American Academy of Ophthalmology
The Eye M.D. Association

Long-term Natural History of Dry Eye Disease from the Patient's Perspective

Jeffrey P. Lienert, MS,[1] Laura Tarko, MSc,[2] Miki Uchino, MD, PhD,[3] William G. Christen, ScD,[4] Debra A. Schaumberg, ScD, OD[1,4,5]

Purpose: To describe the natural history of dry eye disease (DED), which chronically affects millions of people in the United States.

Design: This study is based on the Women's Health Study and Physicians' Health Studies, and uses questionnaires and medical records.

Participants: A total of 398 men and 386 women who reported a diagnosis of DED and responded to a questionnaire about change in disease since diagnosis.

Methods: Three subscales were developed using factor analysis of questionnaire responses: ocular surface symptoms, vision-related symptoms, and social impact. We examined correlates of worsening on each subscale, obtained medical records from a subset of 261 study participants, and examined changes in clinical signs of DED over time.

Main Outcome Measures: Worsening in ocular surface symptoms, vision-related symptoms, and social impact plus clinical signs.

Results: The average duration of DED of 10.5 years (standard deviation, 9.5 years). Worsening was reported by 24% for ocular surface symptoms, 29% for vision-related symptoms, and 10% for social impact. Factors associated with worsening on at least 2 of 3 subscales included a previous report of severe DED symptoms (odds ratio [OR], 2.17 for ocular surface symptoms; OR, 2.35 for vision-related symptoms), spending >$20 per month on DED treatments (OR, 1.80 for ocular surface symptoms; OR, 1.99 for vision-related symptoms), history of blepharitis or meibomian gland dysfunction (MGD) (OR, 1.57 for vision-related symptoms; OR, 2.12 for social impact), and use of systemic beta-blockers (OR, 1.62 for ocular surface symptoms; OR, 1.84 for vision-related symptoms; OR, 1.86 for the social impact of DED). Presence of corneal staining based on review of medical records was associated with use of level 2 or higher DED treatments (OR, 1.54; confidence interval [CI], 1.01−2.36), a previous report of severe DED symptoms (OR, 1.79; CI, 1.07−3.00), having a tear break-up test performed (OR, 2.73; CI, 1.72−4.36), and having blepharitis or MGD (OR, 0.59; CI, 0.35−0.98).

Conclusions: A proportion of patients with DED experience worsening over time, tending to report with more severe symptoms earlier in the disease. Forthcoming data on the natural history of DED from prospective studies should help clarify some of the limitations of this retrospective study. *Ophthalmology 2015;■:1−9 © 2015 by the American Academy of Ophthalmology.*

Dry eye disease (DED) is a pervasive disorder affecting an estimated 3.2 million women and 1.68 million men aged 50 years or more in the United States.[1,2] The disease is thought to progress via a series of events initiated by reduced tear production or increased tear evaporation, resulting in a destabilization of the cornea-tear interface and often accompanied by characteristic ocular surface inflammation.[3]

The diagnosis is achieved primarily through patient-reported symptoms[4] supported by clinical findings, most commonly evaluation of ocular surface staining and less commonly the Schirmer test and tear break-up time.[5] Clinical tests in DED tend to have poor reproducibility, and symptoms and signs may fluctuate. Newer techniques such as in vivo confocal microscopy and tear osmolarity also have limitations.[6]

The most common treatment for DED is artificial tears, with beneficial short-term effects on symptomatology.[7] Other therapies include topical cyclosporine A (Restasis, Allergan Inc, Dublin, Ireland),[7] topical steroids, certain antibiotics, punctual occlusion, and dietary supplementation with omega-3 fatty acids. Even with therapy, DED tends to persist, but despite data supporting the importance of DED as a public health problem,[1,2] the long-term course of the disease is not yet well characterized. The present study, using data from the well-characterized Women's Health Study and Physicians' Health Study cohorts, aims to provide needed data on this issue.

Methods

Study participants were recruited from 2 large longitudinal studies of healthcare professionals in the United States: the Women's Health Study and the Physicians' Health Studies I and II, in which we previously assessed diagnoses of DED and DED symptoms using a short questionnaire.[8,9] From these cohorts, we selected 4000 participants (N = 2500 women and N = 1500 men) who previously

http://dx.doi.org/10.1016/j.ophtha.2015.10.011
ISSN 0161-6420/15

reported a diagnosis of DED or severe dry eye symptoms. We sent this group an expanded DED questionnaire to obtain a more detailed ascertainment of DED symptoms using the Ocular Surface Disease Index (OSDI) and Symptom Assessment in Dry Eye questionnaires; comorbid conditions; dry eye treatments; cost of dry eye treatments; other medication use; patient satisfaction with DED treatments; and the impact of DED on quality of life. We classified DED medications as Level 1 or Level 2 or higher according to the schema of the International Dry Eye Workshop (2007).[3]

Approximately 1 year later, we distributed a second questionnaire to a selected subgroup of 1000 DED study participants (N = 500 women and N = 500 men) who completed the expanded DED questionnaire and had reconfirmed a diagnosis of DED. The second questionnaire (DED-Change questionnaire) ascertained patient-reported data changes in DED relative to when it was first diagnosed. Participants were oriented by asking them to think about how they feel now and then to indicate how much change they experienced (better or worse) compared with when they were first diagnosed. Responses ranged from "much worse" to "much better" and were scored on a 7-point Likert scale centered on "no change." Because of concerns about overall participant burden in these very active and comprehensive cohorts, we sent only a single request for response to the DED-Change questionnaire.

To compare and supplement the patient-reported data, we reviewed the medical records of a subset of participants who completed the DED-Change questionnaire and provided consent. The a priori goal was to review records of 250 participants. To achieve this goal, we sent out a single request for permission to review medical records to all participants who responded to the DED-Change questionnaire and received informed consent from 533. We contacted these participants' eye doctors and obtained medical record information on dry eye from 261 participants. Medical records from the remainder were not pursued. For all clinical visits on record, we abstracted data on the presence of symptoms, treatments used, clinical examination findings (e.g., ocular surface evaluation, tear break-up time, Schirmer test), and diagnoses and treatment recommendations. The study was approved by the Institutional Review Board at Partners Health Care, is Health Insurance Portability and Accountability Act compliant, and adheres to the tenets of the Declaration of Helsinki.

We performed statistical analyses using SAS v9.2 (SAS Inc, Cary, NC). We performed factor analysis, resulting in the identification of 3 subscales: ocular surface symptoms, vision-related symptoms, and social impact of DED. The subscale for ocular surface symptoms was composed of the questions on frequency and severity of symptoms, satisfaction with treatment, and overall severity of condition. The questions pertaining to vision quality, visual fluctuation, ability to work, ability to read, ability to drive during the day and at night, overall eye health, and working with a computer or automated teller machine (ATM) comprised the vision-related symptom subscale. The social impact subscale was formed from questions pertaining to work satisfaction, ability to socialize, satisfaction with socializing, overall mood, irritableness, quality of marriage, quality of friendships, and overall health. For each subscale, we summed the responses to each relevant question and then divided by the number of questions answered for that subscale, rounding to the nearest integer value. Subscale scores formed outcomes for further analyses.

For our primary analysis, we dichotomized subscale scores to compare subjects who experienced any degree of worsening with those who experienced no change or improvement. Multivariate logistic regression models were used to calculate odds ratios (ORs) and 95% confidence intervals (CI) for associations of variables with the measures of patient perceptions of change. We also explored models comparing improvement versus no change and worsening, as well as ordinal logistic regression models using collapsed scores of worsening, no change, and improvement, and models preserving the 7-point Likert scale. The latter 2 methods were found to violate the proportional odds assumptions and were therefore abandoned. The first 2 methods gave qualitatively similar results, so we report results based on any worsening versus no change or improvement.

We selected variables for consideration a priori based on the literature and our knowledge of DED. We adjusted for age and sex, and then extended models initially using a stepwise procedure to consider inclusion of use of level 2 or higher DED treatments,[3] frequency of use of artificial tears, spending at least $20 per month on DED treatment, history of blepharitis or meibomian gland dysfunction (MGD), corneal ulcer, use of topical glaucoma medications, ocular surgery (cataract, strabismus, glaucoma, refractive surgery), history of dry mouth, allergy, rosacea, autoimmune disease (Sjögren's, lupus, and rheumatoid arthritis), fibromyalgia, diabetes, hypertension, anxiety, treated and untreated depression, use of systemic beta-blockers and antihistamines, and an indicator of overall self-reported health. A history of severe symptoms was ascertained from participant responses of experiencing *both* symptoms of dryness and irritation constantly or often on the short dry eye symptom questionnaire we periodically administered since 1997. As we have previously done, we classified participants as having severe symptoms if they reported.[1] After fitting an initial set of stepwise models, we manually added and excluded variables on the basis of clinical knowledge and past literature. Although statistical significance varied between one outcome and another, relationships between covariates and each outcome were qualitatively consistent, so we consequently used a homogenous set of covariates for each outcome measure to enhance comparability.

For clinical record data, we used longitudinal generalized estimating equations to obtain estimates of the probability of an observed change in the frequency of corneal staining/superficial punctate keratopathy (SPK) over time. In these models, we used a logit link function and binomial distribution, compared exchangeable and autoregressive covariance matrices, and observed little change in the empirical standard error estimates.

Results

We received responses from 784 of 1000 (78%) men (N = 398) and women (N = 386) who were sent a single request to complete the DED-Change questionnaire. There was no significant difference in OSDI scores among those who did versus did not return the DED-Change questionnaire ($P = 0.53$). Men were aged 60.2 to 97.3 years and had an average duration of DED of 10.5 years (standard deviation, 9.5 years). Women were aged 61.2 to 89.9 years, with an average duration of DED of 14.5 years (standard deviation, 7.7 years) (Table 1). More women (68.1%) than men (34.7%) had a history of severe DED symptoms ($P < 0.0001$).

Patient-Reported Outcomes

Overall, the median scores were zero for responses to all DED-Change questions, and only nighttime driving showed significant ($P < 0.05$) worsening by single-sample *t* test (data not shown). The 3 DED-Change subscale scores were correlated with one another (correlation coefficients ranging from 0.50 to 0.76). Consistent with the median scores, the most common response of study participants was to report no change since the time of their initial DED diagnosis (Fig 1): 32.0% for ocular surface symptoms, 52.3% for vision-related symptoms, and 71.1% for social impact. Some