Original Article

Effect of Diabetes Mellitus on Central Corneal Thickness – A Comparative Study

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Purpose: To compare central corneal thickness (CCT) of diabetes Mellitus (DM) patientswith age matched subjects without DM and to evaluate the correlation of CCT with glycemic status, duration of DM and severity of diabetic retinopathy (DR).

Study Design: Cross sectional comparative study.

Place and duration of study: Eye Department, PNS Shifa Karachi from March 2016 to February 2017.

Material and Methods: Patients with ages between 20 to 80 years of either gender who were diagnosed to have DM were recruited in the study. Control group comprised of age matched healthy volunteers who did not have DM. CCT was evaluated in each subject with non-contact specular microscope (SP-3000 P, Topcon Corporation, Japan) and all the findings were endorsed on a pre designed performa. SPSS version 13.0 was used for analysis of data.

Result: Two hundred and fifty two eyes (126 diabetic patients and 126 healthy controls) were evaluated. Both groups were age and gender matched ($p > 0.05$). Mean CCT of diabetic population was 512.21 ± 32.68 µm while mean CCT of control group was 498.83 ± 28.98 µm ($p = 0.001$). Difference in CCT values between subgroups of patients with no DR, with NPDR and PDR was statistically non-significant ($p = 0.810$). Pearson's correlation analysis showed that duration of DM ($r = 0.022$, $p = 0.809$), HbA1c ($r = 0.103$, $p = 0.251$), and severity of DR ($r = 0.022$, $p = 0.805$) did not show any significant correlation with CCT.

Conclusion: Significantly thicker CCT was found in patients with DM as compared to healthy age matched controls.

Key words: Specular Microscopy, Central Corneal Thickness, Diabetes Mellitus.

With the advent of precise and better non-invasive measurement tools, central corneal thickness (CCT) measurement has become a vital ocular parameter due to its importance as an indicator of corneal health and integrity. Accurate CCT measurement (Pachymetry) has diagnostic and therapeutic implications in various conditions like ectatic corneal dystrophies (Keratoconus, Pellucid marginal degeneration), contact lens related problems, dry eyes, diabetes mellitus, glaucoma and refractive surgery (LASIK)[1]. For years, ultrasound pachymetry remains the gold standard method for measurement of CCT, but newer non-invasive methods of pachymetry like Scheimpflug system, specular microscopy, spectral domain OCT demonstrated acceptable repeatability and reproducibility. Corneal morphological parameters including CCT vary with age, gender, race and ethnicity. Tayyab et al and Islam et al reported mean CCT of normal Pakistani population using specular microscope as 503.96 µm and 505.72 µm respectively[2,3].

Diabetic keratopathy is a known entity that affects approximately 70% of diabetic population and include decrease in corneal endothelial cell density (CED) and hexagonality, increase in CCT, polymegethism, pleomorphism, higher corneal auto fluorescence and

lower corneal sensitivity[4,5]. CCT has a positive correlation with intra ocular pressure (IOP) measured by Goldman Applanation tonometry and this effect on measured IOP can be clinically significant6. Thicker CCT in diabetes mellitus should be taken into consideration while measuring IOP in diabetics. Several studies had showed variable results while comparing CCT measurements in diabetics with normal subjects. Significantly higher CCT values in diabetic population as compared to healthy age matched controls had been reported by various authors[4,7-9]. However, there are studies that showed no significant difference in CCT values between diabetics and normal population[5,10,11]. Available data from Pakistan on the subject is limited. This study was aimed to compare CCT between patients with DM and non-diabetic control subjects and to analyze the correlation of CCT in relation to diabetes duration, glycemic status and severity of DR.

MATERIALS AND METHODS

This was a cross sectional comparative study conducted at Eye Department, PNS Shifa Naval hospital Karachi from March 2016 to February 2017. Patients with ages between 20 to 80 years of either gender who were diagnosed to have DM were recruited in the study through non probability convenience sampling, after approval by ethical review committee of hospital. Written informed consent was obtained from each subject before enrolment and study was conducted in accordance with the declaration of Helsinki[12]. Sample size was found to be 126 in each group using power of test as 80, level of significance as 0.5, mean CCT value as 566.7 µm in DR group, and 550µm in control group and population SD as 35.7[7]. The diagnosis of DM was based on criteria of the American Diabetes Association (ADA) and included all the patients who were already under treatment of physician[13]. Control group comprised of age matched healthy volunteers who did not have DM (subjects with fasting blood sugar of less than 110 mg/dL). Subjects with history of intraocular surgery / trauma / retinal laser, corneal opacity or dystrophy, glaucoma, pseudoexfoliation, uveitis, use of contact lens, and use of topical eye drops were excluded. Sub groups of patients included those with no DR, non-proliferative DR (NPDR) and with proliferative DR (PDR) on the basis of diagnosis by a consultant ophthalmologist. Complete ocular examination including visual acuity assessment, auto refraction, slit lamp bio microscopic examination and non-contact IOP measurement was done in each subject. CCT was evaluated in each subject with non-contact specular microscope (SP-3000 P, Topcon Corporation, Japan) by a single experienced examiner between 09:00 – 11:00 AM. Three images from central cornea of eye with worse retinopathy stage in diabetic group and randomly selected one eye in control group were captured. An average of three readings was used for final analysis. All the findings including demographic data, glycemic status and CCT were endorsed on a pre designed proforma.

SPSS version 13.0 was used for analysis of data that was tested for normality before analysis. For quantitative variables descriptive statistics i.e. means ± standard deviation (SD) and for qualitative variables frequencies and percentages were used. Chi square test was used to compare frequencies and percentages, while Independent sample 't' test and One way analysis of variance (ANOVA) were used to compare means ± SD between groups. Association of CCT with DM duration, HbA1c, and severity of DR was analyzed using Pearson's correlation coefficient test. A p value < 0.05 was considered statistically significant.

RESULTS

Data of 252 eyes (126 diabetic patients and 126 healthy controls) was evaluated. Mean age of diabetic population was 54.16 ± 9.70 years (range: 30-75 years), while mean age of control group was 52.00 ± 12.37 years (range: 32 – 80 years). Demographic and clinical profile of both groups is given in table 1. Both groups were matched in terms of age (p = 0.12) and gender (p = 0.30). Mean fasting plasma glucose level was significantly higher in diabetic group (p < 0.01). Mean CCT of diabetic population was 512.21 ± 32.68 µm (range: 403 – 623 µm), while mean CCT of control group was 498.83 ± 28.98 µm (range: 412 – 559 µm) [p = 0.001]. Patients with no DR, with NPDR and PDR did not show statistically significant difference in mean CCT values (table 2). However, patients with no DR were significantly younger and had lower HbA1c levels as compared to patients with NPDR and PDR (table 2). Moreover, comparison CCT values between diabetic groups according to duration of DM and/or HbA1c levels did not showed significant difference (table 3). Duration of DM was significantly correlated with type of DR (r = - 0.421, p < 0.01), HbA1c level (r = 0.175, p = 0.050), age (r = 0.305, p < 0.01) and severity of DR (r = 0.616, p < 0.01). However, Pearson's correlation analysis showed that duration of DM,

Table 1: Demographic and Clinical Profile of Study Population.

Parameter	Diabetic (n = 126)	Control (n = 126)	P value
Age (years)	54.16 ± 9.70	52.00 ± 12.37	0.125
Gender			
Male	76 (60.31%)	67 (53.17%)	0.309
Female	50 (39.68%)	59 (46.82%)	
Type of DM			
Type 1	44 (34.90%)	-	-
Type 2	82 (65.10%)	-	-
Duration of DM			
< 10 years	60 (47.60%)	-	-
> 10 years	66 (52.40%)	-	-
Plasma Glucose (F) mg/dL	184.73 ± 75.90	97.52 ± 12.41	< 0.01
HbA1c Level (%)	6.97 ± 1.12	-	-

Table 2: Clinical Profile and CCT Values according to severity of DR.

Parameter	No DR (n = 42)	NPDR (n = 46)	PDR (n = 38)	P value
Age (years)	49.74 ± 10.76	56.80 ± 8.49	55.84 ± 8.24	0.001
Plasma Glucose (mg/dL)	180.00 ± 83.56	179.76 ± 71.16	196.00 ± 73.33	0.553
HbA1c (%)	6.51 ± 1.07	7.06 ± 1.23	7.36 ± 0.86	0.002
CCT (μm) mean ± SD	512.60 ± 37.01	509.91 ± 28.24	514.55 ± 33.30	0.810

Table 3: Comparison of groups according to DM duration and HbA1c level.

Parameter	Age (Years)	Glucose (mg/dL)	CCT (μm)
Duration (years)			
< 10 years	52.08 ±10.91	181.06 ± 73.71	513.99 ± 33.20
> 10 years	56.05 ± 8.08	188.07 ± 78.25	510.59 ± 32.38
p value	0.021	0.607	0.563
HbA1c (%)			
≤ 7.5	53.78 ± 9.79	158.03 ± 57.95	510.98 ± 31.74
>7.5	54.98 ± 9.57	242.15 ± 78.68	514.85 ± 34.89
p value	0.522	< 0.01	0.538

HbA1c, and severity of DR did not showed any significant correlation with CCT. Moreover, plasma glucose level showed weak but significant correlation with CCT (r = 0.155, p = 0.014).

DISCUSSION

The relationship between DM and CCT is very important as the current burden of DM in Pakistan is approximately 7.0 million people and this figure is expected to rise by the year 2040 to an alarming 14.4

million making Pakistan the 8th highest country in terms of burden of DM[14]. It is postulated that hyperglycemia may cause endothelial dysfunction with resultant stromal hydration and swelling of cornea that leads to higher CCT values in diabetic population[15]. Evaluation of corneal morphological parameters including CCT has been done worldwide with conflicting reports. Corneal morphological parameters do differ among various races and ethnic groups with age being the major confounding factor. In this study, both groups were age matched to eliminate the age related bias in CCT measurement among groups. In our study, Mean CCT of diabetic population was significantly higher as compared to normal controls (512.21 ± 32.68 μm vs. 498.83 ± 28.98; p = 0.001). Significantly Thicker CCT values in diabetic population as compared to healthy controls had been reported in various other studies[4,7-9,15-19]. Modis et al in their study found significantly higher CCT values in type I diabetics as compared to controls, whereas in type II diabetics the difference was not statistically significant[20]. Roszkowska et alreported that pachymetric values were significantly altered in both type 1 and type 2 diabetic groups, with values being higher in type 1 diabetics[21]. On the contrary, there are studies which documented that diabetic subjects did not differ from non-diabetic controls with regard to CCT[5,10,11,22,23]. Habib et al in their study found no significant difference in pachymetry values between diabetic and non-diabetics in Pakistani population[24].

In our study, severity of DR did not have a significant effect on CCT. Ozdamar et al [8], Inoue et al[10] and El-Agamy et al[22] also reported that all diabetic groups (No DR, NPDR and PDR) had no significant difference in pachymetry values. Whereas, Parekh et al reported that CCT values were significantly higher in patients with moderate to severe NPDR and PDR as compared to patients with no or mild DR[23]. Regarding comparison of CCT values in patients with DM duration of ≤ 10 years and those with DM duration of > 10 years, no statistically significant difference was detected. Briggs et al and Habib et al reported thicker corneas in patients with > 10 years of DM but the difference was statistically non significant[18,24]. However, Lee et al and Urban et al reported significantly higher CCT in diabetics with > 10 years of duration[4,25]. In our study, comparison of the mean values of CCT in diabetic patients with HbA1c ≤ 7.5% and those with HbA1c > 7.5% showed no significant difference. Similar results are quoted by El-Agamyet al[22] in their work, whereas, Gupta et al[19] in their study reported significantly thicker corneas in patients with HbA1c levels of > 7.0%.

Correlation between CCT and various systemic and ocular variables such as duration of DM, plasma glucose level, HbA1c level and severity of DR had been extensively evaluated worldwide. In our study, duration of DM, HbA1c, and severity of DR did not showed any significant correlation with CCT. Non-significant correlation of duration of DM, HbA1c, and severity of DR with corneal endothelial parameters had been found in various studies worldwide[5,7,22]. However, there are studies that showed significant correlation of CCT with duration of DM, HbA1c level and severity of DR[4,23,25]

The strength of this study was the appropriate sample size, age matched groups, and prospective data collection. Limitations of the study include lack of multivariate analysis, not performing gold standard test (glucose tolerance test) to exclude diabetes in controls and not taking into account possible confounding factors like smoking, IOP and corneal diameter. Results of this study provide a greater insight into the understanding of corneal morphology in diabetic population especially in the context of pre-operative evaluation and glaucoma diagnosis. In fact, Blue Mountains eye study showed persons with diabetes are thought to be at higher risk of glaucoma[26]. Therefore it is recommended that thicker CCT associated with DM must be taken into consideration while measuring IOP in diabetics.

CONCLUSION

Mean pachymetry values were found to be significantly thicker in diabetic population as compared to healthy controls. However, duration of DM, HbA1c, and severity of DR did not showed any significant correlation with CCT.

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Role of Author

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The conception and design or analysis and interpretation of the data, the drafting of the article or

critical revision for important intellectual content, critical appraisal of findings with literature search and actual write up of manuscript and final approval.

REFERENCES

1. **Almubrad TM, Osuagwu UL, Al Abbadi I, Ogbuehi KC.** Comparison of the precision of the Topcon SP-3000P specular microscope and an ultrasound pachymeter. Clinical Ophthalmology (Auckland, NZ) 2011; 5: 871-876. Doi:10.2147/OPTH.S21247.
2. **Tayyab A, Masrur A, Afzal F, Iqbal F, Naseem K.** Central Corneal Thickness and its Relationship to Intra-Ocular and Epidemiological Determinants. J Coll Physicians Surg Pak. 2016; 26 (6): 494-7. Doi:2349.
3. **Islam QU, Saeed MK, Mehboob MA.** Age related changes in corneal morphological characteristics of healthy Pakistani eyes. Saudi J Ophthalmol 2017. Doi: http://dx.doi.org/10.1016/j.sjopt.2017.02.009. In Press Corrected Proof
4. **Lee JS, Oum BS, Choi HY, Lee JE, Cho BM.** Differences in corneal thickness and corneal endothelium related to duration in Diabetes. Eye 2006; 20, 315–318. Doi: 10.1038/sj.eye.6701868.
5. **Choo MM, Prakash K, Samsudin A, Soong T, Ramli N, Kadir AJ.** Corneal changes in type II diabetes mellitus in Malaysia. Intl J Ophthalmol 2010; 3 (3): 234-236. Doi: 10.3980/j.issn.2222-3959.2010.03.12
6. **Brandt JD, Beiser JA, Kass MA, Gordon MO.** Central corneal thickness in the Ocular Hypertension Treatment Study (OHTS). Ophthalmology, 2001; 108 (10): 1779-88.
7. **Galgauskas S, Laurinavičiūtė G, Norvydaitė D, Stech S, Ašoklis R.** Changes in choroidal thickness and corneal parameters in diabetic eyes. Eur J Ophthalmol 2016; 26(2): 163 – 167. Doi: 10.5301/ejo.5000677.
8. **Ozdamar Y, Cankaya B, Ozalp S, Acaroglu G, Karakaya J, Ozkan SS.** Is there a correlation between diabetes mellitus and central corneal thickness? J Glaucoma, 2010; 19 (9): 613-6. Doi: 10.1097/IJG.0b013e3181ca7c62.
9. **Mathebula SD, Segoati TM.** Is the central corneal thickness of diabetic patients thicker than that of non-diabetics' eyes? Afr Vision Eye Health, 2015; 74 (1): 5 pages. Doi: 10.4102/aveh.v74i1.307.
10. **Inoue K, Kato S, Inoue Y, Amano S, Oshika T.** The corneal endothelium and thickness in type II diabetes mellitus. Jpn J Ophthalmol. 2002 Jan-Feb; 46 (1): 65-9.
11. **Sudhir RR, Raman R, Sharma T.** Changes in the Corneal Endothelial Cell Density and Morphology in Patients with Type 2 Diabetes Mellitus: a Population-Based Study, SankaraNethralaya Diabetic Retinopathy and Molecular Genetics Study (SN-DREAMS, Report 23). Cornea 2012; 31: 1119–1122. Doi: 10.1097/ICO.0b013e31823f8e00.
12. World Medical Association declaration of Helsinki: ethical principles for medical research involving human subjects. J Postgrad Med 2002; 48: 206-8.
13. American Diabetes Association. Classification and diagnosis of diabetes. Sec. 2. In Standards of Medical Care in Diabetes- 2016. Diabetes Care 2016; 39(Suppl. 1): S13–S22 | Doi: 10.2337/dc16-S005.
14. International Diabetes Federation. IDF Diabetes Atlas, 7thedn. Brussels, Belgium: International Diabetes Federation, 2015. http://www.diabetesatlas.org.
15. **Su DH, Wong TY, Wong WL, Saw SM, Tan DT, Shen SY, Loon SC, Foster PJ, Aung T.** Singapore Malay Eye Study Group. Diabetes, hyperglycemia, and central corneal thickness: the Singapore Malay Eye Study. Ophthalmology, 2008; 115 (6): 964-968.
16. **Yakov Goldich, MD, Yaniv Barkana, MD, Yariv Gerber, PhD, AdiRasko, MD, YairMorad, MD, Morris Harstein, MD, Isaac Avni, MD, David Zadok, MD.** Effect of diabetes mellitus on biomechanicalparameters of the cornea. J Cataract Refract Surg. 2009; 35: 715–719. Doi: http://dx.doi.org/10.1016/ j.jcrs.2008.12.013
17. **Storr-Paulsen A, Singh A, Jeppesen H, Norregaard JC, Thulesen J.** Corneal endothelial morphology and central thickness in patients with type II diabetes mellitus. Acta Ophthalmol. 2014: 92: 158–160. Doi: 10.1111/aos.12064.
18. **Briggs S, Osuagwu UL, AlHarthi EM.** Manifestations of type 2 diabetes in corneal endothelial cell density, corneal thickness and intraocular pressure. Journal of Biomedical Research 2016; 30 (1): 46-51. Doi: 10.7555/JBR.30.20140075.
19. **Gupta M, Pandey AN, Tyagi R.** A study of corneal changes – endothelial cell density (ECD) and central corneal thickness (CCT) in Type -2 DM in relation to Hba1c levels and compare it with healthy individuals. Indian Journal of Clinical and Experimental Ophthalmology 2016; 2 (2): 123-127. Doi: 10.5958/2395-1451.2016.00029.9.
20. **Modis L Jr, Szalai E, Kertesz K, Kemeny-Beke A, Kettesy B, Berta A.** Evaluation of the corneal endothelium in patients with diabetes mellitus type I and II. HistolHistopathol 2010; 25 (12): 1531-7 Doi: 10.14670/HH-25.1531.
21. **Roszkowska AM, Tringali CG, Colosi P, Squeri CA, Ferreri G.** Corneal Endothelium Evaluation inType I and Type II Diabetes mellitus. Ophthalmologica 1999; 213: 258–261.
22. **El-Agamy A, Alsubaie S.** Corneal endothelium and central corneal thickness changes in type 2 diabetes mellitus. Clinical Ophthalmology (Auckland, NZ). 2017; 11:481-486. Doi: 10.2147/OPTH.S126217.
23. **Parekh R, Ranganath KN, Suresh KP, Dharmalingam M.** Corneal endothelium count and thickness in diabetes mellitus. Int J Diab Dev Ctries 2006; 26 (1): 24-26.
24. **Habib MK, Zaheer N, Sharif N, Hassan S, Malik H.** Effect of Diabetes on Central Corneal Thickness. Al-Shifa J Ophthalmol. 2014; 10 (2): 77-85.
25. **Urban B, Raczy Nska D, Bakunowicz-Aazarczyk A, RaczyNska K, Krwtowska M.** Evaluation of Corneal

Endothelium in Children and Adolescents with Type 1 Diabetes Mellitus. Mediators Inflamm. 2013.
Article ID 913754, 6 pages
http://dx.doi.org/10.1155/2013/913754

26. **Mitchell P, Smith W, Chey T, Healey PR.** Open-angle glaucomaand diabetes: the Blue Mountains Eye Study, Australia. Ophthalmology, 1997; 104: 712– 8.