ASSOCIATION OF CENTRAL CORNEAL THICKNESS AND CENTRAL CORNEAL ENDOTHELIAL CELL COUNT WITH PROGRESSIVE STAGES OF DIABETIC RETINOPATHY

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ABSTRACT

BACKGROUND

Diabetes mellitus along with its different serious pathological complications are increasing very rapidly in both developed and developing countries and manifesting as an escalating pandemic leading to morbidity and untimely death. This may lead to irreversible socioeconomic and psychosocial damage to the individuals, families and communities, either directly or indirectly. Assessment of Central Corneal Thickness (CCT) and Central Corneal Endothelial Cell Count (CCEC) in different stages of DR would help us to understand how rapidly the disease spreads, which could in turn be used as guidelines for disease screening in patients as risk to developing the disease.

The aim of the study is to understand the association of CCT and CECC with progressive stages of Diabetic Retinopathy (DR) in Diabetes Mellitus type 2 (DM-2).

MATERIALS AND METHODS

A case-control study was performed with a random eye from cases, No Diabetic Retinopathy (NDR), Nonproliferative Diabetic Retinopathy (NPDR) and Proliferative Diabetic Retinopathy (PDR) to determine association of DR with CCT and CECC. Parameters were quantified by ultrasonic pachymeter and specular microscope and results statistically analysed to understand significant association.

RESULTS

Significant increase in CCT was observed in NPDR and PDR compared to controls or NDR. Conversely, NPDR and PDR showed significant decrease compared to controls or NDR. CCT and CECC showed significant inverse correlation in all groups.

CONCLUSION

CCT and CECC showed significant increase and decrease respectively with stages of DR and were inversely correlated with each other. Assessment of CCT and CECC could thus be used as effective indicators of ocular manifestations of DM for early therapeutic intervention.

KEYWORDS

Nonproliferative Diabetic Retinopathy, Proliferative Diabetic Retinopathy, Type 2 Diabetes Mellitus, Central Corneal Thickness.

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BACKGROUND

Diabetes Mellitus Type 2 (DM-2) or insulin-independent DM is a global disease burden and the most common form of diabetes.[1] Diabetes mellitus is increasing at an alarming rate in both developed and developing countries and manifesting as an escalating pandemic leading to morbidity and untimely death.[2] DM-2 is associated with a multitude of other pathological conditions including vascular disorders (stroke, myocardial infarction), microvascular complications (neuropathy, nephropathy, diabetic retinopathy), diabetic foot and ocular alterations (ocular surface diseases such as diabetic keratopathy and dry eye syndrome, diabetic papillopathy, glaucoma and cataract)[3,4] cumulating to irreversible socioeconomic and psychosocial damage to the individuals, families and communities, either directly or indirectly.[2]

Diabetic Retinopathy (DR) is a leading cause of loss of vision worldwide and is an added comorbidity of DM-2 dictating the urgency for its early detection and therapeutic intervention.[5] DR is categorised as Nonproliferative DR (NPDR) or Proliferative DR (PDR) based on neovascularisation into the vitreous through a break in the internal limiting membrane.[6] In addition to the above, increase in Central Corneal Thickness (CCT) also occurs in case of DM-2, in human patients and in animal models of diabetes.[7-9] However, to the best of our knowledge, no study

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till date has determined the association between changes in either CCT or Central Corneal Endothelial Cell (CECC) count in a case-control setup between healthy subjects and patients with DM-2 in progressive stages of diabetic retinopathy.

Our study thus aims to explore how CCT or CECC varies between control and patients with progressive stages of diabetic retinopathy (no diabetic retinopathy- NDR, nonproliferative diabetic retinopathy- NPDR and proliferative diabetic retinopathy- PDR) using quantitative data obtained from pachymeter and specular microscope. Our data indicates similar observations in CCT and CECC for both control and NDR. However, there was significant increase and decrease in CCT and CECC respectively in both NPDR and PDR compared to either control or NDR. Moreover, CCT and CECC were significantly and negatively correlated. Our study thus indicates the importance of early screening and diagnosis of CCT and CECC in patients with DR and necessary therapeutic intervention in order to prevent undue ocular damage and blindness in patients with DM-2.

MATERIALS AND METHODS

Study Population- Participants were selected from patients attending the Outpatient Department at the Regional Institute of Ophthalmology, Medical College, Kolkata. The sample size comprised of 75 healthy controls and 225 cases with DM-2. Confirmation of DM-2 was based on the criteria of the World Health organisation, while absence of diabetes was confirmed by random bold sugar test in controls.[9] Among the cases, there were three subgroups of patients, No Diabetic Retinopathy (NDR), Nonproliferative Diabetic Retinopathy (NPDR) and Proliferative Diabetic Retinopathy (PDR), each comprising of 75 patients. Inclusion criteria included patients above 30 years of age and those who had previously never undergone any treatment or surgical procedure that could affect corneal thickness. Exclusion criteria included subjects with ophthalmic pathologies, hypertension, users of eye drops or tear interfering systemic drugs, systemic illness such as rheumatoid arthritis, pregnancy or wearing contact lenses. Institutional research clearance and written informed consent was obtained from all patients prior to the study.

Demographic Characteristics

Demographic characteristics of the patients such as age and gender were noted for statistical correlation.

Determination of Central Corneal Thickness (CCT) and Corneal Endothelial Cell Count (CECC)

One eye from each patient was randomly selected to determine cornea-associated parameters. CCT was determined using ultrasonic pachymeter (Sonomed Pacscan 300P) under topical anaesthesia with 0.5% proparacaine eye drops. The pachymeter probe was placed horizontally to the cornea at the centre of the pupil and five consecutive readings were recorded. The average was used as the determinant of CCT.[8]

CECC was measured with a specular microscope (Topcon SP 2000P, Topcon Corporation, Japan). Five images from the central region of the cornea was captured and a minimum of 20 cells were counted from the photograph to obtain the mean CECC according to standard procedure.[10]

Clinicopathological Correlation

Estimation of risk associated with demographic features such as gender was determined by Odds ratio using univariate analysis through Fisher's exact test. Chi-square for trend was used to detect the linear variation with subsequent age of patients with DR. Analysis of Variance (ANOVA) followed by Tukey's test was used to analyse significant difference (if any) between control and cases. All statistical tests conducted were two tailed with a Confidence Interval (CI) of 95% and probability (p) value <0.05 was considered significant. Calculations were made using software Epi Info 7 (CDC, Atlanta). Tables were created with the help of Microsoft Excel and PowerPoint (Office 365, Microsoft Corp., USA).[11]

RESULTS

Characteristics	Patient Groups Percentage			
	Control	NDR	NPDR	PDR
No. of Patients	75 (25%)	75 (25%)	75 (25%)	75 (25%)
Age				
30-39	14 (18.67)	12 (16)	14 (18.67)	10 (13.33)
40-49	23 (30.67)	19 (25.33)	23 (30.67)	21 (28)
50-59	31 (41.33)	34 (45.33)	29 (38.67)	32 (42.67)
60-69	7 (9.33)	10 (13.33)	9 (12)	12 (16)
Median age	44.47 ± 9.41	50.18 ± 8.46	48.89 ± 8.62	52.66 ± 7.07
Range	30-67	32-67	32-67	37-68
Gender				
Female	30 (40)	29 (38.67)	26 (34.67)	27 (36)
Male	45 (60)	46 (61.33)	49 (65.33)	48 (64)

Table 1. Demography of the Patients

a. Mean central corneal thickness in different groups. (Abbreviations- NDR- No diabetic retinopathy; NPDR- Non-progressive diabetic retinopathy; PDR- Progressive diabetic retinopathy; CCT- Central corneal thickness). Significantly increased CCT was observed in NPDR and PDR compared to control of NDR. (Represents, p <0.01 as determined by Analysis of Variance (ANOVA), followed by Tukey's test).
b. Mean central corneal endothelial cell count in different groups. (Abbreviations- NDR- No diabetic retinopathy; NPDR- Non-progressive diabetic retinopathy, PDR- Progressive diabetic retinopathy; CCEC- Central corneal endothelial cell count). Significantly decreased CECC was observed in NPDR and PDR compared to control of NDR. (Represents, p<0.01 as determined by ANOVA, followed by Tukey's test).
c. Correlation between CCT and CECC in different groups. (Represents, p<0.01 as determined by Pearson's coefficient, followed by t-test).

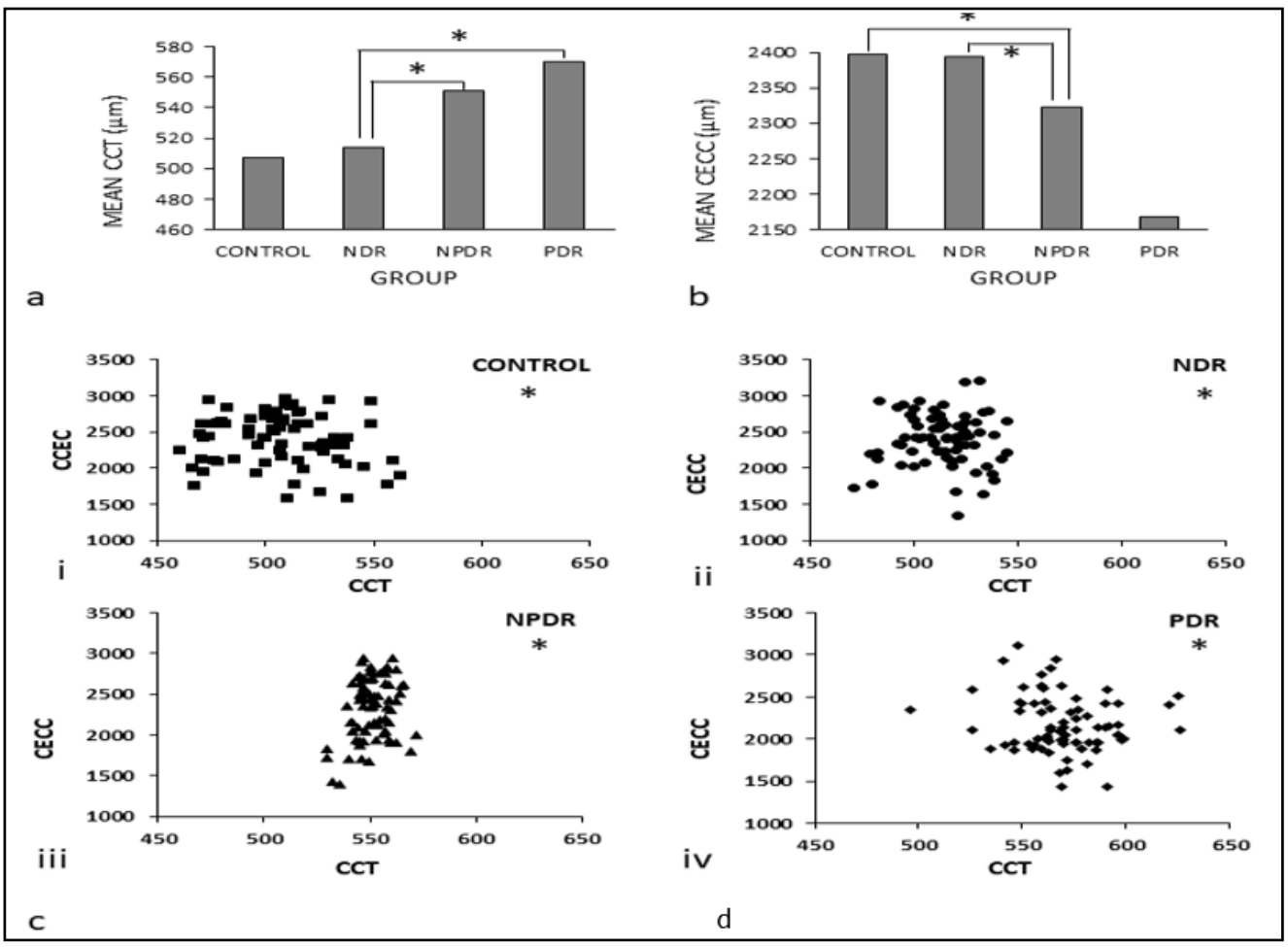

Figure 1. Determination of Corneal Parameters in Controls and Different Stages of Diabetic Retinopathy (DR)

Description of Table and Figure

Demography of the Patients- Differential distribution of the patients was observed in relation to age groups with most patients from control and different diabetes groups belonging to the window of 50-59 years, although no significant linear trend was observed (data not shown, Table 1). Patients in both cases and control was mostly males with no significant correlation in distribution (data not shown, Table 1).

CCT Significantly Increased from Control to Enhancing Diabetes- Associated Ocular Pathological Conditions-

A significantly increasing trend of CCT was observed with progression from control to different stages of ocular alterations in DM-2. While there was no significant difference in mean CCT between control (507.2 µm) and NDR (513.84 µm), there was significant increases ($p < 0.01$) in mean CCT in both NPDR (550.95 µm) and PDR (569.89 µm) compared to either control or NDR (Figure 1a).

CECC Significantly Decreased from Control to Increasing Diabetes-Associated Ocular Pathological Conditions

Control patients showed the highest number of mean CECC (2397.72 cells/sq. mm), comparable to that observed in patients with NDR (2393.87 cells/sq. mm). Significant decrease ($p<0.01$) in mean CECC compared to either control or NDR in both NPDR (2322.12 cells/sq. mm) and PDR (2168.4 cells/sq. mm) was observed (Figure 1b).

Inverse Correlation between CCT and CECC-

Mean CCT and CECC showed significant negative correlation ($p < 0.01$) in controls (Figure 1c I) and all groups of cases (Figure 1c II-IV).

DISCUSSION

The range of complications associated with DM-2 including DR presents a global burden in both developing and developed countries leading to loss of productive years, reduced work efficiency, added expenditure and blindness in extreme cases.[2] It is thus pertinent to explore the pathogenesis of the disease, especially in early cases for effective detection and timely therapy. Moreover, assessment of CCT and CCEC in control and different stages of DR would indicate how rapidly the disease spreads, which could in turn be used as guidelines for disease screening in patients as risk to developing the disease.

Although, the exact molecular mechanism of development of CCT in patients with DM-2 is elusive, structural or functional alterations of the corneal endothelium induced by hydration of cornea due to hyperglycaemia maybe an important aspect in corneal thickening.[12] Others suggested the necessity of corneal

pleomorphism and polymegathism or collagen cross-linking in increasing corneal thickness in DR.[12] It is now proven that the polyol (sorbitol-aldose reductase) pathway plays an important role in altering the morphology of the cornea in diabetic patients.[9] High glucose increases the activity of aldolase reductase leading to accumulation of sorbitol, an osmotic agent in corneal epithelial and endothelial cells and leads to their subsequent swelling. Additionally, Na^+-K^+ ATPase activity is also reduced in the corneal endothelium leading to altered morphology and corneal destruction.[9]

Our study identified participants being predominantly males and in the age group of 50-59 years. Similar age distribution of patients with DR have been reported by other researchers globally.[8,13]

Mean CCT was lowest among control and patients with NDR, while it significantly increased for patients with NPDR and PDR. Our results were concordant with those by other researchers globally, who either showed increased or significantly increased mean CCT in NPDR and PDR compared to control and NDR.[9,12,14-19]

Mean CECC observed by us was similar in control and patients with NDR. Significant reduction in CECC compared to control and NDR was also observed in NPDR and PDR. Similar results were reported by others worldwide.[9,19-24]

Finally, mean CCT and CECC were significantly and negatively correlated in controls and cases, similar to that reported by others.[9,19] Thus, early detection and diagnosis of DR in DM-2 patients was necessary to prevalent added comorbidity and untimely mortality.

CONCLUSION

Diabetes mellitus is increasing at an alarming rate in both developed and developing countries leading to morbidity and untimely death. CCT and CECC showed significant increase and decrease respectively with stages of DR and were inversely correlated with each other. In our study, there is a significant increase in mean CCT in both NPDR and PDR compared to either control or NDR. A significantly increasing trend of CCT has been observed with progression from control to different stages of ocular alterations in DM-2. Assessment of CCT and CECC could thus be used as effective indicators of ocular manifestations of DM for early therapeutic intervention. Assessment of CCT and CCEC in control and different stages of DR would indicate how rapidly the disease spreads, which could in turn be used as guidelines for disease screening in patients as risk to developing the disease.

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