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Effect of glycaemic control on corneal parameters among type 2 diabetes mellitus

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Abstract

Purpose: To study the effect of glycaemic control as demonstrated by the change in HbA1c on corneal parameters among patients with type 2 diabetes mellitus (T2DM). Study design: Prospective study analysing corneal parameters among patients with T2DM along with fluctuations in HbA1c.
Methods: A prospective, single-centre, cohort study was carried out on T2DM patients with HbA1c > 6.5% from Kasturba Hospital, Manipal, India. The subjects underwent a comprehensive eye examination. One-hundred and twenty-two subjects who fulfilled the inclusion criteria were analysed using the Huvitz 9000A to measure anterior corneal curvature followed by ultrasound pachymetry to measure central corneal thickness (CCT) at baseline and after 3 months. A simple linear regression was used to compare the mean corneal parameters, CCT and anterior corneal curvature, for each group with the mean HbA1c. The mean difference was considered statistically significant only if the value was $p < 0.05$.
Results: We observed a significant difference between baseline and follow-up levels of HbA1c ($t = 2.487$; $df = 53$; $p < 0.05$). Simple linear regression analysis showed a positive correlation and revealed a mean increase in CCT of 1.893 µm ($p < 0.001$) and a mean increase in anterior corneal curvature of 0.069 D ($p < 0.005$) for every unit increase in HbA1c.
Conclusions: The present study showed that changes in CCT and anterior corneal curvature occur with respect to changes in HbA1c level. Thus, careful attention is

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required in considering HbA1c status when performing comprehensive eye examinations in diabetic patients.

Keywords: central corneal thickness, corneal curvature, diabetes mellitus type 2, HbA1c

Kesan kawalan glisemik pada parameter kornea di kalangan diabetes mellitus jenis 2

Abstrak

Tujuan: Untuk mengkaji kesan kawalan glisemik seperti yang ditunjukkan oleh perubahan HbA1c pada parameter kornea di kalangan pesakit diabetes mellitus jenis 2 (T2DM).
Reka bentuk kajian: Kajian prospektif menganalisis parameter kornea di kalangan pesakit dengan T2DM bersama-sama dengan perubahan turun naik dalam HbA1c.
Kaedah: Kajian kohort prospektif, pusat tunggal, telah dijalankan ke atas pesakit T2DM dengan HbA1c > 6.5% dari Hospital Kasturba, Manipal, India. Subjek menjalani pemeriksaan mata yang komprehensif. Seratus dua puluh dua subjek yang memenuhi kriteria inklusi dianalisis menggunakan Huvitz 9000A untuk mengukur kelengkungan kornea anterior diikuti oleh pachymetry ultrasound untuk mengukur ketebalan kornea pusat (CCT) pada garis dasar dan selepas 3 bulan. Regresi linear mudah digunakan untuk membandingkan parameter kornea min, CCT dan kelengkungan kornea anterior, bagi setiap kumpulan dengan min HbA1c. Perbezaan min dianggap signifikan secara statistik hanya jika nilainya adalah $p < 0.05$.
Keputusan: Kami melihat perbezaan yang ketara antara tahap asas dan susulan HbA1c (t = 2.487; df = 53; $p < 0.05$). Analisis regresi linear mudah menunjukkan korelasi positif dan mendedahkan peningkatan purata dalam CCT sebanyak 1.893 μm ($p < 0.001$) dan peningkatan purata kelengkungan kornea anterior sebanyak 0.069 D ($p < 0.005$) bagi setiap peningkatan unit dalam HbA1c.
Kesimpulan: Kajian ini menunjukkan bahawa perubahan dalam CCT dan kelengkungan kornea anterior berlaku berkenaan dengan perubahan dalam tahap HbA1c. Oleh itu, perhatian yang teliti diperlukan dalam mempertimbangkan status HbA1c apabila melakukan pemeriksaan mata yang komprehensif dalam pesakit diabetes.

Kata kunci: diabetes mellitus jenis 2, HbA1c, kelengkungan kornea, ketebalan kornea pusat

Introduction

India is the diabetes capital of the world with 65.1 million diabetic individuals in 2013, which is expected to rise to 1.9 million by the year 2035. Several studies have reported the growth of the type 2 diabetes mellitus (T2DM) epidemic in India.[1] A standardized, quality measure for diabetes mellitus (DM) is glycosylated haemoglobin, type A1c (HbA1c). When comparing venous plasma to HbA1c, the latter is much more accurate. HbA1c of 6.5% has a good sensitivity of 65% and specificity of 88% in detecting DM. Hence a cut-off value of 6.5% for HbA1c is a reliable diagnostic factor for classifying a person as DM.[2,3]

Multiple factors such as lifestyle modification, living standards, genetic factors, and an upsurge in urban migration contribute to the aetiology of diabetes among the Indian population. Even though Western countries have risk factors such as high obesity and overweight rates compared to the Indian population—which has a lean body mass index—the Indian population is prone to have a higher rate of DM. One of the causes for this discrepancy could be a genetic predisposition for the development of coronary artery disease, which in turn is due to low levels of high-density lipoproteins and dyslipideamia. Consequently, Indians tend to develop complications of DM in much earlier stages of life.[4]

DM can affect all ocular structures. It is well established that DM plays a crucial role among the leading causes of blindness,[5] and leads to ocular diseases such as diabetic retinopathy (DR), glaucoma, diabetic keratopathy, cataract, eye muscle palsy (especially lateral rectus), and retinal vascular occlusion.[6]

Sukla *et al.* and Huntjens *et al.* have shown a correlation between central corneal thickness (CCT) and HbA1c in 2016 and 2012, respectively.[7,8] Similarly, in 2005 Sonmez *et al.* demonstrated a weak positive correlation between anterior corneal curvature and HbA1c.[9] While the published literature has found an association between corneal parameters and HbA1c, the same is not true regarding the amount of change in corneal parameters with each unit change in HbA1c. Fluctuations in HbA1c may alter corneal thickness and curvature, and these changes may lead to visual degradation. The purpose of this research was to study the effect of glycaemic control as demonstrated by the change in HbA1c on corneal parameters, CCT and anterior corneal curvature, among patients with T2DM invariable of diabetic retinopathy status in the Indian population.

Methods

The study protocol was approved by the Institutional Ethics Committee (IEC) of Kasturba Hospital and Manipal (IEC-227/2016). The study conformed to the tenets of the Declaration of Helsinki. A prospective cohort-observational study was done by including DM patients from Kasturba Hospital. Following an explanation of the procedure in plain terms the subjects could understand and obtaining written informed consent, 160 subjects whose HbA1c was greater than 6.5% underwent a compressive eye examination.

The comprehensive eye examination started with previous ocular history, vision assessment (using logMAR chart), and refraction. Undilated retinal examination was carried out for all the study participants with the help of a Smart scope (Bosch Private Limited, Bangalore, India). Subjects with a history of any previous ocular surgery, chronic use of any ocular medications, contact lens use, retinal photo-coagulation within 1 month of the study, and any other ocular diseases such as pterygium, entropion, or ocular conditions interfering with tearing, such as dry eye, were excluded from the study as they may alter the corneal parameters. Subjects with systemic conditions influencing HbA1c such as anaemia, hemoglobinopathy, pregnancy, hepatic or renal disease, and hypothyroidism were also excluded.

By using the formula $n = [\sigma^2 (Z_{1-\alpha/6} + Z_{1-\beta})^2] / d^2$, we calculated the sample size as 116 along with a dropout percentage of 20%, as this was a prospective study [where, $Z_{1-\alpha/6}$ = 2.39 for 5%; $Z_{1-\beta}$ = 0.84 for 80% power, σ = SD of the observation (from a previous study)[10] d = clinically significant difference). Among the 160 subjects approached, 122 were shortlisted according to the inclusion and exclusion criteria and went on to evaluation. Anterior corneal curvature was measured with the Huvitz 9000A (Huvitz Bldg, Gyeonggi-DO, South Korea). An average of three values was taken for anterior corneal curvature and from that value, the average of flat and steep meridians was considered for analysis. CCT was measured using ultrasound pachymetry. Ten readings were obtained on continuous contact of the probe with the anterior surface of the cornea, two extreme high values and two extreme low values were excluded, and an average of the six readings was taken as one reading. The same procedure was repeated thrice and an average of these three readings recorded for analysis. Since ultrasound pachymetry is a contact procedure that may alter anterior corneal curvature readings, it was performed last. All the readings were taken between 09:00 and 17:00 hours. Intraocular pressure (IOP) was measured only after CCT measurement, as it may alter CCT values.

Although standard protocols outline follow-ups for DM every 6 months, HbA1c values are valid for only 3 months. Therefore, follow-up was shortened to 3 months in our study. In the follow-up visit, after HbA1c was measured, the subjects again underwent the same procedures, namely, Huvitz 9000A and ultrasound pachymetry for anterior corneal curvature and CCT, respectively.

Statistical analysis

Data analysis was done using SPSS software version 16. Paired t-test was used to evaluate the difference in baseline and follow-up values of HbA1c. A simple linear regression was used to compare the mean corneal parameters, CCT and anterior corneal curvature, for each group with the mean HbA1c. The mean difference was considered statistically significant only if the value was $p < 0.05$.

Results

Table 1 shows the demographic details and retinal status between OD and OS. Subjects had a median (interquartile range) spherical equivalent (SE) of 0.13 D (-0.25 to +1.16) and 0.34 D (+0.00 to +1.25) for OD and OS, respectively.

Our study classified DR based on the Internal Classification of Diabetic Retinopathy (ICDR). As shown in Table 1, 7.38–8.20% of eyes had mild non-proliferative diabetic retinopathy (NPDR), 4.10–5.47% of eyes had moderate NPDR, 1.64–2.46% of eyes had severe NPDR, and 0.82–0% of eyes had proliferative diabetic retinopathy (PDR) among the 122 subjects recruited. As the recruited subjects had DM for less than a decade, with a mean duration of DM of 5.59 ± 0.44 years, most eyes were only in the early stages of DR, corresponding to mild and moderate NPDR.

Pearson's correlation between OD and OS was strong for both variables, CCT and anterior corneal curvature (r = 0.957 and 0.939, respectively), with a statistical significance of $p < 0.001$. Hence, only OD was considered for analysis. Paired t-test was done between baseline and follow-up HbA1c levels, which was statistically significant (t = 2.487; df = 53; $p < 0.05$). The correlation between CCT with age, and CCT with DM duration, both were not statistically significant, as it was in the case of anterior corneal curvature with age, and anterior corneal curvature with DM duration, respectively ($p < 0.05$).

Table 1. Demographic details and retinal status between OD and OS

Parameter	OD	OS
Age*	54 ± 9 years	
Sex (M:F)	1.3:1 [male: 57% (n = 69); female: 43% (n = 53)]	
Duration of DM*	5.59 ± 0.44 years	
LogMAR visual acuity*	0.17 ± 0.18	0.16 ± 0.18
Refractive error SE**	+1.28 D (-0.19 to +1.09)	+1.25 D (+0.00 to +1.25)
IOP*	13.93 ± 2.14	14.07 ± 2.13
Retina WNL	69.67% (n = 85)	68.85% (n = 84)
Tessellated retina	22.95% (n = 28)	23.77% (n = 29)
Mild NPDR	7.38% (n = 9)	8.20% (n = 10)
Moderate NPDR	4.10% (n = 5)	5.47% (n = 7)
Severe NPDR	1.64% (n = 2)	2.46% (n = 3)
PDR	0. 82% (n = 1)	0.00% (n = 0)

DM: diabetes mellitus; SE: spherical equivalent; IOP: intraocular pressure; WNL: within normal limits; NPDR: non-proliferative diabetic retinopathy; PDR: proliferative diabetic retinopathy

*Mean ± standard error of the mean

**Interquartile range

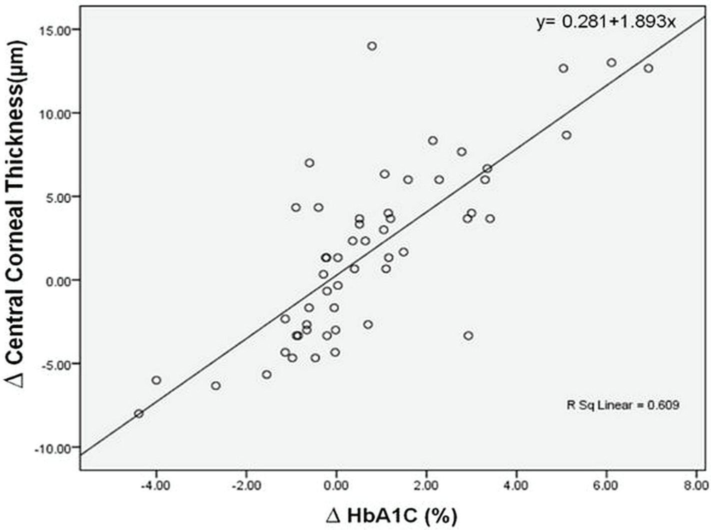

Fig. 1. Scatter plot showing the relationship between ΔCCT and ΔHbA1c.

A simple linear regression analysis was done along with adjustment for mean difference of baseline and follow-up HbA1c levels and the mean difference of baseline and follow-up of CCT for OD. A positive correlation was found between the mean difference of CCT and the mean difference of HbA1c. On average, for every unit increase in difference of HbA1c, there was an increase of 1.893 µm in the difference of CCT ($p < 0.001$), as shown in Figure 1.

To understand the relationship between CCT and HbA1c in depth, further detailed analysis was performed in subgroups based on HbA1c values. Hence, based on the median value of HbA1c (8.605) from the baseline visit, two groups were subdivided: a low HbA1c group (< 8.065) and a high HbA1c group (> 8.065). A simple linear regression analysis was carried for the two groups separately which found that, on average, for a unit increase of difference in HbA1c, CCT increased by 2.563 µm, provided the HbA1c value was less than 8.065. Likewise, on average, for a unit increase of difference in HbA1c, CCT increased by 1.949 µm, provided the HbA1c value was greater than 8.065, as shown in Figure 2.

Even though there was a strong positive correlation between the high HbA1c group and CCT ($r = 0.901$, $p < 0.001$) when compared to the correlation between low HbA1c group and CCT ($r = 0.510$, $p < 0.05$), the amount of change with a unit change in HbA1c was greater in the low HbA1c group than in the high HbA1c group.

The simple linear regression for anterior corneal curvature and HbA1c revealed a weak positive correlation ($r = 0.349$). On average, for every unit increase in difference of HbA1c, there was an increase of 0.069 D in the difference of anterior corneal curvature ($p < 0.05$), as shown in Figure 3.

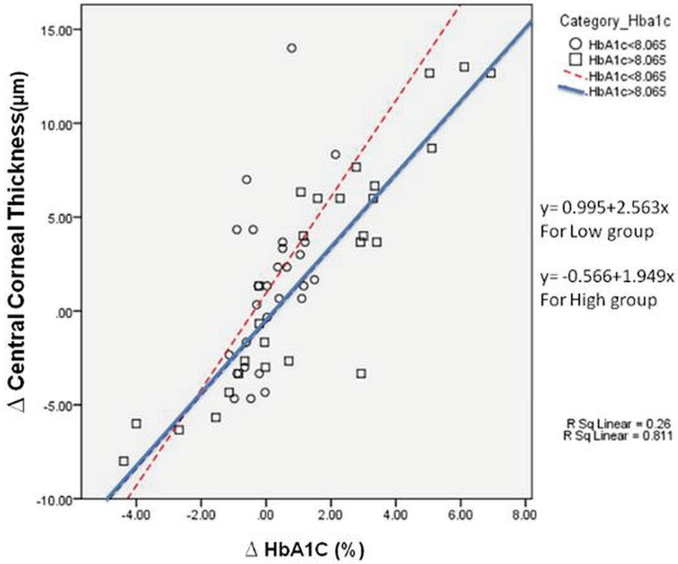

Fig. 2. Scatter plot showing the relationship between ΔCCT and ΔHbA1c among the low and high HbA1c groups.

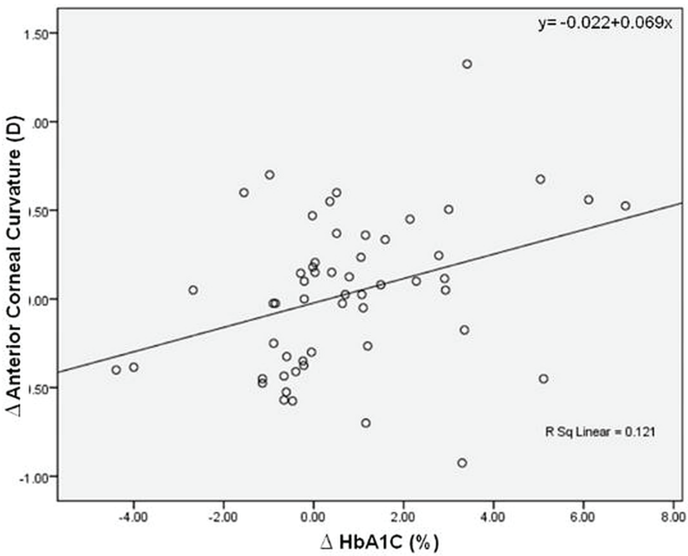

Fig. 3. Scatter plot showing the relationship between Δanterior corneal curvature and ΔHbA1c.

Discussion

The main outcomes of this study demonstrate that both CCT and anterior corneal curvature increase when there is an increase in HbA1c values. Reports have shown an overestimation of IOP in DM patients. This could be due to corneal stiffening caused by high levels of glucose.[5,11] Since our study found a strong positive correlation between CCT and HbA1c, measurement of glucose levels and CCT are necessary to avoid imprecise measurements of true IOP in DM patients.

A study by Shukla *et al.* found a strong correlation between mean CCT and HbA1c values ($r = 0.85$, $p < 0.05$), where analysis was done with only one visit. Our study found a strong correlation between mean difference of CCT (baseline and follow-up) and mean difference of HbA1c ($r = 0.78$, $p < 0.001$). The difference noted between Shukla *et al.* and our study may be due to intrasubject and intersubject variation, where confounding factors such as age and gender might play a role.[7]

Huntjens *et al.* conducted a study with type 1 DM (T1DM) and T2DM patients and found that an increase of 4.5 mM/l would consecutively increase 10 µm of CCT (approximately, a 1% increase in HbA1c corresponds to a 2.2 µm increase in CCT).[8] Our results revealed a mean increase of 1.9 µm in CCT for every unit increase in HbA1c. Given that the clinical features and complications of T1DM and T2DM are different, the discrepancy between our results and those of Huntjens *et al.* may be due to the inclusion of both types of DM in the latter study while we only included T2DM.

While a study by Su *et al.* found an average decrease in CCT of 5.13 µm per decade increase in age,[12] our study found no statistically significant correlation between age and CCT.

Our study found a weak correlation between CCT and DM duration, similar to the findings of Shukla *et al.*[7] Whereas our study found no statistical significance between DM duration and CCT, Lee *et al.*[13] and Pai *et al.*[14] found a statistically significant correlation between DM duration and CCT. The conflicting results between our study and Lee *et al.* and Pai *et al.* may be due to the different ranges of DM duration. Unlike our study, a few other studies found no statistical significance between CCT and glycaemic levels.[8,15,16]

Our study observed a weak positive correlation between anterior corneal curvature and glycaemic levels in DM patients, which is in concordance to Sonmez *et al.*, who noted a statistical difference only at the flattest meridian.[16] In our study, statistical significance was observed regarding the change in average anterior corneal curvature and change in HbA1c levels. In contrast to the present study, Rico *et al.* reported no significant change in anterior corneal curvature with changes in glycaemic levels.[15]

Whereas Huntjens *et al.* did not find a statistically significant change in anterior corneal curvature and glycaemic level,[8] our study found that, on average, a unit increase in HbA1c gives rise to a 0.069 D increase in anterior corneal curvature, which is statistically significant. However, their study considered venous plasma levels for analysis, which could be influenced by medication, diet, and exercise.

The main limitations of the present study were its short duration and not accounting for diurnal variation of corneal thickness for the ease of the study. Further studies should address the comparison of corneal thickness with HbA1c fluctuations in accordance with different types of treatment modalities and a wider range of DM duration, since few studies have found morphological changes in the cornea mostly after 10 years of onset of DM.

Conclusion

We found that blood glucose levels measured in terms of HbA1c have a significant impact on corneal thickness. The present study showed that changes in CCT and anterior corneal curvature occur in correspondence to changes in HbA1c levels. Thus, careful consideration of HbA1c status is required when conducting comprehensive eye examinations in diabetic patients.

Declarations

Ethics approval and consent to participate

The study protocol was approved by the Institutional Ethics Committee (IEC) of Kasturba Hospital and Manipal (IEC-227/2016). The study conformed to the tenets of the Declaration of Helsinki. A prospective cohort-observational study was done by including DM patients from Kasturba Hospital. After an explanation of the procedure in plain terms the subjects could understand, written informed consent was obtained from all participants.

Competing interestes

None to declare.

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None to declare.

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