Androgen Deficiency in Ocular Surface Disease

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Current therapeutic modalities have been helpful in treating many patients with ocular surface disease and dysfunctional tear syndrome. But there remains a subset of patients who continue to have signs and symptoms in spite of aggressive lubricant and anti-inflammatory therapy. Accumulating evidence suggests that meibomian gland dysfunction and ocular surface irritation may be related to systemic androgen deficiency or insensitivity, particularly in women. This article presents evidence supporting this hypothesis and an overview of androgen production, diagnosis and treatment of deficiency states.

Ocular surface disease and dysfunctional tear syndrome comprise a significant proportion of ophthalmic patient concerns and visits,[1] with an estimated prevalence in the United States of 0.4 percent to 0.5 percent.[2] It is more common among women and older adults, and has an estimated 10-year incidence of 21.6 percent among 43- to 86-year-olds.[3] There has been a growing awareness of the importance of inflammation in the etiology of these problems.[4]

Androgen Production and Function

Androgens are a group of hormones that are largely responsible for features of the male phenotype. Systemic symptoms of androgen deficiency can include a decline in muscle mass, increase in body fat, decrease in bone mass, decrease in libido, decrease in overall sense of well-being, lowered mood, dry skin, decline in cognitive skills and increased risk of coronary artery disease.[5] Androgens are produced in the adrenal glands, gonads (ovaries and testes) and through peripheral conversion, such as body fat.

Academy Resources
- Cultural/Linguistic Differences
- Financial Disclosure
- K Card
- OKAP Exam
- Professional Choices/Careers
- Young Ophthalmologists

Other Resources
- ASCRS Post-Refractive Surgery IOL Power Calculator
- Gonioscopy.org
- National Registry of Drug-Induced Ocular Side Effects
- OHTS/EGPS Glaucoma Risk Calculator
- Pediatric Vision Screening
- The Eyes Have It

The androgen levels of men are 10 to 20 times higher than those of women. In women, roughly 50 percent of androgens are produced in the ovaries, with the other half produced in the adrenal glands and through peripheral conversion.[6]

Testosterone and dihydrotestosterone (DHT), which is produced through enzymatic conversion of testosterone via 5-alpha-reductase, are the major biologically active androgens. Testosterone, unlike DHT, can also be converted from estradiol via aromatase. In circulation, nearly all testosterone is bound by sex-hormone binding globulin (SHBG) and, to a lesser degree, albumin. In the adrenal glands, androstenedione, dehydroepiandrosterone (DHEA) and its more stable sulfated variant, dehydroepiandrosterone-sulfate (DHEA-S), are the primary, albeit less potent, androgens produced.

DHEA levels follow a circadian variation, while the stability of DHEA-S provides for more consistent blood levels. DHEA can be further converted into testosterone or estrogens, and this conversion may be more of a factor in women than men. The hypothalamic-pituitary-adrenal axis is the primary regulatory mechanism, but, as estrogens and cortisol are the primary negative feedback hormones in this cycle, there is no direct regulation of testosterone production. As such, exogenous administration of glucocorticoids or estrogens will reduce androgen levels by inhibition of this pathway, as well as by other mechanisms, including increasing SHBG production. This becomes particularly relevant in women who are postmenopausal, have ovarian dysfunction or have had an oophorectomy. Similarly, adrenal deficiencies, adrenalectomy and pituitary dysfunction could all lead to lower androgen levels.

Evidence for Ocular Surface Disease

Basic research has suggested that the meibomian gland is an androgen target organ and that testosterone can influence gene expression in a mouse meibomian gland.[7] Corroborating this finding is that patients with Complete Androgen Insensitivity Syndrome, a condition in which androgen receptors are completely dysfunctional, have altered meibomian gland secretions[8] and possibly an increase in the signs and symptoms of dry eye.[9] Other suggestive evidence includes an increased risk of dry eye syndrome in women taking hormone replacement therapy[10] and women

with premature ovarian failure.[11] While androgen levels were not directly measured in these studies, another study found reduced androgen levels in women with Sjögren syndrome.[12] One small study found that combined esterified estrogen and methyltestosterone therapy improved dry eye symptoms,[13] but androgen levels were not measured in that series either.

Although it seems apparent that hormonal irregularities can contribute to a worsened ocular surface, it is unclear whether specific androgen deficiencies are the cause or whether more complex relationships exist between relative concentrations of androgens and estrogens or other hormones.

Diagnosis and Testing

The diagnosis and management of androgen insufficiency or deficiency is controversial. A proposal has been made for a "female androgen deficiency syndrome," which encompasses symptoms of decreased libido, fatigue and low well-being associated with low bioavailable (loosely, non-SHBG bound) testosterone levels and normal estrogen levels. However, consensus on defining this syndrome has not been achieved as there is no set threshold to define "low" androgen levels, how or which androgens should be measured, or the best supplemental modality.[14]

With this lack of expert consensus, testing and treatment for androgen deficiency should be performed judiciously. The authors typically reserve testing for those who fail standard therapy and either exhibit systemic symptoms of androgen deficiency or have a risk factor for deficiency, such as ovarian dysfunction or long-term use of estrogen replacement therapy with advancing age. In conjunction with the patient's primary care physician, the authors advise testing for free and bioavailable testosterone, SHBG and DHEA-S, as well as routine testing, including for thyroid function and serum electrolytes.

If androgen deficiency is found, supplemental testosterone can be given. The authors' preferred method has been to change an existing estrogen supplement to a combination estrogen-testosterone supplement. If the levels appear normal but a high index of suspicion remains, a trial of compounded DHEA 1% ophthalmic solution can be attempted, usually initiated at one drop four times daily.

Patients should be counseled about the limited clinical data on this regimen and the potential for side effects, including virilization, acne, fluid retention, elevated cholesterol or more serious hepatic and cardiac problems. Pregnant or lactating women should not be treated, given the risk of virilization of female fetuses and infants. Treatment is absolutely contraindicated in any patient with a history of androgen-dependent neoplasia.

It is also important to consider all of the potential causes of low testosterone, and it may be advisable to enlist the aid of an endocrinologist for more extensive testing to rule out pituitary or adrenal dysfunction. This may include testing for cortisol, prolactin, estradiol, luteinizing hormone (LH) and adrenocorticotropic hormone (ACTH) levels.

Case Study

In selected cases, the authors have had success treating patients with supplemental androgen therapy. **Figures 1A and 1B** show the eyes of a 47-year-old woman with peripheral subepithelial corneal fibrosis, severe meibomian gland dysfunction, dry eye syndrome and presumed ocular rosacea, whose right eye (**Figure 1A**) had recently undergone superficial keratectomy. The right eye had a fairly rapid recurrence of fibrosis with peripheral neovascularization in spite of aggressive lubrication, punctal occlusion, oral doxycycline and topical steroid therapy. The left eye (**Figure 1B**) had a pseudo-pterygium with localized limbal stem cell deficiency.

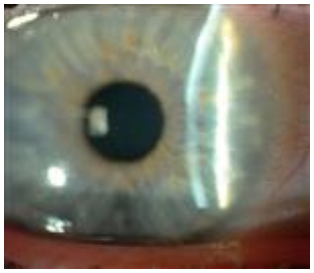

Image courtesy of Ayad A. Farjo, MD, and Qais A. Farjo, MD.

Figure 1A. The right eye, which had recently undergone superficial keratectomy, of a 47-year-old woman with peripheral subepithelial corneal fibrosis, severe meibomian gland dysfunction, dry eye syndrome and presumed ocular rosacea. Note the subepithelial fibrosis highlighted by

the slit beam and the limbal neovascularization nasally.

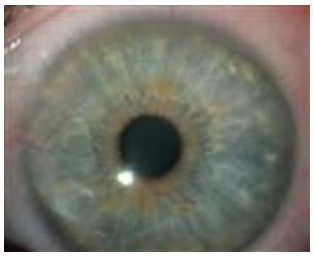

Image courtesy of Ayad A. Farjo, MD, and Qais A. Farjo, MD.

Figure 1B. A pseudopterygium is present nasally in the same patient's left eye.

The patient's medical history was notable for "premature menopause" diagnosed at age 35 by abnormal menstrual cycles, elevated follicle stimulating hormone (FSH) levels and estrogen deficiency symptoms, including hot flashes and vaginal dryness. She was treated with oral contraceptives since then, cycling every three months. At age 39, she began developing hair loss of the scalp, as well as loss of axillary and pubic hair. A review of symptoms was otherwise notable for fatigue and depression.

Given the constellation of findings, androgen deficiency was suspected and the patient referred to her primary care physician and subsequently an endocrinologist for further evaluation. Free serum testosterone levels were undetectable and additional testing led to the diagnosis of premature ovarian failure, most likely autoimmune in etiology. She was prescribed oral 0.625 mg esterified estrogen/1.25 mg methyltestosterone (Estratest) daily and oral 100 mg micronized progesterone (Prometrium) twice daily.

After three months of therapy, she noted improvement in her ocular symptoms and reduced ocular irritation, as well as overall improvement in her well-being. Clinical examination demonstrated marked improvement in meibomian gland function, with no progression of the subepithelial fibrosis in either eye or neovascularization in the left eye and elimination of the need for topical steroids.

Conclusion

Androgen insufficiency appears to play a role in some cases of ocular surface disease, and ophthalmologists may be important in diagnosing

these cases. Current evidence, while tantalizing, is insufficient. Further study is warranted to determine the significance of androgen insufficiency in ocular surface disease, as well as the best methods for diagnosis and treatment of such cases. In patients with ocular surface disease who do not respond to standard therapy, particularly perimenopausal women with risk factors for androgen deficiency, consideration should be given to the possibility of reduced androgen levels.

References

1. Brewitt H, Sistani F. Dry eye disease: the scale of the problem. *Surv Ophthalmol.* 2001;45 Suppl 2:S199-202.
2. Pflugfelder SC. Prevalence, burden, and pharmacoeconomics of dry eye disease. *Am J Manag Care.* 2008;14(3 Suppl):S102-106.
3. Moss SE, Klein R, Klein BE. Long-term incidence of dry eye in an older population. *Optom Vis Sci.* 2008;85:668-674.
4. Stern ME, Gao J, Siemasko, et al. The role of the lacrimal functional unit in the pathophysiology of dry eye. *Exp Eye Research*. 2004;78:409-416.
5. Rivera-Woll LM, Papalia M, Davis SR, Burger HG. Androgen insufficiency in women: diagnostic and therapeutic implications. *Hum Reprod Update*. 2004;10:421-432.
6. Mazer NA. Testosterone deficiency in women: etiologies, diagnosis, and emerging treatments. *Int J Fertil Womens Med*. 2002;47:77-86.
7. Schirra F, Suzuki T, Richards SM, et al. Androgen control of gene expression in the mouse meibomian gland. *Invest Ophthalmol Vis Sci*. 2005;46:3666-3675.
8. Sullivan BD, Evans JE, Cermak JM, Krenzer KL, Dana MR, Sullivan DA. Complete androgen insensitivity syndrome: effect on human meibomian gland secretions. *Arch Ophthalmol*. 2002;120:1689-1699.
9. Cermak JM, Krenzer KL, Sullivan RM, Dana MR, Sullivan DA. Is complete androgen insensitivity syndrome associated with

alterations in the meibomian gland and ocular surface? *Cornea*. 2003;22:516-521.

10. Schaumberg DA, Buring JE, Sullivan DA, Dana MR. Hormone replacement therapy and dry eye syndrome. *JAMA*. 2001;286:2114-2119.
11. Smith JA, Vitale S, Reed GF, et al. Dry eye signs and symptoms in women with premature ovarian failure. *Arch Ophthalmol*. 2004;122:151-156.
12. Sullivan DA, Bélanger A, Cermak JM, et al. Are women with Sjögren's syndrome androgen-deficient? *J Rheumatol*. 2003;30:2413-2419.
13. Scott G, Yiu SC, Wasilweski D, Song J, Smith RE. Combined esterified estrogen and methyltestosterone treatment for dry eye syndrome in postmenopausal women. *Am J Ophthalmol*. 2005;139:1109-1110.
14. Bhasin S. Female Androgen Deficiency Syndrome-An Unproven Hypothesis. *J Clin Endocrinol Metab*. 2005;90:4970-4972.