

The Relationship between Habitual Patient-Reported Symptoms and Clinical Signs among Patients with Dry Eye of Varying Severity

Carolyn G. Begley,¹ Robin L. Chalmers,² Linda Abetz,³ Kitty Venkataraman,⁴ Polyxane Mertzanis,³ Barbara A. Caffery,⁵ Christopher Snyder,⁶ Timothy Edrington,⁷ Daniel Nelson,⁸ and Trefford Simpson⁹

PURPOSE. To investigate symptom profiles and clinical signs in subjects with dry eye and normal subjects in a cross-sectional multicenter study.

METHODS. Subjects aged 35 to 65 were recruited according to dry eye diagnostic codes and telephone interview and completed the Dry Eye Questionnaire 2001, among others, and underwent dry eye clinical tests.

RESULTS. Subjects (122) included 28 control subjects (C), 73 with non-Sjögren's keratoconjunctivitis sicca (non-SS KCS) and 21 with Sjögren's syndrome (SS). Subjects with SS or non-SS KCS reported discomfort and dryness most frequently and that many symptoms worsened over the day and were quite bothersome. Groups were significantly different in corneal fluorescein staining, conjunctival lissamine green staining, Schirmer 1 tear test, and tear break-up time (TBUT; χ^2 and Kruskal-Wallis, $P < 0.0001$). Statistically significant, but moderate, correlations were found between the frequency and evening intensity of dryness and discomfort and TBUT, Schirmer's tear test, overall corneal fluorescein staining, and temporal lissamine green conjunctival staining (Spearman $r = 0.31-0.45$, $P < 0.01$). Symptoms were moderately to highly correlated with the clinician's global grading of severity and highly correlated to patient's self-assessment of severity ($r = 0.46-0.86$, $P < 0.0001$), whereas signs showed lower correlations ($r = 0.22-0.46$, $P < 0.0001$).

CONCLUSIONS. Subjects with SS or non-SS KCS reported frequent and intense ocular surface symptoms in the evening, some of which correlated moderately with clinical test results. The global clinician grade of dry eye correlated more highly with patient symptoms than did clinical signs, suggesting that patient symptoms influence dry eye diagnosis and grading of dry

eye more than clinical test results. (*Invest Ophthalmol Vis Sci.* 2003;44:4753-4761) DOI:10.1167/iovs.03-0270

Dry eye is a prevalent condition that remains a diagnostic challenge.¹⁻³ The National Eye Institute Industry Workshop defined dry eye as a "tear deficiency or excessive tear evaporation that causes damage to the interpalpebral ocular surface and is associated with symptoms of ocular discomfort," but it was acknowledged that clinical signs or symptoms may be absent.⁴ Many researchers have shown that clinical tests measuring tear deficiency and surface damage are only weakly associated with patient symptoms,^{2,3,5} and many symptomatic patients without Sjögren's syndrome (SS) may demonstrate few clinical signs.^{1,6}

Primary SS is a severe form of aqueous-deficient dry eye that is usually found in combination with xerostomia, the presence of autoantibodies, and a positive salivary gland biopsy.^{7,8} Most SS patients show decreased lacrimal function and ocular surface damage, and clinical signs are therefore usually positive in these patients. However, even among these severely affected patients, there can be a poor correlation between symptoms and clinical signs.⁵

This lack of agreement between the severity of dry eye symptoms and clinical signs renders symptoms an important component of the dry eye diagnosis.^{9,10} Although several dry eye questionnaires are available, most do not extensively measure dry eye symptoms,^{1,3,5,8,11,12} and such an appraisal may be necessary to discover associations between symptoms and signs. In earlier studies, we have shown the Dry Eye Questionnaire (DEQ) to be a useful tool for measuring a distinct symptom profile in groups of patients with SS or non-SS dry eye and normal subjects. In contrast to other dry eye questionnaires, the DEQ extensively queries both symptom frequency and diurnal intensity and has demonstrated that many patients with dry eye report an increase in symptoms of ocular irritation at the end of the day^{13,14} (Begley CG, et al. *IOVS* 2002;43:ARVO E-Abstract 77).

In this investigation, a revised version of the questionnaire, the DEQ 2001, was tested in patients who received concurrent clinical examinations. The purpose of this study was to measure the habitual patient-reported symptom profile among patients with dry eye and compare to clinical measures. The data were gathered as part of a larger study designed to develop and validate a comprehensive patient-reported instrument for measuring the impact of dry eye on everyday life (Mertzanis P, et al. *IOVS* 2002;43:ARVO E-Abstract 74).

METHODS

This study was conducted in six clinical sites in North America and included 161 subjects with dry eye and 49 control subjects. After approval by local investigational review boards, each clinic recruited up to 43 subjects older than 18 years. Recruited subjects with dry eye

From the ¹School of Optometry, Indiana University, Bloomington, Indiana; ²Atlanta, Georgia; ³MAPI Values, Boston, Massachusetts; ⁴Alcon Research, Ltd., Fort Worth, Texas; ⁵Toronto, Ontario, Canada; the ⁶School of Optometry, University of Alabama at Birmingham, Birmingham, Alabama; the ⁷Southern California College of Optometry, Fullerton, California; the ⁸Department of Ophthalmology, University of Minnesota, Minneapolis, Minnesota; and the ⁹School of Optometry, University of Waterloo, Waterloo, Ontario, Canada.

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Corresponding author: Carolyn G. Begley, Indiana University, School of Optometry, 800 E. Atwater Street, Bloomington, IN 47405; cbegley@indiana.edu.

were typical of the participating clinic's patient base. Thus, some centers primarily recruited subjects with SS, and other clinics primarily recruited subjects with non-Sjögren's syndrome keratoconjunctivitis sicca (non-SS KCS). Control subjects were recruited from five of the six clinical sites. Because some dry eye symptoms and many ocular signs may be affected by age, this analysis includes data only from subjects in the age range between 35 and 65 years, inclusive. Subjects outside this age range were excluded.

Subject Recruitment

Potential study participants with non-SS KCS were contacted by interviewers at each site, from lists of patients whose records showed dry eye diagnostic codes (International Classification of Diseases [ICD]-9-CM 370.33 or 375.15), and screened by telephone, with a series of questions about the frequency of dryness, previous dry eye diagnosis, and self-assessment of dry eye. Subjects with non-SS KCS were included only if they were symptomatic at least "sometimes," and either reported a previous clinical diagnosis of dry eye or self-assessed presence of dry eye. Potential subjects with SS were contacted if their record showed the ICD-9 diagnostic code for SS (710.2) with evidence of meeting the San Diego criterion,⁷ including a positive salivary gland biopsy. For inclusion in the study, subjects with SS were screened with the same minimum criteria for answers to the screening questions as subjects with non-SS KCS.

Control subjects were recruited from lists of patients who did not have diagnostic codes for dry eye. These patients were asked the same series of screening questions, except that, to be included in the study, they had to report the symptom of dryness less often than "sometimes." They could have no previous dry eye diagnosis and no self-assessment of the presence of dry eye. Therefore, although control subjects were not completely asymptomatic, they were intentionally recruited with no history of dry eye and a distinctly lower symptom profile than the subjects with dry eye. Current contact lens wearers and any subjects with a language limitation that would affect understanding and responding to written questionnaires were excluded from the study.

Study Visit Procedures

Qualified subjects were scheduled for two study visits: a baseline visit and a second visit approximately 2 weeks later. At the baseline visit, informed consent was obtained and subjects completed questionnaires and underwent a series of clinical tests for dry eye. The second study visit involved only the completion of questionnaires. The study adhered to the tenets of the Declaration of Helsinki and was approved by each site's Institutional Review Board. Questionnaires included, in the order administered, a demographic form (first visit only), the Impact of Dry Eye on Everyday Life (IDEEL) questionnaire (Mertzanis P, et al. *IOVS* 2002;43:ARVO E-Abstract 74), the Short Form-36 (SF-36),¹⁵ a revised Dry Eye Questionnaire (DEQ 2001), the Eye Questionnaire-5D (EQ-5D; Mertzanis P, et al. *IOVS* 2002;43:ARVO E-Abstract 74), and the dry eye change scale (second visit only). The DEQ 2001 is a slight revision of the DEQ, which was validated in a large unselected clinical population and against dry eye diagnosis.^{13,14} The content of the habitual symptom questions cited herein has not changed, except that questions regarding how much symptoms "bothered" subjects have been added. The DEQ 2001 is a self-administered habitual symptom questionnaire that includes categorical scales to measure the frequency, diurnal intensity, and intrusiveness of common ocular surface symptoms. A sample habitual symptom question is illustrated in Figure 1.

During the first study visit, dry eye clinical tests were performed by clinicians masked as to the recruited subject group (control [C], non-SS KCS, or SS). These tests were performed in the following order: biomicroscopic grading of bulbar redness,¹⁷ the Schirmer 1 tear test without anesthesia, fluorescein tear break-up time (TBUT), overall and zone-by-zone grade of corneal fluorescein staining,^{18,19} Oxford grading²⁰ of conjunctival lissamine green staining (observed with a no. 25 red Hoya filter), grading of lid redness and crusting,¹⁷ the number of

6. Questions about EYE DISCOMFORT:

a. During a typical day in the past week, **how often** did your eyes feel discomfort?

- 0 Never
- 1 Rarely
- 2 Sometimes
- 3 Frequently
- 4 Constantly

When your eyes felt discomfort, **how intense** was this feeling of discomfort...

b. Within the first two hours of getting up in the morning?

Never <u>have it</u>	Not at All <u>Intense</u>			Very <u>Intense</u>	
0	1	2	3	4	5

c. At the end of the day, within two hours of going to bed?

Never <u>have it</u>	Not at All <u>Intense</u>			Very <u>Intense</u>	
0	1	2	3	4	5

d. When your eyes felt discomfort, **how much** did the discomfort bother you?

Never <u>have it</u>	Not at All <u>bothered</u>			Extremely <u>bothered</u>	
0	1	2	3	4	5

FIGURE 1. A sample habitual symptom question from the DEQ 2001.

plugged meibomian glands out of four glands,²¹ and lid margin irregularity. All clinical grading used a 0 to 4 scale, and the Schirmer 1 tear test and TBUT were timed with a stopwatch. Lid margin irregularity was graded as present or absent.

The clinician then discussed the subject's symptoms after completing all clinical tests and without discussing the subject's assignment to a study group. A global clinician assessment of the severity of the dry eye condition was made, grading it as none, mild, moderate, or severe. Data from subject global self-assessment of dry eye were included on the demographic form and were gathered before any clinical testing. The present analysis includes only the DEQ 2001 questionnaire and the

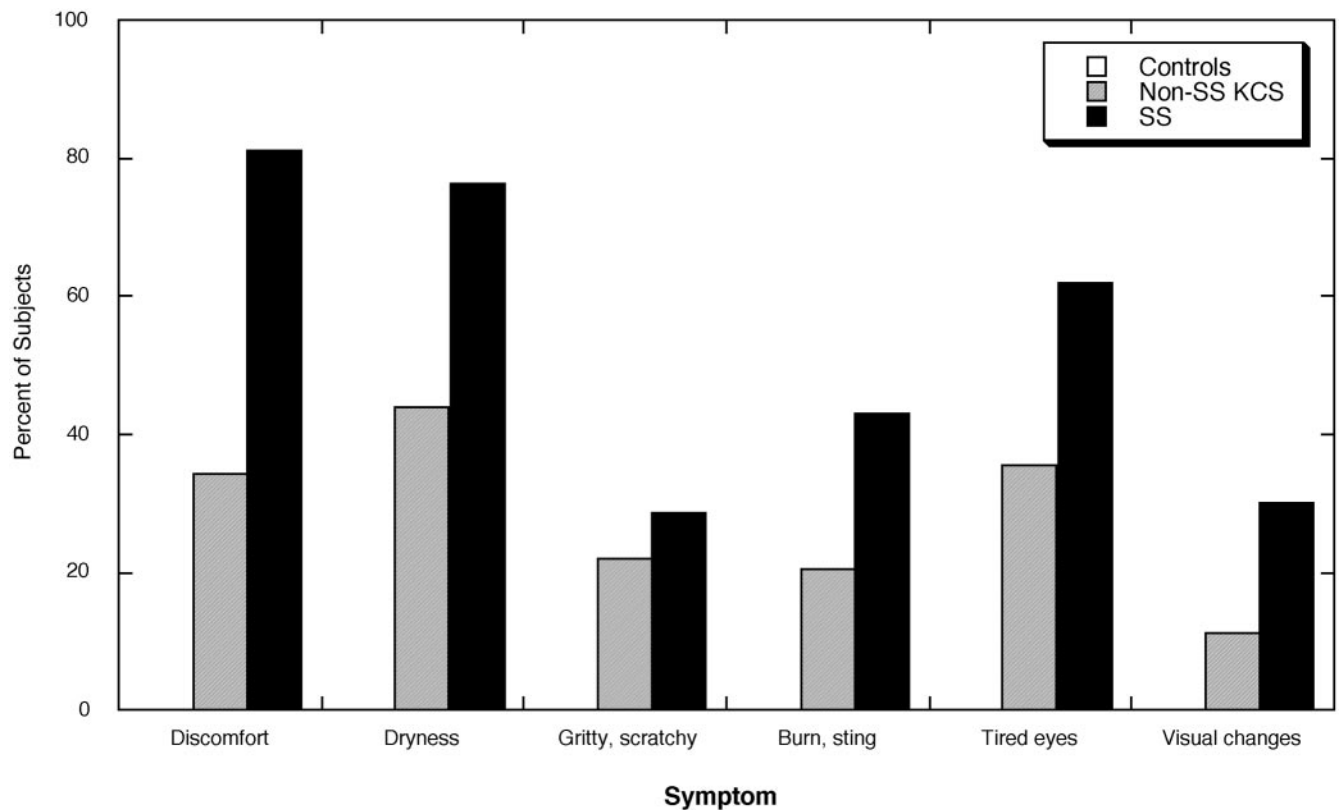


FIGURE 2. Frequency of frequently occurring to constantly occurring symptoms.

clinical and self-assessment data gathered at the first study visit. Other data will be presented elsewhere.

Statistical Analysis

Data are analyzed by recruited severity for subjects with SS or non-SS KCS and control subjects. For analysis of clinical signs, one eye of each subject was randomly selected to avoid data collection bias.

Pearson χ^2 tests were used to analyze symptom data and clinical grading variables. Corneal fluorescein staining zones were analyzed by the Friedman ANOVA by ranks, and nasal and temporal conjunctival lissamine green staining was compared using the Wilcoxon signed ranks test. The Kruskal-Wallis ANOVA was used to compare Schirmer 1 test results and TBUTs among groups, and, if significant, paired comparisons were made using the Bonferroni *t* procedure. The Spearman rank correlation was used to determine correlations between graded variables.

RESULTS

The 122 subjects in the age-restricted group included 28 C, 73 non-SS KCS, and 21 SS. Ages were similar across recruited groups, but gender distributions were unequal among groups. Sixty-eight percent of C, 87% of non-SS KCS, and 100% of the SS group were women, with average ages of 47, 52, and 53 years, respectively. Data were analyzed and are displayed by recruited group severity, which was in close agreement with clinical grading. Ninety percent of control subjects received a clinician grade of "none," with 10% receiving a "mild" grade. Among subjects with non-SS KCS, 8% were graded as none and 92% as mild (66%) or moderate (26%). Twenty-four percent (24%) of the subjects with SS received clinician grades of mild, 19% moderate, and 57% severe.

Symptoms

DEQ 2001 habitual symptom questions queried frequency, morning and evening intensity, and how much the symptom bothered subjects (Fig. 1). Figure 2 shows the percentage of subjects with frequent to constant symptoms for all symptoms queried in the DEQ2001. As the figure illustrates, none of the control subjects reported frequent to constant symptoms. The most frequently reported symptom among subjects with non-SS KCS was eye dryness, followed by discomfort and tired eyes. The same three symptoms were reported at a much higher frequency among subjects with SS. For all symptoms, recruited groups reported symptoms at significantly different rates (χ^2 range: 38.4–112.1, $P < 0.0001$).

The DEQ 2001 asked subjects to report the intensity of their symptoms within 2 hours of getting up in the morning and at the end of the day (Fig. 1). Figure 3 illustrates the diurnal change in the proportion of subjects who reported moderate to severe symptoms (intensity rating, 3–5) for all subject groups. For all symptoms, both SS and non-SS KCS groups showed an increase in the number of subjects who reported moderate to severely intense symptoms in the evening. For example, 67% of subjects with SS and 32% of those with non-SS KCS reported moderate to severe discomfort in the morning versus 90% in the SS group and 60% non-SS KCS group in the evening. The symptom of tired eyes also increased markedly over the course of the day in both the SS and non-SS KCS groups. Some symptoms, such as dryness among subjects with SS, did not increase as markedly, due to the large percentage of subjects already highly symptomatic in the morning. Most control subjects, who were originally selected for minimal dry eye symptoms, did not show moderate to severely intense symptoms during either period.

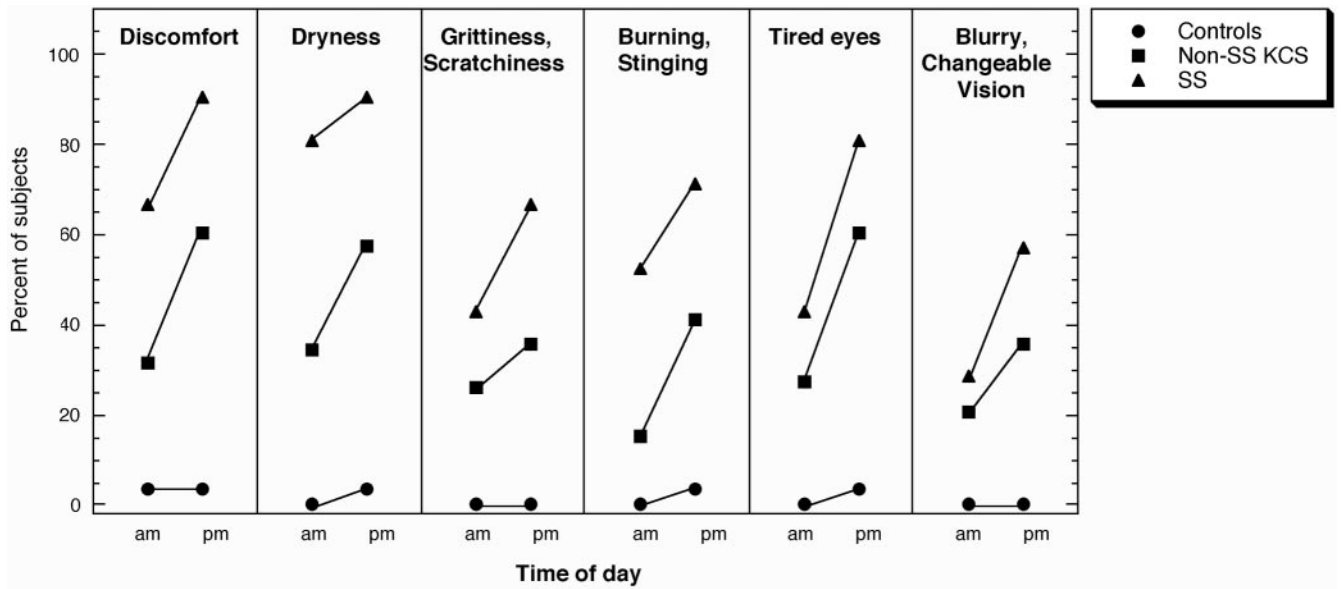


FIGURE 3. Frequency of moderate to intense symptoms at two times of day.

Figure 4 shows the percentage of subjects who reported being moderately to extremely bothered by symptoms (ratings, 3-5). As with symptom frequency and intensity, more subjects with SS reported being bothered by symptoms than did those with non-SS KCS. More than 75% of subjects with SS and 55% of those with non-SS KCS reported being moderately to extremely bothered by discomfort, dryness, or tired eyes. In both groups, visual changes were reported as the least bothersome symptom. Note that the relative frequency of symptoms was

often far less than the degree to which subjects with dry eye reported being bothered by symptoms. As Figure 4 shows, few control subjects reported symptoms to be moderately to extremely bothersome.

Clinical Signs

Schirmer 1 tear test results are shown in Figure 5A. Box-and-whisker plots are used to display Schirmer tear test and TBUT

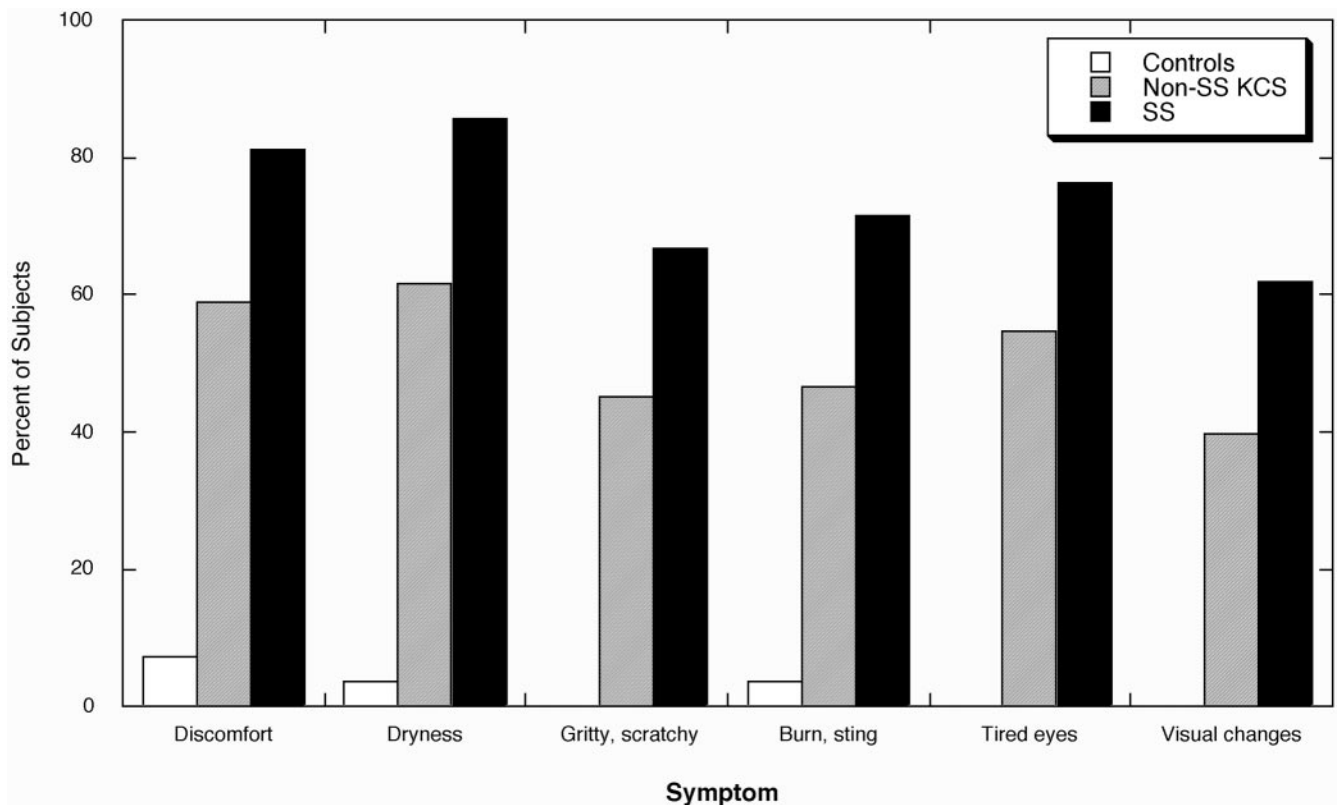


FIGURE 4. Frequency of moderately to extremely bothersome symptoms.

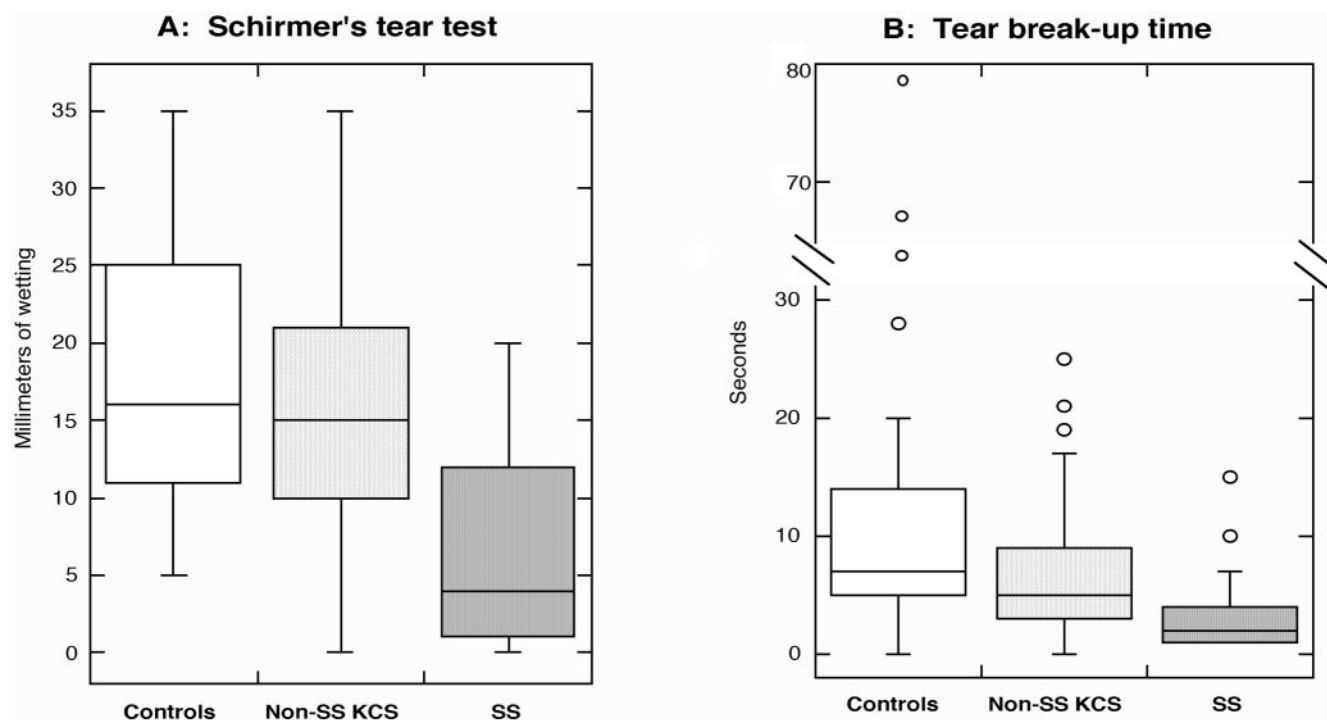


FIGURE 5. Box-and-whisker plots of (A) Schirmer 1 tear test results and (B) TBUT.

data because of unequal sample sizes among groups and skewed distributions. Median wetting values are shown by horizontal lines in Figure 5A. Average wetting values were 6.8 ± 6.5 mm for SS, 17.1 ± 10.0 mm for non-SS KCS, and 18.1 ± 9.6 mm for C subjects. There was a significant difference among groups (Kruskal-Wallis ANOVA, $P < 0.0001$), with SS subjects showing significantly lower Schirmer 1 test scores than the other two groups (Bonferroni multiple comparisons, $P < 0.0001$).

The box-and-whisker plots in Figure 5B illustrate TBUTs for the three groups. The average TBUT for the subjects with SS was 3.7 ± 3.7 seconds; for patients with non-SS KCS, 6.6 ± 5.5 seconds; and for the C subjects, 14.4 ± 19 seconds, with a significant difference between all groups (Kruskal-Wallis ANOVA, $P < 0.0001$; Bonferroni multiple comparisons, $P < 0.001$).

Figure 6 shows frequency distributions for the clinical signs graded on a 0 to 4 scale. Slit lamp biomicroscopic evaluation of bulbar redness showed that subjects with SS had significantly higher grades than the other two groups (Fig. 6A, Pearson $\chi^2 = 15.3$, $P = 0.018$). However, there was great overlap among groups; the statistical significance appeared to be due to the lack of subjects with SS who had grade 0 bulbar redness.

The overall grades of fluorescein staining for C subjects and subjects with non-SS KCS or SS are shown in Figure 7. There was a significant difference among groups (Pearson $\chi^2 = 30.5$, $P = 0.0001$). Very few C subjects or subjects with non-SS KCS had grade 2 corneal fluorescein staining, whereas 42.9% of the subjects with SS had grade 2 or higher staining. Figure 7 shows the percentage of subjects with grade 2 or higher corneal fluorescein staining in each corneal zone. Among C subjects, almost none had grade 2 or higher nasal and inferior corneal staining. More subjects with non-SS KCS showed central and inferior corneal staining (6%–14%), and a yet higher percentage of subjects with SS showed nasal and inferior corneal staining (29%–43%). When all grades of corneal staining were considered, there was a significant difference among corneal zones in all subject groups (Friedman, $P < 0.02$).

Temporal and nasal lissamine green staining is shown in Figures 6D and 6E, respectively, and was significantly different among subject groups (Pearson's χ^2 temporal = 43.0, $P = 0.0001$; nasal = 47.3, $P = 0.0001$). Grades 3 to 4 nasal lissamine green staining were present in 57.1% of the subjects with SS, whereas only 8.2% of those with non-SS KCS and no C subjects showed staining at that severity (Fig. 6E). The temporal zone showed slightly less severe staining, with 48% of the SS and 7% of non-SS KCS groups and none of the C group showing staining at grades 3 to 4 (Fig. 6D). When nasal and temporal zones of lissamine green staining were compared within each group, all showed a significant difference between zones (Wilcoxon signed ranks, $P < 0.001$).

There was no significant difference among groups in the degree of lid redness (data not shown), with 14% of the SS and non-SS KCS groups having redness at grade 2, whereas 7% of the C subjects had grade 2 redness. (Pearson's $\chi^2 = 2.9$, $P = 0.57$). There was also no difference among groups in the degree of lid crusting, with approximately 9% of the dry eye groups and 4% of C having grade 2 crusting or greater (Fig. 6C, Pearson $\chi^2 = 8.6$, $P = 0.20$). Figure 6F shows the number of plugged meibomian glands out of four glands on the lower lid margin; there was no significant difference among groups (Pearson $\chi^2 = 5.6$, $P = 0.69$). C subjects had slightly less lid margin irregularity than subjects with dry eye, with approximately 40% of C subjects with lid margin irregularity compared with 65% of subjects with non-SS KCS and 58% those with SS (Pearson $\chi^2 = 4.2$, $P = 0.12$).

Correlations between Variables

Table 1 shows the correlations among all subjects between some of the clinical signs measured in this study. Many of the clinical signs, including the lid assessments, showed very low and nonsignificant correlations with other signs and are not represented. The highest correlation was between the overall and inferior zone corneal staining grade. Other corneal zones are not listed, but many correlated highly with each other and

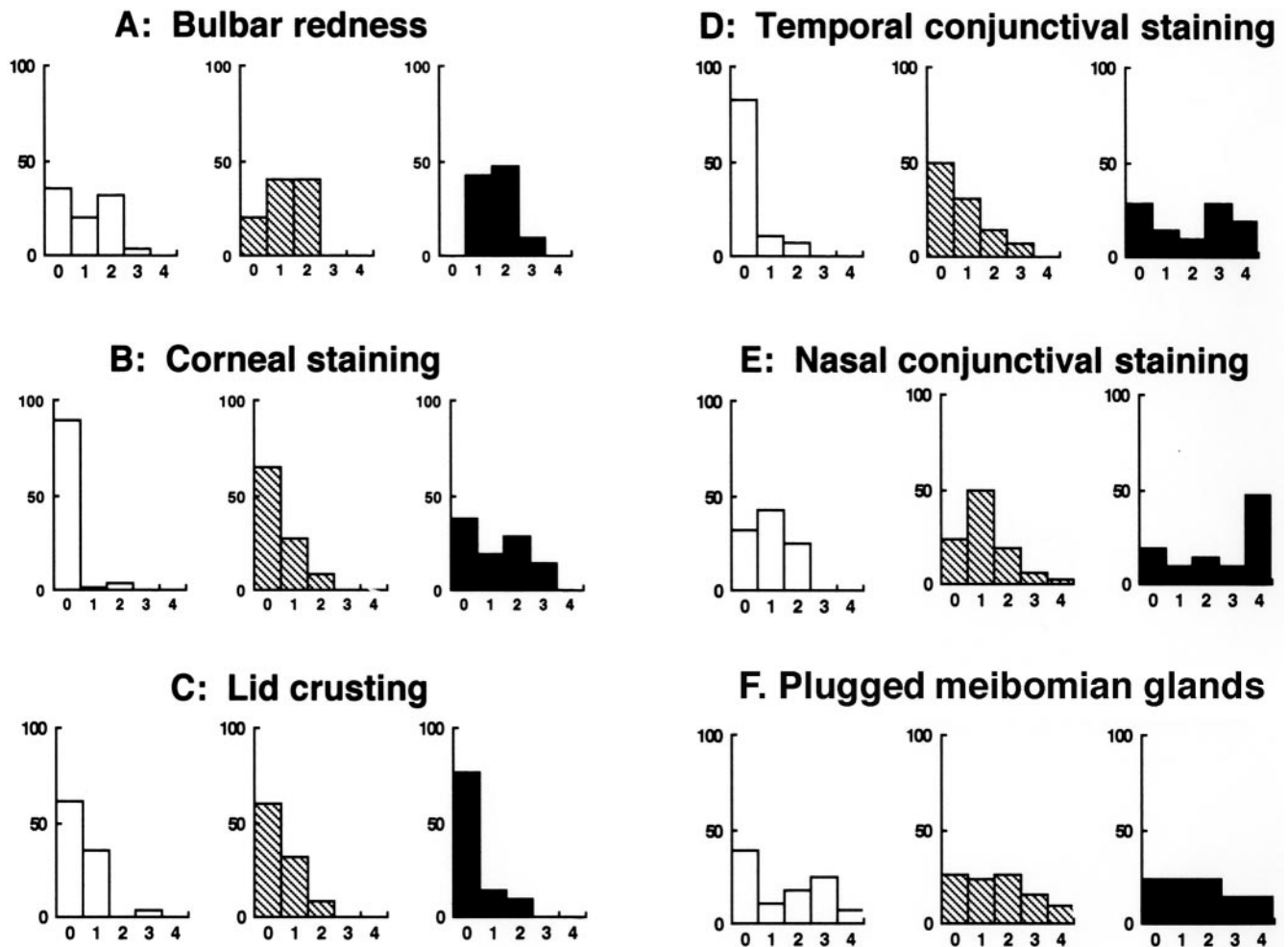


FIGURE 6. Frequency distributions of graded clinical signs: (□) C, (▨) non-SS KCS, and (■) SS. (A) Bulbar redness, (B) overall corneal fluorescein staining, (C) lid crusting, (D) temporal lissamine green conjunctival staining, (E) nasal lissamine green conjunctival staining, and (F) number of plugged meibomian glands of the four glands.

the overall grade of corneal staining. For example, intensity of nasal zone corneal staining correlated highly with the inferior zone (Spearman, $r = 0.625, P < 0.0001$) and overall staining (Spearman, $r = 0.663, P < 0.0001$), whereas superior and central zone staining showed a range of correlations with other zones (Spearman, $0.207 < r < 0.589, P < 0.02$).

As Table 1 shows, corneal staining had a low to moderate correlation with TBUT and conjunctival lissamine green staining. There were also statistically significant, but low correlations between other signs, as noted in Table 1. Bulbar redness was included in Table 1 as an example of a clinical sign with very low correlation to other clinical tests. Lid assessments of

redness, crusting, plugged meibomian glands, and irregular margins showed similar patterns of low to no statistically significant correlation with other test results. Many clinical signs demonstrated low to moderate correlation with the global clinician grade of dry eye severity, but poorer correlation with the subjects' self-assessment of severity.

Table 2 shows the correlation between clinical signs and a sample of the most highly correlated habitual symptoms. Although many correlations were statistically significant, the highest correlations were moderate and occurred between inferior corneal zone staining and the frequency and evening intensity of discomfort and dryness. Similar low to moderate

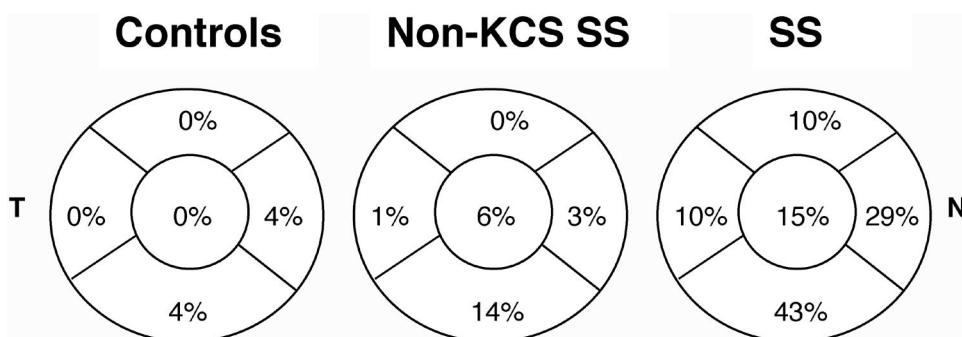


FIGURE 7. Percentage of subjects having grade 2 or higher corneal fluorescein staining.

TABLE 1. Correlations among Clinical Signs

	Bulbar Redness	Schirmer Test	Fluorescein Break-up Time	Overall Fluorescein Staining	Inferior Fluorescein Staining	Nasal Lissamine Green Staining	Temporal Lissamine Green Staining	Clinician Grade	Self-Assessed Severity
Bulbar redness									
Schirmer test	-0.053								
Fluorescein break-up time	-0.293**	0.264**							
Overall fluorescein staining	0.201*	-0.197*	-0.439**						
Inferior fluorescein staining	0.208*	-0.148	-0.415**	0.794**					
Nasal lissamine green staining	0.111	-0.291**	-0.223**	0.305**	0.325**				
Temporal lissamine green staining	0.161	-0.271**	-0.386**	0.412**	0.381**	-0.535**			
Clinician grade	0.262**	-0.394**	-0.482**	0.447**	0.464**	0.429**	0.453**		
Self-assessed severity	0.242**	-0.323**	-0.353**	0.273**	0.351**	0.220*	0.336**	0.780**	

Bold signifies moderate to high correlation (>0.400); * $P \leq 0.05$; ** $P \leq 0.01$.

correlations occurred between those symptoms and the Schirmer tear test results, TBUT, and overall corneal staining. Intensity of morning dryness correlated the most highly with the Schirmer test result. There were also low to moderate correlations between inferior zone corneal staining and tired eyes in the evening and between temporal lissamine green staining and the frequency of dryness. Other correlations between clinical signs and symptoms in Table 2 were often low, although statistically significant. However, Table 2 shows that the clinician grading of dry eye severity correlated highly with the frequency and intensity of many symptoms. Indeed, the correlation of 0.460 with tired eyes in the morning (Table 2) was the lowest correlation between clinician grade and response to any symptom. The correlations between clinical signs and how much symptoms bothered subjects was not included in Table 2, but correlations were similar to those of frequency and intensity questions. Self-assessment of dry eye correlated even more highly with all dimensions of habitual symptoms, compared with the clinician global grade.

DISCUSSION

We selected subjects with dry eye for this study based on previous dry eye diagnosis and current symptoms and com-

pared them with carefully selected control subjects with few or no symptoms of ocular irritation. This design yielded a control population that was much less symptomatic than subjects with dry eye, but these distinctions were less evident by many of the standard clinical measures. These results, in combination with the low to moderate correlations between symptoms and signs, reinforce the idea that symptomatic patients with dry eye are not always identifiable based on positive clinical signs, and that standardized, precise measurement of symptoms is an important part of a dry eye diagnosis.^{9,10}

The three recruited groups of subjects in this study—C, non-SS KCS, and SS—provided a broad range of disease severity, from the mostly asymptomatic control subjects to mild, moderate, and severely affected subjects with dry eye. This study design allowed for a sharp distinction between the symptoms of control subjects and subjects with dry eye and appears to be an effective method for recruiting clearly defined groups for clinical studies. In this study, control subjects were recruited according to their dissimilarity to the subjects with dry eye, and were therefore less symptomatic than an unselected clinical population surveyed in a previous study.¹³ We displayed and analyzed the data by recruited group, which showed 90% or higher agreement with masked clinical grading.

TABLE 2. Correlations between Clinical Signs and Habitual Symptoms

	Discomfort			Dryness			Tired Eyes		
	Frequency	AM Intensity	PM Intensity	Frequency	AM Intensity	PM Intensity	Frequency	AM Intensity	PM Intensity
Bulbar redness	0.168	0.165	0.144	0.133	0.168	0.132	0.103	0.079	0.137
Schirmer test	-0.307**	-0.323**	-0.338**	-0.321**	-0.396**	-0.317**	-0.195*	-0.240**	-0.192*
Fluorescein break-up time	-0.316**	-0.252**	-0.366**	-0.354**	-0.273**	-0.341**	-0.215*	-0.200*	-0.240**
Overall fluorescein staining	0.369**	0.211*	0.367**	0.354**	-0.312**	0.345**	0.230*	0.228*	0.242**
Inferior fluorescein staining	0.406**	0.254**	0.454**	0.405**	0.283**	0.420**	0.254*	0.296**	0.338**
Nasal lissamine green staining	0.127	0.073	0.165	0.168	0.131	0.158	0.110	0.007	0.038
Temporal lissamine green staining	0.281**	0.160	0.282**	0.330**	0.218*	0.286**	0.200*	0.159	0.164
Clinician grade	0.749**	0.604**	0.704**	0.760**	0.676**	0.738**	0.518**	0.460**	0.574**
Self-assessed severity	0.786**	0.727**	0.783**	0.856**	0.783**	0.796**	0.631**	0.623**	0.674**

Bold signifies moderate to high correlation (>0.400); * $P \leq 0.05$; ** $P \leq 0.01$.

As expected, the most symptomatic group of subjects in this study entered with a diagnosis of SS. Many subjects with SS reported that the symptoms queried on the DEQ 2001 were frequent, intense, and bothersome. Among these severely affected subjects, clinical signs were generally positive. Many current dry eye clinical tests were originally developed to measure tear stability, aqueous deficiency, and ocular surface damage in severely affected patients. Our results were consistent with other studies, in which patients with SS typically demonstrated aqueous deficiency and surface damage, resulting in minimal wetting of the Schirmer's tear strip, low TBUTs, and positive conjunctival surface staining.^{4,5,8,21} We used lissamine green dye, rather than rose bengal, to stain damaged conjunctiva,²² due to its similar staining pattern and greater patient acceptance.^{20,23} All clinical sites also used a red filter to enhance viewing of conjunctival staining,²⁴ and used the log-linear Oxford scale to assess the grade.²⁰ Although this combination of methods may have affected our results and made them difficult to compare to studies using the method developed by van Bijsterveld,²⁵ our conjunctival staining results are very similar in trend to many other studies.^{2,5,8,21}

Although others have reported that corneal fluorescein staining among patients with SS can be high,²¹ our results are the first, to our knowledge, to demonstrate that most of the clinically significant staining (grade ≥ 2) occurs in the inferior and nasal quadrants of corneas in subjects with SS. The reason for this distribution is unclear, but it is notable that lissamine green staining was also generally greater in the nasal than in the temporal conjunctiva of subjects with SS. This corneal and conjunctival staining distribution may be due to a number of factors, including rubbing of irritated eyes in the nasal and inferior interpalpebral area. The autoimmune etiology of SS could also play a role.²⁶ Inflammatory by-products in the tears of patients with SS may be in contact with the nasal and inferior portions of the cornea longer because of tear drainage routes, and the contact may be prolonged by the reduced tear turnover in these patients.²¹

The clinical test results for the subjects with non-SS KCS showed less severe and, in some cases, more variable disease. Although many in the non-SS KCS group were symptomatic, they had a wide range of Schirmer 1 test scores, TBUTs, and ocular surface staining. Because the Schirmer 1 test is considered specific for aqueous-deficient dry eye⁴ and was not required for entrance in this study, it is not surprising that subjects with non-SS KCS did not show significantly lower Schirmer 1 values than control subjects. This result is similar to other studies involving symptomatic patients with dry eye who had less severe conditions.^{1,2} Those with non-SS KCS in our study also showed lower TBUTs and increased corneal nasal lissamine green staining over temporal staining, although the degree was not as severe as among subjects with SS. Patients with non-SS KCS showed increased fluorescein staining in the inferior corneal zone, which has been noted among normal patients¹⁸ and contact lens wearers.¹⁹

Some clinical tests were more useful than others as clinical criteria to categorize patients with dry eye. Although subjects with SS had more bulbar redness, there was no significant difference among groups. Thus, there was not a clear criterion for use in a clinical setting. The lid signs provided similar overlap among groups, perhaps because we did not specifically seek a group of subjects with meibomian gland disease.²¹ Corneal fluorescein staining, as measured in an overall judgment, correlated highly with inferior zone staining, and thus gave a similar ability to differentiate between the groups.¹⁹

In this study, the highest correlations between clinical signs occurred between measures of corneal and conjunctival staining, which correlated inversely with TBUT. This is an interesting finding because TBUT measures tear stability over the

corneal surface only. It is unknown how it may relate to stability of the tear film over the conjunctival surface. When symptoms were also considered, ocular discomfort and dryness showed higher correlations with corneal compared to conjunctival staining and correlated inversely with TBUT and the Schirmer 1 test. This pattern of correlations suggests that patients with an unstable or inadequate tear film report more symptoms of ocular irritation,²¹ but that resultant damage to the more sensitive cornea is more likely to produce symptoms.

In this study, subject recruitment was partially based on symptoms, and it is therefore not surprising that symptoms were greater among subjects with dry eye than control subjects. However, a small number of control subjects were symptomatic, despite recruitment efforts. This may be because our recruitment was based on the frequency of dryness. Although none of the control subjects reported frequent to constant dryness, a few control subjects reported a moderate to intense level of symptoms, perhaps indicating that frequency and intensity questions are not interchangeable.

In the SS and non-SS KCS groups, discomfort and dryness were the most frequent and intense symptoms. Subjects with dry eye reported that their symptoms increased later in the day, as we have reported in other studies,^{13,14} suggesting an environment- or task-related etiology for dry eye symptoms.²⁷⁻²⁹ The diurnal increase may be related to the symptom of tired eyes, which also increased markedly in intensity at the end of the day and is similar to the symptom of ocular fatigue described by Toda et al.³⁰ The symptoms queried by the DEQ 2001 appeared to bother many subjects with dry eye at least moderately, even if symptom frequency was relatively low.

The clinicians in this study apparently used both signs and symptoms to arrive at their global assessment of severity, but the higher correlations between patient symptoms and clinician grade indicate that symptoms were given greater weight. In this study, the protocol directed clinicians to discuss symptoms with the patient after signs were gathered. Although useful in a study, this is an artificial situation that could bias toward more attention being paid to symptoms than may occur in a busy clinical setting and may have affected our results. The patient's self-assessment of dry eye severity correlated even more highly with symptoms than did the clinician grade, indicating the relative importance of the symptoms to the patient.

A next step in the development of the DEQ will be determination of the best habitual symptom questions for screening patients with dry eye and for discriminating between types of dry eye. This streamlining process will, by design, leave the research tool intact to measure a full range of potential symptoms while still offering a clinically useful tool. Standardization of symptom measures such as the DEQ will allow for generalization of results between studies, and the ability to measure the effects of dry eye treatment on symptoms. A standard symptom measure is especially necessary in the area of dry eye, because no widely accepted gold standard clinical test exists.²

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References

- McCarty CA, Bansal AK, Livingston PM, Stanislavsky YL, Taylor HR. The epidemiology of dry eye in Melbourne, Australia. *Ophthalmology*. 1998;105:1114-1118.

2. Schein OD, Tielsch JM, Munoz B, Baqndeen-Roche K, West S. Relation between signs and symptoms of dry eye in the elderly. *Ophthalmology*. 1997;104:1395-1401.
3. Hay EM, Pal TB, Hajeer A, Chambers H, Silman AJ. Weak association between subjective symptoms of and objective testing for dry eyes and dry mouth: results from a population based study. *Ann Rheum Dis*. 1998;57:20-24.
4. Lemp MA. Report of the National Eye Institute/Industry workshop on clinical trials in dry eyes. *CLAO J*. 1995;21:221-232.
5. Bjerrum KB. Test and symptoms in keratoconjunctivitis sicca and their correlation. *Acta Ophthalmol Scand*. 1996;74:436-441.
6. Schein OD, Munoz B, Tielsch JM, Bandeen-Roche B, West S. Prevalence of dry eye among the elderly: a population-based perspective. *Am J Ophthalmol*. 1997;124:723-728.
7. Daniels TE. Labial salivary gland biopsy in Sjögren's syndrome. *Arthritis Rheum*. 1984;27:147-156.
8. Vitali C, Moutsopoulos HM, Bombardieri S. The European Community Study Group on Diagnostic Criteria for Sjögren's Syndrome. sensitivity and specificity of tests for ocular and oral involvement in Sjögren's syndrome. *Ann Rheum Dis*. 1994;53:637-647.
9. Korb DR. Survey of preferred tests for diagnosis of the tear film and dry eye. *Cornea*. 2000;19:483-486.
10. Nichols KK, Nichols JJ, Zadnik K. Frequency of dry eye diagnostic test procedures used in various modes of ophthalmic practice. *Cornea*. 2000;19:477-482.
11. McMonnies CW. Key questions in a dry eye history. *J Am Optom Assoc*. 1986;57:512-517.
12. Bandeen-Roche K, Muñoz B, Tielsch JM, West SK, Schein OD. Self-reported assessment of dry eye in a population-based setting. *Invest Ophthalmol Vis Sci*. 1997;38:2469-2475.
13. Begley CG, Chalmers RL, Mitchell GL, et al. Characterization of ocular surface symptoms from optometric practices in North America. *Cornea*. 2001;20:610-618.
14. Begley CG, Caffery BA, Chalmers RL, Mitchell GL. Use of the Dry Eye Questionnaire (DEQ) to measure symptoms of ocular irritation in patients with aqueous tear deficient dry eye. *Cornea*. 2002;21:664-670.
15. Ware JE, Sherbourne CD. The MOS 36-Item Short Form Health Survey (SF-36): I. Conceptual framework and item selection. *Med Care*. 1992;30:473-483.
16. Russel LB, Gold MR, Siegel JE, et al. The role of cost-effectiveness analysis in health and medicine. *JAMA*. 1996;276:1180.
17. Efron NA. *Contact Lenses A-Z*. Oxford: Butterworth-Heinemann; 2002:213.
18. Josephson JE, Caffery BE. Corneal staining characteristics after sequential instillations of fluorescein. *Optom Vis Sci*. 1992;69:570-573.
19. Begley CG, Barr JT, Edrington TB, Long WD, McKenney CD, Chalmers RL. Characteristics of corneal staining in hydrogel contact lens wearers. *Optom Vis Sci*. 1996;73:193-200.
20. Bron AJ. The Doyne Lecture. Reflections on the tears. *Eye*. 1997;11:583-602.
21. Plugfelder SC, Tseng SCG, Sanabria O, et al. Evaluation of subjective assessments and objective diagnostic tests for diagnosing tear-film disorders known to cause ocular irritation. *Cornea*. 1998;17:38-56.
22. Chodosh J, Dix RD, Howell RC, Stroop WG, Tseng SC. Staining characteristics and antiviral activity of sulforhodamine B and lissamine green B. *Invest Ophthalmol Vis Sci*. 1994;35:1046-1058.
23. Manning FJ, Wehrly SR, Foulks GN. Patient tolerance and ocular surface staining characteristics of lissamine green versus rose bengal. *Ophthalmology*. 1995;102:1953-1957.
24. Song A, Schmidlap B, Bradley A, Begley C. Filters for enhanced viewing of conjunctival staining with rose bengal, lissamine green, and fluorescein. *Optom Vis Sci*. 1999;77(12s):231.
25. van Bijsterveld OP. Diagnostic tests in the sicca syndrome. *Arch Ophthalmol*. 1969;82:10-14.
26. Stern ME, Beuerman RW, Fox RI, Gao J, Mircheff AK, Pflugfelder SC. The pathology of dry eye: the interaction between the ocular surface and lacrimal glands. *Cornea*. 1998;17:584-589.
27. Versura P, Profazio V, Cellini M, Torreggiani A, Caramazza R. Eye discomfort and air pollution. *Ophthalmologica*. 1999;213:103-109.
28. Acosta MC, Gallar J, Belmonte C. The influence of eye solutions on blinking and ocular comfort at rest and during work at video display terminals. *Exp Eye Res*. 1999;68:663-669.
29. Hikichi T, Yoshida A, Ri M, et al. Prevalence of dry eye in Japanese eye centers. *Graefes Arch Clin Exp Ophthalmol*. 1995;233:555-558.
30. Toda I, Fujishima H, Tsubota K. Ocular fatigue is the major symptom of dry eye. *Acta Ophthalmol*. 1993;71:347-352.