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TFOS Lifestyle: Impact of elective medications and procedures on the ocular surface

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ABSTRACT

The word "elective" refers to medications and procedures undertaken by choice or with a lower grade of prioritization. Patients usually use elective medications or undergo elective procedures to treat pathologic conditions or for cosmetic enhancement, impacting their lifestyle positively and, thus, improving their quality of life. However, those interventions can affect the homeostasis of the tear film and ocular surface. Consequently, they generate signs and symptoms that could impair the patient's quality of life. This report describes the impact of elective topical and systemic medications and procedures on the ocular surface and the underlying mechanisms. Moreover, elective procedures performed for ocular diseases, cosmetic enhancement, and non-ophthalmic interventions, such as radiotherapy and bariatric surgery, are discussed. The report also evaluates significant anatomical and biological consequences of non-urgent interventions to the ocular surface, such as neuropathic and neurotrophic keratopathies. Besides that, it provides an overview of the prophylaxis and management of pathological conditions resulting from the studied interventions and suggests areas for future research. The report also contains a systematic review investigating the quality of life among people who have undergone small incision lenticule extraction (SMILE). Overall, SMILE refractive surgery seems to cause more vision disturbances than LASIK in the first month post-surgery, but less dry eye symptoms in long-term follow up.

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1. Introduction

This report on the effect of elective mediations and procedures on the ocular surface was part of the Tear Film & Ocular Surface Society (TFOS; www.tearfilm.org) Workshop entitled 'A Lifestyle Epidemic: Ocular Surface Disease' which was undertaken to establish the direct and indirect impacts that everyday lifestyle choices and challenges have on ocular surface health. For the purpose of this Workshop, the ocular surface is defined as the cornea, limbus, conjunctiva, eyelids and eyelashes, lacrimal apparatus and tear film, along with their associated glands and muscular, vascular, lymphatic and neural support. Ocular surface disease includes established diseases affecting any of the listed structures, as well as etiologically-related perturbations and responses associated with these diseases. Disease is considered from an etiological perspective to include infection, inflammation, allergy, trauma, neoplasia, dysfunction, degeneration and inherited conditions.

Aside from a medical indication, patients can choose to use medications or undergo procedures to maintain a healthy state and improve their quality of life. The term 'elective' in the medical field is defined as planned or undertaken by choice with a lower grade of prioritization (not urgent) [1,2]. These options are neither compulsory nor essential for life but benefit lifestyle. Elective medications or procedures, local or systemic, may induce ocular surface changes, particularly dry eye disease [3,4] (Tables 1 and 2). Some medications, such as antibiotics or anti-allergic agents, can be classified as essential for life in some situations or as elective medications in others.

According to the American Society of Cosmetic Surgeons, there continues to be an upward trend in elective procedures in the uptake of elective procedures including those that target the periocular region such as eyelid lifts (blepharoplasty) and botulinum toxin injections [5]. As patients become more cosmetically aware, and want more ease and convenience, surgical and non-surgical procedures (Table 2), such as keratorefractive or intraocular refractive surgery [1,6], are increasingly favored. Yet, their full impact on the ocular surface is not known. Similarly, elective medications and devices used topically or systemically (Table 1) for lid disease, allergies, protection from ultraviolet radiation, acne, weight loss, depression, and more, may also have ramifications on the ocular surface. Many procedures and medications were identified in the Tear Film Ocular Surface Society's second Dry Eye Workshop (TFOS DEWS II) report as iatrogenic factors that can contribute to the development of dry eye disease and have a negative impact on a patient's quality of life [3,4].

The present report used an evidence-based approach to evaluate the anatomical and biological impact of elective medications and procedures on ocular surface homeostasis and the potential pathological conditions triggered by such interventions. It includes a narrative review divided into topical ocular and periocular medications, systemic medications and elective procedures of the eyelids and periorbital region, conjunctiva, cornea (including keratorefractive surgery), lens, and other surgeries. It also summarizes the anatomical and biological neurosensorial consequences on the ocular surface, proposes areas for future research, and increases awareness of patients' choices when considering these options.Wherever possible, the report authors sought to refer to outcomes from high quality systematic review (Level I) evidence, and the reliability of cited systematic reviews was factored into their reporting in the narrative review. In alignment with the other *TFOS Lifestyle Workshop* reports, the Evidence Quality Subcommittee (EQS) provided a comprehensive database of appraised Level 1 evidence judged to be of potential relevance to the report, which was considered

Table 1
Elective topical and systemic medications and devices that risk affecting the ocular surface.

Topical medication	Ophthalmic	Artificial tears, gels, ointments
		Complementary and alternative medicines
		Anti-allergic eye drops (antihistamines, mast cell stabilizers, dual action drugs, Non-Steroidal Antiinflammatory Drugs
		Topical alpha-adrenergic agonists
		Eyewashes
	Periocular	Eyelid hygiene (e.g. tea tree oil based and other ingredients)
		Eyelid warming masks
		Sunscreen
		Ointment for blepharodermatitis
		Ivermectin
		Acne medication (e.g. glycolic acid, salicylic acid, retinoids)
Systemic medication		Corticosteroids and non-steroidal anti-inflammatories
		Antimicrobials
		Omega 3 and 6
		Vitamin supplements
		Hormonal replacement
		Anti-androgens
		Tamsulosin
		Anabolics
		Antihistamines/anticholinergic drugs
		Medication for acne/rosacea (e.g. Isotretinoin)
		Antidepressants and anxiolytics
		Naltrexone
		Cannabis
		Others

Table 2
Ophthalmic and non-ophthalmic surgical and non-surgical procedures and devices that risk affecting the ocular surface.

	Target tissue	Types
Ophthalmic surgical procedures	Lids and periorbital	Blepharoplasty
		Ptosis
		Canthoplasty
		Brow surgery
	Conjunctiva	Pterygium and Pinguecula
		Conjunctivochalasis
		Benign tumor resection (e.g. naevi)
		Eye whitening
	Cornea	Keratorefractive surgery
		Laser-assisted *in situ* keratomileusis (LASIK)
		Photorefractive keratectomy
		Small incision lenticule extraction (SMILE)
		Keratotomy
		Intracorneal ring segments
		Corneal inlays for presbyopia
		Corneal cross-linking
		Cosmetic keratoplasty
		Phototherapeutic keratectomy
		Corneal tattooing
	Lens and anterior and posterior chamber	Phacorefractive surgery
		Phacoemulsification with intraocular lens
		Femtosecond laser assisted cataract surgery
		Phakic intraocular lens
Non-ophthalmic surgical procedures		Neurosurgical procedures
		Bariatric surgery
		Radiation therapy
Non-surgical ophthalmic procedures and devices		Punctal occlusion
		Botulinum toxin
		Cosmetic Lasers
		High frequency radio waves
		High frequency ultrasound
		Microblepharoexfoliation
		Thermal pulsation treatment
		Meibomian gland probing
		Intense pulsed light therapy
		Low-level light therapy
		Plasma discharge therapy
		Transcutaneous periorbital electrical stimulation
		Acupuncture and Moxibustion

by the report authors when writing the narrative review [7]. In addition, the report includes a systematic review about the impact of a relatively new corneal refractive procedure, Small Incision Lenticule Extraction (SMILE), on the ocular surface.

2. The impacts of topical medication on the ocular surface

2.1. Topical ocular products

Various topical ocular medications and formulations may cause problems at the ocular surface. Mechanisms of damage include ocular toxicity from preservatives, ingredients and excipients as well as pH and tonicity of the formulations. Artificial tears, gels and ointments, complementary and alternative medicines including honey eye drops or gels and Aloe vera, anti-allergic topical ocular therapy, and eye washes may be hazardous to the ocular surface. Topical alpha-adrenergic agonists used in the management of ocular allergies, but also frequently chronically (ab)used as eye-whiteners, may lead to ocular surface damage over time [3,4].

2.1.1. Mechanisms of ocular surface damage

2.1.1.1. Toxicity of preservatives. Many elective topical medications contain preservatives. These may act at the ocular surface through various mechanisms, exerting allergic, toxic and immune-inflammatory effects, or by chemical interactions with different components of the ocular surface. Possible targets of preservative toxicity are the tear film, either by disrupting the lipid layer through detergent tensioactive effects, by reducing aqueous secretion or adversely affecting the conjunctival goblet cells, conjunctival and corneal epithelia, the corneal nerves through neurotoxic effects, or the eyelids at the skin or the meibomian glands [8-12] (Fig. 1). Experimental data demonstrate an increase in tear film osmolarity and direct pro-inflammatory effects of benzalkonium chloride, with release of inflammatory cytokines or increased expression of chemokine receptors [13-15]. Clinically higher expression of human leukocyte antigen-DR isotype and a significantly increased infiltration of dendritic inflammatory cells into the central cornea have been observed with the use of benzalkonium chloride-containing eye drops [16,17].

The results from crossover trials where patients were switched from preserved to non-preserved preparations consistently show improvement in reported symptoms and signs of ocular surface disease [18-20]. The only review comparing preserved to non-preserved lubricants evaluated four studies and could not find a significant difference in symptoms and signs of ocular surface disease between groups [21]. However, in three of the four trials Polyquad or Chlorobutanol were used as preservative, rather than benzalkonium chloride. So-called "soft" or "disappearing/vanishing" preservatives such as Polyquad®, sodium perborate, Purite® or SofZia® are known to cause significantly lower cytotoxic effects to the ocular surface than benzalkonium chloride [8,14]. However, their possible effects on the tear film and symptoms have not been fully investigated.

2.1.1.2. pH, tonicity of topical formulations. Only a few brands of topical eye drops disclose the chemical properties of their products, such as pH and tonicity. These may impact the tear film and influence local tolerance on instillation. Hypotonic sodium hyaluronate eye drops are more effective than isotonic drops in improving corneal staining, increasing goblet cell count and decreasing inflammation [22,23].

2.1.1.3. Excipients included in topical formulations. Other common excipients in ophthalmic formulations such as surfactants, co-solubilizers, and preservative aids [24] could also contribute to adverse effects [3]. To the authors' knowledge, there are no specific studies evaluating the adverse effects of these ingredients.

2.1.2. Categories of topical elective medications

2.1.2.1. Artificial tears, gels and ointments. A systematic review of published trials in the management of dry eye disease revealed 49 controlled trials involving 5189 patients [25]. The most frequent category of drugs studied were artificial tears. Although 116 studies were completed according to clinical trial registries, only 15.5% of them were published [25]. This reporting bias clearly demonstrates the difficulty in objectively evaluating efficacy and safety of topical lubricants.

Artificial tears are used to supplement a patient's natural tears and increase eye lubrication by mimicking the tear film. Besides being considered the mainstay treatment option for dry eye disease, they are also used to dampen ocular redness, to provide moisture to contact lenses, to wash out allergens in allergic conjunctivitis, as part of the postsurgical treatment algorithm, and in eye examinations to obtain a regular optical surface on the cornea [25].

Preparations can contain a variety of components, commonly including, but not limited to, polyvinyl alcohol, carboxymethyl cellulose, hydroxypropyl methylcellulose, hydroxypropyl cellulose, hydroxypropyl-guar and hyaluronic acid [25]. According to two meta-analyses, the literature indicates that most over-the-counter artificial tears may have similar efficacies [26,27]. However, a meta-analysis published in 2021 showed a superiority of hyaluronic acid containing artificial tears compared to non-hyaluronic acid eye drops [28].

The most common side effect of artificial tears is transiently blurred vision [26]. Minor burning, stinging or irritation, foreign body sensation and hyperemia may occur. Change in taste after the instillation of the drop has been observed. Topical and/or systemic allergic reactions have also been reported, especially with carbomer preparations [26].

In lipid-containing lubricants, a burning sensation on initial application has been reported to occur in 23.8% of patients in one study [29].

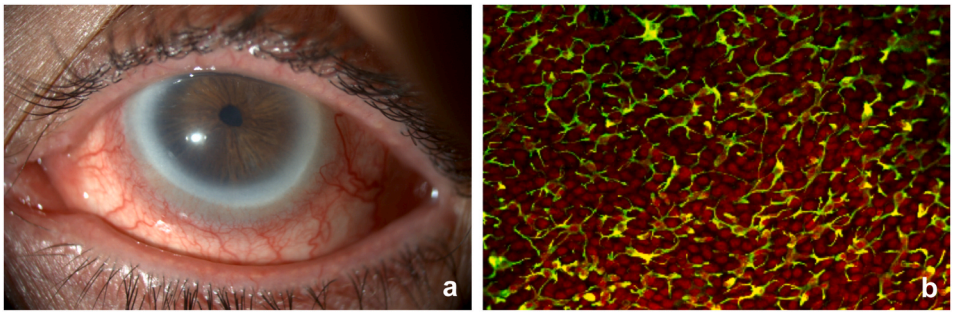

Fig. 1. a) Slit lamp photo of ocular surface inflammation caused by a preserved anti-glaucomatous topical medication. b) Immunofluorescence image of the conjunctiva from a patient using preserved anti-glaucomatous topical medication showing a high number of dendritic cells (in green). Courtesy: Christophe Baudouin, MD, PhD.

Another study observed blurred vision or grittiness in three (11.1%) of 27 participants using castor oil-containing eye drops [30]. Blurring or grittiness lasting 2.5 min after instillation of a castor oil emulsion has been reported [31]. Conversely, no ocular adverse events related to treatment with a carbomer-based lipid-containing gel were seen in a study [32]. Other studies on lipid-based tear supplements do not comment on symptoms and side effects [33,34].

Mucin secretagogues such as diquafasol 3%, a P2Y2 receptor agonist, or rebamipide, a quinolone derivative, are approved in some countries to treat dry eye disease. Burning and stinging on installation as well as mild eye irritation, discharge and itching have been reported in 12.2% of a study population during the use of diquafosol [35]. With rebamipide, eye irritation, nasopharyngitis and especially dysgeusia have been frequently observed, but were generally mild [36,37].

2.1.2.2. Complementary and alternative medicines. Natural products have been used long before the introduction of modern drug therapies and are still in use worldwide as topical ocular preparations.

2.1.2.2.1. Honey eye drops/gel. Honey has been used for millennia as a natural health remedy due to its antimicrobial and wound-healing properties [38]. The most widely known medicinal honey is Manuka honey, and two standardized *Leptospermum* spp. antibacterial medical honey products have received regulatory approval as adjunctive therapy for dry eye disease-associated meibomian gland dysfunction in Australia and Europe [39,40]. These honey products are commercially available as an ophthalmic gel (98% Manuka honey, non-preserved) or as eye drops (16% Manuka honey, non-benzalkonium chloride preserved), are low cost, over-the-counter and sterile. Recipes to produce home-made honey eye drops are also available online [41]. However, such preparations may pose a hazard to the eye as microbial contamination, or the presence of potentially toxic excipients cannot be ruled out [42,43].

Commercially available honey eye drops or gels have been reported to significantly improve ocular surface staining, meibomian gland expressibility and bacterial colony counts, whilst reducing the need for lubricants in patients with meibomian gland dysfunction [39]. Adverse effects noted in a study were temporary redness and stinging [39]. Additionally, protracted conjunctival inflammation and late-stage reactions are possible with Manuka honey ophthalmic products [39]. These products are not suitable for people with allergies to bee stings or bee products, food gums, benzoate preservatives, and are not recommended for children under the age of 12 years [44].

2.1.2.2.2. Aloe vera. Aloe vera is a plant of the *Liliaceae* family that has been used as an herbal remedy since ancient times. It is thought to facilitate wound-healing through the regulation of proteases, especially matrix metalloproteinases, and has been shown to possess antibacterial, antifungal and antiviral properties *in vitro* [45]. In corneal epithelial cell cultures, diluted Aloe accelerated epithelial wound healing [46], reduced nitric oxide production and decreased proinflammatory cytokines such as interleukin (IL)-1b, IL-6, tumor necrosis factor (TNF)-α and IL-10 [47]. In an alkali-burn rabbit model, Aloe vera treatment also promoted epithelial healing and prevented the loss of keratocytes. However, the inflammatory response in the corneal stroma was significantly higher with use of Aloe vera to controls [48].

The Aloe plant contains various polysaccharides and phenolic chemicals, notably anthraquinones. Ingestion of Aloe preparations is associated with diarrhea, hypokalemia, pseudomelanosis coli, kidney failure, as well as phototoxicity and hypersensitive reactions [49]. Recently, Aloe vera whole leaf extract showed clear evidence of carcinogenic activity in rats and was classified by the International Agency for Research on Cancer as a possible human carcinogen (Group 2B) [49].

Aloe vera ocular preparations are marketed for allergic eye disease, dry eye disease symptoms, and following contact lens overwear [50]. Aloe vera eye drops are produced inconsistently using different extraction methods and they may contain different concentrations of aloin A and aloe emodin as well as other chemicals. Recipes to produce a home-made eye gel from an Aloe vera leaf are accessible on the internet. No controlled trials to support the ophthalmic use of Aloe vera are available [45]. Adverse effects reported online include ocular allergies, especially in people allergic to latex (which is part of the plant's skin), ocular redness, irritation and burning sensation on application [51]. As described below, Aloe vera is also used in formulas for periocular application (1.2.2.1. Eyelid hygiene).

2.1.2.3. Anti-allergic therapy. Antihistamines and mast cell stabilizers show good treatment effects in ocular allergy compared to placebo [52]. They are generally safe and well tolerated [53]. In studies evaluating anti-allergic topical therapy, adverse effects were usually included among the secondary outcomes. Therefore, only a few studies are powered to provide reliable evidence about the safety of drugs under investigation [54].

2.1.2.3.1. Antihistamines. The pharmacological effects of antihistamines are based on their ability to block histamine H1 receptors. H1 receptors are activated by histamine, which has many actions. Histamine mediates the tissue response to injury (for example mechanical, thermal or infection damage) [55]. It is also a mediator of gastric acid secretion and may serve as a neurotransmitter. With respect to conjunctivitis, the action of antihistamines is to antagonize the vasoconstrictor, and, to a lesser extent, the vasodilator effects of histamine [55].

Antihistamines are known for their rapid onset symptom relief in allergic conjunctivitis [56]. The antihistamines azelastine hydrochloride, emedastine, antazoline phosphate and alcaftadine did not cause any major side effects in clinical studies [52]. However, pharmacological data sheets discuss ocular irritation and dysgeusia as side effects for azelastine and emedastine. Furthermore, ocular burning and stinging, itching, dry eye, epiphora as well as visual disturbances are acknowledged side effects of emedastine [56]. Antazoline phosphate eye drops are typically manufactured in combination with tetryzoline. Thus, the reported side effects may be partly caused by the topical alpha-adrenergic receptor agonist tetryzoline and include conjunctival irritation and hyperemia, burning, dry eye and visual disturbances (pharmacological data sheet for antazoline and tetryzoline) [3].

In a meta-analysis of five randomized clinical trials of 990 patients with allergic rhinitis, the use of oral antihistamines used as an adjuvant to intranasal corticosteroid resulted in comparable relief of ocular symptoms to intranasal corticosteroid alone [57]. However, systemic antihistamines can decrease aqueous and mucin production from the lacrimal gland and goblet cells respectively, and induce vasoconstriction of lacrimal gland blood vessels. This ultimately leads to decreased tear production and dry eye disease manifestations [58]. Topical antihistamines are more favorable than systemic antihistamines in these cases as they contribute less to dry eye disease. The effects of oral antihistamines are usually reversible and correctable with prompt halting of their use. In a recent study of allergic conjunctivitis, topical cetirizine caused ocular side effects in 22.9% of study patients, however this was not greater than that of the vehicle group (25.1%) [59]. The most common ocular problems following topical cetirizine were conjunctival hyperemia and instillation site pain. Blurred vision, dry eye and eye discharge were rare and occurred with topical cetirizine and the vehicle placebo [59].

2.1.2.3.2. Mast cell stabilizers. Mast cell stabilizers inhibit degranulation by interrupting the normal chain of intracellular signals resulting from the cross-linking and activation of the immunoglobulin E receptor by an allergen [60]. By inhibiting mast cell degranulation, they inhibit release of histamine and the other preformed mediators, and the arachidonic acid cascade [61].

Mast cell stabilizers require multiple daily doses and have a delayed onset of action [56]. Stinging on instillation, dysgeusia, itching, burning, foreign body sensation, conjunctival chemosis and dry eye have been reported after the use of the mast cell stabilizers sodium cromoglycate

and nedocromil sodium [52,55]. For the mast cell stabilizers lodoxamide tromethamine and levocabastine, there were no reported adverse effects in clinical studies [52,55]. However, ocular irritation, eye congestion, eyelid inflammation and blurred vision are reported as side effects in pharmacological data sheets for levocabastine [62]. Data sheets for lodoxamide mention ocular irritation, dry eye, ocular itching, foreign body sensation, epiphora and conjunctival hyperemia, as well as disturbed vision as undesirable effects [63].

2.1.2.3.3. Dual-acting anti-allergy drugs. Dual-acting anti-allergy drugs provide a combined mast cell stabilizer and antihistaminic function (selective H1 receptor antagonist), thus providing improved symptom control than single-action drugs [56,64]. Mild stinging and blurred vision may be seen with the use of dual-acting anti-allergy drugs [55,64]. Topical epinastine, ketotifen and olopatadine did not induce short-term drying and did not worsen signs and symptoms of mild-to-moderate dry eye disease in clinical studies [65-67].

In a randomized, placebo-controlled, double-masked study of olopatadine 0.2% eye drops in allergic conjunctivitis, only three ocular adverse events (ocular discomfort, ocular dryness and ocular fatigue) were reported with the olopatadine 0.2% therapy [68]. No patient was discontinued from the study because of a treatment-related adverse event. A prospective study compared patient preference between olopatadine and ketotifen in 100 patients with allergic conjunctivitis [69] and found that a significant percentage of patients selected olopatadine as more comfortable (81%) than ketotifen (18%) ($p < 0.0001$) [61]. Another study [70] that compared ketotifen and levocabastine to placebo in seasonal allergic conjunctivitis observed that all treatments were generally well tolerated; the type and frequency of adverse events were similar across treatment groups, and the majority of adverse events (76.7%) were of mild or moderate severity. Rare side effects included blurred vision, burning and stinging with instillation and thereafter, eye pain, itching, dry eye and photophobia [70]. However, the dropout rate due to adverse events was lower in the ketotifen group (4.7%; $n = 8$) compared with either placebo (8.7%; $n = 15$) or levocabastine (8.6%; $n = 15$) [70].

2.1.2.3.4. Non-steroidal anti-inflammatory drugs. The primary purpose of non-steroidal anti-inflammatories is to counteract ocular inflammation by the reduction of prostaglandins produced by cyclooxygenases within target ocular tissues [71]. Ketorolac tromethamine has been shown to reduce mast cell degranulation as demonstrated by significantly decreased tryptase tear levels, and reduced the numbers of inflammatory cells such as eosinophils, neutrophils and lymphocytes in tears [72]. In addition, non-steroidal anti-inflammatories are steroid-sparing. In allergic conjunctivitis, non-steroidal anti-inflammatories are effective in reducing conjunctival injection and itching but do not effect conjunctival chemosis, mucus production, eyelid swelling or corneal complications [73].

Non-steroidal anti-inflammatories are rarely used in the treatment of ocular allergy due to their local side effects on instillation [56,73]. These include conjunctival hyperemia, burning, stinging due to inherent properties of the free compounds which alone can adversely impact the unprotected mucous membrane [71]. Further local effects include contact dermatitis, which may appear weeks to months following the use of topical non-steroidal anti-inflammatories due to delayed hypersensitivity reactions.

A local anesthetic effect has been demonstrated by the non-steroidal anti-inflammatory diclofenac due to selective binding to inactive sodium channels within the corneal epithelium [74]. The topical non-steroidal anti-inflammatories diclofenac 0.1%, indomethacin 0.1%, flurbiprofen 0.03% and ketorolac 0.5% compared to placebo and the anesthetic oxybuprocaine 0.4% caused no epithelial damage. All medications caused a reported burning sensation. Diclofenac, unlike the other tested non-steroidal anti-inflammatories, produced a significant decrease in corneal sensitivity for at least 1 h [75]. Another study reported diclofenac-associated superficial punctate keratitis and corneal epithelial defects [76].

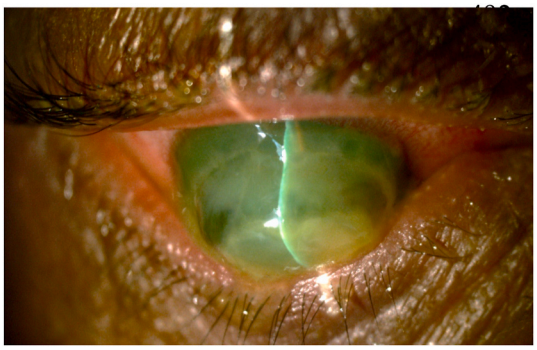

Fig. 2. Slit lamp photo of corneal melting developed in the first week post-operatively after corneal crosslinking and abusive use of topical non-steroidal anti-inflammatory eyedrops (ketorolac 0.5% q2hs). Reprinted from Exp Eye Res, 203, Gomes JAP & Milhomens Filho JAP, Iatrogenic corneal diseases or conditions. Article number 108376. Copyright (2021), with permission from Elsevier.

Corneal melt is the most serious side effect of topical non-steroidal anti-inflammatories [73,77] (Fig. 2). Corneal melting can be observed with any of the approved ocular non-steroidal anti-inflammatories and occurs usually in patients whose cornea is compromised by ocular surgery, diabetes or autoimmune disease. Its true incidence remains unknown, but non-steroidal anti-inflammatory dose and duration of treatment may be important [77]. The events include a corneal epithelial defect caused by a direct apoptotic effect of the non-steroidal anti-inflammatory on corneal epithelial cells, corneal hypoesthesia, decreased substance P content of human tears, reduced prostaglandin E2 levels, increased cyclooxygenase-2 activity, leukocyte infiltration and matrix metalloproteinase-facilitated desquamation (epithelial stage) and degradation of stromal collagen by activated matrix metalloproteinases (stromal phase) [71,77]. Corneal hypoxia seems to be a risk factor for non-steroidal anti-inflammatory-induced injury [71].

2.1.2.4. Topical alpha-adrenergic receptor agonists. In allergy, topical alpha-adrenergic agonists are often used as first line treatment due to their over-the-counter availability. They improve hyperemia, but have little to no effect on itching, and have a short duration of action [56]. More often, topical over-the-counter ocular decongestants are used for non-specific minor eye irritation and redness with no apparent pathology. First generation ocular topical anticongestants include phenylephrine (a sympathomimetic amine with selective affinity for α1-adrenergic receptors) and tetrahydrozoline (an imidazole derivative and selective α1-adrenergic receptor agonist). Second generation alpha-adrenergic receptor agonists are naphazoline (an imidazole derivative and mixed α1/α2 receptor agonist with a binding affinity of 2:1 for α2:α1 receptors) and oxymetazoline (an imidazole derivative with an affinity of 5:1 for α2:α1 receptors) [78].

Brimonidine tartrate is a third-generation adrenergic receptor agonist with noticeably increased binding affinity for α2 receptors relative to α1 receptors (1000:1) and is the first selective α2-adrenergic receptor agonist approved for treatment of ocular redness. In 1996, it received US Food and Drug Administration approval for lowering intraocular pressure in a concentration of 0.2%, in 2013 as a topical gel 0.33% for facial erythema in rosacea [79], and in 2017 as an ophthalmic solution 0.025% for the reduction of ocular redness. Selective α2 receptor agonists are thought to have their primary action on conjunctival venules [78]. It was shown to significantly reduce ocular redness for up

to 8 h [80,81].

Ocular decongestants may cause decreased visual acuity, pain at the site of instillation, burning, irritation, mild transient stinging, nasal discomfort, and rhinitis in some patients [80-82]. These side effects led to discontinuation of brimonidine 0.025% in 7.8% of patients in one study [82]. Common side effects of sustained use of mixed α1/α2 adrenergic agonists include rebound hyperemia, chronic toxic follicular conjunctivitis, (eczematoid) blepharoconjunctivitis, and tachyphylaxis [52,56,78,83]. Tachyphylaxis (the acute sudden decrease in response to a drug after its administration) is thought to be mainly due to a tolerance-related reduction of the α1 adrenergic response [84], and has been documented after repeated daily use of tetrahydrozoline over as few as 5–10 days, risking its overuse [85]. Tachyphylaxis was not observed with brimonidine 0.025% over the one-month treatment period studied [81].

Rebound redness was observed upon discontinuation of naphazoline or tetrahydrozoline after days, weeks or months of continuous use [86]. In 1988, the US Food and Drug Administration decided to include the warning for all over-the-counter products containing vasoconstrictors in use at that time: “Overuse of this product increases redness of the eye”. A “minimal rebound redness” was observed following discontinuation of brimonidine 0.025% [80,81].

Allergy rates in glaucoma patients who received brimonidine 0.2% were 17.6% over 18 months [87]. A delayed hypersensitivity reaction to brimonidine tartrate eye drops resembling a follicular viral conjunctivitis may occur many months after initiation and was reported to cause discontinuation of the drug in up to 15% of patients [88]. Individual patients treated with brimonidine 0.025% reported possible allergic side effects in short-term studies [81]. Long-term evaluations are necessary to fully understand the risk of allergic reactions with low dose brimonidine.

More evidence is needed to provide additional information regarding long-term efficacy and a complete safety profile of brimonidine 0.025%, particularly for adverse events that infrequently occur or long-term side effects. Although brimonidine 0.025% does not cause tachyphylaxis and rebound hyperemia to the same extent as α1 adrenergic receptor agonists, a potential for abuse and overuse is present and has been communicated by many US ophthalmologists. Additional concern exists as brimonidine 0.025% contains the epithelial toxic preservative benzalkonium chloride known to cause damage to the ocular surface epithelium and the tear film (see section 1.1.1.1) and thus has the potential to induce ocular surface damage in otherwise healthy eyes [89].

2.1.2.5. Eyewashes. Eyewashes are used in allergic conjunctivitis, contact lens wear and dry eye disease [90-92]. Historically, eyewash solutions were preserved. The use of these solutions has been associated with corneal epitheliopathy, damage to the mucin layer of the tear film, dry eye and infection [92]. In eyewash solutions lacking benzalkonium chloride, corneal epithelial disorders and changes to the mucin layer were not observed [92]. In a randomized trial in healthy individuals, an eyewash solution containing dipotassium glycyrrhizinate, chlorpheniramine maleate, taurine, pyridoxine hydrochloride, cyanocobalamin, chondroitin sulfate and other excipients was used up to six times/day for one month and for up to 30 s per administration [92]. The eyewash group reported a significant decrease in Dry Eye-Related Quality of Life Score compared to the non-wash group. No significant changes were observed in tear breakup time, ocular staining scores, or expression of mucin 5AC and mucin 16 in conjunctival impression cytology samples compared to controls [92]. Whether longer term use or overuse of eyewashes causes ocular surface damage through tear film depletion is currently unknown.

2.2. Topical periocular products

A wide range of products can be used on the periocular area, which for the purpose of the *TFOS Lifestyle Workshop* has been defined as the area around the eyeball, but within the orbital region [93]. These may include products for eyelid hygiene, eyelid warm compresses, sunscreens, and creams or ointments for eyelid inflammation, acne or rosacea. Some may be recommended by healthcare practitioners, while others are chosen by the patient with no formal consultation. Regardless, products used peri-ocularly have the potential to interact with the ocular surface facilitated by the action of the blink or simply due to the proximity of the relevant anatomical structures. This section will describe commonly used periocular products and evidence of their impact, if any, on the ocular surface. This TFOS workshop mostly concentrated on products used to treat diseases or conditions (such as blepharitis, meibomian gland dysfunction and infections). Information on the use of cosmetics and their excipients on the ocular surface is given in the *TFOS Lifestyle: Impact of cosmetics on the ocular surface* report [94].

A retrospective analysis of ocular exposures to cosmetic and personal care products reported between 2000 and 2018 to the US National Poison Center, revealed that the highest prevalence of ocular exposures was in young children <6 years old (51.6%), followed by adults >20 years old (28.9%) and older children 6–19 years old (19.5%). No sex difference was noted for young children, but with increasing age females were more often exposed, reaching a ratio of 3.9:1 for adults [95]. The majority (90.6%) of exposures linked to cosmetic and personal care products occurred in the home with minimal effects (53.9%) and were managed principally on-site (86.3% for children and 61.7% for adults) [95]. Exposure to these products can induce a variety of reactions including ocular irritation or pain, red eye, conjunctivitis, corneal abrasion, tearing, and blurred vision [95].

2.2.1. Mechanisms of ocular surface damage

Many of the products applied to the periocular area contain a combination of chemical, organic or synthetic compounds, preservatives, buffers, surfactants, fragrances, dyes and other excipients [96,97]. These products can affect the eyelids, eyelid margins, tear film and ocular surface epithelium. Eyelid microbiota, obstruction of eyelid margin gland orifices, tear film pH, tear osmolarity, tear stability, ocular surface integrity can be altered. This may lead to temporary and local irritation, allergic contact reactions, and dry eye disease [98] (Fig. 3).

In a study examining 88 dermatology patients presenting with periorbital dermatitis, the predominant cause was allergic contact dermatitis [98]. Shampoos have historically been advocated as a cost-effective alternative for eyelid hygiene, however a study on 179 shampoos found that their fragrance and cocamidopropyl betaine were common allergens associated with eyelid dermatitis [99-101]. Between 1.7 and 4.1% of the general population test positive on patch testing for fragrances [101-103].

This raises the question of whether periocular products should be fragrant, dye and preservative-free to limit potential sensitivity. More studies are needed to identify potential allergens in products applied to the periocular region and how these affect the eye.

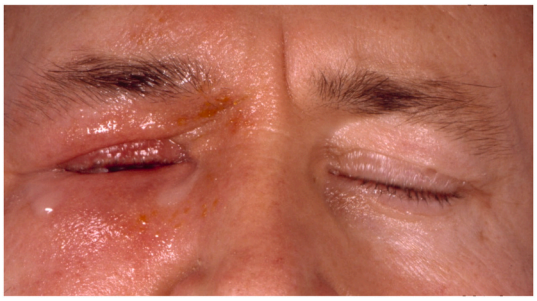

Fig. 3. Clinical case of allergic contact dermatitis and conjunctivitis following topical use of antibiotic eyedrops. Courtesy: Elisabeth M. Messmer, MD.

2.2.2. Categories

2.2.2.1. Eyelid hygiene. Eyelid hygiene is recommended as primary or adjunct therapy for the management of blepharitis, dry eye disease, meibomian gland dysfunction and for preoperative care [104-107]. The therapeutic objective of eyelid hygiene is to reduce the bioburden along the lid margins to help curb inflammatory responses [108]. Although the pathophysiology of blepharitis is not yet completely understood, root causes include microbial (bacterial, fungal, viral or parasitic) infections, immunological conditions (dermatitis, Stevens-Johnson syndrome, graft versus host disease), eyelid tumors, trauma (chemical, thermal, radiation) and toxins (medicamentosa) [108]. The microbiome in anterior blepharitis has been found to be similar to that in mixed blepharitis, but different from that in posterior blepharitis [109]. Studies have highlighted the antimicrobial properties of several eyelid hygiene products including those containing coconut oil [110], 4-terpineol, hypochlorous acid, extracts from *Abelmoschus esculentus* (okra) [111], Manuka honey and Aloe vera [112].

Numerous commercial products are available for the purposes of eyelid hygiene. However, there is a paucity of clinical studies supporting their efficacy. Lid hygiene products are formulated for a variety of delivery systems including pre-moistened towelettes, foams, gels, sprays or suspensions to meet the needs and preferences of the patient [113].

Eyelid scrubs using diluted baby shampoo onto a cotton pad or swab have been the most widely recommended at-home eyelid hygiene therapy, probably due to low cost, accessibility and convenience for patients [107,108]. However when baby shampoo was used as an eyelid scrub it did not show improvement in symptoms and did not reduce matrix metalloproteinase-9 production [107,108]. Furthermore, it can reduce ocular surface mucin expression, important for tear film homeostasis, during a 28-day comparison against a dedicated eyelid hygiene product [114]. When compared to eyelid hygiene products with antimicrobials, such as tea tree oil or 4-terpineol, baby shampoo underperforms with respect to symptoms, assessed with the Blepharitis Symptom questionnaire, and ocular surface staining [115] after a treatment of 8 weeks [116,117]. This difference remains even following a discontinuation period. As the underlying causes of blepharitis continue to be unraveled, baby shampoo needs further exploration to assess its benefits relative to its risks.

2.2.2.1.1. Tea-tree oil and derivatives. Tea tree oil, from the *Melaleuca alternifolia* tree, is well documented for its antimicrobial and anti-inflammatory properties [118]. Eyelid hygiene products containing tea tree oil reduce mite counts in Demodex blepharitis [119,120]. A systematic review and meta-analysis included 19 studies on the efficacy of different topical and systemic treatments for Demodex, including topical application of tea tree oil [121]. All treatments were found to be effective at reducing mite counts with no influence of age and gender. Thirteen studies were included for assessment of reduction of symptoms revealing an overall effect size of 0.76 (0.59–0.90), with no influence of age and gender [121]. However, most studies were limited to short-term use and long-term studies are needed [122]. Skin patch tests have shown that tea tree oil is well tolerated when used below 10% but can be irritating at higher concentrations (100%), although additional work is required to determine the extent of contact dermatitis or allergic reactions [123-125]. Limited randomized clinical studies have investigated the effects of tea tree oil-based eyelid hygiene products on the ocular surface. Some have reported no adverse effects [120,126-129], while others reported short-lived ocular discomfort (a few minutes), with the exception of 50% tea tree oil, which caused the time to open the eyes comfortably to be increased and reduced tear film stability [130]. It is recommended to counsel patients on the potential short-term discomfort of certain eyelid hygiene products, such as those with tea tree oil, especially when initiating treatment for Demodex blepharitis [130,131].

Terpinen-4-ol is the most active ingredient in tea tree oil and possesses the highest anti-demodectic activity [132-134]. Demodex mite counts were significantly reduced after two months use of eyelid scrubs containing terpinen-4-ol combined with microblepharoexfoliation versus control, but no differences ($p > 0.05$) in other ocular parameters (Ocular Surface Disease Index score, tear osmolarity, matrix metalloproteinase-9 levels, corneal and conjunctival staining, gland expression) were found [135]. Terpinen-4-ol, even at extremely low concentrations, is toxic to meibomian gland epithelial cells *in vitro*, affecting their morphology, signaling ability, survival and differentiation, as quickly as 15 min after exposure [136]. Further studies are warranted to explore short- and long-term effects of terpinen-4-ol on meibomian gland function *in vivo*.

2.2.2.1.2. Other ingredients. Linalool is a colorless terpene alcohol derived from flowers and spice plants (such as Lavender, rosewood, sage, bergamot, jasmine, geranium) with multiple commercial applications, such as personal care products and household products [137]. Linalool can readily oxidized when exposed to air and can be an allergen [138,139]. One of the primary benefits of linalool is its antimicrobial and anti-inflammatory properties [133,137,140]. During 28 days of use of eyelid scrubs containing linalool compared to baby shampoo there was improvement in symptoms and several ocular signs (lipid layer, matrix metalloproteinase-9 expression, inferior lid wiper epitheliopathy, cylindrical dandruff) with no reported adverse effects [114]. Further testing is needed to investigate if linalool negatively affects the ocular or periocular structures.

Hypochlorous acid is naturally produced during the human's immune response and has potent antimicrobial properties when applied in the management of burns, wound care and skin conditions [141]. As an eyelid cleanser, hypochlorous acid can significantly reduce the bacterial load on the periocular skin without altering the diversity of the bacterial species, which has been advocated as an advantage over other eyelid hygiene products [142,143]. Different concentrations of hypochlorous acid exist for eyelid hygiene, varying from 0.01 to 0.20%, all available as a spray. One study investigated the comfort of a 0.01% hypochlorous acid-containing eyelid hygiene product, which seemed to be well tolerated and helped reduce the signs and symptoms of blepharitis and Herpes zoster ophthalmicus [144]. Further studies are warranted to investigate tolerability for higher concentrations of hypochlorous acid.

Okra (*Abelmoschus esculentus*), formally known as *Hibiscus esculentus*, is a common vegetable, rich in polysaccharides and other compounds that can be antibacterial and anti-inflammatory [145]. The addition of okra extract in an eyelid wipe formulation was evaluated against a tea tree oil-based product for its anti-demodectic activity [111]. The okra-based product reduced the Demodex mite count similarly to tea tree oil at 1 and 3 months of treatment but with significantly reduced corneal fluorescein staining at both of those time points relative to the tea tree oil group. The authors did not report adverse events with the okra-based product, and it seemed to be well tolerated, whereas 4/25 (16%) of participants in the tea tree oil group reported mild-to-moderate irritation. This may be an alternative for the management of Demodex blepharitis for those with ocular sensitivities. Further studies are needed to investigate any effects on the ocular and periocular area.

Aloe vera is a common medicinal plant known for its spectrum of biological and pharmacological activities [146,147]. It has also been used as an elective topical medication (part 1.1.2.2.2) *In vitro,* an eyelid wipe containing Aloe vera had robust bactericidal and fungicidal activity [112], which may prove to be useful in cases of microbial overgrowth contributing to blepharitis or as prophylaxis prior to ocular surgery. In a randomized controlled study with patients with meibomian gland dysfunction, eyelid wipes containing a combination of Aloe, tea tree oil and hyaluronic acid used twice daily over 4 weeks improved the signs of meibomian gland dysfunction compared to use of wet and warm gauze [148].

Capryloyl glycine, a lipid amino acid derivative of glycine, can restrict the growth of bacteria and control excessive secretion of sebum, suggesting a potential application in the management of skin conditions

and blepharitis [149-151]. Two studies have investigated the benefits of eyelid hygiene products containing capryloyl glycine at improving symptoms, comfort and eyelid margin appearance in patients with blepharitis and meibomian gland dysfunction when used twice a day for 3 weeks [150,151]. These studies found no adverse events related to the capryloyl glycine containing wipes. Another study reported that a capryloyl glycine product significantly reduced the microbial load on the eyelids after 3 or 5 days of use, with less reduction to the conjunctival microbiota [106]. The reduction was comparable to that of a topical antibiotic application, suggesting that eyelid wipes containing capryloyl glycine may be an alternative for prophylactic use prior to ocular surgery. The study did not report adverse events.

Other ingredients that may be found in eyelid hygiene products include sodium hyaluronate, extracts of *Calendula officinalis, Euphrasia officinalis, Centella asiatica* and *Iris florentina*, and argan oil. There was no information available in the literature on the impact these products have on the ocular surface; however, several have been investigated for their benefits in ophthalmology and dermatology [152-154].

Overall, there is a paucity of studies on the impact of eyelid hygiene products on the ocular surface and their effects on patients' lifestyles, suggesting an opportunity for future research [130,155-157]. Additional challenges in studying eyelid hygiene products may be that not all ingredients are divulged, such as perfumes or other inactive ingredients. This may be due to geographic legislative differences in reporting ingredients and labelling of pharmaceutical versus over-the-counter products. There continues to be no universally accepted guidelines or peer-reviewed evidence for cleaning eyelids, although some have been proposed [158] suggesting that this is an area worthy of study.

2.2.2.2. Eyelid warm compresses. Eyelid warm compresses are globally part of the first line recommendations in the management of evaporative dry eye and meibomian gland dysfunction [107,159]. The therapeutic objective is to soften the meibum in the glands so that it can be expressed more easily during a blink. The melting point of normal meibum ranges between 32 and 40 °C, and it is typically liquid at body temperature, whereas it melts at 3 °C higher in abnormal secretions [160] meaning it may be solid in the meibomian glands, at body temperature. Warm compresses have been shown to improve symptoms of dry eye disease, increase tear film lipid layer thickness, reduce tear evaporation, improve tear film stability, improve meibomian gland obstruction, improve contact lens comfort and reduce partial blink rates [161-172]. Unconventional warm compresses, such as the use of boiled eggs [173], bags of rice [174], hot potatoes, heated wooden spoons and others, have been reported by patients and in online forums but only two have been evaluated in clinical trials. The heat and pressure from warm compresses coupled with eyelid massage can result in changes in the Fisher-Schweitzer reflex contributing to transient visual blur and corneal distortion [175].

A facecloth, warmed with tap water and placed on the closed eyelids for several minutes, has been traditionally recommended due to its convenience, accessibility and low cost for patients [107]. However, a temperature of 40–42.5 °C is needed to adequately soften meibum, but facecloths, heated once, rapidly dissipate heat within 1 min and fail to maintain the therapeutic temperature [176,177]. Bundling several facecloths and heating them in a microwave increases the heat retention and can be an alternative for meibomian gland dysfunction therapy, although the method is more labor intensive [174].

Industry has developed numerous warm eyelid compresses including masks heated electrically, those heated with a microwave or those that are self-heating [161,162,166,178-180]. A few cases of skin burns with warm compresses overheated in the microwave have been reported, hence patient education cannot be overstated [107]. In controlled studies, most eyelid warming compresses provide a stable heat retention over 10–15 min with temperature ranges of 35–45 °C [163,164,166,167,174,177,180-182]. However, there are few comparative studies on the different warming masks [113,174,182]. There is no consensus or evidence as to which type of heat delivery is more efficacious or preferred by patients. Eye masks may or may not be washable or have an antimicrobial cover, rendering them prone to contamination from cosmetics and after repeated use. However, heating for 30 s in a 800W microwave oven did significantly reduce the load of applied *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Streptococcus pyogenes* on flaxseed-filled masks, but not to sterility [165,174]. It is recommended to wash hands, remove make-up and sanitize (60 s in an 800W microwave) prior to using reusable eye masks and allow them to cool prior to applying for treatment.

Further studies are warranted to investigate the heat retention, the long-term clinical efficacy, and the side effects of warm compresses; as well as the maintenance, storage and disinfection methods for reusable eye masks.

2.2.2.3. Sunscreens. Sunscreens are used to protect the skin from ultraviolet A and B light exposure. However, variability exists in claims made regarding the breadth of protection for each sunscreen [183]. The US Food and Drug Administration provided a report in June 2011 that addressed the testing and labelling of sunscreen products [184]. Sunscreen may be considered in some markets as a cosmetic while in other markets as a drug, rendering the regulation of ingredients and the reporting of potential side effects inconsistent [185]. Sunscreens and suntan products accounted for 11.2% of reported ocular exposures to cosmetic and personal care products in all age groups, with young children accounting for the most exposures (77.9%) [95].

Numerous ingredients can be found in sunscreen products, with some considered safer than others. Nanoparticles of titanium dioxide and zinc oxide, commonly found in sunscreen products, have been found to be cytotoxic to corneal cells in animal models [186-189]. Titanium dioxide nanoparticle exposure affected the corneas of experimental dry eye rats more than normal controls, suggesting that the ocular surface in dry eye disease is more vulnerable to the effects of these particles [190]. A water-in-oil emulsion sunscreen formulation caused mild irritation, signs of inflammation (bulbar and tarsal conjunctival irritation) for the first 5 min after exposure and these resolved within 1 h [191]. Corneal superficial punctate staining, lacrimation and tear breakup time remained unchanged with application of the test formulation. Other ingredients, such as poly(ε-caprolactone) nano capsules, seem promising with low cytotoxicity and irritation profiles for the ocular surface [192]. More studies are warranted to explore the effects of titanium dioxide, zinc oxide and other ingredients on the ocular and periocular surface in humans.

2.2.2.4. Corticosteroids. Topical ocular corticosteroids in the form of eye drops or ointment are used to curb signs and symptoms of a variety of inflammatory eye conditions [193-195]. Together with systemic corticosteroids, they have well-documented ocular adverse effects and have been associated with glaucoma and cataract [196,197]. Topical corticosteroids (i.e. hydrocortisone) used for inflammatory conditions of the periocular area (blepharodermatitis) have been reported to cause elevated intraocular pressures and reduced visual function [198]. Other ocular effects can include production of allergies (to the corticosteroid or preservatives), decreased wound healing and increased susceptibility to infections [199]. Topical corticosteroids can be combined with systemic or other topical medication to enhance their effectiveness in the treatment of periocular dermatitis [200]. Transdermal absorption depends on the potency of the steroid, physical status of the skin, frequency of application and duration of treatment. Extreme caution is needed when prescribing corticosteroids in infants due to the risk of local and systemic absorption [201]. Additionally, the skin of the eyelid is amongst the thinnest in the body [202,203], increasing its potential for transdermal absorption.

A retrospective analysis, spanning 10 years, of outpatients with a

diagnosis of atopic dermatitis or eczema treated with periocular steroid ointment, revealed no significant change in intraocular pressure for the entire cohort ($n = 31$, $p > 0.05$) [204]. However, of those treated with a baseline intraocular pressure of >14 mmHg, an increase of +0.73 mmHg/year ($p = 0.032$) was noted [204]. Clinicians are encouraged to monitor intraocular pressure when prescribing periocular corticosteroids in patients at greatest risk of steroid response.

Corticosteroids can also trigger hypersensitivity reactions such as allergic contact dermatitis [205]. A 2-year Italian study patch tested 12682 consecutive patients for sensitivity to hydrocortisone, which is a low-dose corticosteroid, and the authors found a low prevalence (0.08%) of allergy [206]. Considering that topical hydrocortisone ointment is available over-the-counter in some markets, more studies are warranted to explore its effects on the ocular and periocular surface.

2.2.2.5. Ivermectin. Ivermectin, a synthetic derivative of avermectin, is a broad spectrum antiparasitic used in dermatology (rosacea, head lice), tropical medicine (river fever), ophthalmology (demodicosis) and more recently for Coronavirus disease 2019 (COVID-19) [207-211]. It is an endectocide, acting on both endo- and ecto-parasites by binding to neurotransmitter receptors and causing paralysis [207]. Ivermectin is available orally or in as a topical cream. Adverse effects of systemic ivermectin may include fever, myalgia, nausea, headache, abdominal pain and postural hypotension. Topical ivermectin may cause conjunctivitis, ocular hyperemia, burning sensation and eye irritation [207,208, 212-214].

Ivermectin is used in the management of demodicosis, especially in refractory cases, such as those found in immunocompromised patients [207,215]. Combination therapy of ivermectin with metronidazole has been reported to be more effective than ivermectin alone at reducing mite counts with minimal to no adverse effects [210,216]. A meta-analysis of 19 studies (14 observational and 5 randomized clinical trials) on the efficacy of local versus systemic treatments for Demodex, revealed no difference for mite counts, eradication rate or symptom improvement [121]. Another meta-analysis on the effectiveness of interventions for Demodex, which included 18 studies with 29 interventions in 1195 participants, found that pharmacological interventions were superior to thermal, mechanical or light therapy [217]. Due to the potential of side effects of systemic treatment with ivermectin, local treatment options should be prioritized, especially in early presentations of Demodex.

2.2.2.6. Acne medication. Important therapeutic options for topical treatment of acne vulgaris are alpha hydroxy acid (glycolic acid), beta hydroxy acid (salicylic acid) and retinoids. There have been no reports on effects of topical alpha or beta hydroxy acid specifically on the ocular surface. However, it is well known that systemic retinoid therapy affects the ocular surface (see section 3.2.9).

A trial on 43 patients with mild to moderate acne vulgaris topically treated with a combination of the retinoid isotretinoin and antibiotic erythromycin, found that the combination resulted in significant increases in signs and symptoms of dry eye disease [218]. There was a significant increase in tear osmolarity, a significant worsening of the Ocular Surface Disease Index score, a decrease in fluorescein break-up time and a prevalence of 51% in punctate epitheliopathy after one month of once daily treatment. However, there was no significant change in Schirmer test results, which the authors explained as being compatible with the absence of signs of aqueous deficiency in patients treated with systemic retinoids [219].

Dry eye disease in patients treated with retinoids, whether topical or systemic, seems to be due to decreased meibomian gland function and consequently increased tear film evaporation and osmolarity [220].

3. Systemic medications impact on the ocular surface

Systemic therapies such as anti-inflammatories, immunomodulatory and antimicrobial drugs have been used to treat dry eye disease [221]. However, elective systemic therapies can have deleterious effects on ocular surface health. There are many reports that describe ocular adverse drug events stemming from systemic drugs, but there is a lack of high quality evidence [222]. This section reviews how elective use of systemic medications can negatively impact the ocular surface.

3.1. General mechanisms of systemic drugs in causing ocular surface disease

Elective systemic medications can affect the ocular surface through different mechanisms, including their impact on meibomian glands, lacrimal glands and goblet cells, which may result in dry eye disease [58]. Their effect on the secretory glands of the lacrimal functional unit can result from the direct deposition but also through affecting innervation or regulation of blood vessels that, ultimately, lead to reduced functioning and effectiveness of the target organs [58]. Also, squamous metaplastic changes to the conjunctival epithelium can occur [223]. Some of these medications contribute to amplifying the immune system and increasing inflammation and subsequent inflammatory markers that contribute to the degeneration of ocular surface health [224]. They can lead to reduced sensitivity or increased pain of the ocular surface, leading to exacerbation of dry eye disease signs and symptoms [224].

3.2. Systemic drug categories and types

3.2.1. Corticosteroids and non-steroidal anti-inflammatories

Systemic corticosteroids and non-steroidal anti-inflammatories are widely used to treat diverse systemic inflammatory disorders. Prolonged oral corticosteroid use may have several ophthalmologic side effects, including increased risk of glaucoma or ocular hypertension, as well as posterior subcapsular cataract formation [224-226]. More importantly, extensive use of oral corticosteroids might lead to corticosteroid dependence and rebound of the ocular surface inflammation when tapered, causing conjunctival hyperemia and dry eye disease symptoms [224]. An Australian study of 1174 patients evaluated the presence and severity of dry eye disease symptoms in an interview for administered questionnaire associations [227]. After adjusting variables, one of the factors significantly associated with dry eye disease symptoms was the use of corticosteroids, with an odds ratio of between 1.2 and 1.7 [227]. Interestingly, intranasal corticosteroid use has not been correlated with dry eye disease, despite several case reports that described other ocular side effects such as increased intraocular pressure and cataract in patients taking intranasal steroids [225].

The deleterious effect of non-steroidal anti-inflammatories on the ocular surface has been researched less frequently. Selective cyclooxygenase-2 inhibitors, mainly celecoxib, have been associated with increased conjunctivitis and blurred vision, as evidenced by a retrospective series of a total of 1006 reports collected at the National Registry of Drug-Induced Ocular Side Effects [228].

Hydroxychloroquine can be used in Sjögren syndrome for reduction of arthralgias and fatigue, but also for other conditions as an anti-inflammatory agent. Hydroxychloroquine has been found to be excreted in the tear film and can exacerbate dry eye disease [229]. This might explain why literature lacks strong evidence for the efficacy of this treatment for dry eye disease [230]. A study on 120 patients with Sjögren syndrome showed no clinical benefit of hydroxychloroquine in xerophthalmia [231]. Similarly, in another study its use did not improve tear production, corneal staining, or inflammatory markers after 12-week period [231]. The conflicting evidence regarding its benefits comes from the fact that it is commonly used to treat autoimmune disorders, which may underlie dry eye disease [230].

3.2.2. Antimicrobials

Antimicrobials have been used electively for the treatment of local and systemic infections. Ocular surface damage caused by their elective use has not been extensively studied and no systematic reviews evaluating this association exist in literature. The largest association is when antibiotics are the causative agents of Stevens-Johnson Syndrome. In a large multinational study on drug use and onset of Stevens-Johnson Syndrome, the use of trimethoprim–sulfamethoxazole and other sulfonamide antibiotics, aminopenicillins, quinolones and cephalosporins were significant risk factors for developing Stevens-Johnson Syndrome and potentially severe ocular surface alterations [232]. Another potential complication of oral antibiotic use is risk of antibiotic resistance developing in the microbes causing the infections or resident in the eye [233]. Whilst long term (over 4 years) ocular dosing with azithromycin (a macrolide) for prevention of trachoma can lead to selection of genes involved in macrolide resistance [233], short term (3 months) use of tobramycin (an aminoglycoside) in topical ocular drops was not associated with selection of resistant microbes in the throat, which would have been exposed to potentially sub-inhibitory concentrations of the antibiotic via its draining through the nasolacrimal ducts [234].

Oral macrolides such as azithromycin, and tetracyclines such as doxycycline and minocycline, have been used to treat acne and meibomian gland dysfunction [235]. They also have anti-collagenolytic and anti-inflammatory effects on the ocular surface and have been used in combination with other systemic and topical drugs in the management of different ocular surface diseases [236,237]. In contrast with these benefits, this category of antibiotics has also been shown to cause drug-induced reactions [238] and antibiotic resistance [233]. Although systematic reviews are not widely available regarding this association, case reports have shown Stevens-Johnson Syndrome arising from use of azithromycin, minocycline [239], and doxycycline [240].

Some antivirals used in the treatment of chronic hepatitis C have been shown to induce dry eye disease and ocular surface squamous metaplasia [241]. Patients undergoing a course of interferon alfa-2b with ribavirin therapy showed increased dry eye symptoms in comparison to controls, with peak symptoms occurring at around 6 months of therapy [241]. Mean Schirmer test values showed a significant reduction after 1 month of treatment and 21% had advanced conjunctival squamous metaplasia [241]. The effects were reversible after cessation of therapy. Patients treated with sofosbuvir showed increased Ocular Surface Disease Index scores, which also returned to baseline after cessation of therapy. Schirmer test and tear breakup time values were also negatively affected by the medication, showing association between sofosbuvir use and dry eye disease [242].

3.2.3. Omega 3 and 6 supplements

The body can synthetize all the fatty acids it needs except for the "essential" polyunsaturated fatty acids omega-3 and omega-6. Supplementation with these has been a focus of interest for their anti-inflammatory properties, although large clinical trials and meta-analysis results have observed contradictory findings.

The largest meta-analysis to date regarding the effects of omega-3 and omega-6 polyunsaturated fatty acids alone or combined with other therapies is a Cochrane review, which studied 34 randomized clinical trials involving 4314 patients with dry eye disease [243]. This study demonstrated that exclusive omega-3 polyunsaturated fatty acid supplementation increased Schirmer test results and reduced tear osmolarity compared to placebo, but did not demonstrate improvement of dry eye disease symptoms. Beneficial effects in decreasing dry eye disease were only evident with concomitant conventional therapy administration (i.e., warm compresses and eyelid scrubs), suggesting the possibility that the positive results stemmed from conventional dry eye disease therapy [243].

However, as reported in the TFOS DEWS II Epidemiological report, a study of over 32,000 women found that a higher ratio of omega-6 to omega-3 levels (>15 to 1) showed a significantly increased risk of dry eye disease than a lower ratio (<4 to 1), suggesting that omega-6 has a proinflammatory effect while omega-3 might have an anti-inflammatory effect [244]. The *TFOS Lifestyle: Impact of nutrition on the ocular surface* report provides further in-depth analysis of the use of omega fatty acids in the diet to control ocular surface disease [245].

3.2.4. Vitamin supplements

Dry eye disease has an association with oxidative imbalance, as there are increased oxidative products and decreased antioxidant agents in patients with this condition [246]. As such, the role of antioxidants and more specifically nutraceuticals such as vitamins have gained interest in managing dry eye and ocular surface diseases. Overall, vitamins appear to be well-tolerated and have shown positive effects in treating dry eye disease symptoms and signs, especially when used as adjuncts to standard therapy. Their use reduced reactive oxidant species, expression of human leukocyte antigen-DR conjunctival inflammatory markers, and dry eye disease symptoms in comparison to placebo [247].

Although there are no systematic reviews that evaluate the association between vitamin intake and dry eye disease or concomitant ocular surface disorders, elective use of high doses of antioxidants and vitamins, such as vitamin B6, can be neurotoxic and can result in small fiber neuropathy and corneal neuropathy leading to reduced corneal light touch sensation, affecting ocular surface health and increasing signs of dry eye disease [248]. However, major limitations are the fact that most of these studies either have short follow up times, or that background diets act as a confounder, whereby positive results may stem from other dietary practices within populations [249]. It has been shown that 13-*cis* retinoic acid (isotretinoin), a metabolite of vitamin A, added topically to or near the eye can affect the meibomian glands, causing keratinization, glandular atrophy and abnormal secretions [250] (see section 2.2.9). Whether dietary vitamin A is converted to 13-*cis* retinoic acid and causes these adverse effects has yet to be studied.

Most of studies of the use of vitamins either have short follow up times, or background diets act as a confounder, whereby positive results may stem from other dietary practices within populations [249]. The effect of vitamins in the diet on the ocular surface is also covered in the *TFOS Lifestyle: Impact of nutrition on the ocular surface* report [245].

3.2.5. Hormonal replacement therapy

Dry eye disease commonly affects postmenopausal women, and an imbalance in estrogen hormone has been posed as a potential etiologic factor [244,251]. Many women use hormone replacement therapy (either estrogen alone or estrogen combined with progesterone or progestin) for menopausal symptom relief. However, as elaborated in the TFOS DEWS II Epidemiology Report, estrogen replacement therapy after menopause has been associated with increased incidence of dry eye disease in a cohort study done of 25,665 women [244,251]. Multivariate odds ratios for risk of dry eye disease were 1.69 for estrogen use alone, and 1.29 for combined estrogen and progesterone or progestin use, compared with no hormone replacement therapy. For each additional 3 years of hormone replacement therapy use, there was a significant 15% increase in dry eye disease. In that same study, prospective analysis confirmed that the onset of dry eye disease was associated with the initiation of estrogen therapy [244,251]. It is hypothesized that estrogen causes dry eye disease through induction of regression of lacrimal glands, reduced metabolic function and consequent tear output [227, 251], but there are as yet no studies confirming this.

3.2.6. Anti-androgens

Anti-androgens can be used for the elective treatment of hair loss in men and hirsutism and acne in women (225). It has been theorized that androgens regulate meibomian gland function by promoting meibum production. As such, it has been postulated that androgen deficiency may contribute to meibomian gland dysfunction (225).

A controlled study on patients taking different anti-androgenic drugs demonstrated that, compared to controls, these patients had a higher

rate of tear film abnormalities, meibomian gland dysfunction, altered relative amounts of lipids in meibomian glands secretions, increased corneal staining, decreased tear breakup time and were more symptomatic [252]. In addition, sex hormone (and more particularly androgen) deficiency has been associated with dry eye disease. This association has been evaluated in settings of direct anti-androgen medications, but also as a result of different medical entities with androgen deficiency such as congenital androgen insufficiency [244].

3.2.7. Tamsulosin (prostate hypertrophy)

Tamsulosin is an alpha 1 receptor blocker commonly used to treat benign prostatic hyperplasia (BPH), but is also for ureteral stones, prostatitis, and female voiding dysfunction. A cross-sectional epidemiological study among 25,444 men found that both the presence of BPH and the use of medications to treat BPH were associated with increased risk of dry eye disease [253]. These findings were likely linked to the fact that the conjunctiva overexpresses α1 receptors in patients using tamsulosin, or even due to the use of anti-androgenic drugs, which have been shown to impact several measures of ocular surface health, as previously discussed [253]. Limitations of these studies include a lack of information related to concomitant drug use [252].

3.2.8. Antihistamines/anticholinergic drugs

Oral antihistamines and anticholinergic drugs are widely available and used by the general population for allergies and rhinitis. The effects of topical antihistamines on the ocular surface have been described in sections 1.1.2.3.1. and 1.1.2.3.3. The combination of 120 mg of the decongestant pseudoephedrine and 5 mg of systemic cetirizine antihistamine increased dryness in eyes and mouth than the use of either cetirizine or pseudoephedrine alone [254].

Anticholinergics can be used for overactive bladder and have similar modes of action to antihistamines (described in section 1.1.2.3.1) on peripheral muscarinic receptors. Oxybutynin and tolterodine, both anticholinergics used for overactive bladder, have been studied in a randomized longitudinal study and both caused a significant reduction in tear breakup time, and were also associated with increased symptoms of foreign body sensation, eye burning and dryness [254]. A double-masked randomized placebo-controlled trial evaluating another anticholinergic medication, solifenacin, used for overactive bladders found significantly greater dry eye signs and symptoms in the solifenacin group consisting of 377 individuals, in comparison to the placebo group consisting of 374 individuals [255].

3.2.9. Isotretinoin

Oral isotretinoin, 13-cis-retinoic acid, use has been shown to be associated with dry eye disease and meibomian gland dysfunction. A systematic review on eleven trials of individuals with moderate-to-severe acne showed that ocular adverse events were twice as likely in the group treated with isotretinoin in comparison to the control group but only represented 7.2% of all adverse events for those treated with isotretinoin [256]. The most frequent side effects were eye dryness, irritation and conjunctival injection [257]. Moreover, isotretinoin is a well-known risk factor for the development of meibomian gland dysfunction due to its reduction of proliferation and differentiation of glandular epithelial cells [258]. This can lead to subsequent glandular atrophy, keratinization of ducts, acinar cell degeneration and peri-acinar cell fibrosis [258] (Fig. 4). These effects are due to isotretinoin's mode of action that is useful for the treatment of acne, that is reducing both the development and function of epithelial cells in sebaceous glands [258].

Isotretinoin can also cause small fiber neuropathy and induce corneal neuropathy [259]. This prospective case series of 50 patients showed decreased corneal sensitivity after isotretinoin use for 3 months, with the effect being more pronounced in women and in older ages [259]. Extensive research and further systematic reviews need to be conducted to corroborate this effect.

3.2.10. Antidepressants and anxiolytics

Although the occurrence of dry eye disease is not a common report in the safety profile of antidepressants, the use of antidepressant medications has been strongly associated with prevalence of dry eye disease [253]. A systematic review found that antidepressant use was associated with increased dry eye disease signs and symptoms [260]. One study in the review evaluating patients with depression treated with antidepressants versus placebo showed that, after 90 days, the antidepressant group had significantly worse dry eye disease, as seen on Ocular Surface Disease Index score, tear breakup time score and corneal fluorescence staining [260]. Association between depression and the ocular surface is covered in the *TFOS Lifestyle: Impacts of societal challenges on the ocular surface* report [261] and *TFOS Lifestyle: Impacts of lifestyle challenges on the ocular surface* report [262].

The possible mechanisms for the effects of antidepressants on dry eye disease may be due to their anticholinergic effects [58]. Another plausible theory is that their production of increased serotonin and inflammatory mediators leads to sensitization of corneal nerve endings and reduced pain thresholds, causing symptoms that overlap with those of dry eye disease [260]. Newer generations of antidepressants used with patients on selective serotonin reuptake inhibitors reduced Schirmer test scores (i.e. lower tear volume) more than patients on serotonin-norepinephrine reuptake inhibitors, while both drug regimens resulted in increased signs and symptoms of dry eye disease [263].

Antianxiety medications, or anxiolytics, have shown similar effects as antidepressants. A study evaluating different sociodemographic parameters affecting dry eye disease found that the incidence of dry eye significantly increased with the use of antianxiety medications [263]. They most likely produce dry eye disease through their anticholinergic effect that reduces lacrimal gland secretions [58]. On the other hand, there is a reported positive correlation between insomnia and dry eye disease [264]. The authors postulated that treatment of depression, anxiety and disturbed sleep can in turn improve dry eye symptoms. This is an important area for future studies.

3.2.11. Opioid antagonists

Patients with dry eye disease may have a neuropathic component of pain and discomfort, which is commonly refractory to conventional dry eye therapies. Opioid antagonists (i.e. oral low dose naltrexone) can be used to treat patients with chronic centralized neuropathic pain [265]. It can also act as an antagonist to Toll-like receptor 4, thus suppressing inflammation by decreasing proinflammatory cytokine release in the

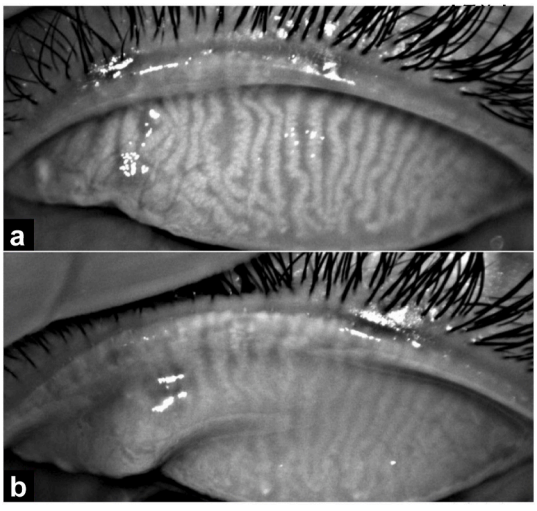

Fig. 4. Upper tarsal meibography of a patient before (a) and after (b) use of oral isotretinoin (0.5 mg/kg/day) for 16 weeks. Observe attenuation in contrast of the meibomian glands induced by the systemic use of isotretinoin. Courtesy: Fabio MX Andrade, MD.

central nervous system. There are no reports regarding deleterious effects of low-dose naltrexone or other systemic opioid antagonists on the ocular surface and dry eye disease. The effect of the use and abuse of opioids on the ocular surface is covered in both the *TFOS Lifestyle: Impacts of lifestyle challenges on the ocular surface* report [262] and *TFOS Lifestyle: Impacts of societal challenges on the ocular surface* report [261].

3.2.12. Cannabis

Cannabis as a risk factor for the development of dry eye disease is still controversial. Although no solid scientific evidence exists as to the direct association between cannabis and ocular surface disease, studies have noted that dry eye can occur as a side effect of inhaled cannabis use [266]. This has been hypothesized to be similar to the effects of smoking tobacco on dry eye disease. Tobacco smoke can increase symptoms of dryness, increase tear osmolarity, reduce the tear lipid layer, reduce tear breakup time, reduce corneal sensitivity and reduce goblet cell density [267]. Further details of effects of cannabis on the ocular surface can be found in the *TFOS Lifestyle: Impacts of lifestyle challenges on the ocular surface* report [262] and *TFOS Lifestyle: Impacts of societal challenges on the ocular surface* report [261].

3.3. Drug-induced immune reactions

Systemic drugs have been associated with immune reactions, such as erythema multiforme, Stevens-Johnson Syndrome, and Toxic Epidermal Necrolysis [268]. The latter conditions, Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis, are severe acute vesiculo-bullous disorders that affect mucocutaneous tissues, including the ocular surface [268]. The incidence of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis are extremely low (0.4–6 cases per million persons per year), however, mortality rates are as high as 1–5% for Stevens-Johnson Syndrome and 25–35% for Toxic Epidermal Necrolysis [268]. These patients develop severe ocular surface complications and can present with dry eye disease, chronic conjunctival inflammation, symblepharon, trichiasis, limbal stem cell deficiency, corneal conjunctivalization and chronic epithelial defects [269-271] (Fig. 5). An extensive systemic review focused on drug-induced Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis in an Indian population has shown that the use of antimicrobial and anti-inflammatory drugs was associated with 37% and 16% respectively of all drug-induced Stevens-Johnson Syndrome/-Toxic Epidermal Necrolysis cases studied [268].

Another important class of medications associated with drug-induced immune reactions are anticonvulsants and neuroleptics. Although these drugs are usually prescribed for seizure disorders, they can also be used electively by patients for neuropathic pain relief, or mood stabilizers and modulators [272]. The use of antiepileptics has been associated with 36% of cases of Stevens-Johnson Syndrome with Toxic Epidermal Necrolysis [268]. Carbamazepine (an anti-convulsant) showed the highest association with Stevens-Johnson Syndrome with Toxic Epidermal Necrolysis amongst individual drug use comparison and was implicated in approximately 18% of cases [268]. Moreover, valproic acid is associated with the development of Stevens-Johnson Syndrome with Toxic Epidermal Necrolysis. Although the correlation of the use of valproic acid with Stevens-Johnson Syndrome with Toxic Epidermal Necrolysis was associated with concomitant use of other antiepileptic drugs such as lamotrigine and carbamazepine, some reports observed the development of Stevens-Johnson Syndrome with Toxic Epidermal Necrolysis with valproic use alone [273].

Elective medications such as over-the-counter non-steroidal anti-inflammatories and multi-ingredient cold medications have also been associated with drug-induced ocular surface immune reactions such as Stevens-Johnson Syndrome with Toxic Epidermal Necrolysis. A systematic review demonstrated a significant association between cold medications and development of Stevens-Johnson Syndrome with Toxic Epidermal Necrolysis [269]. Although these conditions are not prevalent, patients should be aware of this association in order to take decisions on use of elective medications.

Allopurinol is a systemic medication used for management of gout but also used electively for management and prevention of kidney stones. It has been associated in a systematic review with increased ocular immune reactions such as Stevens-Johnson Syndrome [271]. Ocular signs ranged from early-onset conjunctival hyperemia to late-onset keratinization, limbal stem cell deficiency, symblepharon and epithelial defects [270].

4. Elective procedures impact on the ocular surface

4.1. Eyelid and periorbital elective procedures

4.1.1. Eyelids and brow surgery

The periorbital region with the eyelid-brow complex is considered key to the expression and esthetics of a face. Age-related eyelid changes may have a negative impact on self-esteem and body image, and make the affected individual feel less attractive [274]. Surgical procedures aimed at rejuvenating the periorbital area often comprise treatment to both the upper and lower eyelid as well as the brow [275]. Upper eyelid surgery can counteract the effects of aging through excision of eyelid tissue, and also provide a functional improvement of the superior visual field, as well as improvement in headache- and vision-related quality of life [276-278].

The most common surgical method for rejuvenating the eyelids is blepharoplasty [279]. Several surgical techniques that involve removal of different amounts of skin, muscle and fat have been described [280]. In case of upper eyelid dermatochalasis associated with involutional

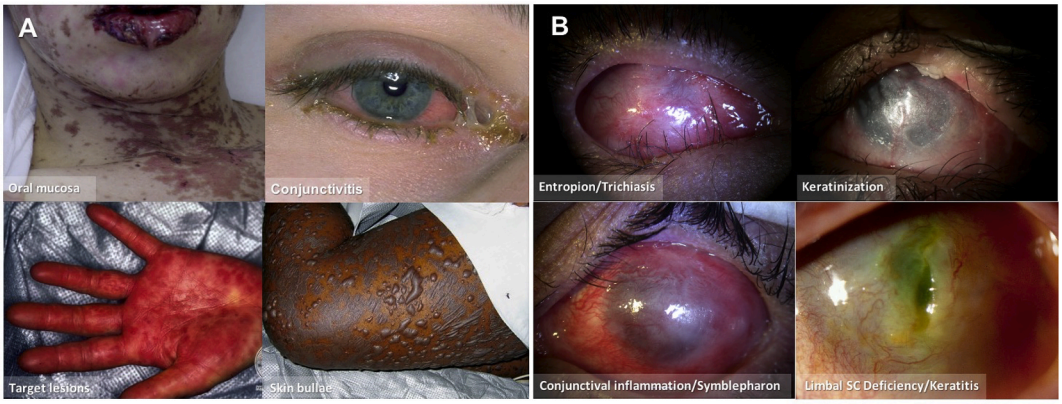

Fig. 5. Clinical aspects and ocular surface sequelae of acute (A) and chronic (B) Stevens-Johnson syndrome/Toxic epidermic necrolysis. (A) courtesy: José AP Gomes, MD, PhD, and (B) courtesy: Dept. of Ophthalmology and Visual Sciences, Paulista School of Medicine, Federal University of São Paulo, Brazil.

blepharoptosis, ptosis repair is also needed [281]. Blepharoplasty is usually undertaken simultaneously in both the upper and the lower eyelid [282]. Lower blepharoplasty is one of the more challenging procedures in plastic surgery [283] and is performed through a transconjunctival or transcutaneous route [284]. Lateral canthal laxity with lateral canthal dystopia can be addressed by performing canthopexy or canthoplasty [285]. Occasionally, lifting of the eyebrows and midface, or laser and chemical skin resurfacing, may be used simultaneously for rejuvenation [282].

Periocular surgery aims for an esthetic outcome whilst maintaining functional eyelids and a healthy ocular surface. Complications that have been reported range from an unsatisfactory cosmetic results to orbital hematomas and vision loss [275]. Since the eyelids are directly responsible for eye protection and lubrication, periocular cosmetic surgery may also affect the ocular surface and tear film depending on the location (upper, lower, both eyelids), technique, amount of tissue removed, preoperative risk factors and time after surgery [281,286].

4.1.1.1. Mechanisms of anatomical and biological damage on the ocular surface. Corneal abrasion following periorbital surgery can result from drying of the corneal surface or direct trauma causing a defect in the corneal epithelial surface [275,287].

Lacrimal gland injury can occur during upper blepharoplasty if the gland is inadvertently mistaken for lateral eyelid fat and resected, especially when it is prolapsed out of the orbit [288,289], and during ptosis surgery with damage to the accessory lacrimal glands, lacrimal gland ductules or ostia [290,291]. This results in diminished tear production and long-term deleterious effects on the ocular surface [290,291]. Cosmetic lateral canthoplasty may cause an outward redirection or direct injury of the lacrimal ductules resulting in a lacrimal fistula and excessive tearing [292]. Excessive epicanthoplasty causes unwanted results, including overcorrection [202], and possible damage to the lacrimal canaliculus during tissue removal [293].

Conjunctival chemosis can develop in the early or intermediate postoperative period after blepharoplasty due to incomplete eyelid closure and conjunctival exposure, ocular allergy, or surgical dissection causing conjunctival edema from increased vascular permeability and disruption of lymphatic venous channels [283,288,294,295]. It is more commonly seen following a transconjunctival lower blepharoplasty or as a complication of an overly aggressive lateral canthal dissection [286,288].

Upper eyelid malposition, known as lagophthalmos or incomplete closure of the eyelids, can be a temporary or permanent sequela of blepharoplasty, especially when combined with ptosis repair and brow-lifting (Fig. 6). Transient lagophthalmos is commonly present in the postoperative period owing to upper eyelid edema and a reduction in orbicularis tone due to surgical trauma. Lagophthalmos persisting for longer than two weeks can be caused by excessive upper eyelid skin resection (anterior lamellar deficiency), incorporation of the septal fibers into the wound/skin closure, orbicularis trauma, or peripheral facial nerve injury [275,287,288]. Ptosis overcorrection may also lead to lagophthalmos [296], especially after frontalis muscle flap suspension surgery [297]. Lagophthalmos is also seen following overly aggressive lateral canthal dissection when a lower eyelid blepharoplasty is combined with a midface-lift due to damage to branches of the facial nerve [286].

Lower eyelid malposition and lateral canthal dystopia or dysfunction are well-recognized complications of surgery involving the lower eyelid, periorbital region, or even the midface. Common causes include adhesions of the orbital septum, excessive lid laxity, inadequate lid suspension, and excess skin or muscle removal [286,298]. Postoperative complications of several lateral canthoplasty techniques include misalignment of the mucocutaneous junction at the lateral canthus, asymmetry, displeasing contours, rounded lateral canthus, and conjunctival exposure and scleral show [299-302].

A symptomatic eyelid closure disorder resulting in a concentric blinking movement, resembling the mouth closure of a fish and termed "fishmouthing" syndrome, is due to dysfunction and/or dehiscence of the lateral canthus after blepharoplasty [303]. This condition should be diagnosed by dynamic evaluation during active blinking. Muscle strip resection of, on average, ≥11 mm in upper blepharoplasty compared to skin only resection has been associated with sluggish eyelid closure but this can resolve two to six weeks after surgery [304]. A prospective study on 110 eyes of 55 young female patients who had undergone transcutaneous Asian double-eyelid blepharoplasty confirmed these time-dependent postoperative blink alterations and showed significantly decreased numbers of blinks as well as increased numbers of partial blinks one week after surgery, although this returned to baseline after one month [305].

Surgical modifications of the eyelid anatomy following periorbital surgery can alter the position of the upper and lower eyelid, eyelid closure and blinking, and thus promote corneal exposure and the development of evaporative tear loss leading to dry eye disease [275]. The decrease in mechanical tear film distribution and clearance of the tear film may lead to chronic build-up of inflammatory factors and breakdown in the corneal and conjunctival epithelium with significant discomfort, pain and visual compromise [275,283,297,306,307]. Resection of tear-producing or tear-stability-supportive structures (damage to the lacrimal gland/ductules, resection of the conjunctiva with goblet cells and its accessory lacrimal glands) is theoretically possible, and may decrease lubrication and lead to dry eye disease [308].

Epiphora commonly occurs on the days following eyelid surgery and can be accompanied by chemosis, dry eye symptoms and exposure keratopathy, triggering tear hypersecretion or an impaired lacrimal drainage pump [286,301].

Exposure may place the ocular surface at risk of infection and scarring, and could lead to further morbidity such as keratopathy, corneal ulceration, perforation, and eventually permanent visual impairment, particularly in patients with a poor Bell's phenomenon [296,309].

Suture-related complications such as granulomas may occur from the use of delayed absorbable sutures, powder from surgical gloves, make-

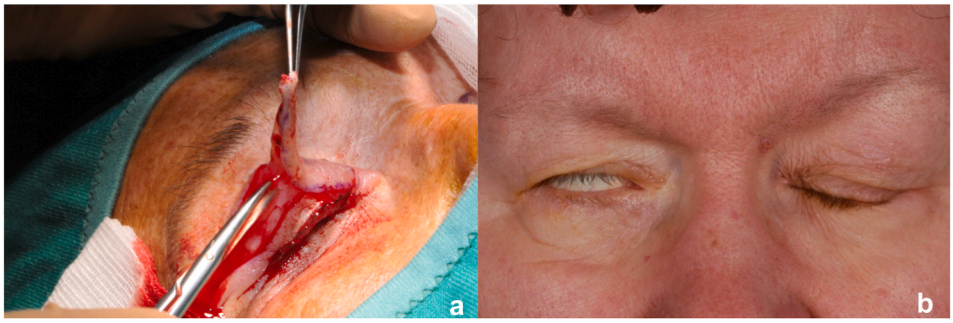

Fig. 6. Upper blepharoplasty (a) and lagophthalmos (b) induced by blepharoplasty. Courtesy: Jutta Horwath-Winter, MD, PD and Elisabeth M. Messmer, MD.

up, retained ophthalmic ointment, or liquefied fat following eyelid surgery [285,287,298]. Exposed sutures after ptosis surgery can result in corneal injury such as epithelial punctate and corneal ulcer, and even a penetrating eye injury and endophthalmitis have been reported [310].

Due to the favorable vascular anatomy of the periorbital region, infections following surgery involving the eyelids or the face are generally not common. However, an increasing number of these infections have been associated with methicillin-resistant *Staphylococcus aureus* [287], which are often resistant to multiple antibiotics. Perioperative hypersensitivity reactions have been observed and typically present as distinct erythema or conjunctivitis. They are most commonly attributed to benzalkonium chloride found in preservative eye drops or to neomycin in some ointments [298].

The occurrence of diplopia and symblepharon following conjunctival Muellerectomy for ptosis repair has been reported in three patients using chronic antiglaucoma treatment [311,312]. However, the relevance of the antiglaucoma treatment in the production of these remains unclear.

4.1.1.2. Types of surgeries

4.1.1.2.1. Blepharoplasty. A retrospective study of 892 blepharoplasty patients found that dry eye disease symptoms at follow up occurred in 26.5% of patients [307]. Simultaneous upper and lower blepharoplasty was more likely to cause the dry eye disease symptoms (31.3%) than lower or upper blepharoplasty alone (21.4% and 12.9%, respectively). The time lapse from surgery to the reporting of symptoms ranged from one to 132 months (median: 7 months) [307].

A systematic review found that an upper blepharoplasty alone may potentially alleviate subjective complaints of dry eyes [276]. These results were confirmed by a randomized controlled trial from the same group that showed subjective symptoms (Ocular Surface Disease Index questionnaire) to be reduced significantly twelve months after upper blepharoplasty in 54 patients with or without muscle resection of 3–4 mm, while the pre- and post-operative outcomes of the objective tear dynamics did not differ [313]. However, muscle strip resection in upper blepharoplasty compared to skin only resection was associated with initially higher ophthalmological morbidity including dry eye disease symptoms (50% vs. 17%), irritation, sluggish eye closure and lagophthalmos after one week [279,304,314]. The width of the orbicularis oculi muscle strip and older age were found to be associated with these complications. A strip wider than 9 mm was associated with dry eye disease and irritation; a width of at least 11 mm, with sluggish eye closure; and one of at least 13 mm, with lagophthalmos.

In comparison with Caucasian lids, Asian upper eyelids are often characterized by the lack of an upper eyelid crease, more preaponeurotic fat, a medial epicanthic fold and a reduced horizontal length of the palpebral fissure [293]. Asian double-eyelid blepharoplasty, a cosmetic technique that creates a supratarsal crease on the upper eyelids, is the most popular esthetic procedure performed in Asia and among Asian Americans [315,316]. After full incisional cosmetic double-eyelid blepharoplasty in 120 young Asian females, the incidence rates of dry eye disease symptoms after one week, one and three months were 12.5%, 32.5% and 16.7%, respectively [315]. Lagophthalmos developed in 3.3% one week postoperatively but had subsided by one month postoperatively [315]. Lower eyelid malposition ranging from mild inferior scleral show to ectropion is a common complication reported after lower eyelid blepharoplasty and the most common cause for re-operative surgery [283,301]. Other complications include chemosis, hemorrhage, infection and diplopia [307,317-319].

4.1.1.2.2. Ptosis surgery. Depending on the degree and severity, ptosis surgery can be an elective or therapeutic procedure. Several study cohorts have shown no significant changes in dry eye disease symptoms following ptosis surgery [320-323]. However, in one study 23% of patients (7/30) who underwent Müller's muscle conjunctival resection were bothered by symptoms of dry eye disease and scored worse on the Schirmer test and Ocular Surface Disease Index. This worsening was only temporary and had subsided with two months following surgery [324]. Another study reported a transient increase in dry eye disease symptoms in at least one eye in 29% (11/38) of patients immediately after surgery. In 16% (6/38) of patients that were followed up for a longer period of time, dry eye disease symptoms worsened or appeared in one or both eyes [325]. Lagophthalmos has been reported to complicate ptosis surgery in 6%–40% of the patients [326,327]. Approximately 6% (3/47) of those who had undergone congenital ptosis surgery presented with symptomatic dry eye disease at some point during their follow up [326]. Exposure keratopathy has been detected in 3%–11% after congenital ptosis surgery [327-329].

Following Fasanella Servat surgery, dry eye disease symptoms and newly diagnosed keratopathy were detected in almost 20% and almost 7% of patients, respectively [330]. The presence of lacrimal gland tissue in the resected tarsus did not correlate significantly with dry eye symptoms or corneal epitheliopathy [330].

New onset dry eye disease symptoms have been observed in 5.6% of patients after transcutaneous levator advancement surgery, with a postoperative decrease in tear volume [291]. Overcorrection in sling surgery may be associated with dry eye disease and keratopathy [306, 331]. Frontalis suspension affected tear breakup time, blink frequency and eyelid closure much more than levator advancement [297]. The varying degrees of lagophthalmos after frontalis suspension tended to gradually decrease with time [297]. Other complications include infection after sling surgery, extrusion of the sling material, entropion, and corneal epithelial defects [332].

When blepharoplasty and ptosis surgery with Müller's muscle conjunctival resection or anterior levator resection were performed concomitantly, an increase in dry eye disease signs and symptoms has been noted [281,333]. Whereas another study showed that Müller's muscle conjunctival resection in combination with upper eyelid blepharoplasty did not worsen ocular surface scores or dry eye disease symptoms [334]. This is an area for further research to understand the strength of associations.

4.1.1.2.3. Canthoplasty. Persistent chemosis due to lymphedema may be an unavoidable complication following lateral canthal surgery [300]. Misalignment of the mucocutaneous junction at the lateral canthus can also occur [300]. Further lower frequency complications of lateral canthoplasty have been reported that include lacrimal cysts, minor infections, lateral canthus deformity, and suture granulomas [335,336].

4.1.1.2.4. Brow surgery. Lagophthalmos has been observed in 2.7% of patients after endoscopic brow surgery techniques involving subperiosteal dissection [337]. Other complications of brow-lift techniques were alopecia, motor branch nerve injury, paresthesia/dysesthesia, hematomas, edema, infection, and cosmetically unacceptable scarring [337]. Injury to the temporal branch of the facial nerve led to temporary neurapraxia in about 1% of cases, but only one patient in over 1200 cases developed permanent paresis [337-339]. Following *trans*--palpebral browpexy and concomitant upper blepharoplasty, 2% of patients (two patients) experienced prolonged edema and 1% (one patient) periodic eruptions of chalazia along the upper eyelids [340].

4.1.2. Punctal occlusion

An option to retain tear fluid, lubricants or other topical medication on the ocular surface is lacrimal occlusion with plugs inserted into the lacrimal puncta and canaliculi [341,342]. These plugs are made of collagen, silicone, hydrogels, polydioxanone or acrylics and can be subdivided into punctal and canalicular plugs (depending on their localization) and temporary or permanent plugs (depending on their durability) [341,342].

Indications for punctal occlusion are dry eye disease associated with contact lens wear, superior limbic keratoconjunctivitis or refractive surgery [341,342]. In addition, plugs play a role in the management of recurrent corneal erosions and neurotrophic keratopathy [341,342]. Perforated plugs can treat acquired punctal stenosis, and

drug-containing punctal or canalicular plugs can be used as drug delivery systems [341,342]. Due to possible complications, they are contraindicated in patients with active ocular infection, especially keratoconjunctivitis and blepharitis, lacrimal obstruction and ectropion [341-343].

There is no effect of sex/gender, race or ethnicity on punctal plug treatment outcomes. However, certain plug types are associated with higher rates of plug loss in elderly populations with lid laxity [344]. The rate of punctal plug implantation in the elderly has declined in the last years after reaching a plateau in 2003 [345].

Punctal plugs can be associated with ocular surface erosions due to plug extrusion; microbial contamination and infection of the ocular surface due to biofilm formation on the plug; canaliculitis or dacryocystitis commonly associated with distal migration or primary intracanalicular plug position [341,342]; and stagnation of tear fluid containing cytokines and inflammatory mediators that lead to ocular surface inflammation [346]. The risk of extrusion is commonly associated with silicone punctal plugs, with rates up to 50% reported [341]. An intracanalicular position has been associated with infection and the need for plug removal [341]. Herrick plugs especially can lead to complications necessitating removal, which is often not possible simply with lacrimal irrigation but requires surgical treatment with canaliculotomy or dacryocystorhinostomy [341].

Prophylaxis against extrusion includes choosing a larger size punctal plug, suturing the punctal plug to hold it in position, and placing the plug only in the inferior lacrimal punctum, as superior punctal plugs are more often associated with extrusion [341,342]. In cases of recurrent loss with concurrent punctum enlargement, canalicular plugs or thermal cauterization may be management options [341,342]. To minimize the risk of infection, punctal plugs should be preferred to canalicular plugs [342]. Herrick Lacrimal Plug® and SmartPLUG® canalicular plugs have been associated with higher rates of infection [341,342]. Management of infection consists of surgical plug removal, as canalicular irrigation rarely works effectively, and of antibiotic therapy [341]. Anti-inflammatory treatment prior to plug placement may be prophylactic against toxic tear syndrome [346].

In summary, punctal plugs seem to be efficacious and thus have a positive impact on the patients' quality of life, but a Cochrane Review on punctal occlusion for dry eye disease found that their effectiveness for the treatment of dry eye disease could not be adequately assessed due to high methodological and clinical heterogeneity in the literature [347].

4.1.3. Botulinum toxin

Botulinum toxin is a natural chemical produced by *Clostridium botulinum* that prevents the release of the neurotransmitter acetylcholine from nerve endings. Therapeutic effects of Botulinum toxin originate from chemical denervation of neuromuscular synapses and autonomic cholinergic nerve fibers of the sweat, lacrimal and salivary glands [3,348]. Two types of Botulinum toxin have been approved for clinical use: type A, being the most commonly used, and type B [349].

Botulinum toxin is administered peri-ocularly in a wide spectrum of clinical disorders, predominantly as the first-line treatment in patients with blepharospasm and hemifacial spasm. Furthermore, it is used for protective ptosis, eyelid retraction, entropion, strabismus, abducens paralysis, nystagmus, dry eye disease and epiphora [3,350-352]. It is increasingly utilized electively for facial rejuvenation [3,353,354], and details of this use are outlined in the *TFOS Lifestyle: Impact of cosmetics on the ocular surface* report [94].

Botulinum toxin treatment significantly relieves blepharospasm symptoms in 96% of patients [355]. This effect lasted for approximately 11 weeks [356,357]. Diminished response to the treatment was observed in clinically anxious or depressed individuals [355]. A Cochrane review concluded that Botulinum toxin treatment improved the severity of overall blepharospasm-specific status with a moderate confidence and blepharospasm-specific disability status with low-certainty evidence [356].

Side effects such as transient tearing (5–10%), dry eye disease (3–7.5%), photophobia (2%) and ectropion (1%) have been reported after Botulinum toxin treatment for blepharospasm [357]. Meta-analysis showed transient eyelid ptosis in 8.4–13.4% of patients [357]. Ptosis was more common in pre-septal than pre-tarsal applications [348,357]. However, the lagophthalmos rate was higher in pre-tarsal compared to pre-septal injections [358,359]. Furthermore, a Cochrane review reported an increased risk of visual complaints (diplopia, blurred vision, and visual disturbance) but no increase in xerophthalmia in patients treated with Botulinum toxin [356].

Botulinum toxin treatment studies have not reported permanent serious adverse events. All side effects subsided spontaneously and depended strongly on the injection technique and practitioner's experience. The occurrence of side effects among a group of 235 patients within the first year was 37% and dropped to 12% during the tenth year of the Botulinum toxin treatment [348]. Incidence of ptosis in Botulinum toxin treatment for blepharospasm was estimated at less than 1% for the experienced practitioners, but at 5.4% for the inexperienced practitioners [360].

The application of Botulinum toxin to the medial part of the eyelids can induce muscle paralysis and eyelid malposition which can lead to retention of the tear film and therefore to an improvement of ocular surface diseases [350,351,359]. However, studies report contradictory Botulinum toxin effects on the meibomian glands and on lipid layer thickness [359,361]. More research is needed to better understand the impact of Botulinum toxin on these anatomical structures and on any changes in blink patterns [357,359].

Epiphora treatment with Botulinum toxin injection into the lacrimal gland has been reported to last up to 30 weeks, with a low rate of side effects that can occur due to Botulinum toxin diffusion into surrounding tissue (ptosis, diplopia) [352]. Botulinum toxin injection may be a more accessible alternative to conjunctivodacryocystorhinostomy [352]. Moreover, conjunctivitis and dry eye disease are rarely reported. Interestingly, in experimental studies in rats and rabbits, lacrimal gland dissection revealed no inflammatory or structural changes after Botulinum toxin injections into the lacrimal gland [352,359].

In order to limit potential side-effects, injections of reduced volumes should be placed not less than 1 cm over the orbital rim and 1.5 cm to the side of the outer canthus [349,360,362]. After the procedure, it is important that patients remain in an upright position and do not rub or massage the affected area to avoid spreading the toxin. Exercise of the treated muscles to fasten the toxin uptake may also be of benefit [349,360,362].

There are several treatment options for Botulinum toxin-induced ptosis. Oxymetazoline hydrochloride, apraclonidine and phenylephrine hydrochloride ophthalmic drops reduce ptosis by 1–3 mm by stimulating the Müller's muscle via α-adrenergic receptors. Furthermore, systemic anticholinesterases demonstrated some benefit [349,360,363].

Botulinum toxin treatment generally has good patient-satisfaction and safety profiles. However, standardized questionnaires on the treatment effect and side effects are lacking [364]. It would also be interesting to assess the psychological aspects of Botulinum toxin treatment considering the reports on reduced effects in clinically anxious or depressed patients.

4.1.4. Cosmetic laser lid surgery

Ablative laser resurfacing is one of the earliest methods of non-surgical treatment for periorbital rhytides [365]. With this treatment, the entire epidermis and part of the dermis are vaporized. This leads to shrinkage, an increase in the production of collagen, and remodeling of tissue through healing. The carbon dioxide (CO_2) laser and 2940-nm Er:YAG laser are two ablative devices used for this procedure. Laser treatments are especially desirable because they can target precise components of the epidermis and achieve precise depths [366]. There is a risk of demarcation lines using laser ablation, and therefore full-face

treatment is recommended.

4.1.4.1. CO_2 laser. High-energy, microsecond-domain pulsed CO_2 laser resurfacing procedure can reduce wrinkles in the perioral and periorbital regions. An average wrinkle score reduction of 2.34 for the perioral region and 2.25 for the periorbital region, using a 9 point system which was developed to describe severity of photodamage and wrinkling present, has been reported [367]. Tightening of loosened and folded skin was also reported. Ultrapulse high-energy CO_2 laser systems provide better improvement of periorbital rhytids when compared to the surgipulse high-energy CO_2 laser systems [368].

The efficacy and safety of CO_2 lasers have been established in combination with lower eyelid transconjunctival blepharoplasty. Transconjunctival blepharoplasty only has been compared to transconjunctival blepharoplasty and CO_2 laser treatment in 44 subjects in a randomized clinical trial. The subjects were prospectively assigned to one of two treatment groups with a masked grader observing postoperative photographs [369]. Transconjunctival blepharoplasty alone improved eyelid bulging in 92% of subjects; however, wrinkling in the lower eyelid also increased in 46% of participants in this group. When CO_2 laser resurfacing was included, a significant reduction in wrinkling was observed ($P < 0.0005$) [369].

Glabellar, perioral and periorbital rhytids can be improved safely using a CO_2 laser with a scanning beam. Minor complications including transient post inflammatory hyperpigmentation and milia formation have been reported [370]. One patient experienced minor focal skin atrophy. There were no reported permanent pigmentation changes or hypertrophic scarring [370].

Many lasers operate within the spectrum of 400 nm–1400 nm, which consequently is in the visible to near-infrared spectrum, to which the retina is especially vulnerable [371-373]. Minor thermal corneal injuries may occur and be painful [374], but do not affect ocular function if the injury is limited to the epithelium [375] (Fig. 7). Corneal ulceration, bullous keratopathy and intrastromal hemorrhage have resulted from use of CO_2 laser skin resurfacing of the upper and lower eyelids as well as the full face. As the patient was given eye protection, the injury was deemed most likely the result of the metal corneal shields overheating throughout the lengthy procedure, as well as lack of cooling between the pulses of the laser [376,377].

4.1.4.2. Erbium:Yttrium-Aluminum-Garnet (Er:YAG) laser. Periorbital wrinkles are also improved with application of Er:YAG laser, which reaches superficial ablation depths. As pulsed char-free CO_2 lasers may result in prolonged wound healing and thermal damage, despite effectiveness of treating rhytids [371], a study of 20 patients examined the use of Er:YAG laser in order to propose the device as an alternative to CO_2. Perioral, periorbital and forehead rhytids were treated using the Er:YAG laser and improvement in rhytids was reported for all patients [371]. It took between 4 and 10 days for re-epithelization, less than 2 weeks for postoperative erythema to resolve, and 3–8 weeks for clinical improvement, post-treatment [371]. The Er:YAG laser had lower morbidity than the CO_2 laser, and both are effective at laser skin resurfacing [371]. Deep wrinkles can be most effectively treated using a combination of both laser types to minimize deeper erbium resurfacing bleeding [372]. Complications appear to be rare using the Er:YAG laser, but may include skin hyperpigmentation or hypopigmentation (related to depth of resurfacing), temporary scleral show and synechiae on the lower eyelid [377].

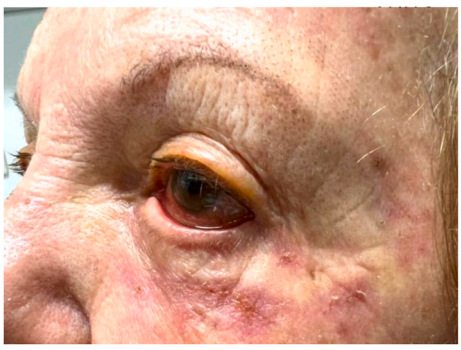

Fig. 7. Ectropion, conjunctival hyperemia, and chemosis 3 days after full face fractional CO_2 laser. Courtesy: Tadaaki Yamada, MD.

4.1.5. High frequency radio waves

High frequency radio waves have been used for tightening of eyelid skin and conjunctivochalasis treatment. Animal studies have demonstrated that the soft tissue effects and ocular temperature change during treatment were acceptable. Using ocular protection with a plastic corneoscleral lens, a 0.25 cm^2 treatment tip could be used without injury to the eyelids or eyes [142,378]. In an examination of eight patients who had high-frequency radio-wave electrosurgery for conjunctivochalasis, none exhibited inflammatory reaction, particle migration or complications (including granuloma) [379].

As the demand for skin rejuvenation therapies has increased, several newer devices have emerged, including micro-insulated needle radiofrequency systems, Polaris WRA™ and ReFirme ST™ [380-382]. The Polaris WRA™ consists of a diode light and radiofrequency. ReFirme ST™ consists of infrared and bipolar radiofrequency. When both were tested on fourteen Korean volunteers with the application of three treatments in 3-week intervals, both appeared to be safe. However, the Polaris WRA™ use of diode light and radiofrequency seemed to be more effective at reducing the appearance of wrinkles and pores [380]. When a 4-MHz radiofrequency treatment was applied to the periorbital, frontal and midface skin of 32 patients, there was a reduction of periorbital and midface rhytides. The most commonly noticed adverse reaction was transient erythema (62.5%) lasting from a few hours to a day [383].

High-frequency radio wave electrosurgery has been refined to produce a blended cut-coagulation effect (by Ellman Surgitron®) [384]. When treated using this method, the germinal cells of the hair follicles were destroyed with only minimal tissue change whereas the Hyfrecator® resulted in more tissue change due to the wide heat spread [384].

A comparison of reported pain has been made between individuals who had prior experience with non-ablative skin tightening energy devices with those who did not. Twenty individuals, 10 naïve and 10 non-naïve, were injected at four sites at two anatomic locations with needles, pulsed dye laser, radiofrequency, and ultrasound in a random sequence [385]. Individuals did not report significant differences in pain. Two-hundred-and-ninety patients were assessed for adverse reactions after non-ablative monopolar radiofrequency treatment. The average energy setting for treatments was 81J/cm (2), 1-cm^2 tip with 2.3-s pulse. In 757 treatments on 290 patients, 11.5% reported that treatments were painful, 2.7% had second-degree burns, and some had incidents of erythema, headache, scarring, edema, and other adverse reactions [386]. It has been recommended that care should be taken during treatments to ensure use of moderate energy settings and no overlapping treatment areas to decrease overheating and the potential for adverse side effects [386].

4.1.6. High frequency ultrasound

Ultrasound devices can be used for portable, non-invasive, high-resolution imaging or as a focused energy source to target specific tissues in order to shape or sculpt them [387]. They have a wide range of uses from breast, head and neck microsurgery and reconstruction, to skin for tightening, adipose tissue removal, rejuvenation of the face (including periocular area), promotion of neocollagenesis, and even bone healing. High frequency ultrasound has been used extensively as a diagnostic tool in ophthalmology with a relatively safe ocular surface profile. Ultrasound therapy has been included in routine clinical practice in plastic surgery with a high success and low complication rates [387,388].

4.1.7. Microblepharoexfoliation

Microblepharoexfoliation is an in-office procedure, that aims to remove the accumulated bioburden from the lid margin and debris from the eyelashes with a rapidly spinning sterile sponge-tipped micro brush and a foam cleanser [128,135]. As the bioburden accumulates with age and the associated microorganism population densities along the lid margin increase [389], the treatment is more likely indicated for older individuals [390]. However, it has been used with contact lens wearers [391], which tend to have a young demographic. Microblepharoexfoliation can reduce the appearance of anterior blepharitis, increase meibomian gland expression and meibum appearance, and reduce palpebral conjunctival hyperemia [391].

Reported damage to the ocular surface by microblepharoexfoliation and its impact on quality of life seems negligible [128,135,391,392]. Potential side effects may include allergic reaction to the foam cleanser used and risk of trauma to the cornea from the rotating brush on accidental contact with the ocular surface.

4.1.8. Thermal pulsation treatment

Lipiflow(R) automated thermal pulsation treatment provides a controlled method to express obstructed meibomian glands by applying heat to the upper and lower palpebral conjunctival surfaces while simultaneously applying intermittent pulsing pressure to the cutaneous eyelid surfaces [393], and may be used to improve their appearance. Systane® iLux® also simultaneously applies localized heat combined with manual compression/decompression of the meibomian glands under topical anesthesia [394]. With this device, the eyelid margin can be observed throughout the procedure using the built-in magnifying lens [394].

No information is available either on the prevalence of ocular surface disease induced by thermal pulsation treatment or on its impact on quality of life. The mean discomfort score during thermal pulsation treatment was 1.4 on a scale of 0–10 and within the category of awareness of pressure without pain [393]. The most common device-related event has been reported to be eye/eyelid discomfort in 1.5% of patients [395]. Slit lamp findings observed immediately after thermal pulsation treatment included eyelid edema, conjunctival edema, conjunctival hyperemia and petechiae, and superficial punctate keratitis [396]. All immediate post-treatment findings were transient and did not require medical treatment [396].

4.1.9. Meibomian gland probing

Intraductal meibomian gland probing is an invasive orifice penetration procedure that targets hyperkeratinization of ductal epithelium, intraductal fibrovascular tissue, periductal fibrosis, and orifice squamous metaplasia that can occur in meibomian gland dysfunction [397,398]. After topical anesthesia with 8% lidocaine to the eyelid margin, or sometimes infiltrative anesthesia, sterile blunt probes of 1–6 mm and 76 μm in diameter are inserted through the orifice and into the central duct to penetrate obstructions and release sequestered meibum from the gland [397,398].

Meibomian gland probing is reported to be a relatively safe procedure, at least in the short term [178]. However, a randomized-controlled study found that it lacked efficacy to restore gland function [399]. The procedure may be quite uncomfortable, and patients with chronic meibomian gland obstruction may report more pain [397]. It typically induces dot hemorrhages at the gland orifice with probing. Dot hemorrhages are hypothesized to occur from relief of disorganized periductal fibrovascular tissue [178,398]. These hemorrhages are usually self-limiting, but there is a hypothetical risk of subsequent fibrosis. Subconjunctival hemorrhages have also been reported [397]. A major concern is the damage to the gland by the probe creating a false passage, especially with longer probes. However, small open label studies using *in vivo* confocal microscopy and meibography could not document any adverse effect on the gland architecture [400,401]. Further independent and randomized studies are warranted to especially evaluate long term effect and safety of meibomian gland probing.

4.1.10. Intense pulsed light therapy

Intense pulsed light therapy uses a non-laser high intensity light source with a high-performance flash lamp to emit non-coherent large-wavelength light (500–1200 nm). The light is directed to the skin tissue and is then absorbed by the targeted structure, resulting in the production of heat (>80 °C) [402]. Appropriate wavelengths can be selected for different targets depending on the absorption behavior and the penetration depth of the light emitted, and specific filters can be chosen to limit the delivery of wavelengths to the treatment area resulting in selective thermal delivery [403].

Intense pulsed light has been widely used in dermatology to treat facial telangiectasias and erythema caused by rosacea [404]. Using specific filters in the handpiece, the light emitted from the flash lamp can be selectively absorbed by oxyhemoglobin. The light energy is converted to heat and induces ablation of small vascular structures. This process is one of the proposed mechanisms of action of intense pulsed light for dry eye disease, the destruction of fine telangiectasias along the eyelid inhibits access of inflammatory mediators to the meibomian glands [404]. It may also induce hypoxic conditions needed for optimal meibomian gland function. Other proposed mechanisms include a local warming effect to allow better meibum expression and destruction of bacteria and Demodex mites that might cause inflammation of the eyelid margin and meibomian glands [403,405-410].

Several devices are available that apply intense pulsed light with or without coupling gels and with or without low-level laser therapy, an athermic, atraumatic photoactivation of cells in both eyelids [411]. For the treatment of meibomian gland dysfunction, five or more pulses are applied along the inferior orbital rim without the necessity of topical anesthesia [402]. In patients with rosacea, some devices allow the concomitant treatment of periorbital/facial skin teleangiectasia. Emerging clinical data regarding the efficacy of intense pulsed light treatment for meibomian gland dysfunction suggests that a series of two or more treatments can improve symptoms, tear film characteristics, including tear breakup time, and clinical signs of meibomian gland dysfunction [402-404,410,412-415].

Most trials do not specifically report adverse events of intense pulsed light treatment. It is not usually recommended for use with dark or deeply pigmented skin (Skin Fitzpatrick scale V/VI) as this can be prone to skin damage, such as discoloration or scarring after intense pulsed light treatment [416], although some devices may be used on dark skin types [417]. The treatment can affect the skin of the eyelid, the ocular surface and pigmented intraocular structures. A retrospective study evaluated 2282 patients after intense pulsed light combined with meibomian gland expression. The rate of mild to moderate adverse events was 3.24% [418]. Side effects of the skin were observed in 1.05% patients and included skin erythema, skin vesicles, skin tingling, pain or burning, and pigmentary changes [418-420]. Loss or thinning of eyelashes and eyebrows may be experienced, however no incidence data are available [419-421]. Corneal epithelial defects have been reported in 0.74% of people following intense pulsed light and meibomian gland expression with ocular protection [418]. Conjunctival irritation and corneal complications may occur with the use of corneal shields, especially in the hands of non-eye care professionals [422], and the use of external eye shields may be preferred.

Anterior uveitis, anterior synechiae, distorted pupils and iris transillumination defects have been reported after intense pulsed light use for photochemo-rejuvenation [423-425]. Failure to use appropriate eye protection was thought to be responsible in these cases. However, there are reports of single cases of recurrent Herpes simplex keratitis, recurrent glaucomatocyclitic crisis and recurrent iridocyclitis after intense pulsed light performed with adequate ocular protection (382). An activation of latent Herpes simplex virus from the trigeminal ganglion stimulated by transient hyperthermia of intense pulsed light was

suggested as a triggering mechanism [418]. Increased phototoxicity, as induced for instance by tetracycline-derivatives, may lead the physician to pause the medication during the treatment cycle [418]. A history of uveitis and/or Herpes simplex virus infection should be considered an exclusion criterion for intense pulsed light treatment [418].

Intense pulsed light devices for hair removal at home have no recognized international standards to limit eye hazard. The International Electrotechnical Commission Report (IEC TR 60825-9) should be used by manufacturers to ensure that the weighted radiance values are less than the exposure limit values for corneal and retinal thermal hazard [426].

4.1.11. Low-level light therapy

Low-level light therapy is based on principles of photobiomodulation, which utilizes a light source (laser, LED, or broadband) for the athermal and atraumatic treatment of pain, inflammation and to promote tissue repair [427] Wavelengths in the visible (390–700 nm) and near infra-red (780–1100 nm) spectral range are chosen depending on the depth of the target tissue being treated. Although the mechanisms of action have not been completely elucidated, it is hypothesized that the near red and red light is absorbed by mitochondrial chromophores which then, by a series of cellular activity, activate the production of adenosine triphosphate, well known for providing energy for numerous cellular metabolic processes.

More recently low-level light therapy has been used for the management of dry eye disease, specifically for meibomian gland dysfunction, where it is believed that the stimulation of adenosine triphosphate in the glands result in endogenous heating which softens the meibum. The low-level light therapy is delivered non-invasively using a face mask with light-emitting diodes with no threat of exposure effects to the ocular surface or surrounding skin [428,429]. More recently, a randomized observer-masked study with a group receiving low-level light therapy twice a week for 3 weeks (total 6 sessions), revealed a significant improvement in the primary endpoint (i.e. corneal staining) after 4 weeks compared to a placebo group [430]. Other positive outcomes were observed in lissamine green staining, Schirmer test and meibography scores, while other parameters (tear film stability, debris, swelling, telangiectasia, meibomian gland secretion and expressibility scores) were not significantly altered. No serious adverse events were reported during that study.

Low-level light therapy has also been used in combination with intense pulsed light for dry eye and meibomian gland dysfunction [431]. A systematic review reported on 6 retrospective case-series studies published between 2019 and 2021, representing 990 eyes from 495 patients having the combined therapy [432]. The review revealed that combination therapy improves symptoms (using the ocular surface disease index), meibomian gland score, tear film stability, and lipid layer thickness. No change was reported for tear volume, Schirmer test scores or tear meniscus height, whereas contradictory outcomes were found for corneal staining and tear osmolarity. A retrospective chart review included 52 eyes of 26 patients having a combined therapy of low-level light therapy and intense pulsed light also reported significant improvement in symptoms, tear film stability and meiboscore scale with no reported adverse events [431], while others report a benefit of intense pulsed light but no strong benefit of low-level light therapy [433].

As new technologies enter the market, further studies are warranted for comparative data. Low-light level therapy on its own or in combination with intense pulsed light shows promising results in the management of meibomian gland dysfunction, however larger, well-designed studies are warranted.

4.1.12. Plasma discharge therapy

Plasma discharge therapy has been successfully used in dermatology for smoothing wrinkles, blunt blepharoplasty and thermal ablation for superficial skin layers [434]. In ophthalmology, this technology may be used to remove hyperkeratinization from the lid margin to unblock meibomian gland ducts to enhance meibum delivery, to partially thrombose telangiectatic vessels and thus reduce pro-inflammatory markers, and to reduce the bacterial microbiota at the lid margin [435]. Two techniques are available, the non-contact technique with a golden applicator for severe non-responsive meibomian gland dysfunction, and the contact technique applied through a silver tip for mild to moderate disease. The procedure is performed under sterile conditions under the operating microscope [434]. As the non-contact method may be quite painful, anesthetic must be injected and the globe protected by an ocular shield. The intensity on the device is set to 6–7, and the golden tip is applied above and under the line of meibomian glands orifices 3 times. For the contact method, topical anesthesia drops are sufficient, the intensity is set to 5–7, and the silver applicator is applied above and under the line of MG orifices for around 2 min. The contact technique needs several treatment sessions (4 sessions over 4 weeks).

Information on side effects on the ocular surface and impact on quality of life is not available. The non-contact treatment is very unpleasant and painful, and infiltration anesthesia is necessary [434]. An ocular protection shield must be inserted.

4.1.13. Transcutaneous periorbital electrical stimulation – quantum molecular resonance

Quantum molecular resonance is a technique in which low-intensity, high-frequency (a spectrum of frequencies ranging from 4 to 64 MHz) electric currents are administered to tissue through contact electrodes. Quantum molecular resonance has been used for years in the treatment of cutaneous ulcers [436], has been shown to increase the secretion of salivary glands [437] by stimulation of the ethmoidal nerve [438] without any significant side effects.

A patended device (Rexon Eye (R)) is on the marked for ocular treatment. It includes a goggle electrode with electronic board, temperature sensors, active electrodes, an external plastic shell, an internal rubber layer and internal sponge filling as well as an electrical generator. The device applies stimulation on the epidermis of closed eyelids up to the eyelid margin by means of the above-described goggles. It may act through an anti-inflammatory effect, as quantum molecular resonance is known to significantly reduce the expression of proinflammatory markers such as matrix metalloproteinases [436]. A previous version of the device used for meibomian gland dysfunction induced transitory cutaneous erythema in 2 out of 27 patients [439]. The recently developed and approved device is reported in an open-label trial to significantly reduces symptoms and signs associated with meibomian gland dysfunction, with no reported adverse events and an excellent patient tolerability [440].

4.1.14. Acupuncture and moxibustion

Acupuncture is a 2000-year-old Chinese non-drug physical therapy that has grown in popularity over the past few decades [441]. Specific areas on the body, the so-called acupoints, are targeted with fine, sterile needles, electroacupuncture or soft lasers [442-444]. The advantage of laser acupuncture is that it takes less time and is painless [445]. Histologically, acupoints show an increased density of nerve components and endings, stimuli-perceiving mast cells and a higher concentration of vascular elements [446].

Moxibustion is a special type of acupuncture that stimulates acupoints using heat generated when herbs containing *Artemisia vulgaris* are burnt [447]. Shaped into a moxa stick or cone, these herbs burn slowly releasing heat, radiation and smoke either directly or indirectly onto the skin [448]. Thunder-fire moxibustion is the predominant method used for treating dry eye disease [449]. In addition to moxibustion with a moxa stick, various traditional Chinese ingredients are added to the mixture to increase its effectiveness [450,451].

The American Academy of Medical Acupuncture and the World Health Organization recommend acupuncture in ophthalmology for acute conjunctivitis, cataract (without complications), myopia and

central retinitis [452]. Two systematic Cochrane Reviews on glaucoma and myopia progression show current data to be inconclusive regarding the effectiveness of acupuncture for these conditions [453,454]. In contrast, acupuncture in an acute hordeolum was advantageous compared to conventional therapy but insufficient data on adverse events made the benefit of treating a hordeolum with acupuncture uncertain [455].

Bladder 1 and 2, Gallbladder 1, Stomach 1, Triple Energizer 23, and Extra Point of Head 5 are the acupoints most used to treat dry eye disease. A meta-analysis of 11 randomized clinical trials demonstrated that acupuncture of body acupoints in addition to periocular points gave greater improvement of tear breakup time, Ocular Surface Disease Index score and Schirmer 1 test result [456].

In a two-center randomized clinical trial, laser acupuncture treatment three times a week for twelve weeks led to a significant improvement in Ocular Surface Disease Index score, tear breakup time and Schirmer 1 test compared to a sham control group [457]. There was also a significant difference in eye discomfort measured through a visual analog scale [457]. However, a placebo-controlled study of verum versus sham acupuncture showed no significant differences between the groups for Ocular Surface Disease Index score, visual analog scale score (or value), tear break up time or Schirmer 1 test result. There was a significant improvement in Ocular Surface Disease Index score and symptoms measured on a visual analog scale after three weeks of treatment in both groups, which suggests bias arising from patients' desire for the treatment to be successful [458]. A superior effect of acupuncture in both Sjögren syndrome and non-Sjögren syndrome patients has been reported in one systematic review and meta-analysis, but another systematic review recommended further high-quality studies on primary Sjögren syndrome [459,460].

In a systematic review, the effect of moxibustion on the symptoms and parameters of dry eye disease was confirmed on the basis of 12 randomized clinical trials, but the authors found the available literature to be insufficient to make strong conclusions [461]. The thunder-fire method of moxibustion at periocular points improved signs of dry eye including tear break up time [462].

Four large-scale survey studies among acupuncture practitioners confirmed that serious adverse events rarely occurred [463-466]. The low risk of serious adverse events was substantiated by two further reviews [467,468]. The high level of experience of acupuncturists might be the reason for the low occurrence of side effects [469]. However, as an invasive procedure, acupuncture using needles bears potential risks such as bleeding, hematoma, infections (e.g. hepatitis C), local pain, allergies and tissue damage. Rarely, this can also lead to organ puncture [470-475]. There is one case report about an open globe penetration due to acupuncture needling in the orbital rim for left-sided headache [476].

Adverse effects are more common in men and elderly patients. The frequency of at least one side effect is between 3.8% and 7.4%, but with only 1.9% requiring treatment [469,477,478]. Silicone-based compounds are used for implants and prostheses and as a coating for syringes and needles [479]. Granulomas can appear decades after initial treatment [479,480], with a periorbital silicone granulomatosis reported 30 years after acupuncture [481].

Burns are the main side effect of moxibustion. However, allergies and infections also occur [482]. One study reported on a patient who had developed an ectropion due to an injury to the superficial nerves and blood vessels during treatment of facial paresis with moxibustion in the periorbital area [483].

4.2. Conjunctival procedures

The conjunctiva is the mucous membrane of the eye and, together with the cornea and limbus, forms the ocular surface epithelium. It has fundamental roles in maintaining the ocular surface homeostasis because of its contribution to the tear film composition and adherence, and its highly committed local immune defense system, part of the mucosal associated lymphoid tissue [484].

4.2.1. Mechanism of anatomical and biological damage

Conjunctival surgery, especially removal of a large part of the conjunctiva such as during excision of large pterygia or nevi, could lead to iatrogenic dry eye disease, inflammation and formation of scars which might compromise ocular surface homeostasis, corneal transparency and, consequently, visual function. This effect can arise with the adjunct use of antifibrotic agents, sutures or excessive cauterization.

4.2.2. Types of conjunctival surgeries

4.2.2.1. Pterygia and pingueculae. A pinguecula is characterized by a fibrofatty degenerative change in the bulbar conjunctiva within the palpebral aperture. A pterygium is a fibrovascular tissue of a triangular shape that grows from the peribulbar conjunctiva towards the cornea [485]. The estimated prevalence of pterygium is variable, ranging from 2.8% to 58.8% [486,487], and for pinguecula the prevalence ranges from 22.5% to 97% [488]. Some environmental factors are believed to exacerbate the risk of developing pingueculae and pterygia, among them, exposure to ultraviolet light and dry eye disease [485,489].

4.2.2.1.1. Surgical techniques and their impact on the ocular surface. Because of the smaller size and usually accepted cosmetic appearance, most ophthalmologists do not recommend a surgical approach for pinguecula, and indicate clinical treatment with the topical use of lubricants, anti-inflammatories and, eventually, vasoconstrictors. As pterygium is a more prominent lesion, surgical removal is the method of choice. An observational survey among the members of the Cornea Society queried the current preferences of corneal experts regarding the indication for primary pterygium excision and found that proximity of the pterygium to the visual axis, eye discomfort, eye movement restriction, induction of astigmatism, and cosmesis were the common factors [490].

The association between the pterygium and dry eye disease and its corresponding symptoms is well established [491-493]. However, only a few studies have evaluated the effects of pingueculae and pterygium excision on the signs and symptoms of dry eye disease. The only study that used the Ocular Surface Disease Index questionnaire before and after surgery demonstrated a significant improvement in Ocular Surface Disease Index scores after pterygium excision [494]. Twelve studies that analyzed tear breakup time before and after pterygium excision demonstrated increased tear breakup time at 1 month after the excision, which improved by an average of 1.5 s by 12 months postoperatively [494-505]. Four studies compared tear osmolarity before and after post-pterygium excision [498,500,502,504]. One study [498] reported no difference, while the others [500,502,504] demonstrated osmolarity reduction. Eleven studies used the Schirmer test to compare tear secretion before and at least 3 months after pterygium excision [494-498, 500-502,504-507]. All 11 demonstrated improvement post-surgery, but that finding was statistically significant in only 1 study [501]. There are only a few published studies on the association between pinguecula excision and dry eye disease with more than 3 months of follow up [508-510]. Their results also showed some positive effects of the excision on dry eye disease signs and symptoms.

Overall, two strategies can be adopted for pterygium or pinguecula surgery: the destructive approach, which enhances the effect of excision by radiation and chemotherapy (mitomycin C, thiotepa, 5-fluorouracil, beta-irradiation) and the reconstructive approach, namely transplantation of various tissue grafts (conjunctival autograft, amniotic membrane transplantation, mucous membrane graft, conjunctival limbal transplantation). Recurrences after conjunctival autograft vary from 0% to 39% [511-517] and from 0% to 70% after adjunctive chemotherapy. Most studies have demonstrated that conjunctival autograft and mitomycin C application are highly successful and equally effective (0%–38% recurrence rate) [515,516,518-520]. However, severe

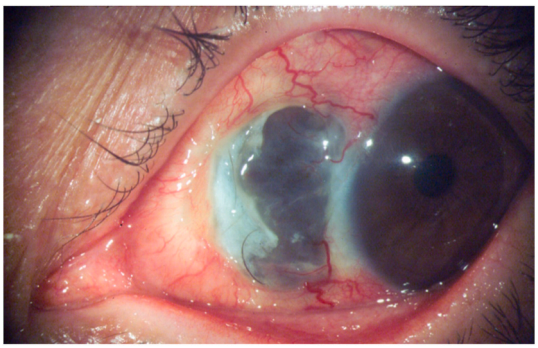

Fig. 8. Slit lamp photo of scleromalacia caused by pterygium surgery with intraoperative use of mitomycin C. Courtesy: Ernesto J Otero, MD.

complications may occur following mitomycin C therapy, such as melting of the conjunctiva and sclera, and even perforation of the globe [521-523] (Fig. 8).

Several studies have demonstrated that conjunctival autograft is the best method to avoid recurrence of pterygia [511,516,524,525]. To date the most common surgical methods of attaching conjunctival autografts to the sclera are through suturing or fibrin glue. In a systematic review, conjunctival autograft was compared to amniotic membrane transplantation for the treatment of pterygium [526]. In total, 20 randomized clinical trials were analyzed reporting 1947 eyes from 1866 participants. The recurrence rate after 6 months of follow up ranged from 3.3% to 16.7% in the conjunctival autograft group and from 6.4% to 42.3% in the amniotic membrane transplantation group. Thirteen trials reported few adverse effects that included conjunctival edema, inflammation, corneal scar, graft reaction, pyogenic granuloma, punctate epithelial erosions, eyelid edema and symblepharon. Pain, diplopia, increased intraocular pressure and restriction of eye movements were also reported. No significant differences were observed between the two procedures [526].

In another systematic review, fibrin glue was compared to sutures for conjunctival autografting in primary pterygium surgery [527]. Fourteen randomized clinical trials from 2004 to 2016 were included, with 372 patients in the fibrin glue group and 439 patients in the suture group. Whilst the use of fibrin glue reduced the recurrence of pterygium (risk ratio 0.47, 95% CI 0.27 to 0.82), it may be associated with more complications compared with sutures (risk ratio 1.92; 95% CI 1.22 to 3.02) [527]. Those complications depended on graft preparation, graft manipulation, surgical experience and participant selection. In the fibrin glue group, graft dehiscence was the most common complication (7 patients), being associated with eye trauma and eye rubbing. Other complications included graft retraction, granuloma, subconjunctival hemorrhage, graft loss, conjunctival inclusion cyst and dellen [527]. The most common complication in the suture group was granuloma (11 patients), followed by graft retraction, dellen, graft dehiscence and graft overlying the limbus [527].

A systematic review compared anti-fibrotic, anti-VEGF or radiotherapy to placebo as adjuvant treatments to pterygium excision [528]. The authors analyzed 34 randomized clinical trials, with a total of 2483 patients. The use of bevacizumab, mitomycin C and β-radiation therapy benefited patients after surgery, reducing the chance of recurrence of pterygium, while the other comparisons showed no significant difference between the procedures. It was also concluded that the use of adjuvants made the surgical procedures more complicated, added economic burden, and side effects might challenge the benefit-risk ratio, which may decrease the acceptability of adjuvants [528]. However, the review did not report on adverse effects and was not prospectively registered on a public systematic review registry.

4.2.2.2. Conjunctivochalasis. Conjunctivochalasis is characterized by the presence of loose and redundant conjunctival folds. It is often overlooked and undertreated, resulting in chronic tearing, foreign body sensation, burning, irritation, ocular surface irritation, blurry vision, and pain [507,529,530].

The association between conjunctivochalasis with dry eye disease and its corresponding symptoms is well established [507,529]. Asymptomatic conjunctivochalasis requires no treatment beyond observation. Symptomatic conjunctivochalasis may be addressed by medical therapy consisting of topical lubricants and topical corticosteroids. In advanced cases, surgical approaches, such as conjunctival excision, cauterization, or radio-wave electrosurgery should be considered. However, there is no consensus on the best procedure [531].

There are only a few published studies on the effect of symptomatic conjunctivochalasis treatment on dry eye disease signs and symptoms [531-548]. Studies have identified a significant improvement in Ocular Surface Disease Index and Canadian Dry Eye Assessment scores postoperatively versus the baseline preoperative scores [532-541]. Other studies identified a significant improvement in ocular symptoms and signs (corneal fluorescein staining scores and tear breakup time) [537, 538].

However, complications of conjunctivochalasis treatment have also been reported [531]. Conjunctival cauterization may need to be repeated causing scarring and ischemia. Conjunctival over resection may cause a compromised inferior fornix, cicatricial entropion or limited ocular movement, whilst under resection might be non-therapeutic. Furthermore, the need for suture placement not only prolongs the operating time and delays healing, but it also predisposes the patient to develop suture-related complications such as postoperative discomfort, foreign body sensation, pyogenic granuloma formation, giant papillary conjunctivitis and induction of inflammation.

Lid-parallel conjunctival folds may represent a mild form of conjunctivochalasis [549]. Lid-parallel conjunctival folds have been correlated with non-invasive tear break-up time, the phenol red thread test (a measure of tear volume) and Ocular Surface Index score [549]. Furthermore, lid-parallel conjunctival folds correlate with comfort during contact lens wear, tear evaporation rate, health of meibomian glands and the palpebral conjunctiva [550]. Microblepharexfoliation can reduce lid-parallel conjunctival folds [391].

4.2.2.3. Conjunctival naevus removal and ocular surface neoplasia. The removal of naevi or ocular surface neoplasia can cause lesion on the ocular surface. Large lesions disrupt the ocular surface tear film and may cause dry eye disease. Typically the conjunctival defect following conjunctival naevus removal is repaired using a conjunctival autograft [551].

Ocular surface neoplasia can also cause dry eye disease due to several different mechanisms. Inflammation from the ocular surface lesion can exacerbate underlying dry eye disease and topical chemotherapeutic drugs may induce dry eye disease [551]. Topical lubricants are advised during the use of chemotherapeutic drugs. In addition, cyclical dosing regimens may reduce the ocular surface side effects. Extensive conjunctival resection can cause additional adverse events such as fibrosis and scar formation, chronic inflammation and limbal stem cell deficiency. Topical therapy with lubricants and immunomodulators can alleviate symptoms [551].

4.2.2.4. Eye whitening. The last decade has witnessed a rise in cosmetic bleaching of the sclera ("eye whitening") that employ subconjunctival mitomycin C injections, conjunctival resection, and tenonectomy with intra- or postoperative antimetabolites, such as mitomycin C and bevacizumab injections. Eye-whitening procedures were pioneered in South Korea and the USA [552].

A study has reported on data retrieved from the medical records of consecutive patients who were reported to have undergone regional eye-whitening procedures by a single surgeon at a single center [552]. Of the

1713 patients, 82.9% developed postoperative complications. Notably, whilst only 2.8% had initially presented with dry eye disease, 32.4% of them were diagnosed with dry eye disease postoperatively [552]. Dry eye disease development following cosmetic eye whitening surgery may stem from the disruption of the function of goblet cells and the conjunctiva, fibrovascular proliferation, keratitis and induction of limbal stem cell deficiency [552].

A review of 10 articles published from 2009 to 2017, found that the most frequent side effects after cosmetic eye whitening were chronic conjunctival epithelial defects, scleral thinning, calcific plaques, dry eye disease, diplopia (occasionally requiring strabismus surgery) and increased intraocular pressure [553]. In another review that included 7 articles, complication rates were fibrovascular proliferation (13%), elevation of intraocular pressure (4.2%), calcific plaque formation (2.9%), recurrence of conjunctival hyperemia (2.1%), scleral thinning (1.8%) and diplopia (1.2%). It was concluded that eye-whitening procedures have complication rates comparable to other ocular surface reconstructive surgeries, such as pterygium excision [554,555].

In minor case reports and case series, the negative outcomes reported matched those observed in the reviews. Additionally, they included other post-operative complications such as necrotizing scleritis [556], infectious and non-infectious scleritis, infectious endophthalmitis [557], and scleromalacia [558], demanding further treatments and surgeries.

4.3. Corneal and keratorefractive surgery

Corneal and refractive surgical procedures have experienced rapid changes and growth over the past decades. Surgical techniques, success rates and visual outcomes have continued to improve, while the rates of vision threatening complications have continued to decrease. However, ocular surface disease signs and symptoms remain common in the early postoperative period.

Laser-assisted *in situ* keratomileusis (LASIK) remains the most popular of refractive surgery procedures in many countries. Its safety is excellent, but induction of dry eye remains one of the main reasons for patients' dissatisfaction after LASIK [559,560]. The incidence of dry eye after LASIK has been estimated at approximately 50% of cases at one week, 40% at one month, then reducing to between 12.5 and 48% up to the 6th postoperative month [561,562]. Photorefractive keratectomy patients also experience a significant reduction in tear secretion early postoperatively [563]. Patient-reported dry eye disease symptoms were found in 43% of patients after photorefractive keratectomy up to 6 months postoperatively [562]. Most of the patients recover, but a small percentage of patients develop a chronic dry eye or experience ocular neuropathic pain [564].

Other sources of harm to the ocular surface after corneal and refractive surgery include the toxicity from drops. In corneal transplantation, local anesthetic and povidone iodine drops may lead to severe ocular surface toxicity and induce inflammation [565-567]. In addition, most of the drops used, such as dilating drops and topical local anesthetics, may contain preservatives such as benzalkonium chloride, which causes toxicity to the corneal nerves, triggers inflammation, damages the goblet cells and causes dry eye disease (see section (1.1.1.1) [8,11,568]. Improved tear film parameters have been reported after changing to non-preserved topical medications [569].

Adverse events may occur after corneal cross-linking surgery, with the most common being temporary corneal haze, but others, including sterile infiltrates, photophobia, stromal edema, blurred vision, ocular pain and irritation, epithelial defects and corneal erosions, increased tearing and dry eye are all reported side-effects of the procedure [570-572].

4.3.1. Mechanism of damage

Corneal and refractive surgery is associated with dry eye disease through various mechanisms. Surgical transection of the corneal nerves by the corneal flap, ablation, incisions or trephination is a common mechanism by which corneal surgical techniques cause postoperative dry eye disease [3]. This is reflected in both a reduction in corneal sensitivity and impact on corneal trophic function. Corneal sensitivity can remain reduced after corneal incisions for as long as 1 year after surgery [573-576].

In LASIK, reduction of corneal sensitivity is a universal phenomenon due to the amputation of the corneal nerves, in creating a flap, and after photorefractive keratectomy due to the ablation of nerves sprouting in the superficial stroma [577-579]. After LASIK there is a marked reduction in the subbasal nerve plexus density and pattern, which may take more than 5 years to recover to standard values as evaluated with in vivo confocal microscopy [580]. Reduced corneal nerve sensory function reduces feedback to the lacrimal gland and basal tear secretion [577-579]. Additionally, centripetal neural function would be affected, decreasing the blinking reflex and blinking frequency. Tear film stability is reduced due to altered corneal shape and, perhaps mostly, due to impaired mucin secretion by damaged goblet cells of the ocular surface [581]. Goblet cell damage is attributed mostly to the action of the microkeratome suction in LASIK, but it has also been demonstrated in photorefractive keratectomy, indicating that other parameters such as the toxicity of drops and inflammation may contribute to goblet cell damage [582-584].

Predisposing factors to postoperative dry eye disease include preoperative dry eye disease and meibomian gland dysfunction. Accordingly, preoperative treatment of meibomian gland dysfunction may improve the postoperative outcomes [585,586]. As mentioned previously in this report, the postoperative use of preserved medications such as steroids (section 1.2.2.4) and antibiotics (section 2.2.2) may exacerbate the ocular surface disease by causing corneal nerve injury, and goblet cell and meibomian gland toxicity. Reductions in goblet cells and meibomian glands contribute to the reduced postoperative tear film stability and lead to worsening evaporative dry eye.

4.3.2. Types of surgery

4.3.2.1. Keratorefractive surgery

4.3.2.1.1. Laser-assisted in situ keratomileusis (LASIK). LASIK remains the most popular refractive surgery procedure in many countries [587]. LASIK-induced neurotrophic epitheliopathy is a clinical entity that may develop in up to 4% of post LASIK patients, more commonly in patients with pre-existing severe dry eyes [588]. This condition, that tends to resolve by around 6 months postoperatively, is consistent with the mechanism that causes post LASIK dry eye disease [589]. Patients develop staining of the ocular surface that in the case of LASIK might be more prominent on the corneal flap, short tear break up time, reduced basic tear secretion and reduced blinking reflex (Fig. 9). This may be due

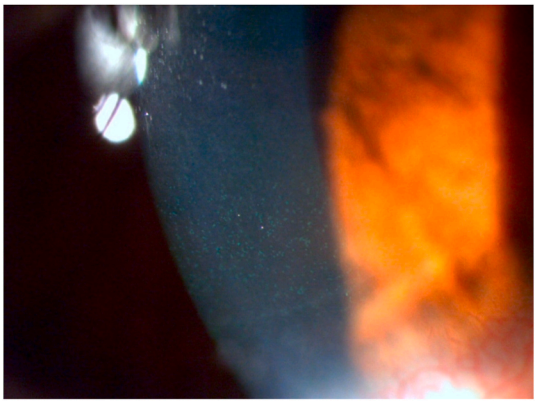

Fig. 9. Post-keratorefractive surgery dry eye and neurotrophic epitheliopathy: slit lamp detail with typical punctate fluorescein staining 3 weeks after LASIK surgery. Courtesy: Renato Ambrósio Jr., MD, PhD.

to loss of trophic factors as the result of loss of corneal nerves [580].

There is an apparent lower risk for dry eye disease when flaps are created with a femtosecond laser versus a mechanical microkeratome [590], with eyes having better tear break up time than those treated by mechanical microkeratome treated eyes in the early postoperative period, although femtosecond laser LASIK group had worse Ocular Surface Disease Index score 1 month postoperatively [590], a finding that was not confirmed in another study [591]. Thin flap LASIK with femtosecond laser showed improved tear break up time, tear secretion and Ocular Surface Disease Index score in comparison to microkeratome flaps [592]. A prospective trial [593] found increased incidence of dry eye disease in microkeratome-treated eyes despite the increased spherical equivalent correction in the femtosecond laser group and the increased suction time. However, another comparative study did not confirm any difference in risk for dry eye disease between femtosecond-treated and mechanical microkeratome-treated eyes [594].

The configuration of the flap has been studied as a modifiable parameter for the reduction of dry eye disease risk after LASIK. Hinge position and size is a parameter considered to contribute, with regard to the number of corneal nerves that are spared from amputation. A temporal hinge was found to have less effect on sensitivity and less postoperative dry eye disease than a superior in some studies [595,596]. However, other comparative studies found no difference with regard to hinge location [597-599]. Other parameters that seem to protect from dry eye disease after LASIK are a wider flap hinge, thinner flap and decreased flap/corneal diameter ratio [598,600-602].

4.3.2.1.2. Photorefractive keratectomy. The pathogenesis of dry eye disease after photorefractive keratectomy is multifactorial and involves a neurotrophic and inflammatory component, toxic action of drops, direct mechanical damage to the ocular surface and change in surface fluidics due to the altered corneal contour [581-584,589]. Patients treated with photorefractive keratectomy develop dry eye disease to a lesser extent than LASIK and for a shorter period of time [603]. The main cause of the dry eye disease development is the severing of the corneal nerves that happens due to the ablation in photorefractive keratectomy, as opposed to LASIK where it is due to amputation of corneal nerves from the flap creation and the ablation of the underlying corneal stroma. In photorefractive keratectomy subbasal nerves fully recover in almost two years [578,580], and the restoration of corneal sensory in photorefractive keratectomy takes approximately 3–6 months, whereas in LASIK it takes six months to more than a year [577].

There is a smaller decrease in Schirmer test value and tear breakup time compared to that following LASIK [604-607]. Affected tear secretion and stability has been found in all types of surface ablation techniques. Evidence from comparative trials is lacking, but the method of epithelium removal does not seem to influence the development of dry eye disease [604-607].

4.3.2.1.3. Small incision lenticule extraction (SMILE). Small incision lenticule extraction (SMILE) refractive surgery involves the use of a femtosecond laser to sculpt a refractive lenticule within the corneal stroma, which is separated from the rest of the stroma by spatula dissection, then removed with forceps through a small incision also created by the laser. Compared with LASIK, SMILE does not require the creation of a flap and therefore should induce less damage to corneal nerves and inflammation, which should result in a relatively lower risk of patients developing dry eye disease [608].

The anterior cornea of patients who undergo SMILE receives only a 2–3 mm incision in the superficial cornea. Therefore, it induces less denervation and less reduction of corneal sensation than LASIK in the postoperative period [609-616] (Fig. 10). For example, one contralateral eye study that involved 28 myopic patients (who underwent LASIK in one eye and SMILE in the other) found that both procedures reduced corneal sensation after surgery; that sensation in both groups returned to baseline levels after 6 months, but at the 1-week, 1-month and 3-months visits, corneal sensation was higher in the SMILE-treated eyes [610]. One meta-analysis that compared corneal sensation in patients who had undergone SMILE or LASIK found that greater sensation at 3 months postoperatively had recovered faster in SMILE-treated eyes compared to LASIK-treated eyes, although there was no significant difference in sensitivity at 6 months [617].

Some studies have found that these anatomical and corneal sensitivity advantages of SMILE over LASIK do not translate into significant differences in objective tear film parameters [610,618], whereas others have found that SMILE is associated with significantly better tear film stability [609,619] and lower dry eye disease symptom severity of shorter duration [620]. One study found that postoperative tear film osmolarity was higher in patients who had undergone LASIK than in those who had undergone SMILE, and that SMILE-treated eyes had significantly longer tear film break-up times [621]. Several meta-analyses and systematic reviews have examined the extent of dry eye disease after refractive surgery [622-625]. However, these found a lack of high-quality randomized controlled trials that examined the ocular surface outcomes after laser refractive surgery to “make concrete conclusions about dry eye disease parameters after refractive surgery” [623]. With the aim of investigating the impact of SMILE on quality of life, a systematic review was included in this report (see item 6).

4.3.2.1.4. Keratotomy. Radial and arcuate keratotomies are techniques nowadays used for a very restricted group of patients. The use of a femtosecond laser for the creation of arcuate incisions has improved the accuracy of astigmatic keratotomy. Incisional techniques can cut corneal nerves and result in decreased corneal sensitivity and trophic nerve function. This effect is more potent with arcuate cuts in comparison to radial cuts, especially in the area central to the incision [626].

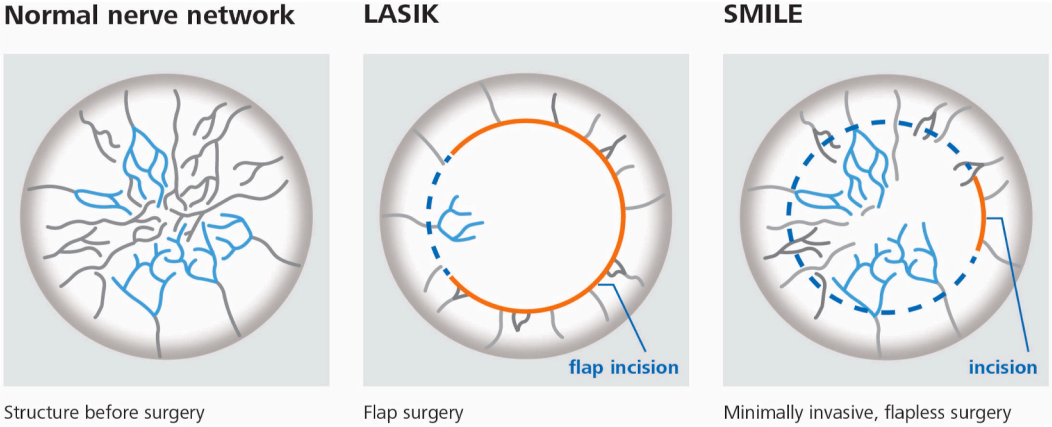

Fig. 10. Schematic changes in corneal nerve network after LASIK and SMILE vs. normal. Courtesy of Carl Zeiss Meditec.

Tear film stability is also significantly reduced due to the surface shape irregularity at the location of the incisions [581].

Dry eye disease has been implicated in the development of late onset corneal ulcers following radial keratotomy, usually over incisions located inferiorly within the interpalpebral fissure. The underlying mechanism has been hypothesized to include bacterial attachment, proliferation and invasion in areas over the incisions of abnormal and ridged epithelium with localized tear film instability [626]. In addition, epithelial basement membrane changes have been found to develop in the early postoperative period after radial keratotomy that may persist up to 12 months postoperatively and trigger epithelial erosions [627].

4.3.2.1.5. Intracorneal ring segments. Intracorneal implants were originally created for myopia correction [628]. In the 2000s, intracorneal ring segments were suggested for the treatment of keratoconus as an alternative to keratoplasty which, at the time, was associated with complications including corneal graft rejection [629]. The implants change the corneal curvature and thereby reduce higher-order aberrations of the cornea through regularizing the surface of the cornea [630]. A comparison of post-surgical outcomes, including visual acuity, refraction, keratometry, and higher-order aberrations, at 6 months and 1 year after implementation of either Intacts® SK intracorneal ring segments (107 eyes) found that both devices improved visual acuity significantly with no major complications [631].

An evaluation of 409 eyes with paracentral keratoconus assessed Snellen uncorrected and best-corrected visual acuity at baseline and post-surgery (Ferrara-type intracorneal ring segments), found improvement in mean uncorrected distance logMAR visual acuity from 0.19±0.19 before implementation to 0.42±0.30 after ($P < 0.0001$) [632]. Safety index was reported to be 1.13 and there was a significant and steep decline in spherical equivalent after surgery (also $P < 0.0001$) [632].

A systematic review and meta-analysis, that included 95 case series studies with 4560 study participants, proposed that intracorneal ring segments with corneal cross-linking and photorefractive keratectomy was a less invasive combination of treatments than intracorneal ring segments with intraocular lens implantation for younger patients in particular [633].

A meta-analysis has been performed to assess the outcomes of MyoRing® and intracorneal ring segment implantations to treat corneal ectasia and evaluate the use of mechanical or femtosecond laser-assisted surgery. In the 115 studies included in the analysis, implantation of both devices resulted in meaningful improvements in keratometric outcomes as well as visual and refractive measurements. Mechanical dissection resulted in higher complication rates when compared to femtosecond laser assisted surgery [634].

4.3.2.1.6. Corneal inlays for presbyopia. Intracorneal inlays are used to increase corneal curvature or to act as a pinhole to restore near vision. They can also minimize the impact of aberrations and even improve the vision in eyes that have corneal irregularities, scars, and iris damage. A benefit of these is that they are reversible [635].

Improved biomaterials and surgical techniques have resulted in the KAMRA™ inlay which has a pupil with a pinhole effect that improves the depth of focus and near vision. Clinical studies have concluded significant improvement in both near and intermediate vision after monocular implantation (non-dominant eye) [636].

A systematic review investigated the visual outcome, satisfaction, and frequency of complications for cases of refractive corneal inlay implantation in 10 case series published between 2011 and 2020 [637]. The review included 308 eyes from 308 participants and in 77.5% of the eyes, the postoperative near visual acuity of 20/32 or better and the inlay-implanted eyes had an uncorrected distance visual acuity of 20/20 or better [637]. The most common complications experienced were halos, poor distance visual acuity, pain, and photophobia. A total of 8.7% of participating eyes had to have the lenses removed because of complications. Overall, the refractive corneal inlays were generally successful, fairly safe, and the participants were mostly satisfied [637]. However, in the long term, there are reports of inlays having been removed due to haze in the visual axis [638].

4.3.2.2. Corneal cross-linking. Corneal ectasias such as keratoconus involve progressive biomechanical weakening and thinning of the cornea, with consequences for patients' vision (increasing irregular astigmatism, myopia, and decreased visual quality) and the ocular surface. Corneal thinning alters corneal nerve morphology, resulting in reduced corneal sensitivity [639-641], and that reductions in corneal sensitivity may alter ocular surface integrity [642].

Corneal cross-linking has become a standard treatment option for progressive corneal ectasias where keratoplasty is not yet necessary and has been in use clinically for 20 years [643]. Corneal cross-linking is an effective method of halting ectasia progression and has been shown to flatten the cornea when used in patients with keratoconus or post-operative ectasia, and this can be associated with a degree of improvement in vision [570,571]. One Cochrane review that included 219 eyes from three studies found that on average eyes treated with corneal cross-linking had 1.92 D lower maximum keratometry values compared with untreated eyes, and better uncorrected visual acuity, by approximately 2 lines, at 12 months [572].

Nevertheless, adverse events may occur after corneal cross-linking surgery, with the most common being temporary corneal haze, but others, including sterile infiltrates, photophobia, stromal edema, blurred vision, ocular pain and irritation, epithelial defects and corneal erosions, increased tearing and dry eye have been reported [570-572]. Transient corneal haze is the most common adverse event, which usually peaks at approximately 3 months after surgery, decreases significantly by 6 months, and usually resolves by 12 months [644]. Haze that persists for more than 12 months is called "permanent haze" which histologically represents a fibrotic scar in the stroma. Treatment with topical steroid can reduce the occurrence of corneal haze [645].

The other potential adverse events are either extremely rare (sterile infiltrates, stromal edema, epithelial defects or corneal erosions) or are typically limited to the immediate days after surgery, in which case they are either self-limiting (photophobia) or managed with topical lubrication, analgesic or anti-inflammatory therapy in the weeks to months after the procedure.

Due to the fact that riboflavin needs to penetrate the stroma for successful cross-linking to occur, and the fact that the corneal epithelium forms an effective barrier, epithelial debridement is required prior to riboflavin application, with epithelial cells proliferating and repopulating the surface over 3–7 days after surgery [643]. However, this is associated with postoperative pain and a small increase in the risk of infection [646]. It has been hypothesized that the corneal denervation associated with epithelial cell debridement may in theory result in decreased blinking rates, increased tear film evaporation, and development of dry eye disease-related symptoms [647-649].

Since 2009, "epi-on" corneal cross-linking using iontophoresis or penetration enhancers (or a combination of both) has been investigated to transport the riboflavin through the epithelium to the stroma. Initially less effective at stopping ectasia progression than standard epi-off techniques, transepithelial corneal cross-linking is now approaching the same level of efficacy [650].

4.3.2.2.1. The ocular surface after corneal cross-linking. Scientific evidence regarding the effect of corneal cross-linking on the ocular surface is limited [651]. Two Cochrane reviews have been published on corneal cross-linking to date, the first reported no ocular surface-related outcomes [572], and the most recent [652], which compared transepithelial and epithelium-off cross-linking procedures, identified only one publication [653] that measured subjective visual function parameters using the Ocular Surface Disease Index. In this publication, transepithelial corneal cross-linking was associated with significantly fewer symptoms on Ocular Surface Disease Index relative to epi-off corneal cross-linking 1 month after surgery.

One potential explanation for the differences in outcome between epi-off and transepithelial corneal cross-linking comes from a report [654] of a prospective randomized impression cytology study. After one month, compared to the control group, corneal cross-linking-treated patients had significantly decreased goblet cell densities in the superior conjunctiva (a region not exposed to UV during corneal cross-linking), but not in the temporal conjunctiva (which is exposed to UV during corneal cross-linking) or the cornea [654]. Epithelial cell morphology appeared to be better in the control group than the corneal cross-linking-treatment group, as control eyes displayed improved epithelial cell-to-cell contact profiles and reduced keratinization on the temporal conjunctiva. However, there were no overall difference between the groups when comparing impression scores [654].

4.3.2.2.2. Corneal cross-linking plus - extra procedures. Certain patients with corneal ectasias can be candidates for corneal cross-linking and wavefront-guided surface ablation with an excimer laser, with the intention of regularizing the corneal surface to give patients a better quality of corrected vision. Approaches like this have been at times called the "Athens" [655] or "Cretan" [656] protocols. In other cases, candidates for cosmetic refractive laser surgery and biomechanically suspect corneas may undergo extra procedures. Despite many of the publications on this topic mentioning the theoretical benefits of SMILE in causing less dry eye disease relative to LASIK surgery, due to the severing of fewer corneal nerves (see section 3.3.2.1.3), very few publications describing these techniques have assessed the ocular surface. A report on the outcomes of accelerated corneal cross-linking in patients with thin corneas (mean pre-surgical central corneal thickness: 501 μm) who first underwent SMILE surgery [657] found no significant difference in Schirmer test scores pre- and postoperatively at day 1 and months 3, 6, and 12.

4.3.2.3. Cosmetic keratoplasty. The leading reasons for penetrating keratoplasty include infectious keratitis (37.1%), herpes simplex keratitis (19.1%), keratoconus (11.2%), bullous keratopathy (8.5%), regrafting (6.7%). Only 4.8% of penetrating keratoplasty are reported to be due to removal of corneal scarring, a more cosmetic reason [658-662].

In cases of anterior scar in patients without visual prognosis, elective anterior lamellar keratoplasty can be performed. A retrospective, comparative, interventional case series found that patients who underwent anterior lamellar keratoplasty experienced advantages over penetrating keratoplasty, including no allograft rejection, longer survival of graft, earlier withdrawal of topical steroids, fewer follow up visits and a reduced recurrence of herpes simplex keratitis, making it the preferable choice for patients with corneal scarring (in the presence of a healthy endothelium and without medical history of perforation) [663]. A Cochrane systematic review found no significant differences between penetrating keratoplasty and anterior lamellar keratoplasty in terms of epithelial defects and other ocular surface complications after the two procedures [664].

4.3.2.4. Phototherapeutic keratectomy. A study reported on the clinical data of 23 eyes of 21 patients suffering from anterior corneal scarring and examined the safety and efficacy of Fourier domain optical coherence tomography-guided phototherapeutic keratectomy and photorefractive keratectomy with the excimer laser [665]. Corneal pathologies included viral keratitis (7 eyes), band keratopathy (4 eyes), traumatic corneal disease (2 eyes), and chemical injury (6 eyes). This surgical procedure when used for removal of anterior corneal scarring had no complications during follow up (mean 10.65 mo, range 3–9 mo) and successfully eliminated or reduced corneal opacities [665].

4.3.2.5. Corneal tattooing. A different approach for cosmetic keratoplasties due to corneal scarring is kerato-pigmentation, also known as corneal tattooing, which consists of permanently staining the cornea by using pigments or chemical products and has been performed with different techniques for centuries [666,667].

Kerato-pigmentation may have a functional purpose of alleviating symptomatic bullous keratopathy, monocular diplopia and photophobia in cases of iris defects and aniridia [667-674] or an esthetic purpose in patients with partial or total irreversible corneal opacities, proving to be safe, cheap and effective [667,675-679]. Combining techniques is also possible, in which stromal tattooing can be combined with anterior lamellar keratoplasty in patients with irregular corneal surfaces and total leukoma [680,681].

The practice of kerato-pigmentation can involve different techniques. The pigment can be injected into the cornea in various forms of inks and dyes through stromal manual or automated punctures or associated with keratectomy or lamellar manual or femtosecond assisted dissection [666,667]. Most studies use micronized mineral or organic tattooing inks as they are marketed for dermatological use, although in some countries it is possible to find inks registered specifically for corneal staining purposes [667,682,683].

The surface pigmentation technique using a chemical reaction with iron oxide, gold chloride or platinum chloride yields colors varying from black to brown, with the advantage of reduced risk of corneal perforation that is inherent to the other methods [676,684]. However, the use of heavy metals such as iron can cause magnetic resonance imaging alterations [667,685] and possibly induce siderosis bulbi [682]. Other complications that have been reported for kerato-pigmentation include color fading, infection, epithelial defects, corneal perforation, intraocular injection of pigment, uveitis and corneal melt [667,685,686].

Generally, most studies demonstrate esthetic satisfaction of patients with the chosen method for kerato-pigmentation as well as an improvement in psychosocial aspects of their lives [667,673,687,688]. The use of tattooing for cosmesis of the eyelid, eyebrow and conjunctiva are covered in the *TFOS Lifestyle: Impact of cosmetics on the ocular surface* report [94].

4.4. Intraocular refractive surgery: phacoemulsification and phakic intraocular lens implantation

4.4.1. Phacoemulsification with intraocular lens

Cataract surgery has been significantly refined over the past decades, evolving to a fast and safe day-surgery procedure, with very low rates of vision threatening complications. The changes have been from large incision intracapsular extraction, with postoperative aphakia to phacoemulsification surgery with sutureless incisions, with intraocular lens implantation. There has been a tremendous transformation in the procedure itself with respect to the speed of recovery of the patients, the intraocular lens technology, and the potential for excellent postoperative vision. In addition to the development of the surgical techniques and intraocular lenses, there has also been a shift in the indications for surgery, from advanced visual loss due to cataract, to dysfunctional lens syndrome and correction of ametropias in the form of refractive lens exchange. Especially in patients already passed the presbyopic age, when cataract formation is anticipated, or the lens already shows early signs of dysfunctionality in the form of light scatter, the procedure of choice for refractive correction is usually lens exchange with phacoemulsification surgery. Non-standard intraocular lenses (i.e. toric intraocular lens) offer a very sophisticated alternative for correction of sphere and astigmatism without compromising quality of vision. In addition, premium multifocal intraocular lenses (e.g. diffractive/refractive intraocular lenses) and extended depth of focus lenses for the management of presbyopia have gained increasing popularity and are continuously evolving. Consequently, phacoemulsification with premium intraocular lens implantation is a common elective procedure used for the correction of presbyopia and ametropias with or without the existence of a visually significant cataract.

Signs and symptoms of dry eye disease are common in the early postoperative period with a peak at about 1 week after surgery.

Incidence of dry eye disease post-cataract surgery has been reported from 8% to 42% of patients 7 days postoperatively [689-692]. Improvement is evident usually at 3 months postoperatively, although some studies report longer rehabilitation time of up to 6 months or more [574,585,689,691-698]. Objective and subjective parameters that are affected include increased dry eye symptoms (Ocular Surface Disease Index), reduced vision-related quality of life, increased tear osmolarity, reduced tear breakup time, reduced Schirmer test scores and increased ocular surface staining (National Eye Institute and Oxford Scores), as well as reduced goblet cell density and meibomian gland function [504, 574,585,586,693,695,697,699,700] (Fig. 11). Patients with diabetes may experience dry eye disease post-cataract surgery more frequently than non-diabetics [689,701], although a recent meta-analysis does not confirm these studies [702].

4.4.2. Mechanisms of damage

Phacoemulsification surgery is associated with dry eye disease through various mechanisms. Surgical transection of the corneal nerves by the corneal incision is a mechanism common to corneal surgical techniques and a causative factor of postoperative dry eye disease [3]. Reduction in both corneal sensitivity and corneal trophic function are the two main components of this effect. Corneal sensitivity after cataract surgery can be reduced for more than 3 months postoperatively before returning to preoperative status [574-576], and the corneal nerve fiber length remains affected 1 year postoperatively [573]. The size and shape of incisions may influence the amount nerves transected, with smaller incisions of modern phacoemulsification surgery introducing less damage to the nerves and favoring faster rehabilitation, while grooved incisions somewhat aggravate postoperative signs [699,703].

Other important surgical parameters related to damage of the ocular surface are the exposure of the ocular surface during surgery and phototoxicity from the surgical microscope light [704]. The duration of exposure to the microscope light has been correlated to post cataract surgery dry eye disease in clinical studies [699,700]. Additionally, in an animal model, light can directly damage the ocular surface and the goblet cells [705]. Active prevention of drying of the ocular surface during surgery protects from developing postoperative dry eye signs. Moreover, use of an aspiration speculum has been shown to worsen dry eye disease temporarily postoperatively [706], and intraoperative coating of the ocular surface with an ophthalmic visco-surgical device has been found to improve tear film parameters (tear breakup time and Schirmer test score) postoperatively, when compared to intraoperative irrigation with balanced salt solution [707,708].

Other sources of harm to the ocular surface include toxicity from drops used during and after phacoemulsification surgery [709]. Local anesthetic and povidone iodine drops can exhibit a direct toxic effect to the ocular surface and induce inflammation [565-567]. In addition, most of the drops used, such as dilating drops and topical local anesthetics, are preserved. As noted previously (section 1.1.1.1), the preservative benzalkonium chloride can cause toxicity to the ocular surface and corneal nerves by triggering inflammation, damaging the goblet cells, and causing increases in dry eye signs and symptoms [8,11,568, 710,711]. Furthermore, usually postoperatively, there is frequent application of topical steroid and antibiotic drops, that are also typically preserved with benzalkonium chloride. A study that explored the effect of non-preserved postoperative treatment for patients with preoperative dry eye disease, found improved tear film parameters in comparison to patients treated with preserved drops [569]. The inflammation and the toxic effect of the drops is also involved in meibomian gland dysfunction after cataract surgery particularly in the early postoperative period [586,697,712]. Preoperative dry eye disease and meibomian gland dysfunction are predisposing factors, and preoperative treatment of meibomian gland dysfunction can protect from further postoperative damage to meibomian glands [585,586].

4.4.3. Other considerations

Femtosecond laser assisted cataract surgery is a more recent development in crystalline lens surgical techniques. Several femtosecond laser platforms exist that aim to create corneal incisions, incisions to correct astigmatism, the capsulorhexis, and to soften the lens and prepare for easier phacoemulsification and aspiration [713]. The laser docking system, as in LASIK surgery, relies on a suction ring that applies a vacuum at the limbus and conjunctiva in order to maintain fixation of the globe and stabilize the laser delivery. After delivering the laser pulses, the surgery continues under the microscope as in conventional phacoemulsification. Dry eye disease signs after femtosecond laser assisted cataract surgery have been demonstrated in clinical studies and may be even more aggravated in the early postoperative period than in conventional phacoemulsification, especially in patients with preoperative dry eye disease [694,714,715], although this effect has not been confirmed by all studies [716]. The suction ring may cause several issues on the conjunctiva including hyperemia, inflammation and damage to goblet cells. These effects have been previously demonstrated by using the suction ring in LASIK, which might have a role in worsening dry eye disease symptoms following the procedure [582,717].

A significant concern regarding patients undergoing elective phacoemulsification surgery is that preoperative untreated dry eye disease might affect the refractive result of the procedure because of reduced accuracy of biometry. Patients with hyperosmolarity of the tears have increased variability in keratometry measurements [718]. Likewise, decreased tear breakup time is correlated with increased variability in axial length measurements [719]. These are significant factors affecting the biometry precision, thereby reducing the refractive predictability of the surgery. Indeed, a study of dry eye disease patients undergoing cataract surgery found that if preoperative dry eye disease was not treated there was significantly reduced refractive predictability [720]. Consequently, patients' increased expectations from surgery might not be met due to failure to achieve the desired refractive result if they have preoperative dry eye disease that has not been managed.

Another factor that must be taken into consideration with regard to postoperative dry eye disease is the increasing demand for use of multifocal lenses for the management of presbyopia in modern cataract

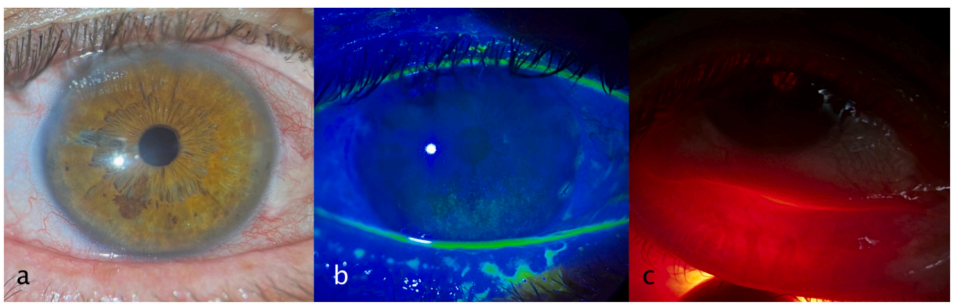

Fig. 11. Slit lamp photo of a patient 1 day after phacoemulsification and IOL implantation (a), with significant corneal staining that developed postoperatively (b), and meibomian gland dysfunction that already existed preoperatively as seen by the loss of meibomian glands (c). Courtesy: Georgios A. Kontadakis, MD, PhD.

surgery. Due to their complex optical properties, these lenses can only function properly in an optimal undisturbed optical system [721]. Dry eye disease can significantly increase corneal aberrations, decrease contrast sensitivity and cause fluctuations of vision [722-724]. This can compromise the performance of multifocal lenses and significantly reduce quality of vision in patients that have been implanted with such lenses. Postoperative dry eye disease in patients implanted with trifocal and extended depth of focus lenses remains one of the main causes of dissatisfaction with visual outcome following surgery [725-727].

4.4.4. Phakic intraocular lens implantation

A relatively common intraocular elective procedure for refractive correction is the implantation of a phakic intraocular lens. This is usually employed in cases where corneal refractive surgery is contraindicated, such as thin corneas or ametropia outside the range of laser treatment. There are two types of phakic intraocular lenses currently approved by the US Food and Drug Administration, a posterior chamber phakic intraocular lens and an iris claw phakic intraocular lens [728]. Both are implanted via a corneal incision in a procedure performed in the operating room under the surgical microscope. Although phakic intraocular lens implantation is considered to be safer than laser refractive procedures for the ocular surface, there is still a risk of dry eye possibly related to the same mechanisms as in phacoemulsification surgery [729]. Corneal incision formation, ocular surface exposure under the operating microscope and use of drops with surface toxicity are involved in this procedure similarly to phacoemulsification.

There only limited data in the literature on dry eye after phakic intraocular lens implantation demonstrating a lower postoperative incidence of dry eye in comparison to laser surgery. A recent prospective study of 60 patients implanted with the posterior chamber phakic intraocular lens showed a marked average change in subjective and objective metrics of dry eye 1 month postoperatively that partially recovered after 3 months [730]. Moreover, the patients who had preoperative dry eye symptoms in this study were significantly more affected postoperatively [730]. Another study that did not account for preoperative tear film status of the patients, found that dry eye symptoms peaked at three months affecting 29% of eyes, and demonstrated subsequent improvement with only one out of 55 patients reporting bilateral dry eye symptoms at twelve months [731]. Other studies with refractive primary outcomes reported dry eye symptoms in 3–5% of patients after phakic intraocular lens implantation [732,733].Consequently, aggravation of dry eye symptoms after phakic intraocular lens implantation is a concern mostly in the early postoperative period, but may persist in the long term in patients that dry eye had been present preoperatively.

4.5. Other surgeries

4.5.1. Neurosurgical procedures

Dry eye disease and neurotrophic keratopathy are known complications of specific neurosurgical procedures. Dry eye disease has been reported as one of the main complications after gamma knife radiosurgery for trigeminal neuralgia [734,735]. There is a high incidence of dry eye disease after repeat procedures [736]. However, treatment of vestibular schwannomas with the gamma knife results in only 13.2% of cases of dry eye disease compared to 25.3% with microsurgery [737]. Persistent dry eye disease without keratopathy has been reported after removal of trigeminal schwannomas due to damage to the vidian nerve [738]. Endoscopic trans-nasal trans-pterygoid can also cause dry eye disease due to damage to the vidian nerve [739,740].

4.5.2. Bariatric surgery

Bariatric surgery is a group of surgical techniques that are increasingly used for the treatment for severe obesity [741]. The procedures are categorized as malabsorptive or restrictive, or a combination of both techniques. Despite the high efficacy of the procedures, there is a range of possible complications that includes malabsorption of vitamin A due to several reasons such as vomiting, food intolerance, reduced gastric secretion and detour of the intestinal absorption area [742].

Vitamin A deficiency is the leading source of xeropthalmia and night blindness. Several such cases following bariatric procedures have been reported. The symptoms in these cases developed months to years after the bariatric procedures [743-745]. Corneal perforation due to xeropthalmia was recently reported in two cases [746], as well as a cornel melt in a patient that underwent LASIK surgery 8 years after bariatric surgery [747]. The patients in both reports failed to use vitamin supplements and developed severe vitamin A deficiency.

The incidence of vitamin A deficiency after bariatric surgery varies among studies depending on the surgical technique. It has been estimated at around 52% at 1 year and 69% at 4 years after biliopancreatic diversion with a duodenal switch technique [748] and at around 11% after Roux-en-Y gastric bypass [749]. In contrast, another study failed to confirm an effect on vitamin A levels after bariatric surgery in patients either using or not using food supplements [750]. In the same study, with the use of a questionnaire, the incidence of symptomatic dry eye disease was 60.7% while the ocular surface of the patients was clinically normal [750].

Other investigators also reported apparently normal ocular surfaces in their group of patients who have undergone bariatric surgery [751]. However, in another study, the tear breakup time of all patients undergoing bariatric surgery was low and the findings were modified by a protein diet. A questionnaire demonstrated a tendency to dry eye disease in that study [752]. Discrepancies among studies might rise from the different surgical techniques used. Nevertheless, patients undergoing bariatric surgery should be followed for possible ocular complications.

The *TFOS Lifestyle: Impact of nutrition on the ocular surface* report also reviews bariatric surgery and the evidence for the effect of this surgery on the ocular surface, as well as providing information via a systematic review on the effect of bariatric surgery as an intentional food restriction on the ocular surface [245]. That systematic review found very low certainty evidence for no changes to Ocular Surface Disease Index scores or tear film break up time 12 months after bariatric surgery, and fair or poor quality reports of post-surgical significant improvements in corneal nerve fiber density, branch density, and fiber length [245].

4.5.3. Radiation therapy

Radiation therapy has a well-established association with the development of dry eye disease. Treatment of head and neck malignancies as well as Graves Ophthalmopathy with radiation can affect the lacrimal apparatus and aggravate dry eye disease in a significant percentage of patients [3].

The incidence of dry eye disease after such treatment varies depending on the proximity of the radiation target to the orbital structures and the dose of the radiation. The incidence of severe dry eye disease, retinopathy and optic neuropathy appears to increase steeply after doses of 40, 50, and 60 Gy, respectively [753]. Dry eye disease following radiation therapy can be a consequence of damage to any of the structures of the lacrimal apparatus, the lacrimal gland, the goblet cells or the meibomian glands. The onset can be a few months after the procedure [754].

5. Ocular surface nerves and elective procedures

Many elective medications and procedures have anatomical and biological impacts on ocular surface nerves (see sections 2.1.1.1, 3.1, 4.1.1.1, 4.1.1.2.4, 4.1.3, 4.1.12, 4.1.13, 4.3.1, 4.3.2.1, 4.4.2, 4.5.1). Therefore, this section focusses on ocular nerve physiology and diagnosis of the consequences of changes to ocular nerves.

The ocular surface is densely innervated by sensory fibers of the ophthalmic branch of the trigeminal nerve. While the conjunctiva receives modest innervation, the cornea is the most densely innervated tissue of the body and, as such, of all ocular tissues.

Corneal innervation arises from midstromal nerve bundles that enter the cornea in a radial fashion from the limbus and subsequently branch [230,755,756], forming a stromal plexus in the anterior one-third of the stroma [756]. Most stromal axons then penetrate the Bowman's layer and from the subbasal plexus below the basal epithelium, terminate within the epithelial layers. In addition, nerves from the pericorneal plexus directly innervate the epithelium [756]. While some axons terminate as free nerve endings [756], others proceed in close anatomical proximity to stromal keratocytes, macrophages, conventional dendritic cells and plasmacytoid dendritic cells [757-760].

The subbasal plexus constitutes the most dense layer of corneal innervation and can be visualized in patients by *in vivo* confocal microscopy and quantified for both nerve density and morphology at a quasi-histological level [761-764]. These images allow detailed *in vivo* studies on anatomical and biological levels of ocular surface diseases, such as dry eye disease, neurotrophic keratopathy, neuropathic corneal pain, and the assessment of elective procedures, such as laser vision correction surgery, and penetrating keratoplasty on corneal innervation [763-769]. Corneal subbasal nerve density in the normal central human cornea ranges from 18 to 27 mm/mm^2 as assessed by *in vivo* confocal microscopy [221,770] to 40–55 mm/mm^2 as assessed by immunohistochemical staining [756]. Electrophysiological recordings of sensory corneal nerve fibers have demonstrated the presence of different types of ocular sensory neurons at a functional level. These can be classified as polymodal nociceptors, cold thermoreceptor neurons and mechano-nociceptors [771,772], each with a specific molecular phenotype and morphology [773].

The conjunctiva is innervated by myelinated and unmyelinated axons with free peripheral endings, containing calcitonin-related gene peptide and substance P [774-781]. The free nerve endings are typically located around blood vessels, but are also found in the epithelium, around meibomian gland acini and lymph follicles [775,776,778,780,782]. Comparisons of corneal and conjunctival sensitivity to mechanical or acidic stimuli has demonstrated that the bulbar conjunctiva is less sensitive to both stimuli than the cornea [783,784]. Activation of conjunctival polymodal receptors with acidic stimulation can evoke irritation and pain [785], while cooling stimuli produced cold sensations [785].

5.1. Neuropathic corneal pain

Neuropathic corneal pain has been identified as a complication of laser vision correction surgeries [786-789], cataract surgery [698,790,791] and glaucoma surgery [792]. Neuropathic corneal pain is caused by injury or disease affecting the corneal somatosensory pathways [786,793-800]. It is characterized by non-specific ocular symptoms, including pain, discomfort, burning, grittiness, irritation, dryness, light sensitivity, hyperalgesia (enhanced pain response to infra-threshold noxious stimuli) and allodynia (pain caused by non-noxious stimuli), which occur out of proportion to what could be expected from the ocular surface findings [786,793]. This lack of specific symptoms as well as lack of clinical findings and techniques to evaluate corneal nerve morphology during a routine visit make the diagnosis challenging [786,793]. Neuropathic corneal pain can occur as a result of complex pathophysiological mechanisms affecting not only peripheral sensory nerves, but also higher order somatosensory pain pathways, thalamus, sensory cortex and inhibitory pain pathways [786,793-800]. Peripheral nerve damage and inflammation may result in increased nerve sensitivity and augment peripheral pain [786,793-800]. Over time, the central neurons may become more highly responsive to stimuli, in addition to spontaneous discharges, suggesting central sensitization [786,793-800]. Peripheral and central sensitization result in development of chronic, persistent symptoms including hyperalgesia and allodynia [786,793-800].

The patient satisfaction rates after laser vision correction surgeries are reportedly over 95% [801,802]. However, after suboptimal vision, dry eye disease and ocular discomfort are the next most common dissatisfaction reasons after laser vision correction surgery, and these are reported to be present in 20–40% of postoperative cases [559,589,803]. Although post-LASIK dry eye disease or tear film disorders can be temporary [589,804,805], 20% of patients complain of persistent symptoms and 2–3% of the patients describe these symptoms as bothersome [801,806]. Additionally, the incidence of chronic dry eye disease after refractive surgery of at least 6 months in duration is 0.8% [807]. A retrospective study of 16,000 cases demonstrated a prevalence of neuropathic corneal pain after laser vision correction surgery of 1 in 900 cases [564]. These numbers are comparable to other well-known refractive surgery complications, such as corneal ectasia (0.2% incidence), infection (0%–1.5% incidence), and mechanical complications (0.16%–15.0% incidence). Previous dry eye disease, ocular surface disease and the presence of systemic autoimmune disease or chronic pain conditions are considered the main risks for neuropathic corneal pain development [564].

Understanding the potential underlying mechanisms is important to the management of post-laser vision correction surgery neuropathic corneal pain. Damage to corneal nerves during laser vision correction surgery alters the afferent stimuli of the neural reflux arc, resulting in decreased tear production and quality, and low tear breakup time [773,805]. Further, decreased tear fluorescein clearance, blinking rates, increased tear evaporation, and osmolarity can also occur [805]. Changed tear composition and increased tear osmolarity, together with other underlying risk factors, may activate inflammatory cascades or prevent their resolution. There might be a loop effect, with inflammation developing as a result of disruption of the neuronal arc, and neuroinflammation contributing to the inflammatory process in post-operative patients [805,808]. Corneal nerve regeneration may be impaired, resulting in aberrant nerve regeneration and the development of micro-neuromas [808], contributing to neuropathic pain.

Detection of corneal nerve dysfunction, such as decreased stimulation thresholds, peripheral and central sensitization, is important in neuropathic corneal pain diagnosis and management [786]. Corneal esthesiometers such as the Cochet-Bonnet and Belmonte esthesiometers have been previously used for this purpose [809-811]. The Cochet-Bonnet contact esthesiometer evaluates only mechanical stimulation, and the Belmonte esthesiometer is expensive and relatively complex to use, and is not commercially available [810,812].

In clinical practice, especially in refractive surgery clinics, physicians need inexpensive, feasible and easy to interpret methods. As polymodal nociceptors of cornea can be stimulated by 5% hypertonic sodium chloride [813], patients can be asked to assess discomfort levels based on visual analogue scales after applying a drop of 5% hypertonic saline [814,815]. Twenty seconds after the drop, patients are asked to re-evaluate their pain level. Exaggerated pain response and pain level higher than baseline at 20 s after drop instillation can be interpreted as presence of probable functional alterations of corneal sensorial nerves [814,815], and suggestive of hyperalgesia or corneal hypersensitivity. Another test, the proparacaine challenge test, has been proposed to differentiate peripheral and central sensitization [786,793,797]. In this test, patients are asked to report their discomfort level based on a visual analogue scale after one drop of 0.5% proparacaine eye drop has been instilled. After 90 s, patients re-evaluate their pain level. Total pain relief, partial relief and unchanged or exaggerated pain level are interpreted as peripheral, mixed, and central sensitization, respectively [786,793,797].

The observation and objective assessment of corneal nerves by slit-lamp examination is not possible. Laser *in vivo* confocal microscopy (HRT3/RCM, Heidelberg Engineering, Heidelberg, Germany) is a non-invasive, high-resolution device, providing optical biopsies, allowing real-time visualization of corneal structures at the cellular level, including corneal nerves and dendritiform cells [761,763,816,817]. Decreased corneal nerve density, increased tortuosity, beading and reflectivity have been identified as morphological abnormalities of corneal nerves in various diseases [761,763,817] (Fig. 12). The presence

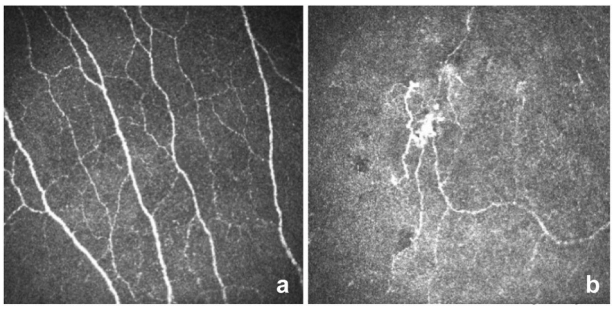

Fig. 12. *In vivo* confocal microscopy of the cornea from (a) a normal eye and (b) a patient with neuropathic pain showing typical changes in the corneal nerve network – beading, tortuosity, increased reflectivity and micro-neuromas. Courtesy: Pedram Hamrah, MD.

of micro-neuromas, visualized as hyper-reflective enlargement of injured nerve endings, are believed to be a marker of nerve damage and aberrant regeneration [764,786,818]. There is an association between decreased corneal nerve density and allodynia and photoallodynia in post-LASIK neuropathic corneal pain patients [789,819]. Further, the presence of micro-neuromas has been reported to be highly specific for neuropathic corneal pain [789,819]. However, neuropathic corneal pain after laser vision correction surgery may develop early in the post-operative phase, during which time the central subepithelial corneal nerve plexus may appear to be totally absent. Therefore, in patients with laser vision correction surgery-related pain, lack of corneal nerves might be considered as an early sign of neuropathic corneal pain if there is appropriate clinical correlation. Furthermore, increased dendritiform cell density in the cornea in asymptomatic contact lens wearers [820] and in the absence of apparent clinical inflammation in meibomian gland dysfunction [821] suggests that *in vivo* confocal microscopy can detect subclinical inflammation.

The diagnosis of neuropathic corneal pain remains challenging, due to a lack of objective findings on slit-lamp biomicroscopy. Therefore, preoperative and postoperative evaluation of corneal nerve function using the hypertonic saline response or proparacaine challenge test, and assessment of corneal nerve morphology and corneal inflammation by in vivo confocal microscopy are most promising diagnostic tools. Detailed preoperative evaluation to identify risk factors may reduce the risk of development of this condition in the future. Current treatment strategies include control of inflammation and suppression of central mechanisms of pain.

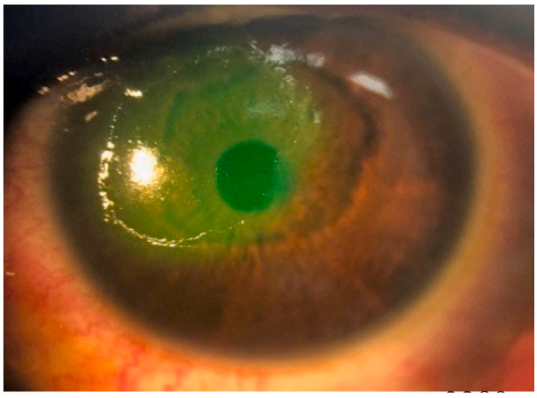

Fig. 13. Slit lamp photo of a grade 2 neurotrophic keratopathy showing round epithelial defect surrounded by smooth and rolled edges with loose corneal epithelium. Courtesy: Maria EXS Araújo, MD PhD.

5.2. Neurotrophic keratopathy

Elective procedures, resulting in corneal nerve damage, can result in neurotrophic keratopathy when nerve damage is persistent. Neurotrophic keratopathy has been identified as a complication of contact lens misuse, ocular surgeries, in particular laser vision correction surgeries [822,823], cataract [824] and glaucoma surgery [825], or due to drug toxicity from elective medications [792,826,827]. Neurotrophic keratopathy is characterized by impaired corneal nerves, resulting in loss of corneal sensation (corneal hypoesthesia or anesthesia) and subsequent corneal epitheliopathy and persistent epithelial defects [828] (Fig. 13). Further, loss of corneal sensation causes patient-reported symptoms of discomfort to be disproportionately milder than expected based on the objective clinical findings on slit-lamp examination [829]. Neurotrophic keratopathy can be progressive and, if left untreated, may cause significant visual compromise, stromal melting, and potentially corneal perforation. In particular, early-stage neurotrophic keratopathy can often go undiagnosed or be misdiagnosed [830].

Neurotrophic keratopathy is caused by compromised corneal nerves. Corneal nerves typically release neurotransmitters, neuropeptides (e.g. substance P, calcitonin gene-related peptide), neurotrophins (e.g. nerve growth factor, brain-derived neurotrophic factor), and growth factors (e.g. epidermal growth factor) that are critical to corneal epithelial differentiation, proliferation and migration, as well as corneal collagen production [831]. Therefore, impairment of corneal nerves in neurotrophic keratopathy can disrupt epithelial homeostasis, reducing the ability of the corneal epithelial layer to heal and maintain its integrity [832].

As stimulation of the ocular surface sensory nerves via the trigeminal ganglion and the trigeminal nucleus of the brainstem results in stimulation of the lacrimal gland via the parasympathetic nerves [773], compromise to the ocular surface nerves might result in abnormal lacrimation and may induce tear film instability and hyperosmolarity [826]. Abnormal innervation further results in a reduction in the amount of nerve and epidermal growth factors as well as other nerve-derived factors, impacting the integrity of the corneal epithelium [826]. Impaired epithelial integrity results in mild, moderate or severe superficial punctate epitheliopathy, which can progress to epithelial defects. Moreover, the natural tear exchange may be hindered, resulting in a build-up of harmful agents and pro-inflammatory cytokines on the ocular surface, which is only exacerbated by a reduced blink reflex [826]. The hyperosmotic environment may induce cell death and an increased level of matrix metalloproteinases, which may lead to the involvement of the stromal layer in the form of stromal melts/perforation, as observed in later stages of the disease [826].

Neurotrophic keratopathy, given its nature, does not commonly result in symptoms of discomfort compared to dry eye disease and other ocular surface diseases. Instead, patients typically report with visual complaints due to the poor quality epithelium and tear film and a significantly reduced blink rate [829]. The patient's past medical history and onset of current disease should first be evaluated for any potential etiologies related to neurotrophic keratopathy. Examination of patients with potential neurotrophic keratopathy should involve a careful examination of the cornea and ocular surface by slit-lamp biomicroscopy. Superficial punctate epitheliopathy is common in neurotrophic keratopathy [829]. However, epitheliopathy is also common in a number of other ocular surface diseases, such as dry eye disease, exposure keratopathy, and toxic keratoconjunctivitis, among others [833]. Punctate staining associated with neurotrophic keratopathy is most commonly found in the central cornea, which is different from the inferior or interpalpebral locations associated with dry eye disease and exposure keratopathy. The presence of a persistent epithelial defect is also characteristic of neurotrophic keratopathy [829]. The stroma underlying the defect may be edematous with accompanying Descemet's folds, but stromal involvement is seen only in the late stages of the disease [826]. Other findings that are common in neurotrophic keratopathy include a

discordant extent of conjunctival inflammation relative to the corneal findings, and localized areas of superficial neovascularization from previous epithelial defects. Iris atrophy and stromal scarring may be noted and could suggest an initial herpetic etiology [826].

A potential neurotrophic keratopathy diagnosis should be confirmed by corneal esthesiometry [829]. A Cochet-Bonnet esthesiometer allows for separate quantitative sensitivity measures of central, superior, inferior, nasal and temporal corneal areas, which can be used in comparisons during follow up visits. In the absence of a Cochet-Bonnet esthesiometer, a cotton wisp test (cotton wisp is touched to the cornea) may allow for a gross corneal sensation evaluation. However, assessment will only be able to be made comparatively between eyes. *In vivo* confocal microscopy can confirm decreased density of corneal nerves. These nerve abnormalities are much more pronounced in neurotrophic keratopathy than in dry eye disease or other ocular surface diseases. Furthermore, asymmetry in corneal nerve loss is typically apparent in cases with unilateral neurotrophic keratopathy.

The Mackie classification is the most commonly used classification of neurotrophic keratopathy and characterizes the disease into three stages based on clinical presentation [834]. In stage I neurotrophic keratopathy, patients typically show unilateral or bilateral vital dye staining of the central cornea or diffuse superficial punctate staining of the corneal epithelium. Signs of compromise to the tear film may include increased viscosity of the tear mucus, which usually manifests as discharge on the lashes, and decreased tear break-up time. Patients with neurotrophic keratopathy also may present with epithelial hyperplasia and irregularity, which is not commonly seen in dry eye disease. Patients who go untreated in stage I often develop neovascularization and stromal scarring in the areas of staining. Gaule spots may also be observed, which are small, scattered areas of dried epithelium. Corneal dellen have also been observed in these early-stage patients. Stage II neurotrophic keratopathy is characterized by a non-healing corneal epithelial defect. At times there also may be an anterior chamber reaction or a sterile hypopyon, but these signs are rare. Stage III neurotrophic keratopathy includes persistent epithelial defects with presence of stromal melting and/or perforation. Treatment of neurotrophic keratopathy should be tailored according to disease stage and severity [826,835]. The goals of treatment are to promote epithelial healing, prevent progression of stromal melting, and/or to induce corneal nerve growth.

6. Prophylaxis and management

The prophylaxis and management of individual iatrogenic causes of dry eye disease and other ocular surface disorders will vary depending on the inciting cause [3]. However, there are some general guidelines that may apply. For example, the management of dry eye disease prior to corneal refractive surgery and cataract maybe similar, despite the fact that the severity of dry eye disease following both procedures is different [3].

6.1. Topical drugs

A subtraction strategy can be helpful. The identification of the offending drug is the first step, which may be challenging, since side effects may occur late, the patient maybe on polypharmacy, the ocular surface may have pre-morbid morbidity, or the treatment cannot be stopped without endangering health. If possible, stopping or switching to a preservative-free or low-toxicity preservative formulation of the drug should be attempted, as benzalkonium chloride toxicity is dose-dependent [18,300]. Alternatively, more invasive procedures may be options in multiple polypharmacy cases [14,836]. In cases of patients with associated dry eye disease, options without benzalkonium chloride should offered right from the initiation of treatment.

6.2. Systemic drugs

Recognition of the culpable agent can often be derived from prior knowledge of the dry eye disease side effects of systemic medications. However, definitive evidence can be obtained by withdrawing and then rechallenging the individual. In certain cases when this is not possible, a chronological history with respect to the timing of the first dose to onset of symptoms may be helpful. It may not be feasible to simply stop the offending medication, hence alternatives with different mechanisms of action, may be sought. If this is not possible, a dose adjustment or concomitant use of topical lubricants or other topical therapies may be considered [107,837]. Reducing systemic side effects may be achievable with better drug design and formulation (e.g. increasing target specificity, use of pro-drugs, sustained release systems, or allowing localized high concentration delivery).

6.3. Surgical and non-surgical procedures

6.3.1. Eyelids and periorbital region

Pre-procedural eyelid disease and dry eye disease should be actively treated [286]. Following an oculoplastic procedure, typically the first step in the management of iatrogenic induced dry eye disease is medical therapy e.g. artificial lubrication (non-preserved), eyelid hygiene, topical low-potency steroids, and cyclosporine A [275,298]. In more persistent cases of dry eye disease, punctal occlusion may be considered. In more advanced cases, innovative devices such as thermal pulsation [393] and intense pulsed light therapy [402] may provide additional benefit, especially in evaporative dry eye disease.

Intraoperative intravenous systemic steroids may help shorten the postoperative inflammatory response [838]. Ocular chemosis can be managed by cold compression, head elevation, massage and eye patching [838]. Topical steroids or phenylephrine with or without oral steroids may also offer benefit in protracted cases [839]. Lagophthalmos and lower eyelid retraction may be managed by massage with steroid ointments, eyelid traction, and taping [840]. For more severe cases, surgical intervention may be required, such as medial or lateral tarsorrhaphy, canthal tendon repair or reconstruction, and surgical revision of the scar with a skin graft.

6.3.2. Conjunctiva

Extensive reconstruction of the conjunctival surface following removal of large ocular surface lesions can put the patient at risk of iatrogenic dry eye disease [3,4]. In addition, topical adjuvants used in tumor removal (e.g. mitomycin C and 5-fluorouracil) are known to be toxic to the epithelium of the ocular surface [515,516,518-523]. Therefore, the ocular surface should be optimized prior to these surgical procedures, since a negative impact can be predicted in the early post-operative period.

The most common ocular surface procedure, pterygium removal with conjunctival autograft, is known to have significant effects on the ocular surface [502]. Pterygium-associated tear hyperosmolarity and abnormal tear film function can improve after its surgical removal, but increases in hyperosmolarity have been noted in recurrent cases. Following conjunctivochalasis surgery, there can be an improvement in objective and subjective dry eye disease [507].

6.3.3. Cornea

The management of dry eye disease prior to any corneal procedure (laser or surgical) is important for a reproducible and consistent outcome following surgery [822,841,842]. Topical preservative-free lubricants, cyclosporine A, dietary alpha omega fatty acids, maintaining a humidity >40–50%, punctal plugs and even autologous serum drops are helpful adjuvants [608,841]. Concomitant infections such as ocular rosacea and lid margin disease associated with Demodex may need specific treatments in the form of lid warming and compression, or administration of doxycycline or azithromycin. The treatment should be

started preoperatively and last at least 6 months from the last surgical or laser procedure [588].

Iatrogenic neurotrophic dry eye disease is very common after all forms of corneal laser refractive procedures. Typically the symptoms will resolve in the majority of cases by 6 months postoperatively, but they can continue for longer in some patients [822]. Enhancement surgery is often associated with recurrence of dry eye disease symptoms and signs, and the ocular surface should be actively treated, with the aforementioned options prior to, and after, enhancement.

6.3.4. Intraocular refractive surgery

It is important to optimize the ocular surface prior to intraocular refractive surgery to improve the accuracy of ocular biometry, in addition to reducing the risk of postoperative patient dissatisfaction [718]. Preoperatively, patients with eyelid margin disease require eyelid hygiene, warm compression, oral or topical antibiotics and an anti-inflammatory administration [843]. Postoperatively, artificial tear lubricants can improve tear breakup time, corneal fluorescein staining and dry eye disease symptoms. Ocular surface inflammatory modulators such as cyclosporine and lifitegrast may enhance tear breakup time, reduce corneal fluorescein staining, improve Schirmer test results, and symptoms, and reduce corneal aberrations [844-846].

6.3.5. Other areas

Intraoperative strategies to minimize ocular surface damage include gentle manipulation of ocular surface tissue, preservation of the conjunctival architecture post-peritomy, secure wound closure, minimal thermal cautery use, reduced surgical time to avoid prolonged corneal exposure, use of a corneal light shield, frequent instillation of balanced salt solution and coating of the ocular surface with an ophthalmic viscosurgical device [3,4,707,708].

For glaucoma patients with pre-existing ocular surface disease, the use of preservative-free medication or laser should be considered as first-line treatment options [847]. For retinal surgery, small gauge 25/27 pars plana vitrectomy is preferred over conventional 20/23g systems, in order to reduce the ocular surface disturbance and allow for faster healing. Non-contact viewing systems are also preferred, to reduce corneal damage [848,849].

For diabetic patients, who are particularly at risk of ocular surface problems postoperatively, pre-surgery glucose levels should be optimized and maintained for as long as possible. Procedures that compromise the ocular surface (e.g. epithelial debridement and exposure to anti-metabolites) should be kept to a minimum. The use of topical rebamipide, aldose reductase can increase goblet cells density and or matrix metalloproteinase inhibitors can improve the rate of corneal wound healing [850-852].

For radiation-induced dry eye disease, topical treatment includes the use of preservative-free topical artificial lubricants, autologous serum and immunomodulators such as cyclosporine [853-855]. In more severe cases, therapeutic contact lenses, amniotic membrane patch and/or graft, and surgical tarsorrhaphy may be required. Pre-radiation therapy with erythropoietin has been shown to have a protective effect on the corneal epithelium in mice through its anti-oxidative stress effect [854]. It has been shown to allow some recovery of lacrimal gland function following radiation, but more studies are required to validate this hypothesis prior to use in humans.

7. Systematic review: The impact of SMILE on quality of life

7.1. Introduction

Keratorefractive laser surgical procedures, including photorefractive keratectomy, LASIK and SMILE, together with phakic intraocular lens implantation, have benefited from continued innovations over the past decades [612,856,857]. The rates of vision-threatening complications have decreased, and the visual outcomes have continued to improve [559,560,858]. However, surgically-induced higher order aberrations and optical irregularities, together with postoperative dry eye and ocular surface disease, have been associated with reductions in patients' quality of vision and quality of life [608]. Asymptomatic patients experiencing improved quality of vision following refractive surgery often report improvements in their quality of life [857].

Surgical transection of the corneal nerves is a common mechanism of corneal surgical techniques and a causative factor of postoperative dry eye [3]. As described in section 4.3.2.1.3, SMILE is a refractive surgery involving a femtosecond laser to create a small incision and delineate a refractive lenticule within the corneal stroma. The lenticule is separated from the rest of the stroma by spatula dissection and then removed with forceps through the laser incision [611]. SMILE induces less afferent nerve fiber damage than other laser refractive surgeries [610-616,859].

Several systematic reviews have evaluated the quality of life after surgical procedures, but quality of life after SMILE is not well understood. This systematic review assessed the literature relating to quality of life following SMILE.

7.2. Methods

The review was conducted by four of the authors (REH, EB, JAPG and DTA) and was written in accordance with the Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) [860] statement. The protocol was registered prospectively in PROSPERO (CRD42022301818) [861].

7.2.1. Search methods

The search strategy is provided in PROSPERO protocol [861]. In brief, PubMed and Ovid Embase electronic databases were searched from inception to January 13th, 2022.

7.2.2. Eligibility criteria

The population of interest was adult patients undergoing refractive surgery. Initially all types of refractive surgeries were to be included in the review. However, this was modified to focus on studies evaluating SMILE. To be included in the review, studies needed to assess quality of vision or quality of life as an outcome at some time point and using any measure.

The studies included randomized controlled trials, non-randomized interventional studies, quasi-randomized clinical trials, systematic reviews, case series (i.e., case studies including two or more participants), and observational studies (e.g., cohort studies, case-control studies). Studies were excluded if they were case reports and studies of refractive surgery as a therapeutic treatment for conditions (such as corneal dystrophy, keratoconus, etc.), as well as studies of incisional surgery, intracorneal implants, ring segments and surgery for non-refractive purposes (e.g., cataract surgery).

7.2.3. Study selection

The online review management software (Covidence, Veritas Health Innovation, Melbourne, Australia) was used for study selection. Titles and abstracts of studies identified by the electronic searches were reviewed and classified as potentially eligible or ineligible by two independent reviewers who were masked to each other's initial decisions. Discrepancies were resolved by a third reviewer. Full text articles of potentially eligible studies were obtained and classified as included or excluded by two independent reviewers. Discrepancies were resolved by a third reviewer, if necessary.

7.2.4. Data extraction and management

Data extraction was performed by two independent reviewers and disagreements were resolved through consensus with a third reviewer. The data extraction form was piloted before beginning complete extraction and data extraction in Covidence.

The extracted characteristics of the studies were: study type,

location, number of participants, trial registry details, participant description, treatments received with number per group, baseline characteristics, study dates or duration, types of quality of life outcomes, sample size, analysis methods, change in quality of life score or comparison in quality of life score between trial arms and adverse event occurrence.

7.2.5. Risk of bias assessment

Depending on the study design the following risk of bias tools were applied, using data collection forms set-up within Covidence. This was performed independently by two reviewers with a third providing the consensus decisions. The following risk of bias tools were used.

- Randomized clinical trial: Risk of Bias 2.0 tool [862].
- Non-randomized intervention studies: Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) tool [863].
- Cohort and case-control studies: Newcastle Ottawa Cohort Scale and Newcastle Ottawa for Case-Control Scale [864].
- Pre-Post Studies with No Control Group: NIH Assessment Tool for Case series/Before-After studies [865].
- Systematic Reviews: Assessment of Multiple Systematic Reviews (AMSTAR) Checklist [866].

7.2.6. Primary outcome

(i) Health related quality of life (any metric and time point)
(ii) Vision-related quality of life (any metric and time point)

7.2.7. Secondary outcomes

(i) Patient-reported outcomes closely related to quality of life. Potential domains included activity limitation, mobility, convenience, health concerns, visual symptoms, ocular-comfort symptoms such as pain and dry eye symptoms, general symptoms, cosmetic appearance of the eyelid and orbit, emotional well-being, and social and economic factors at the pre-specified time points. Special attention was given to immediate postoperative findings (less than 6 weeks) and to outcomes that persisted for 6 weeks or more.
(ii) All adverse outcomes reported in studies that reported health related quality of life or vision related quality of life questionnaires were recorded, including serious adverse events or adverse events related or unrelated to the trial or intervention studied.

7.2.8. Data synthesis and analysis

Meta-analyses were performed for each of the primary and secondary outcomes, for each intervention vs comparison, if there were at least two studies reporting data in a consistent format and if a pooled analysis was deemed clinically appropriate (i.e., if the clinical populations in the studies were similar). Forest plots were produced to show the outcomes of the meta-analyses. If more than three randomized clinical trials were included in each meta-analysis, a random-effects model was used, otherwise a fixed-effect model was used. If there were insufficient numbers of included studies, inconsistency between the study results or if meta-analyses were deemed inappropriate, a tabular or narrative summary of the key findings was provided.

7.3. Results

The electronic search yielded 6830 references, from which 1232 duplicates were removed, leaving 5598 studies to be screened for title and abstract content. In total, 4872 studies were excluded based on titles and abstracts and 548 studies based on full-text evaluation, resulting in 178 studies meeting the pre-specified eligibility criteria. Studies were excluded at the full-text stage most commonly because of outcome measures and interventions that were not in the outlined objectives of this review. Fig. 14 shows the PRISMA flow diagram with reasons for exclusion after full text review documented.

To enable a more focused clinical question to be answered, it was decided that only articles evaluating SMILE would be analyzed and assessed for the current analysis. After applying the additional requirement of SMILE as an intervention, 23 articles remained and were included and proceeded to the data extraction phase [609,625,858,867-886] (Fig. 14).

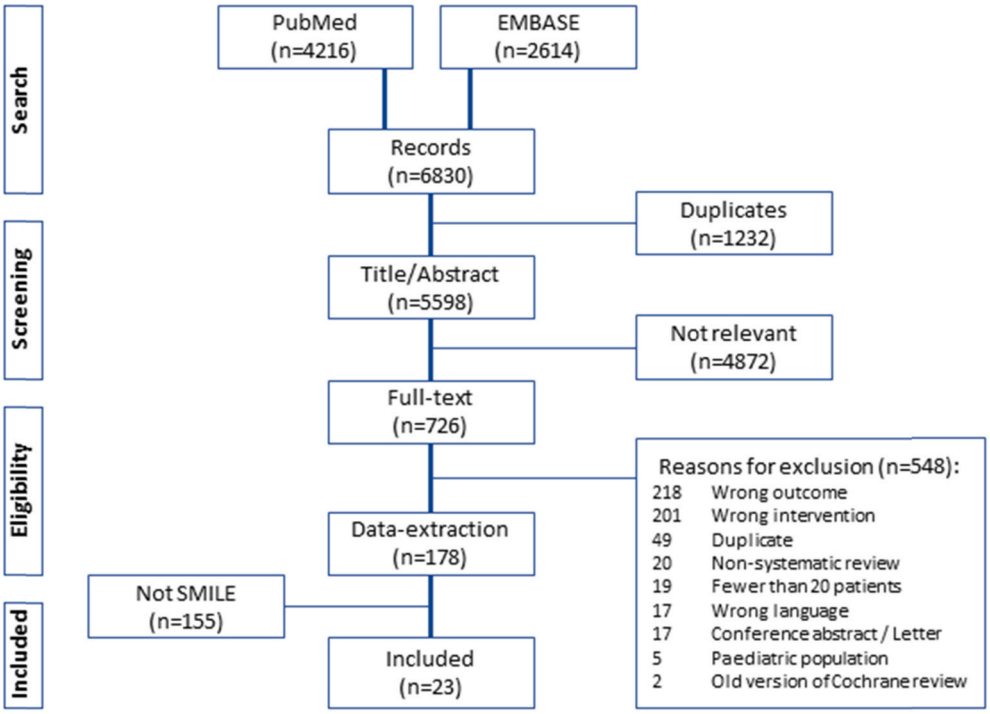

Fig. 14. PRISMA diagram showing rational for included studies.

Table 3
Characteristics of included studies organized by study design.

Study and Location	Interventions assessed	Follow up (months)	Total number of studies *Total number of participants/eyes*	Included study types	Quality of Life/Vision Questionnaires		Summary of results	Comments
Systematic Review								
Zhang 2016, China [625]	SMILE vs. FS-LASIK	Range: 3 - 6	Studies: 11 *Eyes: 532 SMILE; 569 FS-LASIK*	Randomized Controlled Trial; Non-randomized Clinical Trial; Cohort	Subjective symptoms and post-operative vision-related quality of life		3 studies reported postoperative subjective assessment. One showed no difference at 3 months. One reported a higher complaint score in FS-LASIK than SMILE and the other showed that patient reported vision related quality of life was significantly impaired in the FS-LASIK group.	Review search is not comprehensive; 2/3 included studies reporting post-operative assessment also included in our review.
Study and Location	Interventions assessed	Follow up (months)	Total number of Participants *Number eyes per group*	Age, mean (SD)	Percent male	Quality of Life/ Vision Questionnaires	Summary of results	Adverse events
Randomized Controlled Trial								
Damgaard 2018, Singapore [869]	SMILE vs. FS-LASIK	3	Participants:70 *Eyes: 70 SMILE; 70 FS-LASIK*	28.3 (5.2) Overall	36%	Custom Questionnaire[a]	At 1-month, visual blurring was less severe in eyes treated with FS-LASIK compared to SMILE, similar levels at 3 months. The remaining evaluated visual symptoms were equally scored in eyes treated with FS-LASIK and SMILE at the 1- and 3-month examinations.	Dry eye; Halos; Glare
Non-randomized Intervention Study								
Aruma 2021, China [867]	SMILE vs. PCP IOL	12	Participants: 39 *Eyes: 35 SMILE; 32 PCP IOL*	28.8 (4.2) SMILE; 28.6 (5.2) PCP IOL	10%	Quality of vision	No difference frequency, severity, or bothersome nature of visual symptoms between the two groups.	Halos; Glare
Wei 2020, China [885]	SMILE vs. PCP IOL	6	Participants: 114 *Eyes: 103 SMILE; 94 PCP IOL*	28.7 (5.0) SMILE; 27.0 (5.3) PCP IOL	19%	Quality of vision and Custom Questionnaire	Haloes had significantly higher incidence, frequency, and bothersomeness in PCP IOL group than in the SMILE group. SMILE patients were also less distressed by starbursts. No difference in satisfaction or recommendation at 6 months between groups.	Halos; Glare; Double vision; Blurred vision
Klokova 2019, Russia [877]	SMILE vs. FS-LASIK	6	Participants: 118 *Eyes: 56 SMILE; 62 FS-LASIK*	26.0 (3.2) SMILE; 28.1 (2.0) FS-LASIK	64%	Quality of life impact of refractive correction	Change in Quality of life impact of refractive correction score greater in SMILE compared to FS-LASIK though both significantly improved compared to preoperative levels. Change reaching maximum value at 6 months.	Halos; Glare
Ganesh 2018, India [872]	SMILE vs. PRK	3	Participants: 60 *Eyes: 60 SMILE; 60 PRK*	26.8 (4.7) SMILE; 25.8 (4.7) PRK	43%	Custom Questionnaire[b]	The mean scores for pain, hazy vision and night glare were significantly higher in PRK group compared to SMILE group 96% patients were extremely satisfied in the SMILE group with the quality of vision and said would recommend this procedure to their friends versus 78% patients in PRK group.	SMILE: none PRK: 4 eyes mild interface haze, 2 eyes recurrent epithelial defect after BCL removal which eventually healed.
Ganesh 2017, India [858]	SMILE vs. FS-LASIK vs. PPC IOL	12	Participants: 90 *Eyes: 30 SMILE; 30 LASIK; 30 PCP IOL*	28.9 (5.2) SMILE; 27.6 (5.0) LASIK; 26.4 (2.4) PCP IOL	Not reported	Custom Questionnaire[c]	SMILE and posterior chamber lens patients reported excellent satisfaction with their quality of vision at 1 year, but FS-LASIK patients reported low satisfaction due to persistent dryness and the need for lubricant eye drops.	In PCP IOL group, 3 eyes required lens exchange due to frequent rotation and excessive high vault. 2 FS-LASIK eyes lost visual acuity due to micro wrinkles. No complications in SMILE group.

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Table 3 (*continued*)

Ang 2015, Singapore [883]	SMILE vs. FS-LASIK	3	Participants: 860 eyes *Eyes: 172 SMILE; 688 FS-LASIK*	32.0 (7.0) SMILE; 32.0 (8.0) FS-LASIK	Not reported	Quality of life impact of refractive correction and Quality of vision	Blurring of vision and fluctuations in vision were worse in SMILE than FS-LASIK at 1 month, no difference at 3 months. No other differences between groups.	Flap complications; Interface debris
Denoyer 2015, France [870]	SMILE vs. FS-LASIK	6	Participants: 60 *Eyes: 60 SMILE; 60 FS-LASIK*	31.1 (4.7) SMILE; 32.2 (7.5) FS-LASIK	47%	Ocular Surface Disease Index Questionnaire	Patient-reported vision-related quality of life (Ocular Surface Disease Index) was significantly impaired in the FS-LASIK group compared with the SMILE group.	Dry eye
Li 2013, China [609]	SMILE vs. FS-LASIK	6	Participants: 71 *Eyes: 38 SMILE; 33 FS-LASIK*	28.2 (7.0) SMILE; 27.3 (6.6) FS-LASIK	26%	Ocular Surface Disease Index Questionnaire	Ocular Surface Disease Index scores in both SMILE group and FS-LASIK groups at 1 week compared with preoperative values, but returned to preoperative level at 1 month.	Dry eye
Cohort study								
Ding 2021, China [871]	SMILE (high myopic astigmatism (MA)) vs. SMILE (low myopic astigmatism) correction	6	Participants: 70 *Eyes: 30 High MA; 40 Low MA*	27.5 (5.7) High MA; 27.9 (4.3) Low MA	41%	Quality of life impact of refractive correction	No differences in overall in total Quality of life impact of refractive correction score or individual items between groups.	Not reported
Lang 2021, China [878]	SMILE vs. Spectacles	60	Participants: 60 *Eyes: 60 SMILE; 60 Spectacles*	22.5 SMILE; 27.0 Spectacles	42%	NEI VFQ-25	NEI-VFQ 25 composite score significantly higher than control group, all subscales with the exception of general health were significantly higher in the SMILE group.	Not reported
Siedlecki 2020, Germany [881]	SMILE vs. ICL PCP IOL	>3 (range 3–69)	Participants: 40 *Eyes: 40 SMILE; 40 ICL PCP IOL*	32.2 (7.6) SMILE; 33.9 (6.4) ICL PCP IOL	38%	Quality of vision	Visual symptom frequency and severity: no difference. Bothersome score: significantly lower in ICL PCP IOL patients.	SMILE: Starbursts; Fluctuations in vision; Halos; Glare; Blurred vision; Double or multiple images ICL PCP IOL: Halos; Glare; Starbursts
Han 2020, China [874]	SMILE vs. FS-LASIK	36	Participants: 98 *Eyes: 49 SMILE; 49 FS-LASIK*	29.9 (6.2) Overall	–	Quality of life impact of refractive correction	No difference between groups in total Quality of life impact of refractive correction score or in satisfaction or recommendation between groups. FS-LASIK had more glare and severe dryness than SMILE.	Dry eye; Halos; Glare; Double vision
Case Series								
Gyldenkerne 2019, Denmark [873]	SMILE	3	Participants: 51 *Eyes: 51*	38.3 (8.6)	43%	Custom Questionnaire[d]	Symptom score increased immediately after surgery but decreased to near the preoperative level at 3 months	Dry eye; Glare; Double vision
Schmelter 2019, Germany [880]	SMILE	24	Participants: 394 *Eyes: 394*	Not reported	41%	Quality of vision	Patients over 40 report more severe symptoms, those with best pre-operative acuity had highest bothersome score. No association between Quality of vision when stratified by binocular or monocular visual acuity. Patients who lost one or more lines of vision were more bothered by visual disturbances than those who gained vision.	Dry eye; Halos; Glare; Vision loss; Fluctuations in vision
Sia 2021, United States [886]	SMILE	3	Participants: 37 *Eyes: 74*	28.3 (5.4)	78%	NEI RQL-42; Patient satisfaction	Significant Improvements in work productivity and reductions in activity impairment and activity limitation at 3 months. Significant improvements in double images and starbursts but no significant differences in halos or glare. 95% would undergo the procedure again.	Dry eye; Halos; Glare; Double vision; Other
Chiche 2018, France [868]	SMILE vs. FS-LASIK	1	Participants: 46 *Eyes: 23 SMILE; 22 FS-LASIK*	30.1 (4.6) SMILE; 30.6 (7.9) FS-LASIK	60%	Quality of vision	SMILE patients reported statistically more visual symptoms specifically trouble focusing, halos and fog at 1 week but no difference between groups at 1 month and no difference in overall satisfaction at any timepoint.	Halos; Glare

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Table 3 (*continued*)

Han 2016, China [875]	SMILE vs. Spectacles	46	Participants: 73 *Eyes: 19 SMILE; 54 Spectacles*	29.0 (7.2) Overall	41%	Quality of life impact of refractive correction	Surgery group showed a significantly higher total score, higher visual function, more convenience and higher well-being score than spectacles.	Not reported
Qiu 2016, China [879]	SMILE	3	Participants: 97 *Eyes: 193*	22.6 (5.1)	–	Custom Questionnaire[e]	Compared to preoperative data, symptoms of dryness, photophobia and foreign body sensation significantly increased at 1 week however these all decreased by 3 months.	Dry eye
Ivarsen 2014, Denmark [876]	SMILE	3	Participants: 922 *Eyes: 1800*	38.0 (8.0)	39%	Custom Questionnaire[f]	At 3 months 6 patients had scores indicating dissatisfaction.	Dry eye; Halos; Glare; Double vision
Siedlecki 2020 Germany [882]	SMILE	24	Participants: 197 *Eyes: 394*	32.4 (7.7)	41%	Quality of vision	Most commonly reported symptoms were fluctuation in vision and glare, these were also perceived as the most severe and bothersome visual disturbances.	Halos; Glare
Ang 2016, Singapore [883]	SMILE (low myopia) vs. SMILE (moderate-high myopia)	3	Participants: 50 eyes *Eyes: 20 Low; 30 High*	29.0 (5.0) Overall	52%	Quality of life impact of refractive correction	No differences in postoperative quality of life impact of refractive correction scores between groups. Most patients had no visual symptoms by 3 months	Halos; Glare; Starburst

Abbreviations: **SMILE**: Small Incision Lenticule Extraction, **LASIK**: Laser Assisted In-Situ Keratomileusis, **FS**: Femtosecond-assisted, **PCP**: Posterior chamber phakic, **IOL**: Intraocular Lens, **PRK**: Photorefractive keratectomy, **ICL**: Implantable Collamer Lens, **QoV**: The Quality of Vision questionnaire, **OSDI**: Ocular Surface Disease Index, **NEI VFQ-25**: National Eye Institute Visual Function Questionnaire 25, **NEI RQL-42**: National Eye Institute Refractive Error Quality of Life instrument, **QIRC**: The Quality of Life Impact of Refractive Correction questionnaire.

Notes: Studies organized by study design and sorted in order of descending quality/risk of bias (see Table 2), followed by reverse chronologically, and alphabetically. **a** - Questionnaire included light sensitivity, eye discomfort, eye dryness, excessive tearing, gritty sensation, glare, halos, blurring, and fluctuations in vision. Severity of headache and night driving problems were also registered. **b** - A subjective questionnaire assessing the symptoms of postoperative pain, hazy vision and night glare was administered, patients were asked to rate these symptoms on a scale of 10, the higher values indicating worse result. **c** - Symptoms and satisfaction recorded- details not provided. **d** - Patients were asked to grade their eye symptoms from 0 to 3 in the following manner: 0 (no symptoms), 1 (mild symptoms), 2 (moderate symptoms), and 3 (severe symptoms). The listed symptoms were glare, starbursts, cloudy vision, blurred vision, and double vision; an "others" category was listed for cases in which the patient perceived another problem. The presence of night-vision problems (yes/no) was also recorded. **e** - Questionnaire evaluating 3 symptoms dryness, foreign body sensation and photophobia. **f** - Patient satisfaction was evaluated on a questionnaire with a score ranging from 0 to 10, with 10 being maximal satisfaction.

7.3.1. Characteristics of included studies

The 23 included studies [609,625,858,867-886] were published between 2013 and 2022 and their characteristics are shown in Table 3. The studies are arranged by (i) risk of bias, (ii) reverse chronologically and (iii) alphabetically within their study types so that the best quality and most recent publications are presented first.

Length of follow up ranged from one to 60 months. Most studies were case series (9/23) or comparative cohort studies (12/23). Only one randomized clinical trial [869] and one systematic review [625] were identified. The sample size of the included studies ranged from 37 to 922 participants with the systematic review including 11 studies and a total of 1101 eyes [625]. Males and females were included in all studies, with males comprising 10–78% of participants among included studies. The studies were conducted around the world, but most were conducted in Asia (13/23) including China, Singapore and India, followed by Europe (8/23) including France, Germany, Denmark, and Russia. Fifteen studies (65%) focused on patients with myopia only, and the rest considered those with myopic astigmatism or myopia.

The most common measures used to quantify quality of life across the studies were the quality of vision (7/23) and Quality of Life Impact of Refractive Correction questionnaire (6/23). Seven studies developed their own customized questionnaire, most often comprising questions about subjective experience of symptoms and satisfaction with treatment. None of the studies used a health-related quality of life instrument.

Despite multiple studies using the same quality of life questionnaire, the study designs and comparisons were too clinically and methodologically heterogeneous to permit a meta-analysis. The studies are therefore summarized qualitatively in chronological order, groups by the intervention and comparator types.

7.3.2. Risk of bias

All studies were assessed using an appropriate risk of bias tool to the study type. Most studies were judged to be of high or serious risk of bias. The primary cause for this determination was that the outcome of interest, quality of life, is subjective and necessitates masking the outcome assessor for a fair and unbiased judgment. As a result, most of the studies were unmasked, participants knew which intervention they had received, and they were also their own outcome assessors for their perceived quality of life. Tables 4a–4e present the risk of bias judgments for all studies.

7.3.3. SMILE in myopia: quality of life and adverse events

Ten studies published between 2014 and 2021 evaluated SMILE in myopia and their characteristics are shown in Table 3 [871,873,875,876,878-880,882,884,886]. In 2014, one study [876] reported that 9 out of 1036 eyes (0.87%) had satisfaction scores of 5 or less (range, 1–10), indicating a small number of patients were dissatisfied with SMILE in a 3-month follow up. Adverse events observed in 1800 operated eyes were haze grade 0.5 to 1 (127 eyes, 7.05%), dry eye disease (75 eyes; 4.2%), epithelial islands at incision (10 eyes; 0.55%), monocular ghost images (6 eyes; 0.33%), fiber in the interface (6 eyes; 0.33%), infiltrates/keratitis (5 eyes; 0.28%) and interface inflammation (4 eyes; 0.22%).

In 2016, a study [884] found no differences in postoperative quality of life scores between low and moderate-high myopia groups treated with SMILE. In this study, most patients had minimal or no visual symptoms by 3 months; adverse events observed were reports of halos, glare and starburst. SMILE patients showed a significantly higher total quality of life score, higher visual function, more convenience and higher well-being score than compared with spectacle correction in a 46-month follow up [883]. No adverse effects were reported in any of the 19 patients who underwent SMILE. An evaluation of subjective ocular symptoms (dryness, photophobia and foreign body sensation) in 193 eyes of 97 consecutive patients who underwent SMILE used a specific dry eye questionnaire [879]. Compared to preoperative data, dry

eye symptoms significantly increased at 1 week after surgery in 56% of the patients [879]. However, these symptoms all returned to near pre-operative levels by 3 months. No visually threatening complications were observed.

In a study from 2019, patients over 40 years-old perceived visual symptoms more severely compared to those younger, and those with best pre-operative acuity had the highest bothersome scores [880]. A quality of vision questionnaire was used, which rated 10 symptoms in each of three scales (frequency, severity and bothersomeness). No association between quality of vision was found when the results were stratified by binocular or monocular visual acuity. Patients who lost one or more lines of uncorrected distance vision were more bothered by visual disturbances than those who gained vision. The most common and severely experienced visual disturbances were glare (129/197 patients; 65.5%) and vision fluctuation (144/197 patients; 73.1%). Similar findings were confirmed in two other publications by the same group [882]. Another study [873] found that visual symptoms scores increased immediately after SMILE surgery performed in 51 eyes of 51 patients, but decreased to near preoperative levels by 3 months. The same authors described 19.0% reported glare (10 patients), 52.9% reported starbursts (27 patients), 3.9% reported blurred vision (2 patients), 5.9% reported problems seeing at night (3 patients) and 2.0% reported double vision (1 patient) [873].

A report from 2021 [886] applied the National Eye Institute Refractive Error Quality of Life instrument (NEI-RQL-42) and satisfaction questionnaires in 37 patients (74 eyes) who had SMILE surgery. The patients reported significant improvements in work productivity and reductions in activity impairment and activity limitation at 3 months. They also noted significant improvements in double images and starbursts but no significant differences in halos or glare. Most (95%) reported they would undergo the procedure again. Adverse events reported were dry eye symptoms (5 patients), halos, glare, and double vision. A 2021 cohort study compared quality of life outcomes between SMILE treatment vs. spectacles wear in 30 patients (60 eyes). The NEI-Visual Function Questionnaire 25 composite score revealed that all subscales, with the exception of general health, were significantly higher in the SMILE group. No adverse events were reported. In the same year, visual quality evaluations of SMILE surgery for high (30 eyes of 30 patients) vs. low (40 eyes of 40 patients) myopic astigmatism correction were compared [871]. There were no differences in overall total Impact of Refractive Correction Questionnaire score or individual items between groups, and no adverse events were found.

7.3.4. SMILE vs. LASIK vs. photorefractive keratectomy: quality of life and adverse events

Nine studies between 2013 and 2020 compared SMILE with other corneal refractive procedures. In a comparative cohort study published in 2013, SMILE and FS-LASIK were compared in 71 eyes of 71 patients using the Ocular Surface Disease Index questionnaire over a 6-month follow up period [609]. Ocular Surface Disease Index scores in both SMILE and FS-LASIK groups increased after 1 week compared to pre-operative values, but both outcomes returned to baseline levels 1 month after the intervention. Symptoms of dry eye such as dryness, burning, foreign body sensation, pain, photophobia and visual fluctuation were also noted, but the authors did not report data on these. A cross-sectional study compared quality of life and satisfaction outcomes in 98 patients treated with SMILE (49 patients) or FS-LASIK (49 patients), followed up over 36 months [874]. Quality of life outcome was assessed using the Impact of Refractive Correction Questionnaire. There were no differences in total Impact of Refractive Correction Questionnaire score, satisfaction or degree of surgery recommendation. The reported adverse effects were daytime and nighttime glare, haze, halos, daytime and nighttime clarity, reduction in visual acuity, dry eye symptoms, gritty sensation, visual fluctuation, and double vision. Compared to the SMILE group, the FS-LASIK group had more glare and dryness.

A prospective, consecutive cohort study was published in 2015 [883], in which 860 eyes were assessed over 3 months after interventions with SMILE (172 eyes) and FS-LASIK (688 eyes). Quality of life outcomes were assessed using Impact of Refractive Correction Questionnaire and quality of vision questionnaires. Blurring and fluctuations in vision were worse with SMILE than FS-LASIK treatment at 1-month post-surgery, but there was no difference between groups at 3-months follow up. As for adverse effects, the study described a similar safety profile in both groups, without major intraoperative or post-operative complications that affected visual outcomes. In the FS-LASIK group, there was 1 eye (0.38%) that had interface debris removed the following postoperative day. In the SMILE group, there were 2 (0.23%) cases of suction loss intraoperatively. The same group published a randomized, prospective study comparing SMILE and FS-LASIK in 70 patients [869]. Quality of life outcomes were assessed using a custom questionnaire at 1 and 3 months follow up. At 1 month, patients experienced more blurring after SMILE than FS-LASIK. In contrast, all the other visual symptoms (light sensitivity, eye discomfort, eye dryness, excessive tearing, gritty sensation, glare, halos and fluctuation in vision) were similar at the same follow up time point. No differences in any of the visual symptoms were observed between SMILE and FS-LASIK after 3 months.

In a study comparing SMILE and FS-LASIK in a comparative cohort study involving 60 patients (120 eyes) [870], the Ocular Surface Disease Index questionnaire was administered at 1 and 6 months post-operatively. One month after the surgery, a high rate of dry eye symptoms was reported in both groups, but without a significant difference between the groups. However, at 6 months follow up, the Ocular Surface Disease Index scores were significantly lower in the FS-LASIK group compared to the SMILE group.

A systematic review comparing SMILE to FS-LASIK in 1101 eyes has been published [625]. Three studies were included in the final assessment and reported postoperative subjective outcomes [616,621,870]. One study found no difference between groups after 3 months [616]. Another study reported a higher complaint score with FS-LASIK than SMILE, with the main complaints being redness, pain, watering and pricking sensation [870]. The third study showed that patient-reported-vision-related quality of life was significantly impaired in the FS-LASIK group but not in the SMILE group [621]. Only one study reported adverse effects, and the only one described was dry eye symptoms, which were better in the SMILE group compared to the FS-LASIK group [870].

A case series comparing SMILE and FS-LASIK in 46 eyes from 23 patients was published in 2018 [868]. Quality of life assessment was evaluated using the quality of vision questionnaire 1 day, 7 days and 1 month postoperatively. The questionnaire included 10 symptoms (glare, halos, starbursts, hazy vision, blurred vision, distortion, multiple images, fluctuations in vision, focusing difficulties and judging distance). A supplemental question about overall satisfaction patient was added, with the score ranging from 0 (dissatisfied) to 5 (very satisfied). Compared to those treated with FS-LASIK, participants treated with SMILE reported significantly more visual symptoms at 1 week, specifically trouble focusing, halos and fog. However, no difference was found between groups at 1 month follow up and there were no differences in overall satisfaction at any time points.

Table 4
Study quality and risk of bias assessment: (a) systematic reviews (b) randomized controlled trials (c) non-randomized interventions (d) cohort studies (e) case series.

Table 4a. AMSTAR[a] assessment for included systematic reviews

Study	Research questions and eligibility criteria include patient/problem, intervention, comparison and outcome components	Explicit statement that methods pre-specified	Explanation of choice of study design(s) for inclusion	Comprehensive literature search strategy	Study selection performed in duplicate	Data extraction performed in duplicate	List of excluded studies provided and justified	Included studies described in appropriate detail
Zhang 2016 [625]	Yes	No	Yes	No	Yes	Yes	No	Yes

Overall Quality/ Risk of Bias Score	Satisfactory technique to assess risk-of-bias of included studies	Reported sources of funding for included studies	Appropriate methods for statistical combination of results	Assessed potential impact of risk-of-bias on results of meta-analyses	Accounted for risk-of-bias of individual studies when discussing review results	Provided satisfactory explanation for heterogeneity in results	Adequate investigation of publication bias and potential impact on results	Reported any potential conflicts of interest including funding received
High quality	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes

Table 4b. Risk of Bias 2.0 assessment for included randomized controlled trials

Study; Overall Quality/Risk of Bias Score	Risk-of-bias arising from the randomization process	Risk-of-bias due to deviations from intended interventions	Risk-of-bias due to missing outcome data	Risk-of-bias in measurement of the outcome	Risk-of-bias in selection of the reported result
Damgaard 2018 [869]; High Risk of Bias	Low	Low	Some concerns	Low	High

Table 4c. ROBINS-I[b] assessment for included non-randomized studies of interventions

Study; Overall Quality/ Risk of Bias Score	Risk-of-bias due to confounding	Risk-of-bias in selection of participants into study	Risk-of-bias in classification of interventions	Risk-of-bias due to deviations from intended interventions	Risk-of-bias due to missing data	Risk-of-bias due to measurement of outcomes	Risk-of-bias in selection of the reported result
Aruma 2021 [867]; Serious risk of bias	Moderate risk of bias	Critical risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Serious risk of bias	Serious risk of bias
Wei 2020 [885]; Serious risk of bias	Moderate risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Serious risk of bias	Moderate risk of bias
Klokova 2019 [877]; Serious risk of bias	Moderate risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Serious risk of bias	Moderate risk of bias
Ganesh 2018 [872]; Serious risk of bias	Moderate risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Serious risk of bias	Moderate risk of bias
Ganesh 2017 [858]; Serious risk of bias	Moderate risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Serious risk of bias	Moderate risk of bias
Ang 2015 [883]; Serious risk of bias	Moderate risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Serious risk of bias	Moderate risk of bias
Denoyer 2015 [870]; Serious risk of bias	Moderate risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Serious risk of bias	Moderate risk of bias
Li 2013 [609]; Serious risk of bias	Moderate risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Serious risk of bias	Moderate risk of bias

Table 4d. Newcastle-Ottawa Cohort Scale assessment for included cohort studies

Study; Overall Quality or Risk of Bias Score	Exposed cohort representative	Selection of non-exposed cohort	Ascertainment of exposure	Outcome not present at start of study	Comparable cohorts on design or analysis	Ascertainment of outcome	Sufficient follow-up for outcome occurrence	Loss to follow-up
Ding 2021 [871]; 7 – High quality	Somewhat representative of the average cohort in the community	Drawn from the same community as the exposed cohort	Secure record (e.g. surgical records)	Yes	Study controls for any additional factors	Self-report	Yes	Complete follow-up: all subjects accounted for
Lang 2021 [878]; 5 – High risk of bias	No description of the derivation of the cohort (how participants were selected from all surgeries)	Drawn from the same community as the exposed cohort	Secure record (e.g. surgical records)	Yes	Inadequate degree of control	Self-report	Yes	Complete follow-up: all subjects accounted for

(*continued on next page*)

Table 4 (*continued*)

Table 4d. Newcastle-Ottawa Cohort Scale assessment for included cohort studies

Study; Overall Quality or Risk of Bias Score	Exposed cohort representative	Selection of non-exposed cohort	Ascertainment of exposure	Outcome not present at start of study	Comparable cohorts on design or analysis	Ascertainment of outcome	Sufficient follow-up for outcome occurrence	Loss to follow-up
Siedlecki 2020 [881]; 6 – High risk of bias	No description of the derivation of the cohort (how participants were selected from all surgeries)	Drawn from the same community as the exposed cohort	Secure record (e.g. surgical records)	Yes	Study controls for any additional factors	Self-report	Yes	Complete follow-up: all subjects accounted for
Han 2020 [874]; 6 – High risk of bias	Somewhat representative of the average cohort in the community	Drawn from the same community as the exposed cohort	Secure record (e.g. surgical records)	Yes	Study controls for confounding (propensity score matching)	Self-report	Yes	Unclear

Table 4e. National Institutes of Health assessment[c] for included case series

Study; Overall Quality or Risk of Bias Score	Study question or objective clearly stated	Eligibility or selection criteria prespecified and clearly described	Study sample representative of those who would be eligible in target population	All eligible participants meeting criteria enrolled	Sample size sufficient to provide confidence in findings	Intervention clearly described and consistently delivered across study	Outcome measures clearly defined, valid, reliable, and consistently assessed across study	Outcome assessors masked to exposure or interventions	Loss to follow-up 20% or less	Change from baseline (pre/post) assessed	Outcomes measured multiple times before and after intervention
Gyldenkerne 2019 [873]; Good	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	No	Yes	Yes	No
Schmelter 2019 [880]; Good	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No
Sia 2021 [886]; Fair	Yes	Yes	No	Unclear	Yes	Yes	Yes	No	Yes	Yes	No
Chiche 2018 [868]; Fair	Yes	Yes	Yes	Unclear	No	Yes	Yes	No	Yes	Yes	No
Han 2016 [875]; Fair	Yes	Yes	Yes	Unclear	No	Yes	Yes	No	Yes	Yes	No
Qiu 2016 [879]; Fair	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	No
Ivarsen 2014 [876]; Fair	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	No
Siedlecki 2020 [882]; Poor	Yes	No	Unclear	Yes	Yes	Yes	Yes	No	Yes	Yes	No
Ang 2016 [884]; Poor	Yes	Yes	No	Yes	No	Yes	Yes	No	Yes	Yes	No

[a] AMSTAR: Assessment of Multiple Systematic Reviews.
[b] ROBINS-I: Risk of Bias in Non-randomized Studies of Interventions.
[c] Last item of NIH assessment, pertaining to clustered interventions, omitted because not applicable as all interventions are individual.

A cohort study comparing 56 patients treated with SMILE and 62 with FS-LASIK was published in 2019 [877]. Quality of life was assessed using the Impact of Refractive Correction Questionnaire preoperatively and at 1, 3, and 6 months postoperatively. The overall quality of life indicators significantly exceeded preoperative values 1 month after both FS-LASIK and SMILE. The maximum values were observed at the end of the follow up period (6 months). The SMILE group had a more significant change in Quality of Life Impact of Refractive Correction scores than the FS-LASIK group. No complications or adverse events were observed in any patient during the follow up.

A comparative cohort study was conducted in 2018 comparing SMILE and photorefractive keratectomy in 60 patients (120 eyes) [872]. A subjective questionnaire on a 10-point scale assessing postoperative symptoms was administered at 3 months postoperatively. Mean scores for eye pain (photorefractive keratectomy 6.25 vs. SMILE 0.5), hazy vision (photorefractive keratectomy 4.5 vs. SMILE 2.8), and night glare (photorefractive keratectomy 4.8 vs. SMILE 2.5) were significantly higher in the photorefractive keratectomy group compared to the SMILE group. In the SMILE group, 96% of patients were extremely satisfied with their quality of vision and indicated that they would recommend the procedure to their friends. In contrast, in the photorefractive keratectomy group, only 78% of the patients responded as such. There were no complications reported in the SMILE group, but in the photorefractive keratectomy group, 4 eyes had mild subepithelial haze and 2 eyes experienced recurrent epithelial defect after bandage contact lens removal, which eventually healed.

7.3.5. SMILE vs. posterior chamber phakic intraocular lens implantation: quality of life and adverse events

Four studies between 2017 and 2021 compared SMILE with posterior chamber phakic intraocular lens implantation. A cohort study in 2017 [858] compared SMILE, FS-LASIK and posterior chamber phakic intraocular lens implantation. In total, 90 eyes from 90 patients were analyzed and a custom questionnaire was applied over the course of a 12 month follow up. Both the SMILE and posterior chamber phakic intraocular lens groups reported excellent satisfaction with their quality of vision at 1 year, whilst the LASIK group reported low satisfaction due to persistent eye dryness and, thus, the need for lubricant eye drops. As for adverse effects, there were 3 eyes in the posterior chamber phakic intraocular lens group that required lens exchange due to frequent rotation and excessive high vault. Moreover, 2 FS-LASIK-treated eyes lost corrected distance visual acuity due to corneal micro-wrinkles. There were no complications described in the SMILE group.

A study published in 2020 [881] found no difference between visual symptom frequency and severity between 40 eyes (20 patients) treated with SMILE and 40 eyes (20 patients) with posterior chamber phakic intraocular lens implantation. Still, the quality of vision questionnaire bothersomeness score was significantly lower in posterior chamber phakic intraocular lens patients. For adverse effects, 20% of the SMILE group lost one line in the corrected distance visual acuity, whereas no eye lost corrected distance visual acuity in the posterior chamber phakic intraocular lens group. The main complaints in the SMILE group were fluctuations in vision (80% of participants), starburst (65%), glare (50%), difficulty focusing (40%) and halos (35%), blurred vision and double or multiple images. The most common complaints in the posterior chamber phakic intraocular lens group were halos (80%), glare (60%), fluctuations in vision (60%), difficulty focusing (55%) and starburst (30%) [881].

Six-month postoperative data from a study comparing a posterior chamber phakic intraocular lens group (94 eyes, 57 patients) and a SMILE group (103 eyes, 57 patients), found that the posterior chamber phakic intraocular lens group had significantly higher incidence of halo severity and bothersomeness, and SMILE patients were less distressed by starburst [885]. Moreover, there was no difference in patient satisfaction or recommendation between groups after 6 months. The most common visual complaints in the posterior chamber phakic intraocular lens group were halos (93.5% of participants), glare (65.2%), and blurred vision (44.6%). In the SMILE group, the most common symptoms were blurred vision (56.3%), glare (54.4%), and halos (54.4%). The same research group [867] reported that at 1 year, the most common vision complaints were halos after posterior chamber phakic intraocular lens implantation (32 eyes, 20 patients), and starburst and blurred vision after SMILE treatment (35 eyes, 19 patients). Other complaints recorded were glare, hazy vision, distortion, multiple images, visual fluctuation, difficulty focusing, and difficulty with depth perception. It was reported that there was no difference in the frequency, severity, or bothersomeness of visual symptoms between the groups.

7.3.6. Overall analysis of the impact of SMILE on quality of life

Evidence for an improvement in vision-related quality of life from SMILE relative to LASIK or another comparator (e.g., posterior chamber phakic intraocular lens implantation, photorefractive keratectomy, and spectacles) was not uniform, but most studies found that any differences between SMILE and other treatments had disappeared by 3–6 months.

There was no defined pattern in direction of effect or findings based on the quality or risk of bias of the studies. For example, of the studies that evaluated the clinical effectiveness of SMILE versus FS-LASIK to correct myopia, three studies assessed quality of life, with one finding no difference, one finding a higher complaint score in LASIK than SMILE, and one finding impaired quality of life in the LASIK group.

7.4. Systematic review discussion and conclusion

This systematic review evaluating quality of life after SMILE identified and summarized the results of 23 relevant articles, published between 2013 and 2022. The overall satisfaction index seemed to be high, and most patients would choose to undergo the procedure again [886].

While the current review found improved quality of life in some SMILE articles, many other articles reported a moderately high rate of adverse events [609,625,858,867-875,877-883,885,886]. The quality of life changes may be related, in part, to the postoperative corneal topography and wavefront aberrations adverse events, which have direct impact on quality of vision after SMILE. Residual astigmatism after SMILE may also affect the quality of vision and quality of life.

Corneal and refractive surgery are associated with dry eye and ocular surface disease [585,586,609,625,858,867-886]. Predisposing factors for ocular surface disease after SMILE included preoperative dry eye and meibomian gland dysfunction [585,586].

An interesting finding in this systematic review was that SMILE seems to cause more vision disturbances than LASIK in the first month but less dry eye symptoms in long-term follow up [609,625,868-870, 875,877]. This has been attributed, in part, to the 2–3 mm size of the anterior stromal incision in SMILE, which is much smaller than that in LASIK [580,611]. However, the anatomical and corneal sensitivity advantages of SMILE over LASIK may not result in significant differences in objective tear film stability [609,610,618,619], and lower dry eye disease symptom severity [620]. Tear film osmolarity was reported to be higher in patients who had undergone LASIK as compared to SMILE [618,621-623,625,887].

The data in this systematic review also show that relative to photorefractive keratectomy, SMILE caused fewer eye discomfort symptoms in

the immediate postoperative period and has a similar quality of vision outcome. SMILE has similar vision-related outcomes to posterior chamber phakic intraocular lens implantation, but patients present fewer vision-related disturbances, such as blurred and unstable vision, glare, halos and starburst.

There are several limitations to this systematic review. The review initially began with a broader purview that sought to comment on quality of life after a wide range of refractive surgical procedures, but was narrowed to focus on SMILE specifically. Case reports were excluded; it is not known if any of the excluded publications contained relevant information on quality of life or post-surgical adverse events. It was also noted that none of the identified studies managed to mask the staff recording the responses to the quality of life questionnaires, which increased the risk of bias assessment. This is not specific to this context and is a logistical limitation of the majority of quality of life studies.

The current review did not focus on the pathogenetic mechanisms of postoperative side effects. The study was designed to evaluate the quality of life after SMILE and compare it with three other refractive surgical procedures: LASIK, photorefractive keratectomy and posterior chamber phakic intraocular lens. Excluded were refractive surgical procedures for corneal dystrophy and keratoconus, incisional surgery, intracorneal implants and ring segments and intraocular lens surgery for non-refractive purposes. This approach will help inform similar systematic reviews in the future to evaluate quality of life outcomes after other refractive procedures.

8. Overall conclusions and future directions from the *TFOS Lifestyle: Impact of elective medications and procedures on the ocular surface* report

Patients often undergo non-urgent elective procedures or use topical and/or systemic medications to improve their quality of life or cosmetic appearance, but sometimes these interventions are followed by ocular surface disease that paradoxically negatively affects (the subject of the sentence at this point is ocular surface disease) their quality of life.

Several topical medications, including vasoconstrictors and those containing benzalkonium chloride or other topical preservatives, may cause worsening of the visual outcomes especially when used chronically or after ocular procedures. They exert allergic, chemical, toxic, and immune-inflammatory effects on the cornea, conjunctiva, tear film and corneal nerves. They also reduce aqueous secretion and may destroy goblet cells, conjunctival and corneal epithelia, and meibomian glands [8,10-12,54]. Topical ophthalmic corticosteroids can be used to curb signs and symptoms of ocular surface inflammation associated with dry eye disease, but can cause elevated intraocular pressure, cataract allergies, decreased wound healing and increased susceptibility to infections.

Also, regarding the homeostasis of the ocular surface, systemic medication plays a critical role in regulating inflammatory responses and promoting cell differentiation, development and correct function [888]. The duration of such effects has not been explored, and no prospective studies are available that correct the results for long-term micronutrient plasma level and dietary intake modifications in patients receiving mass treatment [888-891]. Additionally, elective systemic medications such as cold medicine have been associated with potentially sight-threatening drug-induced ocular surface immune reactions [269]. Patients should be aware of this association to make decisions on using elective medications without necessity.

The eyelids and the conjunctiva are directly responsible for eye protection and lubrication and, consequently, periocular cosmetic and conjunctival surgery may be complicated by tear film abnormalities and ocular surface disease [275,287,359,361]. Additional complications of oculoplastic and conjunctival surgery include corneal abrasions [275, 287], lacrimal gland injury [290,291], granuloma formation, subconjunctival hemorrhage, edema, corneal dellen, conjunctival scarring and ischemia [531]. Better and less invasive procedures, including the use of laser and adjunct medications, have been developed to decrease the adverse effects of these surgeries on the ocular surface.

Periocular procedures such as cosmetic lasers, plasma discharge and high-frequency radio waves are usually safe but carry a potential risk for ocular surface damage, including burning and hyper- or hypopigmentation [370,386]. The same is true for procedures that treat meibomian gland dysfunction and dry eye disease, such as thermal pulsation and intense pulsed light [396,418-420]. To prevent complications of these treatments, patients with contraindications must be excluded from a specific procedure. Care should be taken during treatments to protect the eyes and periocular skin, moderating energy to protect against overheating and adverse side effects [386]. New technologies and the combination of these procedures have been proposed to improve efficacy and decrease the impact on the ocular surface.

Dry eye disease frequently occurs after LASIK and photorefractive keratectomy and is primarily attributed to corneal nerve injury, reduced tear secretion, decreased blinking and medicamentosa [608]. Predisposing factors include preoperative dry eye disease and meibomian gland dysfunction. Compared with LASIK, SMILE does not require the creation of a flap and therefore induces less damage to corneal nerves, which might result in a lower risk of patients triggering a loss of tear film homeostasis and developing dry eye disease [608].

The data in the systematic review in the present report showed that relative to photorefractive keratectomy, SMILE caused fewer eye discomfort symptoms in the postoperative period but has a similar quality of vision outcome [609,625,858,867-875,877-883,885,886]. SMILE has similar vision-related outcomes to phakic intraocular lens implantation, but patients present fewer vision-related disturbances. Overall, because of the improvement in quality of life and the lesser impact of SMILE on the ocular surface, SMILE compares favorably to other refractive surgical procedures.

Signs and symptoms of dry eye disease are also very common in the early postoperative period after corneal transplantation and in other ophthalmic surgical procedures such as cataract surgery and phakic intraocular lens implantation. Perioperative use of topical anesthetic and povidone-iodine drops can lead to severe ocular surface toxicity and induce inflammation. Surgical transection of the corneal nerves by the corneal incision is a mechanism common to corneal surgical techniques and a causative factor in postoperative dry eye disease. Patients with diabetes and those with previous corneal-refractive procedures may experience more significant postoperative dry eye symptoms following cataract surgery [329,689,701].

Femtosecond laser-assisted cataract surgery seems beneficial in some groups of patients with low baseline endothelial cell count or those planning to receive a multifocal intraocular lens [892]. Nevertheless, more standardized visual-related quality of life scoring systems are needed to understand if the impact of femtosecond laser surgery on the ocular surface is clinically meaningful in both outcomes and the duration of any potential benefit.

Elective medications and procedures can compromise the innervation of the ocular surface, jeopardizing its anatomical and functional integrity. Clinically, this can result in ocular surface diseases and chronic pain of inflammatory or neuropathic etiology, or neurotrophic keratopathy. Treating corneal neuralgia has been challenging since it involves local and systemic neuronal interactions [786,793-800]. Current strategies include control of inflammation, nerve regeneration, and

suppression of mechanisms of pain. As for neurotrophic keratopathy, treatment aims to stimulate epithelial healing, prevent the progression of stromal thinning, and induce corneal nerve growth [826,835]. Identifying the time frame for corneal nerve reinnervation and discovering more particular targets and signaling pathways within the nociceptor could allow us to define better therapeutic management of these conditions [893,894].

As the cosmetic and refractive surgery industries continue to expand worldwide, evidence-based knowledge regarding patient outcomes also should be incorporated into management decisions. Since postsurgical alterations of the ocular surface and tear film may change over time, longer follow up durations may be necessary to fully capture ocular surface effects of the wide range of ocular and periocular procedures [320]. The power of these data is amplified when it is systematically coordinated, collected, analyzed, and published, ideally in a registry. This could help ensure that postoperative care regimens are quickly and effectively optimized after new interventions or variations in existing techniques are deployed.

Similarly, screening for perioperative risk factors for patients would significantly reduce the risk of developing persistent adverse reactions. While examinations like *in vivo* confocal microscopy to assess the state of the ocular surface and its recovery after surgery [895] generate valuable information, less costly, simpler approaches, such as the inclusion of disease or intervention-specific questionnaire assessments, and routinely performing and recording the results from standard dry eye assessments like the Schirmer test, tear breakup time assessments and matrix metalloproteinase-9 evaluations at follow up visits can generate extremely meaningful data [895,896].

In summary, elective medications, ocular and periocular procedures, and surgical interventions may cause ocular surface damage that can impact the patient's quality of life. Increasing awareness of the potential risks, benefits, and consequences will help patients make the right decisions when considering these options. Additionally, it will furnish clinicians with the relevant information to help patients make informed decisions and drive research that might help make such procedures safer.

Declaration of competing interest

José Alvaro P. Gomes: Alcon (F,C), Allergan (F,C), Johnson & Johnson (F,C), Latinofarma/Cristália (F,C), Ofta Vision Health/EMS (F, C), Bausch-Lomb (F), Novartis (C), Ophthalmos (C).

Dimitri T. Azar: Twenty/Twenty Therapeutics (F,I,P,E).

Christophe Baudouin: Horus Pharma (F,C), Pharma (F), Santen (F,C), Théa (F,C), Opia (P), Alcon (C), Allergan (C), Oculis (C), Aerie Pharmaceuticals (C).

Etty Bitton: Johnson & Johnson Vision (F), I-Med Pharma (F), Shire (F,C), Valeant (F), Alcon (C), Aequus Pharmaceuticals (C), Brio (C), Labtician-Théa (C), Novartis (C), Snell Communications (C).

Wei Chen: Santen (C).

Farhad Hafezi: Light for Sight Foundation (F), Schwind Eye Tech Solutions (F), VELUX Foundation (F), Gelbert Foundation (F), SOOFT Italia (F), EMAGine AG (I), ELZA Institute (E), GmbH-Switzerland (C).

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Ruth E. Hogg: Okko Healthcare (F), Roche (C).

Jutta Horwath-Winter: Bausch + Lomb (C), Allergan (C), Croma-Pharma (C), MC2 Therapeutics (C), Omnivision (C) Santen (C), Théa (C), TRB Chemedica (C), Ursapharma (C), Shire (C).

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