

Dry eye disease in patients with metabolic syndrome

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ABSTRACT

الأهداف: تقييم مدى خطورة مرض العين الجافة (DED) في المرضى الذين يعانون من متلازمة التمثيل الغذائي (MetS) ومقارنة مع الأفراد الأصحاء.

الطريقة: أجريت هذه الدراسة في طب العيون والغدد الصماء في مستشفى باجشيلار للتعليم والأبحاث، اسطنبول، تركيا خلال الفترة من يناير وديسمبر 2015م. في هذه الدراسة المستقبلية أجريت اختبارات مرض جفاف العين على 44 مريض من متلازمة التمثيل الغذائي و 43 شخص سليم. استخدم نظام الأسمولية، والذي يعد تقنية الشرائح المدمجة للمختبر تستخدم لقياس الأسمولية المسيلة للدموع، كما أجري McMonnies واستبيان أعراض Ho واختبار شيرمر واختبار TFBUT. أجري التقييم الإحصائي والاختبار المستقل.

النتائج: لم يكن هناك فروق ذات دلالة إحصائية في الأسمولية المسيلة للدموع، TFBUT، و McMonnies نقاط استبيان Ho بين مجموعة متلازمة التمثيل الغذائي والضبط. مع ذلك، كان اختبار شيرمر أعلى بشكل إحصائي في مجموعة متلازمة التمثيل الغذائي (14.8±9.4 mm مقابل 20.4±9.4)، $p=0.007$. في مجموعة النساء، كانت الأسمولية المسيلة للدموع أعلى بكثير في مجموعة متلازمة التمثيل الغذائي مقارنة مع مجموعة ضبط وعلى قطع يسجل 308 ملي أوزمول (309.4±13.1 mOsm/L مقابل 301.2±8.7 mOsm/L)، $p=0.012$.

الخاتمة: أن المرضى الذين يعانون من متلازمة التمثيل الغذائي لديهم انخفاض في حجم الدموع وارتفاع حالات ضعف الغدة الدمعية من أفراد المجموعة الضابطة المشابهين. كما أظهرت الدراسة أن النساء مع متلازمة التمثيل الغذائي لديهم الأسمولية المسيلة للدموع أعلى، مما يعرقل الدور الطبيعي للأسطح البصرية ويسبب التهاب. ينبغي للأطباء أن يكونون على بينة من ارتفاع معدلات مرض العين الجافة في المرضى الذين يعانون من متلازمة التمثيل الغذائي لتلقي العلاج في وقت مبكر لمنع المضاعفات البصرية الخطيرة.

Objectives: To evaluate dry eye disease (DED) in patients with metabolic syndrome (MetS) and compare with healthy individuals.

Methods: The study was conducted in the Ophthalmology and Endocrinology Department of Bagcilar Education and Research Hospital, a tertiary care center in Istanbul, Turkey, between January and December 2015. In this prospective case-controlled study, dry eye disease tests were performed on 44 patients with MetS and 43 healthy controls. TearLab Osmolarity System, which is a lab-on-a-chip technology, was used to measure tear osmolarity. McMonnies & Ho symptoms questionnaire along with Schirmer I test and tear film break-up time (TFBUT) test were also performed. Statistical evaluation was performed by students' independent test.

Results: There was no statistically significant difference in tear osmolarity, TFBUT, and McMonnies & Ho questionnaire scores between MetS and normal group. However, Schirmer I test was significantly higher in MetS group (14.8±9.4mm versus 20.4±9.4, $p=0.007$). In women subgroup, tear osmolarity was significantly higher in MetS group compared to the normal group and over the cut-off score 308 mOsm/L (309.4±13.1 mOsm/L versus 301.2±8.7mOsm/L, $p=0.012$).

Conclusion: Patients with MetS present with lower tear volumes and a higher incidence of lacrimal gland hypofunction than age-matched controls. Especially women with MetS have higher tear osmolarities, which disrupt the normal functioning of the ocular surface and cause inflammation. Clinicians should be aware of higher DED incidence in patients with MetS for early treatment to prevent serious ocular complications.

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With a 35% prevalence in the general population, dry eye disease (DED) is a prevalent public health issue that significantly affects quality of life. As defined by the International Dry Eye Workshop (DEWS), “dry eye is a multifactorial disease of the tears and ocular surface that results in the following symptoms: discomfort, visual disturbance, and tear film instability with potential damage to the ocular surface. It is also accompanied by increased osmolarity of the tear film and inflammation of the ocular surface”.¹ Risk factors for dry eye include being female, being of older age, receiving estrogen therapy after menopause, using computers, insufficient intake of omega-3 essential fatty acids or excessive intake of omega-6 to omega-3 fatty acids, vitamin A deficiency, having refractive surgery, receiving radiation therapy, receiving systemic therapy for cancer, with a bone marrow transplant, diabetes mellitus, HIV and human T-cell lymphotropic virus-1 infection, suffering from connective tissue diseases, hepatitis C, and the intake of systemic and ocular medications, including antihistamines, antidepressants, anxiolytics, beta-blockers, isotretinoin, and diuretics.^{2,3} Although no direct method of diagnosis is available, dry eye questionnaires are used for objective evaluation.⁴ However, symptoms and signs may not always match with the result of these tests.⁵ Tear film break up time (TFBUT), corneal staining, tear film assessment, conjunctival staining, and the Schirmer test are the most frequently used tests for subjective evaluation in support of a dry eye diagnosis.⁴ The hyperosmolarity of the tear film accepted the core mechanism underlying ocular surface inflammation, damage, symptoms, and triggering compensatory events in DED.⁶ Considering this, the measurement of tear osmolarity via lab-on-a-chip technology, namely TearLab (TearLab Corporation, San Diego, CA, USA), is regarded as the most accurate way of subjectively evaluating DED, with up to 95% sensitivity.⁷ Metabolic syndrome (MetS) is a complex disorder that carries a high socio-economic cost. It is defined by a group of interconnected factors that directly increase the risk of cardiovascular diseases, as well as type 2 diabetes mellitus.⁸ The main indications of the syndrome are dyslipidemia, the elevation of the arterial blood pressure, abdominal obesity, dysregulated glucose homeostasis, and/or resistance to insulin. Although many diseases have been associated with DED, only

a few papers in the literature have investigated the relationship between DED and MetS. Kawashima et al⁹ reported a likely influence on the part of MetS on the increasing prevalence of DED using only the Schirmer I test. Park et al¹⁰ observed no significant association between DED and MetS in their population-based study, but DED diagnosis was restricted to symptoms only. We aim to investigate DED in MetS patients using conventional dry eye tests, including McMonnies and Ho's questionnaire, the Schirmer I, TFBUT, and a novel diagnostic test, tear osmolarity.

Methods. The study was conducted in the Ophthalmology and Endocrinology Department of Bagcilar Education and Research Hospital, a tertiary care center in Istanbul, Turkey, between January and December 2015. The study design was a prospective cross-sectional. We prospectively enrolled 44 consecutive newly diagnosed patients with MetS and 43 healthy controls. All procedures performed with humans were in compliance with the Institutional Research Committee's ethical standards, the World Medical Association Declaration of Helsinki developed in 1964 and its amendments and other comparable ethical standards. Before conducting any procedure, permission was obtained from all the participants.

Laboratory evaluations and physical examinations were performed for each subject. Participants who had ≥ 3 of the following criteria, based on the guidelines of the National Cholesterol Education Program Adult Treatment Panel (NCEP ATP III) 2005, were defined as having MetS:¹¹ 1) Abdominal obesity: waist circumference >102 cm in men or >88 cm in women. 2) Hypertriglyceridemia: >150 mg/dl. 3) Low high-density lipoprotein (HDL) cholesterol: <40 mg/dl in men and <50 mg/dl in women. 4) High blood pressure: $>130/85$ mm Hg, or using antihypertensive drugs. 5) High fasting glucose: >100 mg/dl.

Individuals with known diabetes were excluded due to the confusion risk posed by diabetic eye complications. The use of medications, or any other systemic or ocular disease that could affect tear quality or production, the use of ocular medications, a history of anterior segment surgery, refractive procedures, contact lens wear, ocular allergy, glaucoma, diabetic or hypertensive retinopathy, ocular trauma, eyelid pathologies, nasolachrymal drainage obstruction, pregnancy, and lactation were the exclusion criteria. All of the participants also underwent thorough ophthalmological examinations. Snellen's chart was used to measure the visual acuity of both eyes. A biomicroscopic anterior segment examination was performed to observe the tear film, cornea, conjunctiva,

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and adnexa. A biomicroscopic posterior segment examination was carried out to exclude any posterior segment pathology. The study population completed McMonnies&Ho questionnaire, a tear osmolarity test, a tear film break-up time test (TFBUT), and the Schirmer I; all were performed on the same day by a single ophthalmologist. All tests were performed using a randomization table for one eye, and all examinations were performed daily between 15:00 and 16:00 under the same physical conditions to provide diagnostic accuracy.

The dry eye symptoms of the patients were evaluated with McMonnies&Ho questionnaire. Any score over 14.5 indicated a strong likelihood of dry eye disease.¹² Tear osmolarity was measured using laboratory on-a-chip technology, a TearLab™ Osmolarity System (TearLab Corporation, 9980 Huennekens St., Ste 100, San Diego, CA 92121, 1-855-832-7522, USA). The measurements were performed at a stable room temperature of 25-25.5°C, and the room humidity was 50-55%. At the beginning of each day of patient testing, reusable electronic check cards, which were provided by the manufacturer to confirm the calibration and functioning of the TearLab™ Osmolarity System, were used to perform quality control checks. The participants were asked not to wear any makeup on their eyelids. From the inferior lateral tear meniscus of the ocular surface, a tear sample of approximately 50 nl was collected. The cut-off score was 308 mOsm/L. The diagnostic value showed 75% sensitivity and 88% specificity for tear osmolarity in cases of mild/moderate disease, while it was 95% sensitive in cases of severe disease.¹³ The TFBUT is the standard test for estimating tear film stability. The TFBUT was performed by installing an impregnated fluorescein strip moistened with non-preserved saline into the lower fornix. The patient was asked to blink several times for 10-30 seconds and then stare straight ahead. The TFBUT measures the interval between the patient's last blink and the first appearance of a random dry spot.^{14,15} The TFBUT values of more than 10 seconds were considered normal, <10 seconds was considered moderate, and <5 seconds was considered severe dry eye disease.¹⁶ The Schirmer I test is commonly used to measure the basal and reflex volume of aqueous tears. The filter paper was inserted at the junction of the medium and lateral third of the lower lid for 5 minutes. Less than 10 mm of wetting is considered mild, while less than 5mm of wetting is considered to indicate severe DED.¹

Statistical Package for the Social Sciences (SPSS, SPSS Inc., Chicago, IL, USA) Version 21.0 was used to perform the statistical analyses. Descriptive statistics

were summarized as means ± SDs or percentages. A student's independent t-test was used to compare the MetS and normal groups. A *p*-value of <0.05 was regarded as statistically significant.

Results. We prospectively enrolled 44 consecutive metabolic syndrome patients (27 females and 17 males) and 43 controls (24 females and 19 males). The mean age was 44.5 ± 11.1 years old in MetS group and 43.2±11.6 in the normal group. Dry eye test scores and gender ratios of the study participants were summarized in Table 1.

There was no statistically significant difference in tear osmolarity, TFBUT, and McMonnies&Ho scores between the MetS and normal groups. However, the Schirmer I test values were significantly lower in the MetS group (Table 2). Due to the greater prevalence of dry eye in women as compared to men,³ we also subgrouped patients according to gender. In the women subgroup, tear osmolarity was significantly higher in the MetS group and over the cut-off score

Table 1 - Dry eye test scores and gender ratios of 44 consecutive metabolic syndrome patients (27 females and 17 males) and 43 controls (24 females and 19 males).

Dry eye tests	MetS*		Normal	
	F:M ratio	%	F:M ratio	%
<i>Tear osmolarity (mOsm/l)</i>				
>308	09:07	36	06:04	32
<i>TBUT (seconds)</i>				
>10	14:04	41	08:10	42
5-10	08:08	36	04:06	23
≤5	05:05	23	12:03	35
<i>Schirmer I (mm)</i>				
>10	11:12	52	21:14	81
5-10	06:05	25	01:02	7
≤5	10:00	23	01:04	11

*MetS - metabolic syndrome, F:M - female to male ratio, TBUT - tear break-up time

Table 2 - Comparison of dry eye tests in 44 consecutive metabolic syndrome patients (MetS) and normal control groups.

Dry eye tests	MetS*	Normal	<i>P</i> -value†
Tear osmolarity (mOsm/l)	305.9 ± 13.4	303.1 ± 15.5	0.368
TBUT (seconds)	9.5 ± 3.8	8.6 ± 4.1	0.284
Schirmer I (mm)	14.8 ± 9.4	20.4 ± 9.4	0.007
McMonnies and Ho	10.9 ± 4.7	10.4 ± 4.8	0.584

*MetS - metabolic syndrome, TFBUT - tear film break-up time.
†Student's independent t-test.

Table 3 - Comparison of dry eye tests in the women and men subgroup.

Dry eye tests	MetS*	Normal	P-value†
<i>Women</i>			
Tear osmolarity (mOsm/l)	309.4 ± 13.1	301.2 ± 8.7	0.012
TBUT (seconds)	8.3 ± 3.9	7.9 ± 4.3	0.691
Schirmer I (mm)	15.3 ± 9.1	15.3 ± 9.1	0.011
McMonnies and Ho	11.1 ± 4.9	10.5 ± 5	0.703
<i>Men</i>			
Tear osmolarity (mOsm/l)	300 ± 12.3	305.4 ± 21.4	0.391
TBUT (seconds)	11.5 ± 2.9	9.6 ± 3.7	0.1
Schirmer I (mm)	14 ± 9.9	18.6 ± 10.3	0.192
McMonnies and Ho	10.7 ± 4.5	10.1 ± 4.7	0.723

*MetS - metabolic syndrome, TFBUT - tear film break-up time,
†Student's independent t-test.

at 308 mOsm/l ($p=0.012$) (Table 3). There were no significant differences in tear osmolarity, TFBUT, or the Schirmer test between the MetS and normal groups in the men subgroup (Table 3).

Discussion. Both metabolic syndrome and dry eye disease are common and important health problems in the general population. In an effort to investigate DED in patients with MetS, we performed tear osmolarity measurements, Schirmer I, TFBUT, and the McMonnies&Ho questionnaire in 44 consecutive new diagnosed MetS patient.

In our study, there was no significant difference between the tear osmolarity of the MetS and normal groups (305.9±13.1 mOsm/l and 303.1±15.5 mOsm/l, $p=0.368$). There are many studies showing higher tear osmolarity levels in patients with type 2 diabetes mellitus,¹⁷⁻¹⁹ mainly due to the angiopathic and neuropathic complications of diabetes.²⁰ Excluded patients with diabetes from our study may be the reason for these different results.

In our study, no difference in terms of TFBUT measurements was found when comparing the MetS and normal groups ($p=0.284$). There were significant differences between diabetics and non-diabetic controls regarding the TFBUT in most of the studies.²¹ The TFBUT is commonly used to diagnose evaporative dry eye, but TFBUT testing is very non-specific regarding the determination of tear film stability and the diagnosis of meibomian gland disease. Tear film instability is one of the main mechanisms of dry eye, and it may be responsible for an initiating event.^{6,22} As a result, we can say that MetS does not affect meibomian gland function. The Schirmer I test values were significantly lower in the MetS group (14.8±9.4) than in the normal group (20.4±9.4, $p=0.007$). Most of

the studies revealed decreased Schirmer test readings in diabetic patients as compared with healthy subjects.²¹ In the sole study evaluating DED in patients with MetS, Kawashima et al⁹ enrolled 47 MetS patients and 264 healthy subjects. They showed a significant decrease in Schirmer I test values in MetS patients, which is compatible with our results (MetS: 11.0±9.7mm, normal: 18.5±11.9mm, $p=0.000$). There was no significant difference between the symptoms, as assessed by the McMonnies and Ho questionnaire of the MetS and healthy groups ($p=0.584$), which is parallel to the findings of Park et al.¹⁰ In our study, we subgrouped the patients according to the gender to avoid bias in the comparison between females and males.³ In the women subgroup, there was no significant difference in Schirmer I test values, TFBUT values, or McMonnies and Ho questionnaire results, but tear osmolarity was significantly higher in the MetS group as compared to the normal group (309.4±13.1, 301.2±8.7, $p=0.012$.) According to the Schirmer I test, we detected severe dry eye (Schirmer test ≤5mm) in 23% (F:M=10:0) of the MetS group and 11% of the normal group (F:M=1:4) (Table 1). Neither in the Osaka study nor in the DED studies with diabetes were patients evaluated in terms of gender.^{9,17-21} Park et al¹⁰ observed no significant difference between DED symptoms and MetS based on gender.¹⁰ There was no significant difference between MetS and normal men in terms of all dry eye tests.

Study limitations. First, as MetS is related to the diets of the patients²³ and DED is associated with an insufficient intake of omega-3 essential fatty acids, or an excessive intake of omega-6 to omega-3 fatty acids, as well as vitamin A deficiency, the differences in tear osmolarity affected by this association. Further studies considering the possible effects of the dietary habits of patients with MetS and DED are required. Second, tear film components may vary across the menstrual cycle.³ The assessment of tear film components in women during the same period of the menstrual cycle will be valuable.

In conclusion, it is known that patients with MetS present with lower tear volumes and a higher incidence of lacrimal gland hypofunction than age-matched controls and that DED symptoms are similar in MetS patients and the healthy population. Our study confirms both of these findings and reveals, for the first time, that women with MetS have especially high tear osmolarities, which disrupts the normal functioning of the ocular surface and causes inflammation.²⁴ Because the symptoms were the same as those seen in healthy

people, clinicians should be aware of the higher DED incidence in patients with MetS as early treatment may prevent serious ocular complications.

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