Research Article

Correlation of Central Corneal Thickness, Central Macular Thickness, and Corneal Endothelial Cell Parameters with Severity of Diabetic Retinopathy and HbA1c Levels in Type 2 Diabetes Mellitus

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Abstract

Purpose: The aim of this study is to evaluate the association of central corneal thickness (CCT), corneal endothelial cell parameters, and central macular thickness (CMT) with the severity of diabetic retinopathy (DR) and glycaemic control in patients with type 2 diabetes mellitus (T2DM).

Methodology: This cross-sectional observational study was conducted over 12 months at a tertiary care centre and included 100 patients with T2DM. All participants underwent comprehensive ophthalmic evaluation, including fundus examination for grading of DR, specular microscopy for endothelial cell density (ECD), coefficient of variation (CV), and hexagonality, pachymetry for CCT, and optical coherence tomography for CMT. Glycaemic control was assessed using HbA1c levels. Associations between ocular parameters, DR severity, and HbA1c were analyzed using appropriate statistical tests.

Results: Of the 100 patients studied, 29% had diabetic retinopathy. A statistically significant inverse relationship was observed between ECD and increasing severity of DR ($p < 0.001$). Progressive worsening of DR was associated with a significant increase in CV and a reduction in hexagonality ($p < 0.05$). Central corneal thickness increased significantly with advancing DR severity ($p = 0.012$). Central macular thickness showed a progressive and significant increase from patients without DR to those with proliferative DR ($p < 0.001$). Patients with poor glycaemic control (HbA1c > 7.5%) demonstrated significantly lower ECD, higher CV, reduced hexagonality, increased CCT, and increased CMT.

Conclusion: Corneal endothelial alterations, increased central corneal thickness, and macular thickening correlate significantly with the severity of diabetic retinopathy and poor glycaemic control. Comprehensive assessment of both anterior and posterior segment parameters may aid in early detection of ocular involvement and improve clinical management of patients with type 2 diabetes mellitus.

Keywords: Central Corneal Thickness, Central Macular Thickness, Central Macular Thickness, Diabetic Retinopathy, Type 2 Diabetes Mellitus.

Introduction

Diabetes mellitus (DM) is a major global public health concern, with its prevalence increasing rapidly, particularly in developing countries such as India. Chronic hyperglycaemia in diabetes leads to progressive microvascular complications, among which diabetic retinopathy (DR) remains the most common cause of vision loss in the working-age population.[1] While retinal involvement has been extensively studied, diabetes is increasingly recognized as a systemic ocular disease affecting multiple structures of the eye.

The cornea, a metabolically active and avascular tissue, is particularly vulnerable to the effects of prolonged hyperglycaemia. Diabetic keratopathy encompasses a spectrum of corneal abnormalities, including impaired epithelial healing, reduced corneal sensitivity, endothelial

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dysfunction, and increased susceptibility to corneal edema.[2-4] These changes assume greater clinical relevance in diabetic patients undergoing intraocular procedures, where compromised corneal reserve may adversely affect surgical outcomes.

The corneal endothelium plays a critical role in maintaining corneal transparency by regulating stromal hydration through its pump and barrier functions.[2] Endothelial cells are non-regenerative, and any metabolic or surgical insult results in permanent cell loss. In diabetes, activation of the polyol pathway, accumulation of advanced glycation end products, oxidative stress, and reduced Na^+/K^+-ATPase activity have been implicated in endothelial dysfunction. These alterations may manifest as reduced endothelial cell density, increased polymegathism, decreased hexagonality, and increased central corneal thickness (CCT).

In addition to anterior segment changes, diabetes also affects the macula through disruption of the blood–retinal barrier, capillary leakage, and retinal ischemia. Central macular thickness (CMT), measured using optical coherence tomography (OCT), serves as an objective marker of macular involvement. Subclinical increases in CMT may precede clinically apparent diabetic macular edema and reflect early retinal microangiopathy.[5-15]

Glycaemic control, commonly assessed using glycated hemoglobin (HbA1c), is a well-established determinant of the development and progression of diabetic microvascular complications.[6] Poor glycaemic control has been associated with worsening severity of DR and structural changes in both the cornea and macula. However, data correlating corneal endothelial parameters, CCT, CMT, DR severity, and HbA1c levels remain limited, particularly in the Indian population.

Therefore, this study was undertaken to evaluate the correlation between central corneal thickness, corneal endothelial parameters, and central macular thickness with the severity of diabetic retinopathy and HbA1c levels in patients with Type 2 Diabetes Mellitus.

Materials and Methods

Study Design

This study is a cross-sectional, observational study conducted to evaluate the correlation between central corneal thickness (CCT), central macular thickness (CMT), endothelial cell count (ECC), and the severity of diabetic retinopathy (DR) and HbA1c levels in patients with Type 2 Diabetes Mellitus (T2DM).

Study Setting

The study was conducted at the Department of Ophthalmology, LN Medical College, Bhopal.

Ethical Clearance

Ethical approval for this study was obtained from the Institutional Ethics Committee (IEC) of LN Medical College, Bhopal. All procedures were conducted in accordance with the ethical guidelines of the Declaration of Helsinki.

Study Duration

The study was conducted over a period of 12 months.

Study Outcomes

The primary outcomes of this study include

- Correlation of CCT, CMT, and ECC with the severity of DR in patients with type 2 diabetes mellitus.
- Association of these ocular parameters with HbA1c levels to assess the impact of glycemic control on structural changes in the eye.

Measurement of the Outcome

- CCT was measured using a pachymeter.
- CMT was assessed using optical coherence tomography (OCT).
- ECC was evaluated using specular microscopy.
- Severity of DR was graded based on the ETDRS diabetic retinopathy classification using fundus examination.
- HbA1c levels were determined through venous blood sampling and laboratory analysis.

Dependent and Independent Variables

Dependent Variables

Severity of diabetic retinopathy (graded as mild, moderate, severe, or proliferative DR), HbA1c levels.

Independent Variables

CCT, CMT, ECC, age, duration of diabetes, presence of diabetic macular edema.

Definition of the Exposure/Intervention

The study examines the natural variations in corneal and macular thickness, endothelial cell count, and their association with DR severity and HbA1c levels in diabetic patients.

Study Participants

The study population comprised all diagnosed type 2 diabetes mellitus patients attending the Department of Ophthalmology at LN Medical College, Bhopal during the study period.

Study Participants

A total of 100 patients with type 2 diabetes mellitus meeting the inclusion criteria were enrolled.

Inclusion Criteria

- Patients diagnosed with type 2 diabetes mellitus (T2DM).
- Age ≥18 years.
- Presence of any stage of diabetic retinopathy based on fundus examination.
- Patients who provided written informed consent.

Exclusion Criteria

- History of previous ocular surgeries (e.g., cataract surgery, vitrectomy, or refractive surgery).
- Presence of glaucoma, corneal dystrophies, or keratoconus.
- Co-existing retinal diseases (e.g., age-related macular degeneration, retinal vein occlusion).
- Use of systemic corticosteroids or other drugs affecting corneal/endothelial function.

- Pregnant or lactating women.

Sampling Methodology

A consecutive sampling technique was used, where all eligible patients who visited the Ophthalmology department during the study period were recruited until the required sample size was achieved.

Allocation to Groups

Patients were categorised into groups based on the severity of diabetic retinopathy as per the ETDRS diabetic retinopathy classification

- No DR
- Mild non-proliferative DR (NPDR)
- Moderate NPDR
- Severe NPDR
- Proliferative DR (PDR)

Participant Recruitment

Patients attending the Ophthalmology OPD at LN Medical College, Bhopal, were screened for eligibility based on history, clinical examination, and investigations. Eligible patients were enrolled after obtaining informed consent.

Obtaining Informed Consent

All participants were informed about the purpose, procedures, risks, and benefits of the study. Written informed consent was obtained before enrollment.

Designing & Pilot Testing Data Collection Tool

A structured data collection form was designed to record demographic details, clinical history, ocular parameters (CCT, CMT, ECC), and laboratory findings (HbA1c). A pilot study was conducted on 10 patients to test the feasibility of the study design and data collection procedures.

Data Sources

- Patient records (demographic details, diabetes duration, HbA1c levels).
- Fundus examination reports (ETDRS DR severity classification).
- OCT scans (CMT measurement).
- Pachymetry results (CCT measurement).
- Specular microscopy results (ECC measurement).

Data Collection Procedure

- Patient evaluation: All eligible patients underwent a comprehensive ophthalmic examination, including visual acuity, slit-lamp biomicroscopy, intraocular pressure measurement, and dilated fundus examination.
- OCT imaging: Central macular thickness (CMT) was measured using spectral-domain OCT.
- Pachymetry: CCT was measured using ultrasound or optical pachymetry.
- Specular Microscopy: Endothelial cell count was measured using non-contact specular microscopy.
- HbA1c Testing: A venous blood sample was collected, and HbA1c levels were determined using high-performance liquid chromatography (HPLC).

Statistical Analysis Plan

Descriptive statistics (mean, standard deviation, frequency) were used for baseline characteristics. Pearson's/Spearman's correlation analysis was performed to assess relationships between CCT, CMT, ECC, and DR severity/HbA1c levels. A p-value <0.05 was considered statistically significant.

Results

Demographic and Clinical Profile

The present study included 100 patients with Type 2 Diabetes Mellitus (T2DM). The mean age of participants was 50.06 ± 7.78 years (range: 34–81 years), with a slight male predominance (54% males, 46% females). The mean duration of diabetes was 8.97 ± 7.22 years.

The mean HbA1c level of the study population was 7.9 ± 2.1%, ranging from 5.6% to 11.4%, indicating overall suboptimal glycaemic control (Figure 1).

Treatment Status

The majority of the participants (60%) were on oral hypoglycemic agents (OHA). A significant proportion (15%) was not on any treatment at the time of evaluation; 12% of the patients were receiving Human Actrapid Insulin (HAI), while 6% were on a combination of OHA and HAI. Other treatment regimens included Mixtard insulin (3%), insulin alone (2%), OHA & HAI (1%), and OHA & insulin (1%).

The mean HbA1c level among the study population was 7.9 (±2.1), with values ranging from 5.6 to 11.4 (Figure 1).

Distribution of Diabetic Retinopathy

Out of 100 patients, 29% showed features of diabetic retinopathy, while 71% had no retinopathy. Among patients with DR, mild NPDR was the most common subtype (11%), followed by moderate NPDR (8%), severe NPDR (6%), and proliferative diabetic retinopathy (4%) (Figure 2).

Association of DR Severity with Endothelial Parameters, CCT, and CMT

A statistically significant inverse relationship was observed between endothelial cell density (ECD) and increasing severity of DR. Mean ECD progressively decreased from

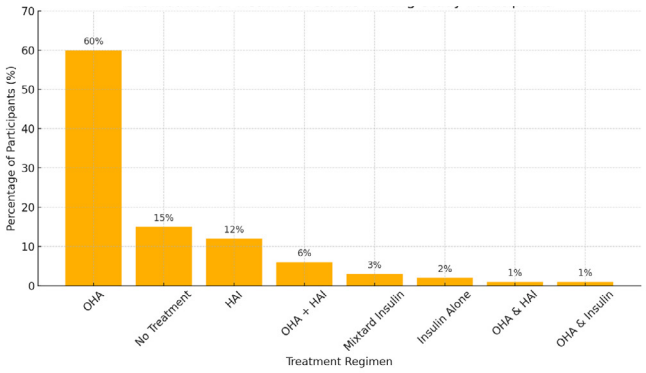

Figure 1: Distribution of Treatment Status Among Study Participants

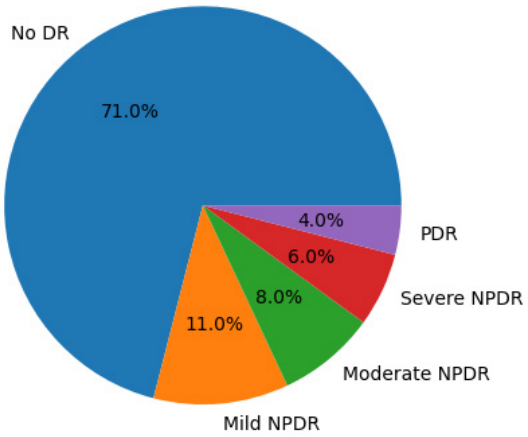

Figure 2: Distribution of Diabetic Retinopathy Severity (n=100)

2538.2 ± 282.4 cells/mm² in patients without DR to 2315.4 ± 305.6 cells/mm² in patients with PDR ($p < 0.001$).

The coefficient of variation (CV), indicating endothelial polymegathism, showed a significant increasing trend with DR severity ($p = 0.009$). Conversely, hexagonality percentage (Hex) demonstrated a significant decline with advancing DR ($p = 0.004$), reflecting worsening endothelial pleomorphism. Central corneal thickness (CCT) increased progressively with DR severity, from 508.7 ± 35.9 µm in patients without DR to 534.5 ± 37.4 µm in PDR, showing a statistically significant association ($p = 0.012$) (Table 1).

Central Macular Thickness and DR Severity

A progressive increase in central macular thickness (CMT) was observed with worsening DR severity. Mean CMT increased from 310 ± 26 µm in patients without DR to 382 ± 37 µm in patients with PDR. This trend was highly statistically significant ($p < 0.001$) (Figure 3).

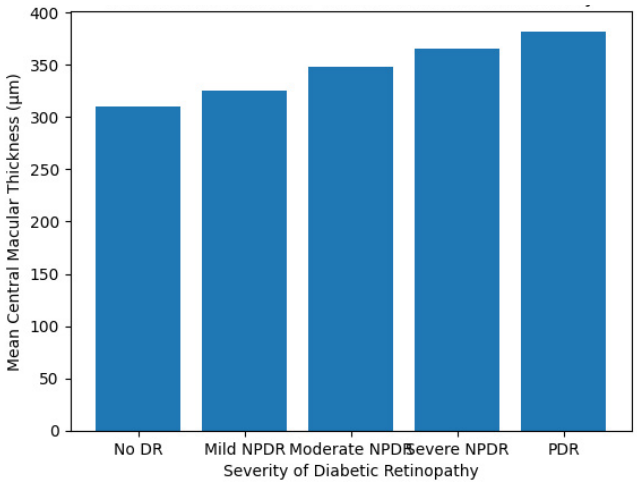

Figure 3: Mean Central Macular Thickness Across DR Severity

Association of Glycaemic Control with Ocular Parameters

Patients with poor glycaemic control (HbA1c > 7.5%) demonstrated:

- Significantly lower ECD
- Higher CV
- Reduced hexagonality
- Increased CCT and CMT

The median CMT was significantly higher in the poor glycaemic control group (342 µm) compared to the good control group (311 µm) ($p = 0.001$), indicating a strong association between hyperglycaemia and macular thickening (Table 2).

Discussion

Diabetes mellitus is a chronic metabolic disorder characterized by progressive microvascular damage, with diabetic retinopathy (DR) being the most vision-threatening ocular complication. While retinal involvement has been extensively investigated, increasing evidence suggests that diabetes affects the eye in a more generalized manner, involving both anterior and posterior segment structures. The present study assessed the relationship between central corneal thickness (CCT), corneal endothelial characteristics, central macular thickness (CMT), severity of DR, and glycaemic status in patients with type 2 diabetes mellitus (T2DM).

The demographic profile of the study population, comprising predominantly middle-aged individuals with long-standing diabetes, is consistent with previously reported patterns of diabetic retinopathy. The mean duration of diabetes approaching nine years reflects prolonged metabolic exposure, which is a known determinant of microvascular damage.

A significant and consistent decline in endothelial cell density (ECD) was observed with increasing severity of diabetic retinopathy. Patients with proliferative DR demonstrated the lowest ECD values, indicating progressive corneal endothelial involvement with advancing retinal disease. Additionally, increasing DR severity was associated with a rise in the coefficient of variation and a reduction in hexagonality percentage, reflecting increasing endothelial polymegathism and pleomorphism. These findings suggest that corneal endothelial morphology deteriorates in parallel with retinal microangiopathy, reinforcing the concept that diabetic ocular involvement is not confined to the retina alone. The endothelial alterations observed in this study may be attributed to sustained hyperglycaemia-induced metabolic stress, including activation of the polyol pathway, intracellular sorbitol accumulation, oxidative damage, and impaired Na^+/K^+-ATPase activity. As corneal endothelial cells lack regenerative capacity, these changes assume particular clinical significance, especially in patients requiring intraocular surgical interventions where endothelial reserve plays a critical role.

Central corneal thickness demonstrated a statistically significant increase with both worsening severity of diabetic

Table 1: Association of severity of DR with endothelial cell changes, CCT, CMT

DR status	*ECD (cells/mm²) Mean ± SD*	*CV (%) Mean ± SD*	*Hex (%) Mean ± SD*	*CCT (µm) Mean ± SD*	*CMT(µm) Mean ± SD*
No DR (n = 71)	2538.2 ± 282.4	39.5 ± 5.8	40.9 ± 5.4	508.7 ± 35.9	310 ± 26
Mild NPDR (n = 11)	2486.7 ± 276.3	40.7 ± 6.5	39.7 ± 4.9	515.3 ± 34.6	325 ± 28
Moderate NPDR (n = 8)	2430.5 ± 264.1	41.2 ± 5.9	38.9 ± 5.1	521.6 ± 33.7	348 ± 30
Severe NPDR (n = 6)	2378.9 ± 298.0	42.1 ± 6.2	38.2 ± 4.8	527.2 ± 36.1	365 ± 34
PDR (n = 4)	2315.4 ± 305.6	42.9 ± 6.8	37.6 ± 4.5	534.5 ± 37.4	382 ± 37
P value	<0.001	0.009	0.004	0.012	<0.001

Table 2: Association of glycaemic control and endothelial parameters, CCT, CMT

HbA1c (%)	*≤7.5%(n = 67) Median (Q1–Q3)*	*>7.5% (n = 33) Median (Q1–Q3)*	*p-value*
Endothelial cell density [cells/mm²]	2543 (2385–2725)	2452 (2230–2640)	<0.001
CV of cell area [%]	39 (36–42)	41 (37–44)	0.002
Hexagonality [%]	41 (38–43)	39 (36–42)	0.005
Central corneal thickness [µm]	515 (498–540)	527 (505–552)	<0.001
Central macular thickness [µm]	311 (287–335)	342 (307–377)	0.001

retinopathy and elevated HbA1c levels. Patients with proliferative disease and poor glycaemic control exhibited the greatest corneal thickness. This increase in CCT is likely secondary to endothelial dysfunction resulting in altered corneal hydration. Clinically, increased corneal thickness in diabetic patients may influence intraocular pressure estimation and should be considered during surgical planning, particularly in glaucoma and refractive surgery candidates.

Central macular thickness showed a progressive and significant increase with advancing DR severity. The highest CMT values were noted in patients with proliferative diabetic retinopathy. Furthermore, patients with poor glycaemic control demonstrated significantly greater macular thickness compared to those with better metabolic control. These findings highlight the role of chronic hyperglycaemia in promoting retinal structural changes through disruption of the blood–retinal barrier and increased vascular permeability. Importantly, increased CMT was observed even in the absence of clinically apparent macular edema, suggesting that OCT-based macular thickness assessment may detect early retinal involvement before overt clinical manifestations.

Overall, the findings of this study demonstrate a strong association between corneal endothelial parameters, central corneal thickness, central macular thickness, severity of diabetic retinopathy, and glycaemic status. Incorporation of these objective measurements into routine ophthalmic evaluation may provide a more comprehensive assessment of ocular involvement in patients with T2DM.

Conclusion

This study establishes a significant association between corneal endothelial morphology, central corneal thickness, central macular thickness, severity of diabetic retinopathy, and glycaemic control in patients with type 2 diabetes mellitus. Progressive worsening of diabetic retinopathy is accompanied by a reduction in endothelial cell density and hexagonality, an increase in endothelial cell size variability, thickening of the cornea, and increasing macular thickness.

Poor glycaemic control is independently associated with adverse corneal endothelial changes and increased central macular thickness, underscoring the importance of optimal metabolic regulation in limiting ocular microvascular damage. Routine assessment of corneal endothelial parameters using specular microscopy, along with evaluation of corneal and macular thickness using pachymetry and optical coherence tomography, may serve as valuable adjuncts to standard diabetic retinopathy screening. Such an approach can facilitate early detection of subclinical changes, improve surgical risk assessment, and contribute to better long-term visual outcomes in patients with type 2 diabetes mellitus.

Funding

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Conflict of Interest

The authors declare no conflicts of interest in this study.

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