ORIGINAL ARTICLE – OPEN ACCESS

Correlation Between Androgen Levels and Dry Eye Parameters in Male Patients with Chronic Obstructive Pulmonary Disease

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ABSTRACT

Objective: To investigate the effects of chronic obstructive pulmonary disease (COPD) in the dry eye status in men and to determine whether the hypoandrogenic status has any concomitant impact.

Materials and Methods: We enrolled 80 patients with stable COPD and healthy volunteers individually matched on the basis of body mass index (BMI), age, and sex. Ocular surface testing included ocular surface disease index (OSDI) questionnaire, evaluation of meibomian gland dysfunction (MGD), tear fluorescein break-up time (TF-BUT), ocular surface staining with lissamine green (LG), Schirmer test with topical anesthesia, and Sirius meibographic analysis of meibomian gland area (MGA) loss. Bioavailable testosterone and free testosterone were measured using the measured total testosterone (TT), albumin, and sex hormone binding globulin (SHBG) levels.

Results: Patients with COPD had lower levels of circulating androgens, decreased TF-BUT, and lower Schirmer score and greater LG staining score, MGD grade, and MG area loss than healthy controls ($p<0.01$). Forced expiratory volume in 1-second (FEV1), FEV1/forced expiratory vital capacity (FVC), and circulating androgen levels were inversely correlated to the OSDI score, LG staining, MGD grade, and MGA loss and showed positive correlation with TF-BUT and Schirmer score in COPD patients ($p<0.01$). However, when adjusted for androgen levels, FEV1 and FEV1/FVC ratio were negatively correlated to the Schirmer score ($p<0.05$).

Conclusion: Male COPD patients had worse tear film parameters, and this finding was more notable in patients with lower androgen levels. Hypoandrogenic status in COPD patients attributes to the dry eye status of the patients, irrespective of their FEV1 and FEV1/FVC status.

Keywords: Androgens, dry eye, hormones, ocular surface, sex steroids

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INTRODUCTION

Dry eye disease (DED) is a very common ocular surface disease. Although there are various subtypes of DED, such as aqueous and lipid deficiency, the clinical entities commonly occur together. DED treatments are mostly symptomatic and expensive; moreover, these treatments do not cure the underlying pathology.

Sex hormones play a critical function in the modulation of both, adnexal tissues and ocular surface; they also influence the difference in DED prevalence based on sex (1). Although DED is more common in women, men with androgen deficiency may also be prone to both, evaporative-type and aqueous-deficient type DED (2). Few studies have investigated the role of sex hormones in DED in men.

Meibomian glands block the evaporation of the preocular tear film and support its stability. Androgens increase lipogenesis and decrease tissue keratinization; androgen deficiency can cause meibomian gland dysfunction (MGD) and evaporative-type DED. Previous studies have shown that MGD and evaporative-type DED often occur in menopause, Sjögren syndrome, and with aging in both the sexes; all these conditions being related to androgen deficiency (3). Moreover, androgens may have an impact on the lacrimal gland, and their deficiency may promote aqueous tear deficiency (4). Clinical and experimental studies have shown that serum androgen levels play an important role in the structure and functioning of the lacrimal gland (5). In this order, we believe that androgen deficiency is related to both, evaporative dry eye (EDE) and aqueous-deficient dry eye (ADDE). Further, the TFOS DEWS II report states that as per the most recent evidence, ADDE and EDE exist as a continuum in a continuous sequence based on their pathology (6).

Harmful gases and particles that cause nearly irreversible airflow obstruction lead to the development of a common progressive disease, chronic obstructive pulmonary disease (COPD). This disease causes systemic alterations in organ functions, one of them being neuroendocrine system changes. Hypoandrogenic status in male COPD patients has been demonstrated in many studies, and there is a relation between androgen deficiency severity and COPD du-

ration (7). The Massachusetts Male Aging Study estimated that nearly 6% of men aged 40–69 y in the United States of America have symptomatic testosterone deficiency (8). When signs and symptoms were not considered, the prevalence studies showed that 10%–25% of the general population had testosterone deficiency (9). In COPD, the prevalence of hypogonadism in men varied from 22% to 69% in several reports (9). In addition, male COPD patients have lower serum testosterone levels than older males with normal pulmonary function (10). In this study, we hypothesized that hypoandrogenic status in COPD affects the dry eye status in male patients.

MATERIALS and METHODS

The Erciyes University Faculty of Medicine Local Ethics Committee approved this case-control study (number: 2017/271, date: 05.26.2017), and all participants signed informed consent.

This cross-sectional study involved 80 patients with stable COPD, confirmed as per the "Global Initiative for Chronic Obstructive Lung Disease" 2017 guideline, who were followed-up at the Erciyes University Faculty of Medicine, Pulmonary Medicine Clinic during 2018 (11). Each patient was matched individually with a volunteered control participant recruited from the ophthalmology clinic for body mass index (BMI), age, and sex. All the healthy volunteers also underwent a complete pulmonary examination, and the results confirmed that they were healthy. All the participants underwent spirometry tests with Sensormedics Vmax 20C (Sensormedics, Yorba Linda, CA, USA), and forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC) values were obtained during spirometry. The American Thoracic Society and the Global Initiative for Chronic Obstructive Lung Disease (GOLD) have provided staging systems that were used to assess the airflow obstruction severity and staging COPD based on the presence of obstruction (FEV1/FVC <70%) and its severity, as estimated using the percentage of predicted FEV1 (11).

All COPD patients received single or combinations of inhaled anticholinergic or ß$_2$ agonists. Inhaled anticholinergics were used as monotherapy in 16 patients (20%), while combinations of inhaled anticholinergic and ß$_2$ agonists were used for 64 (80%) patients. None of the patients received oxygen support or were admitted to hospital because of COPD exacerbation in the previous 3 wk. The exclusion criteria for all the participants were coexisting ocular disease, history of ocular/periocular/intraocular surgery or trauma at any time, scatricial conjunctivitis (i.e., trachoma, ocular pemphigoid, erythema multiforme), mechanical palpebral abnormalities, intraocular inflammation, lacrimal obstructions, pterygium, admission of topical/systemic anti-inflammatory, antibiotic or hormonal therapies, contact lens use, diabetes mellitus, collagen vascular disease, and acne rosacea. In addition, patients with lung diseases other than COPD (i.e., asthma, bronchiectasis, tuberculosis, interstitial lung diseases) were excluded.

Ophthalmic Examination
All the patients and control subjects underwent a complete ophthalmological examination, including best corrected visual acuity, slit-lamp biomicroscopy examination of the anterior segment, intraocular pressure measurement with Goldmann applanation tonometry, and fundus examination with +90 D lens.

All ocular surface examinations were performed by the same experienced clinician who was masked to patient diagnoses. Only one eye per patient was selected randomly for data analyses. The assessments were implemented in the following order:

1. Symptom severity was evaluated using the ocular surface disease index (OSDI) (Allergan Inc., Irvine, CA) questionnaire (sum of scores are multiplied by 25 and divided by the total number of answered questions; then, the result was scored on a scale of 0 to 100.) Patients were classified as having normal scores if the score was <13, mild symptomatic dry eye if the score was 13–s22, moderate symptomatic dry eye if the score was 23–32, and severe symptomatic dry eye if the score was ≥33 (12).

2. Determination and grading of conjunctivochalasis (CCh): The conjunctival laxity location was recorded as nasal, middle, or temporal for each patient.

grade 1: redundant conjunctiva is located in the temporal region

grade 2: redundant conjunctiva is located in two different locations

grade 3: involvement of the entire inferior lid margin (13)

3. Observation of eyelid margins and establishment of the irregularities.

4. Evaluation for the existence of MGD in the lower eyelids and staging if existed, as described by the International Workshop on Meibomian Gland Dysfunction Staging guidelines based on clinical severity was performed as follows (14):

stage 1: expressibility and secretion quality are minimally altered without corneal staining and symptoms

stage 2: secretion quality and expressibility are mildly altered with minimal and mild symptoms and none to limited corneal staining

stage 3: expressibility and secretion quality are moderately altered with mild to moderate, mainly peripheral corneal staining and moderate symptoms

stage 4: expressibility and secretion quality are severely altered with marked central corneal staining and symptoms

"Plus" disease was also defined if there was an accompanying or coexisting disorders of the eyelids and/or ocular surface.

5. Invasive fluorescein-tear break-up time (TF-BUT): Calculated seconds between the final blink and the surfacing of strips wetted with artificial tears (Refresh eye drops; Allergan Inc.). It is the calculated time interval, expressed in seconds, between the first corneal dry spot after the instillation of artificial tears wetted fluorescein strips and the last blink. Measures of ≥10 s were considered normal, those <10 s were considered non-normal, and those <3 s were considered to indicate severe EDE (15).

6. Ocular surface staining with Lissamine green (LG): Conjunctival sac was instilled with LG strips and, conjunctival and corneal staining was graded between grades 0 and 5 as per the Oxford scheme, using the white light (6).

7. Schirmer test with topical anesthesia (proparacaine hydrochloride 0.5%, Alcaine; Alcon Laboratories Inc., Belgium): Topical anesthesia was instilled twice at 1-minute interval, and after 5 min, strips were placed. The amount of wetting in millimeters with the

Table 1. Demographic and clinical characteristics of COPD patients and controls

Variables	Groups		
	Control (n=80)	COPD (n=80)	p
Age (y)	66.88±13.32	68.90±9.29	0.348
Disease duration (y)	–	6.01±5.87	
Smoking (yes)	26 (32.5)	28 (35)	0.986
Smoking (pack–years)	50.0 (37.5–73.0)	50.0 (40.0–64.0)	0.920
Body mass index (kg/m^2)	24.38±5.42	24.66±5.03	0.758
FEV1 (lt)	3.01±0.57	1.58±0.61	<0.001
FEV1 (% of predicted)	100.39±16.02	54.98±17.77	<0.001
FVC (lt)	3.72±0.84	2.71±0.60	<0.001
FVC (% of predicted)	104.22±19.98	74.92±14.44	<0.001
FEV1/FVC	80.80 (76.45–84.31)	56.0 (46.0–65.0)	<0.001
Total testosterone (ng/dL)	538.8 (447.0–638.5)	246.6 (136.8–464.0)	<0.001
Calculated free testosterone (ng/dL)	6.90 (5.82–8.45)	4.51 (2.59–6.03)	<0.001
Bioavailable testosterone (ng/dL)	152.0 (134.0–202.0)	98.5 (49.5–144.0)	<0.001
Sex hormone binding globulin (nmol/L)	64.34 (50.29–86.78)	46.86 (26.94–55.59)	<0.001
Albumin (g/dL)	4.23 (3.96–4.5)	3.90 (3.55–4.40)	0.001
Intra ocular pressure (mmHg)	12.87±1.32	12.99±1.25	0.751

Values are expressed as n (%), mean±SD or median values (1st–3rd quartiles). FEV1: Forced expiratory volume in 1–second; FEV1 (%): Percentage of predicted values FEV1; FVC: Forced expiratory vital capacity; COPD: Chronic obstructive pulmonary disease

patient's eyes closed was determined after 5 min of the placement of the paper strips in the inferotemporal fornix. Schirmer test value <5 mms was considered as aqueous tear deficiency (16).

8. Meibography, using the Sirius topography device (Costruzione Strumenti Oftalmici, Florence, Italy): Meibomian glands were imaged with Sirius Scheimplug rotating camera system that has a built-in infrared camera. The images were gathered from the lower eye lids of both the eyes; analysis of MGD and the assessment of MGA loss severity were performed automatically.

BMI Calculation and Laboratory Blood Analysis
Weight and height were measured by the same medical staff. The patients were weighed after they urinated; the patients were required to be wearing only underclothing for all the measurements. The weight was divided by the square of the height for the calculation of the BMI (kg/m^2).

The blood samples of patients and volunteers were obtained at 8 AM after a 12-hour fasting period for fasting plasma hormone profile of total testosterone (TT), sex hormone binding globulin (SHBG), and albumin. TT and SHBG levels were measured with the Cobas 8000, e602 module, using an electrochemiluminescence immunoassay (ECLIA) kit (Roche Diagnostics, Mannheim, Germany). Bioavailable testosterone was calculated with the measured TT, albumin, and SHBG levels (17).

Statistical Analyses
For assessing the normality of the data, histogram and q-q plots were examined, and Levene test was applied to test the homogeneity of variance. Quantitative variables were expressed as num-

bers with percentages and mean+standard deviation or median values. For comparing the groups, student t test or Mann-Whitney U test was used for continuous variables, and Pearson χ^2 square analysis or Fisher's exact test was used for categorical variables. Spearman and partial correlation coefficients were calculated to assess the relationship between the variables. To identify the predictive ability of bioavailable testosterone on LG staining of the ocular surface (grade) ≥3, presence of MGD, TF-BUT <10 s, and TF-BUT <3 s; receiver operating characteristic (ROC) curves were constructed. R.3.2.1 (www.r-project.org) and easy ROC software were used for data analyses (18). A p value <0.05 was considered to indicate statistical significance.

RESULTS

There was no significant difference in terms of patient age, current smoking status, cumulative smoking history, and BMI between patients with COPD and control subjects (Table 1). Table 1 shows the serum levels of TT, free testosterone (fT), and bioavailable testosterone of the two groups. Sex hormones were significantly lower in male COPD patients than in healthy controls (p<0.001).

TF-BUT scores, number of patients with TF-BUT <10 s and 3 s, LG staining grades, number of patients with LG staining grade ≥3, MGD stage, number of patients with MGD "plus" disease, meibomian gland area (MGA) loss percent, and grade were significantly higher, while Schirmer test values and number of patients with Schirmer test value <5 mm were significantly lower in COPD patients than in healthy controls. There were no significant differences between the two groups with respect to the OSDI scores, number of patients with OSDI score ≥33 and grade of CCh (Table 2).

Table 2. Comparisons of dry eye symptoms and scores between the two groups

Variables	Groups		
	Control (n=80)	COPD (n=80)	p
OSDI score	8.0 (3.0–14.0)	9.4 (2.5–41.7)	0.383
OSDI score ≥33 (number of patients)	21 (26.3)	24 (30)	0.103
Conjunctivochalasis (grade)	0.0 (0.0–1.0)	0.0 (0.0–1.0)	0.238
Tear film brea-up time (seconds)	11.0 (8.0–13.0)	6.0 (3.0–11.0)	*<0.001
Tear film break-up time <10 seconds (number of patients)	15 (18.7)	58 (72.5)	*<0.001
Tear film break-up time <3 seconds (number of patients)	3 (3.7)	25 (31.2)	*<0.001
Schirmer score (mm)	11.0 (9.0–14.0)	9.0 (4.0–14.0)	*0.035
Schirmer score <5 mm (number of patients)	5 (6.2)	21 (26.2)	*0.003
Lissamine green staining (grade)	0.0 (0.0–1.0)	1.0 (1.0–2.0)	*<0.001
Lissamine green staining (grade) ≥3 (number of patients)	3 (3.7)	19 (23.7)	*0.002
Meibomian gland dysfunction (stage)	0.0 (0.0–1.0)	2.0 (1.0–3.0)	*<0.001
Meibomian gland dysfunction "plus" disease (number of patients)	6 (7.5)	27 (33.7)	*<0.001
Meibomian gland area loss (%)	6.0 (3.0–14.0)	33.2 (13.4–55.2)	*<0.001
Meibomian gland area loss (grade)	0.0 (0.0–1.0)	2.0 (1.0–3.0)	*0.023

Values are expressed as n (%) or median values (1st–3rd quartiles). COPD: Chronic obstructive pulmonary disease; OSDI: Ocular surface disease index

Table 3. Partial correlation coefficients between dry eye symptoms and tear film parameters with androgen levels and spirometric values in COPD patients

Variables	OSDI score	Tear film break-up time (s)	Schirmer score (mm)	Lissamine green staining (grade)	MGD (stage)
FEV1	-0.121	0.201*	-0.421*	-0.301*	-0.329*
FEV1/FVC	-0.039	0.046	-0.279*	-0.127	-0.054
Total testosterone (ng/dL)	-0.261*	0.826**	0.635**	-0.602**	-0.723**
Calculated free testosterone (ng/dL)	-0.158	0.782**	0.644**	-0.673**	-0.777**
Bioavailable testosterone (ng/dL)	-0.198	0.793**	0.692**	-0.694**	-0.796**

*: $p<0.05$; **: $p<0.01$. The correlations among FEV1 and FEV1/FVC ratio, and tear film parameters were assessed after adjusting for all androgen levels. The correlations among each androgen level and tear film parameters were assessed after adjusting for FEV1 and FEV1/FVC. OSDI: Ocular surface disease index; MGD: Meibomian gland dysfunction; FEV1: Forced expiratory volume in 1-second; FVC: Forced expiratory vital capacity; COPD: Chronic obstructive pulmonary disease

The associations among FEV1 and FEV1/FVC ratio, and OSDI score, TF-BUT, Schirmer score, LG staining, and MGD stage were assessed using the partial correlation coefficients after adjusting for TT, fT, and bioavailable testosterone levels. Same associations were also assessed among TT, fT, and bioavailable testosterone levels, and OSDI score, TF-BUT, Schirmer score, LG staining and MGD stage after adjusting for FEV1 and FEV1/FVC ratio (Table 3). While only slight correlations among FEV1 and FEV1/FVC ratio and dry eye parameters existed, there were significant and strong correlations between hormone levels and various dry eye parameters including TF-BUT, Schirmer score, LG staining grades and MGD stages when adjustments were performed.

Statistical diagnostic measures of the different bioavailable testosterone cutoffs were defined for the dry eye parameters that showed a strong difference between COPD and controls. For the patients with severe staining [LG (grade) ≥3], the area under the ROC curve for bioavailable testosterone was 0.76, and the significant cut-off value was 99.9 ng/dL with 76% sensitivity and 73% specificity (Table 4, Fig. 1). The cut-off values of bioavailable testosterone levels were 121 ng/dL for patients with MGD, 120 ng/dL for patients with EDE (TF-BUT ≤10 s), and 77.3 ng/dL for patients with severe EDE (TF-BUT <3 s). These optimal cut-off values were determined using the Youden index. We observed that bioavailable testosterone levels had the best diagnostic criteria for LG staining grades.

DISCUSSION

In the present study, COPD patients had lower levels of circulating androgens and worse TF-BUT, Schirmer and LG staining scores, MGD stage, and MGA loss than healthy controls. Moreover, FEV1/FVC, which represents the COPD severity, and circulating androgen levels were inversely correlated to OSDI scores, LG staining, and MGD stage; further, this ratio showed a positive correlation with TF-BUT and Schirmer score in COPD patients COPD. However, when adjusted for androgen levels, the FEV1/FVC ratio was

Table 4. ROC statistics and statistical diagnostic measures of different bioavailable testosterone cutoffs

	ROC statistics		Statistical diagnostic measures			
	AUC	p	SEN	SPE	PPV	NPV
Lissamine green staining (grade) ≥3	0.76 (0.54–0.87)	<0.001	0.76 (0.53–0.92)	0.73 (0.64–0.81)	0.36 (0.26–0.66)	0.94 (0.85–0.96)
Meibomian gland dysfunction	0.69 (0.60–0.78)	<0.001	0.67 (0.52–0.79)	0.67 (0.56–0.77)	0.57 (0.45–0.71)	0.76 (0.63–0.84)
Tear film break-up time ≤10 s	0.69 (0.60–0.78)	<0.001	0.43 (0.31–0.55)	0.90 (0.79–0.96)	0.84 (0.69–0.89)	0.55 (0.43–0.78)
Tear film break-up time <3 s	0.70 (0.59–0.80)	0.002	0.74 (0.54–0.89)	0.64 (0.54–0.73)	0.35 (0.26–0.60)	0.90 (0.79–0.94)

Values in the parenthesis are 95% confidence interval for the related statistical measure. ROC: Receiver operating characteristic; AUC: Area under curve; SEN: Sensitivity; SPE: Specificity; PPV: Positive predictive value; NPV: Negative predictive value
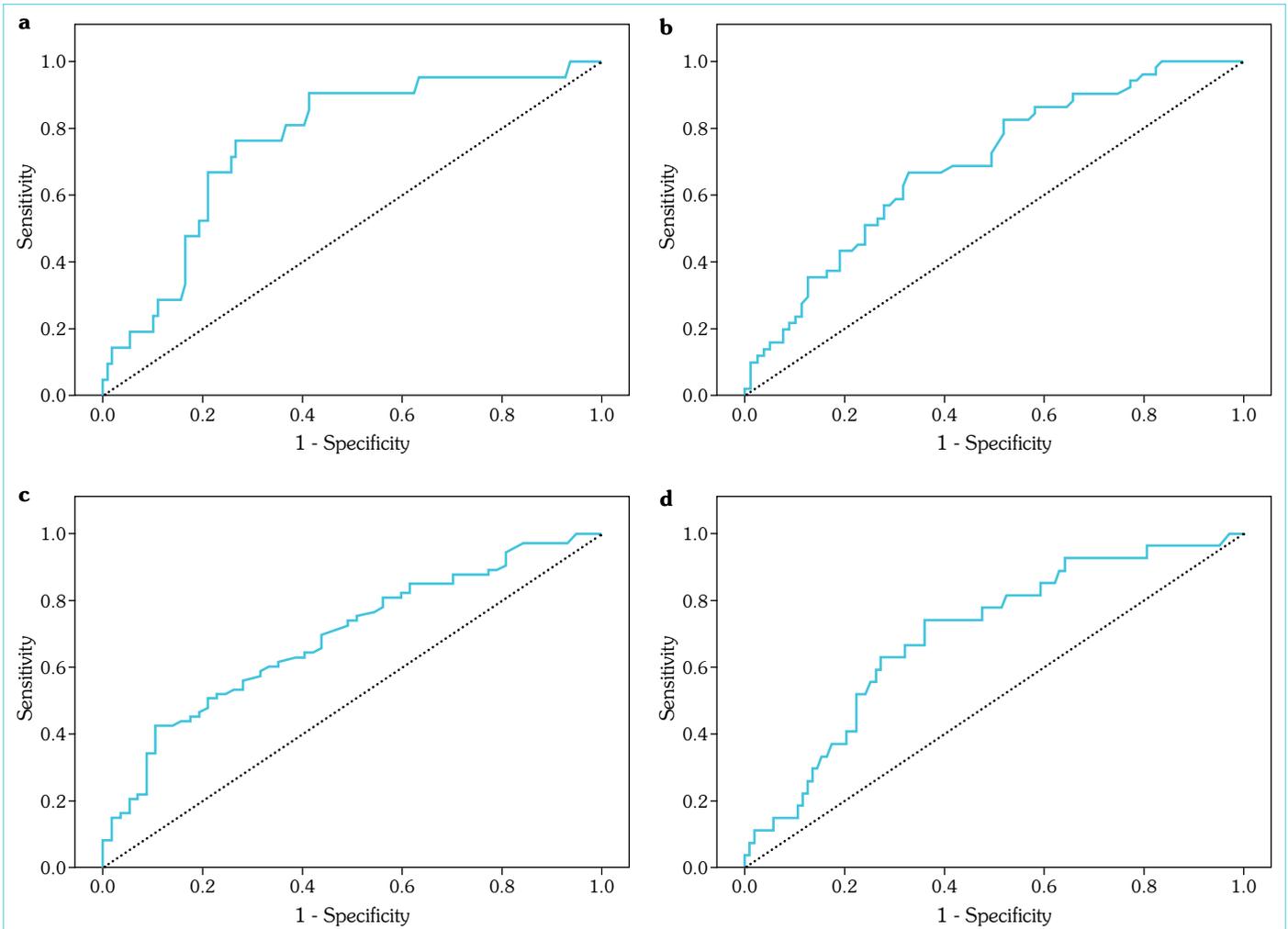
Figure 1. ROC curves demonstrating the predictive performance of bioavailable testosterone on (a) Lissamine green (grade) ≥3, (b) Meibomian gland dysfunction, (c) Tear film break-up time ≤10 seconds, (d) Tear film break-up time <3 seconds

not significantly correlated with any parameters other than Schirmer score; the positive correlation with Schirmer score was shown to become a negative correlation. The present results show that the hypoandrogenic status in COPD patients attributes to EDE status of the patients, irrespective of their FEV1/FVC status.

The effects of sex hormones and patient sex on the physiology of the lacrimal gland and the pathogenesis of DED have been demonstrated in previous studies (2, 5, 19, 20). In a recent study that

enrolled men aged >50 y and aimed to evaluate the relationship between the measures of DED and androgen levels, the authors found healthier global, lipid, and aqueous tear film parameters with higher levels of androstenedione; however, the correlation was weak (19). Further, in a patient with complete androgen insensitivity syndrome (CAIS), conjunctival immunohistochemical studies showed alterations in the mucous layer accompanied by a reduction in TF-BUT. Functional dry eye for lipid tear film instability and MGD have been also shown in patients with CAIS (21). Chronic

androgen deficiency was found to be related with dry eye and MGD in a study that compared subjects consuming antiandrogen medicines with age-matched controls (22). Another study showed that the androgen pool was markedly depleted in non-autoimmune dry eye patients with MGD compared to that in non-MGD patients and controls (23). The outcomes of these studies support our results.

In this study, we measured the bioavailable testosterone using the measured TT, albumin, and SHBG levels because of the high validity of this method demonstrated in previous research (24). However, this study has the following limitation. The serum testosterone volume constitutes a small fraction of the total androgen pool in human males, and studies with conjugated dihydrotestosterone metabolites would provide more accurate results.

Androgen deficiency in men should be regarded as a new systemic pathogenetic mechanism that complicates the clinical course of COPD, prognosis of the disease, and the accompanying pathologies. Known consequences of low androgen levels in COPD patients include loss of muscle mass, worse pulmonary function, depression, reduced sexual function, and low bone density (9). Both, the levels of circulating testosterone and dihydrotestosterone levels were independently associated with FEV1 and FVC; thus, androgen levels were suggested as biomarkers for evaluating the lung function in men (25). Moreover, this is compatible with our results that men with deteriorated FEV1 and FEV1/FVC had lower androgen levels. It is known that topical antiandrogen treatment causes a significant decrease in the ocular lipid profile, and the administration of sex hormones, such as dehydroepiandrosterone, stimulates lipid production in the meibomian glands and increases the TF-BUT accordingly (26). Transdermal androgen patches also improve TF-BUT and Schirmer test scores and quality of life in aging patients with dry eye, without any serious adverse effects (27). Studies related to the replacement of testosterone were based on the thought that male COPD patients have lower circulating androgen levels. However, male COPD patients generally had normal testosterone levels (or lower-normal range levels). Thus, androgen is not used for replacement therapy, but more in a pharmacological manner. The present results suggest that androgen replacement therapy may also improve the dry eye status of COPD patients with low systemic androgen levels.

In a very recent cross-sectional study, the authors evaluated the association between serum metabolites and DED to show decreased levels of the metabolites androsterone sulfate and epiandrosterone sulfate with DED, especially with the symptoms of dryness and irritation (28). However, in our COPD patients, the androgen levels were more strongly associated with the clinical diagnoses than with the symptoms. In our study, lower androgen levels were strongly correlated with dry eye clinical diagnostic parameters, while the OSDI score was weakly correlated only with TT. It is known that, there exist various related manifestations as non-obvious disease. For example, neuropathic pain and some other neurotrophic conditions have no marked ocular surface signs, but can be symptomatic (6). Peripheral neuropathy, predominantly sensory axonal polyneuropathy, in patients with stable COPD is established with electrophysiological evaluation in various studies owing to possible chronic hypoxemia or cigarette smoking (29). The well-known neuropathy in COPD patients may be the cause of the lack of their symptoms in the present study population. Meibum lipids maintain the health

and integrity of the ocular surface and support the tear film stability. Thus, MGD may cause lipid insufficiency, hyperosmolarity, instability, and increased evaporation of tear film. The outcomes of our study suggest that deficiency in androgens in COPD patients may lead to a dysfunction of the meibomian glands, leading to EDE.

There are several methods to determine the function of meibomian glands. One of the limitations of our study is that we were unable to perform measurements related to tear osmolarity and non-invasive TBUT, as suggested in TFOS DEWS II reports. In this study, clinically observed MGD and MGA loss determined with meibography were examined. Recent technological advances have led to the development of various automated scoring scales, such as the quantitative evaluation of MGA visualized using meibography. Such quantitative evaluation has been applied for MGD diagnosis. However, meibography alone is insufficient for MGD diagnosis, and interpretation with other clinical parameters is recommended. Thus, in our study, we combined meibography with clinical parameters for MGD diagnosis. Lipid layer thickness was not evaluated directly in this study; however, the hypothesis that the androgen deficit causes a decrease in the lipid component secreted mainly from the meibomian glands is supported by the meibography findings. Compensatory increased tear fluid secretion in MGD patients devoid of meibomian glands has been reported in previous trials and was significantly reduced in COPD patients with low serum androgen levels in our study (30). This could be the underlying reason of the findings in this set of COPD patients where Schirmer scores were not as affected as other EDE parameters. TF-BUT, LG staining, and MGD stages were more strongly correlated with the androgen levels than with Schirmer scores.

CONCLUSION
Less healthy tear film was related to COPD, especially in COPD patients with lower serum androgen levels. Various strong correlations were found between the serum androgen levels and DED symptoms, suggesting that lower serum androgen levels in COPD patients may cause DED. Further studies that evaluate the changes in ocular surface parameters in COPD patients with low androgen status after androgen replacement therapy would provide more insight into the role of sex hormone levels in the pathogenesis of DED in COPD patients. In the future, the therapeutic and/or preventive use of androgens for DED may be possible and recommended.

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