Sex, sex steroids & dry eye syndromes: The impact of androgen deficiency
D.A. Sullivan
Schepens Eye Research Institute and Harvard Medical School, Boston, MA, USA

Sex steroid deficiency has been linked to the development and/or progression of a wide variety of clinical disorders, including cardiovascular disease, osteoporosis, obesity, insulin resistance and certain cancers. We hypothesize that sex steroid deficiency specifically that of androgens, may also be a critical pathogenetic factor in the etiology of dry eye syndromes. Dry eye syndromes are a leading cause of patient visits to eye care practitioners and are classified into two major types: aqueous-deficient and evaporative. Aqueous-deficient dry eye is due to a lack of aqueous tear secretion by lacrimal tissue. An example is Sjögren's syndrome, an autoimmune disorder that afflicts predominantly women. This syndrome is associated with extensive inflammation in lacrimal glands, an immune-mediated dysfunction and/or destruction of acinar and ductal epithelial cells, and a significant decline in aqueous tear output. Sjögren's syndrome may be either primary (i.e. no associated connective tissue disease) or secondary (e.g. people 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 decreased stability of the tear film. This form of dry eye is also found 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 67% of all dry eye patients.

The rationale for our hypothesis linking androgen deficiency with dry eye syndromes is two-fold. First, androgens control 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, physiology, molecular biology and immunology of this tissue. However, women with Sjögren's syndrome have an androgen deficiency, and this hormone deficit may predispose to lacrimal gland dysfunction, attenuated tear secretion and aqueous-deficient dry eye. Consistent with this hypothesis is the observation 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 patients with Sjögren's syndrome. The mechanism by which androgens suppress lacrimal gland autoimmune disease seems 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.

Second, the meibomian gland, like all other sebaceous glands, is an androgen target organ. Androgens regulate the development, differentiation and lipid production of sebaceous glands throughout the body. Similarly, androgens appear to control 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. These hormone effects seem 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 (decrease in secretion of adrenal androgen precursors), aging in both sexes (decline 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 pharmaceuticals (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 individuals 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 elaboration 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.

Overall, research indicates that androgen deficiency may be a critical pathogenetic factor in the etiology 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 people. Whether this approach is useful may soon be determined by clinical trials in the USA that are testing the efficacy of topical androgens for the treatment of dry eye. (This research summary was supported by NIH grant EY05612)