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Systemic Conditions Associated with Severity of Dry Eye Signs and Symptoms in the Dry Eye Assessment and Management (DREAM) Study

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Abstract

OBJECTIVE: Certain systemic conditions are reported to be risk factors for dry eye disease (DED), but their associations with DED severity are not well-studied. We evaluated whether systemic conditions reported to be DED risk factors are associated with severity of DED signs and symptoms.

DESIGN: Secondary analysis of data from the DREAM Study, a large-scale multi-center randomized clinical trial of patients with moderate-to-severe DED.

SUBJECTS: 535 adult patients with moderate-to-severe DED from 27 US centers.

METHODS: Patients reported their medical history at baseline. They underwent ocular surface exams and symptom evaluation using standardized protocols at baseline, 6 months, and 12 months. We analyzed the associations of systemic conditions (a systemic disease or smoking history) reported as potential DED risk factors with the severity of DED signs and symptoms using generalized linear regression models adjusted by age, sex, race, and visit. To be included, conditions had at least 25 patients.

MAIN OUTCOME MEASURES: DED symptoms assessed using the Ocular Surface Disease Index (OSDI), six DED signs (tear break-up time, anesthetized Schirmer testing, corneal

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fluorescein staining, conjunctival lissamine green staining, tear osmolarity, and meibomian gland dysfunction), and a composite signs severity score with range 0-1 (1 most severe) calculated from the six DED signs.

RESULTS: The mean±SD age was 58±13.2 years, and 81% were female. More severe DED signs were significantly associated with Sjögren's syndrome (mean±SD of composite signs severity score: 0.52±0.17 with disease vs. 0.43±0.13 without disease, p<0.001), facial rosacea (0.47±0.13 vs. 0.43±0.13, p=0.002), rheumatoid arthritis (0.47±0.14 vs. 0.42±0.12, p=0.002), peripheral artery disease (0.50±0.14 vs. 0.43±0.13, p<0.001), and daily smoking history (0.45±0.13 vs. 0.43±0.13, p=0.047). Thyroid dysfunction, osteoarthritis, diabetes, irritable bowel syndrome, hypercholesterolemia, hypertension, and hypertriglyceridemia were not significantly associated with DED signs. No conditions were significantly associated with OSDI.

CONCLUSION: In this large, well-characterized cohort of DED patients assessed under standardized procedures, patients with certain systemic diseases and smoking had more severe DED signs compared to patients without the condition. The profile of significant DED signs varied by systemic condition, reflecting different DED etiologies. Understanding the systemic conditions and underlying etiologies that predispose some patients to severe DED can improve management.

Keywords

Dry Eye Risk Factors; Dry Eye Syndromes; Keratoconjunctivitis Sicca; Peripheral Artery Disease; Rheumatoid Arthritis; Rosacea; Smoking; Thyroid Dysfunction

INTRODUCTION

Dry eye disease (DED) is a common chronic, inflammatory, multifactorial disease of the tears and ocular surface causing ocular discomfort, fatigue, and visual disturbances.[1, 2] The disease is associated with a substantial negative impact on quality of life, such as interference with reading, computer use, and driving, and is estimated to cost the U.S. economy more than $55 billion annually.[3-7] DED prevalence is estimated at 8.7-30.1% of adults in the United States, with higher rates among women and with increasing age.[2]

DED is often characterized as aqueous tear deficient and/or evaporative.[1] Aqueous tear deficiency results from decreased aqueous tear production, such as seen in Sjögren's syndrome (SS). Evaporative dry eye results from any condition that increases the evaporation rate of tears, such as meibomian gland dysfunction (MGD). Many patients have components of both aqueous tear deficient and evaporative dry eye; irrespective of etiology, DED is also characterized by ocular surface inflammation that further exacerbates the disease.[8, 9] This produces classic symptoms such as chronic eye pain, eye irritation, foreign body sensation, fluctuating vision, burning, and/or stinging.[1, 2] Patients also exhibit various signs of dry eye including decreased aqueous tear production, decreased tear break-up time, ocular surface staining with vital dyes such as fluorescein and lissamine green, tear hyperosmolarity, and evidence of MGD as demonstrated by plugging or lid secretions.[1, 9-11]

Risk factors for the prevalence of DED in population studies include demographic characteristics, systemic diseases, environmental conditions, and medications. The 2017 Dry Eye Workshop (DEWS II) Epidemiology subcommittee classified risk factors into

consistent, probable, and inconclusive based on evidence from at least one adequately powered study, a plausible biological rationale, and corroborating basic research or clinical data.[2] Consistent risk factors for the prevalence of DED include increased age,[12–16] female sex,[4, 12, 13, 16, 17] Asian race,[13,16] MGD,[18] connective tissue diseases such as rheumatoid arthritis (RA),[4, 12–14, 16, 19, 20] and SS.[13, 21] Probable factors include diabetes,[12, 13, 16, 19, 22–24] rosacea,[13, 16, 22, 25, 26] and thyroid disease.[4, 12, 13, 16, 19, 20] Inconclusive factors include smoking.[12, 15, 16, 27–31] In addition, other risk factors for dry eye that have been reported in the literature but were not mentioned in the DEWS II report include osteoarthritis,[12, 14, 16, 20] peripheral artery disease,[19] dyslipidemias,[12, 16, 19, 20, 32–34] hypertension,[16, 17, 35] and irritable bowel syndrome.[14, 36]

While risk factors for DED prevalence have been investigated in many studies, there are few large studies evaluating the association of systemic diseases with DED severity. The Dry Eye Assessment and Management (DREAM) study was a large, multi-center randomized clinical trial to assess the efficacy and safety of an oral omega-3 supplement for the treatment of dry eye. As part of the study, DREAM participants provided information about their medical history and underwent ocular surface exams using standardized protocols. We used the well-characterized DREAM study cohort to determine whether systemic conditions reported as risk factors for DED prevalence are associated with the severity of DED signs and symptoms.

PATIENTS AND METHODS

Study patients

The DREAM study (NCT02128763), funded by the National Eye Institute, National Institutes of Health, enrolled 535 adult patients with DED from 27 centers in the United States.[37] Patients were randomized 2:1 to an active oral omega-3 fatty acid supplement group (2000 mg EPA and 1000 mg DHA per day) or a placebo group (refined olive oil). The study was approved by the Institutional Review Board/Ethics Committee, followed the tenets of the Declaration of Helsinki, and obtained written informed consent from all patients.

The DREAM study was designed to include a broad spectrum of patients with symptomatic moderate-to-severe DED. Major eligibility criteria were age ≥18 years, reported dry eye-related ocular symptoms for at least 6 months before the screening visit, use or desire to use artificial tears on average of at least 2 times per day in the 2 weeks preceding the screening visit, and a score on the Ocular Surface Disease Index (OSDI) of 25 to 80 at the screening visit and of 21 to 80 at the baseline visit. Patients also had to satisfy at least 2 of the following 4 criteria for dry eye signs in the same eye at screening and baseline visits: 1) conjunctival lissamine green staining score ≥1 (on a scale of 0 to 6); 2) corneal fluorescein staining score ≥4 (on a scale of 0 to 15); 3) tear film break up time (TBUT) ≤7 seconds; and 4) anesthetized Schirmer's test ≥1 to ≤7 mm/5min. Patients that were unwilling to commit to no use of contact lenses for the duration of the study and within the last 30 days prior to the Screening Visit, as well as patients that used EPA/DHA supplements in excess of 1200 mg/day, were excluded from the study. Full details on inclusion and exclusion criteria can be found in the DREAM study protocol.[37]

At the screening visit, patients were asked about their medical history for 58 systemic or extraocular diagnoses as told to them by a doctor or other health professional within the past two years. Possible answers were no history, past history, or ongoing disease. At each visit, a clinician evaluated patients for the presence or absence of facial rosacea. At the baseline visit, patients were asked whether they had ever smoked cigarettes on a daily basis, and if so, for how many years and whether they currently smoke.

Outcome measures

The outcome measures were dry eye symptoms using the OSDI, six dry eye signs (TBUT, Schirmer testing with anesthesia, corneal fluorescein staining, conjunctival lissamine green staining, tear osmolarity, and MGD), and a composite signs severity score. These were measured at baseline, 6 months, and 12 months.

Scores on the 12-item OSDI range from 0 to 100, with a score of 0 indicating no ocular symptoms and higher scores indicating greater symptom severity. The minimal clinically meaningful change in score for an individual is 10 points.[38, 39] Dry eye signs are measured per eye. The TBUT measures time (in seconds) from a blink to the appearance of gaps in the tear film, with shorter times indicating greater tear film instability. The average of 3 repeated TBUT measurements was used. The Schirmer's test measures the length of wetting of paper strips placed in the inferior cul de sac of the lower eyelid in mm/5 minutes, with shorter lengths indicating less tear production. Corneal fluorescein staining and conjunctival lissamine green staining evaluate ocular surface damage. Corneal staining was assessed using the NEI scale whereby five areas of the cornea are graded 0 to 3, for a total possible score of 0 to 15 per eye.[40] Conjunctival staining was assessed on a scale of 0 to 3 in the nasal and temporal areas for a total possible score of 0 to 6 per eye. Tear osmolarity measures the concentration of solutes in the tear film on a scale of 275 to 400 mOsm/L. Patients (N=405) who enrolled at centers with a TearLab™ Osmolarity System (San Diego, California) had tear osmolarity measured. MGD was evaluated for plugging and lid secretion on a scale of 0 to 3 using the TearScience Meibomian Gland Evaluator™ at slit lamp. The average of the scores for plugging and lid secretion was used. For corneal and conjunctival staining, tear osmolarity, and MGD, higher scores indicate greater abnormality.

A composite severity score for the six dry eye signs was computed using an adapted method from past studies.[41–43] Each of the six signs was transformed to a common unit severity score from 0 to 1, where 0 indicates no DED and 1 indicates the most severe DED, according to the discrete severity grading system of the DEWS report[1] (Supplemental Table 1, available at http://www.aaojournal.org). Scores between the quartile points were linearly interpolated. A composite signs severity score was calculated per eye by taking the mean of the severity scores of the six independent signs. The composite score did not include osmolarity for patients without osmolarity score measurements (N=130).

Statistical analysis

We evaluated whether the presence of a systemic condition (a systemic disease or daily smoking history) is associated with the severity of dry eye signs and symptoms using multivariate generalized linear regression models. Models were adjusted by age, sex,

and race since these variables were significantly associated with the outcome measures (Supplemental Table 2, available at http://www.aaojournal.org) and are consistent DED risk factors according to the DEWS II report.[2] We conducted a combined analysis of three visits (baseline, 6 months, and 12 months) for greater power, as well as separate analyses for each visit to confirm consistency of associations across time points. For the combined analysis, we adjusted by visit (baseline, 6 months, and 12 months) since mean OSDI and some DED signs decreased significantly over the course of the DREAM study.[44] We used the generalized estimating equations (GEE) approach to account for both inter-visit correlations within the same eye and inter-eye correlations within the same subject,[45] performed using the R package geepack version 1.3-1.[46] Two-sided $p<0.05$ was considered to be statistically significant.

Our criteria to analyze a systemic condition were: 1) at least one prior study reporting the condition as a risk factor for DED; and 2) a minimum of 25 subjects with ongoing disease (or daily smoking history). For the RA analysis, we excluded 52 patients with SS meeting the 2012 American College of Rheumatology (ACR) criteria[47] and 27 patients with indeterminate SS status, because RA can cause secondary SS. SS status was identified via self-report and SS antibody profile, using the method described previously by Bunya et al.[48] For the analysis of each systemic disease, patients with only a past history were excluded. Because the DREAM study found no significant difference in dry eye symptoms and signs between the active treatment and placebo groups,[44] we combined patients in the two treatment groups for statistical analysis.

RESULTS

Baseline characteristics

The baseline characteristics of the 535 study patients satisfying criteria for moderate-to-severe DED are summarized in Table 1. The mean±SD age was 58±13.2 years, with the majority of participants being female (81%) and white (74%). The mean±SD for OSDI score was 42.1±15.5. The mean±SD for dry eye signs was 3.1±1.8 seconds for TBUT, 9.6±7.0 mm/5min for Schirmer testing, 3.8±3.0 for corneal fluorescein staining, 2.9±1.5 for conjunctival lissamine green staining, 302.7±16.2 mOsm/L for tear osmolarity, 1.54±0.92 for MGD, and 0.46±0.12 for the composite signs severity score. Mean OSDI decreased to 32.2±19.1 at 6 months and 30.5±18.6 at 12 months. The number of patients who reported ongoing disease at enrollment was 109 (20.4%) for rosacea, 47 (8.8%) for RA, 47 (8.8%) for peripheral artery disease, 94 (17.6%) for thyroid dysfunction, 134 (25.0%) for osteoarthritis, 57 (10.7%) for diabetes, 44 (8.2%) for irritable bowel syndrome, 171 (32.0%) for hypercholesterolemia, 149 (27.9%) for hypertension, and 25 (4.7%) for hypertriglyceridemia. 168 (31.4%) patients reported ever smoking cigarettes daily, and of those, 26 (4.9%) currently smoke. Fifty-two patients (9.7%) satisfied the 2012 ACR criteria for SS. Of the 47 RA patients, 9 also met 2012 ACR criteria for SS and were excluded from subsequent RA analyses.

Older age and female sex were significantly associated with more severe scores for Schirmer testing, corneal fluorescein staining, and the composite signs severity score (Supplemental Table 2, available at http://www.aaojournal.org). Female sex was also

significantly associated with more severe conjunctival lissamine green staining. The mean score for OSDI, TBUT, Schirmer testing, corneal staining, and conjunctival staining varied significantly by race with different racial groups having more severe scores depending on the DED characteristic.

Association of systemic conditions with dry eye signs

In the combined analysis of all time points (baseline, 6 months, and 12 months), five systemic conditions were significantly associated with a higher composite signs severity score after adjustment for age, sex, race, and visit: SS (mean±SD: 0.52±0.17 with disease vs. 0.43±0.13 without disease, $p<0.001$), rosacea (0.47±0.13 vs. 0.43±0.13, $p=0.002$), RA (0.47±0.14 vs. 0.42±0.12, $p=0.002$), daily smoking history (0.45±0.13 vs. 0.43±0.13, $p=0.047$), and peripheral artery disease (0.50±0.14 vs. 0.43±0.13, $p<0.001$) (Table 2). Rosacea was significantly associated with worse dry eye signs in Schirmer testing (8.2±5.6 vs. 10.2±7.2, $p=0.002$) and MGD (1.77±0.96 vs. 1.39±0.93, $p<0.001$); RA was associated with worse signs in corneal fluorescein staining (4.2±3.4 vs. 3.2±2.7, $p=0.02$); daily smoking history was associated with worse signs in MGD (1.62±0.98 vs. 1.40±0.93, $p=0.003$); and peripheral artery disease was associated with worse signs in TBUT (2.8±1.6 vs. 3.6±2.5, $p<0.001$), Schirmer testing (7.8±6.2 vs. 10.0±7.0, $p=0.005$), corneal fluorescein staining (4.9±3.3 vs. 3.3±2.8, $p<0.001$), and MGD (1.73±0.96 vs. 1.45±0.95, $p=0.02$). For comparison, SS was significantly associated with worse signs in Schirmer testing (7.5±6.7 vs. 10.1±6.9, $p=0.01$), corneal fluorescein staining (5.0±3.9 vs. 3.2±2.7, $p<0.001$), lissamine green conjunctival staining (3.6±1.9 vs. 2.6±1.5, $p<0.001$), and tear osmolarity (310.6±20.8 vs. 302.5±16.5, $p<0.001$). All reported associations were consistent in separate analyses of baseline, 6 months, and 12 months (Supplemental Table 3, available at http://www.aaojournal.org).

Thyroid dysfunction was associated with a higher composite signs severity score in univariate analysis (0.47±0.15 vs. 0.43±0.13, $p=0.02$), but was not significant after adjustment by age, sex, race, and visit ($p=0.09$). Similarly, osteoarthritis was associated with a higher composite signs severity score in univariate analysis (0.46±0.13 vs. 0.43±0.13, $p=0.002$), but was not significant ($p=0.15$) after adjustment. Detailed univariate analysis results for all the systemic conditions are included in Supplemental Table 4 (available at http://www.aaojournal.org). No significant associations were found for diabetes, irritable bowel syndrome, hypercholesterolemia, hypertension, and hypertriglyceridemia (Table 2).

Association of systemic conditions with dry eye symptoms

OSDI was not consistently significantly associated with any of the systemic conditions in the combined analysis (Table 3) nor in separate analyses of baseline, 6 months, and 12 months (Supplemental Table 5, available at http://www.aaojournal.org). Significant isolated associations with worse OSDI were SS at 12 months (36.1±18.6 vs. 29.1±18.1, $p=0.03$), daily smoking history at 6 months (34.4±18.4 vs. 31.1±19.3, $p=0.049$) and 12 months (33.0±18.2 vs. 29.3±18.7, $p=0.04$), and peripheral artery disease at 6 months (38.6±19.0 vs. 31.6±19.0, $p=0.02$).

DISCUSSION

We evaluated the associations of 12 systemic conditions previously reported as potential DED risk factors with the severity of dry eye signs and symptoms in a large cohort of 535 patients with moderate-to-severe dry eye disease. After adjusting for age, sex, race, and visit, patients with SS, rosacea, RA, daily smoking history, or peripheral artery disease had more severe dry eye signs than patients without the condition of interest. We did not find significant associations with severity of DED signs for thyroid dysfunction, osteoarthritis, diabetes, irritable bowel syndrome, hypercholesterolemia, hypertension, or hypertriglyceridemia. Additionally, no consistent significant associations were found with severity of dry eye symptoms measured using the OSDI. Notably, older age also was not associated with higher OSDI score despite its association with more severe dry eye signs. This is congruous with other studies identifying age as a predictor of discordance between dry eye signs and symptoms,[41, 42, 49] perhaps due to reduced corneal sensitivity in older adults.[50]

Sjögren's syndrome

SS is a systemic autoimmune disease that causes dry mouth and dry eye, which can be severe. In fact, the 2016 ACR/EULAR SS classification criteria include an ocular staining score ≥5 and Schirmer's test ≤5mm/5 minutes.[51] Bunya and colleagues previously reported that in the DREAM cohort, the four key signs of dry eye (TBUT, Schirmer testing, corneal staining, and conjunctival staining) were significantly worse in SS vs. non-SS patients at baseline.[48] Similarly, in our study we found SS (52 patients) to be significantly associated with a higher composite dry eye signs severity score, including worse values for Schirmer testing, corneal staining, conjunctival staining, and tear osmolarity. The strength of these associations helps validate our findings for the following systemic conditions.

Rosacea

Rosacea is a chronic cutaneous disorder primarily affecting the cheeks, chin, nose, and central forehead.[52] More than half of patients with cutaneous rosacea have ocular signs,[53] such as blepharitis, conjunctival hyperemia, telangiectasia of the lid margin, recurrent chalazia, superficial punctate keratopathy, and nonspecific symptoms including a foreign body, gritty, or dry sensation or burning, stinging, or tearing.[53–56] Rosacea-associated MGD is a variant of MGD and is usually associated with more severe disease and inflammatory complications of the ocular surface.[53, 54, 57] In our study, twenty percent of patients (109 individuals) with moderate-to-severe DED presented with facial rosacea at enrollment. These patients had a higher composite signs severity score, with the most prominent signs being lower Schirmer scores and MGD, suggesting that cutaneous rosacea is associated with both aqueous tear deficient and evaporative dry eye disease.

Our study agrees with past smaller studies of 18 to 32 rosacea patients that also found lower Schirmer scores and more severe MGD to be associated with the presence of rosacea.[25, 26] One study of 18 rosacea vs. 19 healthy patients additionally found significant associations between rosacea and more severe OSDI scores, decreased TBUT, and increased corneal and conjunctival fluorescein staining.[26] While in our study the associations between rosacea and

OSDI, TBUT, and corneal and conjunctival staining was not significant after adjustment for age, sex, race, and visit, we did observe worse mean scores for each of these measures in patients with rosacea compared to those without rosacea.

Rheumatoid arthritis

Extra-articular symptoms of RA include those of the eye, such as dry eye, episcleritis, scleritis, corneal changes, and retinal vasculitis.[58] RA has been reported to be associated with dry eye even in the absence of SS.[59] In our study, seven percent (38 patients) had RA without SS, and these patients were significantly associated with a more severe composite dry eye signs score. Corneal fluorescein staining was the most prominent sign after adjustment for age, sex, race, and visit. These findings agree with a cross-sectional study of 510 Asian DED patients where RA (25 patients) was associated with more severe superior corneal fluorescein staining after adjustment for age.[49] A different case-control study of 72 RA patients did not find any significant association between severity of dry eye signs and RA.[59] A potential etiology for dry eye in RA is over expression of pro-inflammatory cytokines in the tears.[60]

Cardiovascular Risk Factors

Smoking has been reported to increase risk for DED, [12, 15, 16, 27–31] though other studies report no associations.[27, 61] Cigarette smoking may cause toxic oxidative damage to proteins in the tear film, leading to tear film instability and DED.[28, 30] In our study, thirty-one percent (168 patients) reported smoking cigarettes daily (formerly or currently). Daily smoking history was significantly associated with a higher composite dry eye signs severity score, with MGD as the most prominent sign after adjustment for age, sex, race, and visit. Other studies with 49 to 65 chronic smokers report associations between smoking and decreased TBUT, lower Schirmer scores, and increased corneal and conjunctival staining.[29–31]

While we found a history of ever smoking daily cigarettes to be associated with more severe DED signs, we did not find current daily cigarette smoking (26 patients) to be significantly associated with DED severity, potentially due to limited statistical power. A cohort study of 510 Asian DED patients also did not find any association between current smoking (in 33 individuals) and severity of dry eye signs.[49]

Dyslipidemias, hypertension, and atherosclerotic diseases have also been disputably associated with DED prevalence.[12, 16, 17, 19, 20, 32–35, 61] Increased cholesterol content in meibomian lipids may cause plugging of meibomian glands, with elevated high-density lipoprotein reported to be associated with moderate-to-severe MGD in a retrospective case-control study.[33] In our study, nine percent (47 patients) reported ongoing peripheral artery disease, thirty-two percent (171 patients) reported ongoing hypercholesterolemia, twenty-eight percent (149 patients) reported ongoing hypertension, and five percent (25 patients) reported ongoing hypertriglyceridemia. Peripheral artery disease was significantly associated with a higher composite dry eye signs severity score, with corneal fluorescein staining, TBUT, Schirmer's, and MGD as the most prominent signs. However, hypercholesterolemia, hypertriglyceridemia, and hypertension were not associated with more severe dry eye signs, perhaps suggesting that only dyslipidemias severe enough to

cause symptomatic disease, like peripheral artery disease, are associated with more severe DED.

Diabetes

We did not find any associations between diabetes (57 patients) and severity of dry eye signs and symptoms, consistent with the cohort study of 510 Asian DED patients.[49] While the DEWS II report indicates diabetes as a probable risk factor for DED, only diabetes with complications is significantly associated with DED in most studies.[2, 19, 23, 62–65] Duration of diabetes and the presence of diabetic retinopathy have been found to be associated with higher risk of DED.[62, 63] In our study, only four patients reported diabetic retinopathy/macular edema, and information on the duration of diabetes was not collected. It is therefore reasonable to suspect that no association was found for diabetes in the DREAM study because most patients did not have severe enough diabetes to increase DED severity. Another possibility is that diabetes increases disease severity in mild DED, but this is not detected because the DREAM study cohort only includes patients with moderate-to-severe DED.

Thyroid dysfunction and osteoarthritis

In our study, thyroid dysfunction (94 patients) and osteoarthritis (134 patients) were significantly associated with the severity of dry eye signs only without adjustment for age, sex, race, and visit. This suggests that demographic and other confounding factors may explain previous reports in the literature regarding associations between these two diseases and the presence of DED. Alternatively, thyroid dysfunction, osteoarthritis, and the diseases for which we did not find any associations may only be risk factors for the presence of DED, not for its severity in patients with moderate-to-severe DED. Finally, it is possible that thyroid dysfunction is associated with more severe DED only with thyroid eye disease.[66] We did not collect information on the presence of thyroid eye disease in DREAM study patients.

Strengths and Limitations

While various studies have suggested that certain systemic diseases are risk factors for the development of dry eye, there are few other studies to identify whether these systemic diseases are significantly associated with the severity of dry eye as measured by ocular surface exams and symptom indices. Our study represents a large number of patients from multiple centers and includes a standardized assessment of six dry eye signs and symptoms following the DREAM study protocol, providing not only information on different etiologies of dry eye but also a composite severity score synthesizing the six individual signs. The finding that SS, known to be associated with severe dry eye, was the systemic condition most significantly associated with dry eye signs in our study helps validate our methods.

An important limitation is that our study may underestimate the association of certain systemic conditions with DED severity due to potential bias from co-existing systemic diseases and a study population limited to patients with moderate-to-severe DED. The lack of significant associations for some of the systemic conditions, such as diabetes and thyroid dysfunction, should be interpreted in this context. For example, it is possible that these systemic conditions are associated with mild but not moderate-to-severe DED. Similarly,

it is possible that the significant systemic conditions have stronger associations with DED severity than is reported in this study. Other limitations include use of patients' self-report to determine presence or absence of systemic disease without differentiating severity and duration, as well as possible confounding by multiple testing of 12 systemic conditions and 7 DED signs and symptoms.

In conclusion, the DREAM study, a large-scale randomized clinical trial of 535 well-characterized patients with moderate-to-severe dry eye disease from 27 clinical centers across the US, provides to our knowledge the largest dataset to determine whether systemic diseases and cigarette smoking are associated with DED severity. Based on comprehensive evaluation of DED signs and symptoms following standard study protocol, we found that presence of SS, facial rosacea, RA, peripheral artery disease, and a history of daily cigarette smoking are significantly associated with more severe dry eye signs. This is significant as severe DED warrants more intense treatment strategies. Furthermore, the profile of significant dry eye signs varied by systemic condition, reflecting different dry eye etiologies. Understanding the systemic conditions and underlying etiologies that predispose certain patients to more severe DED, compared to patients without these systemic conditions, can improve management.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Please see the Credit Roster for a list of clinical center personnel and other contributors to the DREAM study (available at http://www.aaojournal.org, http://links.lww.com/ICL/A131).

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In the Dry Eye Assessment and Management Study, patients with Sjögren's syndrome, facial rosacea, rheumatoid arthritis, peripheral artery disease, and daily smoking history exhibited significantly more severe dry eye on ocular surface exams.

Table 1.

Characteristics of study patients at baseline (N=535).

Baseline characteristics		
Age (years)	Mean (SD)	58.0 (13.2)
	Min, Max	18, 87
Sex	Female (%)	434 (81.1)
Race	White (%)	398 (74.4)
	Black (%)	64 (12.0)
	Asian (%)	19 (3.6)
	Other (%)	54 (10.1)
Baseline dry eye signs and symptoms		
Tear Break-up time (seconds)	Mean (SD)	3.1 (1.8)
Schirmer's test (mm/5min)	Mean (SD)	9.6 (7.0)
Fluorescein staining of cornea	Mean (SD)	3.8 (3.0)
Lissamine green staining of conjunctiva	Mean (SD)	2.9 (1.5)
Tear osmolarity (mOsm/L)	Mean (SD)	302.7 (16.2)
Meibomian gland dysfunction: plugging and lid secretion	Mean (SD)	1.54 (0.92)
Composite dry eye severity score based on signs	Mean (SD)	0.46 (0.12)
Ocular Surface Disease Index (OSDI) score	Mean (SD)	42.1 (15.5)
Baseline systemic conditions		**N (%)**
Rosacea (facial)	No	426 (79.6)
	Yes	109 (20.4)
Rheumatoid arthritis	Never	486 (90.8)
	Past history	2 (0.4)
	Ongoing	47 (8.8)
Sjögren's syndrome*	No	456 (85.2)
	Yes	52 (9.7)
	Indeterminate	27 (5.0)
Daily cigarette smoking history	Never	367 (68.6)
	Former	142 (26.5)
	Current	26 (4.9)
Peripheral artery disease	Never	484 (90.5)
	Past history	4 (0.7)
	Ongoing	47 (8.8)
Thyroid dysfunction	Never	427 (79.8)
	Past history	14 (2.6)
	Ongoing	94 (17.6)
Osteoarthritis	Never	394 (73.6)
	Past history	7 (1.3)

Baseline characteristics		
	Ongoing	134 (25.0)
Diabetes	Never	473 (88.4)
	Past history	5 (0.9)
	Ongoing	57 (10.7)
Irritable bowel syndrome	Never	476 (89.0)
	Past history	15 (2.8)
	Ongoing	44 (8.2)
Hypercholesterolemia	Never	344 (64.3)
	Past history	20 (3.7)
	Ongoing	171 (32.0)
Hypertension	Never	380 (71.0)
	Past history	6 (1.1)
	Ongoing	149 (27.9)
Hypertriglyceridemia	Never	503 (94.0)
	Past history	7 (1.3)
	Ongoing	25 (4.7)

*Meeting 2012 ACR criteria for Sjögren's syndrome.

Table 2.

Associations of systemic conditions with severity of dry eye signs from analysis with baseline, 6 months, and 12 months combined.

			Tear break-up time (seconds)	Schirmer's test (mm/ 5min)	Fluorescein staining of cornea	Lissamine green staining of conjunctiva	Tear osmolarity (mOsm/L)	Meibomian gland dysfunction	Composite dry eye severity score based on Signs
Sjögren's syndrome	No (n=456)	Mean (SD)	3.6 (2.5)	10.1 (6.9)	3.2 (2.7)	2.6 (1.5)	302.5 (16.5)	1.45 (0.96)	0.43 (0.13)
	Yes (n=52)	Mean (SD)	3.2 (2.3)	7.5 (6.7)	5.0 (3.9)	3.6 (1.9)	310.6 (20.8)	1.61 (0.93)	0.52 (0.17)
		p*	0.19	0.01	<.001	<.001	<.001	0.16	<.001
Rosacea	No (n=426)	Mean (SD)	3.6 (2.5)	10.2 (7.2)	3.3 (2.9)	2.6 (1.6)	303.3 (17.0)	1.39 (0.93)	0.43 (0.13)
	Yes (n=109)	Mean (SD)	3.2 (1.9)	8.2 (5.6)	3.7 (2.9)	2.8 (1.6)	302.4 (16.6)	1.77 (0.96)	0.47 (0.13)
		p*	0.06	0.002	0.72	0.28	0.35	<.001	0.002
Rheumatoid arthritis †	No (n=417)	Mean (SD)	3.6 (2.5)	10.1 (6.9)	3.2 (2.7)	2.6 (1.5)	302.5 (16.5)	1.44 (0.95)	0.42 (0.12)
	Yes (n=38)	Mean (SD)	3.4 (2.0)	9.7 (7.3)	4.2 (3.4)	3.0 (1.8)	302.7 (17.1)	1.64 (1.03)	0.47 (0.14)
		p*	0.26	0.32	0.02	0.06	0.92	0.18	0.002
Daily smoking history	No (n=367)	Mean (SD)	3.6 (2.5)	10.0 (7.0)	3.3 (2.9)	2.7 (1.6)	303.3 (16.4)	1.40 (0.93)	0.43 (0.13)
	Yes (n=168)	Mean (SD)	3.3 (2.2)	9.3 (6.8)	3.6 (3.0)	2.7 (1.6)	302.6 (17.9)	1.62 (0.98)	0.45 (0.13)
		p*	0.15	0.29	0.63	0.53	0.28	0.003	0.047
Peripheral artery disease	No (n=484)	Mean (SD)	3.6 (2.5)	10.0 (7.0)	3.3 (2.8)	2.7 (1.6)	303.0 (16.8)	1.45 (0.95)	0.43 (0.13)
	Yes (n=47)	Mean (SD)	2.8 (1.6)	7.8 (6.2)	4.9 (3.3)	2.9 (1.7)	304.2 (17.9)	1.73 (0.96)	0.50 (0.14)
		p*	<.001	0.005	<.001	0.22	0.70	0.02	<.001
Thyroid dysfunction	No (n=427)	Mean (SD)	3.6 (2.5)	10.1 (7.1)	3.3 (2.8)	2.6 (1.6)	303.1 (17.1)	1.44 (0.95)	0.43 (0.13)
	Yes (n=94)	Mean (SD)	3.3 (2.3)	8.8 (6.3)	4.1 (3.2)	2.8 (1.7)	303.0 (16.2)	1.61 (0.95)	0.47 (0.15)
		p*	0.48	0.37	0.14	0.26	0.54	0.09	0.09
Osteoarthritis	No (n=394)	Mean (SD)	3.7 (2.6)	10.2 (7.2)	3.2 (2.8)	2.6 (1.6)	302.5 (16.5)	1.45 (0.95)	0.43 (0.13)
	Yes (n=134)	Mean (SD)	3.2 (1.8)	8.5 (5.7)	4.1 (3.2)	2.8 (1.6)	304.8 (18.1)	1.51 (0.98)	0.46 (0.13)
		p*	0.09	0.054	0.10	0.66	0.47	0.75	0.15
Diabetes	No (n=473)	Mean (SD)	3.5 (2.4)	9.7 (6.9)	3.4 (2.9)	2.7 (1.6)	303.0 (16.9)	1.47 (0.95)	0.44 (0.13)
	Yes (n=57)	Mean (SD)	3.6 (2.2)	10.4 (6.8)	3.7 (3.1)	2.5 (1.5)	304.2 (17.5)	1.47 (0.99)	0.43 (0.13)

		p*	0.97	0.92	0.33	0.42	0.83	0.94	0.88
Irritable bowel syndrome	No (n=476)	Mean (SD)	3.6 (2.4)	9.9 (7.0)	3.4 (3.0)	2.7 (1.6)	303.2 (16.9)	1.48 (0.95)	0.44 (0.14)
	Yes (n=44)	Mean (SD)	3.2 (2.2)	9.6 (6.9)	3.5 (2.4)	2.4 (1.5)	302.2 (16.2)	1.48 (1.01)	0.44 (0.11)
		p*	0.21	0.94	0.97	0.19	0.67	0.86	0.89
Hypercholesterolemia	No (n=344)	Mean (SD)	3.5 (2.6)	9.8 (7.1)	3.4(3.0)	2.7 (1.6)	303.0 (17.3)	1.50 (0.95)	0.44 (0.14)
	Yes (n=171)	Mean (SD)	3.5 (2.0)	9.5 (6.4)	3.5 (2.8)	2.6 (1.6)	303.5 (16.4)	1.43 (0.94)	0.43 (0.13)
		p*	0.60	0.93	0.41	0.053	0.68	0.06	0.07
Hypertension	No (n=380)	Mean (SD)	3.5 (2.5)	9.8 (6.9)	3.3 (2.8)	2.7 (1.6)	303.0 (16.7)	1.47 (0.94)	0.44 (0.13)
	Yes (n=149)	Mean (SD)	3.5 (2.2)	9.8 (6.9)	3.6 (3.1)	2.6 (1.6)	303.3 (17.5)	1.42 (0.97)	0.43 (0.14)
		p*	0.89	0.44	0.47	0.72	0.46	0.23	0.76
Hypertriglyceridemia	No (n=503)	Mean (SD)	3.5 (2.4)	9.9 (7.0)	3.4 (2.9)	2.7 (1.6)	302.9 (17.0)	1.48 (0.95)	0.43 (0.13)
	Yes (n=25)	Mean (SD)	3.4 (1.9)	8.7 (6.0)	4.1 (3.1)	2.9 (1.6)	303.4 (13.4)	1.29 (0.93)	0.45 (0.12)
		p*	0.81	0.34	0.40	0.56	0.95	0.18	0.80

*P-values for the statistical significance of association between a systemic condition and the outcome measure of interest were calculated from generalized linear regression models adjusted by age, sex, race, and visit. Generalized estimating equations (GEE) were used to account for inter-visit and inter-eye correlations within the same subject.

†Excluding patients meeting 2012 ACR criteria for Sjögren's syndrome.

Table 3.

Associations of systemic conditions with OSDI at baseline, 6 months, and 12 months combined.

	OSDI		
	No	Yes	
	Mean (SD)	Mean (SD)	p*
Sjögren's syndrome	34.3 (18.4)	38.1 (18.0)	0.16
Rosacea (facial)	34.7 (18.4)	36.8 (18.6)	0.15
Rheumatoid arthritis †	34.0 (18.3)	37.5 (18.6)	0.15
Daily smoking history	34.3 (18.6)	37.0 (18.2)	0.03
Peripheral artery disease	34.9 (18.5)	38.1 (17.8)	0.10
Thyroid dysfunction	35.4 (18.6)	34.4 (18.4)	0.52
Osteoarthritis	35.0 (18.9)	34.7 (16.9)	0.92
Diabetes	35.0 (18.2)	36.3 (19.9)	0.31
Irritable bowel syndrome	34.8 (18.4)	38.2 (19.4)	0.26
Hypercholesterolemia	35.9 (18.7)	34.1 (17.9)	0.32
Hypertension	35.6 (18.7)	34.1 (18.0)	0.65
Hypertriglyceridemia	35.2 (18.6)	34.4 (15.8)	0.84

*P-values for the statistical significance of association between a systemic condition and OSDI were calculated from generalized linear regression models adjusted by age, sex, race, and visit. Generalized estimating equations (GEE) were used to account for inter-visit and inter-eye correlations within the same subject.

†Excluding patients meeting 2012 ACR criteria for Sjögren's syndrome.