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Effect of Androgen Deficiency on the Human Meibomian Gland and Ocular Surface*

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ABSTRACT

The purpose of this study was to determine whether the chronic use of antiandrogen medications leads to meibomian gland dysfunction, altered lipid profiles in meibomian gland secretions, decreased tear film stability, and evaporative dry eye. Subjects taking antiandrogen therapy for prostatic indications, as well as age-related controls, were asked to complete a questionnaire that assessed dry eye symptoms and then were given a complete anterior segment examination. Moreover, meibomian gland secretions were obtained from each eye and analyzed by high-performance liquid chromatography/mass spectrometry for the relative content of cholesterol, cholesterol esters, wax esters, diglycerides, triglycerides, and specific molecular species in the diglyceride fraction. Our results demonstrate that patients taking antiandrogen treatment, compared with age-related controls, had a: 1) significant increase in the frequency of appearance of tear film debris, an abnormal tear film meniscus, irregular posterior lid margins, conjunctival tarsal injection, and orifice metaplasia of the meibomian glands; 2) significant increase in the degree of ocular surface vital dye staining; 3) significant decrease in the tear film breakup time and quality of meibomian gland secretions; and 4) significant increase in the frequency of light sensitivity, painful eyes, and blurred vision. In addition, the use of antiandrogen pharmaceuticals was associated with significant changes in the relative amounts of lipids in meibomian gland secretions. Our findings indicate that chronic androgen deficiency is associated with meibomian gland dysfunction and dry eye. (*J Clin Endocrinol Metab* **85:** 4874–4882, 2000)

THE MEIBOMIAN GLAND plays an essential role in the maintenance of ocular surface integrity and the preservation of visual acuity (1–3). This tissue, through its synthesis and secretion of lipids at the lid margin, is primarily responsible for promoting the stability and preventing the evaporation of the preocular tear film (1–3). Dysfunction of the meibomian gland may result in tear film instability and evaporative dry eye, due to inadequate coverage of the aqueous layer of the tear film, and may ultimately lead to significant corneal pathology and visual impairment (1–3). Of particular interest, meibomian gland dysfunction is believed to be the predominant cause of dry eye syndromes (4), which afflict over 10 million individuals in the United States alone. However, very little information exists concerning the physiological control of this tissue. In fact, the precise etiology of meibomian gland disease, which seems to be a major factor in the dry eye that occurs during menopause, aging, and Sjögren's syndrome (5–7), remains unknown.

We hypothesize that androgens regulate meibomian gland function, enhance the quality and/or quantity of lipids produced by this tissue, and promote the formation of the tear film's lipid layer. We also hypothesize that androgen deficiency is a critical etiologic factor in the pathogenesis of meibomian gland dysfunction and evaporative dry eye. In support of these hypotheses, we and others have discovered that: 1) the meibomian glands of rats, rabbits, and humans are androgen target organs and contain androgen receptor messenger RNA (mRNA) and/or androgen receptor protein within acinar epithelial cell nuclei (8, 9); 2) human meibomian glands contain the mRNAs for both Types 1 and 2 5α-reductase (9), an enzyme that converts testosterone into the potent androgen 5α-dihydrotestosterone (DHT) (10); 3) application of dehydroepiandrosterone, an androgen precursor (10), to the ocular surface of rabbits, dogs, and/or a human stimulates the production and release of meibomian gland lipids and prolongs the tear film breakup time (11); 4) orchiectomy causes a significant alteration in the lipid profile of rabbit meibomian glands, whereas the topical administration of 19-nortestosterone for 2 weeks, but not placebo compounds, begins to restore the lipid pattern to that found in intact animals (12); and 5) the one common denominator in menopause (13), aging in both sexes (10, 13), and primary and secondary Sjögren's syndrome (14–16) seems to be androgen deficiency.

If our hypotheses are correct, we would predict that chronic androgen deficiency, such as induced by the extended use of antiandrogen medications, will lead to meibomian gland dysfunction, altered lipid profiles in meibomian gland secretions, decreased tear film stability, and evaporative dry eye. The purpose of the present investigation was to test this prediction.

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Materials and Methods

Human subjects

Male subjects taking antiandrogen therapy for prostatic indications were recruited from the Departments of Urology at Brigham and Women's Hospital and Boston University Medical Center (Boston, MA). These patients (n = 15), whose average age was 70.9 ± 1.9 yr, had been treated with antiandrogen medications for periods ranging from 3–96 months (median, 36 months). These medications included leuprolide acetate (Lupron), goserelin acetate (Zoladex), bicalutamide (Casodex), flutamide (Eulexin), and/or finasteride (Proscar). Age-related male controls (64.8 ± 1.0 yr old; n = 6), who were not receiving antiandrogen treatment, as well as younger normal individuals (~30 yr old; n = 3 males and 1 female) were recruited from the Boston environs. The ages of the patients and their age-related controls were not significantly different. These studies were approved by the Human Studies Committee of the Schepens Eye Research Institute (Boston, MA) and were conducted in accordance with guidelines established by the Declaration of Helsinki.

Clinical assessment

After providing informed consent, subjects were asked to complete without supervision a questionnaire that assessed dry eye symptoms (Ocular Surface Disease Index; Allergan, Inc., Irvine, CA), as well as to answer questions related to medical histories and current medications (Table 1). Individuals then underwent a complete ocular surface and anterior segment examination of both eyes (Table 2) by corneal external disease subspecialists. This examination, which was based on standard protocols (17–21), included a slit lamp evaluation of the: 1) tear film, for the presence of mucus and debris; 2) tear meniscus, by using 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 typically over 0.3 mm in height (20). An abnormal meniscus is present when a clearly continuous tear film cannot be identified over the ocular surface. An intermediate meniscus is identified as a level between normal and abnormal; 3) lids, for the identification of neovascularization, irregular posterior margins, scurf, sleeve, and collarettes; 4) conjunctiva, for the appearance of bulbar injection, tarsal injection and papillary hypertrophy; 5) cornea, for the existence of punctate epithelial keratitis, adherent mucus, filamentary keratitis, and neovascularization; 6) tear film breakup time, which is a measure of tear film stability and a global criterion for dry eye (17); 7) fluorescein staining of the cornea (graded on a 0-3 scale for each of five areas) (17); and 8) rose bengal staining (graded on a 0-3 scale) of the conjunctiva (six nasal and temporal

TABLE 2. Clinical assessment of the ocular surface and anterior segment

Parameter	Clinical assessment
Tear film mucus	Present or absent
Tear film debris	Present or absent
Tear meniscus	Normal, intermediate, absent
Tear secretion—Schirmer test without anesthesia	mm wetting in 5 min[a]
Tear film breakup time	Seconds
Lid neovascularization	Present or absent
Lid irregular posterior margins	Present or absent
Lid scurf	Present or absent
Lid sleeve	Present or absent
Lid collarette	Present or absent
Metaplasia of meibomian gland orifices	Present or absent
Quality of meibomian gland secretions	Grade 0–3
Conjunctival bulbar injection	Present or absent
Conjunctival tarsal injection	Present or absent
Conjunctival papillary hypertrophy	Present or absent
Rose bengal staining of the conjunctiva	Grade 0–3 for 6 areas
Corneal punctate epithelial keratitis	Present or absent
Corneal adherent mucus	Present or absent
Corneal filamentary keratitis	Present or absent
Corneal neovascularization	Present or absent
Fluorescein staining of the cornea	Grade 0–3 for 5 areas
Rose bengal staining of the cornea	Grade 0–3
Iris and anterior chamber	Normal or abnormal

Ocular surface evaluations of the right and left eyes were performed by following standard protocols (17–21).

[a] The results of the Schirmer test without anesthesia have been previously reported (22).

TABLE 1. Medical histories of control subjects and patients taking antiandrogen medications

Subject	Age (yr)	Medical condition	Antiandrogen medication	Treatment duration (months)
Controls				
1	62	HBP, hypercholesterolemia		
2	63	Rosacea		
3	65	HBP, rosacea		
4	65			
5	65	Heart attack (8 yr previously)		
6	69	HBP, rosacea		
Patients				
1	70	Prostate cancer, DM	Leuprolide acetate	12
2	76	Prostate cancer, HBP	Leuprolide acetate	36
3	66	Prostatic hypertrophy	Finasteride	36
4	79	Prostatic cancer, mild HPB, CVD, macular degeneration	Leuprolide acetate, bicalutamide	24, 1
5	83	Prostatic cancer, HBP	Goserelin acetate, flutamide	48, 3
6	74	Prostate cancer, HBP, DM, glaucoma	Bicalutamide	6
7	75	Prostate hypertrophy, HBP, arthritis	Finasteride	12–24
8	78	Prostate cancer, borderline DM	Leuprolide acetate, bicalutamide	18, 18
9	64	Prostate cancer	Leuprolide acetate	60
10	62	Prostatic hypertrophy, CVD	Finasteride	48
11	57	Prostate cancer, HBP, CVD	Leuprolide acetate	~3
12	64	Prostate cancer	Leuprolide acetate	12
13	75	Prostate cancer, DM, arthritis	Leuprolide acetate	>24
14	74	Prostate cancer, HBP, gout	Leuprolide acetate	96
15	66	Prostatic hypertrophy, HBP, CVD	Finasteride	48

HBP, High blood pressure; DM, diabetes mellitus; CVD, cardiovascular disease.

regions) and the entire cornea (17). The tear film breakup time and fluorescein and rose bengal staining procedures were performed according to published methods (17). For the calculation of staining results, grading scores for ocular surface regions from both eyes were summed, thereby yielding a total score for each patient. Additional parameters that were evaluated included: 1) assessment for metaplasia of the meibomian gland orifices, a condition defined as an abnormal growth and keratinization of duct epithelium (6); 2) analysis of the quality of meibomian gland secretions, according to a published classification system (21). In brief, the grading scheme was '0' for clear excreta with small particles, '1' for opaque excreta with normal viscosity, '2' for opaque excreta with increased viscosity, and '3' for secreta that retained shape after digital expression; and 3) examination of the appearance of the anterior chamber and iris (19).

Following these procedures, meibomian gland secretions were obtained from each eye by gently applying digital pressure against the lower eyelid and collecting the expelled secretions with a chalazion curette. Samples were then placed in glass tubes containing a 2:1 mixture of chloroform-methanol, and these tubes were then capped and stored at −70 C until experimental analysis. These studies were approved by the Human Studies Committee of the Schepens Eye Research Institute (Boston, MA) and were conducted in accordance with guidelines established by the Declaration of Helsinki.

Biochemical procedures

Meibomian gland secretions were analyzed for the relative content of cholesterol, cholesterol esters, wax esters, diglycerides, triglycerides, and specific molecular species in the diglyceride fraction by high-performance liquid chromatography (HPLC; Spectra-Physics Model 8700, Thermo Separation Products, San Jose, CA) and mass spectrometry (MS; Finnigan 4500, Finnigan, San Jose, CA). Samples were separated over a 10 cm × 2 mm Inertsil silica column (Keystone Scientific, Inc., Bellefonte, PA) with a complex, multistep gradient that combined mobile phases of isooctane-tetrahydrofuran (99:1,vol/vol), isopropanol-chloroform (4:1, vol/vol), and isopropanol-water (1:1, vol/vol) and had a linear flow velocity of 0.4 mL/min (23). The vaporizer temperature in the moving-belt interface of the Finnigan HPLC/mass spectrometer was 310 C. MS was conducted in positive ion, chemical ionization mode with ammonia reagent gas, and data were acquired with a Teknivent Vector/Two (Teknivent Corporation, Maryland Heights, MO). The predominant peaks in HPLC/MS elution plots were identified by the use of specific ions [*i.e.* cholesterol and cholesterol esters, mass/charge ratio (m/z) 369; wax esters, m/z 636, 650, 664, and 678; diglycerides and triglycerides, m/z 551, 577, 579, 603, and 605; and squalene, m/z 411], peak areas were determined, and the relative amounts of various lipid fractions were then calculated. Analysis of the m/z ratios of diglyceride fatty acids was facilitated through a time-based decomposition of HPLC/MS elution plots.

Statistical analyses

Statistical analyses of the data were performed by using the unpaired, two-tailed Student's *t*, Mann-Whitney *U*, and χ^2 tests.

Results

Influence of antiandrogen therapy on the anterior segment

To determine whether chronic androgen deficiency is associated with alterations of the meibomian gland and ocular surface, male subjects (n = 15) taking antiandrogen therapy (median, 3 yr) for prostatic indications, as well as their age-related controls (n = 6), were given thorough anterior segment examinations. In addition, subjects and controls completed questionnaires designed to assess dry eye symptoms.

Our results demonstrated that the use of antiandrogen medications is associated with meibomian gland dysfunction, tear film instability, and functional dry eye. Slit lamp examinations revealed that patients taking antiandrogen pharmaceuticals, compared with controls, had a significant increase in the frequency of appearance of tear film debris, an abnormal tear film meniscus, irregular posterior lid margins, lid sleeves and collarettes and conjunctival tarsal injection (Table 3 and Fig. 1). In addition, patients had a significant decrease in their tear film breakup time (Fig. 2) and a significant increase in the degrees of corneal fluorescein and rose bengal staining (Fig. 3) and inferior bulbar conjunctival rose bengal staining (control OD and OS, 0.29 ± 0.11; patient OD and OS, 0.63 ± 0.10; $P < 0.05$, one-tail).

Evaluation of the meibomian glands showed that the fre-

TABLE 3. Frequency of appearance of ocular surface abnormalities in patients taking antiandrogen medications

Clinical examination	Frequency of appearance (%)					
	Right eye		Left eye		Both eyes	
	Control	Patient	Control	Patient	Control	Patient
Tear film						
Mucus	16.7	13.3	16.7	7.1	16.7	10.3
Debris	0.0	35.7	0.0	21.4	0.0	28.6[a]
Lids						
Neovascularization	66.7	86.7	40.0	80.0	54.6	83.3
Irregular posterior margins	16.7	78.6[a]	16.7	92.9[b]	16.7	85.7[c]
Scurf	50.0	53.3	50.0	53.3	50.0	53.3
Sleeve	0.0	33.3	0.0	46.7[a]	0.0	40.0[a]
Collarette	0.0	23.1	0.0	30.8	0.0	26.9[a]
Metaplasia of meibomian gland orifices	33.3	60.0	16.7	60.0	25.0	60.0[a]
Conjunctiva						
Bulbar injection	33.3	53.3	33.3	73.3	33.3	63.3
Tarsal injection	33.3	80.0[a]	16.7	80.0[b]	25.0	80.0[b]
Papillary hypertrophy	16.7	42.9	16.7	40.0	16.7	41.4
Cornea						
Punctate epithelial keratitis	0.0	7.7	0.0	7.7	0.0	7.7
Adherent mucus	0.0	0.0	0.0	0.0	0.0	0.0
Filamentary keratitis	0.0	0.0	0.0	0.0	0.0	0.0
Neovascularization	0.0	0.0	0.0	0.0	0.0	0.0

Ocular surface examinations of the right and left eyes were performed on patients (n = 15) taking antiandrogen medications and their age-matched controls (n = 6). Values represent the frequency of appearance of recorded tear film, lid, conjunctival, and corneal abnormalities.

Frequency was significantly ([a] $P < 0.05$; [b] $P < 0.005$, [c] $P < 0.0005$) greater than corresponding control value.

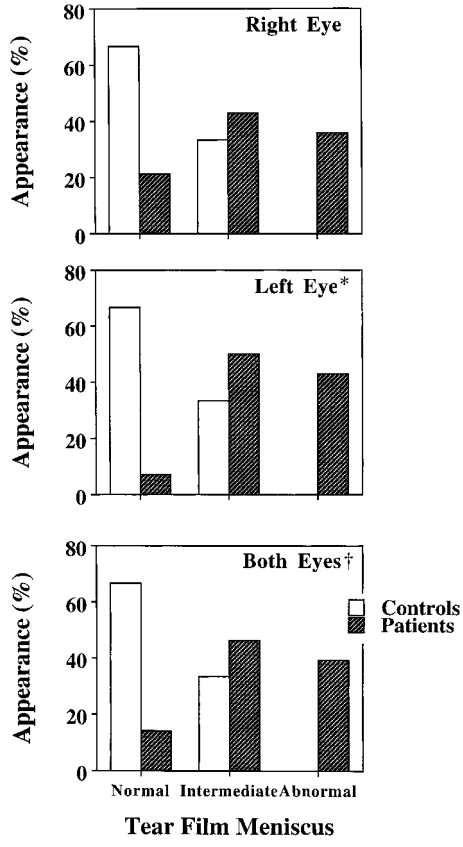

FIG. 1. Impact of antiandrogen therapy on the appearance of the tear film meniscus. Slit lamp examinations of the left and right eyes of patients (n = 15) taking antiandrogen therapy and their age-related controls (n = 6) were performed, and the tear film meniscus of each eye was graded as 'normal,' 'intermediate,' or 'abnormal.' The *columns* represent the frequency of appearance of each grade. Frequencies were significantly (*, $P < 0.05$; †, $P < 0.005$) different between control and patient groups (χ^2 test).

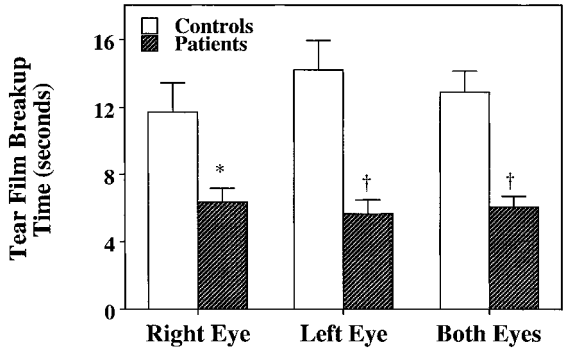

FIG. 2. Influence of antiandrogen treatment on the tear film breakup time. Determinations were made in the left and right eyes of individuals described in the legend to Fig. 1. The *columns* and *bars* equal the mean ± SE. Time was significantly (*, $P < 0.01$; †, $P = 0.0001$) less than value of control group (*t* test).

quency of orifice metaplasia (Table 3) was significantly increased and that the quality of secretions was significantly reduced (*i.e.* higher viscosity; Fig. 4), in patients taking antiandrogen therapy, relative to controls. Moreover, clinical impressions were that the meibomian glands of 'antiandrogen' patients had a much higher frequency of altered appearance (*e.g.* inspissation, cysts) and severe disease. These observations were particularly notable, given that three control individuals had rosacea and that 83% of controls had some evidence of scurf, blocked, or dysfunctional meibomian glands.

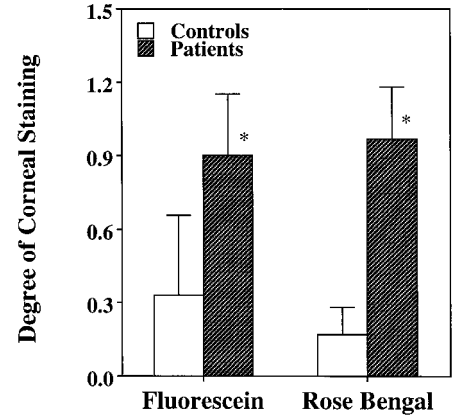

FIG. 3. Effect of antiandrogen therapy on the degrees of corneal fluorescein and rose bengal staining. Evaluations were made in, and data combined from, the left and right eyes of subjects described in the legend to Fig. 1. The *columns* and *bars* represent the mean ± SE. Staining was significantly (*, $P < 0.05$) greater than value of control group (Mann-Whitney *U* test).

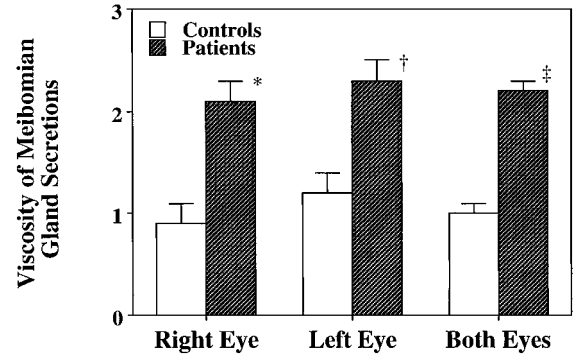

FIG. 4. Impact of antiandrogen medications on the viscosity of meibomian gland secretions. Determinations were made in the left and right eyes of individuals described in the legend to Fig. 1. The *columns* and *bars* equal the mean ± SE. Viscosity significantly (*, $P < 0.005$; †, $P < 0.0005$; ‡, $P = 0.0001$) greater than value of control group (*t* test).

Analysis of the Ocular Surface Disease Index questionnaire results indicated that the use of antiandrogens did not alter the overall 'quality of life' (scores multiplied by 100: controls, 5.16 ± 1.49; patients, 9.25 ± 1.92). However, patients did have a higher frequency of light sensitivity, painful eyes, and blurred vision, compared with controls (Fig. 5).

The appearance of the anterior chamber and iris was normal in both the left and right eyes of the patient and control groups.

We also compared the relative frequency of the signs and symptoms of dry eye between patients taking finasteride (n = 4; age, 67.3 ± 2.8 yr; diagnosis, prostatic hypertrophy; average duration of treatment, ~3 yr) *vs.* other antiandrogen medications (*i.e.* predominantly leuprolide acetate, as well as bicalutamide, goserelin acetate, and flutamide) (n = 11; age, 72.2 ± 2.3 yr; diagnosis, prostatic cancer; average duration of

treatment, ~3 yr). The rationale for this comparison was that finasteride, but not the other antiandrogen compounds, might act to inhibit the local conversion of testosterone to DHT (24). If so, finasteride actions might reflect the importance of local steroidogenesis *per se* in providing potent androgens to ocular surface tissues. These comparisons showed that the left and right eyes of patients taking finasteride had a significantly higher frequency of appearance of conjunctival bulbar injection (finasteride group, 100%; other treatment group, 50%; $P < 0.05$), lid collarettes (finasteride group, 66.7%; other treatment group, 15%; $P < 0.05$), metaplasia of meibomian gland orifices (finasteride group, 100%; other treatment group, 54.6%; $P < 0.01$), and corneal fluorescein staining (finasteride group, 87.5%; other treatment group, 31.8%; $P < 0.01$). Finasteride-treated patients also had a significantly greater sensitivity to wind (finasteride group, 75% positive responses; other treatment group, 0% positive responses; $P < 0.005$). In contrast, patients receiving other antiandrogen therapies had a significantly higher frequency of appearance of conjunctival papillary hypertrophy (finasteride group, 0%; other treatment group, 57.1%; $P < 0.01$%) in their left and right eyes.

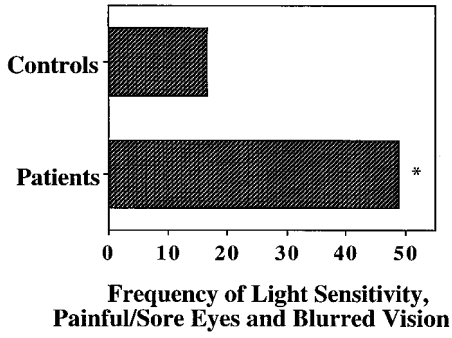

FIG. 5. Influence of antiandrogen treatment on the frequency of dry eye symptoms. Ocular Surface Disease Index questionnaires were given to patient and control groups, which are described in the legend to Fig. 1, and the number of responses indicating the presence (of any degree) of light sensitivity, painful/sore eyes, and blurred vision were recorded. The *columns* represent the frequency of positive responses for one or more of these symptomatic conditions. Frequency was significantly (*, $P < 0.05$) greater than value of control group (χ^2 test).

Effect of antiandrogen treatment on the neutral lipid profile in meibomian gland secretions

To determine whether chronic androgen deficiency is associated with altered neutral lipid profiles in meibomian gland secretions, secretion samples (n = 2/individual) were obtained from the right and left eyes of patients (n = 15) taking antiandrogen medications and their age-related controls (n = 6), as well as younger individuals (n = 4), and analyzed for various lipid fractions by HPLC/MS.

As shown in Fig. 6, the use of antiandrogen pharmaceuticals was associated with significant changes in the relative amounts of lipids in meibomian gland secretions. Patients had a significant attenuation in the levels of cholesterol esters, wax esters, and diglycerides plus triglycerides, relative to those of cholesterol, as well as a significant increase in the percentage of cholesterol. In addition, patients taking antiandrogen therapy had a decreased expression of specific molecular species (*e.g.* m/z 620) in the diglyceride fraction of meibomian gland secretions, compared with that of controls (Fig. 7).

In these studies, no apparent difference existed between

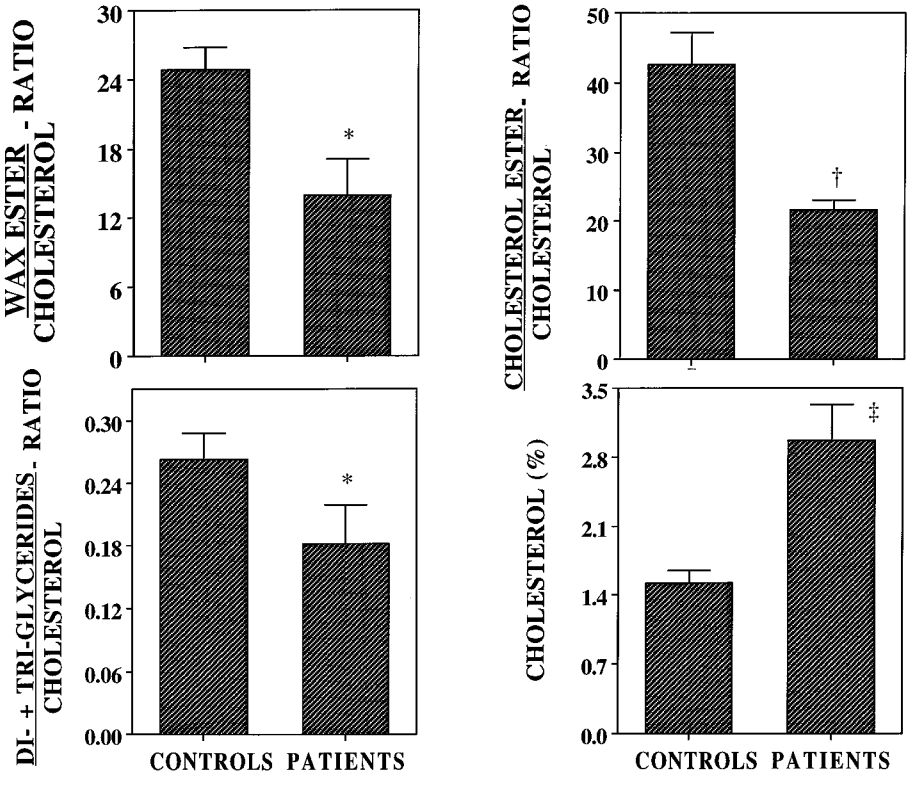

FIG. 6. Effect of antiandrogen therapy on the neutral lipid profile in meibomian gland secretions. Secretions (n = 2 samples/individual) were obtained from the left and right eyes of patients (n = 5) taking antiandrogen therapy and their age-related controls (n = 6) and analyzed (n = 10–12 samples/group) on the same column for the content of cholesterol, cholesterol esters, wax esters, diglycerides, triglycerides, and squalene. Data are expressed in terms of specific lipid to cholesterol ratios, or as the relative amount of cholesterol (%) in the total measured neutral lipid fraction. Additional samples collected from the left and right eyes of patients (n = 10 subjects; n = 2 samples/subject; n = 20 total samples) and younger individuals (n = 4 subjects; n = 1 sample/subject; n = 4 total samples) were analyzed on another column and yielded analogous results. Level was significantly (*, $P < 0.05$; †, $P = 0.0001$) less than the value of control group or significantly ($P < 0.0005$‡) greater than the value of control group (Mann-Whitney U test).

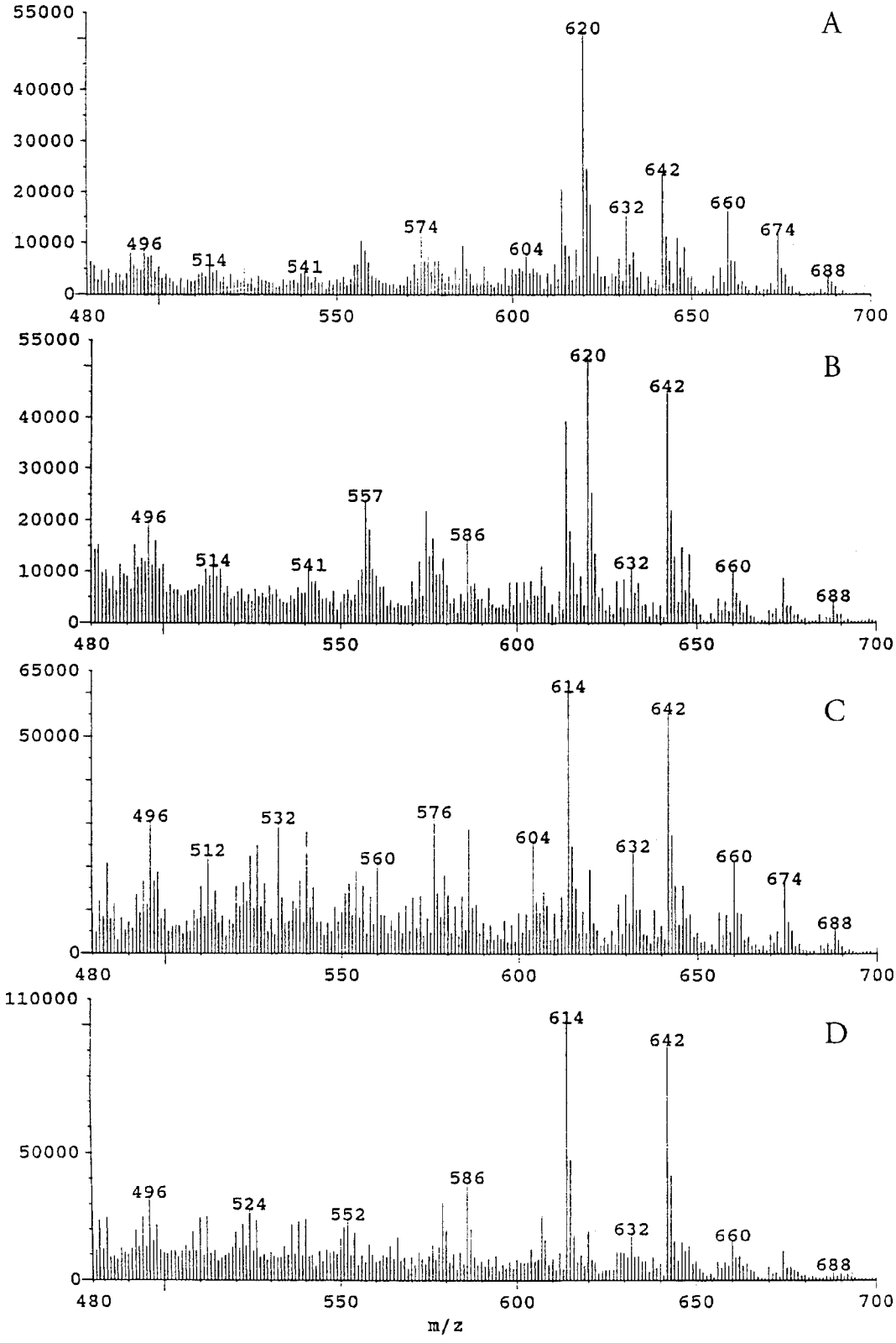

FIG. 7. Influence of antiandrogen treatment on the m/z ratios of fatty acids in the diglyceride fraction of meibomian gland secretions. Samples were obtained as described in the legend to Fig. 6 and processed for HPLC/MS and the analysis of diglyceride molecular species. The plots above show the m/z ratios of different samples from two age-related controls (A and B) and two patients (C and D). The y-axis is in arbitrary units. Note the relative lack of the molecular species of m/z 620 in the patient group. This "m/z 620 ion," which corresponds to a 35-carbon species with four double bonds (25), was prominent in 10 of 12 and medium in 2 of 12 control samples. In contrast, only three patient samples contained medium "m/z 620 peaks," and the rest had low or nondetectable levels of this species.

lipid profiles of patients taking finasteride *vs.* other antiandrogen medications.

Discussion

The present study demonstrates that the use of antiandrogen medications is associated with meibomian gland dysfunction, as measured by both objective and clinical criteria, and an increase in the signs and symptoms of dry eye. Thus, patients taking antiandrogen therapy, compared with controls, had significant changes in their meibomian glands, including orifice metaplasia, a reduced quality of secretions, a striking alteration in the neutral lipid profile of secretions and a morphological appearance consistent with severe disease. In addition, patients had a significantly greater frequency of tear film (*i.e.* debris, abnormal menisci, instability), conjunctival (*i.e.* tarsal injection, inferior staining), corneal (staining), and lid (*i.e.* irregular posterior margins, sleeves, collarettes) abnormalities, as well as an increased appearance of ocular surface symptoms (*i.e.* light sensitivity, painful eyes, blurred vision).

The mechanism by which antiandrogen therapy interferes with meibomian gland function and alters the lipid profile in meibomian gland secretions is undoubtedly due to androgen deficiency. The medications used by the patients in this study included: 1) leuprolide acetate and goserelin acetate, which are analogs of LH-releasing hormone that decrease testicular steroidogenesis and cause a dramatic reduction in the serum levels of testosterone (24); 2) bicalutamide and flutamide, which are nonsteroidal antiandrogens that inhibit androgen uptake and/or binding to nuclear androgen receptors (24); and 3) finasteride, an inhibitor of Type 2 5α-reductase that prevents conversion of testosterone to DHT (24). These treatments would effectively reduce exposure of the meibomian gland to active androgens. Consequently, given that this tissue is an androgen target organ (26), contains both androgen receptor protein and 5α-reductase mRNA (9), and responds to androgens with an enhanced lipid synthesis, production and release (11, 12), it would seem that antiandrogen therapy and the resulting androgen deficiency would lead to meibomian gland dysfunction. In support of this interpretation are two observations. First, the meibomian gland is a large sebaceous gland, and androgens are known to control the development, differentiation, and lipid elaboration of sebaceous glands in nonocular sites (27, 28). Antiandrogen treatment and the related androgen insufficiency, in turn, lead to a marked decline in sebaceous gland activity and lipid output (27, 29). Second, our recent clinical studies on women with complete androgen insensitivity syndrome, which is characterized by the absence of functional androgen receptors (30), have demonstrated that affected individuals have both meibomian gland disease (31) and altered lipid patterns in their meibomian gland secretions (32).

Our finding that antiandrogen treatment changed the neutral lipid profile of meibomian gland secretions might have been anticipated. Androgens have been shown to exert a significant influence on lipid metabolic pathways throughout the body (33–39). This hormone action includes the regulation of genes involved in fatty acid and cholesterol synthesis, the activity of lipogenic enzymes, the incorporation of fatty acids into neutral lipids, the content of cholesterol and other neutral lipids, and the secretion rate of wax esters (33–39). In addition, patients with Sjögren's syndrome, a disease associated with androgen deficiency (14–16), have heightened levels of cholesterol in their tear film (40). In the current study, the antiandrogen patients had a relative decrease in the amount of wax esters, cholesterol esters, and diglycerides and triglycerides in their meibomian gland secretions, and a comparative rise in the quantity of cholesterol. This enhanced cholesterol content would promote tear film instability (2). Moreover, augmented cholesterol increases the melting point and viscosity of meibomian gland secretions, thereby leading to a stagnation and plugging of meibomian glands (2). In fact, these associations may explain the increased prevalence of obstructive meibomitis in these patients, as evidenced by an apparently higher frequency of meibomian gland inspissation and cysts found in individuals taking antiandrogen medications.

The impact of antiandrogen therapy on the conjunctiva, cornea, lid, and ocular surface symptomatology may have been due, in part, to decreased meibomian gland function. Meibomian gland dysfunction typically leads to an increase in the signs and symptoms of evaporative dry eye (1–3, 17). Indeed, this condition has been estimated to be a contributing factor in over 60% of all dry eye patients (4). Of interest, the symptoms associated with meibomian gland dysfunction may or may not be prominent and the ocular surface manifestations are often not correlated with the degree of meibomian gland disease (2). These observations may account for the relatively low score of antiandrogen patients on the Ocular Surface Disease Index questionnaire.

Another consideration in the response of the conjunctiva and cornea to antiandrogen therapy is that these tissues express Types 1 and 2 5α-reductase mRNA and/or androgen receptor mRNA and protein (8, 9). Furthermore, androgens have been shown to influence the functional activity of both the conjunctiva and cornea (41–46). Therefore, the greater tarsal injection and vital dye staining observed in the ocular tissues of antiandrogen patients may have been the consequence not only of meibomian gland dysfunction and evaporative dry eye, but also of androgen deficiency *per se*. Theoretically, it is also possible that the conjunctival and corneal effects might be partially attributed to a decreased tear output from the lacrimal gland. Androgens regulate multiple aspects of lacrimal gland function (47), and investigators have speculated that a loss of androgens may result in an 'aqueous-deficient' dry eye (48). However, this possibility is unlikely, given that we have recently found that androgen insufficiency by itself does not cause aqueous tear deficiency in nonautoimmune humans (22).

The ocular impact of antiandrogen treatment seemed to be influenced by the nature of the medication. Thus, finasteride administration, compared with the analogs of LH-releasing hormone or the nonsteroidal antiandrogens, seemed to be associated with a greater frequency of conjunctival bulbar injection, lid collarettes, metaplasia of meibomian gland orifices, corneal fluorescein staining, and wind sensitivity. In contrast, patients receiving the other antiandrogen therapies had more frequent conjunctival papillary hypertrophy. The reason for these different response patterns remains to be

elucidated. At present, it is known that Types 1 and 2 5α-reductase mRNAs occur in ocular surface tissues (9), but whether, as in other sites, these mRNAs are translated, display tissue-specific degrees of enzymatic activity, or show differential responsiveness to finasteride has yet to be clarified. Similarly, the relative importance of local steroidogenesis (10) *vs.* systemic delivery for the accumulation of androgens in ocular tissues, and the relative activity of classical (*i.e.* nuclear receptor) *vs.* nonclassical mechanisms (49) in mediating androgen action in the eye, are not known. Thus, to explain the differential effects of the various antiandrogen medications (*i.e.* suppressors of testicular androgen synthesis, receptor antagonists, reductase inhibitors), it would seem necessary to first determine the origin, form of metabolism, and mode of action of androgens in ocular tissues. It is of particular interest, though, that our findings extend those of a previous report, which stated that leuprolide acetate administration was associated with ophthalmic problems and blurred vision in some patients (24).

Overall, these observations in patients taking antiandrogen therapy are consistent with our hypothesis that androgen deficiency is a critical etiological factor in the pathogenesis of meibomian gland dysfunction and evaporative dry eye. In further support of our hypothesis are the findings that: 1) reduced serum levels of testosterone are more prevalent in women with dry eye and correlate with the subjective severity of ocular symptoms (50); and 2) serum levels of total androgens decline during menopause (13) and aging in both sexes (10, 13), and these time periods coincide with an increased appearance of meibomian gland dysfunction and dry eye (51–53). As an additional consideration, this apparent interrelationship between androgen deficiency, meibomian gland dysfunction, and dry eye might help to explain why systemic androgen administration has been reported to alleviate the signs and symptoms of dry eye (54–58). Given these results, it is possible that efforts directed at alleviating this endocrine imbalance (*e.g.* topical application of androgens) may prove beneficial as a treatment for meibomian gland dysfunction and the associated evaporative dry eye, in androgen-deficient individuals.

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