,^{31,159} which have to do with CL-related complications^{154,161} and discontinuation.^{23,162} The thickness of the PoLTF at the center location of the cornea is approximately 1 to 3 µm (Fig. 3),^{3,36,64,153,156} in agreement with other studies. In contrast,

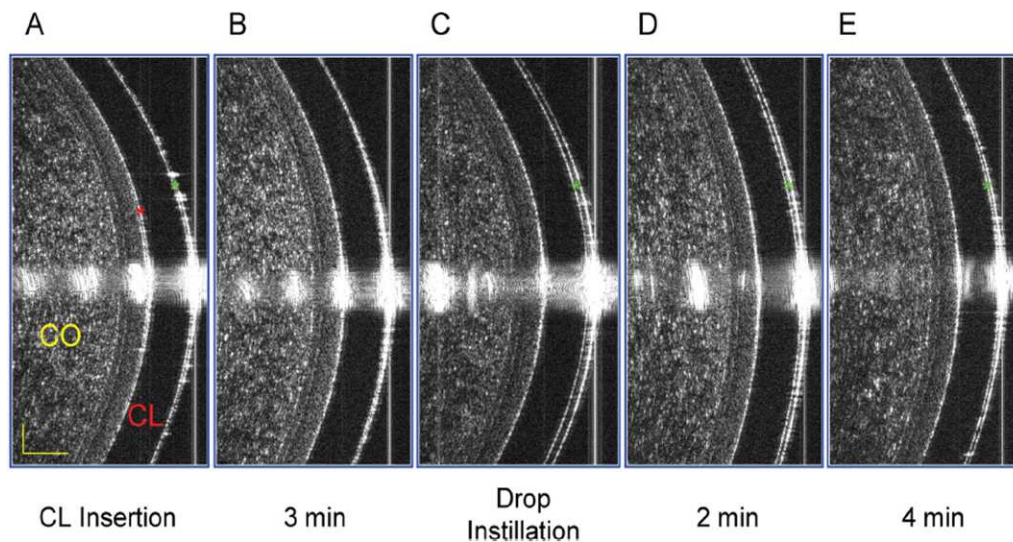


FIGURE 2. Changes in the PLTF and PoLTF after lens insertion followed by one drop of artificial tears on the convex surface of the lens. (A) A soft CL was inserted onto the cornea (CO) without the aid of artificial tears. Immediately afterward, the PLTF (green) and PoLTF (red) were visualized by spectral-domain ocular coherence tomography. (B) Three minutes later, the PLTF and PoLTF were no longer visible, as they became too thin. (C) One drop (35 μ L) of artificial tears instilled onto the lens did not increase the PoLTF, whereas the PLTF was clearly increased immediately afterward. (D, E) In the following minutes, the PoLTF never increased sufficiently to become visible, using ultrahigh-resolution (UHR)-OCT in this study, and the PLTF decreased gradually with blinking. Reproduced from Chen et al. Ultrahigh-resolution measurement by optical coherence tomography of dynamic tear film changes on contact lens. *IOVS*. 2010;51:1988–1993.¹⁵³

Lin and colleagues¹⁶³ found the central PoLTF to be approximately 11.5 μ m using optical pachymetry. It may be slightly thicker at the time of lens insertion, and rapid thinning is evident.^{64,153} The PoLTF remains thin irrespective of the instillation of artificial tears.¹⁵³

Tear Production/Turnover

Quantification of tear production during CL wear has received limited attention, in part because of the technical difficulty of measurement. The earliest attempts by Hamano and colleagues (1983)¹¹⁹ employed a wetting measure, the phenol red thread test, to overcome the problems of repeatability and consistency with the Schirmer test. Thread wetting was not found to increase with CL wear. Sørensen and colleagues (1980)¹⁶⁴ were the first to use tear clearance as a measure of tear flow in 14 individuals before and after 1 month of adaptation to a Soflens CL (Bausch & Lomb, Rochester, NY). They used a gamma camera to assess the rate of new tear production through observation of the elimination of a radioactive tracer, technetium, from the conjunctival sac. The fractional turnover rate with a soft CL presoaked in the technetium solution was similar to the rate with a solution instilled directly into the eye.¹⁶⁴

Other investigators have observed the elimination of a fluorescein dye from the eye to measure tear production during CL wear.^{165–168} Puffer and colleagues (1980)¹⁶⁵ studied 51 normal subjects with a simple method that permitted measurement of the rate of fluorescein loss from the central PTCF. No statistically significant correlations were found between tear elimination coefficient and sex, eye color, or CL wear.¹⁶⁵ Occhipinti and colleagues (1988)¹⁶⁶ were the first to employ the automated scanning fluorophotometer (Fluorotron; OcuMetrics, Mountain View, CA) and found no significant difference in tear turnover rate (TTR) in CL wearers compared with nonwearers.

The use of either an automated scanning fluorophotometer or slit lamp-mounted fluorophotometer offers potentially the most accurate measure of TTR in CL wear without the cost and

inherent restrictions of the gamma camera. The use of small molecular weight fluorescent tracers, however, confounds measurement due to dye penetration into soft CLs.^{168,169,170} Notwithstanding this difficulty, the TTR appears to decrease significantly in CL wear compared with the non-CL-wearing eye.¹⁰⁷ An average TTR of 15.5%/minute is typical of normal young subjects without lenses.^{167,171–175} Further experiments with a more likely nonpenetrating tracer, 70-kDa fluorescein-isothiocyanate (FITC) dextran, were carried out on a group of 20 habitual wearers.¹⁶⁸ The measures with a conventional hydrogel lens, etafilcon A (Acuvue 2; Johnson & Johnson Vision Care, Inc., Jacksonville, FL), and silicone hydrogel lens, balafilcon A (PureVision; Bausch & Lomb), and with no lens showed TTRs of 12.4%/minute, 13.2%/minute, and 16.4%/minute, respectively. Therefore fluorophotometric measurements of TTR with this tracer showed no statistically significant difference in the presence of a CL, consistent with the consensus from previous studies.

In an attempt to relate tear production in CL wear to the discomfort experienced by some CL wearers, Tomlinson and colleagues¹⁷⁶ compared tear physiology in symptomatic and asymptomatic wearers. Subjects with symptoms of CL dry eye (CLDE) had a significantly lower basal TTR (in the absence of a lens) than asymptomatic subjects (Fig. 4); TTR in this study was measured with the Fluorotron (OcuMetrics) immediately after CL removal. This finding is in accord with the speculation of Glasson and colleagues⁹⁰ of reduced tear flow in intolerant wearers. Thai¹⁷⁷ had previously shown that values on CL removal were consistent with the normal basal tear flow rate. No significant differences between the groups were found for tear evaporation, osmolarity, or tear breakup time. The greater basal tear production facility in asymptomatic patients may offset the loss of tear fluid due to the increased tear evaporation rate induced by CL wear.^{104,120,178}

Tear Volume

Tears are secreted by the lacrimal gland and approximately 4.5 μ L is distributed into the cul-de-sac, approximately 2.9 μ L into

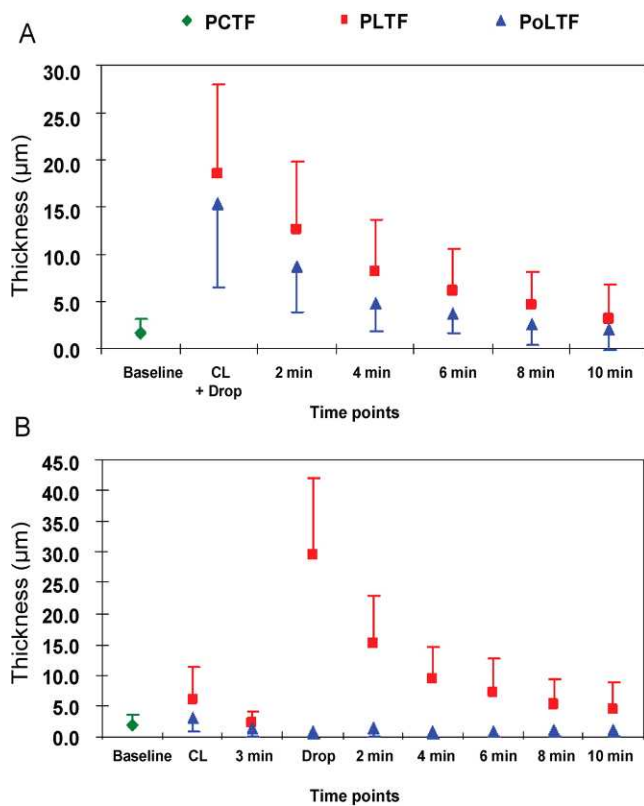


FIGURE 3. Changes in the PLTF and postlens tear film PoLTF after lens insertion. (A) One drop (35 μL) of artificial tears was placed on the concave surface of the lens before insertion. The PLTF and PoLTF were immediately increased compared with the precorneal tear film (PCTF; post hoc tests, $P < 0.05$). The PLTF decreased continuously for the next 8 minutes (post hoc test, $P < 0.05$), and the PoLTF decreased in a similar fashion ($P < 0.05$). (B) After lens insertion without prior application of a drop of artificial tears to the concave surface, the PLTF was immediately thicker than the PCTF at baseline ($P < 0.05$). After 3 minutes of lens wear, both the PLTF and PoLTF decreased significantly compared with the moment of lens insertion ($P < 0.05$). When 35 μL artificial tears was instilled on the lens, the PLTF increased significantly and then decreased gradually in the following 8 minutes ($P < 0.05$). However, the PoLTF did not increase immediately after drop instillation and also did not change in the following 10 minutes (Repeated measures ANOVA, $P > 0.05$). Reproduced from Chen et al. Ultrahigh-resolution measurement by optical coherence tomography of dynamic tear film changes on contact lens. *IOVS*. 2010;51:1988-1993.¹⁵³

the tear menisci, and approximately 1.1 μL into the preocular tear film.¹⁷⁹ During the blinking cycle, some of the tears drain into the drainage system (via the puncta) or evaporate into the air. The volume remains as a dynamic balance so that a certain amount of tears is always available to form the tear film by lid spreading.¹⁵¹ In the normal tear system, as little as 2 to 4 μL of the tear volume on the ocular surface is required for the maintenance of a wet surface.^{151,179} With each blink, the tears are mixed and redistributed.¹⁸⁰ The movement of the eyelids acts as a pump by compressing the canaliculi and lacrimal sac and promoting drainage of tears. The tear volume must maintain a relatively steady state.^{152,179,181-184} Under normal circumstances, the drainage system itself is thought to contain a negligible volume of tears.¹⁸⁵ It appears that only a small variation in the tear menisci occurs during blinking and the small amount of tears constantly available is sufficient to keep the ocular surface wet. While blinking and eye opening have little effect on normal tear volume, spreading during blinking and evaporation during the open-eye period may cause minor

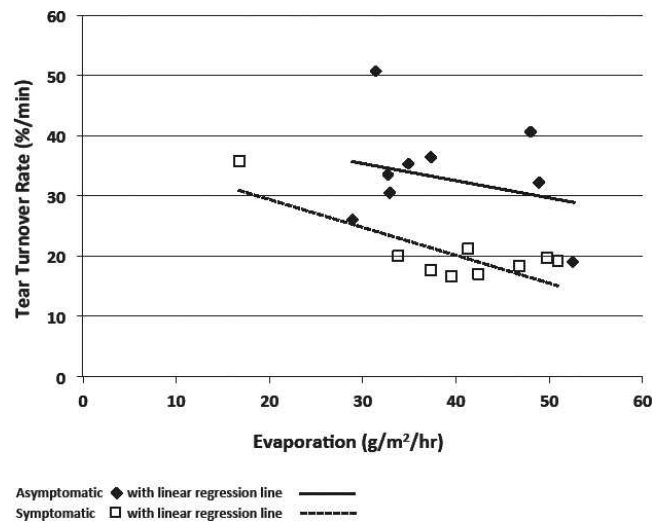


FIGURE 4. Tear turnover and evaporation rates in symptomatic (of contact lens dry eye) and asymptomatic contact lens wearers. Adapted with permission from Tomlinson et al. Why do some contact lens wearers avoid contact lens dry eye symptoms? Poster presented at: 91st Annual Meeting of the American Academy of Optometry; October 24-27, 2012; Phoenix, AZ.¹⁷⁶ Copyright [date if known] [name of copyright holder].

variations in tear distribution (Fig. 5).¹⁵¹ In contrast, the tear volume increases during restricted blinking,¹⁵¹ instillation of artificial tears,¹⁸⁶ and punctal occlusion.¹⁵³ Through overloading of the tear volume with repeated instillation of saline solution, increased blink output into the drainage system is evident.^{151,187,188} The phenomenon indicates that the capacity of the ocular surface to hold excessive tears is limited. It may also indicate that the system may be regulated, presumably by the lower tear meniscus through the drainage system.^{151,152}

Tear volumes with CLs in situ have been estimated by imaging the upper and lower tear menisci using OCT.¹⁵³ Compared to the tear meniscus volume (approximately 1.5 μL) on the ocular surface,¹⁵¹ a reduced tear meniscus volume (approximately 1 μL) on the CL surface is evident.¹⁵³ It is important to note that the tear volume decreases over time during CL wear.¹⁸⁹ Chen and colleagues¹⁸⁹ studied tear meniscus volumes in symptomatic lens wearers, asymptomatic lens wearers, and asymptomatic non-lens wearers. New lenses were worn by these groups for 10 hours, and tear menisci were imaged using OCT. The results showed significant decreases in the tear meniscus volume over the study period (Fig. 6).

In a follow-up study,⁵⁰ a significant relationship between ocular comfort and upper, lower, and total tear meniscus volumes was established following 10 hours of lens wear in symptomatic and asymptomatic lens wearers (Fig. 7). The weak but significant relationships demonstrated a negative impact of the tear meniscus volume on ocular discomfort, although this would suggest, perhaps, that the tear meniscus volume may not be solely responsible for the decreased ocular discomfort.

In summary, there is no direct evidence based on published studies showing the relationship between tear film thickness (pre- or posttear film) and ocular discomfort in CL wearers. However, decreased tear meniscus volumes appear to be related to ocular discomfort at the end of the day.⁵⁰ Similar findings with intolerant CL wearers have been reported by Glasson and colleagues.⁷⁶

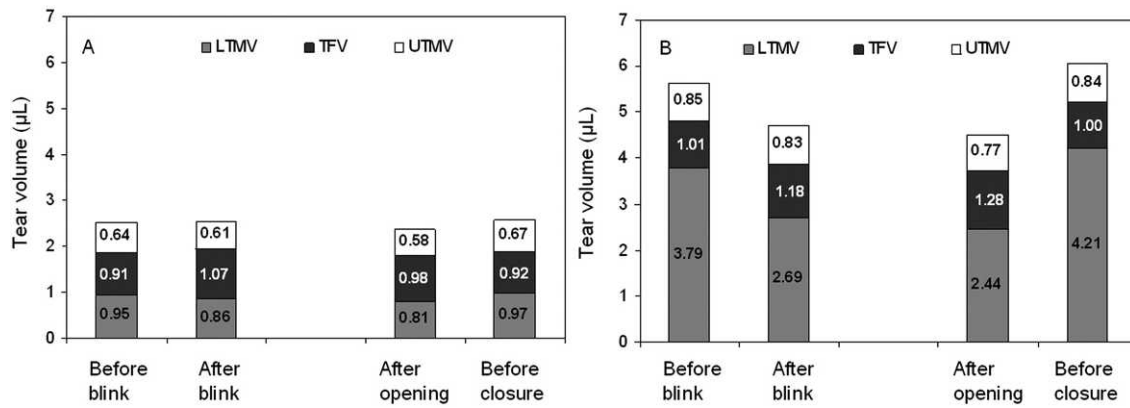


FIGURE 5. Total tear volume during normal and delayed blinks in 21 subjects. The upper tear meniscus volume (UTMV), tear film volume (TFV), and lower tear meniscus volume (LTMV) were estimated during normal (A) and delayed (B) blinks. The tear volume was greater during delayed blinking than during normal blinking ($P < 0.01$). Most of the change was due to increases in the LTMV (B). Both UTMV and LTMV were higher ($P < 0.001$) during delayed blinking (B) compared with normal blinking (A). The UTMV and LTMV increased significantly at the end of the eye-opening period compared with the beginning during delayed blinking ($P < 0.05$). Reproduced from Palakuru et al. Effect of blinking on tear dynamics. *IOVS*. 2007;48:3032-3037.¹⁵¹

Tear Film Profile at the Edge of a Soft CL

Soft CLs cover a portion of conjunctiva, which is soft tissue.⁵⁰ The conjunctiva appears to distort at the lens edge. The interaction between the lens edge and conjunctiva may occur because of different pressure profiles¹⁹⁰ that are produced across the ocular surface underneath each lens.^{191,192} It may be possible to have a tear meniscus around the lens edge at the

point of lens insertion or on instillation of artificial tears.¹⁵⁴ However, the tear meniscus around the soft CL edge appears much smaller than that around the hard lens edge.¹⁵⁴ With excessive tears from tearing or instillation of artificial tears, the tear film can be augmented around the periphery of the lens, with the thickest layers at the inferior portion of the lens due to gravity.

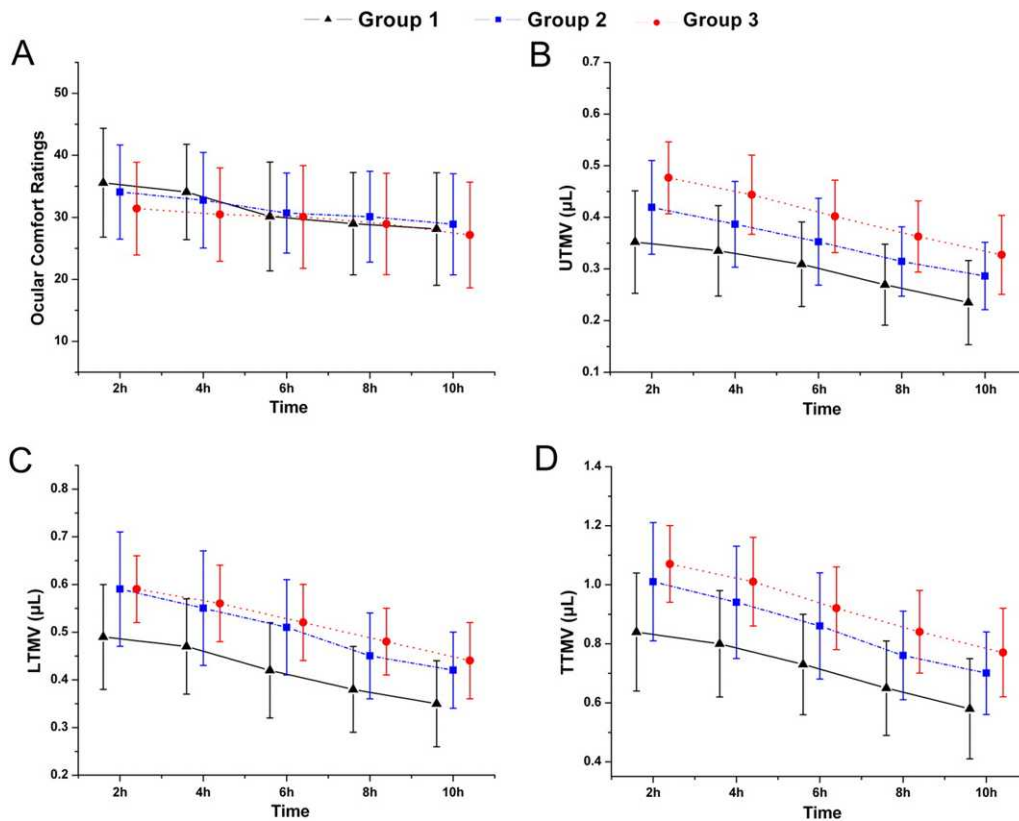


FIGURE 6. Ocular surface comfort ratings (A) and UTMV (B), LTMV (C), and TTMV (D) during 10 hours of contact lens wear. Group 1, experienced contact lens wearers with dry eye complaints; group 2, experienced contact lens wearers without dry eye complaints; group 3, inexperienced contact lens wearers without dry eye complaints. Reproduced from Chen et al. Tear menisci and ocular discomfort in symptomatic wearers. *IOVS*. 2011;52:2175-2180.⁵⁰

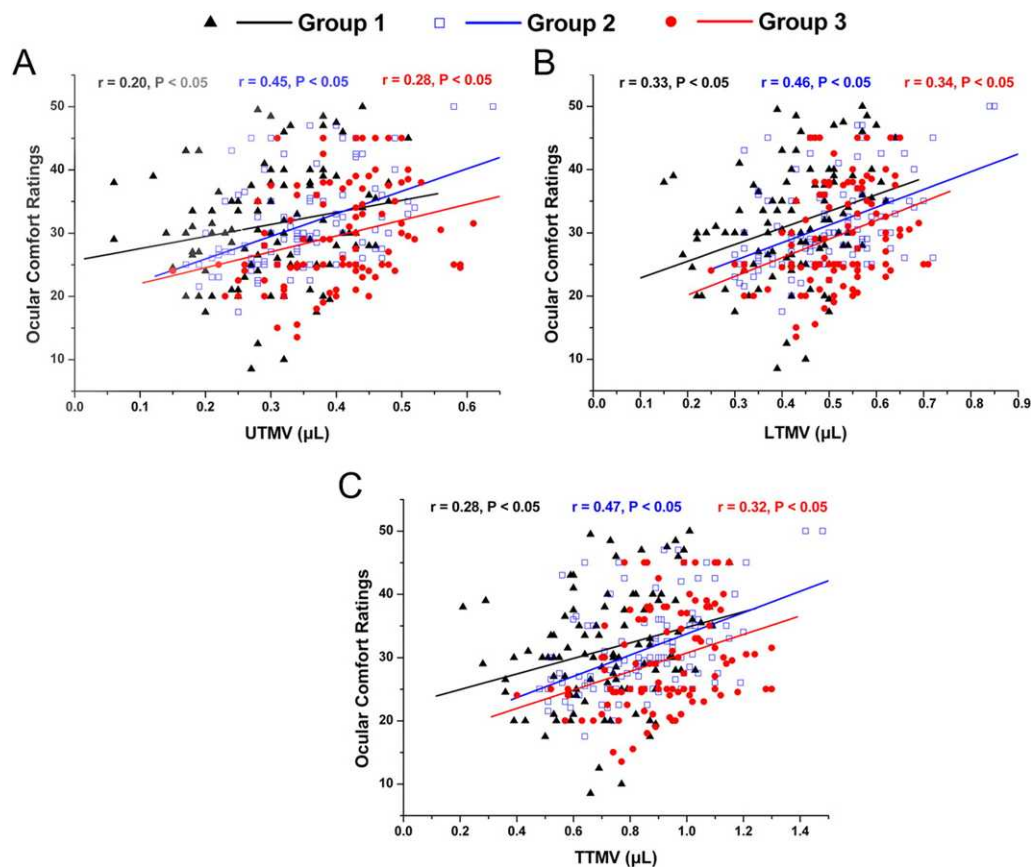


FIGURE 7. Ocular comfort ratings and tear meniscus volumes. Group 1, experienced contact lens wearers with dry eye complaints; group 2, experienced contact lens wearers without dry eye complaints; group 3, inexperienced contact lens wearers without dry eye complaints. For the individuals of each group, the comfort level at each time point during the 10 hours of lens wear was plotted against the simultaneous UTMV (A), LTMV (B), and TTMV (C). During the 10 hours of contact lens wear, there were significant positive correlations between the ocular comfort ratings and each of the calculated volumes ($P < 0.05$). Reproduced from Chen et al. Tear menisci and ocular discomfort in symptomatic wearers. *IOVS*. 2011;52:2175–2180.⁵⁰

Evaluation of the PoLTF peripherally may reveal more information on lens fitting tightness and matching between lens design and ocular surface. Using ultrahigh-resolution OCT, two gaps beneath the lens, filled with PoLTF, can be visualized.^{50,154} One type of PoLTF can be found at the peripheral cornea, and the other one can be found at the limbal junction area. The thickness of the PoLTF beneath the lens edge ranges from several micrometers up to approximately 60 μm .¹⁵⁴ It appears that the PoLTF may vary depending on lens design and material.¹⁸⁹

Tear Exchange

From mathematical formulas, Weissman¹⁹³ inferred that flexure of a -3.0 -diopter (D) lens should exchange approximately 0.01 μL fluid per diopter. Lubrication theory predicted 10% to 20% tear exchange at each blink for a normal blink with the usual tear film thickness.¹⁹⁴ Using fluorophotometry and a nonpenetrating tracer, the measured T95 (time to deplete 95% of a fluorescent dye from beneath a CL) was 27.3 minutes, and the tear exchange turnover rate was calculated to be 9.0%/minute.¹⁹⁵ In another study conducted by McNamara and colleagues,¹⁹⁶ the mean tear mixing rate was 1.82%/minute with a 12-mm-diameter CL, 1.61%/minute with a 12.5-mm-diameter CL, 1.34%/minute with a 13-mm-diameter CL, and 1.24%/minute with a 13.5-mm-diameter CL. Ocular surface OCT has been used to track tear mixing beneath the CL edge (Wang J, et al. *IOVS* 2011;52:ARVO E-Abstract 3628). In a small

sample of five eyes, tear mixing was evident. Preliminary data showed that the 95% decay time was approximately 10 to 20 minutes (Wang J, et al. *IOVS* 2011;52:ARVO E-Abstract 3628). The tear exchange or mixing during lens wear may be regulated by the interrelationships between four variables: lens diameter and movement, the blink, and tear replenishment rate.¹⁹⁶

Osmolarity

Tear osmolarity or the saltiness of tears can be regarded as an indicator of the balance between the production of tears and their elimination via evaporation, drainage, and absorption.¹⁰⁵ The main contributors to tear film osmolarity are the electrolytes of the aqueous phase, principally the cations sodium and potassium and the anions chloride and bicarbonate; proteins and sugars play a minor role only.^{197–199} Mean tear film osmolarity measurements in the normal eye range between 283 and 318 mmol/kg, with an average value of approximately 302 mmol/kg.^{197,200} It must be noted that osmolarity is commonly determined for tears from the lower meniscus, and it has been speculated that the osmolarity across the ocular surface might be significantly higher due to the variable effects of evaporation.^{201,202} Generally, the sex of an individual and the hormonal cycle do not affect tear osmolarity, but increased osmolarity can be observed throughout the day and with increasing age.^{112,172,203–209} While there seems to be agreement that reflex tearing results in decreased tear film

osmolarity, measurements on patients with epiphora remain equivocal.²¹⁰⁻²¹⁵ Tear osmolarity measurements find their most frequent application in the diagnosis of dry eye. The measurement of tear osmolarity has been suggested as a gold standard in the diagnosis of dry eye, as the often observed elevated levels (hyperosmolarity) are considered a core mechanism in symptoms and ocular surface damage in this condition.^{17,63,214} A comprehensive summary of causes and effects of tear film hyperosmolarity in dry eye is provided in the 2007 TFOS Report of the Dry Eye Workshop.¹⁷

During CL wear, tear film osmolarity undergoes a series of changes. Initially, the insertion of a CL results in a reduction of tear film osmolarity, potentially caused by some reflex tearing during the early adaptation to the lens.²¹⁵⁻²¹⁷ This initial reduction has been considered as a cause for PoLTF depletion with subsequent lens adherence and a contributor to corneal swelling, although all osmolarity measurements at the current time are limited to the tear meniscus. A subsequent increase in osmolarity is often observed.²¹⁶⁻²¹⁸ However, there remains some debate as to the level of tear osmolarity over time, the effect of lens type and wear modality, and the effect on ocular comfort. Some authors have reported that tear film osmolarity will return to or remain at its pre-CL insertion level,²¹⁷⁻²¹⁹ while others report an increased level, postremoval, compared to baseline.^{216,220,221} A summary of tear osmolarity values during CL wear is given in Table 3. Farris²²² demonstrated that wear of soft CLs on an extended-wear basis and hard lenses on a daily-wear basis significantly increased tear osmolarity, but such effect was not observed with soft lenses worn on a daily-wear basis. In contrast, other authors have shown significantly increased tear film osmolarity with soft daily-wear lenses.²²¹ So far, no differences in tear osmolarity have been demonstrated between hydrogel and silicone hydrogel CLs.^{219-221,223,224}

Until recently, most studies assessing tear film osmolarity required a large tear volume and consequently the collection of large amounts or dilution of the sample with subsequent recalculation. It must be considered that these requirements may have hindered the observation of subtle differences between lens types. Increased tear film osmolarity during CL wear has been attributed to two main factors: reduced tear production due to reduced corneal sensitivity, and excessive evaporation due to a disrupted tear film and reduced tear film stability.^{214,225} Considering that these mechanisms are similar to those in dry eye, there has been some interest in the impact of tear osmolarity in CL wear on ocular comfort. Nichols and Sinnott⁵⁵ demonstrated significantly higher osmolarity values in participants with CL-induced dryness. Glasson and colleagues⁷⁶ found that symptomatic CL wearers tended to display a high tear film osmolarity even without CLs. However, in a study by Stahl and colleagues,²²¹ an association between tear osmolarity and ocular comfort during CL wear could not be shown.

Ferning

Tear ferning refers to the distinct crystallization pattern that appears when tears are allowed to air dry on a glass slide. This image of fern-like crystals is most commonly assessed, under white light microscopy, on a simple qualitative grading scale from I (complete, uninterrupted ferning pattern with no spaces between ferns) to IV (total absence of ferning),²²⁹⁻²³⁸ although other quantitative methods, such as area assessment through counting the number of micrometer lattice squares^{239,240} or digital image analysis have been applied.^{241,242} As outlined by Golding and Brennan,²⁴³ as well as Pearce and Tomlinson,²⁴⁴ there remains some discussion as to which components of the tear film are responsible for the successful development of tear ferns. However, there seems to

be agreement that it is not the level of a single component but rather the ratio between the organic salts and macromolecules that will determine the quality of the ferning pattern.²⁴³⁻²⁴⁵ The majority of individuals display a tear ferning pattern of grade I or II.^{231,246} An increase in the tear ferning grade, reflecting abnormal tear functionality, can be seen with age,²³⁴ CL wear,²²⁹ in the morning,²³³ and in conditions such as keratoconjunctivitis sicca,^{231,232,246} Sjögren's syndrome,²⁴⁷ Down syndrome,²⁴⁸ and cystic fibrosis.²⁴⁹

The potential benefits of tear ferning in predicting CL tolerance were first described by Kogbe and Liotet.²⁵⁰ Besides being able to predict discomfort, it was also possible to identify individuals with excessive protein deposition, as they would display a grade I ferning pattern but with subtle differences such as big and very closely branched ferns, with the branches being significantly more curved. Defining CL intolerance as cessation of CL wear due to ocular symptoms, deposition, or ocular health issues, Ravazzoni and colleagues²⁵¹ found that grades I and II before the first lens fit can be used as predictors for CL tolerance with a sensitivity of 57.9% and a specificity of 88.5%. With a more strict approach using only grade I as predictive of tolerance, a sensitivity of 78.95% and specificity of 78.35% were achieved. The sensitivity and specificity of the prediction could even be improved further if tear ferning was performed after 1 month of CL wear. Using tear ferning in a group of established CL wearers and nonwearers, Evans and colleagues²²⁹ demonstrated a significantly higher tear ferning grade in lens wearers. However, the authors were not able to show a significant correlation to ocular symptoms, assessed via the Ocular Comfort Index questionnaire, or to demonstrate a difference in tear ferning patterns between symptomatic and asymptomatic lens wearers. The authors concluded that tear ferning provided good accuracy for discriminating between lens wearers and non-lens wearers but that the prediction of dry eye symptoms was rather poor. However, a negative predictive value of 86% indicated that normal tear ferning grades could be considered a good predictor for good ocular comfort during CL wear.

Tear ferning is an indication of tear functionality, and only limited information is available about tear ferning in CL wearers or the relationship to ocular comfort. To draw valuable conclusions about tear ferning in CL wear and the association to ocular comfort, more controlled studies are needed, including studies that assess the correlation between tear ferning in neophytes and ocular comfort during lens wear assessed via questionnaires, the impact of lens type, or the impact of length of lens wear on tear ferning. Currently, Rolando's grading scale is the most commonly used method to assess tear ferning.²³² Although Pensyl and Dillehay²⁵² showed good intra- and interobserver repeatabilities when assessing proportions of tear ferning samples, Rolando's method is based on a subjective grading, and Norn^{239,240} demonstrated poor repeatability using this latter system.

pH Measurement

Different methodological approaches have estimated the pH of the normal tear film to be within the 6.5 to 7.8 range.²⁵³⁻²⁵⁸ The tear film pH varies throughout the day, shifting from acid to alkaline, but such variations are contained within fairly narrow limits, usually a range of approximately 0.6 of a pH unit.^{34,256,259} Stimulation of tear secretion and blinking lead to acidification, whereas eyelid opening leads to alkalization by equilibration with the partial pressure of the CO₂ in the surrounding air.²⁵⁷

The tear film has been shown to be more acidic in CL wearers, decreasing between 0.27 and 0.53 pH units.^{255,258} This decrease has been observed in the tear fluid behind the

TABLE 3. Summary of Tear Film Osmolality Findings During CL Wear

Authors	Subject Group	Tear Osmolarity, mmol/kg	Type of Osmometer
Sarac and colleagues ²¹⁹	Hydrogel	295.0 ± 1.4	In situ tear osmolarity system
	Silicone hydrogel	298.8 ± 7.2	
Stahl and colleagues ²²¹	Baseline	314.4 ± 13.9	Vapor pressure osmometer
	Hydrogel	323.1 ± 13.3	
Glasson and colleagues ²²⁶	Silicone hydrogel	321.5 ± 17.6	Vapor pressure osmometer
	Baseline	322.4 ± 16.7	
Nichols and Sinnott ⁵⁵	Hydrogel	318.1 ± 12.8	Freezing point depression osmometer
	Subjects with CL-induced dry eye	307.7 ± 32.4	
Miller and colleagues ²²³	Subjects without CL-induced dry eye	297.1 ± 31.4	Vapor pressure osmometer
	Control, non-CL wear	305 ± 21	
	Hydrogel daily wear	319 ± 30	
	Silicone hydrogel continuous wear	319 ± 32	
Iskeleli and colleagues ²²⁷	RGP	324 ± 25	Freezing point depression osmometer
	Hydrogel daily wear, 55% H ₂ O	312.2 ± 16.0	
	Hydrogel daily wear, 38.6% H ₂ O	316.5 ± 12.1	
	RGP, 90 Dk	313.1 ± 9.7	
Dabney and colleagues ²²⁴	RGP, 52 Dk	316.4 ± 11.6	Vapor pressure osmometer
	Control, non-CL wear	309.0 ± 17.0	
	Hydrogel	313.7 ± 28.5	
	Silicone hydrogel	324.3 ± 41.7	
Martin ²¹⁶	RGP	317.0 ± 13.0	Freezing point depression osmometer
	Baseline	316	
	Hydrogel lens eye	331	
Farris ²²²	Contralateral eye	320–326	Freezing point depression osmometer
	Aphakic nonwear control	321 ± 9	
	Aphakic extended wear	318 ± 7	
	Phakic RGP daily wear	316 ± 6	
	Phakic hydrogel daily wear	309 ± 8	
	Phakic hydrogel extended wear	318 ± 7	

Dk, oxygen permeability. Defined as the amount of oxygen passing through a contact lens material over a defined period of time and pressure difference, unit is 10^{-11} (cm³ O₂ cm)/(cm³ sec mmHg). Although studies have used different osmometers and therefore units varied, for simplification, all units are considered as mmol/kg. Adapted from Stahl U, Willcox M, Stapleton F. Osmolality and tear film dynamics. *Clin Exp Optom.* 2012;95:3–11. Copyright 2012 John Wiley & Sons, Inc.²²⁸

CL, both in gas-permeable and impermeable lenses, and has been attributed to the lens preventing CO₂ loss from the eye.²⁵⁵

There is limited evidence to support the notion that alteration in tear film pH affects CLD. It has been suggested that acidic changes in pH during CL wear could contribute to tight lens syndrome, based on data demonstrating decreased hydration of soft CLs induced by acidification.^{256,260}

Viscosity

Natural tears display non-Newtonian behavior, dependent upon the shear rate.²⁶¹ This shear-thinning behavior with higher-viscosity fluids at low shear rates, as occurs during the open-eye state, is necessary for the tears to contribute to the lubrication of the ocular surface without damage during a high shear rate situation such as blinking. Viscosity values of normal human tears have been reported in the range of 1 mPa·s at high shear rate (~ 120 s⁻¹) to up to 10 mPa·s at lowest shear rate (~ 0 s⁻¹).^{261–264} The underlying mechanism is not well understood, and the components involved are still questioned. It was originally thought that soluble mucins were the main components contributing to the viscosity of tears,^{261,262,265} but more recently the involvement of tear proteins and lipids has been suggested.^{262–264} Loss of shear-thinning behavior has been reported if the tear lipids are removed, but artificial mixtures of proteins containing lysozyme or lactoferrin can also exhibit shear-thinning behavior^{263,264}; subsequently, Gouveia and Tiffany²⁶⁴ have proposed an interactive role between the proteins and lipids with protein-protein and protein-lipid

interactions responsible for the viscous properties of tears.²⁶³ Slight differences in viscosity have been reported with dry eye disease²⁶³; however, the effect of CL wear on tear film viscosity is currently unknown, and it is not known whether there is a change in viscosity with CLD.

Surface Tension

The stability and spreading of the tear film is governed by the balance of the interfacial forces acting at the air-tear film, tear film–cornea, and cornea–air interfaces. A negative correlation has been shown between surface tension measures of the tear film and the rate of tear film breakup; that is, the higher the surface tension, the quicker the tear film breakup.²⁶⁶ The tear film surface tension is approximately two-thirds that of water²⁶⁷ or saline.²⁶⁸ Therefore, evaluation of the equilibrium surface tension (pressure) at the air-tear film interface is important for understanding the stability of tear film and its ability to spread.²⁶⁹

At one time it was believed that mucin in tears was a major contributor to surface tension,²⁷⁰ but more recent evidence suggests that the concentration of mucin needed (0.5% or 5 mg/mL)^{268,270} exceeds that present in normal tears (estimated as 32 ng/mL Mucin 5AC a protein encoded by the gene *MUC5AC*).²⁷¹ Another possible confounder of previous results was the use of nonocular mucin (often bovine submaxillary mucin or porcine gastric mucin) in place of ocular mucin. Tests have shown that purified bovine ocular mucin has no surface activity even at concentrations 100 times higher than those normally occurring in tears²⁷² and that purified rabbit ocular

mucin has only weak surface activity.²⁷³ Furthermore, the initial assays demonstrating that removal of tears and mucin from the cornea left a hydrophobic surface^{274,275} have been questioned, as the treatments were harsh. Using more gentle removal of mucin has been shown to leave behind a wettable hydrophilic epithelium.²⁷⁶⁻²⁸¹ The tear film lipids are likely to be the most important contributors to the surface tension of tears, as delipidating tears increases their surface tension, and adding back the lipids restores this to its previous value.²⁷³ The polar components of the tear film with their amphipathic nature are likely to be key contributors to the spread of the lipid layer upon the aqueous component of tears.

There are several methods available to measure surface tension. These include a Wilhelmy plate used together with a Langmuir trough for tension measurements at a planar air-water interface^{272,282,283}; an axisymmetric drop/bubble shape analysis for tension determination at curved surfaces of pendant drops^{284,285} or sessile bubbles.²⁸⁶⁻²⁸⁸ Using a capillary tube and determining the pressure needed to flatten a meniscus of tears, the surface tension of reflex or basal tears collected by capillary tubes is 42 to 46 mN/m^{273,289} and is 46.6 ± 3.8 mN/m using a Wilhelmy balance.²⁶⁸

Data using an artificial TFL²⁹⁰ have shown that during increases in surface pressures (as would be seen during blinking),²⁹¹ the area/molecule may be too small to accommodate all lipids (polar and nonpolar) at the air-aqueous interface, and it is most likely that the nonpolar lipids deposit upon the polar lipids. These *in vitro* data also demonstrated that at all pressures the lipid layer was most likely inhomogeneous, with condensed domains of nonpolar lipids above a layer of polar lipids.²⁹⁰ Results of other *in vitro* experiments, performed by adding saturated or unsaturated cholesterol or wax esters to lipid films made of human meibum, have been taken to indicate that the bulk nonpolar layer of the tear film contains liquid crystals of cholesterol esters interacting with wax esters. To date, work on the polar tear film lipids has focused on the role of phospholipids. Phosphatidylcholine or sphingomyelin can restore the surface tension of delipidated tears²⁷³ in a capillary meniscus model, and dipalmitoylphosphatidylcholine can interact strongly with meibum lipids.²⁹²

Although the role of mucin in the surface tension of tears has been largely discredited (see above), there may be a role for tear film proteins. Several investigations using monolayers of meibomian gland lipids have shown that proteins or mucins can penetrate them, and some proteins change the associated surface pressure.^{272,283,285,293,294} Lipocalins in tears have been shown to have some surface activity,²⁸⁵ and adding back a mimic of tear film lipocalin (bovine beta-lactoglobulin) with lipids can improve the surface tension of saline.²⁷³ Millar and colleagues²⁹⁵ concluded that the effect of lipocalin on the TFL was complex and depended on the types of lipids present in the lipid film and adsorbed to lipocalin. Proteins that can be isolated by high-performance liquid chromatography (HPLC) in the 23-minute fraction (likely to be lipophilins) from rabbit tears are surface active and can decrease tear surface tension. They are associated with increases in tear breakup time *in vitro*.²⁹⁶ The presence of divalent cations in rabbit tears may also influence tear film stability, as chelators of these can decrease the tear film surface pressure and decrease the breakup time of rabbit tears on eye, but these ions do not appear to play the same role in human tears.²⁹⁷

Most of the studies discussed above have used monolayers of lipids, but lipids derived from the meibomian glands form multilayers, not monolayers,²⁹² and have a thickness of approximately 20 molecules.^{2,10,298-301} Svitova and Lin²⁶⁹ used lipids extracted from the surface of Iotafilcon A silicone hydrogel CLs (using toluene/isopropyl alcohol) and demonstrated that thick multilayers of these extracted lipids exhibited

a low surface tension (using sessile bubble apparatus) of 32 to 22.5 mN/m (depending on the thickness of the film) compared to monolayers (40 mN/m).^{272,285,294} Addition of lysozyme to these thick lipid layers did not alter their surface tension, but there was evidence that lysozyme could adsorb irreversibly to the lipid layer and increase the relaxation time of the layer.²⁶⁹

There is a paucity of information on the effect of CL wear on the surface tension of tears, or indeed on the components that may influence the surface tension of tears. One study has examined the role of different lipids on the ability of an artificial tear fluid (ATF) to wet the surface of a teflon A Hydroxyethyl methacrylate (HEMA)-based soft CL. Addition of various phospholipids, in particular phosphatidylinositol, was able to improve the ability of the ATF wet the lens surface,³⁰¹ although surface tension of the ATF with or without phospholipids was not measured.

Dry eye tears have increased surface tension, reported as 44 to 53 mN/m compared to 42 to 46 mN/m^{266,273} using the capillary tube method or 52.9 ± 7.4 mN/m compared to 46.6 ± 3.8 mN/m³⁰² using a Wilhelmy balance. As yet there appear to be no studies examining whether any form of CL wear changes the surface tension of tears, or evidence of a link with discomfort associated with CL wear.

Since the CL divides the tear film and creates new interfaces, it is critical that the PLTF components be able to spread over the anterior CL surface. Most hydrophobic tear lipids are unable to spread over the aqueous, and polar lipids are required to attain more favorable spreading conditions. In contrast to the non-CL situation, where tear aqueous components are able to spread over the cornea, in the presence of a CL, tear film aqueous spreading over a surface that is potentially already coated by tear lipids is compromised.³⁰³

Summary of Biophysical Changes to the Tear Film With CL Wear and Their Influence on Comfort

The physical presence of a CL *in situ* divides the tear film into a pre- and a postlens tear film and creates new interfaces with and within the ocular environment. This partition and new interaction has been shown to lead to biophysical changes of the tear film properties, including a decrease in tear film stability, pre-lens lipid layer thickness, and tear volume as well as an increase in evaporation rate, as summarized in Table 4. To date, the effect on comfort of many of these biophysical properties is unknown or inconclusive. However, evidence points toward a link between decreased stability, increased evaporation, reduced tear turnover, and ferning and CLD. Further evidence is required to establish the associations of tear volume, surface tension, osmolarity, pH, and ocular temperature with CLD.

CHANGES IN TEAR COMPOSITION WITH CONTACT LENS WEAR AND THEIR EFFECT ON COMFORT

Biochemistry

Tear Types. Challenges facing analysis of the tear film proteome include the volume and type of tears that can be collected. Tears have been classified into four types: basal, reflex, emotional, and closed-eye tears. Basal³¹³ (sometimes also referred to as open-eye) tears bathe the mucous membranes of the eye during the day and have a turnover rate between 3.4 μL/min³¹⁴ and approximately 1 μL/min,^{183,315} and a volume of approximately 7 μL.^{183,314} Reflex tears are produced upon stimulation of the lacrimal reflex by irritant substances or foreign particles. Emotional tears are produced as a result of various emotions, such as sadness. Closed-eye

TABLE 4. Summary of Major Effects of Contact Lenses on the Tear Film With Evidence, Where Possible, of Links to Contact Lens Discomfort

Parameter	Range in Precorneal Tear Film	Range in CL Wear, Pre-Lens Tear Film	Evidence of Relation to Contact Lens Discomfort
Blink	Interblink interval in healthy eye is 5–15 s. Most of the blinks are complete blinks. In cases of people working on display or exposed to other dry eye factors, interblink time and percentage of incomplete blink increase. ^{32,33,45}	Prolonged CL wear results in increased percentage of incomplete blinks (for rigid CL) and stronger association between tear film instability and percentage of incomplete blinks (for soft CL). CL wear frequently reduces blink frequency. CL wetting solutions can maintain normal blink frequency. ^{25,27–31,34,35}	Reduced blink frequency or increased percentage of incomplete blink resulted in CL discomfort. ^{2,27–30,47,64,72,156}
Lipid layer integrity	TFLL spreading and integrity can be analyzed to evaluate the viscoelasticity of the lipid layer. Elasticity prevails in healthy eyes, while the contribution of viscosity increases in dry eyes. ^{9,11,42,44,304}	TFLL spread depends on the CL material. Prolonged wear of CL frequently delays the kinetics of TFLL spread and worsens the TFLL integrity. ^{2,9,46,49,53,305,306}	Impaired TFLL integrity and spread correlates with CL discomfort. ^{9,44,45,49,50,53,307}
Tear film stability	NIBUT 4.6–>60 ^{43,51,53,54,56,57,59,70,308–311} TBUT 4.2–14.4 s ^{53,54,57,309,311,312}	Soft: 5–10.1 ^{53,66–70} PLTT: 8.23–11.03 ^{2,55,72} RGP: 2–3 s ^{41,66}	Decreased tear film stability associated with CL discomfort ^{70,75,78–86}
Evaporation	Range 0.4–167 g/m ² /h 12,81,96,99,101,103,109,111,114, 119–128	1.2–2.6× ↑ in evaporation ^{98,120,121,126}	Discomfort associated with increased tear evaporation in neophytes fitted with hydrogel CL (but not SiHy) at 18% relative humidity. ¹³⁰
Ocular surface temperature profile	32°C–36°C ¹³¹	Pre-lens tear film: cooler than without CL ¹⁴⁸ Postlens tear film: warmer than without CL ¹³¹	No clear relationship demonstrated between tear film temperature and discomfort in CL wear, although artificially lowering the ocular surface temperature, with cooled (4°C) artificial tears, reduces ocular surface sensitivity and improves comfort. ¹⁵⁰
Tear film thickness	1–7 μm ^{1,3,72,151,154,185,306}	Pre-lens: 1–7 μm ^{3,72,153,154,158,163,306} Postlens: <3 μm ^{3,72,153,154,158,163,306}	No evidence showing a link between tear film thickness and discomfort.
Tear turnover rate	16.9 ± 6.8 ¹⁶⁷ 16.2 ± 5.1 Range = 10.9–22.2 ¹⁰¹ 13.2 ± 4.5 Range = 5–32 ^{168*}	15.6 ± 5.9 ¹⁶⁷ 16.3 ± 7.2 Range = 5–29 ^{168*}	Symptomatic wearers 20.6 ± 6.0 Range = 16–36 Asymptomatic wearers 33.8 ± 8.8 Range = 27–42 ^{175†}
Tear volume	2–4 μL ^{50,151,152,185,188}	1–2 μL ^{185,188}	Lower tear volume has a weak but significant relation to discomfort in CL wear. ^{50,76}
Tear exchange	10%–20% per blink ¹⁹³	9.0%/min ¹⁹⁴ 1.82%/min with a 12-mm-diameter CL, 1.61%/min with a 12.5-mm-diameter CL, 1.34%/min with a 13-mm-diameter CL, and 1.24%/min with a 13.5-mm-diameter CL ¹⁹⁵	No link between tear exchange and ocular discomfort.
Osmolality/electrolytes	280–318 ^{197,200}	297–331 ^{55,216,219,221–224,226,227}	No association between tear film osmolality and ocular comfort has been established, ²²¹ although tendency toward higher tear film osmolality in patients with CL discomfort. ^{55,76}

TABLE 4. Continued

Parameter	Range in Precorneal Tear Film	Range in CL Wear, Pre-Lens Tear Film	Evidence of Relation to Contact Lens Discomfort
Ferning	Grades I to IV ^{231,232,234,235,239,252}	Grades I-IV ²⁵¹ Mean 2.02 ± 0.60 ²²⁹ $0.87 \text{ mm}^2/\mu\text{m}^2$ ⁴⁰	No correlation to comfort assessed via Ocular Comfort Index, but Grades I and II are good predictors for good ocular comfort. ²²⁹ Grades I and II are predictors for CL tolerance. ²⁵¹
pH	6.5–7.8 ^{254–259}	↓ in CL wear ^{255,258}	Limited evidence to support link between pH and discomfort. ^{256,260}
Viscosity	High shear rate 1 mPa·s Low shear rate 10 mPa·s ^{262–265}	No data	No evidence linking tear viscosity with contact lens discomfort.

SiHy, silicone hydrogel lenses.

* With high molecular weight FITC dextran tracer; † ex vivo immediately on CL removal.

tears are those tears that bathe the eye during sleep. The protein component of these tear types is known to be different; for example, the levels of secretory immunoglobulin-A (sIgA) decreases in concentration from closed-eye to basal to reflex tears.^{313,316–320} Other tear proteins such as lactoferrin, lipocalin-I, and lysozyme do not appreciably change their concentration in closed-eye, basal, and reflex tears.^{313,319} These findings led to the classification of different proteins in the tear fluid into constitutive (i.e., those that have a constant level of production and so their concentration decreases during increases in tear fluid production, e.g., sIgA),³¹³ regulated (i.e., those that have changes in production during changes in amount of tears, e.g., lysozyme, lactoferrin, and lipocalin-I),³¹³ and serum derived (which also decrease during increases in tear fluid production, such as albumin).³¹⁷ Emotional tears may differ from reflex tears by containing chemosignals (pheromones) that affect behavior³²¹ and having a slightly higher total protein concentration of 6 mg/mL compared to 4 mg/mL.³²² Table 5 lists the major tear proteins and their changes during CL wear.

Tear Collection Methods. There are essentially three methods for collecting tears: using a microcapillary tube to draw tears into the lumen of the glass tube (it is believed that this causes minimal change to the ocular surface and minimal reflex tearing), using a Schirmer strip placed into the lower fornix to adsorb tears, and using a sponge placed within the fornix to adsorb tears. It is well established that tears collected by Schirmer strip contain higher concentration of serum-derived proteins such as albumin, transferrin, and IgG³²³ compared with those collected by capillary tube. Due to the low volume of tears, even with normal eyes (approximately 7 μL per eye), some researchers have used a flush method to help collect tears. This involves instilling a volume of buffered saline onto the ocular surface, allowing that to interact, and collecting it usually using capillary tubes.³²⁴ While this method does dilute the tear sample, it may have advantages where the tear volume is low or it is difficult to collect sufficient tears for biochemical analysis.

Lipidome

The tear lipids are primarily secreted from the meibomian glands and form the outermost bilayer of the tear film.^{274,300} The TFL has an outer layer of nonpolar lipids at the air interface to retard water evaporation from the tear film and to protect from external contaminants and an inner layer of polar lipids that creates an interface with the aqueous layer to help

the spreading of the outer layer and increase its stability.^{9,12,13,106} The major lipid components of the meibomian gland secretion are nonpolar wax esters, cholesterol esters, diesters, and triacylglycerol, with smaller concentrations of cholesterol, fatty acids, and other polar lipids. Polar lipids account for 5% to 15% of the total lipids and are suggested to include phospholipids (phosphatidylcholine, phosphatidylethanolamine, sphingomyelin), ceramides, and cerebro-sides^{298,325,326} and more recently long chain (O-acyl)-omega-hydroxy fatty acid (OAHFA).^{327,328} The presence of phospholipids in meibum remains controversial,^{329–331} and OAHFAs have been suggested as being responsible for creating the interface between the aqueous and the nonpolar lipid layer instead of phospholipids.^{326,327} Limited information is available on the compositional analyses of tear film lipids. Recent research has shown that the lipid composition of tears is possibly more complex than that of meibum.³³² Nonpolar lipids in tears differ from those found in meibomian secretions.^{332–335} Also, in contrast to meibomian secretion lipids, several researchers have confirmed the presence of phospholipids in tears.^{335–340}

The clinical appearance, thickness, and stability of the pre-lens TFL have been shown to be disrupted by the presence of a CL (refer to section Lipid Layer Interferometry), and lipids are known to deposit on CLs (see TFOS Report from the Contact Lens Materials, Design and Care Subcommittee). Changes in the tear film lipid composition associated with CL wear could be expected; however, compositional analyses of tear film lipids during CL wear are very limited. Young and Hill^{341,342} measured cholesterol levels in normal subjects and subjects with CL problems; the cholesterol levels in the subjects with CL problems ranged from 389 to 435 mg/100 mL whereas the levels measured for normal subjects ranged from 190 to 203 mg/100 mL. In normal subjects, tear cholesterol levels were initially decreased after rigid CL fitting but returned to prefitted levels once adaptation was complete.³⁴² More recently, another study in soft CL wearers reported a negative association between the level of cholesterol esters in tears and the thickness of the lipid layer as well as a positive association between the level of cholesterol esters and dryness symptoms, with higher levels associated with increased dryness symptoms.³⁴³ Yamada and colleagues³⁴⁰ reported concentrations of phospholipids of 186 ± 39 and 162 ± 33 $\mu\text{g/mL}$ in tears of subjects wearing polyacon (group I) and etafilcon A (group IV) CLs, respectively, the latter being significantly lower than for the same subjects when not wearing CLs (220 ± 35 $\mu\text{g/mL}$, $P = 0.0023$). These findings are

TABLE 5. Concentration of Some of the Major Proteins in Tears and the Effect of CL Wear

Protein Type	Reflex	Basal*	Closed Eye	Lens Wear†
Total protein, mg/mL	6.0 ³¹⁹	9.0 ³¹⁹	18.0 ³¹⁹	5.4 ± 0.4 ³⁷²
	3.9–5.0 ³¹⁷	7.3 ³¹⁷	15.5 ± 8.4 ^{373§}	11.9 ± 2.0 ³⁷⁰
	4.6 ± 0.2 ³⁷²	3.4 ± 1.5 ^{373§}		5.6–6.6 ³⁴⁰
		9.4 ± 3.0 ³⁷⁰		7.2 ± 2.3 ³⁶⁷
		5.9 ± 1.5 ³⁴⁰		3.2 ± 1.5 ⁹⁰
		6.9 ± 1.4 ³⁶⁷		
		3.5 ± 1.3 ⁷⁶		
		9.5 ± 1.7 ³⁷¹		
		7.0 ± 1.7 ³⁶⁹		
		2.0 ³¹⁹		
Lysozyme, mg/mL	1.6 ³¹⁹	2.1 ± 0.2 ³¹⁷	1.8 ³¹⁹	4.0 ± 0.6 ³⁷²
	1.3–1.6 ³¹⁷	0.7 ± 0.6 ²²²	3.0 ³⁷⁵	2.9, closed eye, OK RGP ³⁷⁵
	1.5 ± 1.1 ²²²	2.5 ³⁷⁵		3.3 ± 0.4 ³⁷⁶
	2.7 ± 0.3 ³⁷²	3.0 ± 0.3 ³⁷⁶		1.9 ³⁷⁷
		2.2 ³⁷⁷		1.4–1.9 ³⁷⁴
		1.3 ± 0.7 ³⁷⁴		1.1 ± 0.5, RGP‡; 1.2 ±
		0.8 ± 0.4 ⁴²⁶		0.4, high water soft‡; 0.8 ± 0.2,
		1.6 ± 0.2 ⁷⁶		low water soft ⁴²⁶
				1.4 ± 0.3 ⁹⁰
				Decrease, SiHy, RGP ^{425‡}
Lactoferrin, mg/mL	1.8 ³¹⁹	2.6 ³¹⁹	1.8 ³¹⁹	1.5–1.7 ³⁷⁸
	1.3–1.5 ³¹⁷	1.6 ± 0.1 ³¹⁷	3.5 ³⁷⁵	3.3, closed eye, OK RGP ³⁷⁵
	4.0 ± 3.1 ²²²	2.9 ± 2.8 ²²²	1.8 ± 0.1 ³⁷⁹	1.1 ± 0.2 ³⁶⁷
	1.8 ± 0.4 ³⁷⁹	2.5 ± 0.9 ³⁷⁹		1.6 ± 0.9 ³⁶⁸
	1.5–1.8 ³⁸²	3.2 ³⁷⁵		1.6 ± 0.3 ³⁷⁶
		1.1 ± 0.3 ³⁶⁷		0.3–0.8 ³⁷⁴
		1.7 ± 0.5 ³⁶⁸		2.6 ± 1.0 ⁹⁰
		1.7 ± 0.1 ³⁷⁶		
		0.7 ± 0.8 ³⁷⁴		
		2.7 ± 1.1 ⁷⁶		
Lipocalin-1, mg/mL	1.9 ³¹⁹	1.3 ³¹⁹	1.7 ³¹⁹	3.2, closed eye, OK RGP ³⁷⁵
	1.1–1.3 ³¹⁷	1.6 ± 0.1 ³¹⁷	3.3 ³⁷⁵	
		3.5 ³⁷⁵		
		0.5 ± 0.9 ³⁵⁹		
sIgA, mg/mL	0.1 ³¹⁹	2.6 ³¹⁹	10.0 ³¹⁹	0.1 ± 0.1 ³⁸⁰
	0.1–0.2 ³¹⁸	0.2–0.9 ³¹⁸	2.3–8.4 ³¹⁸	5.0, closed eye, OK RGP ³⁷⁵
	0.1–0.4 ³¹⁷	0.9 ± 0.1 ³¹⁷	4.6 ³⁷⁵	1.1 ± 0.5 ³⁷⁰
	0.1 ± 0.1 ³⁸⁰	2.8 ³⁷⁵	0.8 ± 0.3 ⁹⁰	1.6 ± 0.5 ³⁶⁷
		0.8 ± 0.3 ³⁷⁰	3 ± 2 ³⁸³	1.5 ± 0.6 ^{382‡}
		1.7 ± 0.7 ³⁶⁷		1.2 ± 0.2, DW RGP; 0.7 ± 0.1, DW soft;
		2.6 ± 1.8 ³⁸²		0.6 ± 0.1, EW soft ³⁸¹
		0.9 ± 0.1 ³⁸¹		1.1 ± 1.6 ⁴²⁷
		1.3 ± 1.0 ⁴²⁷		0.7 ^{377‡}
		2.4 ³⁷⁷		1 ± 1, closed eye ^{383‡}
Specific sIgA, units	2.1 ± 2.7 (<i>S. epidermidis</i>) ³⁸⁰	82 ± 15 (<i>P. aeruginosa</i>) ³⁸¹		1.3 ± 2.0 (<i>S. epidermidis</i> ; reflex tears) ³⁸⁰
	9.0 ± 12.2 (<i>E. coli</i>) ³⁸⁰	100% (<i>P. aeruginosa</i>) ³⁸³		3.7 ± 3.4 (<i>E. coli</i> ; reflex tears) ^{380‡}
	6.0 ± 12.3 (<i>H. influenzae</i>) ³⁸⁰			2.7 ± 5.8 (<i>H. influenzae</i> ; reflex tears) ³⁸⁰
				67 ± 11, DW RGP; 52 ± 9, DW soft;
Albumin, µg/mL	20 ³¹⁹	100 ³¹⁹	1100 ³¹⁹	38 ± 6, EW soft (<i>P. aeruginosa</i>) ^{381‡}
	3.0–8.4 ³¹⁷	42.0 ± 4.7 ³¹⁷	760–1100 ³¹⁸	20% (<i>P. aeruginosa</i> ; DW and EW) ^{383‡}
	1830 ± 2440 ²¹⁹	380 ± 640 ²¹⁹	200 ³⁷⁵	540, closed eye, OK RGP ^{375‡}
	10–20 ³¹⁸	20–60 ³¹⁸		10.3–24.1 ³⁷⁴
	72.3 ± 71.2 ³⁸⁰	20 ³⁷⁵		49.8 ± 57.1 ³⁸⁰
		14.6 ± 8.6 ³⁶⁷		10.2 ± 3.0 ³⁶⁷
		12.5 ± 5.1 ³⁷⁴		
		14.6 ± 8.6 ³⁶⁷		

OK RGP, rigid gas-permeable lenses designed for orthokeratology.

* Used as default if tear type not mentioned.

† Compared to basal tears unless otherwise stated; soft lenses unless otherwise stated.

‡ Significant effect of contact lens wear.

§ Tears collected using flush method.

in agreement with another study showing an increase in the ratio of nonpolar to polar lipids in the tears of CL wearers.³⁴⁴ Further, a similar finding was reported in non-CL-wearing subjects with dry eye symptoms.³⁴⁵ A low level of phospholipids/polar lipids in tears could conceivably be a contributing factor to the dryness symptoms and discomfort reported during soft CL wear.

When the lipid layer is compromised and no longer able to supply full coverage over the aqueous layer, the tear film stability is significantly decreased and evaporation increased.^{12,98,106,346} Degradation of lipid components by autoxidation (or photooxidation), enzymatic oxidation, or enzymatic lysis is expected to have a deleterious effect on the layer.³⁰³

The presence of one or more double bonds (unsaturation) in the structure of certain lipids makes them susceptible to oxidation due to the availability of the allylic hydrogen.³⁴⁷ Hence, mono- or di-unsaturated fatty acids or esters present in the tears and, in particular, polyunsaturated fatty acids possibly originating from vascular leakage into the tear layer, are susceptible to autoxidation under the effect of light, atmospheric oxygen, and so on.³⁰³ Primary oxidation products, hydroperoxides, can then be further converted into secondary peroxidation products such as hydrocarbons, aldehydes, hydroxyaldehydes, and epoxides.³⁴⁷ Two aldehydes commonly used as markers of oxidative stress are 4-hydroxy-2(E) nonenal (4-HNE), a peroxidation product of linoleic acid (18:2 n-6) or arachidonic acid (20:4 n-6), and malondialdehyde, an end product of the degradation of linolenic acid (18:3).

Phospholipases are lipolytic enzymes found in tears, contributing to their antibacterial properties,³⁴⁸ that are able to degrade phospholipids into diacylglycerols and lysophospholipids; group II phospholipase A2 (sPLA2 GII) is the most abundant in tears and is secreted by both the acinar and ductal cells of the lacrimal gland.³⁴⁹⁻³⁵¹ There have been several reports of PLA2 in tears of CL wearers as well as deposited on hydrogel CL materials³⁵²⁻³⁵⁴ but without consensus on the effect of CL wear, with both no change and a reduction in concentration being reported. Group II phospholipase A2 hydrolyses the ester bond at the sn-2 position of phospholipids, producing a lysophospholipid and a free fatty acid, often arachidonic acid, a precursor in the production of eicosanoids such as prostaglandins and leukotrienes and known to be involved in ocular surface inflammation.^{355,356} The suspected presence of diacylglycerols and the lack of phospholipids in tear samples reported by Campbell and colleagues,³⁵⁷ in conjunction with phospholipase C activity, further highlights the possible role of lipolytic enzymes in modulating tear film lipid composition. In blepharitis patients, PLA2 activity has been shown to be enhanced and is hypothesized to cause the disruption of tear film phospholipids, compromising the function of the polar lipid layer and contributing to a breakdown of tear film structure.³⁵⁸ Intolerant wearers unable to wear their CLs for longer than 6 hours during the day were found to have an increased level of secretory phospholipase A2 (sPLA2) in the tears (1.86 ± 0.05 ng/ μ L, $P = 0.047$) compared to tolerant subjects (1.80 ± 0.08 ng/ μ L), as well as increased levels of degradation products, malondialdehyde and 4-HNE (0.85 ± 1.0 vs. 0.15 ± 0.15 μ M, $P = 0.004$).³⁵⁹ The enzymatic activity of sPLA2 was double (13.5 ± 51 vs. $7.3 \pm 2.4 \times 10^3$ cpm/protein unit, $P = 0.004$) that of tolerant wearers, with a 10-fold increase in the concentration of lipid degradation products. Both findings suggest greater lipid deterioration in intolerant wearers. The accumulation of sPLA2 on CL surfaces may also promote further hydrolysis of tear film phospholipids.

Finally, transfer of skin lipids and lipase not normally present in the tear film onto CLs and subsequent release in the

tear film can create compositional changes detrimental to tear film stability.³⁶⁰

Tear lipid chemistry is likely to be affected by CL wear. This effect will depend upon the characteristics of the CL but also on the individual patient tear composition. Studies of the tear lipid chemistry investigating nonpooled, individual samples are required to further understand the potential role of lipids in CL discomfort.

Proteome

The Tear Film Proteome. The tear film proteome (defined as all the proteins and peptides that can be identified from tears) has not yet been definitively described, although researchers have been examining the proteins of tears for many decades. Various techniques have been used to investigate the tear film proteome. These include one-dimensional polyacrylamide gel electrophoresis (PAGE) and Western blotting to identify and quantify the separated proteins; chromatography and mass-spectrometry (MS) techniques with additions such as isobaric tag for relative and absolute quantitation to enable quantification of proteins in the original sample; and enzyme-linked immunosorbent assays using specific antibodies to quantify proteins in a sample without prior separation of the proteins. The numbers of proteins in the tear proteome have been reported to vary widely. Using sodium dodecyl sulfate (SDS)-PAGE-MS to separate proteins and reverse-phase (RP)³⁶¹ capillary HPLC and matrix-assisted laser desorption/ionization (MALDI)-MS to identify peptides, Funke and colleagues³⁶² identified 267 proteins in tears collected from experienced soft CL wearers. Using nano-HPLC-MS/MS, de Souza and colleagues³⁶³ identified 491 proteins in the tear film of one individual. Zhou and colleagues,³⁶⁴ using various fractions of tears and nano-RP HPLC-MS/MS, identified 1543 proteins in tears collected from four healthy non-CL wearers, with 714 proteins being present in all samples. It has been estimated that the tear film proteome contains approximately 35% of proteins in common with the proteome of plasma,³⁶⁴ 25% of proteins in common with those found in saliva,³⁶⁵ and 24% of proteins in common with those found in urine.³⁶⁶ These findings indicate that tears contain many unique proteins as well as a smaller fraction of proteins in common with other human body fluids.

Table 5 gives details of the major proteins found in the tear film. The basal tear film contains 3.5 to 9.5 mg/mL total protein^{76,317,319,340,367-371} (as with all protein analyses, differences are partly due to collection methods, techniques to quantify proteins [i.e., Lowry, Bradford, bicinchoninic acid or fluorescence-based protein assays], and use of different standards [usually albumin but occasionally, e.g., IgG or soybean trypsin inhibitor]). The total protein concentration does not change significantly in reflex tears (Table 5),^{317,319,372} but does increase during sleep in closed-eye tears to approximately 16 to 18 mg/mL (Table 1).^{319,373} The level of the regulated major tear proteins lysozyme (0.7-3.0 mg/mL),^{76,219,317,319,372,374-377} lactoferrin (0.7-4.0 mg/mL),^{76,222,317,319,367,368,374-376,378,379} and lipocalin-1 (0.5-3.5 mg/mL)^{317,319,359,371,375} does not change in reflex, basal, or closed-eye tears. The constitutive protein sIgA changes from a low concentration in reflex tears, of 0.06 to 0.38 mg/mL,^{317,319,380} to 0.84 to 2.8 mg/mL in basal tears^{76,317,319,367,370,375,377,381,382} and to 3 to 10 mg/mL in closed-eye tears.^{319,375,383} Sullivan and Allansmith³⁸⁴ have shown that all IgA in tears in rats is sIgA. Similarly, the serum-derived proteins albumin, complement C3, complement C4, and complement factor B also increase in concentration from reflex to basal to closed-eye tears.^{317,319,367,374,375,379,380}

TABLE 6. Concentration of Certain of the Inflammatory Proteins, Proteases, and Protease Inhibitors in Tears and Effect of Contact Lens Wear

Protein Type	Reflex	Basal*	Closed Eye	Lens Wear†
Fibronectin, ng/mL		21 ± 25 ⁴²⁹		120 ± 160 ^{429‡}
Complement C3, µg/mL	4.0 ± 5.6 ³⁷⁹	27.4 ± 47.5 ³⁷⁹ 4.4 ± 2.1 ³⁷⁰	106.5 ± 84.3 ³⁷⁹	5.3 ± 1.7 ³⁷⁰
Complement C4, µg/mL	0.2 ± 0.4 ³⁷⁹	1.7 ± 3.1 ³⁷⁹ 0.1 ± 0.1 ³⁷⁰	5.6 ± 5.1 ³⁷⁹	0.1 ± 0.1 ³⁷⁰
Complement factor B, µg/mL	0.1 ± 0.1 ³⁷⁹	4.0 ± 5.0 ³⁷⁹	20.8 ± 8.1 ³⁷⁹	
sPLA2, ng/µL		1.8 ± 0.1 ³⁵⁹ 5.0 ± 0.7 ³⁴⁰		5.0-5.1 ³⁷¹
IL-6, pg/mL	~45 ⁴⁰⁵	~70 ⁴⁰⁵ 2.2 ⁴³¹ 2.2 ⁴³⁰ 7.1 ± 6.4 ⁴³³ 5.8-10.0, keratoconic Px ^{82,432} 1516 ± 497 ⁸² 0 ⁴³⁴ 26.5 ± 21.8 ³⁹³ 13.9 ± 1.1 ³⁸⁹ 3.6 ± 3.4 ³⁹⁸ 110 ± 142 ³⁹⁰ 29.3 ⁴⁰⁶ 31.7 ³⁹⁷ 2.2 ⁴³¹ ~10 ³⁹¹	147 ± 112 ⁴³⁵	3.6, RGP lenses ⁴³¹ 4.7, OK RGP ^{430‡} 33.1 ± 15.0 ^{433‡} 33.2-40.4, keratoconic Px, RGP or soft piggyback ^{432‡} 2505 ± 951 ^{82‡} 43.8 ± 5.3 ^{434‡} 60 ± 32, neophyte‡; 218 ± 45, adapted
IL-8, pg/mL	~400 ⁴⁰⁵	~1200 ⁴⁰⁵ 601.5 ⁴³⁰ 107.4 ± 56.8 ⁴³³ 110.5-156.2, keratoconic Px ⁴³² 176 ± 72 ³⁹³ 37.4 ± 8.7 ³⁸⁹ ~500 ³⁹¹ 572 ± 637 ³⁹⁰ 1084.3 ⁴⁰⁶ 283.0 ³⁹⁷	148 ± 103 ⁴³⁹	935.3, OK RGP ^{430‡} 412.6 ± 104.1 ^{433‡} 372.6-438.2, keratoconic, RGP or soft piggyback lens wear ^{432‡} 70 ± 32, neophyte‡; 229 ± 175, adapted ⁴⁴
TNF-α, pg/mL		1.8 ⁴³¹		4.2, RGP lenses ^{431‡}
EGF, pg/mL		698.1 ⁴³⁰ 1277 ± 619 ³⁹³		2348.7, OK RGP lens wear ^{430‡}
MMP-9, ng/mL		9.8 ± 14.3 ^{373‡} 6.1 ⁴³¹ 39.2 ⁴³⁰ 8.4 ± 4.7 ⁴⁰⁸ 10.5 ± 0.2 ⁴¹⁶	2000.7 ± 1950.7 ^{373‡}	12.9, RGP lenses ^{431‡} 74.3, OK RGP lens wear ^{430‡}
TIMP-1, ng/mL		74.5 ± 39.7 ^{373§}	277.8 ± 282.2 ^{373‡}	
NGAL, ng/mL		680.8 ± 523.3 ^{373§}	3620.3 ± 1832.1 ^{373‡}	

NGAL, Neutrophil gelatinase-associated lipocalin.

* Used as default if tear type not mentioned.

† Compared to basal tears unless otherwise stated; soft lenses unless otherwise stated.

‡ Significant effect of contact lens wear.

§ Tears collected using flush method.

Inflammatory Mediators in Tears. Tears have been shown to contain a variety of inflammatory mediators, including complement (Table 6),³⁷⁹ arachidonic acid metabolites (e.g., leukotriene B₄ and prostaglandin E₂),³⁸⁵⁻³⁸⁶ and a range of different cytokines (Table 6). The range of cytokines differs depending on the study methodology, but the most commonly observed cytokines in tears are interferon (IFN)-γ; interleukin (IL)-1α, IL-1β, IL-4, IL-6, IL-8, IL-10, and IL-12(p70); and tumor necrosis factor (TNF)-α.³⁸⁷⁻³⁹⁸ One of the reasons for differences in the descriptions of the cytokines present in tears may be that not all tear samples contain all cytokines. For example, Enriquez-de-Salamanca and colleagues³⁹⁹ found that epidermal growth factor, CX3CL1, interleukin-1 receptor

agonist and CXCL10 were detected in 100% of basal tear samples; IL-8/CXCL8 and vascular endothelial growth factor were detected in >93% of samples; IL-6 in 65%, IL-10 in 48%, IFN-γ in 30%, IL-1β in 30%, IL-17 in 13%, and IL-13 in 9%; GM-granulocyte-monocyte colony stimulating factor in 7%; and TNF-α in 2% of samples. These inflammatory mediators appear to be tightly regulated, as tears also contain inhibitors of the complement cascade including lactoferrin,^{379,400} decay accelerating factor,^{379,401} and CD59⁴⁰²; soluble receptors of cytokines and growth factors, for example, EGFR,^{394,395} IL-2R,³⁹⁵ IL-6R,^{394,395,403} and TNFR2³⁹⁴; and the IL-1 antagonist IL-1Ra^{387,399,404} as well as certain cytokines (such as IL-10) that are themselves anti-inflammatory.

Table 6 details the changes that occur to some of these inflammatory mediators in different tear types and in CL wear. The concentration of IL-6 and IL-8 decreases in reflex tears compared to basal tears, whereas the concentration of VEGF, Fas ligand (FasL), and monocyte chemoattractant protein (MCP1) does not.⁴⁰⁵ In closed-eye tears, IL-1 β , IL-6, IL-12(p70), and TNF- α increased in concentration,⁴⁰⁶ but there are conflicting reports on whether the concentration of IL-8 and IL-10 increases during sleep,^{385,397,406} partly because, for IL-8, its level is already high in basal tears.

Proteases in Tears. The major proteinase activities of tears are gelatinolytic and collagenolytic.³⁸⁸ Tears contain high levels of cathepsin-C activity, but also cathepsin-B, trypsin-like, and urokinase activity.⁴⁰⁷ The proteomic study by de Souza and colleagues³⁶⁵ showed large numbers of proteases (such as matrix metalloproteinase [MMP]-8, MMP-9, leukocyte elastase, plasminogen, cathepsins, and aminopeptidases) as well as antiproteases (such as α -2-macroglobulin, α -1-microglobulin, cystatins, α -1-antitrypsin, α -1-antichymotrypsin, leukocyte elastase inhibitor, plasminogen activator inhibitor-2, thrombospondin-1, secretory leukocyte protease inhibitor, and tissue inhibitor of matrix metalloproteinase [TIMP]-1).³¹⁸

Research has tended to focus on the presence of MMPs and their inhibitors (such as TIMPs) in tears. Tears have been shown to contain MMP-1 (also known as interstitial collagenase), MMP-2 (gelatinase A), MMP-3 (stromelysin-1), MMP-8 (neutrophil collagenase), MMP-9 (gelatinase B), MMP-10 (stromelysin-2), MMP-13 (collagenase 3), TIMP-1, TIMP-2, and TIMP-4 (Table 6).^{387,388,395,408-411} However, often the active forms of the MMPs have not been demonstrated, and often tears contain only inactive pro-forms^{387,412-414} or low levels of active forms.^{415,416}

Plasmin activity in tears increases during sleep,^{320,417} as does the level of pro-MMP-9.³⁷³ However, the level of protease inhibitors such as α -1-antiprotease, α -1-antichymotrypsin, α -2-macroglobulin, secretory leukocyte protease inhibitor, and cystatin C also increases in closed-eye tears to levels between 3 and 23 times those in reflex tears.^{318,373} In the case of MMP-9 and TIMP-1, there is the potential for activation of MMP-9 during sleep as its level increases by approximately 200-fold whereas the level of its inhibitor TIMP-1 increases only 3-fold.³⁷³

Other Types of Inflammatory Mediators. Tears contain histamine (N-methyl histamine), and its concentration increases from reflex (80 ± 110 pg/mL) to basal (200 ± 140 pg/mL) to closed-eye (840 ± 1150 pg/mL) tears. Its concentration in tears during asymptomatic CL wear (370 ± 80 pg/mL) is not different from that in basal tears of non-lens wearers.⁴¹⁸ Tears also contain the neuromediators: substance P, calcitonin gene-related peptide (CGRP), neuropeptide Y (NPY), vasoactive intestinal peptide, and nerve growth factor (see report from the Subcommittee on Neurobiology for more details).^{386,419-421}

Effect of CL Types and Wear Schedules on the Tear Film Proteome. It is possible that different CLs or the disinfecting/cleaning solutions used with them, as well as the wear schedule on which lenses are worn, can affect the tear film proteome, although there is a general lack of information on the effects of CL wear on the tear film proteome. Tables 5 and 6 outline the publications that have examined the effect of CL wear on the tear film proteome.

Initial studies on total protein in tears by Hill and Uniacke⁴²² and Callender and Morrison⁴²³ showed that, during adaptation to hard CLs, protein concentration decreased, but returned to normal after the first 7 days of lens wear.⁴²³ However, overall there does not appear to be a change in the total protein content or the concentration of lysozyme, lactoferrin, or lysozyme during lens wear (Table 1)^{90,323,340,361,367,368,370,372,374-376,378,422,424} (with the excep-

tions that one study showed a significant decrease in antibody intensity of lysozyme in PAGE from tears of silicone hydrogel and rigid gas-permeable [RGP] lens wearers compared to nonwearers,⁴²⁵ and one other study showed that the level of lysozyme increased in tears from RGP [1.1 ± 0.5 mg/mL] or high water soft lenses [1.2 ± 0.4 mg/mL] compared to no lens wear [0.8 ± 0.4 mg/mL] or wear of low water content soft lenses [0.8 ± 0.2 mg/mL]).⁴²⁶

In contrast, the effect of CL wear on the concentration of sIgA in tears is more controversial. Six studies have reported no effect of lens wear.^{367,370,375,380,381,427} However, Kijlstra and colleagues⁴²⁸ reported that there was a decrease in the concentration of sIgA in tears during the first 3 months of RGP daily lens wear compared to non-lens wear, by approximately 27%, but the concentration returned to normal 1 year after lens fitting. Others have shown a similar effect of a decrease in sIgA concentration in tears of CL wearers (type of lens, wear schedule, or length of wear was not given)³⁶¹ in a mixed group of CL wearers (lens type not given; mixed DW and EW; average 8 years of wear),³⁷⁷ in a group of EW soft lens wearers (at least 6 months lens wear),³⁸² and in the closed-eye tears collected from a group of either daily wear or extended wear soft lens wearers (average length of wear 4 years).³⁸³ In addition, there appears to be a reduction in the concentration of sIgA specific for *Pseudomonas aeruginosa* or *Escherichia coli* but not for *Staphylococcus epidermidis* or *Haemophilus influenzae* in tears.^{380,381,383}

The concentration of albumin in basal tears does not change during relatively long-term wear of RGP³⁶⁷ or soft lenses³⁷⁴ but is increased in closed-eye tears during wear of RGP lenses for orthokeratology.³⁷⁵ The concentration of complement proteins C3 or C4 does not change with DW or EW of soft lenses.³⁷⁰ The concentration of fibronectin in basal tears is increased during EW of soft lenses (average wearing time of 33 months).⁴²⁹ Most studies (with the exception of one measuring the concentration of IL-6 in tears of RGP lens wearers, another measuring the level of IL-6, IL-8, or MMP-9 in the tears of long-term lotrafilcon A silicone hydrogel lens wearers, and one measuring IL-6 in tears after 2 weeks of silicone hydrogel lens wear)^{82,430,431} have found that CL wear in general increases the concentration of IL-6, IL-8, TNF- α , EGF, and MMP-9 in tears,⁴³⁰⁻⁴³⁵ and moreover there appears to be an effect of length of lens wear.⁴³⁵

After collecting tears using the flush method and two-dimensional differential gel electrophoresis (2D-DIGE), Markoulli and colleagues⁴³⁶ found a significant decrease in the level of Zn-alpha2-glycoprotein in the tears of people who had worn silicone hydrogel lenses (lotrafilcon B) on a DW basis compared to their tear film collected prior to lens wear. Kramann and colleagues,⁴²⁵ using wearers of RGP or silicone hydrogel lenses and a semiquantitative analysis, found that there was a significant increase in the concentration of protein S100 A8 in the tears of both lens-wearing groups, and a significant decrease in concentration of secretoglobulin but increase in cystatin in the RGP lens wearers compared to silicone hydrogel or non-lens wearers. There is an increase in plasmin activity in tears during CL wear (soft lens wearers) acknowledged by most⁴³⁷⁻⁴³⁹ but not all studies.⁴¹⁷

Association of CL Discomfort With the Tear Proteome. There has been very little research on whether the tear film proteome changes with CL discomfort (by any definition). No significant difference was found in the concentration of total protein, lysozyme, lactoferrin, or sIgA between tears of tolerant or intolerant CL wearers in the absence of lens wear compared to soft lens wear during 1 day.^{76,90} However, there is an apparent association between the levels of lipocalin-1 or sPLA2 in tears and intolerance to lens wear, with intolerant individuals in the absence of CL wear having increases in both

these proteins (2.40 ± 1.5 vs. 0.45 ± 0.85 , $P < 0.001$; 1.86 ± 0.05 vs. 1.80 ± 0.08 , $P = 0.047$, respectively) compared to tolerant lens wearers.³⁵⁹

Nichols and Green-Church³⁶⁹ analyzed the tears of normal CL wearers and CL wearers classified, using the Contact Lens Dry Eye Questionnaire, as having CL-related dry eye symptoms during lens wear (all wore galyfilcon A silicone hydrogel CLs). Using combinations of SDS-PAGE, 2D-DIGE, and nano-LC-MS/MS, they found that the total protein of tears was significantly reduced in the CL-related dry eye group ($P = 0.02$). Furthermore, the concentrations in tears of β -2-microglobulin, proline-rich protein-4, lacritin, and secretoglobulin 1D1 were found to be decreased, whereas the concentrations of secretoglobulin 2A2, albumin, deleted in malignant brain tumor (DMBT)-1, and prolactin-inducible protein were increased in the tears of the CLDE group compared to the normal CL group.

Mucins and Glycocalyx

Mucins are a family of high molecular weight, heavily glycosylated proteins that form the protective biofilm on the surface of epithelial cells. They are characterized by the presence of multiple tandem repeats of amino acids, rich in serine and threonine, in the central domain of the mucin core peptide; these tandem repeats provide sites for O-glycosylation.^{440,441} Epithelial mucins can be divided in two different classes, transmembrane (or cell surface associated) and secreted. The glycosylated regions of these molecules are hydrophilic and contribute to the prevention of ocular surface desiccation by binding water. On the apical glycocalyx, transmembrane mucins and their O-glycans prevent adhesion and maintain epithelial barrier function through interactions with galectins.²⁰ Other O-glycan-containing glycoproteins, such as lubricin, also promote boundary lubrication between the cornea, conjunctiva, and CL-like materials.⁴⁴²

The normal human tear film contains MUC5AC, a secreted mucin produced by goblet cells within the conjunctival epithelium. The stratified corneal and conjunctival epithelia produce three transmembrane mucins: MUC1, MUC4, and MUC16. Transmembrane mucins are concentrated on the tips of the apical cells' microvilli, forming a dense glycocalyx at the epithelial-tear film interface, but they can also be shed from the cell surface and consequently are found in the tear film.⁴⁴³

Several studies have demonstrated a decrease in the amount of secreted mucin at the ocular surface of CL wearers. MUC5AC messenger ribonucleic acid (mRNA) in the conjunctiva and MUC5AC protein in tears are significantly reduced in subjects wearing both soft and rigid CL.^{82,444-446} Also, levels of sialic acid, a terminal carbohydrate in glycoproteins, is reduced in the tears of CL wearers.⁴⁴⁷ Studies evaluating transmembrane mucins during CL wear have generated more variable results. Binding of the CA 19-9 antibody to a sialic acid on MUC1 in tear samples decreased significantly during CL wear.⁴⁴⁸ Conversely, exposing tear film from CL wearers to immortalized human corneal epithelial cells has resulted in MUC1 upregulation.⁴⁴⁹ This variability could be ascribed to the use of different experimental approaches, methods, or CL types in these studies. For instance, use of CLs with different water contents has been shown to differentially influence the levels of MUC1 mRNA.⁴⁵⁰

Contact lens wear is commonly associated with damage to the ocular surface glycocalyx, including physical changes in the form of thinning or compression and signs of biochemical changes reflected as an increase in the number of carbohydrate receptors.⁴⁵¹ Multipurpose CL solutions further contribute to disruption of the integrity of the glycocalyx, affecting the

shedding of MUC16 from the cell surface and reducing MUC1 and MUC16 mucin gene expression.^{452,453}

Mechanical interaction of the CL with the epithelial surface and the blinking forces of the lid are also involved in formation of so-called mucin balls.⁴⁵⁴ This is a common but innocuous phenomenon that appears to cause spherical indentations in the corneal epithelium after lens removal.⁴⁵⁵⁻⁴⁵⁸ Histology shows that mucin balls are negative for lipids and bacteria, but are periodic acid Schiff positive, indicating that glycoproteins constitute a major component of their content.⁴⁵⁹ The development of mucin balls does not depend on the CL type worn, but lens type does influence the degree of mucin ball formation.⁴⁵⁴ There does not appear to be a link between CLD and mucin ball formation.

A limited number of studies have attempted to correlate mucin expression during CL wear with comfort. Protein analyses have shown that CL wearers with symptoms of discomfort, as measured using the Contact Lens Dry Eye Questionnaire, have decreased levels of MUC5AC in the tear film.⁴⁴⁴ Additional analyses in asymptomatic CL wearers, on the other hand, have produced conflicting results. MUC5AC content in conjunctival goblet cells is low in CL wearers with no subjective symptoms or clinical signs of intolerance compared to healthy controls.⁴⁴⁵ However, data from additional studies have shown no significant changes in the levels of transmembrane or secreted mucins, or in the content of glycosidic residues in non-goblet epithelial cell vesicles in tolerant CL wearers.^{460,461} These discrepancies in mucin expression in asymptomatic wearers could be attributed to long-term differential inflammatory responses, known to affect mucin biosynthesis.⁴⁶⁰ More recently, it has been proposed that the pattern of mucin degradation during CL wear could also affect comfort, since mucin fragmentation in response to a new material has been observed in asymptomatic, but not symptomatic, CL wearers.⁴⁶²

Other Tear Film Components

Tears have antioxidant activity^{463,464} and contain several antioxidant components, including gamma-glutamyl transpeptidase that protects against oxidative stress via glutathione recapture,⁴²¹ cysteine, ascorbic acid/ascorbate, glutathione, uric acid/urate and tyrosine,^{465,466} and superoxide dismutase.¹⁹ Ascorbate and lactate dehydrogenase, but not urate, increase in concentration in tears from basal to closed eye.³⁷⁵

While CL wear increases the level of the antioxidant tyrosine in tears,⁴⁶⁶ it does not increase the concentration of ascorbic acid or the total antioxidant activity.⁴⁶⁷ Wearing a RGP orthokeratology lens for one night significantly increases the concentration of ascorbate and lactate dehydrogenase in tears,³⁷⁵ and lactate dehydrogenase increases with extended wear of highly oxygen-permeable soft or RGP lenses.^{224,468} The magnitude of lactate dehydrogenase increase is dependent on the type of CL and especially on the oxygen permeability of the lens.^{469,470} Tears contain nucleotides and dinucleotides that have a function in controlling tearing and ocular surface wound healing,⁴⁷¹ but the effect of CL wear on the concentration of these in tears is not known.

There is no published information on the relationship between antioxidants or nucleotides on the comfort response during CL wear.

Cellular Content of Tears (PMNs)

The earliest demonstration of white blood cells in tears was by Norn,⁴⁷² who observed a relative leucocytosis, first thing in the morning, in tears collected from the conjunctival sac. Subsequently, others have shown that during sleep the tear film and

ocular surface are infiltrated by large numbers of polymorphonuclear leukocytes/neutrophils (PMN).^{318,435,473-475} This recruitment is likely to be mediated by the increased concentrations of chemokines, such as IL-8 and leukotriene B₄,^{385,476} that are found in closed-eye tears.

Using neophytes to CL wear and placing a CL in one eye only, Wilson and colleagues⁴⁷⁵ demonstrated that there were >6000 leukocytes that could be washed from the ocular surface after sleep and that lens wear did not affect this number. On the other hand, in a study of three separate groups of subjects (non-lens wearers, neophytes to lens wear, and adapted CL wearers), numbers of PMNs were significantly higher from tears/ocular surface wash of neophyte compared to non-lens wearers, but adapted lens wearers had fewer PMNs recovered.⁴³⁵ The number of PMNs recovered from the two CL-wearing groups was also significantly different. These changes were at least partly the result of changes to chemokine levels in tears of the three groups.⁴³⁵ Similarly, Stapleton and colleagues⁴⁷⁴ demonstrated that there was a significant reduction in the numbers of PMNs washed from the corneal surfaces of experienced (adapted) daily-wear soft lens wearers following sleeping in their lenses.

There have been no studies relating the role of PMN recruitment onto the ocular surface during sleep to CLD.

External Components

Multipurpose disinfecting solutions (MPDS) used to clean and disinfect soft CLs overnight often contain surface-active ingredients (e.g., Tetronic, Pluronic),⁴⁷⁷ added to improve cleaning efficiency and CL wettability and to maximize comfort. Surface-active agents have the capacity to emulsify the lipid layer and destabilize the tear film.²⁷⁴ These surfactants are introduced in the tear film upon CL insertion, after overnight soaking in MPDS, and can further destabilize the tear film.^{36,269,274} Svitova and Lin²⁶⁹ have reported some effect of surfactant-containing lens care solutions on the rheological properties of mixed lipids-lysozyme films *in vitro*. Further, any uptake into the CL material during overnight storage will create a slow release of the surface-active substance during wear.^{269,478} No information is currently available on the effect *in vivo* of MPDS on the tear film.

Eye cosmetics, even though applied externally, have been shown to migrate onto the ocular surface and through the tear film⁴⁷⁹ and deposit onto CLs; cosmetic products include a variety of ingredients (oils, waxes, pigments, powder, stearates, surfactants, diluents, preservatives) that can have a potential destabilizing effect on the tear film.⁴⁸⁰ One ingredient commonly found in eye cosmetics, to prevent bacterial growth during storage, is the preservative benzalkonium chloride, which has been associated with a decreased TBUT and dry eye symptoms.^{304,481,482} While deposition of cosmetics on the CL surface is recognized to affect CL comfort,¹²² no information on cosmetics within the tear film, specifically, has been linked to CL-induced discomfort.

FUTURE DIRECTIONS

It is clear from the preceding report that there remain significant gaps in our understanding of the extent to which tear film changes in CL wear might be responsible for inducing symptoms of discomfort in CL wearers. A number of areas in which further research is indicated and should be prioritized to help address the identified shortfalls are described below.

To understand the relationship between CLD and tear film dynamics and composition, possible major directions of research are as follows:

1. Examining associations between biochemical parameters in the tear film with CLD using a consistent definition of comfort, particularly in establishing parameters that may be predictive in neophyte wearers and understanding changes over time.
2. Refining the selection of wetting agents that can be included in CL care solutions to help maintain long-term wettability of the CL surface (e.g., in addition to poloxamer and Tetronic molecules incorporated in current formulations, many other hydrophilic polymers and block copolymer wetting agents require further exploration)
3. Development of novel CL materials that can resist evaporation of water content or can maintain a highly wettable surface after a prolonged wearing time

In terms of lipid layer integrity, major priorities for future research include the following:

1. Elucidating the mechanism of lipid/CL and protein/CL interactions responsible for deposit formation to explore the effect of CL surface charge, roughness, and effect of lens surface modification with phospholipid or polymer coatings, and so on
2. Designing nonadhesive CL surfaces with long-term resistance when worn or to develop lens care formulations improving the CL wettability
3. Gaining an understanding of how wetting agents can modify the spread and the quality of the TFLL over the CL surface

With regard to PLTF stability, future research should be directed toward development of lens materials, designs, and surfaces, with or without the aid of care products that promote biocompatibility, to a level where the tear film can remain stable over the surface. Current evidence leads us to believe that more biocompatible CL surfaces could promote more physiological tear film structure in at least those deemed tolerant of CL wear.⁹⁰

Whether the ocular surface temperature in CL wearers directly impacts comfort has not been established. However, cooled artificial tears have been found, subjectively, to improve comfort in normal non-lens-wearing eyes, suggesting that this area is deserving of further exploration. The close relationship between ocular surface temperature, tear film stability, and tear evaporation would suggest that interventions that modify one aspect will have influence on all.

Contemporary high-resolution technologies such as OCT, allowing detailed observation of the tear film profile during lens wear, have confirmed the significant physical impact of CLs, and particularly rigid CLs, on the tear film. This approach has benefit in optimizing the fitting relationship and edge characteristics of the lens as related to CLD.

Osmolarity is recognized as a key property of the tear film, but its assessment in CL wear has been limited to date, in part by the need for large tear volumes for analysis. The design of osmometers that require only minute amounts of tears may help in more accurately defining location-specific tear film osmolarity changes in the pre- and post-CL tear film, particularly in those suffering from CL-induced dry eye. Although a variety of studies have investigated the effect of CLs on tear film osmolarity, there is limited information on the impact of the osmotic level on ocular comfort, unlike the situation with dry eye disease. Of particular relevance would be studies that not only compare the osmolarity of symptomatic and asymptomatic lens wearers but also assess its correlation to ocular comfort indices in order to improve our understanding of the impact of tear film osmolarity on CL-

induced dryness. Also, if osmolarity of tears does affect comfort, then investigations on the biochemical/chemical changes that occur may provide insight into methods of alleviating the discomfort.

Tests such as tear ferning have shown some potential to discriminate between lens wearers and non-lens wearers and perhaps even predict ocular comfort during CL wear. Availability of digital image analysis may allow for more accurate and objective tear ferning quantification in the future and lend support to the investigation of the relationship between tear ferning and ocular comfort during CL wear.

Clinical investigations have yielded some limited data indicating that CL wear induces a modest decrease in tear film pH. Additional evidence-based data are required to support any mechanistic link between reduced pH in the tear film and CL discomfort.

With regard to the surface tension of tears, there is a lack of data specifically addressing the questions of whether CL wear alters the surface tension of tears, whether this can be related to discomfort during lens wear, and what might be the underlying biochemical and physical changes to the tears that manifest as changes to surface tension. Furthermore, experiments specifically addressing the issue of whether changes to the surface tension of tears are related to the wettability of CLs during wear are lacking.

With the advent of newer proteomic,^{369,425,436} glycomic,^{483,484} and lipidomic^{326,485} techniques, reexamination of the role of the proteins, glycoproteins, mucins, and lipids, as well as nonbiological components of the tears in tear film surface tension and effects of CLs, should be undertaken. In recent years the polar lipids OAHFAs and their esters in meibum have been discovered,⁴⁸⁶ and their concentration is correlated more strongly than that of phospholipids to dry eye severity⁴⁸⁷; therefore an examination of the effect of these lipids and other polar lipids on the spreading behavior of the TFL, surface tension of tears, changes during CL wear, and discomfort is warranted, as well as further evaluation of the effect of tear lipid degradation.

In relation to effect of CLs on tear composition, it is clear that there is probably no effect of CLs on the concentration of total protein, lysozyme, and lactoferrin (at least with soft lens wear). Research needs to be conducted on the effect of lens wear on the concentration of lipocalin-1 in tears, especially given its potential change in tears in intolerant compared to tolerant lens wearers.³⁵⁹ The effect of CL wear on the concentration of total or specific sIgA requires further investigation. It should be noted that while substantial progress has been made in defining the tear proteome, this has not taken into account the changes that are known to occur between the different tear types; this should be addressed in future work.

Concerning the inflammatory mediators in tears, further research on the potential for CL wear to affect arachidonic acid metabolites, neuropeptides, histamine, and other inflammatory mediators would be beneficial. While lens wear does appear to generally increase the level of several cytokines in tears, which if any of these relate to CL discomfort is unknown at present. An effort to relate changes of these mediators, proteases, and all the potential inhibitory factors for inflammatory mediators and proteases in tears with comfort during CL wear is urgently needed. Aside from these major directions, the very large differences in the amount of cytokines reported in tears (see Table 6, IL-6 and IL-8 as examples) also merit investigation. It seems unlikely that these large differences are physiological but are perhaps related to methodological differences,⁴⁸⁸ and further research is required for clarification.

Clinical investigations have yielded some supportive data indicating that symptomatic CL wear might be associated with

decreased levels of secreted mucin in tears. However, there is not complete agreement on whether reduced mucin content contributes to ocular surface discomfort, due to some degree of variability in methods across studies. Contact lens wear is clearly associated with physical and biochemical changes to the epithelial glycocalyx. Future investigations on the integrity of this carbohydrate-rich zone on the cell surface could offer potential new information on the mechanisms leading to discomfort during CL wear. At present, there are insufficient molecular data to demonstrate accurately the presence of either transmembrane or secreted mucins within “mucin balls.”

CONCLUSION

Numerous opportunities exist for further research to be conducted in this area. Answers to these research questions will foster a better understanding of the impact of tear film changes secondary to CL wear on ocular comfort, in order that we might strive to reduce the effects and optimize CL comfort. Evidence suggests that the biophysical properties of the tear film are interrelated, and thus it is likely that no single component can be isolated as responsible for CL discomfort. This theory is supported by the demonstration that the feature with the strongest link to ocular comfort during CL wear is tear film stability, a property recognized to reflect myriad tear film components and interactions.

Acknowledgments

Disclosure: Each workshop participant's disclosure data can be found in the Appendix of the Introduction.

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The TFOS International Workshop on Contact Lens Discomfort: Report of the Subcommittee on Clinical Trial Design and Outcomes

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See the tables in the Introduction for the members of the TFOS International Workshop on Contact Lens Discomfort.

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The goal of this report is to review previously published clinical trials addressing contact lens discomfort (CLD) to identify appropriate trial design and outcome parameters to guide future clinical research that will characterize and investigate possible causes of CLD. A further goal is to identify possible confounding features of clinical trial design and performance in order to reduce bias in conduct of future trials or analysis of data from those trials.

Scope of Report

A contact lens is a foreign body placed on the eye, albeit of compatible material and design, applied to patients with variable biologic risk factors that influence the degree of experienced symptoms. The design of clinical trials and selection of appropriate outcomes that allow examination of CLD should be determined with respect to the specific questions being asked and answered by a specific trial. For example, the duration of a clinical trial to determine the time required for adaptation to a contact lens could be short, but such a time frame is inadequate for evaluation of chronic or persistent episodic discomfort. Similarly, evaluation of care system-related CLD would require control of not only the care system to be evaluated but also the contact lens (material, design, fit, and wearing pattern). Evaluation of symptoms of CLD should be done with questionnaire instruments that probe

parameters of discomfort unique to CLD. For example, a symptom of “dryness” may be an appropriate outcome for CLD if qualified by features of timing, duration, severity, and relationship to lens wear.¹⁻³ If a validated questionnaire is not available for the particular trial design, then visual analogue scales or numerical rating scales of comfort (on 1-100 or 1-10 scales) can be used. Although most of the data gathered from the literature for this report is derived from trials involving soft contact lenses, the principles for clinical trial design also apply to rigid contact lenses.

The proposed evaluation of CLD is for primary discomfort during lens wear. There are clinical conditions that can be produced by prolonged lens wear resulting in discomfort, but these conditions are secondary. For example, giant papillary conjunctivitis can occur in response to contact lens wear and produces symptoms of CLD (perhaps due to mechanical irritation from the edge of the lens or buildup of biological material on the lens), but this conjunctivitis would be considered a separate entity from CLD.⁴⁻⁶

Recognition of the fact that there is great variation in patient acceptance or tolerance of any noxious sensation requires that some qualification of the degree of discomfort be made. Thus a psychometric assessment of enrolled study participants may be required for some clinical trials.^{7,8}

RESULTS OF PRIOR CLINICAL TRIALS

The CLD clinical trial subcommittee searched the PubMed database using the search term “contact lens discomfort” (last searched on January 25, 2013). We included interventional trials involving contact lens wear that collected information about ocular comfort or discomfort, even if this was not the primary aim or outcome of the study. We searched the reference lists of included studies for any additional studies not identified by the electronic search. Clinical trials of contact lens performance may be published in the non-peer-reviewed professional literature (e.g., *Contact Lens Spectrum* or *The Optician*). We did not search non-peer-reviewed literature or any conference proceedings.

A review of published clinical trials assessing CLD is summarized in Table 1.⁹⁻³⁹ These were published between 1999 and 2013 and enrolled 18 to 362 participants. Trials typically were small; only four enrolled 100 or more participants. These participants were followed for 15 minutes to 3 months. It is clear that most prior clinical trials were designed to evaluate performance of certain contact lenses or lens care solutions rather than the specific nature and etiology of CLD. As a result, their ability to elucidate CLD is modest due to inherent weaknesses in the chosen study design. Nonetheless, certain features of CLD can be distilled from those clinical trials. To date, investigations into CLD have primarily focused on sensation, with little attention given to the possible visual disturbance aspect of CLD.

Interventional trials have included examining the effects of lens fitting characteristics,¹³ lens type,^{9,14-17,23,28,29,32,34,35} lubricating^{10,12,18,19,21,23,27,29,30} and therapeutic^{12,26,39} eye drops, and lens care regimen.^{11,22,31,33,36-38} A common limitation of these studies is the poor control of confounding variables such as care regimen, prior lens wear, wear experience, and timelines of reporting symptoms. The extent of visual near tasks or computer/video terminal use should be quantified and characterized. Potential effects of concurrent medications, both topical and systemic, require evaluation, as well as effects of seasonal allergy and climate.

Outcomes and Predictive Factors

Discomfort can be described by a study participant in a clinical trial in various ways. The relative activation by the stimulus of subpopulations of ocular surface sensory fibers evokes different qualities of irritation and pain sensations (see the report of the Neurobiology Subcommittee).^{40,41} Most of this corneal sensory research has been conducted without contact lens wear, so the role of these various nociceptors in CLD is not well established. Dryness is a frequently described sensation of CLD in study participants with reduced tolerance for contact lens wear,¹⁻³ particularly of higher intensity later in the day of wear.^{1,2,42}

Subjective Outcome Measurement

Clinical scientists rely on information in the form of data, some relatively direct (e.g., visual acuity) and other data less so (e.g., feelings of ocular surface dryness). These latter outcomes are often regarded as outcome measures and dealt with as though they are numbers, although whether all of these numbers can be regarded as distinct measurements is still unclear.⁴³ This concern is particularly salient when we do not have direct access to what is being measured and the dimensions or units as well as scaling of the metrics are unknown. This is by no means unique to the vision sciences and occurs frequently in psychometrics⁴⁴⁻⁴⁶ and psychophysics.^{47,48}

Part of the problem with trying to develop and evaluate qualitative or descriptive measurements (so called latent variables) is that they may or may not represent the property being measured. Wearer experience of discomfort is influenced by multiple contextual factors, which adds to the complexity of measurement. When developing new instruments, it is important to consider content validity compared with an established reference, if possible.⁴⁹ If measurements are “the same” as a gold standard, this is an empirical demonstration that the novel metric is as good as the reference (this is not quite a calibration, but it demonstrates that the new and old measures map onto each other in some rational way). If such is not the case, the validity of the measurement needs to be demonstrated in a number of possibly less direct ways.⁴⁶ Distinct from the measurement of a one-dimensional sensation, a patient-reported outcome instrument attempts to capture the patient experience in a more aggregate form. These instruments often have many questions, but are validated to show that they relate to self-assessment of the severity of conditions and change in condition. Not many potential patient-reported outcomes instruments have been used to assess CLD in some quantitative way, and all but one have been tested in only subjects who were not wearing contact lenses. Table 2 summarizes this list.^{1,25,50-62} Only one of these instruments was directly designed to examine symptoms in contact lens wearers,²⁵ and it has recently been validated in a shorter iteration.¹

Generally the direct validation work for ocular surface symptoms has not been on lens wearers specifically and has been descriptive in nature; and there have been a few reports of use of a theory-based assessment of the measurements (all using Rasch Analysis). The only validated contact lens-related dryness symptom measurement tool at the present time is the CLDEQ or its short form, CLDEQ-8.¹ The CLDEQ was validated in 2002 as a measure predictive of a doctor's diagnosis of contact lens dry eye.²⁵ In its long form, it was shown to have a sensitivity of 83% and specificity of 67%.²⁵ Scoring of the CLDEQ-8 involves summation of the items. In the validation work, the ranges for CLDEQ-8 sum score at baseline according to the wearers' overall opinion of their habitual contact lenses was as follows: Fair 17.4 ± 8.7 , Good 13.7 ± 6.4 , Very Good 9.1 ± 4.7 , and Excellent 6.4 ± 3.7 . Thus, using the CLDEQ-8 assessment of the symptoms with habitual lenses may help determine wearers who would benefit from management of their CL-related discomfort, and scores of 13 or above should warrant clinical attention. This version's diagnostic accuracy has not been tested. (Note that the CLDEQ-8 is copyrighted by Indiana University for public use. The university requires only that the copyright be cited in any publication reporting results with the instrument.)

Further assessment of patient symptoms can be done with respect to onset and time course to determine when CLD is occurring. Contact lens discomfort at the beginning of the day, but improving over time with wear, may have a different etiology than CLD with an onset at the end of the day. A further useful measure may be the duration of comfortable lens wear. Evaluation of the frequency and intensity of symptoms should be accomplished using a questionnaire designed to better understand the frequency and intensity of CLD. If a daily diary is used or it is necessary to assess symptoms at a particular point in time, a 0 to 100 visual analogue scale (VAS) or 0 to 10 scales may be more appropriate until alternative metrics can be developed and properly validated.

Clinical Measures That May Describe CLD

In an attempt to assess a number of outcome measures that are not subjective but that may be predictive of CLD, a PubMed

TABLE 1. Assessment of Published Clinical Trials

Study Design (e.g., Placebo- Controlled RCT, Retrospective Cohort) and Reference	Details of Intervention (e.g., Regimen, Composition)	Comfort/Discomfort Outcomes	Disease Definitions/ Criteria (OSDI)	Sample Size, Overall and per Arm	Follow-up Period, From Baseline	Overall Quality Rating
Open label, single group, uncontrolled ¹⁰	Preservative-free hypoosmolar (280 mOsm/L) copolymer, commercially available in Italy (Farmiga, Pisa, Italy); contains 0.2% hyaluronic acid and 0.2% tamarind seed polysaccharide, pH 7.4; 3 times daily on waking with no lens, early afternoon and before bed with lenses in Verbal and written instructions for using a no-rubbing, rinsing lens care regimen following the manufacturer's recommendations	CLD as measured by OSDI	OSDI > 12; tear breakup time (TIBUT) ≤ 10; Schirmer 1 > 10 mm	15	60 d	Weak; high risk of bias (uncontrolled; placebo effect very likely)
Crossover, investigator masked ¹¹		CLD as measured by OSDI	Habitual soft contact lens daily wear for at least the past 6 mo, asymptomatic and satisfied with the vision and comfort of the habitual lenses	72 (65 completed)	10-wk study: 1- wk accrual (adaptation) followed by 2- wk trial × 3 conditions with 1-wk washout between conditions	Weak; high risk of bias (nonvalidated secondary outcome measures, industry funded, bias due to inadequate randomization likely)
Open-label, parallel- group, randomized trial ¹²	Azithromycin: 1 drop to each eye twice a day for the first 2 d, then 1 drop daily for days 3–29 applied in the morning before contact lens application Visine for contacts: 1–2 drops 4 times a day for 29 d spaced by approximately 4 h on each dosing	Comfortable contact lens daily wear time (C/FB) at week 4 (average of days 23–29)	CLDEQ ≥ 2	50 (25 per arm)	4 wk (29 d)	Moderate; intermediate risk of bias (open label), unbalanced, comfortable wear times at baseline may have favored treatment arm)
Open label, single group, uncontrolled, crossover ¹³	Lotrafilcon A was worn, and fit was assessed by observer and by subjective comfort. 8.60 BC,* then 8.40 BC only if fit unsuccessful with 8.60 BC.	Objective assessment of fit and subjective comfort rate (1–10 scale) after 1 and 15 min (lens settling)	Habitual lens wearers	95 subjects (190 eyes), 49 eyes fitted with second lens	6-mo study but paper presents nondispensing fitting data only, 15 min	Weak; high risk of bias (data from 2 eyes of 1 subject considered independent; uncontrolled, unbalanced, industry funded)
Randomized, double- masked, contralateral study ¹⁴	Asymptomatic group: Focus Night & Day (CIBA Vision, Atlanta, GA) vs. Acuvue 2 (Johnson and Johnson Vision Care, Jacksonville, FL). Symptomatic group: Focus Night & Day vs. Acuvue 2 (Johnson and Johnson Vision Care) and Focus Dailies (CIBA Vision) vs. Proclear Compatibles (CooperVision, Pleasanton, CA).	Ocular comfort on 0–100 rating scale	Habitual lens wearers	39 subjects; 20 asymptomatic lens wearers and 19 symptomatic lens wearers	7 h	Moderate; moderate risk of bias (partly industry funded, no run-in prior to enrolment)

TABLE 1. Continued

Study Design (e.g., Placebo- Controlled RCT, Retrospective Cohort) and Reference	Details of Intervention (e.g., Regimen, Composition)	Primary Outcomes	Disease Definitions/ Criteria (OSDI)	Sample Size, Overall and per Arm	Follow-up Period, From Baseline	Overall Quality Rating
Randomized single masked, using deception as control ¹⁵	Habitual daily wear hydrogel lens wearers were refitted with Iotrafilcon A (Focus Night & Day; CIBA Vision) but told they were randomly assigned to wear either low-oxygen or high- oxygen permeability lenses and were "masked" to lens assignment.	Subjective comfort and dryness VAS (0-100)	Habitual lens daily wear with >4 y experience	87 (81 analyzed)	2 mo	Moderate; high risk of bias (open label, habitual lens wear preintervention control likely to favor intervention; analysis not intention to treat; care regimen a potential confounder; industry funded)
Randomized, contralateral, crossover study, open label ¹⁶	Hioxifilcon A lenses (extreme H ₂ O, copolymer GMA-HEMA), diameter 14.2 mm, base curve 8.6-mm, center thickness at 3.00 diopter 0.07 mm, 59% water content, Group 2, high- water nonionic, cast-molded daily wear with fortnightly replacements. Omafilcon A (Proclear Compatibles; CooperVision), diameter 14.2 mm, BC 8.2 or 8.5 mm, center thickness at 3.00 D 0.065 mm, 59% water content, Group 2, high-water nonionic, cast- molded. OPTIFREE Express (Alcon Laboratories) disinfection solution and Clerz Plus Lens Drops (Alcon Laboratories). Patient switched to hydrogen peroxide if solution problems suspected (number not specified)	CLDEQ (frequency and severity of dryness, discomfort, and blurry vision)	Previous diagnosis of mild to moderate dry eye or thinking one has dry eye or symptoms of dry eye AND either tear breakup time < 10 s, Schirmer 1 test \leq 5 mm, staining \geq 1, or bulbar redness	40	6 wk in each arm (crossover), 12 wk total	Moderate; high risk of bias (open label, habitual lens wear preintervention control; use of baseline habitual lens wear control may have favored treatment arms; no washout)
Study 1: multicenter prevalence study Study 2: uncontrolled, single-masked (subjects) intervention study ¹⁷	Study 1: NA Study 2: senofilcon A daily wear lens for 2 wk Continuing with habitual lens care unless advised by investigator (unspecified)	Discomfort: 4-point scale (never, infrequent, frequent, constant)	Problem contact lens patients: difference of >2 h between average and comfortable wear time OR frequent or constant discomfort or dryness symptoms on CLDEQ OR limbal or bulbar hyperemia \geq 2 OR corneal staining \geq 3	Study 1: 1092 Study 2: 257	Study 1: NA Study 2: 2 wk	Moderate; high risk of bias (no washout; trial short; comparison to habitual lens wear control subject to bias; questionable external validity)

TABLE 1. Continued

Study Design (e.g., Placebo- Controlled RCT, Retrospective Cohort) and Reference	Details of Intervention (e.g., Regimen, Composition)	Primary Outcomes	Disease Definitions/ Criteria (OSDI)	Sample Size, Overall and per Arm	Follow-up Period, From Baseline	Overall Quality Rating
Randomized, controlled (no treatment), investigator- masked clinical study ¹⁸	Unpreserved 0.9% sodium chloride (Hydrabak; Laboratoires Thea, Clermont- Ferrand, France) in both eyes 4 times a day for 21 d. All subjects used the same contact lens care solution (type unspecified).	Ocular comfort: 0–100 continuous VAS with anchors “excellent (lenses not felt)” at one end and “very uncomfortable (lenses cause irritation or discomfort)” at the other	Experiencing ocular discomfort (irritation, stinging, burning, or sensation of intermittent blurred vision), TBUT ≥ 10 s, Schirmer 1 ≥ 5 mm in 5 min in both eyes	50; 30 randomized to intervention, 20 to control	21 d	Weak; high risk of bias (no washout; trial short; comparison vs. baseline; lacking no-treatment control; confounders not measured)
Study 1: prospective cross-sectional (3 groups). Study 2: randomized, contralateral, open label, no- treatment control ¹⁹	Study 1: etafilcon A 8.5-mm base curve (Acuvue 1-Day; Johnson and Johnson Vision Care) Study 2: 20- μ L ReNu MultiPlus (Bausch & Lomb, Rochester, NY) rewetting drop	Ocular comfort: 0–50 continuous VAS	Study 2 Symptomatic: self- reporting of at least 1 symptom often or continually on Shippai Eye Study ²⁰ Dry Eye Questionnaire	60 (20 per arm)	Study 1: 10 h Study 2: 30 min	Strong; low risk of bias (no washout; primary outcome poorly described (anchors and descriptors not specified)
Single masked (subject), contralateral, no- treatment control ²¹	2 drops of sterile, isotonic, buffered, solution of carboxymethylcellulose (CMC), sodium chloride, boric acid, potassium chloride, calcium chloride, magnesium chloride, purified water and preserved with PURITE (stabilized oxychlorocomplex) 0.005% (Refresh Contacts; Allergan, Inc., Irvine, CA) on back surface of contact lens prior to insertion vs. straight from packaging in contralateral eye	Ocular comfort on 0–100 rating scale	At least 1 mo of lens wear Symptomatic lens wearers based on answering “no” to “Are you able to wear your lenses for as long as you want?”	61 (59 analyzed): 12 symptomatic, 49 asymptomatic	8 h	Weak; high risk of bias (2 authors employed by industry; investigator not masked; no washout; unequal arms; analysis not ITT; some data [e.g., comfort] not presented)
Crossover, single masked (investigator) ²²	OPTI-FREE Express Lasting Comfort No Rub Formula (Alcon Laboratories) vs. ReNu MultiPlus (Bausch & Lomb)	Comfort (0–100 VAS)	At least 1 y of lens wear, 8 h/d	8	4 wk	Weak; high risk of bias (no washout; not randomized; sample size too low; confounders not controlled [e.g., lens type])

TABLE 1. Continued

Study Design (e.g., Placebo-Controlled RCT, Retrospective Cohort) and Reference	Details of Intervention (e.g., Regimen, Composition)	Primary Outcomes	Disease Definitions/ Criteria (OSDI)	Sample Size, Overall and per Arm	Follow-up Period, From Baseline	Overall Quality Rating
Multisite, uncontrolled, open label ²³	Nelfilcon A containing high molecular weight, nonfunctionalized polyvinyl alcohol (PVA) and packaging saline containing hydroxypropyl methylcellulose and polyethylene glycol (Triple Action Moisture DAILIES AquaComfort Plus; CIBA Vision) worn daily on daily disposable schedule	Frequency and severity of 8 common subjective symptoms (tired eyes, irritated eyes, lens awareness, blurred vision, redness, discomfort, deposits, dryness)	Contact lens wearer reporting at least 2 symptoms often or always	83 (81 completed)	4 wk	Weak; high risk of bias (use of baseline habitual lens wear comparison may have favored treatment arm; no washout; industry sponsored, conducted, written)
Randomized, controlled, double-masked, single-center clinical trial ²⁴	3-mo absorbable glycolic acid and trimethylene carbonate punctal plug (EXTEND Absorbable Synthetic Implants; Odyssey Medical, Memphis, TN) vs. sham procedure	CLDEQ	Symptomatic dry eye contact lens wearers with CLDEQ score > 0.13 ²⁵	32 enrolled, 22 eligible based on CLDEQ score, 19 completed	6 wk	Strong; low risk of bias (sham procedure and blinding well described; regression toward the mean and placebo effect likely)
Randomized, investigator masked, placebo controlled ²⁶	Cyclosporine 0.05% ophthalmic emulsion (Restasis; Allergan, Inc.) twice per day vs. rewetting drops (carboxymethylcellulose 0.5%, Refresh Contacts; Allergan, Inc.), twice per day, to be used before and after lens wear	Subjective evaluation of dryness severity (mild, moderate, severe), OSDI	Self-reported history of contact lens dryness/intolerance	17	5 wk	Medium; moderate risk of bias (patients unmasked; subjective bias likely); demographic data not provided
Randomized, double masked, placebo controlled ³⁹	Cyclosporine 0.05% ophthalmic emulsion vs. Refresh Preservative Free Artificial Tears (Allergan, Inc.) twice a day	OSDI and National Eye Institute Refractive Error Quality of Life Instrument	Chart review to identify contact lens wearers with complaints of dryness including irritation, burning, decreased wearing time	44 (22 per arm)	3 mo	Strong; low risk of bias (continuing use of habitual lens and cleaning regimen potential confounder; no washout)
Randomized, double-blind, parallel-group 15-center study ²⁷	2% polyvinylpyrrolidone (PVP) vs. 0.9% NaCl 1–6 drops per day as required	Overall contact lens comfort (VAS scale)	Contact lens wearers complaining of discomfort and soreness, irritation, smarting, burning, blurred vision aggravated by environmental factors (air conditioning, heating, working conditions, e.g., prolonged use of visual display unit)	45 (25 PVP, 20 NaCl)	28 d	Weak; high risk of bias (unbalanced; industry sponsored, conducted, written; variable dosage confounder)

TABLE 1. Continued

Study Design (e.g., Placebo- Controlled RCT, Retrospective Cohort) and Reference	Details of Intervention (e.g., Regimen, Composition)	Primary Outcomes	Disease Definitions/ Criteria (OSDI)	Sample Size, Overall and per Arm	Follow-up Period, From Baseline	Overall Quality Rating
Single-center, double-masked, randomized, crossover, pilot clinical trial ²⁸	Senofilcon A (Acuvue Oasys with Hydraclear Plus; Johnson and Johnson Vision Care) vs. habitual (control) during 75-min controlled adverse environment (CAE) exposure	Ocular discomfort (0–4 scale)	Soft contact lens wearers with histories of ocular discomfort during lens wear in windy or dry environments	11	75 min	Weak; high risk of bias (use of habitual lens wear control a potential confounder; inadequate sample size; masking not described; industry funded)
Randomized, contralateral, crossover, open- label clinical trial ²⁹	Intervention 1: etafilcon A (1-DAY Acuvue; Johnson & Johnson Vision Care) vs. lotrafilcon A (NIGHT & DAY; CIBA Vision) Intervention 2: NaCl 90 mg/mL (AstraZeneca, North Ryde, NSW, Australia) vs. PVA 14 mg/mL, povidone 6 mg/mL, sodium chloride (Refresh; Allergan, Inc.) vs. carboxymethylcellulose (CMC) 5 mg/mL (Cellufresh; Allergan, Inc.) every 2 h for 6 h	Comfort (100-point scale)	At least 12 mo of lens wear fitted	15	6 h on 4 separate days	Moderate; moderate risk of bias (patients masked for lens type but unmasked for drop type except at insertion; investigators not masked)
Prospective, single- masked (subjects), randomized, crossover study ³⁰	Lotrafilcon A with hypoosmotic (280 mmol/kg) vs. hyperosmotic (380 mmol/kg) saline 15 μ L 4 times a day	Comfort (1–100 scale)	Symptomatic lens wearers with maximum comfortable wearing time < 6 h	15	6 h	Strong; low risk of bias (investigator not masked)
Randomized, double-masked, 19-site study ³¹	OPTI-FREE Replenish (Alcon Laboratories) vs. ReNu MultiPlus No Rub Formula (Bausch & Lomb)	Comfort and dryness scores (0–100 scale)	Symptomatic wearers of group IV soft lenses answering disagree or strongly disagree to “My contacts are comfortable all day long” and agree or strongly agree to one or both of “During the day, I take my contacts out earlier than I like because they become uncomfortable” and “Late in the day, my contacts become uncomfortable but I continue wearing them”	362 (183 OPTI-FREE vs. 179 ReNu MultiPlus)	28 d	Medium; moderate risk of bias (no washout; lens type solution interactions likely confounder)

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TABLE 1. Continued

Study Design (e.g., Placebo- Controlled RCT, Retrospective Cohort) and Reference	Details of Intervention (e.g., Regimen, Composition)	Primary Outcomes	Disease Definitions/ Criteria (OSDI)	Sample Size, Overall and per Arm	Follow-up Period, From Baseline	Overall Quality Rating
Randomized, crossover study, open label ³²	Omafilcon A (Proclear; CooperVision) vs. new habitual lenses (control)	Subjective symptoms VAS (10 cm) scale (comfort and dryness severity; dryness, eye irritation, itchiness, burning, soreness, scratchiness, grittiness, watering, light sensitivity frequency)	Contact lens wearers with dry eyes (NEI definition: Schirmer without anesthesia \leq 5 mm, rose bengal staining \geq 3, fluorescein staining \geq 3, meibomian gland dysfunction \geq 2)	76	6-wk crossover	Weak; high risk of bias (open label likely to favor new lens type; use of more than 1 lens type as control a confounder; industry funded)
Randomized, double- masked, cross- over study ³³	Lotrafilcon B with polyhexamethylene biguanide (PHMB) (Solocare Aqua; CIBA Vision) vs. PHMB with surfactant (Hydro Health, Disop, Spatin) solutions	10-item symptoms questionnaire (0–10 scale); discomfort; blurry vision, lens-handling problems, dryness, redness, tearing, burning, itching, discharge, dissatisfaction + CLDEQ	Daily wear of lotrafilcon B for $>$ 3 mo	54	1-mo crossover	Strong; low risk of bias
Randomized, crossover, single masked (participant) ³⁴	5 silicone hydrogels: galyfilcon A (Acuvue Advance; Johnson & Johnson Vision Care); senofilcon A (Acuvue OASYS; Johnson & Johnson Vision Care); lotrafilcon B (O ₂ Optix; CIBA Vision); lotrafilcon A (NIGHT & DAY; CIBA Vision); balafilcon A (PureVision; Bausch & Lomb) disinfected with ClearCare (AOSEpt Plus; CIBA Vision) for $>$ 6 h	Comfort, burning, dryness, analogue scales (0–100) with verbal anchors at various times (insertion, settling, 8 h, 12 h on days 1, 4, 7, 10, and 14 using handheld wireless communication devices	Adapted soft lens wearers	55 (45 completed and analyzed)	4-wk crossover with 1 d washout	High; low risk of bias (base curve selection for 2 of 5 lens types a potential confounder; single masked only)
Retrospective multistudy, multicenter analysis, open label, uncontrolled ^p	Lotrafilcon A (NIGHT & DAY; CIBA Vision) or lotrafilcon B (O ₂ Optix; CIBA Vision) daily wear or continuous	Dryness during the day and end-of-day from CLDEQ	Adapted soft lens wearers (nonsilicone hydrogel)	259	2 wk (lotrafilcon B) or 1 mo (lotrafilcon A)	Weak; high risk of bias (open label; subject masked to study sponsor only, not to lens type; retrospective; uncontrolled; multiple wear schedule and lens type a confounder)

TABLE 1. Continued

Study Design (e.g., Placebo-Controlled RCT, Retrospective Cohort) and Reference	Details of Intervention (e.g., Regimen, Composition)	Primary Outcomes	Disease Definitions/ Criteria (OSDI)	Sample Size, Overall and per Arm	Follow-up Period, From Baseline	Overall Quality Rating
Contralateral, randomized, double masked ⁵⁵	Etafilcon A (Acuvue; Johnson and Johnson Vision Care) vs. Omafilcon A (Proclear Biocompatibles; CooperVision)	Subjective comfort and dryness (100-mm VAS scale with anchors at 0 = very dry and 100 = no dryness) at 0, 1, 3, 5, and 7 h	Symptomatic: Wearers with symptoms of dryness after 5 h of wear with consequently reduced wearing time and use of lubricating drops at least once daily Asymptomatic: wearers without symptoms of dryness or discomfort who could wear lenses all day without use of lubricants	40 (20 symptomatic, 20 asymptomatic)	7 h	Moderate; moderate risk of bias (no washout; contralateral eye effect potential confounder)
Randomized, investigator-masked, crossover study ³⁶	Hydroxypropyl methylcellulose (HPMC) (COMPLETE ComfortPLUS; Allergan, Inc.) vs. citrate (No Rub OPTIFREE Express; Alcon Laboratories) solution with fresh habitual lenses	Daytime and end-of-day comfort and dryness (50-point continuous scale with anchors 0 = impossible to wear and 50 = excellent)	Experienced daily lens wearers	75 (64 completed)	1-mo crossover with 1-wk washout	Moderate; moderate risk of bias (participants masked only to study sponsor; lens type confounder; industry funded)
Retrospective, 7-site open-label trial ³⁷	Senofilcon A (Johnson & Johnson Vision Care) daily wear with multipurpose solution (MPS) (one of Polyquad/EDTA, Alcon Laboratories; Polyquad/nananoyleDTA, Alcon Laboratories; PHMB/borate, Bausch & Lomb; PHMB/phosphate, CIBA Vision) vs. hydrogen peroxide (H ₂ O ₂) vs. daily disposable (DD)	Comfort and dryness on a 1–10 scale with anchors 1 = poor and 10 = excellent	Previous wear experience not specified	283 (160 MPS, 83 H ₂ O ₂ , 40 DD)	3 mo	Weak; high risk of bias (open label; not randomized; retrospective; multiple MPS and replacement schedule confounders; unbalanced; same participants in more than 1 trial)
Randomized, investigator-masked, 2-site crossover study ³⁸	No Rub OPTIFREE Express (Alcon Laboratories) vs. Complete (Allergan, Inc.) or ReNu MultiPlus (Bausch & Lomb) with Acuvue 2 (Johnson and Johnson Vision Care) or Soflens 66 (Bausch & Lomb)	Subjective preference based on answer to "Did you notice a difference in comfort provided by the study solutions?"	Daily wearers	89 (47 and 42 at each site); 71 completed	2-mo crossover with 72-h washout	Weak; high risk of bias (participants not masked; unequal group sizes; randomization not stratified by site)

For many studies attracting good overall quality rating, a subjective contact lens comfort improvement was found in both the treated and the placebo groups.^{27,33}

* BC, base curve.

TABLE 2. Candidate Outcomes for Clinical Trials

Name, Reference	Validation With a Contact Lens-Wearing Population
Developed for contact lens wear	
Contact Lens Dry Eye Questionnaire (CLDEQ) ²⁵	Yes; screening
CLDEQ-8 ¹	Yes; screening and responsiveness
Contact Lens Impact on Quality of Life (CLIQ) ⁵⁰	Yes; quality of life; keratoconus only
Developed for dry eye without contact lenses	
Dry-Eye Questionnaire (DEQ) ⁵¹	No
DEQ ⁵²	No
Ocular Surface Diseases (OSD) questionnaire (in French) ⁵³	No
Impact of Dry Eye on Everyday Life (IDEEL) questionnaire ⁵⁴	No
McMonnies ⁵⁵	No
Ocular Surface Disease Index (OSDI) ⁵⁶	No
Symptom Assessment in Dry Eye (SANDE) ⁵⁷	No
Subjective Evaluation of Symptom of Dryness (SeSOD) ⁵⁸	No
Short questionnaire for dry eye syndrome (DES) questionnaire ⁵⁹	No
Unnamed questionnaire (in Spanish) ⁶⁰	No
Standard Patient Evaluation of Eye Dryness (SPEED) ⁶¹	No
Texas Eye Research and Technology Center (TERTC) ⁶²	No

literature review was conducted using the search terms “comfort AND contact lenses” with the addition of search terms related to the outcome. The Subcommittee on Clinical Trial Design and Outcomes agreed in advance to investigate a number of outcome measures that fall under the broad categories of staining, hyperemia, tear film changes, vision, ocular sensitivity and contact lens surfaces. The resulting relevant manuscripts were reviewed and evaluated for standardization and agreement. There is a large volume of work reporting on contact lens outcomes, and so a representative list of studies investigating CLD is presented in Table 3. A few “other” assessments/responses to contact lens wear are also described in this section.

Staining of the Cornea. Staining of the cornea is an established method of evaluating the ocular surface.^{37,38,63-72} For corneal staining, sodium fluorescein is generally used, and methods for instillation and observation have been reported.^{73,74} Corneal staining is often measured in studies evaluating CLD; however, it has been reported to be a frequent outcome that is not well understood.^{74,75} With respect to grading corneal staining, there are various systems in use; however, only some have been validated for precision and reliability, such as the Efron scale and the Cornea and Contact Lens Research Unit (CCLRU) scale.⁷⁶ Information related to corneal staining can include its severity, type, and location, which can be used to help identify the etiology for the staining and may be important to understand its impact on CLD. Diffuse staining, when people use daily wear of lenses with multipurpose disinfecting solutions, in a characteristic annular pattern across the entire cornea or concentrated in three or more peripheral quadrants, has been described as solution-induced corneal staining (SICS),⁷⁷ also known as preservative-associated transient corneal hyperfluorescence.⁷⁸ This is quantified mainly on the extent (or % corneal coverage) of corneal staining.^{69,79,80}

Of the studies reviewed, investigations typically compare corneal staining at baseline to staining at follow-up visits, subsequent to an intervention with one or more contact lens types or lens care systems. Baseline visits often occur following a “washout” period of no lens wear or earlier in the day prior to lens insertion. Studies investigating SICS have performed measurements at baseline, then after 2 to 4 hours of lens wear,^{65,79} and then again at the end of the day.

As indicated in Table 3, corneal staining may be related to CLD; however, there have been mixed reports in the literature. The location and type of corneal staining may be important for different aspects of contact lens performance.

It is recommended that studies report method and techniques used to assess staining and that a common grading system be adopted to aid in the interpretation of staining across studies. Grading methodology, such as the methodology proposed in the report of the National Eye Institute and Industry-Sponsored Dry Eye Workshop,⁸¹ may not be adequate to grade corneal staining observed with contact lens wear. With respect to SICS, a better understanding of the uptake and release profiles of excipients in the disinfecting solutions with contact lenses may aid in study design, particularly with respect to determining the optimal times for clinical assessments to be conducted. In fundamental studies, where certain lens characteristics, lens care systems, or other variables are altered, controlling as many other factors as possible is warranted to better understand the relationship between corneal staining and CLD.

Staining and Indentation of the Bulbar Conjunctiva. Changes in the bulbar conjunctiva occur with CL wear.^{71,82-85} Either sodium fluorescein or lissamine green dyes are typically used for the assessment of conjunctival staining; however, lissamine green has been reported to be better at differentiating symptomatic from asymptomatic contact lens wearers.⁸⁴ A number of different grading scales have been used, such as the Efron scale⁸⁶ and the CCLRU scale.⁸⁷ Other scales developed for evaluation of dry eye include the National Eye Institute/Industry Workshop scale,⁸¹ the TFOS Dry Eye Workshop scale,⁸⁸ and the Sicca scale⁸⁹; but these have not been validated for evaluation with contact lens wear. It is recommended that the type of conjunctival staining, such as lens edge-related conjunctival staining^{82-84,90,91} or diffuse conjunctival staining, be specified. As indicated in Table 3, conjunctival staining and indentation may be associated with CLD.

Staining and Roughness of the Palpebral Conjunctiva. Korb et al.⁹² introduced the term “lid wiper” to refer to the area of the upper eyelid that spreads tears over the surface of the cornea (or contact lens) and the term “lid wiper epitheliopathy” (LWE), which refers to the disruption of epithelial cell integrity in this area. A similar area in the lower

TABLE 3. Clinical Measures of CLD

Outcome	Associated With CLD?	Methods	Key Findings
Corneal staining	Yes	Data obtained from 7 prospective trials, $n = 283$; 4 groups wore senofilcon A lens material on a daily-wear basis using multipurpose solutions (DW-MPS, $n = 160$), 2 groups using hydrogen peroxide (DW-H ₂ O ₂ , $n = 83$), and 1 group wearing the lens on a daily disposable basis ($n = 40$). Participants were followed for 3 mo using the same protocol.	Comfort at insertion and end of day, and end-of-day dryness scores, were significantly lower for participants who experienced solution-induced corneal staining (SICS; 8.2 ± 1.6 , 7.0 ± 1.9 , and 7.0 ± 2.2) than for those who did not (8.8 ± 1.2 , $P = 0.004$; 7.9 ± 1.7 , $P = 0.002$; and 7.9 ± 1.8 , $P = 0.003$, respectively). ³⁷
	Yes	Ninety-day, randomized, concurrently controlled, double-masked, multisite study involved 573 subjects at 30 investigational sites in the United States, using 1 of 2 multipurpose disinfecting solutions.	Differences noted in the level of corneal staining (SICS) between the 2 disinfecting solutions, and the solution that gave most SICS was rated worse for subjective comfort (insertion, removal, overall). ⁶⁶
	Yes	Retrospective analysis of a series of open-label studies conducted with 24 groups of approximately 40 participants, each wearing 1 of 6 silicone hydrogel contact lenses with 1 of 4 lens care products bilaterally for 3 mo of daily wear.	Participants with SICS had lower levels of comfort during the day (7.9 ± 1.7 vs. 8.5 ± 1.4 , $P = 0.03$), comfort at the end of the day (6.6 ± 2.1 vs. 7.4 ± 1.9 , $P = 0.03$), overall dryness (7.4 ± 1.9 vs. 8.0 ± 1.7 , $P = 0.04$), dryness at the end of the day (6.7 ± 2.2 vs. 7.5 ± 2.1 , $P = 0.01$), feelings of burning and stinging (8.5 ± 2.0 vs. 8.9 ± 1.8 , $P = 0.02$), and overall vision (8.2 ± 1.6 vs. 8.7 ± 1.3 , $P < 0.001$). ⁶⁴
	Yes	Two sites conducted a randomized, investigator-masked, 2-mo crossover study; $n = 45$ used regimen 1 and 2 for 1 mo each (study 1), and $n = 44$ used regimen 1 and 3 for 1 mo each (study 1). 1 of 2 soft lens types was randomly assigned, and the same lens type was worn throughout the study.	Significantly more subjects preferred the comfort of an MPS that gave low levels of corneal staining (SICS) (61.8%) to that of regimen 3 (11.8%). ³⁸
	Possibly	One-week, daily-wear, subject-masked, bilateral, parallel-group study with subjects ($n = 282$) randomly assigned to 1 of 2 daily disposable soft contact lenses.	There was a weak correlation between corneal staining and comfort for 1 lens ($r = 0.27$, $P = 0.002$, $n = 136$), but not the other ($r = -0.11$, $P = 0.18$, $n = 140$). ⁷⁰
	Possibly	Observational, single-visit, investigator-masked study; $n = 89$ wearers of group IV hydrogel or silicone hydrogel lenses who were required to have consistently used a polyhexamethylene biguanide (PHMB)- or polyquaternium-1-based solution for 2 y. Clinical assessments included average and comfortable wear time; overall and end-of-day comfort; signs of dryness, discomfort, burning or stinging, grittiness or scratchiness; corneal staining.	No significant differences between the 2 preservative system groups were noted for overall or end-of-day comfort, discomfort, or burning or stinging. However, grittiness or scratchiness was higher with PHMB-containing system, and so were the level and extent of corneal staining (SICS). ⁷¹
	No	Prospective, bilateral, single-masked (investigator), randomized crossover design with 4 phases (1 for each care system). Each study phase comprised 2 consecutive days of lens wear on which the lenses were inserted on day 1 directly from the blister-packs and worn for over 8 h, then inserted on day 2 after overnight disinfection with 1 of the study lens care systems. $N = 25$ adapted soft contact lens wearers who were able to wear their habitual lenses comfortably for more than 12 h were recruited.	Even though 1 MPS was associated with high levels of corneal staining (SICS), there was no difference between the lens care systems and subjective comfort over a 2-d period. ⁶³
	No	Three-month prospective study; $n = 120$ participants were randomized into 1 of 3 lens types (etafilcon A, narafilcon A, and senofilcon A), all worn bilaterally on a daily disposable regimen; observations were at baseline, 2-wk, and 1- and 3-mo visits.	No differences were found between lenses in the 1-100 rating scale ($P > 0.05$) even though some lenses had statistically worse corneal staining. ⁶⁴
	No	A series of pilot studies using a total of 27 subjects (some of whom were enrolled in 2 or more studies) was conducted over 11 mo using a double-masked, randomized, crossover design. Asymptomatic, adapted, daily-wear soft lens users were included; evaluations were at baseline and after 1 and 2 h of wear.	Significantly increased extent of corneal staining (SICS) was observed at 2 h when subjects used silicone hydrogel lenses soaked an MPS, but significant levels of symptoms were not correlated with extent of staining. ⁶⁵

TABLE 3. Continued

Outcome	Associated With CLD?	Methods	Key Findings
	No	Prospective, double-masked, single-investigator study; $n = 20$ participants were recruited for 2 visits with lenses worn bilaterally for 2 h.	Comfort scores did not differ between eyes ($P > 0.05$) despite significantly less corneal staining (SICS) in 1 eye compared to the other. ⁶⁸
	No	Double-masked, randomized, 1-mo crossover study; $n = 50$ adapted soft lens wearers.	Significantly different ($P < 0.01$) levels of relatively asymptomatic corneal staining (SICS) were observed with 1 lens care solution (37%) compared to the other (2%); symptoms were not correlated with the degree of staining. ⁶⁹
	No	Observational study; $n = 50$ (19 men, 31 women; mean age, 32.1 ± 11.4 y) adapted lens wearers. Comfort was evaluated using the Contact Lens Dry Eye Questionnaire. Corneal staining was assessed in the right eyes. Nonparametric analyses were used to study differences between groups and correlations between objective tests and symptoms.	No difference in corneal staining observed between asymptomatic and symptomatic lens wearers. ⁷²
Conjunctival staining	Yes	The study was conducted on a cohort population of 27 established soft contact lens wearers, who wore each contact lens type, in a random order, for a period of 10 (± 2) days. Circumlimbal staining was measured in a double-masked fashion through image analysis of digital photographs of lissamine green taken under controlled experimental conditions.	An inverse association between circumlimbal staining and contact lens comfort was demonstrated. Lenses with a rounded edge design produced the lowest comfort (72 of 100) whereas lenses with a knife-edge design produced the highest (87 of 100). ⁸²
	Yes	Overall staining, as well as staining at 5 separate sites (limbal, nasal band, temporal band, superior, and inferior), was graded on an analogue scale in 48 contact lens-wearing subjects and 50 control non-lens wearers. The degree to which subjects experienced sensations of dryness, wateriness, itchiness, grittiness, and comfort was also assessed using analogue scales.	In regression analysis, overall conjunctival staining was associated with the degree of dryness and the amount of itchiness. ⁸³
	Yes	Lissamine green and sodium fluorescein conjunctival staining were assessed in 102 soft contact lens wearers and 79 non-contact lens wearers.	Lissamine green staining (\geq grade 1) could discriminate symptomatic from asymptomatic lens wearers ($P = 0.007$). ⁸⁴
	No/possibly	Observational, single-visit, investigator-masked study; $n = 89$ wearers of group IV hydrogel or silicone hydrogel lenses who were required to have consistently used a PHMB- or polyquaternium-1-based solution for 2 y. Clinical assessments included average and comfortable wear time; overall and end-of-day comfort; signs of dryness, discomfort, burning or stinging, grittiness or scratchiness; conjunctival staining.	Nasal and temporal conjunctival staining was significantly higher for users of PHMB-containing systems ($P < 0.05$). No significant differences between the 2 preservative system groups were noted for overall or end-of-day comfort, discomfort, or burning or stinging; but grittiness or scratchiness was significantly higher with the PHMB-containing system. ⁷¹
Conjunctival indentation	Yes	A new method to measure contact lens osmolality was validated by testing for repeatability and by evaluating independence of lens material, power, and osmolality value of the lens. This method was then used in a clinical study. 15 subjects wore each of 9 different lens types. Osmolality, tear film, and ocular surface parameters were tested for their association with comfort using linear mixed model.	Comfort was associated with conjunctival indentation ($P = 0.002$, $r = -0.37$) (Stahl U, et al. <i>IOVS</i> 2009;50:ARVO E-Abstract 2611).
Palpebral conjunctival staining, including lid wiper staining and lid parallel conjunctival folds	Yes	Subjects were divided into 2 groups based on the presence or absence of dry eye symptoms. The lid wiper of asymptomatic ($n = 75$) and symptomatic ($n = 30$) soft contact lens wearers was examined following the instillation of fluorescein and rose bengal dyes. Lid wiper staining was graded zero to 3.	Eighty percent of the symptomatic subjects displayed lid wiper staining compared to 13% of the asymptomatic subjects ($P < 0.0001$). ⁹²

TABLE 3. Continued

Outcome	Associated With CLD?	Methods	Key Findings
	Yes	Observational study; $n = 50$ (19 men, 31 women; mean age, 32.1 ± 11.4 y) adapted lens wearers. Comfort was evaluated using the Contact Lens Dry Eye Questionnaire. Corneal staining, lid wiper epitheliopathy, and lid parallel conjunctival folds were assessed in the right eyes. Nonparametric analyses were used to study differences between groups and correlations between objective tests and symptoms.	Lid wiper epitheliopathy and lid parallel conjunctival folds were significantly increased ($P < 0.035$) in the symptomatic lens wearers. ⁷²
Palpebral roughness	No/possibly	Observational, single-visit, investigator-masked study; $n = 89$ wearers of group IV hydrogel or silicone hydrogel lenses who were required to have consistently used a PHMB- or polyquaternium-1-based solution for 2 y. Clinical assessments included average and comfortable wear time; overall and end-of-day comfort; signs of dryness, discomfort, burning or stinging, grittiness or scratchiness; palpebral roughness.	No significant differences between the 2 preservative system groups were noted for overall or end-of-day comfort, discomfort, burning or stinging, but there was an increase in grittiness or scratchiness ($P = 0.045$) for the PHMB system and also an increased level of palpebral roughness ($P = 0.014$). ⁷¹
Conjunctival hyperemia	Yes	Cross-sectional study on 415 contact lens wearers in which a number of tear film, contact lens, and patient-related factors were measured and examined in relation to dry eye status. Univariate and multivariate logistic regression models were used, and data from 360 of the 415 subjects were used in the analyses.	Several factors were shown to be related to dry eye status in multivariate modeling, including limbal injection ($P = 0.03$). ⁷⁵
	No	Prospective, randomized, parallel-group, 3-mo study; $n = 120$ participants (40 in each group) wore 1 of 3 lens types (etafilcon A, narafilcon A, and senofilcon A), all worn bilaterally on a DD regimen. Participants were observed at baseline, 2-wk, and 1- and 3-mo visits in which ocular physiology and lens performance variables were collected on a 0–4 grading scale in 0.1 increments. Subjective comfort and vision ratings were collected on a 1–100 rating scale and in the form of symptom severity.	Even though 1 lens type was associated with significantly more limbal redness ($P < 0.01$), there were no differences in comfort between lenses ($P > 0.05$). ⁷²
Limbal hyperemia	No	Observational, single-visit, investigator-masked study; $n = 89$ wearers of group IV hydrogel or silicone hydrogel lenses who were required to have consistently used a PHMB- or polyquaternium-1-based solution for 2 y. Clinical assessments included average and comfortable wear time; overall and end-of-day comfort; signs of dryness, discomfort, burning or stinging, grittiness or scratchiness; limbal and bulbar hyperemia.	No significant differences between the 2 preservative system groups were noted for overall or end-of-day comfort, discomfort, burning or stinging (except grittiness or scratchiness), or for limbal or bulbar hyperemia. ⁷¹
Tear film stability	Yes	Thirty-eight subjects participated; 20 were successful contact lens wearers and 18 had discontinued contact lens wear because of discomfort. Baseline tear film (no lens wear) was analyzed with a range of clinical measurements and protein analyses (lactoferrin, sIgA, and lysozyme). Comfort was determined after 6 h of lens wear, and differences in tear film characteristics between subject groups were determined. Tests were performed in absence of contact lens wear.	Tear stability (noninvasive tear breakup time) was significantly reduced in intolerant wearers ($P < 0.05$). ¹⁰⁷
	Yes	Cross-sectional study on 415 contact lens wearers in which a number of tear film, contact lens, and patient-related factors were measured and examined in relation to dry eye status. Univariate and multivariate logistic regression models were used, and data from 360 of the 415 subjects were used in the analyses.	Several factors were shown to be related to dry eye status in multivariate modeling, including rapid pre-lens tear film thinning time ($P = 0.008$). ⁷⁵

TABLE 3. Continued

Outcome	Associated With CLD?	Methods	Key Findings
	Possibly	Randomized, double-masked, contralateral, 7-h nondispensing study; $n = 40$ (20 symptomatic and 20 asymptomatic lens wearers). Lens water content was measured before and after 7 h of lens wear, and pre-lens noninvasive tear film breakup time (NITBUT) was measured immediately after insertion and after 5 h of lens wear. Subjective comfort and dryness were rated at 0, 1, 3, 5, and 7 h of lens wear.	Symptomatic hydrogel contact lens wearers with decreased wearing time had measurably reduced NITBUT. ³⁵
	Possibly	Randomized, subject-masked bilateral crossover study of silicone hydrogel lenses in 24 adapted soft contact lens wearers.	Tear film stability was superior for 1 lens over the other, and the authors concluded that this was associated with an overall better comfort for this lens. ¹⁰⁵
	No	Prospective, 8-h nondispensing study; $n = 30$ adapted soft contact lens wearers (16 symptomatic and 14 asymptomatic) were fitted with etafilcon A lenses. In vivo wettability, NITBUT, and subjective symptoms (vision, comfort, and dryness) were assessed at baseline and after 2, 4, 6, and 8 h. After 2-, 4-, 6-, and 8-h time points, lenses were collected, and total protein, total lysozyme, and active lysozyme deposition were assessed.	There was no significant difference in the NITBUT values between the 2 groups at any time point ($P > 0.05$), but the 8-h time point was significantly lower than the baseline measurement in both the symptomatic and asymptomatic groups ($P = 0.032$). ¹⁰⁶
	No	Observational, single-visit, investigator-masked study; $n = 89$ wearers of group IV hydrogel or silicone hydrogel lenses were required to have consistently used a PHMB- or polyquaternium-1-based solution for 2 y. Clinical assessments included average and comfortable wear time; overall and end-of-day comfort; signs of dryness, discomfort, burning or stinging, grittiness or scratchiness; noninvasive and fluorescein breakup time.	No significant difference between 2 preservative system groups was noted for overall or end-of-day comfort, discomfort, burning or stinging (except grittiness or scratchiness) or for tear breakup times. ⁷¹
Tear film volume	Yes	Thirty-eight subjects participated; 20 were successful contact lens wearers and 18 had discontinued contact lens wear because of discomfort. Baseline tear film (no lens wear) was analyzed with a range of clinical measurements and protein analyses (lactoferrin, sIgA, and lysozyme). Comfort was determined after 6 h of lens wear, and differences in tear film characteristics between subject groups were determined. Tests were conducted in absence of contact lens wear.	Tear volume (meniscus height and phenol red thread test) were significantly reduced in intolerant wearers ($P < 0.05$). ¹⁰⁷
	No	Observational, single-visit, investigator-masked study; $n = 89$ wearers of group IV hydrogel or silicone hydrogel lenses were required to have consistently used a PHMB- or polyquaternium-1-based solution for 2 y. Clinical assessments included average and comfortable wear time; overall and end-of-day comfort; signs of dryness, discomfort, burning or stinging, grittiness or scratchiness; tear meniscus height, Schirmer, and fluorescein clearance tests.	No significant difference noted between the 2 preservative system groups for overall or end-of-day comfort, discomfort, burning or stinging (except grittiness or scratchiness), and tear meniscus height, Schirmer test, or fluorescein clearance. ⁷¹
Tear lipid layer	Possibly	Randomized, subject-masked bilateral crossover study of silicone hydrogel lenses in 24 adapted soft contact lens wearers.	Lipid layer thickness was superior for 1 lens over the other, and the authors stated that this may have been a reason for the better comfort for that lens over the other. ¹⁰⁵
	No	Observational, single-visit, investigator-masked study; $n = 89$ wearers of group IV hydrogel or silicone hydrogel lenses were required to have consistently used a PHMB- or polyquaternium-1-based solution for 2 y. Clinical assessments included average and comfortable wear time; overall and end-of-day comfort; signs of dryness, discomfort, burning or stinging, grittiness or scratchiness; preocular tear film lipids.	No significant differences between the 2 preservative system groups were noted for overall or end-of-day comfort, discomfort, burning or stinging, except grittiness or scratchiness, and no difference in clinical assessment of tear film lipid layer. ⁷¹

TABLE 3. Continued

Outcome	Associated With CLD?	Methods	Key Findings
Tear film osmolality	Yes	Cross-sectional study on 415 contact lens wearers in which a number of tear film, contact lens, and patient-related factors were measured and examined in relation to dry eye status. Univariate and multivariate logistic regression models were used, and data from 360 of the 415 subjects were used in the analyses.	Several factors were shown to be related to dry eye status in multivariate modeling, including increased tear film osmolality ($P = 0.05$). ⁷⁵
	No	Prospective, 8-h nondispensing, crossover study; the right eyes of 15 neophytes were included. Tear osmolality was measured before and after 4 and 8 h of each contact lens wear. Ocular comfort was assessed after 4 and 8 h of each contact lens wear.	Tear osmolality was not associated with ocular comfort. ¹¹⁴
	No	Thirty-eight subjects participated; 20 were successful contact lens wearers and 18 had discontinued contact lens wear because of discomfort. Baseline tear film (no lens wear) was analyzed with a range of clinical measurements and protein analyses (lactoferrin, sIgA, and lysozyme). Comfort was determined after 6 h of lens wear, and differences in tear film characteristics between subject groups were determined.	Tear osmolality was not statistically significantly different between tolerant and intolerant contact lens wearers (osmolality [mOsmol/kg] 317.4 and 324.4, respectively, $P = 0.069$), even though intolerant wearers had a greater number of symptoms than tolerant wearers ($P < 0.05$). ¹⁰⁷
	No	A new method to measure contact lens osmolality was validated by testing for repeatability and by evaluating independence of lens material, power, and osmolality value of the lens. This method was then used in a clinical study. 15 subjects wore each of 9 different lens types. Osmolality, tear film, and ocular surface parameters were tested for their association with comfort using linear mixed model.	Comfort after 6 h of lens wear was not associated with tear osmolality after lens wear ($P = 0.993$). ⁸⁵
Contact lens osmolality	Yes	A new method to measure contact lens osmolality was validated by testing for repeatability and by evaluating independence of lens material, power, and osmolality value of the lens. This method was then used in a clinical study. 15 subjects wore each of 9 different lens types. Osmolality, tear film, and ocular surface parameters were tested for their association with comfort using linear mixed model.	Comfort after 6 h of lens wear was associated with the osmolality of the worn lens ($P = 0.006$, $r = -0.41$). Osmolality of worn lenses significantly correlated with tear film breakup time ($P = 0.003$, $r = -0.22$), lens water content ($P < 0.001$, $r = -0.58$), conjunctival indentation ($P < 0.001$, $r = 0.45$), and ocular sensitivity ($P < 0.05$) after 6-h lens wear. ⁸⁵
Optical quality	No peer reviewed publications on this topic		
Corneal sensitivity	Yes	$N = 32$ symptomatic and 29 asymptomatic contact lens wearers (aged 20–42 y, 6 males and 26 females; and 21–36 y, 9 males and 20 females, respectively). Mechanical stimulus thresholds of the cornea were determined using a Belmonte pneumatic esthesiometer and the ascending method of limits. Then 3 stimulus intensity groups (subthreshold, threshold, and suprathreshold) were applied to the eye in random order, each 20 times. Subjects rated the intensity of the stimuli using a scale of zero to 4. The rating data from the 2 groups were compared by Friedman nonparametric ANOVA. Adaptation was defined as the reduction in subsequent ratings compared with earlier ones.	Adaptation was found to suprathreshold mechanical stimuli in the asymptomatic group but not in the symptomatic group ¹²¹ ; in other words, the symptomatic group responded as much to the first suprathreshold stimulus as the last and never gained “tolerance” to the stimulus. ¹²¹
	No	Non-contact lens wearers and subjects who had worn soft contact lenses for more than 1 y were recruited and were divided into 3 groups: (1) normal controls, (2) contact lens wearers without dry eye, (3) contact lens wearers with dry eye. Corneal sensitivity was measured with a Cochet-Bonnet esthesiometer. Nerve density and branching in the subepithelial plexus were measured using in vivo confocal microscopy. Tear nerve growth factor and tissue growth factor-beta1 levels were measured with an enzyme immunoassay.	Both sets of contact lens wearers had reduced corneal sensitivity ($P = 0.032$) compared to the normal controls, ¹²² but there was no difference in sensitivity between contact lens wearers with and without dry eye complaints.

TABLE 3. Continued

Outcome	Associated With CLD?	Methods	Key Findings
Conjunctival sensitivity	Yes	Fifteen subjects, 9 lens types, lenses worn for 6 h; sensitivity measured with an air jet aesthesiometer at baseline and following lens removal.	Comfort associated with a change in corneal and conjunctival sensitivity. ¹⁵⁹
In vivo contact lens wettability	No	Prospective, randomized, bilateral, crossover study; $n = 15$. Initial comfort and surface wettability were compared between 3 lens types (Novalens [Ocu-Tec, Bellshill, North Lanarkshire, UK], ENVISION [Bausch & Lomb], and D3X4 [Wesley-Jessen, Des Plaines, IL]).	Initial comfort was significantly better with the D3X4 lens; no significant difference was found between the 2 rigid lens materials. No significant difference in lens surface wettability was found between the 3 materials. ¹²⁴
	No	Prospective, 8-h nondispensing study; $n = 30$ adapted soft contact lens wearers (16 symptomatic and 14 asymptomatic) were fitted with etafilcon A lenses. In vivo wettability, NITBUT, and subjective symptoms (vision, comfort, and dryness) were assessed at baseline and after 2, 4, 6, and 8 h. After 2-, 4-, 6-, and 8-h time points, lenses were collected, and total protein, total lysozyme, and active lysozyme deposition were assessed.	In vivo wettability was reduced over the course of the day for both groups, but was not statistically significant ($P > 0.05$). There was also no significant difference in wettability between the 2 groups at any time point ($P > 0.05$). ¹⁰⁶
	No	Observational, single-visit, investigator-masked study; $n = 89$ wearers of group IV hydrogel or silicone hydrogel lenses were required to have consistently used a PHMB- or polyquaternium-1-based solution for 2 y. Clinical assessments included average and comfortable wear time; overall and end-of-day comfort; signs of dryness, discomfort, burning or stinging, grittiness or scratchiness, and visual changes; noninvasive and fluorescein breakup time; precorneal tear film lipids, tear meniscus height, Schirmer, and fluorescein clearance tests; limbal and bulbar hyperemia; palpebral roughness; corneal and conjunctival staining; lens front surface wetting; and lens film deposits.	Front surface lens wettability was significantly better for group IV polyquaternium-1 users compared to PHMB users ($P = 0.008$), with 84% vs. 72%, respectively, with lenses graded by the investigator as having "good" or "excellent" wettability. No significant differences between the 2 preservative system groups were noted for overall or end-of-day comfort, discomfort, burning or stinging, grittiness or scratchiness. ⁷¹
Ex vivo wettability	Possibly	Randomized, single-masked study, $n = 6$; test and control lenses were soaked for 12 h in either saline or 1% aqueous solution of poloxamine 1107. The advancing and receding contact angles were determined ex vivo after various periods of wear.	Control saline-soaked lenses exhibited no change in wetting angles over time, indicating a lack of surface modification by components within the tear film. Poloxamine-soaked lenses exhibited a significantly reduced advancing angle ($P < 0.001$) and hysteresis angle ($P < 0.001$) when compared with control lenses. In addition, treated lenses were consistently rated as more comfortable than control lenses ($P = 0.04$). ¹²⁵

eyelid margin has also been identified.⁹³ The suspected etiology of this epitheliopathy is increased friction between the lid wiper area and the surface of the cornea or contact lens as a result of inadequate lubrication⁹⁴; however, this etiology still needs to be tested.

There are studies suggesting that LWE is more frequent in individuals reporting CLD; however, there have been no studies showing that the amount of LWE is related to the level of symptoms. Confirmatory studies are necessary to determine whether LWE is a good outcome measure of CLD. Standardization of dye instillation and assessment are also warranted since various methodologies have been reported.^{92,95} There is one study that showed a possible effect of palpebral roughness on the symptoms of grittiness and scratchiness during contact lens wear.⁷¹

Lid Parallel Conjunctival Folds. Lid parallel conjunctival folds (LIPCOF) have been described by Hoh et al.⁹⁶ and are defined as subclinical folds parallel to the upper and/or lower eyelid margin in the temporal and nasal areas of the bulbar conjunctiva. Lid parallel conjunctival folds have been shown to be significantly increased in symptomatic contact lens wear-

ers⁹⁶⁻⁹⁸ and to be positively correlated with LWE.⁹⁷ While LIPCOF may be predictive of CLD, prospective studies to investigate onset and recovery and whether the severity of LIPCOF is related to the severity of CLD are warranted.

Conjunctival and Limbal Hyperemia. Vascular dilatation can occur with CL wear.^{67,75} Conjunctival hyperemia is often increased with contact lens wear compared to non-lens-wearing eyes.^{99,100} However, since conjunctival hyperemia is affected by a number of factors, such as corneal hypoxia,¹⁰¹ protein adsorption with lens overwear,¹⁰² and lens fit,¹⁰³ it has generally not been a good outcome measure or predictor of CLD.

Tear Film Stability. Changes in tear film stability occur with CL wear.^{35,71,75,104-106} There have been mixed reports about the relationship between tear film stability and contact lens comfort. Reduced tear film stability has been reported in symptomatic and intolerant contact lens wearers,^{75,107} while Fonn et al.,³⁵ Guillon and Maissa,³⁶ and Guillon et al.¹⁰⁸ report no difference in tear stability between symptomatic and asymptomatic contact lens wearers in the absence of lens wear. Various techniques are used to assess tear film stability,

and it has been noted that endpoint criterion used for measurements can also differ.^{109,110} Standardization in methodology would be helpful to further evaluate the relationship between tear film stability and CLD. No optimal method for assessing tear film stability has yet been defined or validated, and this is needed.

Tear Volume. Tear volume can vary with CL wear.^{71,104} Tear volume has been measured noninvasively by measuring tear meniscus height, which has been done with use of a slit lamp and grading system or with more sensitive measurement techniques, such as optical coherence tomography (OCT). Tear meniscus height as measured by OCT has been reported to contribute to ocular comfort in both symptomatic and asymptomatic wearers.¹⁹ Glasson et al.¹⁰⁷ have shown that tear meniscus height (and area) is different between tolerant and intolerant lens wearers and that contact lens intolerance was best predicted by a combination of clinical variables, including tear film stability, tear volume, and the number of symptoms reported.

Tear Film Lipid Layer. The tear film lipid layer is affected by CL wear.^{71,105} The lipid layer is generally graded on a scale that uses interference patterns to estimate the thickness of the layer.^{108,111} The thickness of the lipid layer has been correlated with the evaporation rate of the tear film.¹¹² As contact lens wear increases the evaporation of the tear film,¹¹³ it has been assumed that there may be a relation between lipid layer thickness and CLD. Nichols and Sinnott⁷⁵ showed in a sample of 360 lens wearers that reduced lipid layer thickness was predictive of contact lens dry eye, in addition to being correlated with an increase in pre-lens tear thinning (a surrogate for evaporation). However, that relationship, if one exists, has not been conclusively shown.

Tear Film Osmolarity. Osmolarity of the tear film is a sensitive marker of tear function.^{75,104,107,114} (Stahl U, et al. *IOVS* 2009;50:ARVO E-Abstract 2611). Tear osmolarity has been shown to change with contact lens wear¹¹⁵; however, there have been mixed results as to whether it can be used to predict CLD. It has been recommended that for bilateral measurements, the more severe measurement be analyzed due to the asymmetric effects of environmental stress.^{115,116} With respect to methodology, it should be indicated whether measurements were completed with the lens on the eye or after it had been removed, since removal may result in reflex tearing and may result in lower values.⁷⁵

While tear film osmolarity has been related to symptoms of dry eye in non-contact lens wearers, its effect on CLD is less clear. However, contact lens osmolarity (i.e., a property of the contact lens itself) has been associated with CLD⁸⁵ (Stahl U, et al. *IOVS* 2009;50:ARVO E-Abstract 2611), and additional studies would be helpful to better understand this potential outcome measure.

Optical Quality. Papas et al. (Papas E, et al. *IOVS* 2003;44:ARVO E-Abstract 3694) suggest that poor optical quality may have a psychological impact on perceived ocular comfort and it may be that lens awareness as a result of reduced optical quality is related to CLD. With contact lens wear, reduced optical quality can be related to a number of factors, including uncorrected refractive error, higher-order aberrations,^{117,118} and poor front surface lens wettability.^{119,120} Currently, there is insufficient information to make conclusions regarding the link between optical quality and CLD; therefore additional research is warranted. Challenges will likely include methods of testing, since subtle vision changes are not adequately measured using traditional visual acuity measures. The development of dynamic vision assessments, taking into account environmental factors and blink patterns, may be warranted.

Ocular Sensitivity. Ocular sensation may be altered by CL wear.^{85,121,122} Trials measuring corneal sensitivity in contact lens wearers have used either the Belmonte pneumatic esthesiometer or the Cochet-Bonnet esthesiometer, and it would be expected that results could be impacted by the measurement technique. Overall, there have been few clinical trials investigating this outcome. Conjunctival hyperesthesia has been reported in dry eye subjects¹²³ but has not been explored in subjects with CLD.

Contact Lens Surface. The surface of the contact lens is a critical interface.^{71,106,109,124,125} The relationship between contact lens wettability and CLD has been unclear, possibly related to the various techniques that are used to assess wettability in vitro and in vivo and their limitations in capturing the dynamic changes that occur with wear and between blinks (for more in-depth analysis see the report of the Contact Lens Materials, Design & Care Subcommittee). Validation of measurement and grading techniques and a better understanding of the variability of in vivo wettability may be beneficial in determining the role that wettability plays in CLD.

Contact Lens Deposition. A correlation has been reported between active lysozyme on worn lenses and subjective comfort ($r = 0.6-0.7$; $P < 0.001$).¹⁰⁶ Additionally, a study of mucin mobility on worn contact lenses has been conducted, and changes in MUC1 breakdown were significantly negatively correlated to the overall Ocular Surface Disease Index score ($r = -0.891$, $P = 0.001$).⁷² However, the overall concentration of protein or cholesterol that can be extracted from contact lenses was weakly if at all correlated to comfort during lens wear (as measured on a VAS).¹²⁶ Additional studies investigating the role of contact lens deposition and CLD are necessary.

A number of studies have measured CLD and clinical signs with contact lens wear but did not determine whether there was a relationship between signs and symptoms.^{15,17,21,23,31,32,38,127-135} This complicates the interpretation of outcomes related to CLD since the specific driver(s) of CLD cannot be determined. In addition, when correlations have been measured, often there is not a test for a direct causative effect. A number of studies have reported changes in clinical outcomes with contact lens wear; however, there has been little evidence or discussion as to whether these findings are clinically relevant.

Studies With the Primary Objective of Predicting CLD. There have been only a few studies with this primary objective. Berry et al.⁷² evaluated signs and symptoms (using the CLDEQ) in 19 men and 31 women (mean age 32.1 ± 11.4 years) and reported that symptomatic contact lens wearers exhibit significantly more LWE and LIPCOF and decreased MUC5AC reactivity. Using a similar study design, Pult et al.⁹⁷ also reported that contact lens wearers with dryness symptoms exhibit significantly more LWE and LIPCOF, but not increased corneal staining, bulbar hyperemia, or decreased pre-lens tear breakup time. In a prospective, 2-month longitudinal study, Michel et al.¹³⁴ investigated new contact lens wearers and grouped them according to their response to the screening CLDEQ questions, resulting in 20 "symptomatic" and 13 "asymptomatic" subjects. They reported that the best combination to predict CLD using logistic regression was LIPCOF sum plus noninvasive tear breakup time (NITBUT) and OSDI scores (positive predictive value, 87%; accuracy, 91%).¹³⁴ Nichols and Sinnott⁷⁵ evaluated data from 360 contact lens wearers (33/360 were gas-permeable lens wearers) from a large cross-sectional study and reported several factors to be related to dry eye status in multivariate modeling, including female sex ($P = 0.007$), lenses with higher nominal water content ($P = 0.002$), rapid pre-lens tear film thinning time ($P = 0.008$), frequent usage of over-the-counter pain medication (P

= 0.02), limbal injection ($P = 0.03$), and increased tear film osmolality ($P = 0.05$). In a prospective, observational multicenter study conducted by Young et al.,¹³⁵ symptomatic soft contact lens wearers reported significant soft contact lens-related dryness using the CLDEQ preceding a protocol-driven dry eye examination. Of the 226 symptomatic wearers examined, 23% were without signs. The wearers classified as “No dry eye signs” had significantly longer prelens breakup time (9.8 vs. 6.6 seconds, $P < 0.0001$), better lens wetting (3.4 vs. 2.4 [0–4 scale], $P < 0.0001$), and lower levels of film deposits on lenses (0.45 vs. 0.92 [0–4 scale], $P < 0.0001$), and most slit-lamp signs. The wearers with no signs of dry eye were significantly more likely to be male (36% vs. 19%, $P = 0.013$), were less likely to have deteriorating comfort during the day (81% vs. 97%, $P = 0.001$), reported longer average hours of comfortable wear (11 ± 3 vs. 9 ± 4 hours, $P = 0.014$), had older contact lenses (18 ± 14 vs. 13 ± 12 days, $P = 0.029$), and had greater intensity of photophobia early and late in the day ($P = 0.043$ and 0.021).¹³⁵ Glasson et al.¹⁰⁷ demonstrated that the type of drying of the tear film (spot versus streak during the interblink period), the number of ocular symptoms in absence of lens wear, and the tear meniscus area best differentiated tolerant from intolerant lens wearers.

The combined results of these studies suggest that the clinical outcome variables of tear stability, tear meniscus height/area, LWE, and LIPCOF are most likely to be predictive of CLD, although predictive factors have yet to be evaluated prior to wear to be able to identify wearers likely to get CLD. However, LWE and LIPCOF may only allow classification of participants in trials into symptomatic and asymptomatic groups and may not be able to predict other aspects such as the increase in symptoms over the course of 1 day of contact lens wear. It would be beneficial if additional testing were completed to determine whether these are good outcome measures of CLD. An ideal outcome measure is one that is a good predictor of the level of CLD and one that is also modifiable in order to confirm the relationship with CLD and to evaluate treatments. Provocative testing may be a strategy to better understand the impact of contact lens wear on clinical measures and to control for confounding factors.

As mentioned previously, many of the clinical trials investigating CLD have focused on the symptoms, but little attention has been given to the visual aspect of CLD. Yang et al.¹¹ investigated the effect of lens care systems on blink rate, ocular discomfort, and visual performance, but did not determine whether there was a relationship between these variables.

Conclusions Regarding Outcome Measures

A goal of future studies should be to establish needed standardization and agreement for the outcome measures related to CLD. An ideal outcome measure would be objective, internally and externally valid, and measurable with minimal bias. To better understand the predictors of CLD, it is recommended that more fundamental, basic clinical trials be conducted in order to at least understand which outcome variables are related to CLD and what level of change is clinically meaningful. Once our understanding of these basic questions is improved, more advanced study designs can be employed to comprehensively evaluate in-eye performance of existing and emerging technologies. A few key considerations for future outcome measures related to CLD are understanding of onset and recovery; cause or effect relationship with symptoms; knowledge of clinically meaningful changes; identification of confounding factors; consideration of timing, so that outcome measures and symptoms are assessed at

similar time points; validation of testing methodology; standardization of grading scales, as well as observation techniques.

Considerations for Clinical Trial Design

Design and performance of clinical trials should follow the guidelines of good clinical practice, which are extensively reviewed in the 2007 Report of the International Dry Eye Workshop and are not repeated herein.¹³⁶ A simple checklist for conduct and reporting of a clinical trial is the CONSORT recommendation (in the public domain at www.consort-statement.org).¹³⁷ Understanding CLD requires careful thought and consideration when it comes to the design of a study. Many factors can have adverse impact upon the variables being measured and thus the results.

The possible interrelationship between lens comfort and many other variables such as lens wearing time, lens care system used, lens material, lens design, form of vision correction (i.e., single vision, toric, or multifocal), current ocular disease, general health of the study participant, or use of medication requires that all these features be carefully controlled and considered. Many other factors about the study participant or the observer may inadvertently introduce bias and again must be considered with regard to the study design.

Trial Design. Consideration must be given to the correct clinical trial design. Prospective design with appropriate randomization of subjects is key. Clinical trials may employ single-eye, fellow (contralateral)-eye,¹³⁸ or crossover designs,^{15,139} but there are advantages and limitations to each trial design depending upon the question being asked and the length and level of supervision of the trial. In any case, avoiding bias is an important consideration when designing a clinical trial, and studies comparing lens comfort performance by collecting data from right and left eyes should consider having participants wear the test lens and control in both eyes. When these methods are used, it is important to consider whether discomfort in one eye can influence assessment made in the other or whether the study participant has a preference toward one eye. When this preference is demonstrated to be strong, the lens wearer should be considered ineligible for the study. To avoid such bias, test and control lenses may have to be crossed over and worn bilaterally, and then comfort assessment would be the mean for each eye.

Appropriate Data Collection. Frequently lens comfort studies collect data that is subjective or opinion based. The tool used to collect these data must be carefully evaluated and crafted, whether the study is using a VAS, a numerical rating scale, a Likert scale, or a questionnaire. Visual analogue scale data may lack sensitivity, as most data points may be skewed toward one end of the scale or artificially enhance sensitivity by scale expansion.¹⁴⁰ The impact of ceiling and floor effects must also be evaluated. Some validated questionnaires thought to be useful in assessing lens comfort may also lack sensitivity due to the different populations that may have been used as part of their validation.¹⁴¹ A specific questionnaire oriented toward lens comfort would be needed. Another consideration is that reported lens comfort changes both over the day of wear and over the life of the lens,^{34,35} making the collection of these data time sensitive. Different methods have been trialed to ensure that data of this type are recorded by the study participant in a timely way. Stone et al.¹⁴² used paper diaries that electronically recorded when data entries were made and found that 90% of the study participants hoarded time-sensitive data to one entry time point, encouraging the conclusion that paper-based diaries were not ideal. The incorporation of electronic devices to collect data directly has also been tried

in various clinical trials with variable levels of compliance pertaining to recording time-sensitive data.^{143,144} Relating to the field of contact lenses, Morgan et al.¹⁴⁵ reported high levels of compliance, with 93% of study participants responding within 30 minutes when requested via SMS messaging; Plowright et al.¹⁴⁶ reported between 76% and 82% responding, but the time delay for the response to their SMS messages was not reported. Woods et al.¹⁴⁷ developed an online Web-based system allowing entry via smartphones and reported a response rate of 97.5%, with 84.1% responding within the allotted time window for time-specific data. The use of smartphones with a data collection method for time-sensitive data would appear to be an obvious recommendation, particularly as their use is now considered to be ubiquitous.¹⁴⁸

Clearly Written Protocols. The process for conducting the study must be clear, and the protocol must describe each step of the study design as well as methods of data collection. It has been reported that CLD is time dependent, in relation to both length of lens wear and diurnal variation, and those features should be considered when one is measuring or differentiating lens comfort.³⁴

Inclusion of Appropriate Controls. Consideration must be given to ensuring that the correct control is used, in addition to the inclusion of an arm in which no change in products is made. Confounding influences must be considered. For a study that is investigating the impact of lens material on comfort, the lens care system being used must be carefully controlled. Studies have reported that different lens materials in combination with lens care systems can influence lens comfort.^{11,139}

Adequate Length of Trial. The length of time a contact lens has been worn (both during 1 day and over the recommended life of the lens in days) has been shown to affect lens comfort.^{34,35} Therefore, comparisons to be made between studies to record end-of-day comfort must be associated with how long the lens has been worn in elapsed hours. The age of the lens also influences discomfort and should be recorded.³⁴

Run-In and Washout Periods. In order to compare the performance of a contact lens, all study participants should be exposed to the same conditions before the study starts as well as during periods between various phases of the study. During a run-in period at the start of a study, the participant's method of vision correction should be consistent, that is, a period of spectacle wear or all participants wearing the same lens type with a consistent lens care system. The same provision is advised for periods between study phases.

Adequate Sample Size. Sample size calculations should be considered before the study begins, except in the case of pilot studies that are intended to generate data from which sample size can be calculated. For determination of sample size it is important to consider the variability of the primary variable being measured and a clinically meaningful difference in the variable.

Prevention of Disclosure of Masking. Frequently, lenses used in studies have engravings or markings on them rendering difficult, if not impossible, any attempt to mask the study participant with regard to the lens being used.¹⁴⁹ Having a research assistant insert and remove the lenses may avoid the study participant's identifying the lens but may not be practical for all study designs. The researcher observing and recording physiological changes should do so with the lens removed by another researcher to maintain the masking. The researcher who assesses lens fit should not collect other data in the study.

Evaluation of Effectiveness of a Treatment/Modification. This type of evaluation is used to assess whether a specific treatment or modification aimed at improving CLD has had an effect. In addition to a better score on the subjective

rating scale used, increased wearing time, increased comfortable wearing time, reduction in the frequency or intensity of symptoms, preference ratings, and quality of life information may all be potential ways of assessing the effectiveness of such a treatment.

Questionnaire Length. When designing a questionnaire, it is important to consider participant fatigue. If the questionnaire is too long, this may encourage bias—habit bias or self-limiting bias (see below). Use of validated questionnaires is advisable.

Collection of Data. When designing a clinical study it is important to consider what the key variables are and not to try to collect every variable possible. This can make the study visits burdensome and induce fatigue, increasing variability. Some variables may affect others, that is, have an order effect. Use of fluorescein to assess corneal staining will affect a subsequent assessment of NITBUT. Repeated NITBUT assessments may affect a subsequent measure of vision.

Appropriate Statistical Analysis. Parametric statistical tests should not be used on data that are not normally distributed or continuous in nature. Careful consideration should be given to the appropriate statistical tests, and this should be described in the study protocol.

Generalizations Outside of Study Results. Reports or discussion in papers should expand only on the results from the study. It is important to remember that the study results relate only to the population tested and that the study population is not likely to be representative of all populations; avoid cohort bias.

Discussion of Potential Bias. Collecting subjective data can lead to various types of bias. Bias can be very difficult to control, so potential types of bias should be evaluated¹⁴⁹ (see later sections on bias).

Evidence- versus opinion-based conclusions: Careful consideration needs to be given to the pyramid of evidence. Randomized clinical trials (RCTs) provide significantly stronger evidence than anecdotal opinions from experts or the authors. Care should be taken to ensure that reporting focuses on factual evidence.

Excessive Reuse of Study Subjects. Subjects who are regularly used by a research center as study participants can effectively become trained observers. If not taken into account, this could lead to bias and skew the study results. When conducting research it is important to monitor the frequency with which study participants are enrolled. Creating a pool of trained participants can be advantageous for a particular investigation. Consideration should be given to reporting the frequency with which study participants have been used in similar study designs.

Ethics/Institutional Review Boards/ClinicalTrials.gov Registration. The data collected from a study are of greater value when the study has been conducted as a RTC. The guidelines of good clinical practice (in the public domain at <http://ichgcp.net>) should be employed. Prior ethical review and approval are mandatory, and registration of the clinical trial is desirable and is becoming mandatory.

Disclosure of Conflicts of Interest. Researchers and authors need to pay careful attention to potential conflicts of interest, and these must be declared.

Study designs that can be used to report on CLD at different phases of development are outlined in Table 4.

AVOIDING BIAS AND ENSURING QUALITY IN CLINICAL TRIAL DESIGN AND PERFORMANCE

There are many sources of potential bias in conducting a clinical trial. If not recognized, the bias can invalidate

TABLE 4. Candidate Designs for Clinical Trials

Design Criteria	Study Phase			
	Lens Design Phase 1	Biocompatibility Phase 2	Dispensing Phase 3	Postmarket Phase 4
Main purpose	Emphasize short-term on-eye performance and comfort, for example, assessment of effects of lens edge, case curve, thickness, optic zone	Emphasize the effect of material/tear film interactions on comfort and vision (variability). Examine the effects of changes to materials, surfaces, packaging solutions.	Measure "normal use" performance over lens life. Emphasize material/tear film interactions on comfort and vision (variability). Measure adverse events during lens wear. Assess effects of changes to material, lens care, lens/surface aging.	Measure use after lenses released for sale. Examine the wearer's experience. Assessment of adverse events during lens wear.
Features	Short-term (minutes to hours) Direct supervision Many sequential comparisons acceptable Account for order effect Contralateral design may be acceptable, but not if this stimulates excess tearing in one eye Questionnaire design—enhance differences Double masking Ensure adequate control/tests for potential false-positive results. That is, if changing from lens A to B and assessing comfort, also include masked change from lens A to lens A.	Short- to midterm (4–12 h) Direct supervision Not often sequential Could assess effects of packaging solution vs. being cycled in lens care Contralateral design may be acceptable but not if it stimulates excess tearing Questionnaire design -Diurnal changes -Recall period Double masking Pre- and postexposure testing of ocular surface staining	Mid- to long-term (days to months) In-home use/dispensing Lens care assigned if using reusable contact lenses Crossover preferred to contralateral design Need to define washout period Questionnaire design -Diurnal changes -Recall period Observer masking more critical; wearer masking if possible Pre- and postexposure testing of ocular surface staining	Cross section Prospective cohort Registry
Essentials	Double masking Ensure adequate control/tests for potential false-positive results. That is, if changing from lens A to B and assessing comfort, also include masked change from lens A to lens A.	Double masking Pre- and postexposure testing of ocular surface staining	Observer masking more critical; wearer masking if possible Pre- and postexposure testing of ocular surface staining	Breadth Variety of clinical settings
Population	Can be asymptomatic wearers to determine whether change is detectable Could select difficult-to-fit subpopulation Understand habitual symptom state	Possible participant groups include poor "wetters," symptoms vs. no symptoms Must be able to attend visits after lens fitting On premises best for new materials in case of need for emergency lens removal Determine clinically meaningful and statistically significant differences Clinic	Possible participant groups include poor "wetters," symptoms or no symptoms Account for adverse events between scheduled visits	Fewer exclusion/inclusion criteria
Outcomes	Decide on meaningful differences with scales Clinic	Determine clinically meaningful and statistically significant differences Clinic	Determine clinically meaningful and statistically significant differences Home use	Determine clinically meaningful and statistically significant differences Home use Remote access
Setting	Clinic	Clinic	Home use	Home use Remote access

conclusions and, even if recognized before data analysis, may not be amenable to compensation in the final analysis. Therefore it is worthwhile to identify and avoid such bias. Bias can be introduced at several junctures in a clinical trial. Bias can be grouped into several categories.¹⁵⁰ These include selection bias, performance bias, detection bias, attrition bias, reporting bias, psychometric bias, and statistical bias.

Selection Bias

This generally concerns a lack of comparability of baseline characteristics between intervention groups. This can be due to lack of random sequence generation to produce comparable groups or due to inadequate allocation concealment—concealment that is insufficient to mask study investigators to forthcoming treatment assignments and could thus result in nonrandom allocation of subjects. One of the most frequent sources of selection bias occurs with entry criteria that fail to segregate a study population into appropriate trial groups. As one example, if a diagnostic test is being validated against other tests and the first diagnostic test is included in the selection process for identifying subjects to be tested, there is a high probability that such a test will perform better than other tests due to the criterion of selection. This bias is occasionally encountered in evaluation of dry eye disease in which multiple contributory factors are responsible for the expression and severity of disease but are not appropriately compared. One way to attempt to avoid such bias is to use a composite (and possibly weighted) index to establish presence of disease.

Another form of selection bias is *spectrum bias*, in which study subjects may be selected from only a portion of the entire spectrum of disease severity. This bias would weigh heavily against an evaluative test that had accuracy over the entire spectrum of disease but not with as great a differential performance as a second test that identified a more limited subset of disease. This bias can be avoided by ensuring that the entire spectrum of a disorder is included in the test population if results are to be generalized to a larger population. It is also necessary to include a large enough population that the entire spectrum of disease is captured.

External validity can be questioned when the study population is not representative of the whole, which is more likely to occur with small sample sizes. One should not assume that the answers to a given survey match those for the whole population if the sample is small. Too many studies have small sample size as noted in the prior summary of published clinical trials.

Performance Bias

This can occur due to inadequate masking of subjects or investigators. Knowledge of the allocated interventions on the part of participants and personnel during the trial may lead to differential provision of care to participants in one group as compared to the other. Inadequacy of masking does not need to be prior to allocation in order to bias results. If subjects or investigators are able to determine which treatment they are on at any point in the trial, this can cause bias (e.g., the patients' reporting of symptoms, as well as the investigators' interpretation of test findings, which in this case is also somewhat subjective—that is, the investigator “grades” some parameter).

Detection Bias

This is due to inadequate masking of outcome assessment for the participants and investigators and subsequent systematic differences in the assessment of study outcomes between randomized intervention groups.

Attrition Bias

This is due to systematic differences between groups in outcome data either in the amount, nature, or handling of incomplete data or to violations of study protocol.

Reporting Bias

This can occur when reporting of outcomes is selective. A type of reporting bias occurs when there are systematic differences between reported and unreported findings (e.g., pulling out and preferentially reporting only statistically significant findings and not reporting those that were analyzed but found not to be statistically significant). This can be referred to as outcome bias or selective reporting bias.

Psychometric Bias

This bias depends upon the responsiveness of the subject and thus is less easily detected and recognized but may be a particularly obstructive effect in the analysis of subjective tests. *Habit bias* occurs when responders stop thinking and answer “Yes,” as all previous answers have been “Yes.” This may be due to fatigue or may occur when the survey is too long or too complex. Habit bias can result in misclassification that will either reduce study power if nondifferential among randomized groups, or may bias study findings if differential among randomized groups.

The Hawthorne effect occurs when respondents respond differently simply because they are being asked the question. This effect tends toward a positive bias: Subjects give the answer they think the investigator wants. This is similar to the bias that occurs simply due to testing a different lens on the eye. For example, subjects might rate a new lens type/design given to them as more comfortable than their previous lens simply because it is new. To minimize this bias, subjects should be randomized to receive a new lens type/design, masked if possible, and also a new lens that is simply a fresh lens of their previous type/design. In other words, in interventional clinical trials, placebo and nocebo effects must be considered. A placebo has been defined as “a substance or procedure . . . that is objectively without specific activity for the condition being treated,” and a “placebo effect” often occurs when the subject has a strong desire for the intervention in question to be successful.¹⁵¹ The opposite effect is seen when a subject who disbelieves in a treatment experiences a worsening of symptoms. This is called a nocebo effect.¹⁵²

Self-Limiting Bias

Self-limiting bias occurs when respondents try to make themselves appear in a positive light: Subjects give the answer they think makes them right. *Recall bias*, in which the participant may get things wrong, has several potential causes, such that the question being asked to collect factual data should not be too complex or rely on extensive memory recall.¹⁵³ The method of asking contact lens wearers what they are wearing (by asking them from memory, or showing a photograph of lens packaging or showing the actual packaging), particularly with respect to the name (brand) of lens and lens care system or manufacturer of products, can result in recall bias.

Statistical Bias

This occurs in several forms. For a clinical trial, internal validity, the extent to which systematic error is minimized, requires control of selection bias (biased allocation to comparison

groups), performance bias (unequal provision of care apart from treatment under evaluation), detection bias (biased assessment of outcome), and attrition bias (biased occurrence and handling of deviations from protocol and loss to follow-up). External validity (the extent to which results of trials provide a correct basis for generalization to other circumstances) requires control of patients' age, sex, severity of disease and risk factors, comorbidity, or the treatment regimen's dosage, timing and route of administration, type of treatment within a class of treatments (concomitant treatments), settings (level of care [primary to tertiary] and experience and specialization of care provider), and modalities of outcomes (type or definition of outcomes and duration of follow-up).¹⁵⁴

A particularly problematic data analysis effect is Simpson's paradox (Yule-Simpson effect).^{155,156} This occurs when a trend that appears in different subgroups of data is not seen when these groups are combined and indeed the reverse trend is demonstrated for the aggregate data. An example of this effect is the sex bias case at a major university alleging bias against women who had applied for admission to graduate schools there. The admission figures showed that men applying were more likely than women to be admitted, and the difference was so large that it was unlikely to be due to chance.^{157,158} In the total cohort there were 8442 male applicants, 44% of whom were admitted to jobs, and 4321 female applicants, 35% of whom were admitted to jobs. But when examining the individual departments, it appeared that no department was significantly biased against women. In fact, most departments had a small but statistically significant bias in favor of women.¹⁵⁸ The research paper by Bickel et al.¹⁵⁷ concluded that women tended to apply to competitive departments with low rates of admission even among qualified applicants (such as the English department), whereas men tended to apply to less competitive departments with high rates of admission among the qualified applicants (such as engineering and chemistry). Alternative impersonal terms for Simpson's paradox are reversal paradox and amalgamation paradox.

An additional feature of data analysis that can occur if a limited number of measurements of outcome values are obtained is regression to the mean. This is the phenomenon in which a variable is extreme on its first measurement but will tend to be closer to the average of its range on subsequent measurements.¹⁵⁸

There are other possible sources of bias, many of which pertain only to particular study designs (e.g., carryover in crossover trials and recruitment bias in cluster randomized trials). At other times, less common types of bias may arise under specific circumstances in a trial (e.g., contamination of intervention groups, whereby the experimental and control interventions get mixed, for example, if participants switch their lens care systems or contact lenses).

Recognizing that there are many potential bias effects in design and conduct of clinical trials is important to help avoid them or correct for them in data analysis.

RECOMMENDATIONS

General recommendations for design of clinical trials that categorizes study by lens design and duration of trials have been summarized in Table 4. The best design is a prospective, randomized, double-masked clinical trial. The question whether these designs should incorporate parallel-group, contralateral-eye, or crossover design as the most appropriate depends upon the specific question being investigated in the trial. Contralateral and crossover trials help to control for variations in subject psychological pain tolerance, but suffer the disadvantage of having the potential of development of

tolerance to any given stimulus in the same subject during the duration of the study. It is also possible that a sensation of pain or discomfort in one eye may have an impact on the reporting of pain or discomfort in the fellow eye.

Regardless of the design, appropriate entry criteria and adequate sample size are critical. Also, appropriate masking of both subject and investigator is critical. In contact lens-related trials, masking can be complicated by the type of lens being evaluated, the cleaning and lubrication solutions employed, and the wearing schedule. Inherent lens characteristics (e.g., markings, tint, and shape) may prohibit true masking of investigators in some instances. Finally, based upon our review of the literature, no specific clinical outcome instrument can be recommended, but the CLDEQ-8 most approaches the best validated device. It is clear that there needs to be more work on developing specific and efficient questionnaires for contact lenses—that they should be specific, that is, for soft, gas-permeable, or scleral lenses—rather than assuming that one questionnaire will work for all. The use of technology that allows easy data entry and time tracking (e.g., smartphone, call-in, online ratings, or other time capture methods) is recommended.

Modern experimental design is generally in two forms—one with fixed characteristics (primarily duration/sample size) and the other with adaptive characteristics (in which critical aspects [e.g., sample size and duration] are defined, a priori, as being modifiable). Under the current circumstances, the most appropriate design would be the former.

What variables will be important to manipulate in order to demonstrate lens-related discomfort effects, inclusion of control/placebo groups, determination of the duration of the experiments and how frequently the intervals will be sampled, what hypotheses are being tested, and what statistical tests to perform are important considerations. Until these at least are tied down, there is no rational way to design experiments. It is also possible that many nontrial experiments need to be done. The lack of an evidence base for many outcomes and predictors might necessitate that pilot validation experiments be conducted before any trial is designed. Finally, the epidemiology of the outcome itself is poorly understood, so it is possible that basic prevalence data are required, as well as population-based long-term incidence studies, before any interventional experiments are designed.

SUMMARY CONCLUSIONS

Prior clinical trials measuring CLD have been focused primarily on lens performance rather than specific characteristics or etiology of the discomfort experienced by the subject. Lessons learned from these published clinical trials nonetheless provide some guidance with respect to future clinical trial designs and performance to investigate CLD. Patient discomfort ranges from awareness of the lens, through sensation of dry eye, to actual pain. Impairment of visual function includes impairment of clarity, instability of vision, or fatigue in performing visual tasks.

Accurate assessment of the symptoms of CLD requires that clinical trial design include an appropriate and representative population of adequate size evaluated by questionnaires that specifically assess a particular clinical question symptom with well-controlled contact lens material, lens design, lens care products, and wearing schedule. Avoidance of bias is necessary in performance of the trial, including care in subject selection, implementation of random intervention group assignments, psychometric testing, and statistical analysis of the data.

At this time no specific clinical outcome instrument can be recommended on the basis of an evidence-based review of the

literature, but the CLDEQ-8 best approaches the most validated device.

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The TFOS International Workshop on Contact Lens Discomfort: Report of the Management and Therapy Subcommittee

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See the tables in the Introduction for the members of the TFOS International Workshop on Contact Lens Discomfort.

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The aim of the subcommittee was to review published evidence and current practice in the management and treatment of contact lens-related discomfort (CLD) in order to present an evidence-based schema for applying the available management and treatment options. To do this, a literature review was undertaken and the results placed in the context of the quality of evidence provided by each relevant study. Categorization of evidence quality was made according to objective criteria for clinical and basic research studies adapted from the American Academy of Ophthalmology Practice Guidelines. These were identical to those used in the previous Tear Film & Ocular Surface Society (TFOS) reports^{1,2} and are shown in Table 1.

The approach presented in this report sets out a clinical framework for use when faced with an individual complaining of CLD. Beginning with history taking, the clinician then moves to identify any confounding conditions, such as coexisting disease, before turning to the examination of the contact lens itself. This conceptual framework is summarized in the Figure. The purpose of all these activities is to arrive at the point where everything has been done to optimize the contact lens environment within the needs and individual

characteristics of the wearer. Only once this has been achieved can the true extent of the underlying CLD be appreciated and the identified remedial actions begun.

SETTING THE STAGE: PRESENT CLINICAL APPROACHES

The only report to address how practitioners diagnose and manage contact lens dry eye is from an online market survey ($n = 457$) conducted in 2012.³ The methods preferred for assessing contact lens dry eye were symptoms assessment (25%), corneal staining (19%), and tear breakup time (11%). In terms of diagnosing contact lens dry eye, practitioners classified most contact lens dry eye patients with evaporative (57%) rather than aqueous-deficient dry eye (43%), using the Dry Eye WorkShop (DEWS) classification schema. Further, most practitioners felt that most cases of contact lens dry eye were mild (65%) in severity, followed by moderate (27%) and severe (8%).

With regard to treating patients with contact lens-related dry eye, nearly half (47%) would refit their patients into a different contact lens as the first mode of treatment. This was followed by refitting into a lens with a more frequent

TABLE 1. Grading Level of Evidence of Clinical and Basic Research Studies

Clinical studies	
Level I	Evidence obtained from at least 1 properly conducted, well-designed randomized controlled trial or evidence from studies applying rigorous statistical approaches
Level II	Evidence obtained from 1 of the following: Well-designed controlled trial without randomization Well-designed cohort or case-control analytic study from 1 (preferably more) center(s) Well-designed study accessible to more rigorous statistical analysis
Level III	Evidence obtained from 1 of the following: Descriptive studies Case reports Reports of expert committees Expert opinion Meeting abstracts, unpublished proceedings
Basic science	
Level I	Well-performed studies confirming a hypothesis with adequate controls published in a peer-reviewed journal
Level II	Preliminary or limited published study
Level III	Meeting abstracts or unpublished presentations

replacement schedule (24%), refitting into a different lens material with the same replacement schedule (23%), recommending topical lubricants (22%), and changing the care solution (15%).

This information provides an understanding of the current mode and practice patterns used in managing and treating the contact lens wearer with discomfort. These and other options are considered further in this evidence-based review and in making appropriate recommendations for management and treatment of CLD.

ESTABLISHING THE CURRENT STATUS OF THE LENS AND ITS RELATIONSHIP WITH THE EYE AND ADNEXA

A full and careful history of the presenting problem and the general status of the patient is a critical first step in the management process for CLD. Detailed information is essential to establish a background against which the reported complaints can be assessed and potential contributory factors identified. Elaboration of the significance of many of these issues is the province of other WorkShop reports, however, important elements to note follow.

Age and Sex

These factors give a context to the complaint, although unlike dry eye, which is more prevalent in females and with increasing age,^{4,5} the data for CLD are mixed.⁶ Although sex has not been found to be a related factor as measured through the use of survey questionnaires,⁷ younger individuals do seem more prone to reporting symptoms than older wearers.⁸⁻¹⁰

Timing and Symptom Onset

Although there is relatively little information on the onset of discomfort with contact lenses, it is apparent that the situation worsens during the day, irrespective of lens type.¹¹ This classic late-day presentation is likely to have a different etiology from the kind of discomfort that becomes evident immediately on insertion, and treatment strategies will also vary as a result.

Type of Lens

It is useful to obtain full details of the lens type (e.g., spherical, toric, multifocal) and material, as these factors will affect the choice and likely benefit of the treatment strategy.

Care System and Lens Replacement Schedule

The components of the care system and the frequency of lens changes need to be established, as these all bear on aspects, such as lens cleanliness and wettability.

Use of Additional Wetting Agents

Establishing whether the wearer's routine incorporates wetting or lubricating drops either as a preconditioner before insertion or during wear is worthwhile.

Wearing Time/Pattern

Many wearers experience a reduction in their comfortable wearing time as a result of CLD^{7,12,13}; as a corollary, improved wearing time may be a useful indicator of treatment efficacy.

Compliance and Adherence to Instructions

Incorrect use of the lenses, their associated care products, and cases can precipitate a host of problems, including discomfort.¹⁴ Patients may be noncompliant because they do not understand the rationale for the care procedures or the potential consequences of misuse. Regardless of modality, compliant patients have better comfort at the end of the day and are more consistent with planned lens replacement,¹⁵ although those who actually dropout of contact lens wear do not appear to have worse compliance than those who remain.¹⁶ Compliance with lens case cleaning procedures influences the osmolarity of the solution in the case-well, which may impact insertion comfort.¹⁷ Discussing the various procedures and why they increase the probability of sustained comfortable and safe lens wear appears to have the potential to strengthen or change patient attitudes toward being more compliant.¹⁸

Occupational Environment

It is important to understand the nature of the surroundings, both habitual and exceptional, in which the wearer is situated. Most will encounter challenging environments from time to time. The frequency and duration of these periods are important facts to consider when assessing the relevance and significance of reported symptoms.

Occupational considerations can influence the type of contact lenses worn and the choice of lens modality and material can influence the severity of discomfort¹⁹⁻²¹; being fully informed on these factors is critical to the choice of management approach.

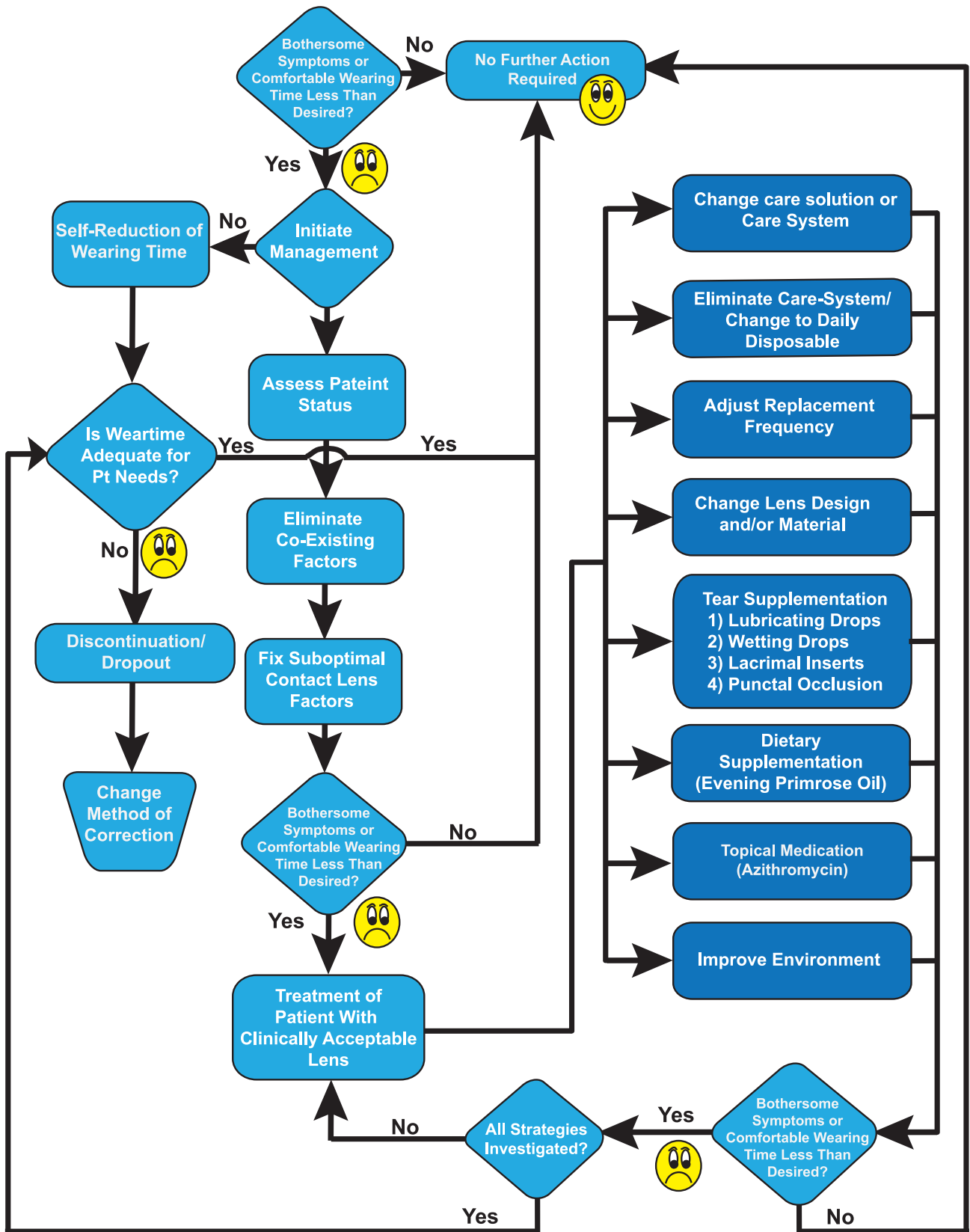


FIGURE. Summary of the management strategies for CLD.

Coexisting Disease

The possibility that the problem may be rooted elsewhere than in the contact lens itself needs to be eliminated; inquiry about relevant, known, current, or past disease should be made. For example, allergic rhino-conjunctivitis may contribute to contact lens intolerance.²² A history of prior treatment for dry eye or allergy is worth eliciting, as well as whether there was impact on contact lens discomfort. As with many of the items discussed in this section, a complete and detailed history will help avoid revisiting previously unsuccessful approaches to management.

Current Medications

Although many contact lens wearers may be perceived as “young and healthy,” such individuals, as well as other demographic groups, can be taking a range of agents, whether over-the-counter (OTC) or prescribed, that affect the ocular surface. It is not uncommon for healthy individuals to be using antihistamines, psychiatric drugs with anticholinergic effects, sex hormones, caffeine, or multivitamins, any of which might contribute to dry eye and discomfort during contact lens wear.^{4,23–26}

IDENTIFYING AND TREATING NONCONTACT LENS—RELATED, COEXISTING, SYSTEMIC, AND OCULAR DISEASES

In crafting a therapeutic plan to treat CLD, it is important to recognize the nonspecificity of the symptom “discomfort.” Because discomfort can result from many sources other than the contact lens, identification of any coexisting pathology that may be responsible for the patient’s symptoms is important. A complete review of all the conditions that can present with patient complaints of discomfort and signs of ocular surface disease is not the purpose of this report and the reader is referred to the relevant textbooks on this subject.^{27,28} What follows is a brief categorical review of noncontact lens-associated diagnoses that should be considered by clinicians in the differential diagnosis of CLD as well as in approaching its treatment.

Medicamentosa

Ocular medicamentosa can be defined as chemical irritation of the ocular surface by a topically applied drug, preservative, or cosmetic.²⁹ Accompanying symptoms may be delayed for weeks or months, either as a consequence of a delayed hypersensitivity (cell-mediated) reaction on the ocular surface or some other unspecified mechanism. The condition presents with diffuse punctate staining of the cornea and/or conjunctiva that is evident with vital dyes, such as sodium fluorescein, rose Bengal, or lissamine green. Chronic epithelial defects (due to toxic inhibition of epithelial healing) are sometimes present with corneal edema, pseudo-dendritic healing ridges, and/or grey stromal haze that can be confused with an infectious infiltrate.³⁰ As discomfort of varying intensity invariably accompanies these events, differential diagnosis relative to CLD is crucial.

It is well known to clinicians that the tear film can be affected in an adverse manner by the use of both topical and systemic medications, and that relief can be obtained simply by ceasing to use the offending agent. It is therefore imperative that the eye care provider evaluating complaints of CLD take a thorough history to identify the use of suspicious, prescribed, or OTC medications.

Systemic antihistamines are the most common oral medication associated with reduced tear film function and ocular discomfort,^{23,25,26,31–34} and these medications are now available OTC in many countries. Patients often do not report their use of such medicines to their caregivers. Other orally administered medicines that can induce tear film abnormalities that mimic CLD include isotretinoin, antipsychotics, and docetaxel.^{35–43}

Much has been published on the ocular surface toxicity of preservatives in topical medications^{44–62} and will not be repeated here. Clinicians should be particularly aware of the impact of timolol, prostaglandin analogues, brimonidine, atropine, acyclovir, neomycin, and nonsteroidal anti-inflammatory agents on the ocular surface.^{49,58,61,63,64}

Systemic Diseases

Autoimmune diseases and systemic atopy can produce abnormalities of the tear film and, consequently, symptoms and signs that mimic CLD. Although Sjögren’s syndrome is perhaps most commonly associated with ocular surface disease, other candidates include rheumatoid arthritis, systemic lupus erythematosus, inflammatory bowel disease, Whipple disease, and thyroiditis.^{65–69} Treatment of these systemic conditions may be necessary to gain control of the ocular surface disease and reviews of treatment strategies are published elsewhere.^{65,70,71} Of course, some patients with these systemic conditions will, at the same time, suffer from CLD and treatment of the two problems must occur simultaneously.

Immunological conditions that cause conjunctival scarring, such as ocular cicatricial pemphigoid, Stevens-Johnson syndrome, graft-versus-host disease, and lichen planus, can also produce symptoms and signs indistinguishable from CLD.^{70–76} In patients with diabetes mellitus, abnormalities of the basement membrane and possibly diminished tear secretion, predispose to superficial punctate keratitis, which may then produce symptoms that are confused with CLD. Although rarely observed in the developed world, systemic vitamin A deficiency in the absence of malabsorption must be considered in the evaluation of xerophthalmia. A thorough history and general physical examination are necessary to identify these important conditions.

Eyelid Disease

Anatomical and physiological abnormalities of the eyelids can produce symptoms similar to those of CLD, and it is often impossible to achieve relief without first treating the eyelid problem. Conditions including entropion, ectropion, lagophthalmos, and trichiasis can each produce conjunctival inflammation, keratitis, and symptoms resembling CLD.^{77,78} Treatment may be palliative, including aggressive lubrication with eye drops or ointments, the use of adhesive tape to “normalize” eyelid malposition, or involve surgical correction of the anatomic abnormality. Details of these treatments are beyond the scope of this article, but are available elsewhere.²⁷

Inflammatory disease of the eyelid, including anterior and posterior blepharitis can also produce a comparable clinical picture. The complex subject of posterior blepharitis or meibomian gland dysfunction has been the subject of an earlier TFOS report,^{79–86} which should be consulted for reviews of current diagnostic and therapeutic approaches.

Tear Film Abnormalities

The overlap between the conditions labeled dry eye, dysfunctional tear syndrome, meibomian gland dysfunction and ocular

surface disease is so great as to prevent discussion of each individually. Earlier TFOS reports, including the DEWS report⁸⁷ and the International Workshop on Meibomian Gland Dysfunction,⁷⁹⁻⁸⁶ have attempted to review state-of-the-art knowledge about these conditions and should be read by all clinicians. With respect to recognition of the presence of either aqueous-deficient or evaporative tear dysfunction, it should be stressed that clinicians must strive to treat these conditions to the best of their ability before attributing residual patient symptoms to a contact lens-associated etiology.

Conjunctival Disease

Anatomic abnormalities of the conjunctiva, such as conjunctivochalasis, pinguecula, or hyperkeratinization (vitamin A deficiency or Bitot's spot), can cause symptoms of ocular discomfort and these may be exacerbated with attempted contact lens wear.^{88,89} It may be necessary to correct these anatomic problems, whether with topical medication or surgically, before it becomes clear whether the contact lens has a specific role in causing symptoms. Likewise, immunologic diseases, such as the atopic family (seasonal and perennial allergic conjunctivitis, atopic and vernal keratoconjunctivitis), and conditions of uncertain etiology, such as superior limbic keratoconjunctivitis, should be considered as potential causes of ocular discomfort in the setting of contact lens wear.⁹⁰

Control of allergic hyper-reactivity with mast cell stabilizers, topical antihistamines, and/or corticosteroids is often necessary to permit atopic patients to successfully wear contact lenses. Moreover, antiglaucoma drops such as topical dorzolamide and brimonidine can cause allergic reactions that may resemble CLD. Ruling out these possibilities is imperative, as intolerance of contact lens wear may result from insufficient control of the allergic process.

Clinicians should evaluate the eyelids for injection and follicular response to establish the contribution of allergic mechanisms, as measurement of tear film IgE is not discriminatory.⁹¹ The diagnosis of superior limbic keratoconjunctivitis is generally not difficult once the clinician is aware of the unique localization of conjunctival inflammation to the superior bulbar conjunctiva. Excellent reviews of the treatment of superior limbic keratoconjunctivitis have been published elsewhere.⁹⁰

Corneal Disease

Diseases that are primarily corneal, as distinguished from those in which keratitis and/or anatomic changes occur secondary to another disease process (e.g., scleritis, dysfunctional tear syndrome, meibomian gland dysfunction (MGD), or peripheral ulcerative keratitis) can cause symptoms resembling CLD. Careful biomicroscopic examination will often reveal abnormalities in the anterior basement membrane that are indicative of recurrent corneal erosion syndrome due either to a dystrophy or following traumatic corneal injury. Because the use of a bandage contact lens is recognized as an effective treatment for corneal erosion syndrome, ordinary contact lens wear may confuse the presentations of CLD and recurrent corneal erosion. The management of corneal erosion syndrome has been reviewed elsewhere, including the use of hypertonic saline ointment and/or eye drops, contact lenses, superficial keratectomy, corneal micropuncture, and phototherapeutic keratectomy.^{92,93} The safety of hypertonic saline eye drops in the presence of a contact lens has not been evaluated.

Salzmann's nodular degeneration is another anatomic corneal disease that can cause discomfort and contact lens intolerance. Published reviews of this condition emphasize the

value of surgical therapy to remove the nodular corneal elevations.⁹⁴

Although it may not seem valuable to undertake a detailed differential diagnosis of the patient with complaints of CLD, consideration of the diagnoses and pathophysiologic processes mentioned above should make it clear that many therapeutic interventions can relieve symptoms of discomfort without the need for changes to the contact lens, its material, design, care solutions, or wear schedules.

TREATING EVIDENT CONTACT LENS-RELATED PROBLEMS

In many instances, the existence of a contact lens-related anomaly would be apparent during the course of the routine examinations suggested above. Whether or not that is the case, a comprehensive assessment of contact lens status is indicated, and the next step is treating and managing problems that then become evident once obvious ocular and systemic issues have been dealt with. The aim is to ensure that the lens in the eye is in a clinically acceptable ocular environment without obvious deficits of either a physical or behavioral nature.

Typical deficiencies can encompass physical defects, such as edge chips and tears, or fitting problems. Anterior and/or posterior surface deposits can also affect contact lens comfort, with the former also contributing to a nonwetting surface⁹⁵; although this can also occur in the absence of visible anterior surface deposition.⁹⁶

Perhaps because defective lenses are such an obvious source of discomfort, little in the way of manuscript citations exist. Standard textbooks provide adequate coverage as part of their discussion on fitting and follow-up care, however.⁹⁷⁻¹⁰⁰ Defective lenses are usually the result of mishandling, aggressive cleaning, or storage case mishaps and are rarely observed on removal from a fresh blister pack. Although biomicroscopic examination of the lens, either in situ or ex vivo, presents the most likely opportunity for detection of defects, other methods, most notably magnifying loupes, phase-contrast microscopes, and shadow boxes can also be used.

The lens-to-cornea fitting relationship can influence the comfort of a contact lens. This can be evaluated using a biomicroscope to judge the lens movement in both primary position and upgaze. Additional information can be gained by applying the standard push-up technique. Fluorescein is essential to the assessment of rigid lens fitting.

Generally speaking, an excessively flat soft lens fit will cause immediate discomfort that worsens on blinking. Lens inversion due to incorrect insertion is a common cause of this problem and usually manifests as an apparently flat fit.⁹⁹ Reversing the contact lens typically provides relief.

Interactions between the lens and the ocular surface or eyelid^{101,102} and design features of the edge may create awareness and discomfort throughout the day. Stiffer lenses, or those with a higher modulus of elasticity (e.g., some silicone hydrogels) can exhibit edge clearance or standoff from the ocular surface. In extreme cases, this appears as fluting of the lens periphery and is most easily appreciated on a blink when discomfort is also more keenly felt.^{95,103-105} On the other hand, steep-fitting lenses may be initially comfortable, but become intolerable due to the build-up of cellular waste beneath the lens and compression onto the bulbar conjunctiva.¹⁰⁶⁻¹⁰⁸ The most apparent solution to either situation is to attempt to optimize the fit in the indicated direction: an apparent flat-fitting uncomfortable lens might be steepened and vice versa.

Surface deposits are another potential cause of CLD and where these are obvious during examination, steps should be

TABLE 2. Summary of Evidence Supporting Various Potential Management Strategies for CLD

Treatment Strategy	Supporting Evidence		
	Level I	Level II	Level III
Adjust replacement frequency		•	
Change material		Insufficient or contradictory evidence	
Add internal wetting agents		Insufficient or contradictory evidence	
Add external wetting agents		•	•
Eliminate the care system		•	
Alter lens design factors	•	◦	•
Change the care system		•	
Use tear supplements, wetting agents, lacrimal inserts		•	
Dietary supplementation (omega-6 FAs/evening primrose oil)	•		
Punctal occlusion		•	•
Topical medication (azithromycin)		•	
Improve environment			•
Alter blink behavior		Insufficient or contradictory evidence	
Switch soft to RGP lens		Insufficient or contradictory evidence	
Switch RGP to soft lens		•	
Orthokeratology		Insufficient or contradictory evidence	
Refractive surgery		Insufficient or contradictory evidence	
Spectacles			•◦

Closed circles (•) refer to soft lenses and open circles (◦) refer to rigid lens. Blank cells indicate no data available.

taken to reduce their accumulation. The predominant type of deposit found on the contact lens surface is dependent on the material. Hydrogels, especially ionic lens materials, attract more protein,⁹⁵ whereas some silicone hydrogels can attract greater levels of lipid.¹⁰⁹⁻¹¹⁴ Both the amount and type of protein deposit can be influenced by the surface charge of the material.¹¹⁵ The connection between deposits and CLD is closely linked to the perturbation of the prelens tear film and associated lack of wettability.^{111,113}

Specifically with regard to protein deposits, however, the literature is inconclusive on the impact of their removal on CLD. One report found no correlation between lens protein and patient comfort, another demonstrated a decrease in comfort with even inconspicuous levels of protein.^{116,117} A more recent study found poor correlation between total protein/lysozyme and any subjective factor ($r < 0.3$; $P > 0.05$), and only weak correlations between dryness and percent active lysozyme ($r = 0.3-0.5$ for all time points). However, stronger correlations were found between active lysozyme and subjective comfort ($r = 0.6-0.7$; $P < 0.001$).¹¹⁸

Frequent replacement of the contact lens and strict compliance with replacement recommendations serve as the first steps in eliminating a deposited lens.^{110,119} In addition, adequate cleaning after removal and subsequent storage in an approved contact lens care solution can prevent contact lens deposits.⁹⁵ Different care systems may have some effect, with polyquaternium (PQ)-containing products demonstrating decreased levels of deposition for Group IV lenses compared to polyhexamethylene biguanide (PHMB).¹²⁰⁻¹²⁴ PQ has also shown a greater level of lipid removal from senofilcon lenses compared with hydrogen peroxide systems.¹²⁵ Citrate in a care system has been found to have efficacy in reducing protein deposition, whereas surfactants and alcohol-based cleaners are useful against lipids.^{126,127} Finally, transfer of contaminants from the hands or other areas (e.g., make-up) to the contact lens may be evident, reinforcing the importance of hand washing before handling.¹²⁸

In terms of refractive correction, poor vision is reported to be a trigger for discontinuation of wear^{129,130} and can also be a sign of contact lens dryness.^{131,132} Although there is some evidence¹³³ that suboptimal vision correction may result in

discontinuation due to visual discomfort and/or disturbance, the question of whether there is a direct association between vision and the comfort of the contact lens itself remains unanswered. Although many practitioners anecdotally express a belief in such a relationship and there is some supporting evidence (Papavas EB, et al. *IOVS* 2003;44:ARVO E-Abstract 3694),¹³⁴ this has yet to appear in the referenced literature. Nevertheless, together with the knowledge that monocular and binocular refractive errors or accommodative insufficiency can result in visual discomfort, it would be prudent to remove the potential for such a problem by ensuring that the contact lens presents as accurate a refractive correction as possible.¹³⁵⁻¹³⁸

TREATMENT OF THE SYMPTOMATIC CONTACT LENS PATIENT WITH A CLINICALLY ACCEPTABLE LENS

Having eliminated possible nonlens-related causes and established that the lens as it sits on the eye is in a clinically acceptable condition, we now turn to the strategies available to manage any remaining symptoms of discomfort. The comments that follow relate primarily to soft contact lenses, except where rigid or rigid gas permeable (RGP) lenses are specifically referred to. A summary of these approaches is given in Table 2.

Adjusting Replacement Frequency

All soft lenses exhibit a gradual reduction in both comfort and wettability over time.¹³⁹⁻¹⁴¹ These changes are potentially linked to deposition of elements from the tear film, such as denatured proteins or nonwetting lipids.¹⁴²⁻¹⁴⁶ Replacing lenses before these effects reach the level at which they become subjectively evident would seem a reasonable approach. Early attempts to implement more frequent replacement among extended wearers did indeed indicate the promise of enhanced subjective performance compared with the annual replacement schedules common until the early 1990s.¹⁴⁷

In looking for evidence of the value of frequent replacement as a means of improving comfort, there have been no high-quality (Level I) studies to date. Although several Level II studies do exist (with most dealing with conventional hydrogels), the balance of evidence is equivocal. For example, although subjects in a cohort of 338 who wore a range of conventional hydrogel materials for 3 years on a no-replacement schedule were slightly less likely to report good comfort than those on frequent replacement schedules, in general, differences between the daily, 1- and 3-month replacement regimens were only marginal (Level II).¹⁴⁸ Other relevant studies have had smaller samples but were controlled in terms of the lens types involved. For Group IV lenses, comfort was better when replacing lenses every 4 weeks compared with 12 weeks and a similar, if smaller, effect was seen for Group II materials (Level II).¹⁴⁹ Later workers failed to confirm this second result, however, finding no difference between monthly and 3-month replacement of Group II lenses (Level II).¹⁵⁰ Likewise Group I lenses have shown no discernible comfort advantage for either every 3-month versus monthly replacement,¹³⁹ or daily as opposed to biweekly replacement (Level II).¹⁵¹

For silicone hydrogels, a large survey of more than 1300 patients across 158 practices found that replacement every 2 weeks was significantly *less* comfortable than monthly replacement; although as the nature of the study did not permit control over lens type, it is possible that factors other than replacement frequency may have been responsible for that outcome (Level II).¹⁵ However, recent work (Level II) with a single silicone hydrogel (senofilcon A) indicated that significantly better end-of-day comfort and dryness accompanied a daily disposable schedule than either (1) 2-week replacement using PHMB- or hydrogen peroxide-based care systems, or (2) 4-week replacement using PQ-based solutions.¹⁵²

In summary, support for increasing the frequency of soft lens replacement from once per month to twice per month is lacking in the current literature. Switching to a daily disposable schedule may be helpful, especially for silicone hydrogels, although data are available for only a single material. This is evidently an area that would benefit from better quality clinical studies. For RGPs, more frequent replacement does not appear to be valuable, at least on a 3-month replacement schedule, as this frequency conferred no comfort benefits compared with nonreplacement (Level I).¹⁵³

Changing Material

Some practitioners may seek to address discomfort issues by changing contact lens materials. The rationale for this is anecdotal and/or experiential, but presumably involves an effort either to increase oxygen transmissibility or enhance wettability. Changes may be made with or without clinical signs and are based on the clinical judgment of the individual practitioner. This may mean changing within material classes (i.e., hydrogel to hydrogel) or between classes (i.e., hydrogel to silicone hydrogel or vice versa).

Influences on comfort that might be produced by particular attributes of the material are difficult to isolate from one another. For example, increasing oxygen transmissibility by switching from a hydrogel to a silicone hydrogel will almost certainly alter other properties, such as modulus of elasticity or wettability. The overall result is, therefore, difficult to ascribe to one parameter in isolation and, not surprisingly, directed studies of these effects are uncommon in the peer-reviewed literature.

Oxygen effects on contact lens discomfort have been mostly studied using atmospheric control. In a small group of

soft hydrogel contact lens wearers, reducing atmospheric pressure, while holding temperature, humidity, carbon dioxide concentration, and illumination constant, influenced comfort levels (Level II: although, as other significant complications arose during this experiment, it is uncertain that the effects were ascribable directly to hypoxia).¹⁵⁴ Other studies of oxygen effects include both simulated and real altitude increases that resulted in a decreased comfort level in soft hydrogel contact lens wearers (Level II and III).^{155,156} In both studies, subjective changes were evident, with an inability to wear contact lenses resulting in at least one case. Again, however, it should be noted that the nature of the experimental set-up makes it impossible to link these effects solely with oxygen changes.

Perhaps of greater relevance to clinicians are the results of studies that have looked at comfort differences between hydrogel and silicone hydrogels; there are several of these in the literature. When patients were converted from hydrogel to silicone hydrogel contact lenses, a slight decrease in dry eye complaints was noted (Level II).¹⁵⁷ However, other work has shown that nearly half of previously symptomatic hydrogel soft contact lens wearers experienced reduced symptoms, mostly dryness, when refitted to silicone hydrogel contact lenses in either a daily or continuous-wear modality (Level III).¹⁵⁸ When refitting subjects into silicone hydrogels for continuous wear it did not appear to matter whether the previous modality was daily or extended wear, as reductions in dryness symptoms occurred in both cases (Level II).¹⁵⁹ This symptomatic change in both frequency and severity was noted within 1 week of being refitted into silicone hydrogel lenses. In a large study, 278 hydrogel contact lens wearers were refitted into a lotrafilcon A silicone hydrogel material and followed for 3 years (Level II).¹⁶⁰ Results showed that symptoms of dryness abated after 1 week of wear and remained consistent throughout the 3-year study period; however, the study could not ascertain the precise reason for the improvement.

Similarly, a survey of 360 contact lens wearers showed that dry eye symptoms occurred with greater frequency among those using hydrogel compared with silicone hydrogel lenses, with high water content hydrogels being more problematic than low water lenses. These differences were thought unlikely to have been due to either corneal desensitization effects induced by relatively low oxygen transmissibility or lens dehydration (Level I).¹⁶¹

Set against these outcomes in favor of silicone hydrogels are several studies that have failed to find any difference in terms of comfort (both Level II),^{13,162} and others in which the reverse was true. For example, one group of lapsed contact lens wearers experienced greater success when refitted in hydrogels from silicone hydrogel lenses (Level I),¹⁶³ although, a direct analysis was difficult because the overwhelming majority of the subjects were refitted into hydrogel contact lenses (271 vs. 16). A decrement in comfort was also observed in daily disposable silicone hydrogels when compared with daily wear disposable hydrogel lenses.¹⁶⁴

As has been pointed out in recent reviews,^{165,166} the outcomes of many of the studies mentioned above depended critically on the methodology used. It is also difficult to separate material effects (i.e., silicone hydrogel versus conventional hydrogel) from other aspects of lens construction, such as design or surface characteristics.¹⁶⁶ Taking all this into account, there is currently no firm consensus on whether silicone hydrogel lenses alone can ameliorate CLD. Although new lens materials and designs continue to emerge, there has not been sufficient peer-reviewed literature on which to base an assessment of their value in solving CLD dilemma.

Incorporation of Internal Wetting Agents

Soft contact lenses have been impregnated with internal wetting agents in an attempt to enhance comfort. Hyaluronic acid (HA) has been successfully incorporated into silicone hydrogel contact lenses.¹⁶⁷ The presence and location of HA can be confirmed by techniques such as x-ray photoelectron spectroscopy, confocal laser scanning microscopy, and Fourier transform infrared spectroscopy-attenuated total reflectance. HA increases the hydrophilicity and the equilibrium water content of hydrogels, generally without affecting transparency. HA also significantly decreases the amount of lysozyme sorption, but has no effect on lysozyme denaturation in hydrogels containing less than 2% by weight methacrylic acid (MAA). Adsorption of proteins is considerably decreased by the presence of cross-linked HA.^{167,168} The presence of small amounts of cross-linked HA has been confirmed in a laboratory study by using material physical property techniques¹⁶⁹ and results in consistently lower water contact angles. This indicates that there is a continued availability at the interface without dissipation over time. There is, however, no direct evidence that HA incorporation leads to enhanced comfort.

Polyvinyl alcohol (PVA) is a successful tear film stabilizer and is widely used in comfort drops and some soft contact lens materials. A PVA-containing lens (nelfilcon A), modified to include additional (nonfunctional) PVA as an internal wetting agent for sustained release onto the ocular surface, achieves consistent near zero-order release beyond 20 hours through polymeric delivery.¹⁷⁰ This approach was found to provide improved lens surface wettability and comfort both initially and at the end of the day (Level II).¹⁷¹ Other studies, however, return a different picture, with the nonfunctional PVA lenses performing worse than other daily disposable contact lenses in terms of comfort, wearing time and comfortable wearing time, corneal staining, and lens fit (Level II, Level III).^{172,173} When this same lens material was used in combination with external wetting agents, enhanced lens surface wettability, measured objectively by using noninvasive tear breakup time, was observed, but comfort still decreased toward the end of the day and wearing time did not increase (Level II).¹⁷⁴ Nevertheless, it was noted that when subjects were refitted from their habitual fortnightly and monthly replaced lenses, common symptoms of discomfort were reduced and biomicroscopy signs, such as bulbar and limbal redness and conjunctival staining improved (Level II).¹⁷⁵ To what extent the observed benefit came from the internal wetting agent as opposed to the new lens material, more frequent lens replacement, or absence of care solution is unclear, however, and the overall value of these agents remains equivocal.

In an effort to enhance the comfort of their RGP lenses, some manufacturers have endeavored to improve the hydration characteristics of the lens surface. One way this has been done is to incorporate what is essentially a water-containing (silicone hydrogel) polymer into the material as a means of providing better hydration at the lens surface. Evaluation of this modality relative to a standard RGP lens did show some significant improvements in subjective ratings of end-of-day comfort, but the authors deemed these to be too small to be of clinical significance (Level D).¹⁷⁶ However, as these comments were based on the group means, it may be that a minority of cases will derive some benefit from this strategy.

Use of External Wetting Agents

Since studies have demonstrated that symptoms of dryness are related to the surface wettability of a soft CL,¹⁷⁷ some

practitioners instruct patients to lubricate their lenses with wetting drops before applying them, especially if the recommended care solution does not itself have an intrinsic wetting agent.¹⁷⁸ For example, prelubrication with methylcellulose or guar to protect the cornea from biocide¹⁵⁶ may increase comfortable wearing time (Level II).¹⁷⁸ Likewise, use of a carboxymethyl cellulose-containing conditioning solution before insertion of a daily disposable lens resulted in improved comfort after insertion and at the end of 1 day of wear (Level II), although only one lens material was studied.¹⁷⁹

During continuous wear, better comfort on insertion, better visual quality, and less mucous discharge on waking were reported when using rewetting drops containing surface active surfactants compared with a saline solution control (Level II).¹⁸⁰ However, the symptom of dryness per se, was not different between treatment groups in this study. It appears that addition of surface-active agents can aid in removal of protein deposits with continuous-wear silicone hydrogel lenses and that this may improve comfort for the wearer.¹⁸⁰ To maximize effectiveness, patients may use wetting drops before the eye feels dry because hydrophobization will increase tear breakup time.⁹⁵

The addition of the ocular lubricant hydroxypropyl methylcellulose (HPMC) to a multipurpose contact lens solution conditions the hydrogel lens surface, but also is adsorbed by both Group I and IV materials, then gradually released beyond 12 hours, improving the wetting of the lens surface and enhancing lens-wearing comfort (Level III).¹⁸¹ Although HA has been shown to be efficacious as an internal wetting agent in laboratory studies¹⁶⁷⁻¹⁶⁹ and is incorporated in some commercially available multipurpose solutions (MPSS), there has been no research that has examined its effect on comfort as a surface wetting agent.¹⁸¹

Certain physical properties of blister pack solutions differ between products¹²¹ and can influence lens comfort, particularly on initial insertion (Level II/III).^{122,124} Where an individual reports unsatisfactory comfort early in the wearing cycle, and particularly with a daily disposable lens, it is possible that the blister pack solution is responsible. Rinsing the lens with sterile saline before insertion can be diagnostic for this problem, as well as being a management option. As residual solution may remain in the lens bulk after rinsing, full resolution may require switching to a different manufacturer, provided that suitable parameters and lens properties are available.

The wettability of lens care solutions can have a positive impact on blink rate and visual comfort, especially visual performance during the interblink interval (Level II).¹⁹ End-of-day discomfort could be related to the solution, but it is often due to poor surface wettability of the contact lens itself.⁹⁵

In summary, although the incorporation of external wetting agents into the lens care solution appears to be useful in increasing wearing comfort, the benefits are mainly evident during the early portion of the daily wearing cycle.

Elimination of the Care System

Care systems and the solutions involved may contribute to contact lens discomfort. One treatment option is to eliminate the care system as a variable by switching to a daily disposable lens. The benefits of daily disposable lenses are discussed in an earlier section but appear to be at least partly due to the removal of the need for a care system, which in turn reduces the potential for interaction between solution components and the ocular surface or lens.¹⁸² These lenses are designed and labeled for single use: the lenses are removed from a blister pack, inserted directly in the eye, and then removed and

discarded after 1 day of wear. A recent analysis of data collected from multiple studies at a single center showed greater comfort and less subjective dryness when a single material was used as a daily disposable compared to when it was worn on a daily wear schedule using any of a range of care systems (Level II).¹⁵² Although one of these systems was hydrogen peroxide based, it should be noted that this did contain a surfactant, so a truly chemical-free system was not achieved. Peroxide disinfection with soak and rinse in saline before insertion, or peroxide disinfection with chemical neutralization involving no additional agents should be studied further.

With that insight it should be borne in mind that switching to a daily disposable with the goal of eliminating the care system is confounded by the presence of the solution in the blister pack. In effect, this fluid is the “care system” of the disposable lens; its contents and physical characteristics vary between manufacturers and potentially may cause problems for individual wearers. Symptomatic daily disposable patients (Group IV) preferred lenses that were preconditioned with carboxymethyl cellulose drops to those fresh from the packaging (Level II).¹⁷⁹ This report highlights that completely eliminating the care system by switching to a daily disposable modality remains confounded by factors intrinsic to any particular lens, such as its material and packaging solution.

Collectively, these data suggest that elimination of the care system may be beneficial to patients with contact lens discomfort and, in most cases, a switch to daily disposables will be beneficial. In cases in which it is desirable to eliminate even the residual packaging solution, preconditioning of either daily wear or daily disposable lenses may be of value for any patient prone to discomfort.

Lens Factors

Soft Lenses. In considering the evidence base for using parameter changes to manipulate lens comfort, it is important to bear in mind the temporal characteristics of the effects that may be induced by various interventions. Thus, although some changes may have an impact on late-day dryness and discomfort, others will be more effective at mitigating insertion and short-term problems.

There is good evidence (Levels I-II) that a thin, knife-point edge is superior to a rounded edge in terms of late-day comfort. The response to a chisel-shaped edge lies between these two extremes.¹⁰¹ Mechanistically, it is suggested that the thinner edge more closely approaches the ocular surface, minimizing the interaction with the eye lid during blinking. While use of knife-edge lenses is likely to be accompanied by increased circumlimbal staining, this does not appear to be a factor in determining the final level of comfort.

Several reports support the strategy of fitting a steeper base curve as a means of improving comfort and, although all deal with only a single lens type, some degree of generalization is possible, as materials vary between the investigations. The most reliable evidence comes from two silicone hydrogel studies (Levels I-II) that agree, showing an advantage for steeper base curves, specifically 8.3 mm versus 8.6 mm¹⁰⁵ or 8.4 mm versus 8.8 mm.¹⁸³ Only in the latter case did the difference reach statistical significance. A third silicone hydrogel study (Levels II-III) indicated that when discomfort resulted from trial fitting the flatter (8.6 mm) of two available base curves (as it did for 26% of the sample), a high proportion of eyes (45 of 49) improved when refitted to the steeper lens (8.4 mm).¹⁰⁴ Similar results were obtained with midwater hydrogel lens (Levels II-III), where the number of comfort complaints diminished significantly as the base curve was steepened from 9.0 to 8.4 mm. Given that this series of studies

includes examples of assessment after short and longer wearing periods, the advantages of steeper base curves appear to apply to both situations.

Larger diameter lenses have been shown to be beneficial in improving short-term comfort¹⁸⁴ (Levels I-II). However, the range of sizes that has been investigated stretches only from 12.0 to 13.5 mm, which represents the lower end of what would be acceptable in contemporary soft lens practice. Although there appears to be an advantage in increasing diameter up to 13.5 mm, the benefit of lenses larger than this has not been formally studied.

Alterations to the back surface shape of the lens (i.e., its design) have been investigated for their impact on comfort,¹⁰⁶ as well as other aspects of fitting (Levels I-II). Designs tested included moncurve, aspheric, and bicurve alternatives and, although short-term comfort differences between these shapes were observed, no systematic pattern emerged. It is difficult to discern an evidence-based strategy for influencing comfort by manipulating the lens back surface shape, other than to say that a moncurve design is least preferred.

The evidence for altering the center thickness as a useful tool for manipulating comfort is very weak. Only one study¹⁸⁵ has assessed this directly (Levels II-III) and, although the authors state that comfort was better with the thinner of the two compared lenses (0.035 mm vs. 0.07 mm), they also found that dryness became worse. This apparently contradictory outcome is likely a reflection of the statistical approach taken during this analysis, as on inspection, the differences in the presented data look unlikely to be either statistically significant or practically useful.

Two important practical considerations must be borne in mind when attempting to use these features. The first is that although it may be desirable to strategically manipulate certain contact lens parameters, it will not be possible (or indeed desirable) to adjust individual elements in isolation from the rest of the lens due to the potential for aspects of behavior other than comfort to be affected in the process. As an example, recall that increasing the diameter usually requires the base curve to be flattened to avoid excessively tightening the fit. The effect of each intervention on overall lens behavior will have to be considered, together with any compensatory adjustments that might be necessary, if satisfactory performance is to be maintained. The second point is that due to the nature of the contemporary marketplace, unless custom-designed lenses are chosen, control over most lens parameters does not reside with the clinician, but is dictated by the manufacturer. In many cases, this will limit the scope for achieving meaningful improvements via these means.

Rigid Lenses. Improving the fit of an RGP lens in cases in which it is deemed to be imperfect can improve comfort. Avoiding excessively steep fitting appears to be of value in the short term, as both optimally fitted and slightly flat lenses were preferred in terms of initial comfort (Level II).¹⁸⁶ In the longer term, having lenses that more accurately approach the shape of the cornea resulted in improved comfort after 2 weeks of wear. It was particularly noted in this study that nonrotationally symmetrical designs (i.e., toric back surfaces or toric peripheries) were beneficial in cases in which significant astigmatism was present (Level III).¹⁸⁷ The implication for clinical practice is that respecting the corneal shape is important when attempting to reduce rigid lens comfort issues.

Other parameters that may confer benefits include larger diameters (i.e., 10 mm) (Level II)¹⁸⁶ and a rounded anterior edge shape (Level II).¹⁸⁸ It may also be advisable to avoid excessively thin lenses that permit flexure (Level I).¹⁸⁹ As the experimental exposure in all of these three cases was for a relatively short period, the potential for longer-term benefits has not been verified.

Changing the Care System

It has long been appreciated that contact lens care systems and solutions may contain ingredients that contribute to hypersensitivity or toxicity, leading to discomfort, intolerance, and ultimately discontinuation of contact lens wear (Level III).¹⁹⁰ Patients with these problems might benefit from switching among care systems in a single category; that is, from one multipurpose solution to another with similar preservatives but different accompanying ingredients, or to a different care system entirely, such as one that is peroxide based. Solutions developed for use with one lens material may have different effects on the user when used with other lenses.

There are conflicting studies regarding the impact of solutions on contact lens discomfort. Beginning with those that were the best conducted, a regression analysis did not find any statistically significant association of solution or disinfecting ingredients in self-reported dry eye among contact lens wearers (Level D).¹⁶¹ Next, studies with daily wear lenses of a single material using two different MPSs, found an increase in symptoms with wear time that again was not related to solution type (Level D).²¹ In more recent work, however, two studies suggest that certain solutions can offer comfort advantages. The first, a controlled, masked comparison of two multipurpose solutions in wearers of various soft lenses, including both silicone hydrogel and hydrogel lenses, showed statistically significant improvements in comfort when the solution specifically developed for use with silicone hydrogels by the study sponsor was used (Level D).¹²⁸ Finally, crossover comparisons of three care systems (two MPS solutions and a peroxide system) with a daily disposable control, found that MPSs containing wetting agents reduced discomfort when assessed using the Ocular Surface Disease Index (Level D).¹⁹

Prolonged use of PHMB solutions does not appear to lead to dry eye as defined by a combination of ocular and lens characteristics (Level II).¹²⁰ Users of PHMB-containing systems did report a significantly higher rate of grittiness or scratchiness.

In a study reporting differences in comfort, as well as corneal sensitivity and staining between two multipurpose solutions, the author reported the seemingly paradoxical finding that the solution associated with reduction in corneal sensitivity was associated with decreased comfort during midday and end-of-day periods (Level III).¹⁹¹ Although this result may appear to support the conjecture that corneal sensitivity and contact lens tolerance are not related, its value must be questioned due to a number of inherent methodological problems.¹⁹²

A very recent study offers a degree of clarity to this rather confusing situation by comparing comfort ratings for several contact lens materials when each was used with a range of different care systems (Level II).¹⁹³ The implication from this study is that for any given lens type, the average comfort response in a population of wearers varies according to the care system in use and that lens manufacturers do not necessarily produce the best solutions for their own lenses. As it has also been shown that optimizing the lens-solution combination can confer comfort benefits that are large enough to be appreciated by many wearers,^{194,195} changing the care system to one more suited to the particular lens type may be a practical strategy to improve comfort. An important point to bear in mind is that the solution offering the best comfort may have drawbacks in other areas, such as an increase in the rate of adverse events.¹⁹³

There is scant evidence that changing care systems can increase RGP contact lens comfort. In a small study involving two systems from the same manufacturer, although there was a preference in favor of the one-bottle MPS system over the two-

bottle cleaner plus conditioner alternative, this was not statistically significant. Furthermore, the wearing schedule involved overnight orthokeratology, which does not offer the best platform for assessing end-of-day discomfort (Level III).¹⁹⁶ However, this lack of formal evidence does not necessarily mean that certain solutions will not perform better with particular materials.

Use of Tear Supplements and Wetting Agents

Although fewer in number relative to studies conducted to establish the usefulness of tear supplements in noncontact lens wearers, there are several published reports that support the use of tear supplements and wetting agents in the management and treatment of CLD.¹⁶¹

Treatment with a preservative-free 0.9% sodium chloride ophthalmic solution has been found to reduce ocular surface discomfort and extend the duration of contact lens wear¹⁹⁷; although wearers of first-generation silicone hydrogel lens material, who were symptomatic for dry eye, preferred saline drops that were hypo-osmotic rather than hyper-osmotic (Level II).¹⁹⁸

An investigation conducted at six clinical sites in North America found that 47% of contact lens wearers reported obtaining moderate relief using rewetting drops (Level II).¹⁹⁹ In a study in which lens hydration was monitored together with discomfort, symptomatic hydroxyethylmethacrylate contact lens wearers gained short- and long-term relief using both lubricants and saline,²⁰⁰ but without any differential benefit between the two. The symptomatic relief provided by the drops was attributed to psychological factors, as there was no substantial hydration effect observed.

A study conducted in a sample of 59 subjects indicated that the use of a carboxymethylcellulose (CMC)-containing conditioning agent with brand new hydrogel lenses provided improved comfort on insertion, although the advantage was no longer significant by the end of the day.¹⁷⁹ Evidence from a comparison of tear supplements with differing viscosity indicates that these drops also helped reduce postinsertion discomfort for both hydrogels and silicone hydrogels during the first 6 hours of wear. Although both lubricants (i.e., drops containing either CMC or PVA) were more effective in reducing the dryness symptoms of silicone hydrogel wearers than the 0.9% saline control (Level III), there was no advantage to having a more viscous drop.²⁰¹ Drops containing surface-active agents also provided greater subjective satisfaction than saline. (Level I).¹⁸⁰

Eliminating preservatives from ocular preparations will avoid possible toxic complications. Preservative-free drops were preferred by hydrogel lens-wearing patients who had symptoms of dryness with habitual lens wear.²⁰² The use of 2% povidone preservative-free eye drops was also associated with an improvement in symptoms of ocular tiredness, dryness, and difficulty during sustained computer use (Level III).²⁰³

When the combination of MPS and rewetting drop was studied, a PQ- and myristamidopropyl dimethylamine-based MPS used in conjunction with a polyethylene glycol 11-containing drop was rated as being more comfortable than the alternative PHMB MPS used with povidone-based drops. However, the difference did not become statistically significant until the 1-month point and, as only one lens type was used in this study, the result may not be generally applicable (Level II).²⁰⁴

It is well established that when any ophthalmic solution is administered to the eye, most of the drop rapidly leaves through the nasolacrimal duct, leaving only a fraction available for absorption by the cornea, conjunctiva, and nasal mucosa. The ocular surface residence time for such drops is short and,

as a consequence, tear supplements usually need to be regularly re-instilled to maintain efficacy throughout the wearing day. Despite this limitation, tear supplements and wetting agents (also referred to as rewetting drops, lubricant drops, or artificial tears) are regarded as the mainstay treatment for CLD. They are widely and easily available OTC and for many sufferers are an effective means of managing the problem.

The development of alternatives that can provide day-long sustained comfort and relief from CLD is a desirable target for future research and this may involve the use of new surface active agents, demulcents, and ingredients, such as hyaluronic acid, which has been proposed to improve comfort and wettability of lenses.^{205,206} Further randomized controlled masked clinical trials are necessary to determine the efficacy of tear supplements across varying levels of severity of CLD.

One other treatment option that bears a mention is the hydroxypropyl cellulose (HPC) ophthalmic insert, which has been available for more than 2 decades. It was shown in multicenter, two-visit, open-label, 4-week registry studies that contact lens patients experienced significant reductions in the mean severity of eye discomfort, burning, dryness, grittiness, and stinging after 1 month's use of this treatment (Level II).^{207,208} Smaller studies and case reports have also indicated similar improvements in patient-reported dryness (Level III).^{209,210} Despite these apparently attractive results, the use of HPC inserts remains limited, presumably due to the relatively invasive nature of the insertion procedure. They do, however, provide a useful alternative for difficult cases.

Nutrition

Most reported nutritional intervention strategies to treat and manage contact lens dry eye are anecdotal and follow the treatments that have been suggested for the general dry eye disease population. As in most other areas of medicine, nutritional interventions fall under the umbrella of alternative and complementary medicine. However, few controlled studies currently exist on which practitioners can base their advice to patients.

Essential Fatty Acids. Long-chain essential fatty acids (FAs) traditionally described as being necessary for ocular health include omega-3 FA isolates, such as eicosapentaenoic acid and docosahexaenoic acid: both are converted to prostaglandin E3 and function as anti-inflammatory agents. The use and indications for omega-3 and omega-6 FAs can be found in the TFOS DEWS report as well as the TFOS MGD workshop.^{79,211}

The use of omega-3 and omega-6 FAs in contact lens dry eye has little in the way of peer-reviewed literature to suggest that it is efficacious. The only relevant study (Level I)²¹² was of 76 female soft contact lens wearers who were randomized to use either a placebo (olive oil) or omega-6 FAs (evening primrose oil). Subjects in the evening primrose oil group demonstrated a significant improvement in dryness symptoms at 3 and 6 months, as well as better overall lens comfort and increased tear meniscus height at 6 months. It was suggested that omega-6 FAs taken as evening primrose oil might be useful as a therapeutic adjunct for contact lens dry eye discomfort.

There is good evidence that omega-3 and omega-6 FAs are useful in decreasing inflammation in the bodily diseased states. Additional evidence supports their use in dry eye, especially severe states such as keratoconjunctivitis sicca and Sjögren's syndrome, and the little that has been published relative to soft contact lens discomfort or dryness is also suggestive of their utility. In summary, although omega-6 FA supplementation may help reduce CLD, the use of omega-3 FAs has not been directly studied.

Hydration. Dietary advice is often given to patients with dry eye and in turn contact lens dry eye relative to hydration status and, indirectly, alcohol consumption. No research exists on the exact amount of water that is needed on a daily basis, although six to eight, 8-ounce glasses per day have been suggested as a target.^{213,214}

The influence of hydration status on the tear film has been studied, but not with any specific reference to contact lens wearers. In one study conducted during the course of fasting, decreases in tear proteins and enzymes were noted,²¹⁵ and in a small interventional study of dry eye sufferers, nearly 76% had decreased symptoms after being asked to increase their daily water intake for a 2-week period.²¹⁶

Alcohol consumption has been shown to significantly shorten tear breakup time, increase fluorescein staining, and increase tear film osmolarity.²¹⁷ However, contact lens-wearing status was not explicitly indicated in this study.

Likewise there is no clear, peer-reviewed evidence addressing the issue of hydration status and contact lens-related discomfort or dryness. Anecdotal suggestions abound in relation to both topics, but more controlled studies are necessary to define the likely influence on contact lens discomfort.

Punctal Occlusion

Punctal occlusion is a therapeutic option for dry eye syndrome and, for the purposes of this review, refers to punctal or canalicular occlusion of the lacrimal drainage system. Either dissolving, intracanalicular, collagen plugs that last only days, or other polymers that may last months, can be used. More permanent, yet reversible, occlusion can be obtained with silicone rubber or conforming polymers, or with silicone rubber plugs that are retained at the punctum. Finally, electrocautery or laser ablation can be used to obtain more permanent and complete occlusion by inducing fibrosis of the canaliculus and or punctum. Occlusion may be partial or total depending on the method chosen and can be applied to either or both of the lower and upper punctal/canaliculi.

A Cochrane review found a relative scarcity of controlled clinical trials assessing the efficacy of punctal occlusion therapy for dry eye, with data suggesting that silicone plugs can provide symptomatic relief in severe dry eye, and that temporary collagen plugs appear similarly effective to silicone plugs on a short-term basis (Level I).²¹⁸ Although contact lens-related discomfort was not addressed in this particular review, other reports have done so.

Occlusion of the lower punctum with a silicone plug resulted in increased wearing times for 18 of 25 symptomatic wearers of soft contact lenses (Level II).²¹⁹ Silicone intracanalicular plug occlusion of upper and lower drainage systems improved symptoms in symptomatic hydrogel contact lens wearers, an effect that decreased over time (Level I).²²⁰ Occlusion of the lower punctum only seemed to induce a short-lasting subjective benefit in contact lens wearers (Level III).²²¹ A study using high-definition OCT demonstrated that occlusion of both upper and lower puncta in symptomatic and asymptomatic contact lens wearers increased tear menisci, and this increased volume was associated with better comfort in both groups (Level II).²²² These positive findings are opposed by one study that found no treatment effect when the lower punctum only was occluded with an absorbable polymer (Level I).²²³ Specifically, there was not a difference in tear film thickness or subjective responses when comparing a group that received punctal plugs and a group that received a sham procedure.

In total, the balance of evidence slightly suggests that punctal occlusion can improve contact lens discomfort and

that silicone plug occlusion is more likely to be effective than dissolvable types. Similarly, occlusion of both upper and lower lids is more likely to be beneficial than the lower lid alone.

This analysis, however, addresses only the effectiveness of punctal occlusion as a strategy for treating contact lens discomfort. Practitioners must also consider the risks, benefits, relative safety, and cost-effectiveness of the various approaches before proceeding.

Topical Medications

Data are very limited on the use of topical medications other than lubricants. However, based on the view that CLD is commonly associated with the evaporative form of dry eye disease, clinicians may consider approaching its management by applying similar treatments to those appropriate for evaporative dry eye. Topical medications may play an important role in this regard. Note that manifest signs of underlying ocular surface disease should already have been detected and treated as described above. A complete review of medications and their properties is beyond the scope of this report, but commonly used ones, their dosages, and their benefits and risks are briefly described.

Azithromycin. Azithromycin is a macrolide antibiotic. As well as being one of the few antibiotic classes that achieve therapeutic concentrations in the eyelids, topical azithromycin is known to have anti-inflammatory properties, having recently been shown to decrease corneal inflammation and inflammatory cytokines in a murine model.²²⁴ Since the introduction of azithromycin ophthalmic solution 1%, a number of groups have investigated its efficacy in the management of blepharitis and associated symptoms.²²⁵⁻²²⁹ Although these studies provide Level II evidence, they do support the use of daily topical azithromycin ophthalmic solution 1% for the improvement of physical findings of blepharitis, which may be a precipitating condition for CLD. They also show concurrent reduction in related dry eye signs and symptoms, without significant treatment side effects.²²⁸ Topical azithromycin ophthalmic solution 1% therapy clearly resulted in the reduction of the signs and symptoms of blepharitis and dry eye findings, with one study showing a sustained effect lasting at least 4 weeks after discontinuation of therapy.²²⁶

To date, only one study has directly considered the safety and efficacy of azithromycin in patients with contact lens-related dry eye (CLDE).²³⁰ This was a 4-week, single-center, open-label clinical trial (Level II) in patients diagnosed using the Contact Lens Dry Eye Questionnaire (CLDEQ). Fifty patients were randomized to use either twice-daily azithromycin ophthalmic solution 1% or a potassium sorbate and edetate disodium preserved contact lens rewetting drop containing hypromellose and glycerin administered four times per day. The azithromycin treatment was well tolerated and resulted in a significant improvement in comfortable contact lens wearing time in the patients with CLDE. However, given the short-term nature of this study and its relatively small sample size, further work is required to confirm the findings, as well as to establish the potential for undesirable side effects, such as the development of bacterial resistance.

Cyclosporine. Cyclosporine A (CsA) is a neutral, hydrophobic, cyclic peptide of amino acids that acts as a selective inhibitor of IL-2 release during the activation of T cells and suppresses the cell-mediated immune response. More specifically, it increases tear production and conjunctival goblet cell density based on its effects on subconjunctival and lacrimal gland inflammation in a significant number of moderate-to-severe dry eye patients.²³¹⁻²³⁷

Reports of the clinical efficacy of topical CsA in CLD are contradictory. A small ($n = 17$), 5-week, randomized, investigator-masked study (Level II)²³⁸ in which CLD patients were randomized to CsA 0.05% or carboxymethylcellulose 0.5% drops twice per day (before and after lens wear), demonstrated a decrease in CLD symptoms and less use of rewetting drops during the day for the CsA users, as well as an increase in wearing time. However, a larger ($n = 44$), longer-duration (3 months) double-masked study (Level I) found that there was no significant difference in signs or symptoms between the CsA treatment group and a control group using a preservative-free tear supplement.²³⁹ At this point in time, there is no strong evidence that CsA treatment is useful in CLD and additional trials are needed.

Steroids. There is still debate regarding the role of topical corticosteroids in the treatment of dry eye and related conditions, as inflammation may be present or absent in these clinical presentations. If, as in CLD, there are no vision-threatening aspects to the disease process, steroid use is especially hard to justify. There are no published studies supporting corticosteroid therapy for CLD.

Nonsteroidal Anti-Inflammatory Drugs. Like corticosteroids, the rationale for considering the use of a nonsteroidal anti-inflammatory drug (NSAID) is to reduce any underlying inflammation. Given that the presence of such inflammation in CLD is controversial, the case for using NSAIDs, like that for corticosteroids, has not been made. There is no evidence supporting NSAID use in the treatment of soft lens-related CLD.

For RGP, two studies evaluated 0.1% diclofenac sodium. In the first, four-times-a-day treatment with 0.1% diclofenac for 3 days before dispensing had no effect in unadapted contact lens subjects (Level II).²⁴⁰ The second investigation involved a contralateral comparison with subjects reporting a preference for the eye that was given 0.1% diclofenac sodium four times a day for 1 week after the initial fitting (Level III).²⁴¹ No difference in corneal or lid sensitivity was reported. Combined, these reports suggest that although diclofenac has no value in ameliorating initial discomfort issues, there may be some longer-term benefit. More evidence is required to confirm this.

Anesthetics. Proparacaine and other topical anesthetics indiscriminately target corneal nerve sodium channels. They are effective at eliminating ocular surface pain, but the effect is short-lived and these agents are prone to abuse. Furthermore, topical anesthetics have been shown to cause delayed wound healing and ulceration in the cornea.²⁴² Although topical anesthesia has been shown to be effective in improving discomfort, both initially and out to 2 weeks of rigid lens wear,²⁴³ there is some resistance among clinicians to using this approach.²⁴⁴ No studies have evaluated the efficacy of these drugs in treating soft contact lens-related discomfort. This notwithstanding, the long-term use of anesthetics as a treatment for any kind of contact lens-related discomfort is not supportable.

Environment

Most contact lens wearers encounter a range of conditions during the course of their daily lives. When asked about circumstances when they “always or frequently” wore lenses, responses from 80% of a large ($n = 496$) group of hydrogel wearers included reading, sitting in an air-conditioned or heated car, using a computer, and driving at night, whereas approximately 30% mentioned more extreme situations, such as airline travel and napping or sleeping.²⁴⁵ Contact lenses that cause only minor symptoms of dryness in a normal environment can precipitate significant discomfort when the wearer

experiences prolonged exposure to adverse conditions (Level III).²⁴⁶ Dust, pollution, or smoke are especially problematic (Level III).²⁴⁵ Refitting the members of this cohort into silicone hydrogel lenses brought about significant comfort improvements in most environments, suggesting that this may be a viable clinical strategy. However, the study design used was prone to Hawthorne-type effects (i.e., subjects respond positively simply because they are being studied), so the outcomes must be interpreted cautiously.

There has been little research on the effects of environmental conditions on CLD *in vivo*. Comfort may be lower when RGPs are worn in low-humidity environments in some patients (Level III).²⁴⁷ In a small pilot study ($n = 6$), dehydration of soft contact lenses was found to be similar after 200 minutes of exposure to arid (5% humidity, 30°C temperature), temperate (70%, 22°C), and arctic (90%, 5°C) environments and there were no differences in subjective comfort (Level II).²⁴⁸

Air quality aboard commercial aircraft varies significantly,²³⁰ and is one situation in which many wearers choose to remove their lenses rather than suffer the ensuing discomfort. Interestingly, contact lenses are well tolerated by military air crews (Level II/III),^{249,250} perhaps suggesting that the air quality within their cockpits or flight suits is of a higher standard, although there may be psychological factors involved as well. Nevertheless, it seems prudent to advise patients to avoid situations in which discomfort is known, or expected, to increase. Where contact with potentially threatening conditions is unavoidable, the use of protective eyewear should be considered.

Blinking Behavior

The suggestion that inadequate wetting of the anterior surface of the contact lens is a factor in precipitating late-day dryness and discomfort has led to scrutiny of the mechanism responsible for achieving the rewetting cycle, namely eyelid blinking. Occupational tasks, such as sustained viewing of a computer screen, for example, can alter the blink rate, causing symptoms, such as discomfort, dryness, and eyestrain.²⁵¹ Inefficient blinking, which may be due to either reduced frequency or amplitude of lid movement relative to the lens surface (or both), has been put forward as a cause of this problem,²⁵² and modification of lid dynamics through blink-efficiency exercises proposed as a treatment. Although detailed instructional material is available for this method,²⁵³ data supporting its efficacy appear to be completely absent. Despite the fact that several authors have proposed the use of exercises in problem cases,^{253–256} there is a paucity of even anecdotal-level reporting on the outcomes of these treatment efforts. Their usefulness in providing symptomatic relief is therefore unknown and this is clearly an area in which well-conducted research is required. In a sample of 360 contact lens wearers, the type of blink was characterized for each subject (as complete, forced, or twitch); the type of blink was not related to contact lens dry eye status.²⁵⁷

There is some evidence (Level II) that blink rate responds to the type of care system used with the contact lens. MPSs that contain wetting agents have been associated with lower blink rates than hydrogen peroxide-based systems, which do not have such additives.¹⁹ However, this slower rate was associated with *better* comfort; the opposite of what would be expected if blinking were the main cause. Although changing care systems may be a valid way of improving comfort, the mechanism involved does not seem to be one that directly influences blink frequency. It is more likely that the solution addresses the underlying comfort problem by some other, unspecified means, and the blink rate slows down as a consequence. Nevertheless, the introduction of additional lubrication to the

ocular environment might well be considered as an option for CLD, as has been covered elsewhere in this report.

ALTERNATIVES

Soft to RGP and Vice Versa

Soft lens patients who wore low-water-content lenses that maintained their hydration generally reported that their eyes “never felt dry” during wear,²⁵⁸ suggesting that preventing lens dehydration is an important factor in reducing symptoms. Repeated failure with soft lenses may prompt consideration of RGP lenses, as they are much less prone to dehydration. There are, however, no recently published evidence-based data on refitting modern-day contact lens wearers with complaints of CLD into RGP contact lenses. On the other hand, there are several reports supporting refitting into soft lenses for those who experience poor comfort in RGP contact lenses. Subjects fitted with a soft lens in one eye and an RGP lens in the other preferred the comfort, although not the vision, of the soft lens after 3 months (Level II).²⁵⁹ Likewise, toric hydrogels were rated as being more comfortable than RGP contact lenses after 3 weeks of wear, with vision preference again in favor of the RGP lens (Level II).²⁶⁰ Younger wearers (8–11 years) experiencing discomfort problems with RGPs might gain, in terms of longer comfortable wearing time and reduced frequency of symptoms, by switching to soft contact lenses. Once again vision was significantly better in the rigid lens modality (Level II).²⁶¹

Clearly, switching uncomfortable RGP lens wearers into soft lenses is a viable approach, but one that may be accompanied by inferior vision. Some wearers may also find the different lens maintenance and handling procedures problematic.

Reduced Wearing Time

Many patients choose to limit their wearing time to avoid periods in which their discomfort is at unacceptable levels. For some, this will involve wearing lenses during working hours, whereas others will choose to favor leisure periods. Although this is often a useful compromise, it is doubtful whether the total daily wearing time can be extended using this method (Stahl U, et al. *IOVS* 2013;54:ARVO E-Abstract 5462).

Orthokeratology

Orthokeratology (OOK) lenses are worn during sleep and are removed on awakening, at which point the refractive error of the unaided eye is reduced or eliminated. In the best case scenario, patients are thus relieved of the need to wear a refractive correction of any kind during their waking hours and so do not experience CLD. It is this aspect that gives OOK its potential as a management option for those with intractable discomfort related to soft contact lens use.

There are no studies that directly compare OOK as an alternative for patients who experience soft contact lens discomfort; however, corneal epithelial health, a potential surrogate for ocular discomfort, has been studied. A crossover study that measured the tear concentration of lactate dehydrogenase before and after overnight OOK wear, found markedly increased levels of the enzyme, suggesting that corneal hypoxia results from OOK overnight wear.²⁶² Similar findings have also been observed after extended-wear soft contact lens use.^{263,264} Tear lactate dehydrogenase levels have not been compared between OOK and soft contact lenses.

OOK is not without its limitations and risks of side effects or complications. The corrective effect from OOK is not

permanent and lenses must be periodically worn overnight to reproduce the effect. Unlike the effect of contact lenses or spectacles, there is slight regression of the effect and a change in refraction from 0.25 to 0.75 diopters can occur throughout the course of the day.²⁶⁵ Like keratorefractive surgery, OOK can cause the induction of higher-order aberrations, such as spherical aberration, which can be more problematic in low-lighting conditions and with pupil dilation. Pigmentation of the cornea has also been reported. Of these complications, microbial keratitis remains the most feared, as it can result in permanent vision loss. There have been more than 20 publications describing microbial keratitis in case reports and case series; however, the relative frequency with which microbial keratitis occurs in OOK as opposed to soft lens wear is not clear. There are no studies that have Level I evidence for microbial keratitis in OOK. In two studies that have Level II evidence, no adverse events were reported after 15 months of OOK use in 65 adult patients,²⁶⁶ or with more than 3 months of follow-up in 14 patients.²⁶⁷

Refractive Surgery

Most practitioners are aware of individuals who have abandoned contact lenses in favor of refractive surgery, and there is good evidence (Level II) that contact lens-related dryness is an important precipitating factor. In a survey of refractive surgery patients who had previously worn contact lenses, 23% cited dry eyes as the reason for their decision to undergo refractive surgery.²⁶⁸ Utilization of refractive surgery as a means of managing CLD requires careful thought and counseling of the individual patient, as there are several aspects that need to be considered before proceeding. Not the least of these is that the procedure itself is commonly associated with dry eye in the postsurgical period.^{269,270} Other potential complications include ocular pain and visual disturbance due to halos, glare, and spherical aberrations.²⁷¹ Faced with these issues, the question of whether the overall situation of the patient will be improved postsurgery is an important one to consider. In a study that assessed the preoperative quality of life and psychological factors that influence decision making in Laser In Situ Keratomileusis (LASIK) surgery, SCL wearers, not interested in LASIK, reported better vision function ($P = 0.001$), felt more attractive ($P = 0.007$), had a lower frequency of disturbing visual and ocular symptoms ($P = 0.027$), and had a higher overall satisfaction with their current optical correction ($P < 0.001$) than patients seeking LASIK surgery (Level II).²⁷² There is some evidence (Level II) that quality of life after LASIK refractive surgery is better overall than that of contact lens wearers.²⁷³ However, no studies have evaluated the change in subjective satisfaction that contact lens wearers with discomfort have *after* opting for surgical refractive correction.

Not all patients are candidates for laser keratorefractive surgery and careful screening is required to eliminate those with keratoconus, herpetic eye disease, and history of autoimmune disease. Serious complications, such as infection and corneal ectasia, can result in significant loss of best-corrected visual acuity (BCVA). In fact, 2.35% of eyes treated with either LASIK or photorefractive keratectomy (PRK) have been shown to lose two or more lines of BCVA.²⁷⁴ Infections are rare after LASIK; however, more than 80 cases have been reported and reports in the literature put the incidence at between 1 per 1000 to 5 per 1000.²⁷¹ This compares with average rates of 0.35 and 3 per 1000 in daily and extended contact lens wear respectively.²⁷⁵

Spectacles

Although there are no published data on spectacle wear as a management strategy for CLD, it is fairly obvious that this will

be the default option for the vast majority of lapsed contact lens wearers. Unarguably, spectacles provide a convenient, accessible, and effective alternative in cases of persistent CLD. Given that freedom from spectacles is the main driver for patients to begin contact lens wear in the first place, an enforced return is unlikely to be viewed positively in most cases, however. For many sufferers, intermittent contact lens wear, interspersed with periods of spectacle wear, will be an acceptable middle ground requiring maintenance of an up-to-date spectacle prescription. It is important to instruct the patient in the care and hygiene conditions that are necessary for contact lenses worn on this sporadic basis. Daily disposables offer advantages in this respect and are the preferred option.

FUTURE POSSIBILITIES

Therapeutics that reduce pain directly or through neuro-modulation potentially could be used to treat contact lens discomfort that exists in the absence of coexisting disease. The treatment of ocular surface pain is an active area of research because safe, prolonged pain relief is difficult to achieve. Furthermore, the sensitive nature of the cornea contributes to the challenge of providing successful analgesia.

In animal studies, other therapeutics have been used to treat ocular surface pain. For example, resiniferatoxin exhibited prolonged analgesia without delaying corneal wound healing in rats and selectively targeted specific cornea sodium channels within nociceptive neurons, which are triggered by irritating chemicals.²⁷⁶

Opioids are another class of drugs that are predominantly administered systemically, affect the central nervous system, and have analgesic effects when administered topically to the eye. Morphine has been found to act on local opioid receptors in the cornea, to decrease corneal inflammation, and lessen corneal hyperalgesia.²⁷⁷ Topical morphine has also been shown to provide corneal analgesia for up to 4 days without causing a delay in re-epithelization.²⁷⁸

Neuromodulation of the cornea is another area of ongoing research that is related to CLD. In this respect, one of the most studied therapeutics is autologous serum tears, which are biological subproducts of blood. Autologous serum tears have been shown to contain significantly more neurotrophic factors than human tears and have been reported to restore corneal sensitivity in eyes that suffer from neurotrophic keratopathy.²⁷⁹ These findings were reported from retrospective noncomparative case series where it was also demonstrated that 20% autologous serum could promote the healing of corneal epithelial defects associated with neurotrophic keratopathy. Although most of the literature published on autologous serum includes predominantly retrospective case series, investigators have performed small prospective, randomized trials. A double-masked randomized prospective crossover clinical trial found that 12 severe dry eye patients had a significant symptomatic improvement when treated with autologous serum compared with artificial tears during a 2-week treatment period. Another small prospective, randomized, masked clinical study demonstrated significantly faster wound healing than hyaluronic acid drops, a commonly used artificial tear product.²⁸⁰ There have not been any published reports on the use of autologous serum specifically for treatment of CLD and its widespread use for this application may be limited by production barriers that include the need for phlebotomy, a standardized manufacturing method compliant with regulatory measures, and long-term storage.

SUMMARY

CLD presents a considerable clinical challenge. Although the causes of the short-term discomfort associated with post-insertion difficulties are generally understood and appropriate remedies relatively easily applied, symptoms of discomfort and dryness that persist and increase toward the end of the day pose a more intractable problem. Managing patients in these circumstances requires careful, individual assessment to eliminate concurrent conditions that may confuse the clinical picture, followed by a determination of the most likely cause or causes and identification of corresponding treatment strategies. The Figure again shows a recommended treatment algorithm for clinicians to follow in managing CLD. With this in mind, it should be appreciated that the subjective effects of these tactics may have reasonably limited magnitude. In many cases, therefore, incremental improvements may be all that can be reasonably expected from any single intervention and the addition of treatments in a stepwise manner may be required to provide the maximum possible relief. Unfortunately, given the current state of knowledge surrounding the condition, a proportion of patients will remain with residual levels of CLD that are sufficiently bothersome, causing them to resort to discontinuation of contact lens wear. Continued research is needed to support the development of technologies that will permit the progressive elimination of the problems experienced by this portion of the contact lens-wearing population.

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