Is the central corneal thickness of diabetic patients thicker than that of non-diabetics’ eyes?

The purpose of the study was to evaluate central corneal thickness in diabetic patients and to compare the results with controls without diabetes mellitus. Sixty-five diabetic patients (65 eyes) constituted the study group, and 50 eyes were from the healthy control group (50 non-diabetic patients). The study group was subdivided into group 1 (no diabetic retinopathy, \( n = 35 \)), group 2 (mild to moderate nonproliferative diabetic retinopathy, \( n = 20 \)), and group 3 (proliferative diabetic retinopathy, \( n = 10 \)). Central corneal thickness measurements in microns were determined using ultrasound pachymetry. The mean central corneal thickness was significantly greater in the study group (567.14 \( \mu m \) ± 14.63 \( \mu m \)) than in the control group (531.14 \( \mu m \) ± 5 \( \mu m \)). In addition, the mean central corneal thickness was found to be greater in group 3 (577 \( \mu m \) ± 12 \( \mu m \)) than in groups 1 (562 \( \mu m \) ± 13 \( \mu m \)) and 2 (566.86 \( \mu m \) ± 15 \( \mu m \)), but the difference did not reach statistical significance. We found that the mean central corneal thickness for diabetic patients was thicker than that of the healthy controls. Thicker central corneas associated with diabetes mellitus should be taken into consideration when obtaining accurate intraocular pressure measurements in diabetics.

Introduction

The cornea is the major refracting component of the eye, accounting for approximately 70% (43 of the 60 D) of the total refraction.\(^{1,2,4}\) The cornea is about 535 \( \mu m \) (0.535 mm) thick, and is composed of five different layers.\(^{5,7,8}\) The outermost layer is the corneal epithelium, responsible for both protecting the eye from foreign material and absorbing oxygen and other nutrients. Bowman’s membrane maintains the integrity of the corneal structure and acts as a barrier against infections. The stroma maintains the transparent cornea and is made up of keratocytes that lie between collagen fibrils within the stroma.\(^8\) The next layer is the Descemet membrane which adheres to the stroma. The main role of the endothelium is to control swelling and stromal hydration in order to maintain corneal transparency.\(^9,10\) Dysfunction in any of these components may result in a loss of transparency and/or function.

The corneal stroma has highly organised arrangements of collagen fibrils that are braced apart by a proteoglycan matrix that maintains uniform spacing.\(^9,10\) The proteoglycan extracellular matrix is hydrophilic and draws in water from the anterior chamber and pre-corneal tear layer via the corneal endothelium and epithelium, respectively. Corneal hydration is maintained at a constant level by a fluid pump mechanism (Na\(^+\)-K\(^+\) ATPase) that is located predominantly on the corneal endothelium but is also present at the corneal epithelium.\(^10\)

Central corneal thickness (CCT) is an important parameter for the evaluation of suitable patients for refractive surgery, when assessing glaucoma risk and evaluating physiological and pathological variations of the corneal structure.\(^11,12\) Various structural and functional abnormalities of the cornea in diabetic patients, especially in the epithelium and endothelium, are called diabetic keratopathy.\(^11,12\)

Diabetes mellitus (DM) is one of the most common metabolic diseases that has become an epidemic of the 21st century.\(^13,14,15\) DM also has significant detrimental effects on the morphology, physiology and clinical appearance of the human cornea. Diabetic changes may manifest in the corneal epithelium, basement membrane, stroma, and endothelium.\(^13,14,15\) Stromal changes include structural alterations produced by collagen crosslinking that may cause increased stiffness of the cornea; this in turn may affect the measurement of intraocular pressure (IOP), causing over-estimation of the true intraocular pressure.\(^14,15\)

The purpose of the present paper is to present the results of central corneal thickness measurements in diabetic patients with or without retinopathy, and compare the results with non-diabetic control patients.
Materials and methods

The study included diabetic eyes for the study or experimental group, and healthy non-diabetic eyes for the controls. As there were good correlations between measurements in both eyes, only the readings from right eyes were used for analysis. If there were asymmetric retinopathies, the more seriously affected eye would be chosen. The study group was divided (stratified) into three subgroups, namely subgroup 1 (no diabetic retinopathy), subgroup 2 (mild to moderate nonproliferative diabetic retinopathy) and subgroup 3 (proliferative diabetic retinopathy). Diabetic retinopathy was classified by the ophthalmologist (TMS) according to the Early Treatment Diabetic Retinopathy Study (ETDRS) criteria. All subjects had clear corneas and anterior chambers without inflammation. The control group had no systemic diabetes and no ocular abnormalities.

Detailed eye examinations were performed including best corrected visual acuity, biomicroscopic evaluation of the anterior segment and dilated fundus examination with a 90-D lens. Central corneal thickness was measured with a Zeiss-Humphrey ultrasound biomicroscope, model number 840 (50 MHz) (Zeiss Humphrey, San Leandro, USA). The average of the last three of four successive measurements of CCT per eye was used for the analysis. Patients with keratoconus, keratoconjunctivitis sicca, ptosis, ocular trauma, glaucoma, retinal laser treatment, and any history of ocular surgery were excluded. Patients with anterior chamber neovascularisation and contact lens wearers were also excluded from the study. The study was conducted according to the Declaration of Helsinki.

Procedure

The central corneal thickness was measured using ultrasound pachymetry, with each subject comfortably seated on a chair with the head upright and eyes in the primary position of gaze, fixating on an optotype chart on a distant wall (6 metres). The probe was sterilised with 70% alcohol and allowed to air dry. A drop of topical anaesthetic (0.4% Novesin) was instilled in the subject’s right eye. As best as could be judged manually, the probe was carefully aligned centrally and perpendicular to the corneal surface whilst lightly applanating the cornea in front of the centre of the pupil. Four consecutive measures or readings were taken but only the last three of them were considered for analysis, and the mean or average was calculated as the measured central corneal thickness in microns (μm). The first measurement was performed only to make the patient feel comfortable with the procedure.

Statistical analyses were performed using SPSS (version 22, SPSS, Chicago, IL, USA). Student’s t-test was used to compare means, and p-values ≤ 0.05 were considered statistically significant.

Results

Overall, 115 eyes were included in the analysis. There were 50 male and 65 female subjects. The study group comprised 65 diabetic patients (30 men and 35 women) with a mean age of 56.08 years, ranging between 38 and 74 years. The average age of the control group of 50 eyes was 57.56 years, ranging between 48 and 68 years. There were 20 men and 30 women in the control group.

For the diabetic patients, the average CCT was 567.14 mm ± 14.63 mm, ranging between 533 μm and 598 μm (Table 1). The increase in CCT found in diabetic patients compared with that of non-diabetic patients was statistically significant (p < 0.005). The mean CCT of Type 1 diabetic patients was 567.15 μm ± 12.7 μm, whilst that for Type 2 was 567.20 μm ± 15.7 μm (Table 2). The mean CCT of subgroup 3 (577 μm ± 11 μm) was thicker than that of subgroups 1 (566.86 μm ± 15 μm) and 2 (562.7 μm ± 13 μm), but the difference was not statistically significant (p > 0.005). Also, the mean CCT measurements in Table 3 were not statistically significantly different between the diabetic patients with retinopathy (subgroups 2 and 3, mean CCT 569 μm ± 12 μm) and those without retinopathy (subgroup 1, mean CCT 566.86 μm ± 15 μm).

Table 1: Mean Central corneal thickness in microns (μm) of diabetic and non-diabetic patients.

<table>
<thead>
<tr>
<th>Patients</th>
<th>n</th>
<th>Central corneal thickness (μm)</th>
<th>Mean</th>
<th>Standard deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetic</td>
<td>65</td>
<td>567.14</td>
<td>14.63</td>
<td></td>
</tr>
<tr>
<td>Non-diabetic</td>
<td>50</td>
<td>531.14</td>
<td>43.4</td>
<td></td>
</tr>
</tbody>
</table>

Table 2: Mean Central corneal thickness of Type 1 and Type 2 diabetic patients.

<table>
<thead>
<tr>
<th>Diabetic type</th>
<th>n</th>
<th>Central corneal thickness (μm)</th>
<th>Mean</th>
<th>Standard deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1</td>
<td>20</td>
<td>567.15</td>
<td>12.7</td>
<td></td>
</tr>
<tr>
<td>Type 2</td>
<td>44</td>
<td>567.20</td>
<td>15.7</td>
<td></td>
</tr>
</tbody>
</table>

Table 3: Central corneal thickness in microns of the subgroups of diabetic patients.

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>Central corneal thickness</th>
<th>Mean</th>
<th>Standard deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subgroup 1</td>
<td>35</td>
<td>566.86</td>
<td>15.0</td>
<td></td>
</tr>
<tr>
<td>Subgroup 2</td>
<td>20</td>
<td>562.70</td>
<td>13.0</td>
<td></td>
</tr>
<tr>
<td>Subgroup 3</td>
<td>10</td>
<td>577.00</td>
<td>11.7</td>
<td></td>
</tr>
</tbody>
</table>

Note: Subgroup 1 represents patients without diabetic retinopathy, subgroup 2 patients with nonproliferative diabetic retinopathy and subgroup 3 patients with proliferative diabetic retinopathy.
Diabetic patients also indicate outliers. Measurements 2, 4, 18, 28, 31 and 32 are deemed to be outliers as they are different to the rest (Figure 1). The boxplot or box-and-whisker plot is a graphical representation of the spread or dispersion of data; such a plot provides some understanding of the shape of the distribution.

The most commonly used methods for investigating the relationship between two quantitative variables are correlation and linear regression;¹⁹ in this study, therefore, correlation and linear regression analyses were performed. Correlation quantifies the strength of the linear relationship between CCTs in diabetic and non-diabetic patients, whereas regression expresses the relationship in the form of an equation (\(y = \beta_0 + \beta_1 x\), where the coefficient \(\beta_0\) is the intercept of the line on the y axis and \(\beta_1\) is the slope or gradient). Once \(\beta_0\) and \(\beta_1\) are known, we can use the equation to predict the value of the CCT of any diabetic patient for any given CCT value in a non-diabetic patient. The coefficient of determination (\(r^2\)) expresses the strength of the relationship between diabetic and non-diabetic variables. It varies from 0 to 1, with values near 1 meaning that the dependent values fall almost on the regression line, whilst values near zero mean there is very little relationship between CCT measurements in diabetics and non-diabetic patients. In the present study, \(y = 629.711 - 0.118x\) (x represents non-diabetic patients), \(r^2 = 0.104\) and \(p = 0.022\) (Figure 3). These figures mean that there is a weak negative relationship between the CCT measurements in diabetic and non-diabetic patients.

Table 4 is presented because the SPSS output for regression analysis is given in the form of analysis of variance (ANOVA) table. The \(p\) value is determined from the \(F\) ratio which is computed from the ANOVA table, and the two values of degrees of freedom are shown in the ANOVA table. ANOVA partitioned the variability amongst all the CCT measurements into one component that arises from variability amongst group means and another component that arises from variability within groups (residual variation). A significant \(F\) value (\(p < 0.05\)) tells us that the population means are probably not equal.

**Discussion**

The measurement of central corneal thickness has become a very exciting ocular parameter owing to its importance as an indicator of corneal health status, and decisions
involved refractive surgery are sometimes dependent on CCT amongst other variables. In the present study, we found a mean CCT of $567.14 \pm 14.6 \mu m$ and $531.14 \pm 43.4 \mu m$ in the diabetic and control groups, respectively, and this difference was statistically significant. There was no statistical or clinical difference between the CCT in Type 1 and Type 2 diabetic subjects. The mean CCT was found to be greater in eyes with proliferative diabetic retinopathy than in eyes with nonproliferative diabetic retinopathy and no diabetic retinopathy; however, the differences were not statistically significant between patients with retinopathy and those without retinopathy. The results of the present study correlate with previous studies done in other countries. For example, Busted et al. also reported that diabetic corneas were significantly thicker than normal corneas in a sample size of 81 diabetic patients. In addition, they did not find any significant correlation between disease duration and CCT. They concluded that higher CCT values could be because of increased hydration of the cornea and corneal endothelial dysfunction. Keolain et al. discovered that diabetic patients frequently had abnormal corneal endothelium in contrast to normal persons. A study by Lee et al. found that diabetic patients have more corneal morphological abnormalities than non-diabetic subjects, and CCT was significantly correlated with the duration of diabetes. They also noticed that older diabetic patients had thicker corneas than young diabetics. The reason is unknown but is believed to be related to the dysfunction of the corneal endothelial pump and increased corneal hydration.

Su et al. conducted a population-based study on 3280 Malay adults, ages ranging from 40 to 80 years. CCT measurements were obtained from the right eye of each subject. The effects of age, gender, duration of DM, mean Hba1c level and fasting blood sugar level on CCT were investigated. They found that hyperglycaemia was associated with thicker central corneas. They further reported that the current Hba1c value was a perfect predictor for CCT measurements. In their study, patients were grouped according to glucose level but the stages of diabetic retinopathy were not considered. They explained that this association could result from corneal endothelial dysfunction, stromal hydration and swelling of the cornea.

Ozdamar et al. conducted a study to investigate the association of CCT with DM and compare it with age- and sex-matched healthy controls. They included measurements of one eye per subject in their analysis in a sample of 245 subjects. There were 100 diabetic patients who constituted the study group and 145 healthy controls. The mean age of the subjects was 58.4 ± 8.6 years (age range 42–79 years) in the study group and 57.3 ± 4.7 years (age range 50–60 years) in the control group. They reported that the CCTs of diabetic patients were thicker than those of non-diabetic patients. However, a study conducted by Wiemer et al. found no differences in the CCT measurements between diabetic and healthy subjects. They measured the CCT with Scheimpflug imaging; therefore, the differences between these studies could be the measuring methods.

Although CCT changes associated with DM have been reported in previous studies, there are differences in the pathogenesis hypothesis. Some possible mechanisms of corneal thickness could include the activation of the polyol pathway, accumulation of advanced glycation end products (AGEs) and increased osmotic stress. In the polyol pathway, the aldose reductase enzyme which is present in the cornea metabolises excess glucose into sorbitol. Sorbitol is a sugar alcohol and strongly hydrophilic, and therefore does not diffuse easily through the cell membrane but accumulates intracellularly with possible osmotic consequences. The build-up of sorbitol leads to the increased production of reactive oxygen species (ROS) within the cell. AGEs arise from non-enzymatic reactions between extracellular proteins and glucose. AGEs alter the cell function by impairing the function of cellular proteins and lipids. AGEs form at a constant but slow rate in a non-diabetic body but their formation is greatly accelerated in diabetes because of the increased availability of glucose. AGEs form irreversible crosslinks with collagen. Collagen crosslinks may lead to increased corneal stiffness and thickness. This is the most likely explanation for the increased central corneal thickness in diabetic patients.

Possible limitations of our study are that the duration of DM, the haemoglobin A1c (Hba1c) level, fasting blood sugar level, hypertension, dyslipidaemia were not measured. Ultrasound pachymetry is probably the most common clinical method for measuring CCT; but the main disadvantages of this method include the use of local anaesthetic which may alter corneal thickness, and the location where the ultrasound probe is applied may vary in repeated measurements because there is no fixation target for controlling eye movements. This method may yield slightly thinner measurements as a result of tissue indentation. Mild patient discomfort and risk of infection are some additional concerns with a contact method. The advantages of this method include ease of use, portability and low cost.

However, several newer noncontact technologies for the measurement of corneal thickness have shown better repeatability and reproducibility. These include the Pentacam, the Orbscan and optical coherence tomography (OCT), amongst others. These devices use light instead of sound to measure corneal thickness and are noncontact systems. Measurement of the CCT with noncontact methods such as OCT probably would be a better option. Another limitation was that we did not include patients with ocular hypertension and glaucoma in the study.

**Conclusion**

Diabetic patients exhibit a greater statistically significant average CCT than non-diabetic patients. The study suggests that diabetic patients show thicker corneas as one of the often unnoticed signs associated with the disease. Thicker central corneas associated with DM should be taken into consideration whilst obtaining accurate IOP measurements.
in diabetic people. Although diabetic retinopathy leads to severe vision loss, keratopathy should also be recognised as a major complication in diabetic patients.

Acknowledgements

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

S.D.M. (University of Limpopo) was responsible for experimental design and statistical analysis. T.M.S. (Netcare Ferncrest Hospital) performed all the experimental data. The authors contributed equally to the study.

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