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A Prospective Study to Correlate Glycosylated Hemoglobin (HBA1C) with Central Corneal Thickness (CCT) and Intraocular Pressure (IOP) in Type 2 Diabetic Patients

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Abstract: ***Purpose: To evaluate the correlation of glycosylated hemoglobin (HbA1c) with central corneal thickness (CCT) and intra ocular pressure (IOP) in type 2 diabetes mellitus patients. Methods: In a prospective study, 200 eyes of 100 patients of type 2 diabetes mellitus, in age group 30 to 80 years of either gender were evaluated for their HbA1c. The cohort was subdivided into 2 groups, with the cut off value of HbA1c of 8%. IOP measurements were obtained by Goldmannapplanation tonometry. Pachymetry was done by NIDEK NT 530P and corrected IOP was calculated using Ehlers equation. The values were compared using correlation coefficient &t-test. Results: HbA1c values had positive correlation with CCT(r=0.27) and Corrected IOP(r=0.22).On comparison on t test, the p values were significant, <0.03 &<0.04 respectively. High CCT values and high IOP were found to have higher prevalence in group with HbA1c>8%. Conclusion: In patients with type 2 diabetes, higher HbA1c values were positively related to higher CCT values and higher CIOPs, in a statistically significant way.***

Keywords: Glycosylated Hemoglobin, Central Corneal Thickness, Intraocular Pressure, Applanation Tonometry

1. Introduction

Diabetes mellitus has emerged as an important cause of concern because of its adverse pathological effects on various tissues. India and China have the largest diabetic populations in the world.[1,2] Main indicators of diabetes in ocular tissues are retinopathy, cataract and glaucoma. In a diabetic patient, visible lesions take years to develop. However, functional abnormalities may be detected long before anatomical changes are evident. Very early in the disease an increased permeability of the capillary endothelium to plasma proteins is found.[3] The corneal changes associated with Diabetes mellitus is known as diabetic keratopathy, a lesser studied pathology.[4] If corneal endothelial function is compromised, corneal hydration and consequently the corneal thickness will increase.[5] An increased serum level of glycosylated hemoglobin increases the predisposition to impaired corneal epithelial barrier function. Advanced milliard products accumulate in collagen proteins result in the formation of covalent cross linking bonds and may lead to increased corneal thickening and biochemical changes. The corneal endothelium in diabetic patients is considered as a tissue under continuous metabolic stress and it has increased coefficient of variation of endothelial cell area, decreased percentage of hexagonality and increased corneal autofluorescence. The central corneal thickness is a sensitive indicator of health of cornea and serves as an index for corneal hydration and metabolism. The range of intraocular pressure (IOP), among the general population, varies from 10-21 mmHg. Although diabetes is associated with higher IOP values in most population studies, the underlying mechanisms are still unclear. This study is aimed to evaluate the effect of diabetes mellitus on central corneal thickness (cct) and Intra ocular pressure (IOP) and association of them with serum levels of HbA1c.

2. Materials and Methods

The study was conducted at the Department of Ophthalmology, Chattrapati Shivaji Subharti Medical College, Meerut. The patients were diagnosed to be having type 2 diabetes mellitus based on HbA1c levels >6.5% (48 mmol/mol), patients with prediabetes (HbA1c ≥5.7%) [39 mmol/mol].FPG ≥126 mg/dL (7.0mmol/L). Fasting is defined as no caloric intake for at least 8 hours. Also, according to latest guidelines of American Diabetes Association (ADA), the cut off value for division of two groups in the study was taken, viz.:- Group 1 - <8 % HbA1c and Group 2 - >8 % HbA1c. The above division was considered because in studies conducted by ADA, it showed that incidence of microvascular complication rates increase in diabetics with HbA1c >8% as compared to lesser values of the same.The patients will be included in the study if they are classified as type 2 diabetics either by a medical officer or on examination. Patients having any corneal disease (pterygium, corneal dystrophies etc.), previous use of hard contact lenses, positive history of glaucoma, previous anterior segment surgery, laser treatment, positive history of systemic hypertension, patients using any topical medications, patient with history of trauma to the eye were not included in the study.

3. Observations and Results

A prospective study was conducted in Department of Ophthalmology, Chattrapati Shivaji Subharti Medical College, Meerut, India, from July 2017 to April 2019 in 200 eyes of 100 patients with type 2 diabetes mellitus. The Institutional review board and the Ethics committee approved the trial. A written informed consent was taken from all the participating patients in accordance with the tenets of declaration of Helsinki.

Table 1: Gender and Age Distribution According to Groups

	Group 1 (HbA1c <8%)	Group 2 (HbA1c >8%)	Average
Males	24	23	23.5
Females	19	34	26.5
Total (n)	43	57	
Mean Age	53.06±8.79	56.85±11.20	

Table 2: Distribution of HbA1c in two groups for 100 patients:

	Group 1	Group2
Range Of HbA1c (%)	6.0-7.9	8.2-13.4
Average	7.2±0.49	9.5±1.30
CCT (microns) Range	447-629	456-621
Average CCT (microns)	540.91±44.72	539.21±37.26
Corrected IOP (mm of Hg) Range	8-24	9-26
Corrected IOP Average (mm of Hg)	14.6±3.25	16.1±3.05

Correlation of HbA1c with central corneal thickness of right eye for 100 patients:

Table 3: HbA1c and CCT of Right Eye for 100 Patients

	HbA1c (%)	Central Corneal Thickness (microns)
Range	6.0-13.4	447-629
Average Values	8.5±1.55	539.8±40.44

a) On applying Karl Pearson's Correlation coefficient for 100 patients, to find out correlation between HbA1c and CCT of right eye, following result was obtained:-
- R- value = 0.207
- P- value = 0.03

Correlation of HbA1c with corrected intraocular pressure of right eye for 100 patients:-

Table 4: HbA1c and corrected intraocular pressure of right eye of 100 patients

	HbA1c (%)	Corrected Intraocular Pressure (mm of Hg)
Range	6.0-13.4	8-26
Average Values	8.5	15.46
Standard Deviation	1.55	3.52

b) On applying Karl Pearson's Correlation coefficient for 100 patients, to find out correlation between HbA1c and CIOP of right eye, following result was obtained:-
- R- value = 0.242
- P- value = 0.15

Correlation of hba1c with central corneal thickness and corrected intraocular pressure of right eye between groups 1 and 2:-

In the following correlations, Karl Pearson's Correlation coefficient has been used to check for presence of a positive or a negative correlation among the parameters.

1) Group 1: HbA1c < 8% :-

a) Correlation of HbA1c and central corneal thickness:
- The R- value obtained = 0.419
- The P- value obtained = 0.005
- In the above result, R-value signifies a positive correlation of central corneal thickness with HbA1c and this relationship is significant at p<0.05 level of significance.

b) Correlation of HbA1c and Corrected IOP:
- The R- value obtained = -0.173
- The P- value obtained = 0.26
- According to the above result, R-value shows no positive correlation among the two parameters at HbA1c<8%, and the relationship is not significant at p<0.05 level of significance.

2) GROUP 2: HbA1c > 8%

a) Correlation of HbA1c and Central Corneal thickness:
- The R- value obtained = 0.276
- The P- value obtained = 0.03
- According to the above result, R- value shows a positive correlation between the two parameters, and the p-value give a significant result at p<0.05 level of significance.

b) Correlation of HbA1c and Corrected Intraocular pressure:
- The R- value obtained = 0.237
- The P- value obtained = 0.04
- As shown by above results, R- value shows a positive correlation between the parameters, the p-value also shows a significant result at p<0.05 level of significance.

4. Discussion

In this study, 100 patients were divided in two groups according to HbA1c values; the age of patients was 30-80 years (Table 1). The mean range of age for group 1 was 53.06+/-8.79 years and for group 2 were 56.85+/-11.20 years (Table 1).

In 2007, Oshitari T et al[6] investigated the effect of chronic hyperglycemia on intraocular pressure and the age group used was 50-80 years. In 2017, Chowdharyet al[7] conducted a study to correlate HbA1c with IOP and CCT in type 2 diabetics, where the mean age was 57.96+/-11.59 years (range 35-82 years). In 2016, Briggs et al[8] compared central corneal thickness, corneal endothelial cell density and intraocular pressure in type 2 diabetics with mean age of 55.8+/-12 years for controls and 55.7+/-11.5 years for cases, with a range of 30-85 years. In this study, out of 100 patients, group 1 had 24 males and 19 females (total 43), while group 2 had 23 males and 34 females (total 57) (Table 1), with an average of 23.5 males and 26.5 females divided between the two groups. Thus, the two groups were matched in reference to age and gender distribution. On comparison of CCT between the two eyes of 100 patients, it was observed that the average CCT in right eye was 539.77±40.44 microns, and for the left eye the average value was 536.90±34.87 microns; also on application of T-test, the t value obtained was 0.52 and the p value was 0.59, which showed that there was no significant correlation between the two eyes and that either of the two eyes could be used to further correlate various parameters of the study. In this study we evaluated CCT of all patients using the right eye and when divided among the two groups, it was observed that the diabetic group with good metabolic control (Group1), had an average CCT value of 540±44.72 microns; while the group with poor metabolic control (group 2) had an average CCT of 539.21±37.26 (Table 2). Therefore, on correlating HbA1c with CCT for right eye of 100 patients, it

was observed that a positive correlation was present between the two and the result was significant at the assigned level of significance. However, when the correlation was divided between the two groups, it was observed that the correlation was more strongly positive for group1 (R-value=0.41) as compared to group 2 (R-value= 0.27). This shows that in early stages of diabetes mellitus, the central corneal thickness gets affected quite rapidly but as the levels of HbA1c increases over the later stages, the correlation becomes weaker, indicating that there is no linear association between HbA1c and CCT and with poor metabolic control and rising levels of HbA1c, the increase in central corneal thickness gets altered and the result becomes variable. Moreover, on comparing the CCT among two groups with T-test, it was observed that there was no significant change in values (t-value=-0.31, p-value=0.75), again signifying that though there is a positive correlation between HbA1c and CCT but with increasing levels of HbA1c, it is not necessary that the central corneal thickness would also increase at the same rate. Claramonte et al [9]reported a mean CCT value of 571.96±26.81µm in diabetic patients. While Su DH et al [10] observe CCT value of 547.2µm in patients with diabetes. Storr Paulsen A et al [11] also observed increased CCT value of 546µm in diabetic patients as compared to controls. In a study by Chowdhary et al [12] mean CCT values of patients with HbA1c <7% and >7% were 527.05±26.46µm and 541.83±30.45 µm respectively. In this study, CIOP was taken for 100 patients for both the eyes, and for right eye the average CIOP was 15.46±3.52 mm of Hg, while for left eye the average value was 15.76±3.27 mm of Hg.The CIOP values were then divided into two groups for right eye; it showed that the group with good metabolic control (Group 1) had average CIOP of 14.6±3.25 mm of Hg, while the group with poor metabolic control (Group 2) had average CIOP of 16.1±3.05 mm of Hg (Table 2).On correlating the values of CIOP with HbA1c for 100 patients for right eye, the result had a positive correlation and was significant at the kept level of significance; also the relationship between the two parameters remained positive with increasing levels of HbA1c. With increasing levels of HbA1c, the values of CIOP were also increasing with a strong positive correlation (R-value= 0.23) and the result was also significant at the assigned level of significance (p-value=0.04). Also, on comparing CIOP between two groups with T-test, a significant result was obtained (t-value=-2.1, p-value=0.03), implicating that CIOP does increase with poorly controlled diabetes and increasing levels of HbA1c. Therefore, in patients with diabetes CIOP can be used as an early marker to check for progression of open angle glaucoma, and with poorly regulated diabetes, the chances of developing glaucoma would also increase.Oshitari T et al [13]observed mean IOP of 15.5±2.5mm of Hg with HbA1c<8% and 16.6±2.4mm of Hg with HbA1c>8%. Khalaj M et al [14] reported a mean IOP of 16.7±1.96 mm of Hg in diabetic patients. Chowdhary et al [15] reported CIOP values for HbA1c <7% and >7% to be 13.93±2.93 mm of Hg and 14.77±3.40 mm of Hg respectively.

5. Conclusion

To conclude, in patients with type 2 diabetes mellitus, due to various unknown mechanisms, the biochemical and viscoelastic properties of the cornea gets altered and this leads to increase in central corneal thickness of the patients but the increment becomes variable on increasing levels of HbA1c. Also, due to changes in trabecular meshwork and various degradation mechanisms affecting the intraocular fluid in anterior chamber, the intraocular pressure also gets affected and the levels consistently increase with increasing levels of HbA1c or with poor metabolic control of diabetes. So in patients with diabetes IOP or CIOP can be used as an early marker to check for progression of open angle glaucoma, and with poorly controlled diabetes, the chances of developing glaucoma would also increase. Therefore, knowledge of these diabetes associated changes in corneal parameters and intraocular pressure and their regular monitoring may prevent vision loss by enabling early detection and treatment.

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