An investigation of the relationship between tear meniscus height and the subjective severity of ocular symptoms in keratoconus

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Keratoconus is a debilitating disease in which the cornea does not develop its characteristic round shape but develops into a conical form affecting both functional vision as well as ocular comfort. Depending on the severity of the keratoconus as well as the presence of any associated conditions, keratoconic individuals may complain of various symptoms that include discomfort, irritation, dryness, reflex tearing and foreign body sensation. There are various subjective and objective measures that can be used to determine the severity of these symptoms. A subjective method that is widely used is the ocular surface disease index (OSDI) which has been shown to be fairly accurate when diagnosing dry eye disease; however, these symptoms do not correlate with objective measures of dry eye. Research has revealed the various structural and biochemical changes that take place within a keratoconic cornea; however, the tear dimensions of keratoconic subjects have not been extensively investigated. It is possible that the symptoms experienced by many keratoconic individuals might be linked to alterations within the quantity of the tears of these patients. The present study compared the symptoms experienced by keratoconic individuals with the symptoms of control patients. The differences in tear meniscus heights between keratoconic individuals and those of control individuals were also compared using the Oculus Keratograph 4 (OK4). The results of the study show the absence of a relationship between the subjective symptoms experienced and the height of the tear meniscus.

Introduction

Keratoconus, one of the most common corneal ectasias, presents with various structural and biochemical changes. Research has suggested that keratoconic patients suffer from severe symptoms of dry eye that include tearing, discomfort, irritation and foreign body sensation. Alterations can be seen within each individual layer of the cornea as well as within the tears of these patients. The exact volume of tears found within the tear meniscus, however, has not been comprehensively investigated in terms of keratoconic patients. The tear meniscus plays a vital role in maintaining ocular physiology as well as providing comfort to the anterior ocular structures. Is there a possibility that the volume of tears could be related to the dry eye symptoms being experienced? The present investigation aimed to determine whether a significant difference exists between the tear meniscus heights of keratoconic individuals and those of controls. If a difference were found, can it be related to the symptoms being experienced by these patients?

Literature review

A healthy human cornea is made up of five distinct layers, each with its own specific structural arrangement necessary to maintain the transparency of the cornea. When this precise arrangement is disturbed in any way, it could have a detrimental effect on vision. Of particular importance in the present study are the effects caused by keratoconus, whereby the cornea takes on a conical shape. Keratoconus may be defined as a non-inflammatory corneal ectasia of unknown origin that is generally bilateral but asymmetric.[1] It is a progressive corneal dystrophy that can be seen by observing a protruding corneal cone and may be characterised by thinning of the corneal tissue both centrally and para-centrally.[1,2] Keratoconus may severely affect the function of the visual system by inducing irregular corneal astigmatism as well as myopia which is not always correctable through the use of spectacle lenses and may require more invasive intervention – that is, surgical procedures.[3] The exact aetiology of keratoconus is unknown; however, evidence has shown a genetic, biochemical as well as an environmental link to keratoconus.[3] Keratoconic individuals often have associated atopy leading to symptoms of irritation. To relieve these symptoms, patients tend to rub their eyes vigorously, further contributing towards the conical shape of the cornea.

Evidence has shown that there are various structural and biochemical changes that can be observed within the corneas of keratoconic individuals versus normal corneas. Numerous studies have shown the central corneal thickness as well as the volume of the cornea to be significantly less in keratoconic corneas as opposed to normal corneas, which would be expected because of the thinning that takes place as the condition progresses.[1] Within the individual layers of the cornea, there are numerous changes that have been revealed. One of the most predominant changes taking place within the corneal structure is apoptosis of the keratocytes situated in the stromal layer.[4,5] Keratocytes are mostly responsible for maintaining the extracellular matrix as well as the structure of the collagen fibrils which is imperative for the transparency of the cornea.[6] Apoptosis, otherwise known as programmed cell death, is thought to occur due to mechanical trauma resulting from the vigorous rubbing of the eyes occurring in the majority of keratoconic patients, usually as a result of allergy.[4,7] The epithelial layer is also affected in the pathophysiology of this condition, which demonstrates degeneration, causing irregularity that can be observed along the epithelial surface with confocal microscopy.[3] Also seen in the corneal epithelium is an accumulation of iron which may result in chemical reactions that produce highly toxic hydroxyl radicals (Fleischer's ring).[8] In conjunction with these changes occurring within the corneal structure, there are also changes taking place within the structure and composition of the tears. Keratoconic individuals display an alteration in tear quality as well as changes within the protein profile of the tears.[9]

In addition to the various visual complaints and distortions experienced by keratoconic subjects, these individuals also suffer from severe symptoms of ocular discomfort, dryness, reflex tearing and foreign body sensation.[10] Symptoms are common in keratoconus, including itching, irritation, photophobia as well as eyestrain.[11] Keratoconus has been shown to be associated with various other clinical conditions, one of which is critically important, namely atopy.[12,13] Atopy is a condition that generally occurs with a history of asthma or hay fever, causing itchiness of the skin that may affect various regions of the body.[12] To relieve these symptoms of irritation, subjects tend to rub their eyes vigorously, thereby causing further mechanical damage to an impaired cornea.[14] Could these symptoms be related to specific changes within the tear structure of these subjects?

When trying to determine the severity of symptoms experienced, one of the most common subjective methods is known as the ocular surface disease index (OSDI). The OSDI is a questionnaire comprising 12 questions related to the severity of dry eye symptoms and how these symptoms affect visual function.[15] Research seems to suggest a lack of correlation between subjective symptoms of dry eye and objective tests; however, the OSDI questionnaire has been shown to be a reliable and valid indicator of symptoms and the effect of these symptoms.[15]

Despite the mounting evidence of changes taking place within the corneal layers of the keratoconic patient, the tear meniscus height (TMH) has not been comprehensively investigated. The tear menisci may be observed at the margins of both the upper and lower lids and are generally a good measure of tear volume.[16] These menisci expand horizontally and are held in place by surface tension, with gravity playing a vital role.[16] The tear meniscus is important in terms of maintaining ocular physiology, along with upholding the comfort of the ocular system. The evaluation of TMH has been shown to be a potential diagnostic factor for aqueous-deficient dry eye.[17] There are numerous factors that may affect the height of the tear meniscus, such as the length of the lid, the punctum location, tear secretion as well as tear drainage.[17] TMH may be measured using various methods, one of which includes photography using the Oculus Keratograph.

With the extensive changes taking place within the structure of the keratoconic cornea, is it safe to assume that the tear meniscus height would remain unchanged? If a change in TMH could be observed, is it likely to be larger or smaller than expected?

Method

Data from 25 keratoconic and 25 control patients were obtained during the present study. Across the sample of 50 subjects, age ranged between 19 and 56, with both groups comprising women predominantly. The keratoconic subject group had a mean age of 24, and the control group a mean age of 19. The keratoconic group consisted of 15 women and 10 men, whilst the control group consisted of 20 women and 5 men. The study as well as its procedures were thoroughly explained to the potential subjects, and written informed consent was received from each before taking part in the study. Within the keratoconic group, the presence of keratoconus was confirmed through the use of corneal topography as well as slitlamp procedures to determine whether clinical signs diagnostic of keratoconus were present. The control group of subjects were screened for the presence of any ocular pathology that might result in exclusion from the study. Each subject was required to complete the OSDI questionnaire consisting of 12 questions for grading the severity of the symptoms experienced by the subject. Following completion of the questionnaire, the score from each individual questionnaire was manually calculated, yielding a percentage which gave an indication of the severity of the symptoms experienced.

TMH measurements were taken, using the OK4. With the subject sitting upright, positioned correctly against both the chin and forehead rest of the OK4, photographs were obtained of the tear meniscus situated on the surface of the lower lid. The subject was asked to blink and, directly following this blink, the photograph was taken. The height of the tear menisci in both the right and left eyes of each subject was obtained, with 5 individual photographs per eye. In an attempt to ensure that constant conditions were maintained, all tear meniscus measurements were taken at approximately the same time in the afternoon with the air conditioning set at a standard setting of 22 degrees Celsius. After completion of the photographs using the OK4, each individual photograph was magnified to

twice its original size in order to view the height of the tear meniscus. Using the tools and software available on the OK4, individual photographs were opened and each height manually measured; these scans were saved with the measurements on them and the OK4 was calibrated so that the measurements were given in millimeters (mm) and could be converted to microns. In an attempt to ensure consistency of measurements, the same individual was responsible for measuring each scan in order to rule out variability amongst different individuals taking measurements. The scans were randomly measured to ensure that the individual taking the measurements was unaware of which subject group the specific scan belonged to.

Once the TMH measurements with the OK4 had been completed, the five measurements from each eye were averaged in order to obtain one TMH value for each eye of the 50 subjects. In an attempt to ensure consistent comparisons between values, the TMH averaged for both the right and left eyes were added together and a global mean was calculated. This was done because of the fact that the severity of the symptoms given by the OSDI scores were reported as one overall value. Symptoms cannot be recorded separately for each eye and therefore the OSDI gives one value for the symptoms experienced. For a valuable comparison to be made, one value was needed to compare the symptoms versus the TMH. To achieve this, the TMH of the right and left eyes were added and averaged (25 sets of eyes were used for each of the two subject groups, resulting in 25 means for the keratoconic subjects and 25 means for the controls). Using these values for the TMH, combined with the percentages calculated from the OSDI questionnaires, a statistical analysis could be done using the SPSS (Statistical Package for Social Sciences) software.

Results

Table 1 presents the results of the Kolmogorov-Smirnov and Shapiro-Wilk tests. These tests were performed for the OSDI scores as well as the TMH obtained using the OK4 for both the subject groups in order to determine whether the data were normally distributed.

TABLE 1: Kolmogorov-Smirnov and Shapiro-Wilk tests for the normality of data.

Subject groups	Kolmogorov-Smirnov		Shapiro-Wilk	
	Statistic	Significance	Statistic	Significance
OSDI score				
Keratoconic	0.091	0.2	0.967	0.176
Control	0.258	0	0.709	0
TMH				
Keratoconic	0.161	0.002	0.854	0
Control	0.106	0.200	0.953	0.044

Note: The test statistics and the significance levels are presented for OSDI scores and TMH for both subject groups.
OSDI, ocular surface disease index; TMH, tear meniscus height.

Using the values obtained from the normality tests, it can be seen that both the OSDI scores and the TMH are mostly shown not to be normally distributed for both sets of subjects. The Kolmogorov-Smirnov results show that the OSDI scores obtained from the keratoconic group and the TMH obtained from the control group can be seen as normally distributed. Shapiro-Wilk results suggest that only the OSDI scores obtained by the keratoconic group can be seen as normally distributed. The remainder of the results were shown not to be normally distributed; consequently, mostly non-parametric statistics could be performed on the data set.

Table 2 presents the descriptive statistics for the data used in the present study with right and left eyes combined. The descriptive data in this table are presented for both the keratoconic and the control group of subjects. These descriptive statistics are given for the OSDI scores as well as the TMH, with the OSDI scores represented as a percentage whilst the TMHs are measured in microns.

When examining the values in Table 2, it can be seen that a large difference exists between the mean and median OSDI scores of the keratoconic versus the control group. The TMH measurements, however, do not seem to exhibit such a large difference. As shown in Table 2, the mean OSDI score for the keratoconic group of 58.47% is almost six times that of the control group, signifying the severity of these symptoms. The mean TMH does not seem to exhibit a large difference between the keratoconic and the control groups, being separated by approximately 20 microns. The medians are separated by only 2 microns; however, it is essential to determine whether these differences are statistically significant.

When assessing the results obtained from the Mann-Whitney U test, it can be seen that the OSDI scores are statistically significantly different, whereas the TMH does not seem to be statistically significantly different. Therefore, although symptoms indicated by the OSDI scores are significantly different between keratoconic subjects and control subjects, with keratoconic subjects displaying a greater severity of symptoms, we cannot conclude that the TMH is significantly different between the two subject groups (Table 4).

Pearson's correlation coefficients were calculated in order to determine whether a correlation exists between the symptoms

TABLE 2: Descriptive statistics for the data collected from the two subject groups.

Descriptive statistics	OSDI score (%)		TMH (μm)	
	Keratoconics	Controls	Keratoconics	Controls
Mean and standard deviation	58.47 ± 20.62	9.44 ± 11.98	268.48 ± 95.29	247.12 ± 42.82
95% confidence interval for the mean	52.61 – 63.33	6.04 – 12.85	241.4 – 295.56	234.95 – 259.29
Median and interquartile range	54.9 ± 28.4	6.3 ± 9.35	238 ± 101	240 ± 59

Note: The results for both the keratoconic and the control groups are presented. The means, standard deviations, confidence intervals, medians and interquartile ranges for both the OSDI scores and TMH readings are presented. The OSDI scores are presented as a percentage whilst the TMH values are expressed in microns (μm).
OSDI, ocular surface disease index; TMH, tear meniscus height.

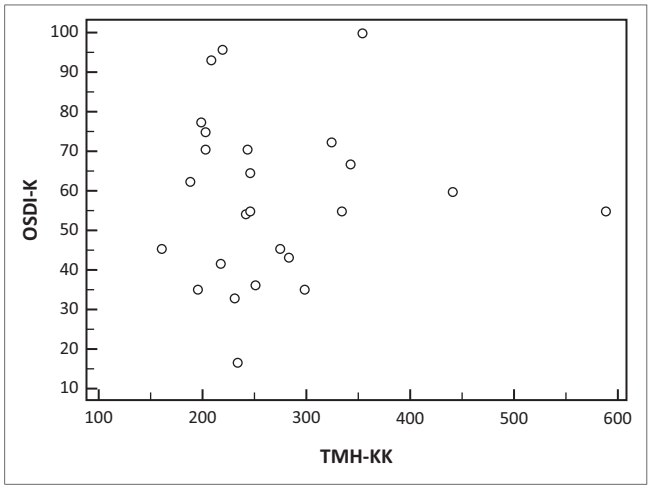
TABLE 3: Mann-Whitney *U* test presenting the test statistics and significance levels for both the keratoconic and the control groups.

Mann-Whitney *U* test	Mann-Whitney *U* score	*Z*	Significance
OSDI	50	-8.288	0
TMH	1207	2482	-0.296

OSDI, ocular surface disease index; TMH, tear meniscus height.

being experienced and the TMH. Both groups showed poor correlation between the symptoms and the TMH that was measured. From the *p* values obtained, it can be seen that in both cases the null hypothesis cannot be rejected, and therefore the correlation is not statistically significant.

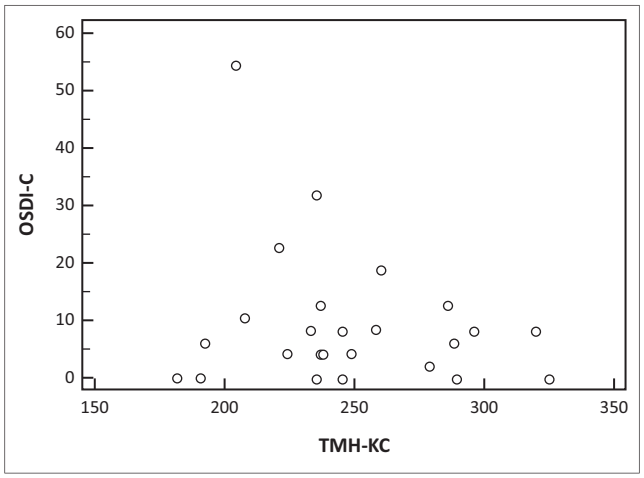
Figures 1 and 2 present the scatter plots for the OSDI scores and the TMH's of the keratoconic versus the control group respectively. The OSDI scores are represented as a percentage, with TMHs expressed in microns.



Note: The OSDI-K axis comprises OSDI scores from the keratoconic group expressed as percentages. The TMH-KK axis represents TMH averages for the keratoconic group expressed in microns (μm), as measured by the OK4.

OSDI, ocular surface disease index; TMH, tear meniscus height.

FIGURE 1: Scatter plot for the keratoconic subjects presenting ocular surface disease index scores versus tear meniscus height readings.



Note: The OSDI-C axis comprises OSDI scores from the control group of subjects expressed as a percentage. The TMH-KC axis represents TMH averages for the control group expressed in microns (μm), as measured by the OK4.

OSDI, ocular surface disease index; TMH, tear meniscus height.

FIGURE 2: Scatter plot for the control subjects presenting ocular surface disease index scores versus tear meniscus height.

TABLE 4: Pearson's correlation coefficients for both the keratoconic and the control groups.

Pearson's correlation	Keratoconic	Control
Correlation coefficient (*r*)	0.0392	-0.2095
p value	0.8525	0.3149
95% confidence interval	-0.3616 – 0.4277	-0.5584 – 0.2024

Note: The table includes the correlation coefficients, significance levels and the values representing 95% confidence intervals for the correlation coefficients.

In Figures 1 and 2, no correlation appears to exist between OSDI scores and TMH. The observed values seem to be scattered randomly, with no specific relationship between the two variables.

Discussion and conclusion

When calculating the statistics for the present study, it was decided that TMH values for the left and right eyes would be combined in order to obtain one value for each of the 50 subjects. One reason for this approach is that the OSDI score gives an overall percentage of the severity of symptoms experienced by a specific subject. OSDI scores cannot be given for right and left eyes separately, and therefore one percentage is calculated per subject. Previous research has indicated that no significant difference exists between the TMH acquired from right and left eyes.[18] In the study by Shen et al.,[18] four measurements of upper and lower TMH were taken 3 hours apart, and measurements were repeated upon awakening the following morning. Shen et al.[18] reported results indicating that there was no significant difference between the tear menisci of the right and left eyes. In a study by Karakosta et al.,[19] 161 published research articles were analysed to determine the effects of combining the right and left eyes when data measurements are analysed. The research articles were categorised according to whether one eye was used, both eyes were used, and whether criteria for eye selection were included.[19] From the results of Karakosta et al.'s study, it was determined that combining the data values for right and left eyes might have a negative effect on the results, especially if the correlation nature of the data had not been accounted for.[19] This combination may result in an underestimation of the true variation within the data set.[19] In a similar study by Armstrong,[20] where research articles were analysed, it was concluded that both eyes could be used and averaged if the correlation was found to be close to one. When calculating the statistics involved in our present study, we were aware of the limitations involved when combining right and left eyes; however, the data sets were easily comparable using one value for each subject, and calculation was therefore done in this way.

The results of the present study suggest that keratoconic individuals have symptoms of greater severity than those of the control group of subjects. As seen in Table 2, the mean OSDI score obtained from the control group is approximately one-sixth that of the keratoconic group, illustrating the severity of the symptoms experienced in keratoconus. The accuracy of these results cannot be comprehensively determined as the OSDI is a subjective technique by which to determine symptom severity. The experience of each subject is entirely

subjective and may be linked to various other causes such as atopy or connective tissue diseases. The severity of these symptoms may be influenced by altered nerve morphology present in keratoconic corneas, changes to the tear structure, the duration of the ocular disorder resulting in increased damage to the ocular surface, as well as various associated conditions such as atopy. As demonstrated in Table 3, the results of the Mann-Whitney U test indicate that a significant difference exists between the two subject groups in terms of the OSDI scores. Therefore, as anticipated, keratoconus does play a vital role in the severity of symptoms experienced by these patients.

Sarac et al.[21] stated that dry eye symptoms have been shown to be present in approximately 81% of keratoconic patients. Sarac et al.'s study[21] found that some of the factors contributing towards dry eye in keratoconic patients included the release of collagen degradation products, a change in corneal sensitivity or changes occurring within the surfacing mechanism of the tears. Rabinowitz[14] found the symptoms in keratoconus to be variable, depending on the progression of the disease, with symptoms being subtle in the early stages and increasing in severity as the disorder progresses. A study by Johnson,[22] in which symptoms and signs of dry eye were compared, indicated that the duration of any specific ocular disease might have an effect on the severity of symptoms. Depending on the duration of the disease, corneal nerves may display an altered nerve response, leading to extreme symptoms of dry eye. When assessing the results of our study, it can be seen that, of the 25 keratoconic subjects, 16 of them (64%) obtained an OSDI score of 50% or more, indicating dry eye symptoms ranging between moderate and severe. In the control group of subjects, however, an OSDI score above 50% was obtained by only one subject (4% of the control group). This finding signifies the severity of symptoms experienced as a result of the presence of keratoconus.

As shown in Table 3, the TMHs of the keratoconic and the control group do not exhibit a statistically significant difference. Therefore, we cannot conclude that a difference in TMH could be observed owing to the presence of keratoconus. In the study by Sarac et al.,[21] the TMHs of keratoconic patients were investigated, and the results indicated that no significant difference existed between the TMH of keratoconic versus control patients. According to Uchida et al.,[23] TMH is a valuable component when diagnosing dry eye disease. In various other conditions, such as Sjögren's syndrome, TMH has been shown to be significantly lower.[24] Owing to the compromise in lacrimal gland function, thereby causing impairment in tear secretion, Sjögren's syndrome patients display lower tear menisci. Shen et al.[18] also reported findings of lower TMH in patients with tear-deficient dry eye. Could one therefore assume that lower TMH might correlate with dry eye symptoms? It has been thought that lower TMH may apply to keratoconus owing to the various structural and biochemical changes taking place within the anterior ocular components. The results displayed in our study, however, show that keratoconus does not seem to have a direct effect on TMH, as no significant difference could be found between the keratoconic and control groups.

Furthermore, no significant correlation exists between the severity of symptoms and the TMH measured, with correlation coefficients that deviate largely from one. These findings relate to other publications demonstrating a lack of correlation between subjective symptoms and characteristic signs of dry eye. Johnson[22] also indicated that there was no statistically significant correlation between subjective symptoms and characteristic signs within the general population. Consequently, it was concluded that objective measures of dry eye cannot be used to predict the symptoms that may be experienced and vice versa.[22] In a study by Morales-Fernández,[25] symptoms obtained from the OSDI questionnaire specifically were compared with objective measures of dry eye to determine whether a significant correlation could be found. Morales-Fernández[25] concluded that no significant correlation could be observed when comparing the symptoms reported to the characteristic signs of dry eye. Similarly, we found no link between OSDI scores and objective measures of TMH. The data points in Figures 1 and 2 appear to be distributed in a random nature with no specific pattern observable. We therefore cannot find any associations between TMHs and the severity of the symptoms experienced. No conclusions can be made regarding changes in TMH as a result of keratoconus.

Limitations of the present study could be the small size of the sample group; a larger sample group consisting of an equal distribution between race and gender might provide a more conclusive finding regarding the relationship between symptoms and TMH.

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Competing interests

The authors declare that they have no financial or personal relationships which may have inappropriately influenced them in writing this article.

Authors' contributions

D.L.N. (University of Johannesburg) was responsible for collection and acquisition of data. Owing to the nature of the data measurements, one individual was responsible for measurement of each separate scan, which was performed by D.L.N. under the supervision of W.D.H.G. (University of Johannesburg). The statistical analysis was performed by Statkon (University of Johannesburg) with the remainder of the content written by D.L.N. under the supervision of W.D.H.G.

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