

DEFICIENCIA ANDROGÉNICA Y SÍNDROMES DE OJO SECO

ANDROGEN DEFICIENCY & DRY EYE SYNDROMES

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Sex steroid deficiency has been linked with the development and/or progression of a wide variety of clinical disorders, including cardiovascular disease, obesity, osteoporosis, insulin resistance and certain cancers (1). We hypothesize that sex steroid deficiency, specifically that of androgens, may also be a critical etiologic factor in the pathogenesis of dry eye syndromes.

Dry eye syndromes are a leading cause of patient visits to ophthalmologists and are classified into two major types: aqueous-deficient and evaporative (2). Aqueous-deficient dry eye is due to a lack of aqueous tear secretion by the lacrimal glands. An example is Sjögren's syndrome, an autoimmune disease that afflicts predominantly women. This disorder is associated with extensive inflammation in lacrimal tissue, an immune-mediated dysfunction and/or destruction of acinar and ductal epithelial cells, and a precipitous decline in aqueous tear output. Sjögren's syndrome may be either primary (i.e. no associated connective tissue disease) or secondary [e.g. individuals with systemic lupus erythematosus (SLE) or rheumatoid arthritis (RA)]. The second type of dry eye is termed evaporative and is most often caused by meibomian gland dysfunction and lipid insufficiency, thereby promoting increased evaporation and reduced stability of the tear film. This form of dry eye is also observed in Sjögren's syndrome, as well as during menopause and aging. Researchers have estimated that meibomian gland disease may be a contributing factor in over 2/3 of all dry eye patients (3).

The rationale for our hypothesis linking androgen deficiency with dry eye syndromes is two-fold:

First, androgens regulate numerous aspects of the lacrimal gland, including epithelial cell morphology, gene expression, protein synthesis, secretory processes and immune function. 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. However, women with Sjögren's syndrome have an androgen deficiency (4), and this hormone deficit may predispose to lacrimal gland dysfunction, decreased tear secretion and aqueous-deficient dry eye. Consistent with this hypothesis is the finding that androgen treatment of female mouse models of Sjögren's syndrome causes a dramatic suppression of the inflammation in, and a significant increase in the functional activity of, lacrimal glands. Similarly, androgen therapy has been reported to alleviate dry eye signs and symptoms, and stimulate tear flow, in Sjögren's syndrome patients. The mechanism by which androgens suppress lacrimal gland autoimmune disease appears to involve hormone binding to nuclear receptors within epithelial cells and a consequent alteration in the activity of specific genes and proteins in lacrimal tissue (5).

Second, the meibomian gland, like other sebaceous glands, is an androgen target organ. Androgens control the development, differentiation and lipid production of sebaceous glands throughout the body. Similarly, androgens appear to regulate meibomian gland function, improve the quality and/or

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Acknowledgments:

Research cited in this editorial was supported in part by grants from United States National Eye Institute [NIH grants EY05612 & 12523], Allergan [USA & Japan], the German Research Society DFG, the Sjögren's Syndrome Foundation, the Massachusetts Lion's Research Fund, the Joint Clinical Research Center of the Schepens Eye Research Institute and the Massachusetts Eye & Ear Infirmary, and the General Clinical Research Center at the University of Chicago Medical Center Foundation).

quantity of lipids produced by this tissue and promote the formation of the tear film's lipid layer. These hormone effects appear to be mediated through androgen receptors within epithelial cell nuclei and to involve the modulation of multiple genes, including those related to lipid, sex steroid and other cellular metabolic pathways. 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. 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). This association between androgen deficiency, meibomian gland dysfunction and evaporative dry eye may help to explain why 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 (6).

Overall, 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. Given these observations, it is possible that efforts directed at alleviating the endocrine imbalance in ocular surface tissues may prove beneficial as a therapy for lacrimal and meibomian gland dysfunction and the associated dry eye in androgen-deficient individuals. Whether this approach is useful may soon be determined by Allergan, which is currently testing in clinical trials in the USA and Europe the efficacy of topical androgens for the treatment of dry eye.

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