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Original Article

Physiology Section

Comparison of Retinal Thickness in Diabetic Patients with Healthy Controls: A Cross-sectional Study

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ABSTRACT

Introduction: Diabetes Mellitus (DM) is a metabolic disorder characterised by chronic hyperglycaemia, leading to systemic complications such as Diabetic Retinopathy (DR). The impact of DM on retinal thickness is of particular interest, as it can serve as an early indicator of DR progression.

Aim: To assess variations in retinal thickness among diabetic patients without systemic involvement and also to correlate retinal thickness with the duration of diabetes and Glycated Haemoglobin (HbA1c) levels.

Materials and Methods: This cross-sectional study was conducted in the Department of Physiology at Geetanjali Medical College and Hospital, a tertiary care centre, from January 2023 to April 2024. A total of 120 participants were included, with 60 individuals in the diabetic group (group D) and 60 in the healthy control group (group N). Group D consisted of participants with a diabetes duration of 1.5-10 years and HbA1c levels above 6.5%, while those with systemic or ocular complications of diabetes were excluded. Retinal thickness was measured using Optical Coherence Tomography (OCT), and HbA1c levels were recorded. Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) version 20.0, employing independent samples t-tests and correlation analysis.

Results: The study included 60 participants in each group, with group N (Control) and group D (Diabetic) having a mean age of 38.67±5.38 years and 48.17±8.76 years, respectively, with the latter being significantly older. The gender distribution varied, with group N having a higher male-to-female ratio (51 males and 9 females) compared to group D (39 males and 21 females). The diabetic group exhibited significantly reduced retinal thickness compared to the controls, with mean values of 190.88±22.33 µm in the right eye and 188.02±19.58 µm in the left eye. In contrast, the control group had mean values of 206.02±21.29 µm in the right eye and 210.33±18.14 µm in the left eye (p-value <0.001). Correlation analysis showed no significant associations between HbA1c levels, duration of diabetes and retinal thickness.

Conclusion: This study highlights significant reductions in retinal thickness among diabetic patients compared to healthy controls. The lack of correlation with HbA1c levels and diabetes duration suggests the need for further investigation into additional factors influencing retinal changes in DM.

Keywords: Diabetic retinopathy, Hyperglycaemia, Optical coherence tomography, Retinal microvasculature

INTRODUCTION

The DM as defined by the World Health Organisation (WHO), is a metabolic disorder characterised by chronic hyperglycaemia, leading to disturbances in carbohydrate, protein and fat metabolism due to deficiencies in insulin secretion, action, or both [1]. The American Diabetes Association (ADA) diagnoses DM based on either a fasting plasma glucose level of ≥126 mg/dL or an HbA1c level of ≥6.5%, emphasising the significance of assessing chronic hyperglycaemia and its associated risks [2]. A National Non Communicable Disease Monitoring Survey (NNMS) reported a DM prevalence of 9.3% in India in 2018, projected to rise to 10.4% by 2030 [3], underscoring the urgent need for effective management strategies.

The DM is a chronic condition that affects multiple systems, with complications such as DR, nephropathy and neuropathy [4]. DR arises from damage to the retinal microvasculature and neurons, typically detected via fundus examination. However, traditional diagnostic methods like slit-lamp biomicroscopy and stereo fundus photography are relatively insensitive to early retinal changes. Fluorescein angiography, while highly sensitive, is invasive and unsuitable for routine screening [5,6]. These limitations highlight the need for advanced diagnostic tools capable of identifying early retinal changes.

Recent advancements in non invasive yet sensitive imaging techniques, such as OCT, OCT-Angiography (OCT-A) and multifocal Electroretinography (mfERG), have demonstrated the ability to detect retinal abnormalities even in patients without visible signs of DR [7-11]. While these tools have significantly enhanced our understanding of retinal changes in diabetes, most existing studies focus on retinal alterations associated with established DR or its complications. Few studies have specifically explored the relationship between retinal thickness, diabetes duration and glycaemic control in individuals without visible DR [12-14].

The present study is novel in its focus on early retinal changes in patients with diabetes who exhibit no visible signs of DR, addressing a critical gap in existing research. Unlike earlier studies, which often emphasise structural or vascular changes in the later stages of DR, this research aims to identify subtle alterations in retinal thickness and their correlation with diabetes duration and HbA1c levels, which may serve as early indicators of disease progression. By targeting a population without visible DR, this study seeks to provide insights into the potential utility of OCT as a screening tool for preclinical detection, thereby contributing to earlier intervention and improved outcomes.

This study aims to address this gap by assessing variations in retinal thickness in diabetic patients without systemic involvement and compare with those of healthy controls. Additionally, it seeks to correlate retinal thickness with the duration of diabetes and HbA1c levels.

MATERIALS AND METHODS

This cross-sectional study was conducted in the Department of Physiology at Geetanjali Medical College and Hospital, a tertiary care institution, Udaipur, Rajasthan, India between January 2023 and April 2024. Approval was obtained from the Human Research

Ethics Committee (IEC number: GU/HREC/2019/679) and informed written consent was collected from all participants. Measures were implemented to ensure the confidentiality of participant data.

Inclusion criteria: Diabetic patients aged 28-52 years with a diabetes duration of between 1.5-10 years, HbA1c levels >6.5% and no systemic or ocular complications were included as cases. Healthy participants with no history of DM were included as controls.

Exclusion criteria: For both groups, subjects with systemic complications of DM (e.g., diabetic neuropathy, nephropathy), overt DR, or ocular conditions such as glaucoma, cataracts, or fundus abnormalities were excluded. Individuals with undiagnosed or subclinical DR were also excluded from the study.

Sample size calculation: The sample size was calculated based on the prevalence of DM in Rajasthan (8.3%) [3], with a 95% confidence level and an allowable error of 10%.

Using the formula:

$$N=Z^2\times p(1-p)/e^2$$

Where Z is the Z-score for a 95% confidence level (1.96), p is the prevalence and e is the allowable error; a minimum of 60 participants was determined for each group.

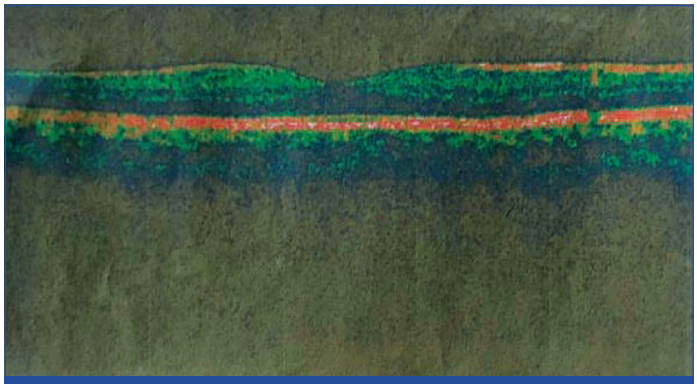
The allocation ratio was set at 1:1, resulting in 60 participants in the case group (group D) and 60 age-matched healthy participants in the control group (group N).

Data collection: All participants underwent a comprehensive ophthalmic examination, including intraocular pressure measurement and OCT. Blood samples were collected early in the morning for HbA1c testing. Body Mass Index (BMI) and pulse rate were also recorded for all participants to ensure comparability between groups. There were no significant differences in these parameters, strengthening the basis for comparison between the diabetic and control groups. This comprehensive assessment helped ensure the robustness of the study design while addressing potential confounders [15].

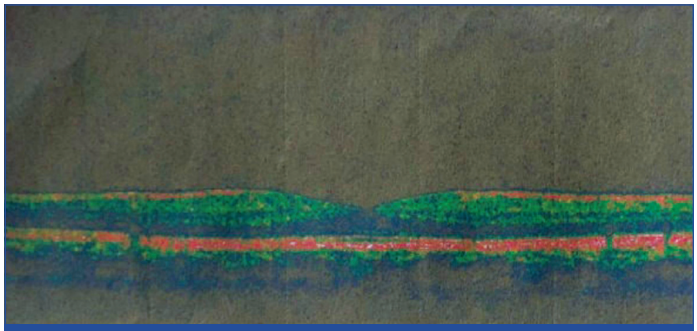
Study Procedure

The retinal images were captured using OCT, specifically employing time-domain software within the Department of Ophthalmology. OCT is an advanced diagnostic imaging technology that provides high-resolution, micrometer-scale visualisation of retinal structures, including retinal thickness. Retinal thickness is defined as the height from the vitreoretinal interface to the Retinal Pigment Epithelium (RPE). The principle of OCT relies on Michelson Interferometry, in which low-coherence infrared light is transmitted through a beam splitter and directed towards the eye along with a reference mirror. This setup enables precise measurement of retinal layers and their thickness using interferometric signals. In this study, OCT was utilised specifically to evaluate retinal thickness. The scanning procedure involved using a Spectral-Domain OCT (SD-OCT) device, which offers enhanced imaging capabilities compared to traditional time-domain OCT. SD-OCT devices provide higher resolution images due to their faster scanning speeds and greater sensitivity to fine details within the retina, allowing for a more detailed assessment of Retinal Nerve Fiber Layer (RNFL) thickness and the optic nerve head [16,17]. For this study, however, only retinal thickness measurements were considered. Time-domain software was used to capture the OCT images.

Procedure: Participants were asked to sit comfortably in front of the OCT machine, resting their chin on the chin rest and instructed to fix their gaze on a green fixation target. Once the participant was properly positioned, the operator selected the desired scan. The resulting image could be either in color or grayscale, with highly reflective tissues appearing in red and white, moderately reflective tissues displayed in green or yellow and low reflective tissues shown in blue and black [18]. Representative images include [Table/Fig-1], which displays an OCT scan measuring retinal thickness of 187 µm at A-scan 1, along with signal strength and a thickness chart and [Table/Fig-2], which shows an OCT image and thickness chart with a retinal thickness of 212 µm at A-scan 1.



[Table/Fig-1]: OCT image displaying retinal thickness measurement of 187 µm at A-scan 1, along with signal strength and a thickness chart.



[Table/Fig-2]: OCT image and thickness chart displaying retinal layer measurement of 212 µm at A-scan 1.

STATISTICAL ANALYSIS

The data was analysed using IBM SPSS version 20. Continuous variables such as age, HbA1c and retinal thickness were presented as mean±SD, as the data were normative. The Karl Pearson correlation coefficient was performed to assess the correlation between HbA1c and retinal thickness in both groups, as well as the duration of diabetes in group D and retinal thickness. A p-value <0.05 was considered statistically significant.

RESULTS

[Table/Fig-3] summarises the demographic and clinical characteristics of the control group (group N) and the diabetic group (group D). Both groups included 60 participants each. The mean age of group D (48.17±8.76 years) was significantly higher than that of group N (38.67±5.38 years; p-value <0.001). The gender distribution showed

Variables	Control (Group N)	Diabetic (Group D)	p-value
Number of participants	60	60	-
Mean age (years)	38.67±5.38	48.17±8.76	<0.001
Males/Females	51/9	39/21	0.020
Mean HbA1c (%)	5.16±0.52	8.19±1.19	<0.001
Intraocular pressure			
Right eye	16±2.58	15.43±3.04	0.270
Left eye	16.22±2.37	15.47±2.95	
Pulse rate	75.85±6.74	75.50±7.16	0.127
Body mass index, n (%)			
<18.9	0	1 (1.67)	0.004
18.9-24.9	46 (76.67)	29 (48.33)	
>24.9	14 (23.33)	30 (50)	
Mean duration of diabetes (years)	-	3.46	-

[Table/Fig-3]: Demographic and clinical characteristics.

more males in group N (51 males vs. 39 in group D). Mean HbA1c levels were markedly elevated in group D (8.19±1.19%) compared to group N (5.16±0.52%; p-value <0.001), reflecting poorer glycaemic control among diabetic participants.

[Table/Fig-4] presents the comparison of retinal thickness measurements between the control group (group N) and the diabetic group (group D) for both the right and left eyes. In both eyes, the control group exhibited significantly higher retinal thickness compared to the diabetic group, with p-values <0.001. These findings highlight the impact of diabetes on retinal structure, indicating thinner retinal measurements in individuals with diabetes, which could be due to microvascular changes associated with the disease.

Retinal thickness (µm)	Control (Group N)	Diabetic (Group D)	p-value
Right eye	206.02±21.29	190.88±22.33	<0.001
Left eye	210.33±18.14	188.02±19.58	<0.001

[Table/Fig-4]: Retinal thickness in right and left eye.

The relationship between the duration of diabetes and retinal thickness was explored in diabetic participants. The correlation between diabetes duration and retinal thickness in the right eye showed an R-value of 0.095, indicating a weak positive association, though this was not statistically significant (p-value >0.05). Similarly, for the left eye, the R-value was 0.004, suggesting a negligible correlation between diabetes duration and retinal thickness, with the result remaining non significant (p-value >0.05) [Table/Fig-5].

Correlation	R-value	p-value
Duration of diabetes (Right eye)	0.095	0.47
Duration of diabetes (Left eye)	0.004	0.975

[Table/Fig-5]: Correlation between diabetes duration and retinal thickness.

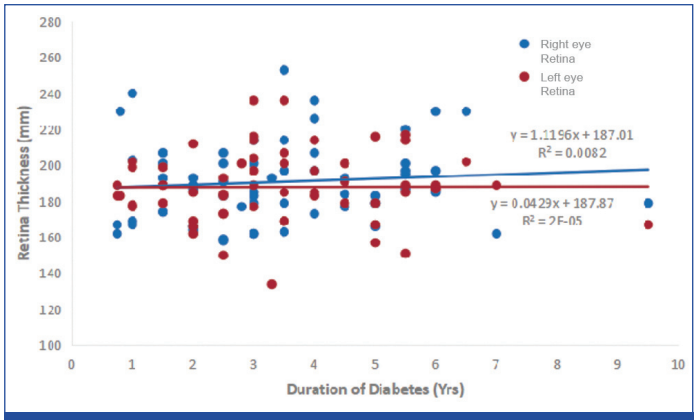
The correlation between HbA1c levels and retinal thickness was examined separately for both the diabetic and control groups. In the diabetic group (group D), the correlation between HbA1c and retinal thickness for the right eye was weak and non significant (R=0.014, p-value >0.05). For the left eye, the correlation was slightly stronger but still non significant (R=0.083, p-value >0.05). In the control group (group N), the correlation for the right eye was weak (R=0.046, p-value >0.05) and for the left eye, there was a slight negative correlation (R=-0.138, p-value >0.05), neither of which reached statistical significance [Table/Fig-6].

Group	Correlation	R-value	p-value
Diabetic (Group D)	HbA1c and retinal thickness (Right eye)	0.014	0.915
Diabetic (Group D)	HbA1c and retinal thickness (Left eye)	0.083	0.528
Control (Group N)	HbA1c and retinal thickness (Right eye)	0.046	0.528
Control (Group N)	HbA1c and retinal thickness (Left eye)	-0.138	0.293

[Table/Fig-6]: Correlation between HbA1c and retinal thickness.

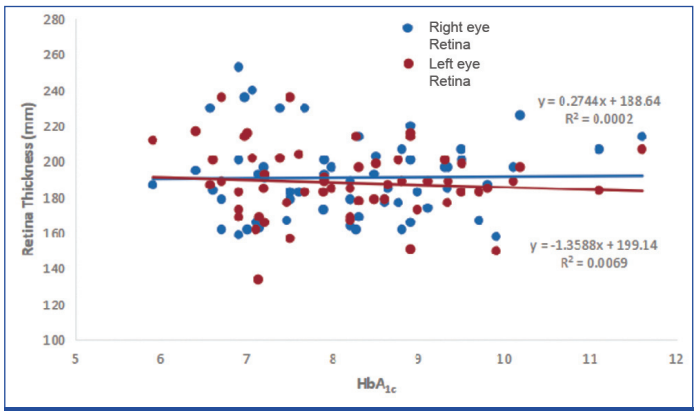
As shown in [Table/Fig-7], no significant correlation was observed between the duration of diabetes (in years) and retinal thickness (in µm) in either eye. The correlation coefficient was r-value=0.095 for the right eye and r-value=0.004 for the left eye, indicating a negligible relationship. These findings imply that retinal thickness does not appear to be significantly influenced by the duration of diabetes, emphasising the role of other contributing factors in retinal changes among diabetic individuals.

[Table/Fig-8] illustrates the correlation between HbA1c (%) and retinal thickness (µm) in the diabetic group (group D), which was found to be insignificant. The correlation coefficients were r-value=0.014 for the right eye and r-value=0.083 for the left eye, indicating a very weak and non significant association. These findings suggest that HbA1c



[Table/Fig-7]: Correlation were assessed between duration of diabetes (years) and retinal thickness (µm) it was not significant (r=0.095 of right eye and r=0.004 left eye).

levels alone may not directly influence retinal thickness in diabetic patients, emphasising the need to investigate other contributing factors to retinal changes.



[Table/Fig-8]: Correlation were assessed between HbA1c (%) and retinal thickness (µm) in Group D, it was not significant (r=0.014 of right eye and r=0.083 left eye).

DISCUSSION

Diabetic retinal changes are subtle and multifaceted, necessitating early detection to prevent progression to DR. OCT studies have illuminated structural alterations in the retina, revealing both thinning and thickening of specific layers. Normal retinal thickness ranges from approximately 212 to 250 µm in healthy individuals, depending on the specific measurement location [18,19]. This study compared retinal thickness in diabetics without overt DR to healthy controls, revealing notable differences. These findings align with the existing literature and highlight the utility of retinal imaging in understanding early neurovascular changes associated with diabetes.

The present study demonstrated a significant reduction in retinal thickness in diabetic participants compared to non diabetic controls, which aligns with findings from several prior studies. For instance, Dumitrescu AG et al., reported that the average macular thickness in the central region was significantly reduced in diabetic individuals (243.5 µm) compared to healthy controls (269.9 µm, p-value <0.001) [12]. These results are consistent with the current study, which found mean retinal thickness values of 190.88±22.33 µm in the right eye and 188.02±19.58 µm in the left eye for the diabetic group, both significantly lower than the respective values of 206.02±21.29 µm and 210.33±18.14 µm in the control group (p-value <0.001). Jiang J et al., also reported significant reductions in retinal thickness across multiple regions in diabetic individuals: foveal (215.8±18.9 µm vs. 222.0±18.6 µm, p-value=0.04), temporal parafovea (319.9±16.7 µm vs. 326.0±14.4 µm, p-value=0.01) and temporal perifovea (276.4±27.9 µm vs. 284.8±17.4 µm, p-value=0.02) [13]. These findings correspond well with the significant reductions observed in the diabetic group of the current study, emphasising the impact of diabetes on the retinal microstructure across various regions. Such changes may indicate underlying pathophysiological

mechanisms, including retinal ischaemia, microvascular dysfunction and neuroretinal degeneration, which are common in diabetes. The consistency of these findings reinforces the importance of retinal thickness as a potential marker for early diabetic changes and highlights the utility of retinal imaging techniques like OCT in detecting and monitoring these changes in clinical practice.

The present study found a significant reduction in retinal thickness among diabetic participants compared to non diabetic controls, indicating early signs of neurodegenerative changes. However, the complex progression of retinal changes in diabetes, especially in the presence of DR, can be discussed in light of the following studies. Pires I et al., observed an increase in macular thickness in diabetic patients with mild Non Proliferative Diabetic Retinopathy (NPDR) without macular oedema, with Central Point Thickness (CPT) and Central Subfield (CSF) thickness measuring 186.6±28.4 µm and 215.2±25 µm, respectively, both significantly higher than in non diabetic controls (p-value <0.001) [20]. Similarly, Sanchez-Tocino H et al., reported increased retinal thickness in all regions in eyes with NPDR or Proliferative Diabetic Retinopathy (PDR), suggesting a progression to vascular complications [5]. These findings contrast with the current study, where all diabetic participants were free from systemic complications or overt DR and retinal thinning was the predominant finding. This discrepancy can be attributed to differences in disease stage and pathological mechanisms. In early diabetes without DR, retinal thinning is thought to result from neurodegenerative processes affecting retinal axonal and glial cells [12-14,19].

As diabetes progresses, the disease transitions from a neurodegenerative to a vascular-dominant pathology. Increased vascular permeability, inflammatory responses and retinal oedema contribute to the thickening of the retinal layers, as seen in the findings of Pires I et al., and Sanchez-Tocino H et al., in eyes with NPDR or PDR [5,20]. This shift is driven by microvascular damage, including capillary leakage and ischaemia, which stimulate inflammatory cytokines and angiogenic factors, causing retinal swelling. The findings of the present study align with those of Dumitrescu AG et al., and Jiang J et al., who reported significant retinal thinning in the absence of overt DR [12,13]. The relationship between neurodegeneration and vascular dysfunction in diabetes underscores the heterogeneity of retinal changes across disease stages. Early-stage diabetes, as studied here, is characterised by predominant thinning, reflecting neuroretinal damage. Conversely, retinal thickening in DR represents a later-stage vascular response. This highlights the need for early detection of subtle retinal changes using advanced imaging modalities like OCT, which can help stratify patients and guide timely interventions to prevent progression to DR. Further studies exploring these transitions are critical to fully elucidate the sequence and mechanisms underlying diabetic retinal alterations.

The present study found no statistically significant correlation between the duration of diabetes and retinal thickness in either eye, aligning with findings from Zhong ZL et al., who suggested that while the duration of diabetes is linked to neurovascular alterations, it does not directly correlate with measurable changes in retinal thickness [21]. Similarly, Jiang J et al., observed subtle regional thinning in the temporal parafoveal area with prolonged diabetes duration, although these changes were not statistically significant [13]. Srinivasan S et al., highlighted progressive functional impairments in individuals with over 10 years of diabetes, indicating neuroretinal dysfunction rather than significant structural thinning [22]. Early-stage diabetes may cause thinning in specific retinal layers, such as the Ganglion Cell Layer (GCL) and Inner Nuclear Layer (INL), even in the absence of DR [23,24]. However, overall macular thickness changes often remain subtle or undetectable at this stage. The mfERG studies, such as those by Srinivasan S et al., reveal functional impairments that precede structural changes, suggesting that neuroretinal dysfunction can develop independently of measurable macular thinning in early diabetes [22]. Studies have shown that individual macular retinal layers can exhibit varying degrees of thinning in diabetic eyes, highlighting the importance of assessing layer-specific changes using advanced imaging techniques [22-24]. The lack of correlation between diabetes duration and retinal thickness observed in the present study aligns with findings suggesting that the progression of retinal changes in diabetes involves a complex interplay of neurovascular alterations rather than being directly influenced by disease duration. Zhong ZL et al., proposed that cumulative neurovascular alterations, including capillary dropout and neural apoptosis, may not uniformly affect macular thickness in the early or mid-stages [21]. Jiang J et al., supported this, showing that regional thinning becomes evident only with extended disease duration [13]. These findings collectively underscore the importance of using advanced diagnostic tools beyond OCT to detect early diabetic alterations.

The study found no significant correlation between HbA1c levels and retinal thickness, a finding that aligns with the results from Srinivasan S et al., and Adhikari P et al., who observed consistent retinal thickness regardless of HbA1c thresholds [22,25]. Asefzadeh B et al., also reported a lack of association between HbA1c and macular thickness [26]. However, contrasting findings from Jiang J et al., and Karakahya RH suggest that higher HbA1c levels are associated with localised thinning in specific retinal regions, such as the temporal and perifoveal areas, as well as reduced RNFL thickness, indicating early neurodegeneration [13,27].

The absence of a significant HbA1c-retinal thickness correlation in this study may be due to the participants being in the early stages of diabetes or maintaining good glycaemic control, where retinal changes have not yet become pronounced. Additional confounders such as blood pressure, lipid profiles and glycaemic variability could influence these outcomes, potentially diluting the direct impact of HbA1c on retinal thickness measurements [13,27].

The findings from this study are consistent with those reported by previous studies; Srinivasan S et al., found no significant differences in retinal thickness measured by OCT or in mfERG measurements between participants with HbA1c levels below 7% and those with HbA1c levels of 7% or higher [22]. Similarly, Adhikari P et al., reported that mfERG amplitude did not show any significant correlation with blood glucose levels [25]. Asefzadeh B et al., also noted no correlation between HbA1c and macular thickness [26].

These results suggest that early-stage or well-managed diabetes may not yet manifest detectable changes in retinal structures due to variations in HbA1c. The complex interplay of factors such as blood pressure and lipid levels may dilute the impact of HbA1c on retinal thickness in these individuals, highlighting the need for further studies to elucidate the underlying mechanisms.

Limitation(s)

However, several limitations should be considered. Potential inaccuracies in self-reported diabetes duration could impact the assessment of correlations with retinal changes, while unaccounted confounding factors, such as systemic blood pressure and lipid levels, may influence retinal findings. The relatively small sample size and the study's focus on early-stage diabetes without advanced retinopathy might limit the detection of subtle retinal alterations. Standardisation of imaging techniques and larger-scale studies are needed to validate these findings and provide a more comprehensive understanding of diabetic retinal changes.

CONCLUSION(S)

The present study highlights the significant impact of diabetes on retinal structure, demonstrating thinner retinal measurements in individuals with diabetes compared to non diabetic controls. Despite the finding of thinner retinas in diabetic participants, there was no significant correlation between the duration of diabetes or

HbA1c levels and retinal thickness. These results suggest that other factors, possibly related to vascular changes or individual variations in retinal sensitivity, may contribute to early retinal alterations in diabetes. Future studies should involve larger cohorts and employ standardised imaging techniques to more accurately capture early retinal changes and assess interventions aimed at protecting the retina in diabetic patients.

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