Dry Eye Workshop Tear Film Committee:

Utility of endocrine markers in the diagnosis of dry eye syndromes (Sullivan)

1. Objective

To discuss the applicability of endocrine markers (i.e. levels of androgens, estrogens and/or prolactin in sera and tears)for the diagnosis and differential diagnosis of dry eye syndromes

2. Measurement of serum androgen levels

2.1. Rationale

Recent research indicates that androgen deficiency may be a critical etiologic factor in the pathogenesis of aqueous-deficient and evaporative dry eye syndromes during menopause, aging and certain autoimmune diseases (e.g. Sjögren'ssyndrome, systemic lupus erythematosus [SLE], rheumatoid arthritis [RA]). The rationale for this indication is as follows:

- androgens regulate numerous aspects of the lacrimal gland, including epithelial cell morphology, gene expression, protein synthesis, secretory processes and immune function.1 Indeed, androgen action appears to account for many of the sex-related differences that exist in the anatomy, molecular biology, physiology and immunology of this tissue.1However, women with Sjögren's syndrome have an androgen deficiency,[2] and this hormone deficit may predispose to(but not cause) lacrimal gland dysfunction, decreased tear secretion and aqueous-deficient dry eye.[1]
- androgens appear to regulate meibomian gland function, improve the quality and/or quantity of lipids produced by this tissue and promote the formation of the tear film's lipid layer.[1] Conversely, androgen deficiency, such as occurs during menopause (decline in secretion of ovarian androgens and adrenal androgen precursors), aging in both sexes (decrease in the total androgen pool), autoimmune disease (e.g. Sjögren's syndrome, SLE, RA), complete androgen insensitivity syndrome (i.e. women with dysfunctional androgen receptors) and the use of anti-androgen medications (e.g. for prostatic hypertrophy or cancer), is associated with meibomian gland dysfunction, tear film instability and a significant increase in dry eye signs and symptoms.1 Androgen-deficient people also have a higher frequency of metaplasia of the meibomian gland orifices and a reduced quality of meibomian gland secretions, as well as significant alterations in the neutral and polar lipid profiles of their meibomian gland secretions (i.e. relative to those of normal male and female controls).[3-6]
- low serum levels of testosterone have been reported to be more prevalent in women with dry eye and to correlate with the subjective severity of ocular symptoms.[7]
- topical or systemic androgen has been reported to alleviate dry eye signs and symptoms, and stimulate tear flow, in Sjögren's syndrome patients.1 In addition, topical or systemic androgen treatment has been reported to help restore intraglandular lipid patterns toward normal in androgen-deficient animals, stimulate the production and secretion of meibomian gland lipids, prolong the tear film breakup time and to decrease the signs and symptoms of dry eye in women and men.[1]

These findings suggest that measurement of serum androgens, such as testosterone, may serve as a marker to identify individuals susceptible to dry eye syndromes. In support of this suggestion is the observation that serum testosterone levels correlate positively with tear function in menopausal (but not pre-menopausal) women.[8]

2.2 Utility of serum androgen measurements for the diagnosis of dry eye

2.2.1. Testosterone and dihydrotestosterone (DHT)

Measurement of serum testosterone levels, particularly in women, is of questionable utility as a marker to identify individuals susceptible to dry eye syndromes. The reason is that serum testosterone levels represent only a very small fraction (< 0.2% in women, < 2% in men) of the total androgen pool in humans.[9,10] Indeed, it appears that the measurement of serum testosterone in women has little or no value except as an index of ovarian activity, and this tissue is not the principal origin of androgens in human females.[9,10]

As shown in the rapidly emerging field of intracrinology, the vast majority of androgens (e.g. 75% before and 100%after menopause) in women, and a significant proportion in men (e.g. 40 to 50%), are synthesized in peripheral tissues from adrenal sex steroid precursors (i.e. dehydroepiandrosterone [DHEA] and DHEA-sulfate [DHEA-S]).[9,10] In fact, humans and primates are unique in possessing adrenal glands that secrete large amounts of DHEA and DHEA-S, which are then converted into potent androgens (e.g. testosterone, DHT) or estrogens by steroidogenic enzymes in peripheral sites and thereby permit target tissues to adjust the formation and metabolism of sex steroids to local requirements.[9,10] This situation contrasts sharply with that in lower mammals (e.g. mice, rats, guinea pigs), in which the ovaries and testes are the exclusive source of active sex steroids.[9,10]

The primary source of androgens (e.g. testosterone, DHT) that act on the human lacrimal gland, meibomian gland, cornea and conjunctiva is most likely the tissue itself (i.e. from intracrine steroid synthesis). These tissues have recently been shown to contain the mRNAs for the key steroidogenic enzymes, including steroid sulfatase, 3b-hydroxysteroiddehydrogenase (**HSD**)-_-5_4-isomerase type 1, 17b-HSD types 1 and 3, aromatase, Types 1 and 2 5a-reductase,glucuronosyltransferase and sulfotransferase.[11,12]

Overall, serum testosterone and DHT are useful as markers of testicular secretion in men and interstitial ovarian secretion in women.[13] Their measurement for dry eye diagnosis, though, does not appear to be warranted.

2.2.2. DHEA and DHEA-S

Similarly, serum measurements of DHEA and DHEA-S would not be useful as specific markers for dry eye syndromes. A variety of conditions that may induce dry eye have been linked to a reduction in the serum levels of DHEA andDHEA-S. Thus, autoimmune diseases, such as primary and secondary Sjögren's syndrome, SLE and RA, are associated with a significant decrease in the serum levels of DHEA and/or DHEA-S.2 Moreover, the aging process is paralleled by a dramatic decline in the serum concentrations of

DHEA and DHEA-S. For example, serum DHEA levels decrease by _ 70%in men and women between the 3rd to 6th decade of life.[13]

However, reductions in serum DHEA and its sulfated form have also been correlated with insulin resistance, obesity, osteoporosis, cardiovascular diseases, loss of muscle mass, depression, immunodeficiency, cancer and other diseases.[14, 15] Levels of DHEA have also been shown to increase with acute stress[16] and moderate alcohol consumption.[17] These conditions, in turn, are not necessarily associated with dry eye syndromes.

2.2.3. Other androgens

The most valid and perhaps the only reliable estimate of the total androgen pool in humans is the serum concentration of the conjugated DHT metabolites, such as androsterone-glucuronide (ADT-G), androstane-3a,17b-diol -G (3a-diol-G),3b-diol-G and ADT-sulfate, which reflect the total intracrine production and metabolism of androgens in peripheral tissues throughout the body.[9,10,13] The serum concentration of these various conjugated androgen metabolites declines by 40.8% to72.8% between the 20- to 30-yr-old and 70- to 80-yr-old age groups in men and women, respectively, and suggests a parallel decrease in the total androgen pool with age.[13] In addition, the serum levels of ADT-G and 3a-diol-G are significantly reduced in women with Sjögren's syndrome.[2]

Measurement of these serum DHT metabolites, such as by liquid chromatography/tandem mass spectrometry using aturboionspray,[18] would demonstrate whether an individual is androgen-deficient. However, such analyses would not necessarily reflect the levels of active androgens within ocular tissues.

3. Measurement of serum estrogen levels

The rationale for the measurement of serum estrogens for dry eye diagnosis is unclear. To explain:

- some researchers have proposed that the topical or systemic administration of estrogens to women with dry eye syndromes elicits a subjective amelioration of symptoms, a decrease in foreign body sensation and redness, an increase in Schirmer test values, an improvement in tear film break-up time, as well as enhanced corneal clarity and visual acuity.[1] This proposition would be consistent with the reported positive correlation between serum estradiol levels and tear function for women 30-39 years of age.[8]
- other investigators have found no demonstrable influence of estrogens on various aspects of the normal or autoimmune lacrimal gland or the tear film.[1]
- and yet other scientists have reported that estrogens, or estrogen-containing oral contraceptives, induce negative actions on the tear film, including lacrimal gland hyposecretion, decreased tear volume, diminished tear film break-up time, attenuated mucous production, foreign body sensation, blurred vision, contact lens intolerance, decreased visual acuity and dryness in humans.[1] Indeed, an epidemiological evaluation of 25,665 postmenopausal women has demonstrated that women using estrogen replacement therapy have a significantly higher prevalence of severe dry eye symptoms and

clinically diagnosed dry eye syndrome.[19] These observations would be consistent with the reported negative correlation between serum estradiol levels and tear function for postmenopausal women.[8]

Given this controversy regarding estrogen's role in the anterior segment, it is not apparent how serum estrogen measurements could accurately reflect tear film function. As an additional consideration, the meaning of a serum estrogen determination is itself questionable, especially in postmenopausal women and men. For example, the ovaries are a principal source of estrogens in premenopausal women. However, in postmenopausal women and in men estrogen is produced almost exclusively in extragonadal tissues (i.e. through the aromatization of androgens). The estrogen then acts locally and is either metabolized or escapes metabolism and enters the circulation.[20-22] In other words high levels of estrogen may be produced within a given tissue (e.g. lacrimal gland), but these amounts may not be reflected at all in the circulation.[23] This is particularly true during inflammation, when elevated amounts of pro-inflammatory cytokines (e.g., IL-1, TNF-a, IL-6) may disrupt the normal activity of steroidogenic enzymes and promote the aromatization of testosterone to 17b-estradiol.[1]

Consequently, the measurement of serum estrogens, especially in postmenopausal women, may not reflect the concentration or activity of these hormones in ocular surface tissues.

4. Measurement of tear androgen and estrogen levels

Investigators have reported that the human tear film contains 17b-estradiol, progesterone and testosterone.[24,25]

Moreover, the tear levels of 17b-estradiol and progesterone appear to correlate with those of serum.[25] The relevance of tear hormone concentrations to dry eye diagnosis, though, is not readily apparent. Endogenous tear steroid (e.g. testosterone) levels would not necessarily reflect the concentration of bioavailable steroid in any specific ocular tissue and, as in other mucosal sites, would be significantly influenced by changes in the rate of steroid metabolism (e.g. during autoimmune disease) in the adjacent ocular adnexa.

5. Measurement of serum and tear prolactin levels

Investigators have reported a negative correlation between serum prolactin levels and tear function, particularly in women taking hormone replacement therapy. The interpretation of this correlation, though, is unclear.

- Prolactin originates not only from the pituitary, but also from lacrimal gland acinar epithelial cells.[26] Prolactin is also secreted by lacrimal tissue into tears.[26] Whether 'pituitary' or 'lacrimal' prolactin species have differential effects on the lacrimal gland or ocular surface is unknown.
- A definitive role for prolactin in lacrimal gland function and tear film dynamics is also unknown. This hormone has no significant influence on tear secretion rates, tear volume or tear protein content.[26]

It may be that prolactin promotes autoimmune disease in the lacrimal gland, given this hormone's pro-inflammatory nature and possible role in the pathogenesis of Sjögren syndrome.[26] However, there is no indication as to why the measurement of serum or tear prolactin levels might be indicative of this activity.

6. Summary

Androgen deficiency may contribute to the development of dry eye syndromes and may be identified by the measurement of glucuronidated DHT metabolites in serum. The value of other possible markers (e.g. serum estrogen and prolactin) for the dry eye diagnosis has yet to be demonstrated.

7. References

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