Association between Depression and Dry Eye Disease in an Elderly Population

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PURPOSE. A population-based cross-sectional study to investigate the association between depression and dry eye disease (DED) in a community-dwelling elderly population.

METHODS. The subjects were 657 Korean elders ≥ 65 years of age randomly selected from an official household registration database in Yongin, Korea. DED symptoms were assessed using the six-item Dry Eye Questionnaire (DEQ). Signs were evaluated using the Schirmer test, fluorescein stain score, tear film break-up time (BUT). Depression was assessed using the Korean version of the Short Geriatric Depression Scale (SGDS-K). The association between DED and depression was evaluated using logistic linear analyses.

RESULTS. The SGDS-K score correlated with the number of positive responses in the Dry Eye Questionnaire (r = 0.229, P < 0.001), but not with tear film break-up time (r = 0.041, P = 0.139) or Schirmer test score (r = 0.048, P = 0.642). In the binary logistic regression model, female sex (P = 0.014), residence in urban areas (P < 0.001), depression (P < 0.001), and Schirmer score of ≤5 mm (P = 0.035) were associated with the risk of DED. Depression was associated with the risk of DED (P < 0.001) in the patients with Schirmer score > 5 mm but not in those with Schirmer score ≤ 5 mm (P = 0.290).

CONCLUSIONS. Depression was associated with DED symptoms in subjects with normal or mildly reduced tear production. (Invest Ophthalmol Vis Sci. 2011;52:7954–7958) DOI:10.1167/ iovs.11-8050

Dry eye disease (DED) is a common condition which has an adverse effect on daily life.1 Along with ocular signs of tear film instability and ocular surface damage, dry eye symptoms such as dryness, discomfort, foreign body sensation, and pain are included in all DED definitions.2–4 Thus, proper evaluation of DED symptom severity is crucial in its diagnosis and management. However, it has been reported that subjective ocular symptom severity often does not correlate with that of objective signs in DED; this may be partly attributed to decreases in corneal sensation from persistent stimulation of the neural reflex arc in chronic DED.5,6 In addition, subjective ocular symptoms can be affected not only by tear film instability or ocular surface damage, but also by characteristics of individual pain perception or psychosomatic aspects including depression, stress, and anxiety.7,8

Female sex, age, and hormonal influence are well-established risk factors for both DED and depression.9,10 Literature has suggested that dry eye symptoms and mood status may influence each other.7,8 Vriezekolk et al.8 demonstrated that depression, fatigue, and pain were common in patients with primary Sjögren syndrome. Other researchers also revealed that depressive mood is one of the underlying causes of subjective dry mouth.11–13 However, few reports have shown a relationship between depression and DED.14,15

The aim of this study was to investigate the association between depression and DED in randomly selected community-dwelling elders. We also sought to evaluate the impact of comorbid depression on the agreement of DED signs and symptoms.

METHODS

Subjects

All subjects were randomly selected community-dwelling Korean elders aged 65 years or older who participated in the Yongin Aging Study (YAS).1 The YAS is a community-based longitudinal cohort study on the memory, mood, and sensory functions of Korean elders.5 Its baseline study was conducted from May 2008 to February 2009. First, 1060 elderly individuals were randomly sampled using the official registration database of Yongin city, and invitation letters were sent to them for general mental and ophthalmologic health evaluation. Specific statements about DED or depression were not included in the letter to avoid selection bias. Of the 1060 subjects, 657 agreed to participate in this study.

Assessments

Depressive symptoms were evaluated using a self-administered Korean version of the Short Geriatric Depression Scale (SGDS-K) for depression.16 Definite depression was defined as having an SGDS-K score of eight or higher.16 Dry eye symptoms were evaluated using the Dry Eye Questionnaire (DEQ) that included six questions pertaining to dry eye symptoms (see Appendix A).9 When a participant indicated the presence of a symptom, she or he was asked to indicate whether the symptom was experienced rarely, sometimes, often, or all the time. DED was defined as having one or more of the symptoms often or all the time. The Schirmer test was measured along with DEQ. Without the instillation of topical anesthetics, a pre-calibrated dry filter strip (Color Bar; EagleVision, Inc., Memphis, TN) was placed temporally in each lower fornix. The strips were removed after 5 minutes, and the amount of wetting (in mm) was recorded.
All 657 subjects who completed the initial field survey were asked to visit the Seoul National University Bundang Hospital and to undergo the second step of the study—further ophthalmologic evaluation for dry eye signs, including a tear film break-up time (BUT) test, fluorescein staining, and slit-lamp examination of the meibomian gland. All tests were performed by one experienced cornea specialist (ERH) blinded to the SGDS-K, DEQ, and Schirmer test results. The diagnostic status of DED was also masked to all study participants. In the secondary evaluation, 21.2% (139/657) of the enrolled subjects visited our center. The tear film BUT was measured three times for each eye and the average was recorded. Fluorescein staining of the cornea was graded as 0 (no staining), 1 (mild staining limited to 1⁄3 of the cornea), 2 (moderate staining of 1⁄2 of the cornea), or 3 (severe staining occupying one half or more of the cornea).

Meibomian gland obstructions were graded 0 (no obstruction with clear meibum), 1 (plugging with translucent serous secretion when compressing the lid margin), 2 (plugging with viscous or waxy white secretion when compressing the lid margin), or 3 (plugging with no secretion when compressing the lid margin). Meibomian gland dysfunction (MGD) was defined as the presence of gland orifice plugging (grade ≥ 1). The cutoff points of abnormal clinical test were defined as tear film BUT ≤ 10 seconds, Schirmer test score ≤ 5 mm, fluorescein score ≤ 1, or the presence of MGD. The study protocol was approved by the Institutional Review Board of Seoul National University Bundang Hospital. This study conformed to the tenets of the Declaration of Helsinki, and informed consent was obtained from all study participants. Statistical Analysis

In each subject, the data from worse eyes were used for analyses. Determination of the eye with worse signs was made based on clinical judgment of the examiner (ERH). Demographic factors, SGDS-K scores, and the prevalence of definite depression were compared between subjects with DED (DED group) and those without DED (non-DED group) using Student’s t-test and the χ² test, as appropriate. The correlation between SGDS-K and dry eye symptoms and/or signs was evaluated using Pearson’s correlation test.

To determine the impact of depression on the risk of DED, binary logistic regression analyses were performed computing other potential risk factors shown previously as well as depression as independent factors. In addition, binary logistic analyses were separately conducted in the low Schirmer score group (Schirmer score ≤ 5 mm) and high Schirmer score group (Schirmer score > 5 mm) to evaluate the differential association between definite depression and symptom-based DED by the presence of DED signs. P values < 0.05 were considered statistically significant. Statistical software (SPSS for Windows, version 15.0; SPSS Inc., Chicago, IL) was used in every statistical analysis.

RESULTS

Of the 657 responders, 650 finished both questionnaires for DED and depression. The mean age of the 650 participants was 71.9 ± 5.8 years (mean ± SD; range 65–95), and 336 (51.7%) were women. Among them, 198 (30.5%) met the diagnostic criteria for DED, and 148 (22.8%) had definite depression defined as having a SGDS-K score ≥ 8.

Mean SGDS-K score was higher (5.63 ± 4.48 vs. 3.73 ± 3.77; P < 0.001) and definite depression was more prevalent (33.3% vs. 18.1%, odds ratio [OR], 2.26; 95% confidence interval [CI], 1.54–3.50; P < 0.001) in the DED group than in the non-DED group.

The number of positive responses in the DEQ representing DED symptom severity was significantly correlated with the SGDS-K score (r = 0.229; P < 0.001) but not with DED sign severity, including tear film BUT (r = 0.041; P = 0.139) and Schirmer test score (r = 0.048; P = 0.642) (Table 1).

In the binary logistic regression model, female sex (OR, 1.57; 95% CI, 1.10–2.24; P = 0.014), residence in urban areas (OR, 2.14; 95% CI, 1.49–3.09; P < 0.001), definite depression (OR, 2.54; 95% CI, 1.70–3.80; P < 0.001), and low Schirmer test score of ≤ 5 mm (OR, 1.51; 95% CI, 1.03–2.22; P = 0.035) were found to be associated with the risk of DED (Table 2).

Multivariate analyses using binary logistic regression revealed that definite depression was associated with the risk of DED (OR, 3.08; 95% CI, 1.93–4.93; P < 0.001) in the high Schirmer score group but not in the low Schirmer score group (OR, 1.52; 95% CI, 0.70–3.30; P = 0.290) (Fig. 1).

Other risk factors for DED were female sex (38.4% in women, 25.8% in men; OR, 1.84; 95% CI, 1.31–2.59; P = 0.013) and urban dwellers (36.4% in urban dwellers, 25.8% in rural dwellers; OR, 1.54; 95% CI, 1.10–2.16; P < 0.001). Subjects with Schirmer scores ≤ 5 mm were more prevalent in the DED group than in the non-DED group (P = 0.042). However, the frequencies of other DED signs including a fluorescein score ≥ 1 and meibomian gland dysfunction were comparable between the two groups.

DISCUSSION

In the present study, we demonstrated that comorbid depression is closely related to dry eye symptoms but not with dry eye

### Table 1. Correlations* between Dry Eye Symptom and Sign Severity and Depression Severity

<table>
<thead>
<tr>
<th>Variables</th>
<th>DEQ</th>
<th>Schirmer Test</th>
<th>Tear Film BUT</th>
<th>SGDS-K</th>
</tr>
</thead>
<tbody>
<tr>
<td>DEQ</td>
<td>—</td>
<td>—0.106</td>
<td>—0.200</td>
<td>0.229†</td>
</tr>
<tr>
<td>Schirmer</td>
<td></td>
<td></td>
<td>—0.196</td>
<td>0.048</td>
</tr>
<tr>
<td>BUT</td>
<td></td>
<td>—</td>
<td>—</td>
<td>0.041</td>
</tr>
<tr>
<td>SGDS-K</td>
<td></td>
<td>—</td>
<td>—</td>
<td></td>
</tr>
</tbody>
</table>

DEQ represented by the number of positive responses to DEQ.
* Pearson correlation coefficient.
† P < 0.001.

### Table 2. Factors Associated with the Risk of Dry Eye Disease

<table>
<thead>
<tr>
<th>Variables</th>
<th>Odds Ratio (95% CI)*</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definite depression†</td>
<td>2.54 (1.70–3.80)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Female sex</td>
<td>1.57 (1.10–2.24)</td>
<td>0.014</td>
</tr>
<tr>
<td>Urban dwellers</td>
<td>2.14 (1.49–3.09)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Schirmer test score ≤ 5 mm</td>
<td>1.51 (1.03–2.22)</td>
<td>0.035</td>
</tr>
</tbody>
</table>

* Binary logistic regression analysis.
† SGDS-K ≥ 8.
the two diseases. Moreover, the association between depression and symptomatic DED was confined to subjects with normal or mildly decreased tear production. Therefore, the symptom-sign discrepancy in DED, which is common in both clinical and research settings, may be attributed at least in part to comorbid depression in DED patients.

Several mechanisms may underlie the association between depression and dry eye symptoms, although they are unclear and yet to be determined. First, the two diseases may have common pathophysiology. The two diseases have common risk factors including female sex and menopause, suggesting the involvement of sex hormones in both diseases. In addition, inflammation plays a crucial role in the development of DED, and the anti-inflammatory potential of ω-3 polyunsaturated fatty acids (PUFAs) has been shown to be helpful in alleviating dry eye signs and symptoms. Interestingly, many researchers have reported decreased levels of ω-3 polyunsaturated fatty acids in patients with depression. Moreover, an increased ω-6:ω-3 ratio in the diet has been suggested to be an important cause of the increased incidence of both DED and major depression. An increased ω-6:ω-3 ratio promotes the production of proinflammatory cytokines including interleukin (IL)-1, IL-6, and tumor necrosis factor (TNF)-α. These cytokines provoke ocular surface inflammation in DED and produce and enhance negative moods by affecting neurotransmissions and signal transductions. Therefore, increased production of inflammatory cytokines may be a cause overlapped in the pathogenesis of the two diseases. As both conditions were known to have multifactorial pathogeneses, we can assume that the two diseases often coexist, especially in the patients with high ω-6:ω-3 ratio. Therefore, further studies are needed to investigate the influence of dietary fatty acids on comorbidity of the two diseases. Second, a depressive mood may aggravate dry eye symptoms. Several researchers have revealed that chronic or longer-term depression itself can enhance both acute and chronic proinflammatory cytokine production, which can worsen DED. Kielland-Glaser et al. demonstrated that the combination of higher level of depressive symptoms and increased ω-6:ω-3 ratio can markedly promote the production of proinflammatory cytokines beyond the contribution provided by either variable alone. In addition, depressive subjects may have a lower threshold for perceiving physical discomfort or pain. Kim et al. recently demonstrated that, at the same stage of osteoarthritis, patients with depression complained of more severe pain than those without depression, suggesting the influence of the depressive mood on the pain perception. Likewise, depressive patients might be more prone to feel dry eye symptoms. Moreover, somatization may play a role in aggravating dry eye symptoms. Somatization is a common condition in depression, that has been documented in up to 80% of patients. The results that depression was closely related to dry eye symptoms but not to dry eye signs supports the idea that DED may be, at least in part, a somatization disorder. Third, dry eye symptoms also can aggravate depressive symptoms. Chronic discomfort and visual impairment caused by dry eye symptoms can often be annoying, and can conceivably worsen depression.

The present study has several limitations. First, history regarding systemic medication was not investigated. Systemic medications including antidepressants, antianxiety medications, antihistamines, diuretics, and antibenign prostate hyper trophy medications were reported to be associated with DED. However, no significant correlation was found between Schirmer and SGDS-K scores (Table 1). Moreover, the association between DED and depression was significant only in the high Schirmer score group; this suggests that the influence of systemic medications was not critical (Fig. 1). However, we believe that the thorough investigation of systemic medication history is necessary in further studies to rule out possible compounding effects. Second, 62.0% (657/1060) of the subjects enrolled in the study sample participated in the initial survey, and only 21.2% (139/657) of them underwent secondary ophthalmologic examinations. This fact may raise a concern about selection bias, although we used the following measures to avoid bias: in the initial survey, specific statements about DED or depression were never included in the invitation process.
letter: all 657 subjects who finished the initial survey were invited for the second step of the study; and in the second step, the diagnostic status of DED was masked to the examiner as well as to all participants. However, multivariate analyses revealed the association between the two diseases (Table 2). The SGDS-K score correlated with the number of positive responses in the DEQ (Table 1), suggesting the correlation between severity of the depressive mood and that of DED symptoms. Moreover, the DED symptoms and depression were evaluated in the initial survey, thus the possible bias due to the small number of participants in the second step had little influence on the determination of association between symptom-based DED and depression. Therefore, we believe that the results demonstrate the association between the two diseases, regardless of the bias. Third, because of the cross-sectional nature, this study could not show a causal relationship. It remains unclear whether depression is a predisposing factor of DED, or vice versa, although we believe that both conditions have an influence on each other. Fourth, the severity of dry eye symptoms was represented by the number of positive responses to DEQ. Subjective symptoms may be better quantified using tools including the visual analog scale and the ocular surface disease index score. However, considering that participants were elders who often have difficulty answering excessive numbers of questions, we evaluated the symptom grade indirectly rather than adding another questionnaire. Fifth, our diagnostic criteria of DED have still limited value. As the lack of association between DED signs and symptoms is well reported, we selected the symptom-based diagnostic criteria as did the recent population-based studies. However, our DEQ may not be specific for DED and also be reflective of other ocular surface diseases including MGD, allergic and chronic infectious conjunctivitis. Moreover, some dry eye symptoms might not be included in our DEQ. Therefore, the development of more accurate diagnostic criteria for DED is necessary. Finally, we did not control for contact lens wear, which is an important risk factor of DED. However, this study included only subjects aged 65 years or older, among which the number of contact lens wearer could be negligible in Korea.

In conclusion, depression was associated with dry eye symptoms in subjects with normal or mildly decreased tear production. These results suggest that depression could be one of the aggravating factors for dry eye symptoms. Thus, screening and management of comorbid depression may be helpful, particularly in subjects with severe dry eye symptoms which are not in accord with mild dry eye signs.

References

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APPENDIX A. The Dry Eye Questionnaire (DEQ)

1. Do your eyes feel dry?
2. Do you feel gritty or sandy sensation in your eyes?
3. Do your eyes ever have a burning sensation?
4. Do your eyes ever feel sticky?
5. Do your eyes ever feel watery or tearing?
6. Are your eyes ever red?

Allowed responses to the questions included “none,” “rarely,” “sometimes,” and “often or all the time.” Dry eye disease was defined as having one or more dry eye symptoms often or all the time.