Cross-sectional Study on Measurement of Central Corneal Thickness in Type 2 Diabetes Mellitus Using Pachymeter

Toshika Dahal[1], Dakki Sherpa[2], Neyaz Kausar Mikarani[2]
[1]Department of Ophthalmology, Lumbini Eye Institute, Bhairahawa, Nepal.
[2]Department of Ophthalmology, Nepal Eye Hospital, Kathmandu, Nepal.

ABSTRACT

INTRODUCTION: Diabetic mellitus causes decrease in corneal endothelial cell density and hexagonality, whereas increases polymegathism, pleomorphism and central corneal thickness. Corneal pachymetry measures corneal thickness, a sensitive indicator of endothelial physiology that correlates well with functional measurements. The increase in Central Cornea Thickness seems to be present very early in the disease and thus may be one of the earliest clinically detectable changes of diabetic eye. The association between increased corneal thickness and severe retinal complications suggests that the corneal thickness may be an indicator of the risk of retinal complications.

METHOD: This was cross-sectional, hospital based cross sectional study in 59 diabetic patient that was done in Nepal Eye hospital general ophthalmology OPD and in Retina Clinic in a time period of 18 months. Patients underwent comprehensive ophthalmic examination including dilated fundus examination with a 90-D lens, Intraocular pressure (IOP) measurement with a Goldmann applanation tonometer and central corneal thickness measured using ultrasound pachymetry (ACCUTOME).

RESULT: The findings revealed statistically significant increase in central corneal thickness with increase duration of diabetes($p=0.043$), random blood sugar more than 200 mg/dl ($p=0.04$), HbA1c more than 6.5($p=0.025$). However, there was no statistically significant change in central corneal thickness in relation to subgroup of diabetic retinopathy patient, age of patient and gender.

CONCLUSION: This study shows that persons with diabetes mellitus or higher glycosylated hemoglobin levels have greater CCT, independent of age, gender. These findings suggest that CCT measurements may be affected by chronic hyperglycemia and, together with future research findings, may aid in understanding the pathophysiological processes in diabetes.

KEYWORDS: central corneal thickness; diabetic retinopathy; pachymetry.

INTRODUCTION

Cornea is the most important refractive element in the human ocular system, providing approximately two-third(40-45D) diopters of power of eye.[1] Corneal thickness is a sensitive indicator of health of cornea and serves as an index for corneal hydration and metabolism.[2]

Correspondence:

Dr Toshika Dahal, Department of Ophthalmology, Lumbini Eye Institute, Bhairahawa, Nepal.

Email: toshikadahal2047@gmail.com

Phone: +977-9841740018

In Nepal, it was found that normal cornea has a central thickness of about 539.10μm(SD ± 33.73).[3] Cornea becomes thicker in paracentral zone and peripheral zone.[4] Cornea composed of five different layers. 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.[5]

The corneal stroma has highly organized arrangements of collagen fibrils that are braced apart by a proteoglycan matrix that maintains uniform spacing. 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.[5–7]

If corneal endothelial function is compromised, corneal hydration and consequently the corneal thickness will increase. 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.[7]

Diabetic keratopathy is a frequent disease that entails several alterations, especially in the epithelium and endothelium, like punctate epithelial keratopathy, recurrent corneal erosions and persistent epithelial defects. Especially the endothelium like decrease in endothelial cell density and hexagonality, as well as increased polymegathism, pleomorphism and central corneal thickness.[8,9]

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.[10–12]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.[13]

Corneal pachymetry measures corneal thickness, a sensitive indicator of endothelial physiology that correlates well with functional measurements. Ultrasound pachymetry is the current standard for corneal thickness measurement.[14]

Diabetes mellitus has a significant effect on morphological, metabolic, physiological, and clinical aspects of the cornea. Measuring Central Cornea Thickness in diabetic patients may help to identify those patients who are at higher risk of developing severe complications thus enabling the ophthalmologist to treat their disease more accurately. The increase in Central Cornea Thickness seems to be present very early in the disease and thus may be one of the earliest clinically detectable changes of diabetic eye. The association between increased corneal thickness and severe retinal complications suggests that the corneal thickness may be an indicator of the risk of retinal complications in diabetic individuals.

METHOD

This was hospital based cross sectional study that was done in Nepal Eye hospital general ophthalmology OPD and in Retina Clinic in a time period of 18 months. Ethical approval was obtained from Institutional Review Committee of National Academy of Medical Sciences and written informed consent was taken. The patients with diagnosed case of type II diabetes mellitus were recruited in this study according to the inclusion and exclusion criteria set for this study. Cochran's formula was used to calculate a representative sample size of 59. Convenience sampling was the sampling procedure used. Patient with FBS level more than 126mg/dl or PP level more than 200mg/dl or RBS more than 200 within 1 month of presentation to hospital, taking oral hypoglycemic or insulin was taken for study. The mean duration of DM of 12.87±8.03 years (range: 1–40 years), mean value of HbA1c of 8.57%±2.09% (range: 6.3%–17.2%) and IOP with Goldmann Applanation Tonometer to be 10-21 mm Hg was taken for study. The central corneal thickness was measured using ultrasound pachymetry (ACCUTOME). To avoid observer bias all measurements were taken by single Ophthalmologist. Independent paired t-test was used to study relation between central corneal thickness (CCT) and gender, Random Blood sugar (RBS), Subgroup of diabetic retinopathy, HbA1c value. ANOVA test was used to study correlation between CCT and age variation of patient.

RESULT

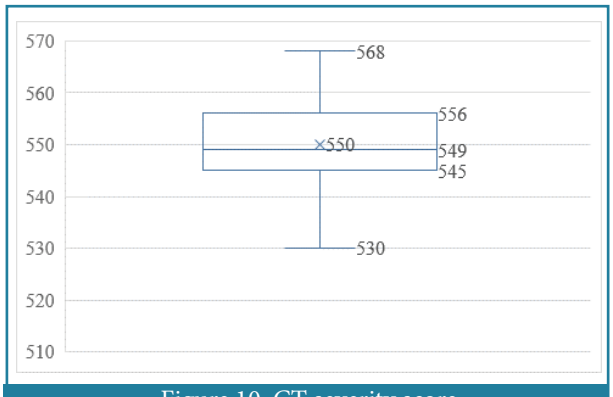

Figure 10: CT severity score

Figure 1: CCT distribution of Type II diabetic patients (in μm)

The average CCT was 550.00 μm ± 8.31 μm, ranging between 530 μm and 568 μm.

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Gender	Mean CCT (μm)	Number	Std. Deviation
Male	550.50	30	8.08

Female	549.48	29	8.66
Total	550.00	59	8.31

Table 1 : Measurement of CCT and Gender variation in Type II Diabetes patients

The mean CCT in male was 550.50 ± 8.08 μm and in female was 549.48 ± 8.66 μm.

There is no clinical significance between CCT and gender (p = 0.64).

Table 2 : Measurement of CCT and Age Variation in Type II DM patients

Age in years	Mean CCT (μm)	Number	Std. Deviation
less than 49	546.92	13	9.50
50 to 59	552.16	25	8.02
more than 60	549.33	21	7.52
Total	550.00	59	8.31

The mean CCT in age group less than 49 years was 546.92 ± 9.50 μm, age group 50- 59 years was 552.16 ± 8.02 μm and more than 60 years was 549.33 ± 8.31 μm. The CCT and age group showed no clinical significance(p = 0.16)

Table 3: Measurement of CCT with value of RBS

RBS	Mean CCT (μm)	Number	Std. Deviation
less than 200	547.71	28	7.23
more than 200	552.06	31	8.79
Total	550.00	59	8.31

The CCT in group less than 200 mg/dl was 547.71 ± 7.23 μm and more than 200 mg/dl was 552.06 ± 8.79 μm. The CCT and the RBS value was clinically significant (p = 0.04)

Table 4: Measurement of CCT with duration of diabetes

Duration of Diabetes	Mean CCT (μm)	Number	Std. Deviation
less than 5 year	545.67	15	7.60
5 to 10 years	550.56	25	8.25
more than 10 years	552.68	19	7.95
Total	550.00	59	8.31

The mean central corneal thickness of diabetic patients for less than 5 years duration was 545.67 ± 7.60 μm, 550.56 ± 8.25 μm for patients with duration 5-10 years, and 552.68 ±7.95 μm for more than 10 years duration. The increase in central corneal thickness with increase duration of diabetes was statistically significant (P= 0.043)

Table 5: Measurement of CCT in Subgroups of Diabetic patients

	Mean CCT (μm)	Number	Std. Deviation
No DR	548.69	36	8.22
DR present	552.04	23	8.21
Total	550.00	59	8.31

36 patients had no retinopathy, 23 had Diabetic retinopathy. The mean CCT in patients with No DR was 549.69 ± 8.22 μm and that of with DR was 552.04 ± 8.21 μm. There was no clinically significant difference found between the corneal thickness of those with diabetic retinopathy as compared to those without any retinopathy. (p- value = 0.132)

Table 6: Measurement of CCT with value of HbA1c in Type II diabetic patients

HbA1c	Mean CCT (μm)	Number	Std. Deviation
less than or equal to 6.5	547.94	34	7.13
more than 6.5	552.80	25	9.10
Total	550.00	59	8.31

34 Diabetic patients with HbA1c less than or equal to 6.5 had mean CCT of 547.94 ± 7.13 μm as compared to 25 patients who had HbA1c more than 552.80 ± 9.10 μm. There was significant co-relation between CCT and HbA1c level (p=0.025).

LIMITATION

Confocal microscopy of corneal endothelium, which would have provided potential insights on underlying corneal thickening changes among individuals with diabetes, was not performed. Part of metabolic syndrome example hyperlipidemia, hypertension which is known to also have effect on CCT which may be a confounding factor in patients with DM II was not considered.

DISCUSSION

Diabetes mellitus is a metabolic disorder characterized by the presence of chronic hyperglycemia, which may develop ocular complications like diabetic retinopathy, cataracts, keratopathy, glaucoma, refractive changes and dysfunctional lacrimal gland. Diabetes causes structural and functional changes in corneal endothelium as reported by McNamara et al, Weston et al and Su et al suggested that hyperglycemia alters endothelial structure leading to hydration of cornea and hence increased corneal thickness. Whereas Lopez et al con-

cluded that diabetics exhibited increase in CCT due to greater pleomorphism and polymegathism in their corneas.[15–17] Collagen crosslinking may be another reason leading to increase in corneal thickening and gradual stiffening of the cornea that consequently affect the accuracy of IOP measurements. It is thought to reduce the activity of endothelial Na+ /K +ATPase and, since this enzyme is a major component of endothelial cells, it may cause morphological and permeability changes in diabetic corneas. McNamara et al. suggested that hyperglycemia might affect certain aspects of corneal hydration and modify CCT in diabetic patients.[15]

In this study the mean central corneal thickness of diabetic patients of less than 5 years duration was 545.67 ± 7.60 μm, 550.56 ± 8.25 μm for patients with duration 5-10 years, and 552.68 ±7.95 μm for more than 10 years duration. The increase in central corneal thickness with increase duration of diabetes was statistically significant (P= 0.043)which was similar to study done by Rajesh et al. where there was significant relationship observed between duration of diabetes and increased CCT. Similarly another study done by Mamta et al. on 2018, CCT with diabetes patients of duration <10 years and > 10 years was 518.98 μm and 544.64 μm. The increase in CCT with duration of diabetes was significant clinically with p=0.021.[18]In a study done by Vivek et al. with duration of diabetes <10 years having CCT 540.73 μm and diabetes duration of >10 years with CCT 574.13 μm , there was clinical significance (p value 0.003) between increase in CCT value with duration of diabetes.[19]

Briggs et al also concluded that CCT was thicker for diabetic with duration of > 10 years than those with duration of < 10 years (p <0.05).[20]

In study done by Prempal et al. including duration of diabetes <10 years with CCT 554.4±79 μm and > 10 years with CCT 576.3 ±21 μm .Central corneal thickness in a group with diabetic duration >10 years was significantly higher than in patients with diabetic age <10years (p =0.015).[21]

In this study the mean CCT in male was 550.50 ± 8.08 μm and in female was 549.48 ± 8.66 μm. There was no clinical significance between CCT and gender. (p = 0.64) Similarly in study done by Mamta Singh et al. the CCT for male subjects in diabetic group was 528.433 ± 30.91 μm and female subjects in the diabetic group had central corneal thickness of 520.97 ± 27.77 μm .The statistical difference between male and female in either group was not significant.[18]Similarly Nagraj et al. also concluded that there was no significant correlation between the male and female group.(p>0.05).[22]Study done by Swarastra et al. concluded that mean CCT was almost higher in males (570.67μm) than females (556.75μm) and the small difference was not significant (p=0.176).

In this study 34 Diabetic patients with HbA1c less than or equal to 6.5 had mean CCT of 547.94 ± 7.13 μm as compared to 25 patients who had HbA1c more than 552.80 ± 9.10 μm. There was significant co-relation between CCT and HbA1c level. (p=0.025) The present study did not find any significant correlation between CCT and HbA1c levels which is considered as an indicator of long-term control of diabetes. Similarly in study done by Prempal Kaur et al. the mean CCT was 548±11.9 μm and 561±9.5 μm in patient with HbA1c <7 and > 7 respectively (p=0.00001).[21]In study of Gupta Manisha et al. when the patients were analyzed in terms of HbA1c levels, patients with HbA1c levels over 7% had thicker corneas than the patients with HbA1c levels under 7% (p=0.031).[23]

In study by Sethia Rajni et al. the mean CCT of patients with HbA1c <7% was 545.3 μm (SD-24.31) and that of patients with HbA1c = 7% was 545.1 μm (SD-24.63). The difference was statistically insignificant (p value = 0.96).[24]

Amira el-agamy et al. study concluded that diabetic patient with HbA1c less than equal to 7.5 had mean CCT 544.33 μm and HbA1c more than 7.5 had CCT 546.54 μm. The difference between 2 group was not clinically significant (p = 0.789).[25] In Vivek Oommen Varghese et al. study the mean CCT among those with HbA1c <6.5 g% was (533.57 ± 2.81 μm), with HbA1c values (6.5–7.9 g%) was (543.83 ± 9.14 μm), and with HbA1c >8 g% was (548.10 ± 8.16 μm).[19] This is similar to the study by Ozdamar which did not show a significant correlation of CCT with respect to the level of glycosylated hemoglobin.[26]

In this study the mean CCT in age group less than 49 was 546.92 ± 9.50 μm, age group 50- 59 μm was 552.16 ± 8.02 μm and > 60 was 549.33 ± 8.31 μm. The CCT and age group showed no clinical significance(p = 0.16).Similarly in study done by Nagaraj G et al. the CCT in age group < 50, 51-60, 61-70 and > 70 was 526.58 μm , 520.70 μm , 514.36 μm, 524.61 μm respectively. There was no clinical significance between the age and CCT (p>0.05).[22]Ana M. Calvo-Maroto et al. study also concluded that there was no correlation between age and CCT.(P= 0.68).[27]In another study done by Rachapalle R. Sudhir et all with age group 40-49 , 50-59 , 60-69 ,>69 years with CCT of 530.15 μm , 523.09 μm, 522.95 μm , 516.56 μm respectively showed no clinical significance between CCT and age (p value= 0.685).[28] Study by Daniel H. W. Su et l. concluded that Central corneal thickness decreases with age(P<0.001) at an average of 5.13um a decade.[17]

In this study 36 patients had no retinopathy, 23 had Diabetic retinopathy. The mean CCT in patient with no Diabetic retinopathy was 549.69 ± 8.22 μm and that of with Diabetic Retinopathy was 552.04± 8.21μm. There was no clinical significant difference found be-

tween the corneal thickness of those with diabetic retinopathy as compared to those without any retinopathy.(p- value = 0.132) Similarly in study done by Prempal Kaur et al. 64 patients in group 1 (No DR) had CCT 566.1 ± 13.35 μm , 47 in group 2 (NPDR) had CCT 569.4 ± 15.04 μm and 9 in group 3(PDR) had CCT 575.1 ± 12.54 μm. Central corneal thickness (μm) values increased from patients with no diabetic retinopathy to those with proliferative retinopathy but the increase was not statistically significant. (p = 0.13).[21]In Study done by Okan TOYGAR et al. concluded that CCT in diabetic patients without retinopathy did not significantly differ from that of patients with retinopathy (P = 0.64). Similarly, there was no significant difference in CCT between nonproliferative and proliferative diabetic retinopathy patients (P = 0.47).[29] In study of Solani D. Mathebula et al. 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 .[13] Ozdamar et al. and Choo et al. reported in their studies that patients with proliferative retinopathy had thicker CCT than those with non-proliferative retinopathy and no retinopathy; however, the difference was not statistically significant.[26] This was similar to our observations. More recent studies by Toygar et al. and Mathebula et al. were also in agreement with the previous studies.[13,29] Busted et al. and Wiemer et al. found that CCT increased in DM regardless of the severity of the retinal disease.[30]

In this study the CCT in group of RBS value less than 200 mg/dl was 547.71 ± 7.23 μm and more than 200 mg/dl was 552.06 ± 8.79 μm. The CCT and the RBS value was clinically significant (p = 0.04). Similarly in study done by Daniel H. W. Su et al. the Central corneal thickness was also greater with higher serum glucose levels (P = 0.023).[17] In study done by Vivek Oommen Varghese et al. the Fasting blood sugar < 110 mg/dl . 110- 125 mg/dl and > 126 mg/dl had CCT of 531.86 μm, 539.55 μm and 551.03 μm. This correlation between FBS and CCT was clinically significant (p = 0.009).[19]

In this study the average CCT was 550.00 μm ± 8.31 μm, ranging between 530 μm and 568 μm.

CONCLUSIONS

In conclusion, our study shows that persons with diabetes mellitus or higher glycosylated hemoglobin levels have greater CCT, independent of age, gender. These findings suggest that CCT measurements may be affected by chronic hyperglycemia and, together with future research findings, may aid in understanding the pathophysiological processes in diabetes.

A significant correlation was found between increase CCT and diabetes, with positive correlation between thick cornea and the duration of the diabetes, indicating that patients with thick corneas are more likely to be found in an advanced stage of the disease.

RECOMMENDATION

Knowledge of these diabetes associated changes in corneal parameter and their monitoring may prevent vision loss by enabling early detection and treatment. Routine assessment of CCT and corneal endothelial structure may be beneficial in all diabetic patients along with their usual retinopathy assessment to prevent visual disability by early detection and management. Measuring CCT in diabetic patients may help to identify those patients who are at higher risk of developing severe complications thus enabling the ophthalmologist to treat their disease more accurately.

CONFLICT OF INTEREST: NONE.

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