Journal of Multidisciplinary Healthcare

Dovepress
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ORIGINAL RESEARCH

Association Between Dry Eye Disease with Anxiety and Depression Among Medical Sciences Students in Qassim Region: Cortisol Levels in Tears as a Stress Biomarker

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Purpose: This study aimed to investigate the relationships between anxiety, depression, and ocular surface health. Cortisol levels were detected in human tears, and their relationship with anxiety levels was determined using a validated questionnaire.

Patients and Methods: In total, 112 participants were recruited for this study. All participants were healthy medical students at the Qassim University. Each participant signed an informed consent form after receiving detailed information about the study. Visual acuity examination, TBUT, Shirmer1 test were performed. Participants were asked to fill out three questionnaires: Taylor Manifest Anxiety Scale, Beck Depression Inventory, and The Ocular Surface Disease Index. Tear samples were extracted from the Schirmer strips and cortisol level was measured using ELISA kits.

Results: A total of 112 college students were included in the study, 58.9% of whom were females. The mean age was 21.9 ± 1.7 years. Subjective reported symptoms of anxiety levels were significantly correlated with depression scores, the OSDI, and reduced Schirmer test measurements. Moreover, cortisol levels detected in tears were positively associated with higher anxiety scores ($r=0.328$, $P<0.05$).

Conclusion: Ocular surface health is associated with symptoms of anxiety and depression. The use of tears to measure cortisol levels could be an interesting way to serve as an anxiety biomarker.

Keywords: anxiety, cortisol, depression, dry eye, OSDI

Introduction

The ocular surface serves as a unit with an important role in vision and it protects the orbit from harmful substances, such as ultraviolet light or any infectious organism. Among all the structures that form the ocular surface, the tear film is a very important component because it also provides oxygen and it contains lysozymes, immunoglobulins, and lactoferrin, all of which highlight the importance of the tear film in controlling inflammation, restraining infections, and maintaining good quality of vision.[1,2] Any alteration or reduction in the volume in tears would disturb the homeostasis of the tear film and result in dry eye disease.[3,4]

Dry eye disease is a worldwide issue, with a prevalence ranging between 5% and 50% of the population, and it is one of the most common reasons for visiting ocular health specialists. Dry eye is defined as

> a multifactorial disease of the ocular surface characterized by loss of homeostasis of the tear film accompanied by ocular symptoms, in which an etiological role is played by instability and hyperosmolarity of the tear film, inflammation and damage to the ocular surface, and neurosensory abnormalities.[5]

Received: 9 August 2024
Accepted: 26 September 2024
Published: 30 September 2024

Individuals with dry eye disease may have a number of discomfort symptoms, such as foreign body sensation, burning, blurry vision, photophobia, visual disturbances, grittiness, and itching. Such symptoms negatively affect the patients' quality of life.[6,7]

The risk factors for developing dry eye vary according to the environment and genetics. A low-humidity environment, air-conditioned rooms, long hours of reading and exposure to screens, contact lens use, and smoking are among the factors that negatively affect the health of the ocular surface.[8] Moreover, non-modifiable risk factors for developing dry eye can be due to age, ethnicity, and sex.[9] Autoimmune diseases can lead to dry eye as well, disorders include Sjögren's syndrome, rheumatoid arthritis, and rosacea.[10] The use of medications, such as beta-blockers, decongestants, selective serotonin reuptake inhibitors, tricyclic antidepressants, oral contraceptives, and anxiolytics, can also lead to dry eye.[11]

Psychological factors are often overlooked as potential causes of ocular surface diseases; however, they are risk factors. It is widely recognized that poor visual output is associated with increased mental stress and social isolation.[12–14] Similarly, research has revealed that the development of dry eye illness can be attributed to both psychological stress and the use of psychiatric medication.[15]

Numerous studies have provided evidence of a connection between the mental health of an individual and the ocular surface condition. To acquire prior knowledge, retrospective investigations were conducted in eye care clinics and/or mental hospitals, using information collected from patients, these studies highlighted the common presentation of depression and anxiety among dry eye patients, and some authors suggested that this correlation might be the reason behind the inconsistency between dry eye signs and symptoms.[16–18] The exact nature of this connection as a cause or consequence remains uncertain; nevertheless, numerous research studies have emphasized the relationship between these variables.[14]

One of the interesting molecules that is upregulated by the Hypothalamic-Pituitary-Adrenal axis in cases of anxiety disorder is cortisol.[19,20] This current study aims to elucidate the correlation between anxiety, depression, and ocular surface health in young university students. Moreover, cortisol levels in tears were measured in the search for possible anxiety biomarkers.

Materials and Methods

Recruitment of Participants

A total of 112 participants were recruited from September 2022 to May 2023 at the Qassim University outpatient optometry clinics. The recruitment was through announcements at the university channels targeting medical health sciences students. To calculate the sample size, the G*Power software version 3.1.9.7 was used for sample size determination. The main statistical analysis to be conducted was linear correlation analysis between anxiety, depression, and research variables. The parameters used to determine sample size were as follows: Two tailed tests, average effect size assumed, 95% Confidence level, and the power (1-β) 0.80. Based on the mentioned assumptions the minimum required sample size was 84 students.

The study included participants enrolled in health-related academic programs such as medicine, optometry, pharmacology, radiology, medical laboratories, dentistry, and nursing. Ethical approval before starting the study was obtained from the Ethics Committee of Qassim University (21–20-09). All the methods used in this study has followed the principles defined in the Declaration of Helsinki.[21] Written informed consent was signed by all the patients. Patients who underwent ocular surgery or had ocular pathologies other than dry eye were excluded from the study. Subjects who were medicated for psychological disorders were also excluded from the study.

Ocular Examination

All participants underwent a series of tests to assess visual capacity and ocular surface health. All tests were done in at the same time range for all participants to avoid diurnal variations; subjects were always examined from 12:00–14:00 hours. First, corrected visual acuity was measured and an auto-refractometer was used as a rough indication of their current refraction status. Afterward, ocular surface examination using slit lamp bio-microscopy and tear breakup time test (TBUT) was done followed by Schirmer's test.

The Schirmer test was done with no anesthesia instillation, it consists of a strip filter that is gently inserted on the lower eyelid close to the lateral margin and patients were asked to have their eyes closed during 5 minutes. The amount

of tears was measured, and the strips were saved in 1.5 mL tubes in ice during the clinical examinations and saved later in −20°C freezer for further analysis.

Finally, tear breakup time was measured using strips of sodium fluorescein dye. The strips were wetted by a single drop of saline solution, and the tear film was observed under blue light in the bio-microscope. The average of three measurements taken for each eye was used to determine the final value. The Ocular Surface Disease Index (OSDI) questionnaire was translated into Arabic and administered to the participants to assess their subjective experiences with dry eye.[22] The questionnaire is self-administered, and the results indicate which category of dry eyes is "normal" for 0–12, "mild" for 13–22, "moderate" for 23–32, and "severe" for 33–100.[23]

Psychological Questionnaires

Two surveys were administered to the participants to measure their subjective depression and anxiety levels. The first questionnaire was the Beck Depression Inventory (BDI), it is self-reported with 21 items used to measure depression in healthy people and people with mental illnesses. The inventory has been translated and validated in Arabic.[24] The tool used in this research was a four-point rating system ranging from 0 to 3, ascending from lack of symptoms to 3 which refers to the presence of severe symptoms. BDI score was calculated by summing the values provided by the patients for each of the items in the questionnaire and the outcomes were categorized into five discrete levels, spanning from a condition of normality to a state of profound depression.

The Taylor Anxiety Test was performed based on the Minnesota Multifaceted Personality Test. The test consisted of 50 statements intended to measure explicit anxiety. After being created by Dr. Janet Taylor and translated into Arabic, it underwent a process of validation to ensure that it was reliable and true.[25]

Cortisol Levels in Tears

The Schirmer strips were kept at −20°C in 1.5 mL tubes until the day of the experiment. Afterwards, the strips were transferred in a 0.5 mL Eppendorf tube. With an 18-gauge needle, holes were made at the bottom of each tube to allow elution through centrifugation. Tubes that had been punctured were placed in larger tubes to facilitate tear collection. The tubes were centrifuged at 13,000 rpm for 5 min to extract tears from the Schirmer strips, as illustrated elsewhere.[26] All the samples were handled either in ice or at 4°C during centrifugation to avoid protein degradation.

Enzyme-linked immunosorbent assay (ELISA) was used to measure the amount of cortisol in tear fluid samples (Abcam, Cambridge, United Kingdom; ab108665). The assay was performed and analyzed according to the manufacturer's instructions. As suggested by the protocol, HEPES buffer (0.1M, pH 7.5) supplemented with 0.1% BSA was used for sample dilution that was set at (1:2) after different experiments to optimize the titration. To ensure precision, duplicate wells were used for each sample.

Data Analysis

Before proceeding with the data analysis process, the collected data were coded and prepared in Excel spreadsheets. SPSS version 25 software was used for statistical analysis. For categorical variables, frequency and percentage measures were employed in descriptive statistics. Statistical measurements such as mean, standard deviation (SD), and interquartile range (IQR) were used to characterize the quantitative variables. The strength and direction of the relationships between ocular surface signs and symptoms and anxiety- and depression-related scores were examined using correlation analysis. Statistical significance was considered when $p \leq 0.05$.

Results

The current study was composed of 112 college students from health and medical colleges, 66 (58.9%) of whom were female and the mean age of all participants was 21.9 years with 1.7 SD. Most students (75.9%) had normal general health, moreover, the percentages of students who take medications and who had a psychological family history were 18.8% and 17.9% respectively. Only five students reported taking psychological medication (Table 1).

The basic descriptive measures of the surface parameters and symptoms reported of anxiety and depression are shown in Table 2. The percentages of participants who suffered from anxiety and depression were 66.96% and 56.25%, respectively. Among all the patients, 11.60%, 17.85%, and 37.50% had mild, moderate, and severe anxiety scores,

Table 1 Basic Characteristics of Participants

Variable	N= 112
College	
Dentistry	14 (12.5)
Laboratory	10 (8.9)
Medicine	32 (28.6)
Nursing	10 (8.9)
Optometry	27 (24.1)
Pharmacy	13 (11.6)
Others	6 (5.3)
Gender	
Female	66 (58.9)
Male	46 (41.1)
Age	21.9± 1.7
General health	
Normal	85 (75.9)
Not normal	27 (24.1)
Medication	
Yes	21 (18.8)
No	91 (81.2)
Psych family history	
Yes	20 (17.9)
No	92 (82.1)
Psych medication	
Yes	5 (4.5)
No	107 (95.5)

Table 2 Measures of Anxiety, Depression, and Ocular Surface Parameters

Parameter	Min	Max	Mean	SD	Q1	Q3
Schirmer	0	35.0	20.3	11.2	11.9	32.5
TBUT	0	14.5	5.6	3.5	3.0	7.9
Anxiety	1	45.0	21.8	9.6	14.7	29.0
Depression	0	43.0	12.9	9.3	7.0	17.0
OSDI	0	68.8	20.4	16.8	6.3	33.3
Cortisol	0.4	25.1	8.7	6.6	2.5	14.3

Notes: Units for the variables are as follows: Schirmer, mm. TBUT, seconds. Anxiety, depression, and OSDI are scores following the protocol for each questionnaire. Cortisol, ng/mL.

respectively. Mild, moderate, and severe depression scale accounted for 25.00%, 21.42%, and 9.82%, respectively. The mean Schirmer test was 5.6 mm (SD = 3.5 SD, the mean TBUT was calculated at 5.6 seconds, and the mean OSDI was 20.4.

Primary analysis showed no significant differences between participants with psychological family history compared to healthy non-medicated subjects. Hence, they were included in the current analysis. The results of the correlation analysis between ocular surface parameters and the anxiety and depression scales are reported in Table 3. Anxiety was significantly correlated with depression (P <0.001), the OSDI, and cortisol levels. Anxiety was positively correlated with OSDI (Figure 1) and cortisol levels, as seen in the scatter plot (Figure 2); the worse dry eye symptoms was correlated with higher anxiety levels and higher cortisol concentration. A significant negative correlation was identified between depression and Schirmer measures (Table 3).

Table 3 Correlation Between Anxiety, Depression, and Ocular Parameters

	Anxiety	Depression	Schirmer	TBUT	OSDI	Cortisol
Anxiety	–					
Depression	0.706**	–				
Schirmer	−0.163	−0.200*	–			
TBUT	−0.140	−0.069	0.109	–		
OSDI	0.219*	0.197*	−0.074	0.038	–	
Cortisol	0.328*	0.128	0.149	0.205	−0.373*	–

Notes: Results in the table are Pearson r and *indicate P<0.05, **P<0.0001.

Depression scores obtained from the Beck Depression Inventory were also positively correlated with OSDI scores and negatively correlated with Schirmer's test results (P <0.05), indicating that participants who suffered from depression also suffered from dry eye symptoms but also showed signs of lower tears production through the Schirmer test. However, cortisol levels in tears showed no relationship with depression scores.

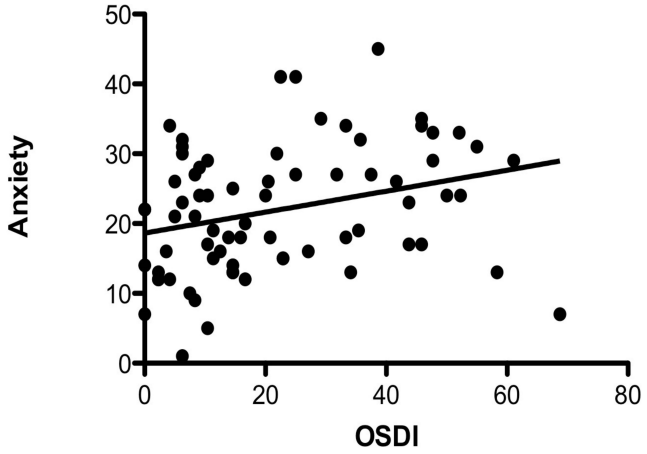

Figure 1 Scatter plot representing the relationship between anxiety levels and OSDI scores. Positive correlation was observed (r= 0.219, P <0.05).

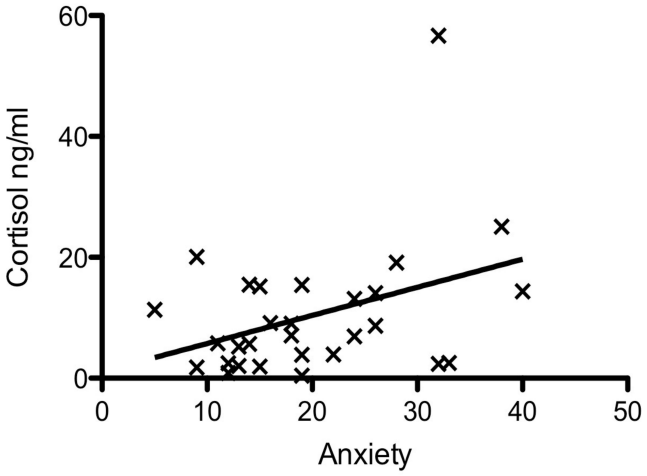

Figure 2 Scatter plot representing the positive correlation between anxiety scores obtained by Taylor anxiety questionnaire and cortisol level measured in human tears (r=0.328, P<0.05).

Discussion

According to the current study, higher scores on the Taylor anxiety scale and/or Beck Depression Scale were positively correlated with individuals' experiences of dry eye symptoms. Furthermore, a significant correlation was observed between elevated cortisol concentration in the tear samples and the aforementioned symptoms. These observations were confirmed by the results. This study shows a potential link between anxiety and/or depression scores seen in young people in good health and who are not clinically and dry eye symptoms. Additionally, the focus has been on examining the levels of cortisol in tears for potential utility as a biomarker for assessing stress levels. Previous studies showed that cortisol levels could be used as a predictor for mental health.[27]

The term "stress" encompasses several stimuli, both of a physical and psychological nature, that disrupt the state of homeostasis. The emergence of the "fight-or-flight" reaction can be attributed to a series of observations and experiments conducted in the early 20th century. The management of stressful events involves intricate processes that affect the physiological and neurological aspects of an individual. When an individual encounters either actual or anticipated dangers, certain chemicals that bind to the receptors located in the outer regions of the brain are released. This process triggers a stress response that ultimately facilitates the restoration of bodily equilibrium.[28] These stressors could range from physical, such as hemorrhage, or physiological, similar to predator-related.[29,30]

Visual impairment is associated with one of the identified stressors. Numerous publications have shown that patients with vision disorders are more prone to anxiety, poor quality of life, and in some cases, other psychological illnesses.[31–33] Although our sample does not include visually impaired subjects, dry eye can lead to discomfort and is known to have a negative impact on the quality of life. Analogous investigations in the current study have shown a correlation between several psychological problems including anxiety, depression, and dry eye. The concept of psychosomatic ophthalmology has become increasingly important.[34]

Medical students have notably elevated levels of anxiety and depression. Multiple survey-based investigations have demonstrated that over 50% of undergraduate medical students experience depression and over 60% experience anxiety.[35] These figures vary depending on the investigation; a study conducted on Chinese medical students revealed a lower prevalence of anxiety, with 30.8% of the sample reporting symptoms.[36] According to another study conducted in Egypt, 65% and 73% of medical students reported anxiety and depression, respectively.[37,38] In Bahrain, results showed that 40% of medical students showed symptoms of depression and 51% suffered from considerable levels of anxiety. Interestingly, the same study showed that Arab ethnicity played a role in depressive symptoms: Arab students had a higher percentage of depressive symptoms than non-Arabs.[39] A possible explanation for the elevated rates of worry and depression in this study is that all the participants were native-born citizens. Furthermore, research has demonstrated that gender affects anxiety and depression substantially more in females than in males, which is consistent with our findings.[40]

Several groups have demonstrated a correlation between psychological morbidities and dry eye. Large-scale retrospective research has found strong correlations between anxiety, depression, and dry eye illness.[41] Consistent with earlier findings, prospective cross-sectional studies have shown that stressed or depressed individuals have a higher likelihood of presenting dry eye illness.[42,43] After establishing that there were no co-occurring conditions that would impact the outcome, we recruited university students to participate in the study. All participants were young adults with good health status. The prevalence of anxiety and depression among medical students in Saudi Arabia has been previously studied; however, no studies to specifically address dry eye syndrome were found. According to Abdullah Alkhani et al, 42% and 53% of medical students experience anxiety and depression, respectively.[44] Anxiety and depression have been identified to be more common in this study as compared to the last one. One plausible explanation for this could be that the COVID-19 epidemic, which caused significant psychological strain and increased screen time as well as social isolation, occurred after our study was conducted.[45,46]

Conclusion

According to the study findings, medical students' ocular surface health, mainly dry eye, was significantly correlated with subjectively reported anxiety and depression. The incidence of anxiety and depression was significantly elevated within this group, emphasizing the importance of mental health services in educational environments. Furthermore, our study

presents an innovative perspective by measuring cortisol levels in tears and establishing a favorable correlation with anxiety scores. More studies to confirm the use of cortisol in tears as a biomarker for anxiety are still in need, as the present study have some limitations such as the sample number and the fact that subjects were not clinically diagnosed by psychology specialists. Also, a depression and cortisol levels were not correlated in our results, and it would be interesting to investigate the mechanism behind the results seen by reduced Schirmer scores and depression, but not cortisol concentration.

Cortisol levels in tears were of interest for the ocular surface in different studies independently of the purpose of the current study. Previous results compared cortisol in healthy subjects' tears and in cases of infectious keratitis and immune-mediated diseases and showed elevated cortisol levels in the presence of ocular surface disease.[47] These results could be indicating that cortisol in tears plays a role in the health and disease of the ocular surface, however, more studies are needed to elucidate this hypothesis.

Investigating the relationship between stress and various health diseases, such as dry eye disease, is of immense value for gaining new insights. Further research with a larger sample size is required to understand the molecular mechanisms underlying these correlations.

Acknowledgments

The author gratefully acknowledges Qassim University, represented by the Deanship of Graduate Studies and Scientific Research at Qassim University, for financial support for this research under the number (CAMS1-2022-1-1-J-26003) during the academic year 1443 AH / 2022 AD.

The authors are grateful to the participants for their time and participation in the study. We would like to sincerely thank the Optometry Department Head, Dr. Sulaiman Aldakhil, for facilitating the clinics to conduct the research, and Dr. Khalid Allemailim, head of the Basic Sciences Department, for facilitating the laboratory and equipment for sample analysis.

Disclosure

The author(s) report no conflicts of interest in this work.

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