Investigation of the psychological aspects of dry eye disease

PhD thesis

Dr. Ildikó Tünde Szakáts

Semmelweis University
Mental Health Sciences Doctoral School

Supervisor: Dr. György Purebl, Ph.D., associate professor

Official reviewers: Dr. Miklós Resch, Ph.D.habil., senior lecturer
Dr. Katalin Barabás, Ph.D.habil., associate professor

Head of the Final Examination Committee:
Dr. Beáta Pethesné Dávid, Ph.D.habil., professor

Members of the Final Examination Committee:
Dr. Ágnes Füst, Ph.D., senior lecturer
Dr. Judit Balázs, Ph.D. habil., associate professor

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1 Introduction

The symptoms of ocular discomfort typical of dry eye disease (DED) are among the leading reasons why patients visit the ophthalmologist. They often persist despite appropriate local therapy, causing continuous frustration for both patient and physician. Diagnosis of dry eye disease, assessment of its severity and associated therapeutic decisions are complicated by the significant variability of the symptoms and signs and the lack of uniform diagnostic criteria. According to the 2007 International Dry Eye Workshop (DEWS) report ocular surface symptoms are included in the definition of dry eye disease. Under the recommendations of the DEWS report diagnosis of dry eye is based on symptom-based questionnaires and objective diagnostic tests.

In addition to objective dry eye tests evaluation of subjective symptoms are also important in clinical research and in clinical practice to screen individuals for the diagnosis of dry eye, or to grade disease severity, or to assess its progression. Several questionnaires have been developed for this purpose. To our knowledge, there was no validated Hungarian dry eye questionnaire available before our study.

Previous studies reported weak or non-existent correlations between symptoms and signs of dry eye disease. Therefore, patients' symptoms and clinical signs are equally important when dry eye is diagnosed, because some patients with mild disease can report severe symptoms, while others with severe dry eye can have minimal symptoms. Several studies have addressed the repeatability and reliability of the subjective symptoms and objective signs of dry eye disease, and have investigated the lack of correlations between its symptoms and signs. Previous studies have shown that the subjective symptoms of dry eye can be influenced not only by the alterations of the ocular surface and the tear film, but also by several psychological factors including depression, anxiety, post-traumatic stress disorder and subjective happiness. The prevalence of sleep and mood disorders has been found to be significantly higher in patients with dry eye. To the best of our knowledge, the health anxiety level of dry eye patients has not been previously investigated.

Diagnosis and research of dry eye disease is further complicated by the known variability and the lack of repeatability of the classical objective tests. Therefore, in recent years, research has turned toward new instrumental testing. Until recently, tear osmolarity measurement has been limited to laboratory instruments. However, since the TearLab osmometer (TearLab Inc., San

Diego, CA, USA) became commercially available in 2009, the measurement became quick and simple. Although it is applicable in the near-patient setting, tear osmolarity determination did not become a routine test in everyday clinical practice. Several clinical studies using the TearLab osmometer have shown that it is a reliable diagnostic tool for dry eye disease. However, taking into account the variability of tear osmorality, which is a known feature of dry eye disease, the diagnostic value of a single measurement is questionable.

Several studies have reported that cataract surgery can lead to the development of dry eye disease or can aggravate existing symptoms and signs of dry eye. Contributing factors can include postoperative inflammation of the ocular surface, prolonged use of medications containing preservatives, corneal irregularities caused by the incisions, and disruption of the corneal nerves potentially leading to decreased tear secretion by the lacrimal gland. It has also been shown that symptoms of dry eye are associated with an adverse impact on vision-related quality of life, potentially leading to patient disappointment after cataract surgery.

Since modern cataract surgery has high success rates, patients' expectations regarding the outcomes of surgery have greatly increased. Despite impeccable surgical technique, rapid rehabilitation and significant improvement in visual acuity, some patients are dissatisfied with their postoperative results. Psychological factors may also influence patients' expectations and satisfaction regarding their outcome after cataract surgery. However, these psychological characteristics are less well studied.

2 Purpose

2.1 Reliability and validity of the Hungarian version of the Ocular Surface Disease Index questionnaire

Our objective was to investigate the psychometric properties of the Hungarian version of the Ocular Surface Disease Index (OSDI) questionnaire. We have examined the reliability and validity of the questionnaire in dry eye patients and healthy volunteers.

2.2 Associations between psychological factors and objective signs in dry eye disease

Our aim was to investigate the psychological characteristics (health anxiety, depressive and anxiety symptoms) of patients with dry eye symptoms and/or dry eye disease and to analyse the correlations between these psychological aspects, the severity of ocular surface symptoms and the objective parameters of dry eye.

Furthermore, the aim of our study was to define tear osmolarity in dry eye disease, to evaluate the diagnostic accuracy of a single measurement, and to analyse the correlations among tear osmolarity, dry eye symptoms and classical dry eye tests.

2.3 Investigation of patient satisfaction after cataract surgery

The purpose of our study was to identify the relationship between patients' satisfaction after cataract surgery, postoperative visual acuity, visual acuity improvement, patient-reported visual functioning, dry eye signs and symptoms and the psychological factors studied (health anxiety and depressive symptoms).

3 Methods

Each study's protocol was approved by the Semmelweis University Regional and Institutional Committee of Science and Research Ethics. All participants received a full explanation of the study and provided their written informed consent. The study adhered to the tenets of the Helsinki Declaration.

3.1 Reliability and validity of the Hungarian version of the Ocular Surface Disease Index questionnaire

The study was conducted at the Department of Ophthalmology of St. Pantaleon Hospital (Dunaújváros, Hungary), between January 2013 and June 2013. The study subjects were patients presenting to our outpatient department with typical dry eye symptoms and asymptomatic volunteers. Patients with the following conditions were ineligible to participate in the study: any other ocular surface and corneal disease, eyelid and lacrimal system disorders, uveitis, glaucoma, ocular surgery within the last six months, contact lens wear, topical treatment, Sjogren's syndrome and connective tissue diseases. 78 patients (58 women,

20 men) participated in the study, mean age: 63.0 years (SD = 10.8 years, range: 37-85 years). Permission to use the OSDI questionnaire for research purposes was granted by Allergan Inc. The official Hungarian version of the questionnaire was used. The translation was performed by Corporate Translations Inc. (Hartford, CT), in accordance with the FDA rules.

After completing the OSDI questionnaire participants underwent ophthalmic examination including the most commonly used objective tests for dry eye: tear-film break-up time (TBUT), ocular surface staining (according to the Oxford scheme) and Schirmer 1 test. Dry eye tests were performed on both eyes; data from the worse eye was used for statistical analysis. In order to determine test-retest reliability of the OSDI, each patient was asked to return in two weeks to complete the questionnaire a second time. On the basis of objective parameters participants were divided into three groups: healthy controls, mild/moderate dry eye and severe dry eye.

Statistical analyses were performed using IBM SPSS 22.0 software. The internal consistency of the OSDI questionnaire and for each subscale was computed with Cronbach-alpha. The test-retest reliability of the instrument was evaluated by computing intraclass correlation coefficient and by performing the Wilcoxon test. Discriminant validity of the OSDI was assessed by comparing the control and the two dry eye groups by Kruskal-Wallis test followed by Dunn's post-hoc test. The control and the total dry eye group were compared using the Mann-Whitney U test. Receiver operating characteristic (ROC) curves were generated to describe the sensitivity and specificity of the OSDI for the diagnosis of dry eye.

Correlations between the OSDI total score and the objective parameters of dry eye were examined by Spearman’s rank correlation test. P values < 0.05 were considered statistically significant.

3.2 Associations between psychological factors and objective signs in dry eye disease

The study was conducted at the Department of Ophthalmology of St. Pantaleon Hospital (Dunaújváros, Hungary), between November 2013 and December 2013. The study subjects were patients presenting to our outpatient department with typical dry eye symptoms and asymptomatic volunteers. Patients with the following conditions were ineligible: any other ocular surface and corneal disease, eyelid and lacrimal system disorders, uveitis, glaucoma,

ocular surgery within the last six months, contact lens wear, topical treatment, Sjogren's syndrome and connective tissue diseases. 84 patients (69 women, 15 men) participated in the study, mean age: 63.7 years (SD = 8.6 years, range: 40-87 years).

Health anxiety was measured using the Shortened Health Anxiety Inventory (SHAI), depressive symptoms were identified using the Shortened Beck Depression Inventory (BDI), non-health-related anxiety was measured using the Beck Anxiety Inventory (BAI). Symptoms of dry eye were evaluated using the Ocular Surface Disease Index (OSDI, Allergan Inc.) questionnaire. The Hungarian validated version was used for each questionnaire. After completing the questionnaires, patients underwent ophthalmic examination. Best spectacle corrected visual acuity (BSCVA) was recorded on ETDRS charts. After visual acuity testing tear osmolarity was measured using the TearLab system (TearLab Inc., San Diego, CA, USA). The tear sample for osmolarity measurement was collected from the inferior lateral tear meniscus. Classical objective tests for dry eye disease were performed in the following order: tear film break-up time (TBUT), ocular surface staining (according to the Oxford scheme), Schirmer 1 test. Grading of meibomian gland dysfunction was performed on a scale ranging from 0 to 4, based on the quality of expressed secretions and eyelid margin abnormalities. Every test was performed according to the recommendations of the 2007 DEWS report and of the 2011 MGD report. Dry eye tests were performed on both eyes; data from the worse eye was used for statistical analysis.

Participants were divided into two groups based on the OSDI score: symptomatic (OSDI score>12) and asymptomatic (OSDI score ≤12). Further subgroups were created based on the objective parameters of dry eye: healthy control and dry eye. Data analyses were performed with IBM SPSS 22.0 software. Groups were compared using the Mann-Whitney U test and the Chi-square test. Correlations between the scores of the questionnaires and the objective parameters of dry eye were analysed utilising the Spearman's rank correlation test. P values < 0.05 were considered statistically significant.

3.3 Investigation of patient satisfaction after cataract surgery

The study was conducted in the Department of Ophthalmology of St. Pantaleon Hospital (Dunaújváros, Hungary) between March 2016 and June 2016. Fifty-four patients (40 women, 14 men, mean age: 68.02 years, SD=8.67 years, range: 51-84 years) who underwent

uneventful phacoemulsification and monofocal, aspherical posterior chamber intraocular lens implantation in our department were included prospectively. The surgical procedures were performed by three surgeons. Exclusion criteria were any ocular surface disease (except dry eye), eyelid malpositions, lacrimal system disorders, Sjogren's syndrome, uveitis, glaucoma, any other ocular surgery within the last six months, contact lens wear, topical treatment, and any fundus pathology affecting visual acuity. Participants with a confirmed diagnosis of major depression, anxiety disorder, Parkinson's disease or dementia were also excluded.

Participants were divided into two groups. Group 1 consisted of 27 patients who were unsatisfied with their postoperative outcome despite significant visual acuity improvement and good postoperative corrected visual acuity (no worse than logMAR 0.1). Group 2 consisted of 27 patients who were satisfied with their postoperative vision-related quality of life. Postoperative visual functioning was assessed using the Visual Function Index-14 (VF-14), symptoms of dry eye were measured using the Ocular Surface Disease Index (OSDI, Allergan Inc.), health anxiety was measured using the Shortened Health Anxiety Inventory (SHAI), depressive symptoms were identified using the Shortened Beck Depression Inventory (BDI). The validated Hungarian version was used for each questionnaire.

After completing the questionnaires, participants underwent ophthalmic examination. All of the assessments were done postoperatively at 2 months after surgery. Uncorrected visual acuity (UCVA) and best corrected visual acuity (BCVA) were measured bilaterally using the ETDRS chart and expressed on a logMAR scale. Visual acuities were also measured before surgery. Refractive error was assessed by an Auto Refracto-Keratometer RT-7000 (Tomey Co., Ltd., Nagoya, Japan), followed by subjective best-corrected refraction.

Lower tear meniscus of the operated eye was measured using Spectral OCT (iVue, Optovue Inc., Fremont, CA) equipped with a corneal adaptor module (CAM). Two images were taken 2 seconds after blinking, centred on the inferior corneal limbus and lower eyelid, and two parameters of the lower tear meniscus were measured: tear meniscus height (TMH) and tear meniscus depth (TMD). Dry eye tests on the operated eye were performed in the following order: measurement of tear film break-up time (TBUT), ocular surface fluorescein staining (according to the Oxford scheme), Schirmer 1 test and meibomian gland dysfunction assessment, graded on a scale ranging from 0 to 4 based on the quality of expressed secretions

and eyelid margin abnormalities. Each test was performed according to the recommendations of the DEWS report and the MGD report.

Statistical analyses were performed using IBM SPSS 22.0 software. The two groups were compared using the Mann-Whitney U test for continuous variables and the chi-square test for categorical variables. Associations between visual acuity, dry eye test results, and the scores of the questionnaires were examined by Spearman's rank correlation test. Multiple binary logistic regression analysis was used to estimate the relationship between patient satisfaction, dry eye symptoms (OSDI score), visual functioning (VF-14 score) and health anxiety (SHAI score). All tests were considered statistically significant at $p<0.05$.

4 Results

4.1 Reliability and validity of the Hungarian version of the Ocular Surface Disease Index questionnaire

The healthy control group included 31 participants (24 women, 7 men, mean age: 58.3 years, SD=9.9 years, range: 40-82 years), the mild to moderate dry eye group included 28 participants (20 women, 8 males, mean age: 64.8 years, SD=9.2 years, range: 40-81 years), the severe dry eye group included 19 participants (14 women, 5 men, mean age: 68.1 years, SD=11.7 years, range: 37-85 years).

The Cronbach alpha for the overall questionnaire and each of the subscales exceeded 0.6. The Cronbach alpha for the total OSDI questionnaire was 0.89. 23 participants (20 women, 3 men, mean age: 64.5 years, SD=9.8 years, range: 40-85 years) completed the questionnaire a second time. The intraclass correlation coefficient between the test and retest scores was 0,907 (95% CI = 0.783-0.960). No significant difference was found between the test and retest scores (Wilcoxon test: $p = 0.422$).

Significantly higher OSDI scores were found in the severe dry eye group than in the healthy control group ($p=0.003$), demonstrating the survey's discriminant validity. However, no significant difference was observed in the OSDI total score between the healthy control and the mild/moderate dry eye group ($p=0.182$), or between the mild/moderate dry eye group and the severe dry eye group ($p=0.253$). Significantly higher OSDI scores were found in the overall dry eye group ($n=47$) than in the healthy control ($n=31$) group ($p=0.003$). According

to the ROC analysis, a threshold of 13 demonstrated the highest sensitivity (74.5%) and specificity (67.7%). The OSDI score demonstrated significant, but weak negative correlations with the tear film break-up time (r=-0.309, p=0.006), and weak positive correlations with the ocular surface staining (r=0.396, p<0.001), but no correlations were found between the OSDI score and the results of the Schirmer 1 test (r=-0.200, p=0.079).

4.2 Associations between psychological factors and objective signs in dry eye disease

Of 84 participants enrolled in the study 56 were symptomatic (mean OSDI score = 39.4, SD=15.5, range: 16.6–72.9) and 28 asymptomatic (mean OSDI score = 6.1, SD=3.8, range: 0–11.36). According to the objective parameters of dry eye 48 out of 56 in the symptomatic group (85.7%) and 23 out of 28 in the asymptomatic group (82.1%) had dry eye disease.

Best corrected visual acuity showed no statistically significant difference between the symptomatic and asymptomatic group (p>0.168). The only objective dry eye test showing a statistically significant difference between these groups was the TBUT (p=0.046). Tear osmolarity showed no statistically significant difference between the two groups (p = 0.605). All of the psychological questionnaires found statistically significant differences between the symptomatic and asymptomatic group (p<0.005). Significantly higher scores were observed in the symptomatic group than in the asymptomatic group. Our study found no significant correlations between the OSDI scores and the objective dry eye test results, except for a weak, negative correlation with the TBUT measurement (r=-0.25, p<0.05). The OSDI scores did, however, show significant correlations with the psychological questionnaire scores (r>0.3, p<0.01). Considering the correlations between the objective dry eye tests, a moderately strong, positive correlation was found between the TBUT and the Schirmer 1 test (r = 0.56, p <0.01). In addition, ocular surface staining showed a significant but weak, negative correlation with the Schirmer 1 test (r = -0.33, p <0.05) and with the TBUT (r = -0.35, p <0.01). Tear osmolarity demonstrated no significant correlations with either the results of the objective tests or the OSDI score (r <0.16, p> 0.05).

4.3 Investigation of patient satisfaction after cataract surgery

Of the total of 54 patients enrolled in the study, 27 (23 women, 4 men, mean age: 69.78 years, SD=9.34 years, range: 53–84 years) were unsatisfied with their postoperative outcome (group 1) and 27 (17 women, 10 men, mean age: 66.26 years, SD=7.71 years, range: 51–83 years) were satisfied (group 2).

After cataract surgery, there was a significant improvement in mean uncorrected distance visual acuity overall (6.7 lines) and in both groups (6.1 lines in group 1 and 7.2 lines in group 2). The mean postoperative UCVA and BCVA for both groups were between 0.0 and 0.1 logMAR (20/20 to 20/25). There was no statistically significant difference ($p>0.9$) between the two groups in terms of postoperative UCVA and BCVA. The same was true for UCVA and BCVA improvement after surgery ($p>0.77$), and for subjective mean spherical equivalent refraction ($p=0.212$).

In terms of the tear meniscus parameters and the objective dry eye tests other than TBUT, there were no statistically significant differences between the two groups ($p>0.130$). However, dry eye symptoms (OSDI scores, $p<0.001$), visual functioning (VF-14 scores, $p=0.002$) and health anxiety (SHAI score, $p<0.001$) showed significant differences between the two groups. In the unsatisfied patient group visual functioning was significantly worse, dry eye symptoms and health anxiety were significantly more pronounced than in the satisfied patient group.

The results of the correlation test showed no significant correlations between visual acuity measures (UCVA, BCVA) and patient-reported visual functioning assessed by the VF-14 questionnaire ($r<0.17$, $p>0.05$). On the other hand, significant negative correlations were found between the VF-14 and OSDI scores ($r=-0.43$, $p<0.01$). In our study population, the classical dry eye tests showed no correlations with either each other, the tear meniscus parameters (TMH, TMD), or the intensity of dry eye symptoms ($r<0.29$, $p>0.05$). Our study found significant, but weak, positive correlations between the OSDI scores and the SHAI scores ($r=0.33$, $p<0.05$). Multiple binary logistic regression analysis found that severity of dry eye symptoms (higher OSDI scores) and decrease in visual functioning (lower VF-14 scores) were significant predictors of patient dissatisfaction after cataract surgery. For the OSDI score, the odds ratio for association with patient satisfaction was 1.46 (95% CI: 1.02–2.09, $p=0.038$), and for the VF14 score, it was 0.78 (95% CI: 0.60–1.0, $p=0.048$). This means that

for a one-unit increase in OSDI score, patients are 46% more likely to be unsatisfied with the results of surgery; for a one-unit increase in VF14 score, they are 22% less likely to be unsatisfied.

5 Conclusions

5.1 Reliability and validity of the Hungarian version of the Ocular Surface Disease Index questionnaire

Evaluation of subjective symptoms and assessment of dry eye signs are also important when dry eye disease is diagnosed or the effects of therapy are determined. To our knowledge, no validated questionnaire to assess dry eye symptoms was available in Hungarian language. The results of our study demonstrate the internal consistency, the test-retest reliability, and the discriminative validity of the Hungarian version of the Ocular Surface Disease Index (Allergan Inc.) questionnaire. Moreover, the OSDI demonstrated good sensitivity and specificity in distinguishing between healthy controls and patients with dry eye. Our study proved for the first time the applicability of the questionnaire in Hungarian patients. In our opinion, the Hungarian version of the OSDI questionnaire is a valuable and useful tool for assessing subjective dry eye symptoms.

5.2 Associations between psychological factors and objective signs in dry eye disease

The discrepancy between the severity of subjective symptoms and the results of objective tests in dry eye disease has already been reported. Recently, the role of psychological background factors emerged as a possible explanation for this discrepancy. Our study found that symptomatic dry eye patients are more predisposed to depressive and anxiety symptoms. To the best of our knowledge, we have investigated for the first time the role of health anxiety in dry eye disease. In our study population we found no significant correlations between the intensity of dry eye symptoms and the severity of dry eye signs. Dry eye symptoms did, however, show significant correlations with health anxiety and depressive and anxiety symptoms. The psychological factors examined in our study may lead to a decreased pain

threshold and an increased sensitivity to physical sensations, which might be a possible cause of the frequent patient-physician encounters. In our opinion, the severity of subjective symptoms of dry eye is largely due to psychological factors, coupled with anomalies of the ocular surface and the tear film as measured by objective tests. Identification and management of the underlying psychological disturbances may aid our understanding of the development and course of dry eye symptoms. It may also complement local therapy in improving patients' subjective ocular surface symptoms and potentially their quality of life.

Furthermore, our investigations confirmed earlier results, that a single measurement of tear osmolarity cannot be employed as a sole marker in dry eye diagnosis. Tear osmolarity should be used in combination with other dry eye test results. Further research is needed to clarify the discrepancies between the results of the studies.

5.3 Investigation of patient satisfaction after cataract surgery

To our knowledge, this is the first simultaneous investigation of objective visual acuity, subjective visual functioning, dry eye signs and symptoms, and psychological characteristics (health anxiety and depressive symptoms) as factors affecting patient satisfaction after cataract surgery.

According to our results, perception of visual functioning correlated with the severity of dry eye symptoms, while dry eye symptoms correlated with the intensity of health anxiety. Our study found that patients' satisfaction after cataract surgery was more closely associated with the severity of dry eye symptoms and with subjective visual functioning, than with postoperative visual acuity or with visual improvement.

The findings of our study may be useful in the postoperative management of patients who have undergone phacoemulsification. They draw attention to the importance of informing patients about the possibility of worsening dry eye symptoms and visual fluctuations after surgery. They also highlight the importance of dry eye evaluation and treatment before and after surgery in order to avoid postoperative patient dissatisfaction.

6 List of author's publications related to the PhD thesis:

Szakáts I, Sebestyén M, Németh J, Birkás E, Purebl G. (2016) The Role of Health Anxiety and Depressive Symptoms in Dry Eye Disease. Curr Eye Res, 41: 1044-9.

IF: 2,238 (2016)

Szakáts I, Sebestyén M, Tóth É, Purebl G. (2017) Dry Eye Symptoms, Patient-Reported Visual Functioning, and Health Anxiety Influencing Patient Satisfaction After Cataract Surgery. Curr Eye Res, 42: 832-6.

IF: 2,238 (2016)

Szakáts I, Sebestyén M, Németh J, Birkás E, Purebl G. (2014) Reliability and validity of the Hungarian version of the Ocular Surface Disease Index questionnaire. Szemészet, 151: 167-71.

Szakáts I, Sebestyén M. (2016) Diagnostic value of a single tear osmolarity measurement in dry eye disease. Szemészet, 153: 75-80.