

Is Complete Androgen Insensitivity Syndrome Associated with Alterations in the Meibomian Gland and Ocular Surface?

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Purpose. This study's purpose was to determine whether complete androgen insensitivity syndrome (CAIS) is associated with alterations in the meibomian gland and ocular surface. **Methods.** Individuals with CAIS, as well as age-matched female and male controls, completed questionnaires which assessed dry eye symptoms and underwent slit lamp evaluations of the tear film, tear meniscus, lids and lid margins and conjunctiva. The quality of meibomian gland secretions was also analyzed. **Results.** Our results demonstrate that CAIS is associated with meibomian gland alterations and a significant increase in dry eye signs and symptoms. Clinical assessment revealed that CAIS women, as compared to controls, had a significant increase in telangiectasia, keratinization, lid erythema and orifice metaplasia of the meibomian glands, and a significant decrease in the tear meniscus and quality of meibomian gland secretions. Questionnaire results showed that dry eye symptoms were increased over twofold in CAIS individuals, as compared to controls, including a significant increase in the sensations of dryness, pain and light sensitivity. **Conclusion.** Our results suggest that androgen insensitivity may promote meibomian gland dysfunction and an increase in the signs and symptoms of dry eye.

Key Words: meibomian gland, ocular surface, dry eye, androgens, complete androgen insensitivity syndrome

The meibomian gland is extremely important in maintaining the health and integrity of the ocular surface.^{1–6} This eyelid tissue, through its production and release of lipids, promotes the stability and prevents the evaporation of the precocular tear film.^{1,3–6} Conversely, meibomian gland dysfunction and the associated lipid insufficiency may cause tear film instability and evaporative dry eye, which may lead to significant corneal pathology and visual

impairment.^{1,3,4,7,8} Of particular interest, meibomian gland dysfunction is believed to be the major cause of dry eye syndromes,⁹ which impact more than 10 million people in the United States.¹⁰

Recently, our research has shown that the meibomian gland is an androgen target organ and that androgen deficiency may be a critical etiologic factor in the pathogenesis of meibomian gland dysfunction and evaporative dry eye.¹¹ Thus, 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.^{12–14} Moreover, androgen deficiency appears to be associated with meibomian gland dysfunction (i.e., evidence of meibomian gland abnormality in morphology or its secretion), altered lipid profiles in meibomian gland secretions, decreased tear film stability, and evaporative dry eye.^{15–17} Of particular interest, meibomian gland disease and evaporative dry eye often occur during menopause, aging in both sexes, and primary and secondary Sjögren syndrome,¹⁸ and a common denominator in these diverse conditions is androgen deficiency.^{19,20}

The precise mechanism(s) underlying this androgen influence on the meibomian gland is unclear. We hypothesize that androgen action is mediated primarily through "classical" intranuclear androgen receptors because such receptors are known to initiate almost all androgen effects throughout the body^{21,22} and have recently been identified within acinar epithelial cell nuclei of human meibomian glands.²³ In addition, we have discovered that the use of antiandrogen medications is associated with meibomian gland dysfunction and an increase in the signs and symptoms of dry eye.¹⁵ However, it is also possible that androgens act on the meibomian gland through "nonclassical" processes. These hormone effects, which are often very rapid (e.g., seconds or minutes), may involve changes in membrane fluidity, regulation of neurotransmitter receptors, and/or interaction with stereospecific plasma membrane receptors.²⁴ Furthermore, androgens could associate with sex-hormone binding globulin, which interacts with a cell surface receptor and stimulates cellular activities through adenylyl cyclase-linked pathways.²⁵

The purpose of this investigation was to test our hypothesis that androgen receptors are important in the androgen regulation of the meibomian gland. Accordingly, we recruited women with complete androgen insensitivity syndrome (CAIS). These CAIS individuals have mutations in their androgen receptor gene that result in totally dysfunctional androgen receptors as well as an inability

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to respond "classically" to androgen action.^{26,27} Given our hypothesis, we predicted that CAIS women would have meibomian gland dysfunction and an increase in the signs and symptoms of dry eye.

METHODS

Human Subjects

Individuals with CAIS (40.4 ± 2.3 years old; $n = 9$) were recruited nationally from the Androgen Insensitivity Syndrome Support Group (San Diego, CA). Age-matched female (40.6 ± 2.7 years old; $n = 10$) and male (36.9 ± 1.4 years old; $n = 11$) controls (combined controls = 38.7 ± 1.5 years old; $n = 21$) without a clinical history of androgen insensitivity were recruited from the Boston area (Boston, MA). Subjects were excluded if they had any active ocular infection, were not in good general health (i.e., cancer, uncontrolled diabetes), or could not understand the study purpose or procedure. These studies were approved by the Human Studies Committees of the Brigham and Women's Hospital (Boston, MA) and the University of Chicago Medical Center (Chicago, IL) and were conducted in accordance with guidelines established by the Declaration of Helsinki.

Clinical Assessment

After giving informed written consent, subjects were asked to complete without supervision two questionnaires that assessed symptoms of ocular irritation consistent with dry eye disease [i.e., the Dry Eye Severity Questionnaire (DESQ) and Ocular Surface Disease Index[®] (OSDI), Allergan, Inc., Irvine, CA]. The DESQ grades symptoms experienced over the previous week on a 0 to 4 scale. A "0" score reflects no specific symptomatology, whereas a "4" score indicates that the subject always noticed the symptom

and that it was uncomfortable and interfered with his/her activities. The DESQ evaluates eight specific ocular surface symptoms, including dryness, sandy or gritty feeling, burning/stinging, pain, itching, sensitivity to light, blurred vision, and tired eyes and also requests subject grading of other unspecified symptoms. The OSDI is a validated set of questions that examine the frequency of ocular symptoms and associated functional impairment during the prior week.

Following completion of the questionnaires, individuals were asked to answer questions related to medical histories and current medications and then underwent an examination of both anterior segments (Table 1) by corneal external disease specialists. This exam, which was based on standard protocols,²⁸⁻³² included a slit-lamp evaluation of the tear film for the presence of mucus and debris and of the tear meniscus by utilizing semiquantitative measurements. A normal meniscus appears as a clear and continuous tear film over the ocular surface adjacent to the lower lid margin and is usually over 0.3 mm in height.³¹ An abnormal meniscus is present when a clearly continuous tear film cannot be distinguished across the inferior lid margin. An intermediate meniscus is identified as a tear film level between normal and abnormal. Lids and lid margins were examined for the identification of erythema, notching, irregular posterior margins, misdirected lashes, loss of lashes, neovascularization, telangiectasia, collarettes, sleeve and scurf, keratinization, and the number of expressible meibomian glands; and conjunctivae were examined for the appearance of erythema, bulbar injection, tarsal injection, and papillary hypertrophy. Lids were also evaluated for the presence of metaplasia of the meibomian gland orifices, a condition defined as an atypical growth and keratinization of duct epithelium.³³ Analysis was done of the quality of meibomian gland secretions, according to a reported classification system (Table 1).²⁹

TABLE 1. Clinical assessment of the anterior segment

Parameter	Clinical assessment	Grading scheme
Tear film		
Mucus	Present or absent	
Debris	Present or absent	
Tear meniscus	Grade 0-2	0 = normal; 1 = intermediate; 2 = abnormal
Lid and lid margin		
Erythema	Grade 0-3	0 = none; 1 = mild, with redness of most of the lid margin; 2 = moderate, with redness of the lid margin and skin; 3 = severe, with marked redness of lid and skin
Notching	Present or absent	
Irregular posterior margins	Present or absent	
Misdirected lashes	Grade 0-3	0 = none; 1 = mild; 2 = moderate; 3 = severe
Loss of lashes	Grade 0-2	0 = none; 1 = some; 2 = extensive
Neovascularization	Grade 0-3	0 = none; 1 = micropannus; 2 = pannus <180°; 3 = pannus >180°
Telangiectasia	Present or absent	
Collarette	Grade 0-2	0 = none; 1 = some; 2 = extensive
Sleeve/scurf	Grade 0-2	0 = none; 1 = some; 2 = extensive
Keratinization	Grade 0-2	0 = none; 1 = some; 2 = extensive
Metaplasia of meibomian gland orifices	Present or absent	
Number of expressible meibomian glands	Out of 10 lower lid glands	
Quality of meibomian gland secretions	Grade 0-3	0 = clear excreta with small particles; 1 = opaque excreta with normal viscosity; 2 = opaque excreta with increased viscosity; 3 = secretions that retained shape after digital expression
Conjunctiva		
Erythema	Grade 0-3	0 = none; 1 = slight localized; 2 = pink color to palpebral/bulbar conjunctiva; 3 = red color to palpebral/bulbar conjunctiva
Bulbar injection	Present or absent	
Tarsal injection	Present or absent	
Papillary hypertrophy	Present or absent	

Ocular surface examinations of the right and left eyes were performed by following standard protocols, as described in the Materials and Methods.

Examinations of individuals with CAIS were performed at the General Clinical Research Center at the University of Chicago Medical Center, whereas evaluations of control subjects were conducted at Brigham and Women's Hospital. One of our corneal external disease specialists conducted all of the clinical examinations in Chicago as well as many of the control evaluations in Boston. The time available for assessment of CAIS individuals was extremely limited. These people, who were attending a national meeting of the Androgen Insensitivity Syndrome Support Group in Chicago, had previously agreed to take part in, and had been scheduled for, a series of nonophthalmic clinical exams at the University of Chicago Medical Center. Consequently, the duration of subject participation in our ophthalmic study was limited to approximately 15 minutes. These time constraints did not permit us to perform, or to obtain Institutional Review Board approval for, additional and time-consuming ocular surface assessments, such as Schirmer tests, tear film breakup time, and vital dye staining.

Statistical Analysis

Data were compared by using unpaired, two-tailed Student's *t* and χ^2 tests.

RESULTS

To determine whether CAIS is associated with meibomian gland alterations and an increase in the signs and symptoms of dry eye, CAIS individuals ($n = 9$) and age-matched female ($n = 10$) and male ($n = 11$) controls were given anterior segment examinations. Moreover, subjects and controls completed questionnaires designed to evaluate dry eye symptoms.

Our results demonstrate that CAIS is associated with a significant increase in dry eye signs and symptoms. Clinical assessment showed that the CAIS group, compared to all controls, had a significantly reduced tear meniscus (Fig. 1) and a significantly increased degree of lid erythema, telangiectasia, and keratinization (Table 2, Fig. 1). Furthermore, examination of the meibomian glands revealed that CAIS individuals had a significant increase in the frequency of orifice metaplasia and a significant decrease in the quality (i.e., higher viscosity) of secretions, relative to all controls (Fig. 1). All of these differences were found whether CAIS group data were compared to those of the female, the male, or the entire control group.

In addition to these observations, CAIS individuals had a greater frequency of collarettes, sleeve/scurf, irregular posterior margins, conjunctival erythema, bulbar injection, and tarsal injection than did all controls (Table 2). In contrast to these findings, control individuals had a higher frequency of misdirected lashes, lid neovascularization, and conjunctival papillary hypertrophy relative to CAIS women (Table 2).

These results could not be attributed solely to interexaminer bias. If comparisons were limited to the CAIS ($n = 9$) and control ($n = 9$) subjects examined by the same investigator, analysis showed that CAIS individuals had an increased degree of lid telangiectasia ($p < 0.05$), keratinization ($p = 0.0001$), and meibomian gland orifice metaplasia ($p = 0.0001$), a reduced tear meniscus ($p = 0.0001$) and quality of meibomian gland secretions ($p = 0.0001$), a decreased number of expressible meibomian glands ($p < 0.05$), and a lower frequency of lid neovascularization ($p < 0.0005$), conjunctival papillary hypertrophy ($p < 0.005$), and misdirected lashes ($p < 0.005$) (data not shown).

Analysis of the DESQ and OSDI questionnaire results showed that dry eye symptoms were significantly increased over twofold

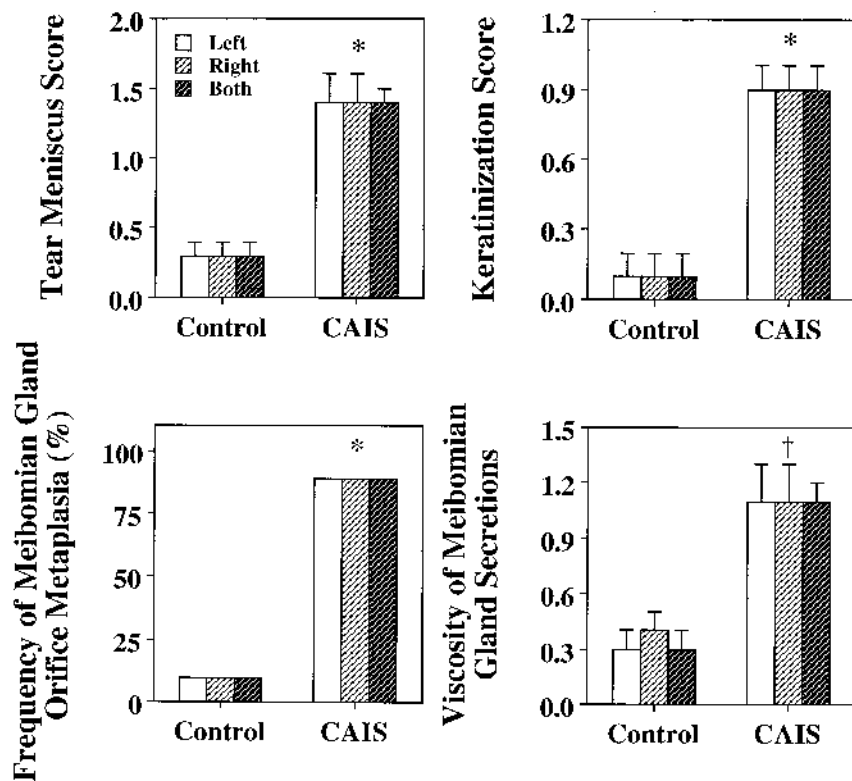


FIGURE 1. Influence of CAIS on the tear film, lid margin, and meibomian gland. Examinations were performed on CAIS individuals ($n = 9$) and their age-matched female and male controls ($n = 21$). The left and right tear film menisci were graded on a scale of 0 (normal), 1 (intermediate), or 2 (abnormal). In three of the graphs (i.e., meniscus, keratinization, and viscosity), the columns and bars represent the mean \pm SE of each group's score. In the remaining graph (i.e., metaplasia), the columns represent the frequency of appearance of metaplasia. *Significantly ($p = 0.0001$) higher in all three categories (i.e., left eye, right eye, and both eyes) than the control values. †Significantly (left, $p < 0.005$; right, $p < 0.0005$; both, $p = 0.0001$) greater than the control values.

TABLE 2. Frequency of ocular surface and lid abnormalities in CAIS individuals

Clinical exam	Controls	CAIS subjects	p Value
Tear film			
Mucus OD	0%	0%	NS
Mucus OS	4.8%	0%	NS
Mucus OD and OS	2.4%	0%	NS
Debris OD	0%	0%	NS
Debris OS	0%	0%	NS
Debris OD and OS	0%	0%	NS
Lid and lid margin			
Erythema OD	0.3 ± 0.1	1.0 ± 0.2	<0.01
Erythema OS	0.4 ± 0.1	1.0 ± 0.2	<0.05
Erythema OD and OS	0.4 ± 0.1	1.0 ± 0.1	<0.0005
Notching OD	0%	0%	NS
Notching OS	0%	11.1%	NS
Notching OD and OS	0%	5.6%	NS
Irregular posterior margin OD	19.1%	44.4%	NS
Irregular posterior margin OS	9.5%	44.4%	<0.05
Irregular posterior margin OD and OS	14.3%	44.4%	<0.05
Misdirected lashes OD	0.4 ± 0.1	0 ± 0	<0.05
Misdirected lashes OS	0.5 ± 0.1	0 ± 0	0.01
Misdirected lashes OD and OS	0.5 ± 0.1	0 ± 0	0.001
Loss of lashes OD	0.1 ± 0.1	0 ± 0	NS
Loss of lashes OS	0.1 ± 0.1	0 ± 0	NS
Loss of lashes OD and OS	0.1 ± 0.1	0 ± 0	NS
Neovascularization OD	0.7 ± 0.2	0.2 ± 0.1	NS
Neovascularization OS	0.7 ± 0.2	0.2 ± 0.1	NS
Neovascularization OD and OS	0.7 ± 0.1	0.2 ± 0.1	<0.05, 1 tail
Telangiectasia OD	28.6%	88.9%	<0.005
Telangiectasia OS	33.3%	88.9%	<0.01
Telangiectasia OD and OS	31.0%	88.9%	0.0001
Collarette OD	0 ± 0	0.1 ± 0.1	NS
Collarette OS	0 ± 0	0.1 ± 0.1	NS
Collarette OD and OS	0 ± 0	0.1 ± 0.1	<0.05
Sleeve/scurf OD	0 ± 0	0.1 ± 0.1	NS
Sleeve/scurf OS	0 ± 0	0.1 ± 0.1	NS
Sleeve/scurf OD and OS	0 ± 0	0.1 ± 0.1	<0.05
No. meib glands expressed OD	7.0 ± 0.5	5.8 ± 0.5	NS
No. meib glands expressed OS	7.0 ± 0.6	6.6 ± 0.6	NS
No. meib glands expr OD and OS	7.0 ± 0.4	6.2 ± 0.4	NS
Conjunctiva			
Erythema OD	0.4 ± 0.1	0.8 ± 0.1	NS
Erythema OS	0.4 ± 0.2	0.8 ± 0.1	NS
Erythema OD and OS	0.4 ± 0.1	0.8 ± 0.1	<0.05
Bulbar injection OD	28.6%	55.6%	NS
Bulbar injection OS	28.6%	66.7%	<0.05, 1 tail
Bulbar injection OD and OS	28.6%	61.1%	<0.05
Tarsal injection OD	28.6%	55.6%	NS
Tarsal injection OS	23.8%	55.6%	<0.05, 1 tail
Tarsal injection OD and OS	26.2%	55.6%	<0.05
Papillary hypertrophy OD	19.1%	0%	NS
Papillary hypertrophy OS	19.1%	0%	NS
Papillary hypertrophy OD and OS	19.1%	0%	<0.05

Ocular signs of individuals with CAIS as compared to age-matched female and male controls. Additional signs are reported in Figure 1. Values equal either the mean ± SE or the frequency (%) of “yes” answers. The latter measurement was used if clinical parameters were evaluated on a present (i.e., yes) or absent (i.e., no) basis. Statistical analyses of data between two groups were conducted with the unpaired, two-tailed Student’s *t* test, as well as χ^2 tests.

Abbreviations: OD, right; OS, left; No., number of; meib, meibomian; expr, expressed.

in CAIS subjects as compared to controls (Fig. 2, Table 3). As concerns specific symptoms, CAIS individuals had a significant increase in dryness, pain, and light sensitivity, relative to female and male controls (Fig. 2). Indeed, 78% of CAIS subjects complained of dryness, as compared to only 14% of controls. The CAIS individuals also had a significant increase in blurred vision and sandy/gritty and itching sensations on their ocular surface as well as a more difficult time reading and a lower tolerance to low humidity and air conditioning, relative to all controls (Table 3).

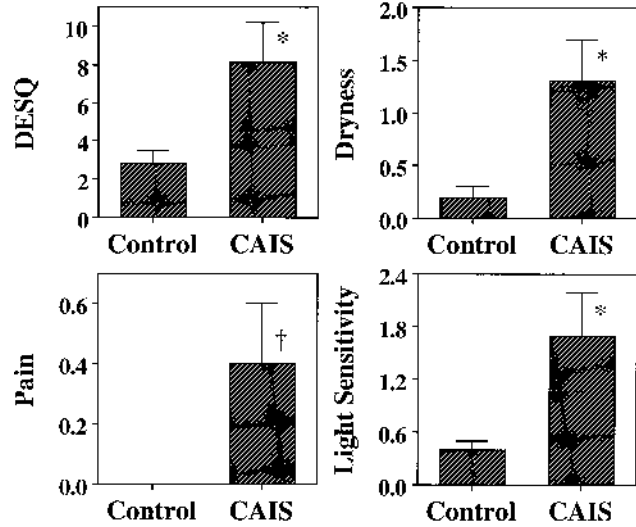


FIGURE 2. Effect of CAIS on the frequency of specific dry eye symptoms. Columns equal the mean ± SE of the total DESQ score as well as the degree of ocular surface dryness, pain, and photophobia. Significantly (**p* < 0.005; †*p* < 0.01) higher than the control values.

DISCUSSION

This investigation demonstrates that androgen receptor absence is associated with significant alterations in the meibomian gland and an increase in the signs and symptoms of dry eye. Women with CAIS, as compared to female and male controls, had a significantly reduced quality of meibomian gland secretions and a significantly increased frequency of meibomian gland orifice metaplasia. Moreover, CAIS individuals had a greater appearance of tear film (i.e., abnormal menisci), conjunctival (erythema, bulbar and tarsal injection), and lid (i.e., telangiectasia, keratinization, erythema, irregular posterior margins) abnormalities and a higher frequency of ocular surface symptoms (e.g., dryness, pain, and light sensitivity) than controls. These anterior segment effects in

TABLE 3. Frequency of specific dry eye symptoms in CAIS individuals

Measure	Controls	CAIS	p Value
DESQ			
Sandy/gritty	0.2 ± 0.1	0.8 ± 0.3	<0.05
Burning/stinging	0.3 ± 0.1	0.8 ± 0.3	NS
Itching	0.6 ± 0.2	1.3 ± 0.3	<0.05
Blurred vision	0.3 ± 0.1	0.9 ± 0.4	<0.05, 1 tail
Tired eyes	0.8 ± 0.2	0.9 ± 0.2	NS
OSDI	4.6 ± 1.8	14.2 ± 5.6	<0.05
Poor vision	0.2 ± 0.2	0.7 ± 0.4	NS
Light sensitive	0.4 ± 0.2	0.9 ± 0.4	NS
Feel gritty	0.2 ± 0.1	0.3 ± 0.2	NS
Feel painful	0.1 ± 0.1	0.2 ± 0.1	NS
Blurred vision	0.1 ± 0.1	0.2 ± 0.1	NS
Reading	0 ± 0	0.3 ± 0.2	<0.05
Night driving	0.3 ± 0.2	0.7 ± 0.3	NS
Computer/ATM	0.1 ± 0.1	0.4 ± 0.2	NS
TV	0.1 ± 0.1	0 ± 0	NS
Windy	0.3 ± 0.1	0.8 ± 0.5	NS
Low humidity	0.2 ± 0.1	0.9 ± 0.5	<0.05
Air conditioning	0.1 ± 0.1	1.5 ± 0.5	<0.0005

Ocular symptoms of individuals with CAIS, as compared to age-matched controls.

Additional symptoms are shown in Figure 2. Values represent the mean ± SE.

CAIS women may be attributed, at least in part, to a decrease in meibomian gland function. Meibomian gland dysfunction increases tear film evaporation^{4,34} and typically leads to a significant rise in the signs and symptoms of dry eye.⁹

The ocular surface sequelae in CAIS women are reminiscent of the influence of antiandrogen therapy in men with prostatic disease.¹⁵ Use of antiandrogen medications is associated with meibomian gland dysfunction, an altered neutral lipid profile in meibomian gland secretions, a reduced tear film breakup time, and functional dry eye.^{15,16} In addition, patients taking antiandrogens, as compared to age-matched controls, have a greater frequency of tear film, conjunctival, lid, corneal, and symptomatic (e.g., photophobia, painful eyes) abnormalities.¹⁵

The specific mechanism by which CAIS and antiandrogen treatment promote dry eye is most likely through a disruption of the receptor-mediated effects of androgens on the meibomian gland and a consequent alteration in the quality and/or quantity of meibomian gland secretions. The meibomian gland is a large sebaceous gland, and androgens are known to regulate the development, differentiation, and lipid production of nonocular sebaceous glands throughout the body.^{35–39} These hormone actions are undoubtedly the result of androgen binding to saturable, high-affinity, and steroid-specific receptors in acinar epithelial cell nuclei and a consequent regulation of gene expression.^{39–42} Conversely, sebaceous gland transcription, activity, and secretion are attenuated by androgen receptor defects, such as in CAIS,⁴³ or by antiandrogen administration.^{44,45} Similarly, the human meibomian gland contains androgen receptor mRNA and protein,^{23,46} and androgens appear to regulate the expression of numerous genes in this tissue.^{47,48} These genomic actions seem to be dependent on the presence of functional androgen receptors.^{48,49} As an additional consideration, we have recently discovered that CAIS is associated with striking changes in the fatty acid profiles of neutral and polar lipids in human meibomian gland secretions.⁵⁰ These alterations may contribute significantly to the tear film instability and evaporative dry eye found in androgen-deficient states.

Another possibility is that the increased dry eye signs and symptoms in CAIS women are caused by lacrimal gland dysfunction and decreased aqueous tear output. Androgens exert a tremendous impact on the architecture of epithelial cells, the expression of specific genes, the synthesis of various proteins, and the extent of certain secretory processes in the lacrimal gland.⁵¹ In fact, androgen actions appear to account for many of the sex-related differences that exist in the anatomy, biochemistry, physiology, immunology, and molecular biology of lacrimal tissue in a variety of species.⁵¹ These androgen effects are apparently mediated through androgen receptors in epithelial cells⁵¹ and should theoretically be disrupted in CAIS. Moreover, some researchers have speculated that androgen deficiency may result in an “aqueous-deficient” dry eye.⁵² However, this possibility is unlikely, given that our previous findings show that androgen insufficiency by itself does not cause aqueous tear deficiency in nonautoimmune humans.⁵³

An alternative consideration is that the dry eye signs and symptoms in CAIS individuals may be caused, at least in part, by the influence of estrogens on the meibomian gland. Thus, the majority (i.e., 78%) of CAIS, but not control, women were taking estrogen supplementation, which would increase the already elevated estrogen levels in CAIS individuals secondary to testosterone aromatization.²⁷ Estrogens, in turn, have been shown to cause a significant decrease in the size, activity, and lipid production of sebaceous

glands in multiple species.^{35,45,54} In addition, the meibomian gland contains estrogen receptor mRNA and protein,^{46,55} and a recent epidemiologic study of over 25,000 postmenopausal women demonstrated that estrogen replacement therapy significantly increases the prevalence of severe dry eye symptoms and clinically diagnosed dry eye syndrome.⁵⁶ However, whether this latter effect of estrogen replacement therapy was mediated through the meibomian or lacrimal gland is unknown. Furthermore, a proposed mechanism by which estrogens interfere with sebaceous gland function is through the antagonism of androgen action,^{57,58} a process that might not be relevant in CAIS women. Consequently, whether estrogens contribute to the increased dry eye signs and symptoms in CAIS individuals remains to be determined.

Overall, our study supports our hypotheses that androgen receptors mediate androgen effects on the meibomian gland and that androgen receptor absence promotes both meibomian gland dysfunction and dry eye. Our ongoing research is designed to delineate the nature and extent of androgen influence on the meibomian gland, in order to advance our understanding of the physiologic mechanisms controlling this tissue in both health and disease.

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