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ORIGINAL RESEARCH ARTICLE

SUBCLINICAL CENTRAL MACULAR THICKNESS AND TOTAL MACULAR VOLUME IN DIABETICS USING SPECTRAL DOMAIN OPTICAL COHERENCE TOMOGRAPHY AND ITS CORRELATION WITH GLYCEMIC INDEX - A CROSS SECTIONAL ANALYTICAL STUDY IN RURAL KARNATAKA

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ABSTRACT

BACKGROUND

To estimate Central macular thickness (CMV), Total macular thickness (TMV) in diabetic patients without diabetic retinopathy (DR) & compare them with nondiabetic patients & correlate with glycosylated hemoglobin (HbA1C) level.

METHOD

In this cross-sectional study, Spectral domain Optical coherence Tomography measurements were taken in 80 subjects with diabetes (>10 years' duration) and 80 controls. The Data of central macular thickness, total macular volume and glycosylated haemoglobin levels were compared in both groups and were presented using frequency, percentage and mean + SD.

RESULTS

The mean age of study group and control group is 64.925 ± 10.674 and 64.6625 ± 9.932 respectively. The mean Central macular thickness was 248.4 ± 38.31; 228.37 ± 15.10; mean Total Macular Volume was 10.83 ± 1.88; 8.33 ± 0.72 & mean glycosylated hemoglobin levels were 7.99 ± 2.35; 5.06 ± 0.41 in study & control group respectively. The study group had significantly higher central macular thickness, total macular volume and glycosylated hemoglobin level was significantly related to them

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CONCLUSION

Our study found that subclinical changes in central macular thickness (CMT) and total macular volume (TMV) may precede overt diabetic retinopathy (DR) alterations. The pronounced elevation of CMT, TMV, and HbA1C levels in the study group suggests a potential link between subclinical macular changes and glycemic control status. This correlation emphasizes the intricate interplay between glycemic control and early macular alterations. Early tight glycemic control prior to the onset of DR may play an important role in preventing the deterioration of macular function by altering the macular hemodynamic

KEYWORDS

CMT: Central Macular Thickness; TMV: Total Macular Volume; SD-OCT: Spectral Domain Optical Coherence Tomography; HbA1C: Glycosylated Hemoglobin.

INTRODUCTION

Diabetes mellitus (DM) is a prevalent microangiopathy with multifaceted impacts on various organs and often leads to serious complications, including diabetic retinopathy (DR).[1] Maintaining tight glycemic control is crucial in mitigating diabetic complications, as emphasized by numerous large-scale studies.[2] Glycosylated hemoglobin (HbA1c) is recognized as the gold standard for evaluating long-term glycemic control, reflecting plasma glucose levels over the preceding three months. This marker reflects the irreversible addition of glucose to the N-terminal end of hemoglobin molecules, a process catalyzed by enzymatic glycosylation. The rate of glycosylation is proportionate to the concentration of glucose in the bloodstream.[3]

For adults without diabetes, the reference range for HbA1c is typically 4.0–5.9%, and a value surpassing 6.5% is indicative of diabetes according to diagnostic criteria.[4,5] Uncontrolled HbA1c levels have been correlated with the development of DR, including retinal hemorrhages, ischemia, neovascularization, and macular edema, among which macular edema is a primary cause of vision loss in individuals with diabetes.[6,7]

Optical coherence tomography (OCT) has revolutionized the assessment of diabetic cystoid macular edema (DCMO), enabling objective monitoring of its progression and providing invaluable insights into this diabetic complication.[2] Screening individuals with diabetes for DR is routine, and OCT has become a pivotal tool in detecting diabetic fundus complications more sensitively than clinical examination alone.[6] Detecting subclinical DME through OCT examination could prompt changes in patient management, such as closer monitoring or focal laser photocoagulation.

Numerous studies have established a correlation between the prevalence of clinically recognized DME and the severity of DR.[8] Limited evidence exists regarding the relationship between the prevalence of subclinical DME and retinopathy severity, highlighting the importance of identifying early warning signs for improved diabetic eye care.

The primary objective of the study is to employ Spectral Domain OCT to measure central macular thickness and total macular volume in diabetic individuals without any DR features and

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in non-diabetic individuals, correlating these measures with participants' glycemic control to contribute valuable insights into macular health, DR, and systemic glucose regulation, potentially revolutionizing diabetic eye care.

MATERIALS & METHODS

This cross-sectional analytical study delves into the nuanced interplay of macular health, diabetic retinopathy (DR), and systemic glycaemic control. Two distinct groups are meticulously delineated – a case group comprising diabetic patients without overt DR and a control group constituted by non-diabetic individuals. The study, conducted at R. L. Jalappa Hospital and Research Centre, Kolar, Karnataka, employs stringent ethical practices, securing written informed consent from participants.

Detailed information on diabetic complications and the standard care available at the institution is provided to participants, fostering an environment of transparency and collaborative engagement. The recruitment strategy focuses on patients attending the Ophthalmology Outpatient Department, ensuring a cohort actively seeking eye care services.

Sample Size Determination

Statistical robustness is underpinned by a thorough estimation of the sample size. Leveraging insights from prior studies, particularly Aitchinson's work, the study aims to detect a mean difference of 0.15 macular thickness. Sample size calculations, performed using the n-master 2.0 software, result in an estimated requirement of 106 subjects per group, considering a 5% alpha error and 80% power.

Inclusion and Exclusion Criteria

The inclusion criteria encompass individuals clinically diagnosed with diabetes mellitus (Type I and Type II) with minimum duration of 10 years and aged 40 years or older without DR, juxtaposed against age and gender-matched non-diabetic counterparts. Exclusion criteria are meticulously designed to mitigate confounding factors, excluding those with hypertension, systemic disorders, high myopia, posterior segment pathologies, previous ocular surgeries, and hazy media.

Clinical Procedure

A structured clinical procedure unfolds, commencing with assessments of visual acuity, refraction, and intraocular pressure using Goldmann Applanation Tonometry. Subsequent examinations include slit-lamp and fundus examinations, executed with precision using slit lamp biomicroscopy with 90D and indirect ophthalmoscopy.

Spectral Domain Optical Coherence Tomography (SD-OCT)

At the heart of the investigative process lies the deployment of Spectral Domain Optical Coherence Tomography (SD-OCT). The advanced SD-OCT Zeiss system, featuring an automatic real-time eye-tracking mode, ensures motion artifact elimination. High-resolution

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horizontal scans and volumetric scans at the macular area are executed, with the selection of images based on quality scores. The calculation of central macular thickness (CMT) and total macular volume (TMV) involves meticulous analysis of the selected images, emphasizing signal-to-noise ratio and high-quality criteria. Total macular volume (TMV), in mm 3, is calculated using the mean thickness, in μm, of each sub-field.

$$TMV = \frac{\pi A}{4000} + \frac{\pi B1 + \pi B2 + \pi B3 + \pi B4}{2000} + \frac{27(\pi C1 + \pi C2 + \pi C3 + \pi C4)}{16000}$$

Blood Sugar Estimation

Beyond ocular assessments, the study extends into systemic parameters with blood sugar estimation. A judicious collection of 2 ml of blood facilitates serum separation, followed by fluoride level estimation using Ion Selective Electrode methodology. By combining ethical considerations, advanced technological applications, and statistical precision, the research aspires to contribute significant insights into the intricate relationship between macular health, diabetic retinopathy, and systemic glucose regulation. Ultimately, the findings hold promise for advancing the landscape of diabetic eye care.

The data were inputted into a Microsoft Excel spreadsheet and analyzed using SPSS 22 software. Categorical data were expressed through frequencies and proportions, with significance tested using either the Chi-square test or Fischer's exact test (for 2x2 tables). Continuous data were presented as mean and standard deviation, with the significance of mean differences between two quantitative variables assessed through the Independent t-test. Pearson Correlation coefficient was employed for correlation analyses.

Graphical representations were generated using MS Excel and MS Word. A P value of <0.05 was considered statistically significant, adhering to all statistical test protocols. The statistical software utilized included MS Excel and SPSS version 22 (IBM SPSS Statistics, Somers NY, USA).

RESULTS

In our comprehensive investigation, the mean age of study group and control group is 64.925±10.674 and 64.6625±9.932 respectively. The mean central macular thickness (CMT) exhibited notable distinctions between the study and control groups, with values of 248.4±38.31 and 228.37±15.10, respectively and was statistically significant. A similar trend emerged in mean total macular volume (TMV), demonstrating values of 10.83±1.88 in the study group and 8.33±0.72 in the control group which was statistically significant. Additionally, our examination included the mean hemoglobin A1C (HbA1C) level, revealing a substantial difference between the two groups with values of 7.99±2.35 in the study group and 5.06±0.41 in the control group. Significantly higher CMT, TMV, and HbA1C levels were observed in the study group, and a notable correlation was established between these parameters.

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		Mean	Std. Deviation	P Value
Subclinical Central Macular Thickness	Cases	248.40	39.363	<0.001
	Control	223.80	20.136	
Total Macular Volume	Cases	10.832500	1.8859088	<0.01
	Control	7.230000	0.6632105	

Table 1: Comparison of mean Subclinical central macular thickness among case and control

There was a statistically significant difference found between case and control with respect to central macular thickness and total macular volume.

			HbA1C level
Among all subjects	Central macular thickness	Pearson Correlation	0.688**
		P value	<0.001
	Total macular volume	Pearson Correlation	0.552**
		P value	<0.001
Among Cases	Central macular thickness	Pearson Correlation	0.715
		P value	<0.01
	Total macular volume	Pearson Correlation	0.082
		P value	0.468

Table 2: Correlation of HbA1C level with Central macular thickness and Total macular volume among all the subjects

Positive strong correlation was found between HbA1C level and Central macular thickness which was statistically significant among all subjects and cases.

Positive moderate correlation was found between HbA1C level and Total macular volume which was statistically significant among all Subjects.

Positive weak correlation was found between HbA1C level and Total macular volume which was not statistically significant among cases.

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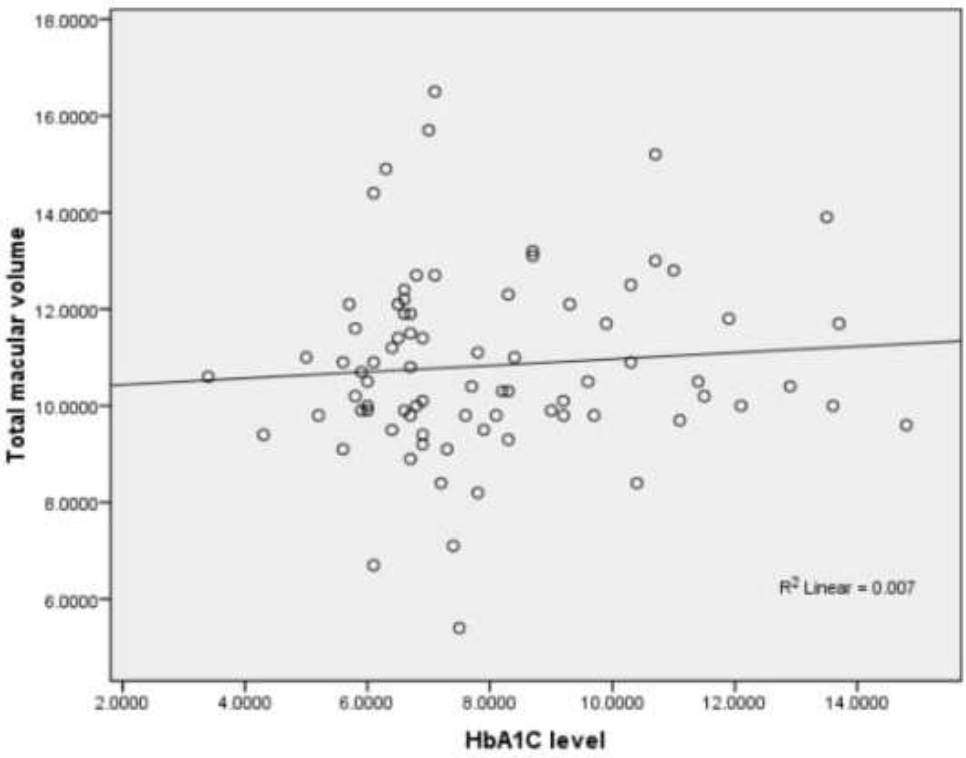

Figure 1a: Scatter plot showing Correlation of HbA1C level with Central macular thickness

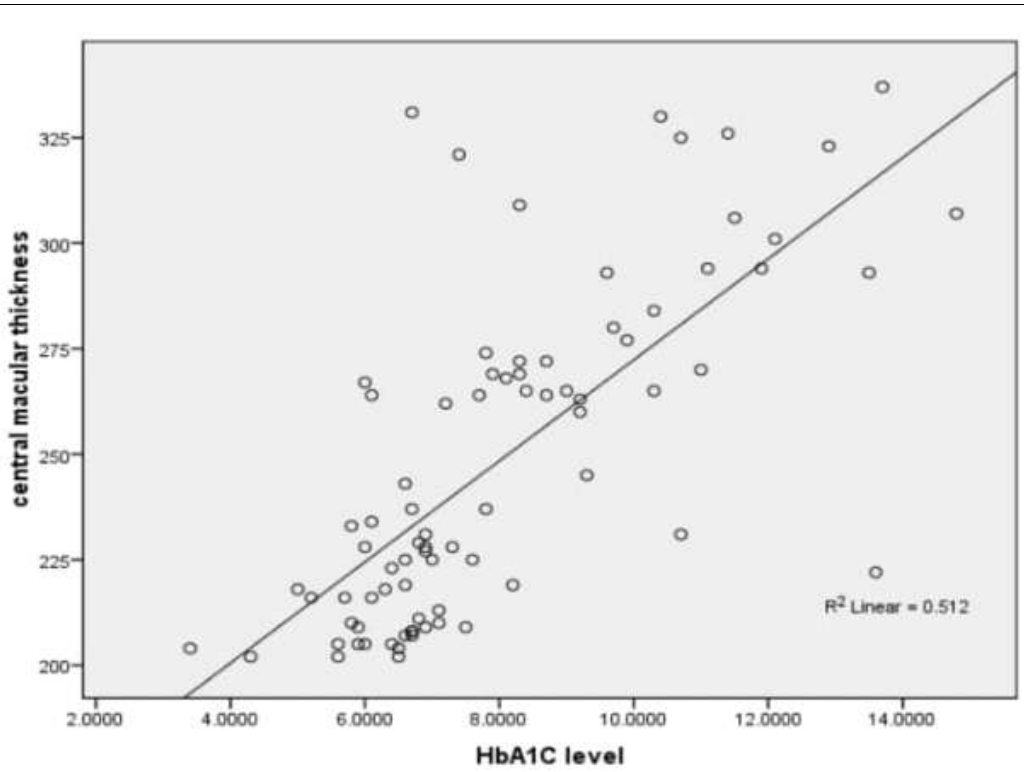

Figure 1b: Scatter plot showing Correlation of HbA1C level with Total macular volume

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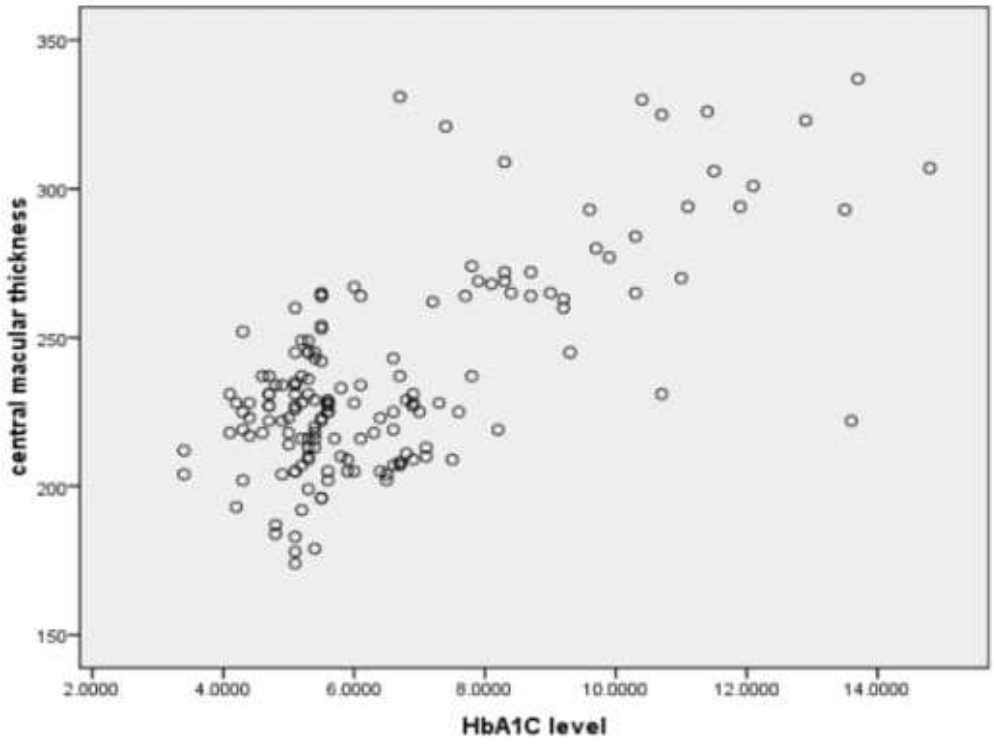

Figure 2a: Scatter plot showing Correlation of HbA1C level with Central macular thickness among cases

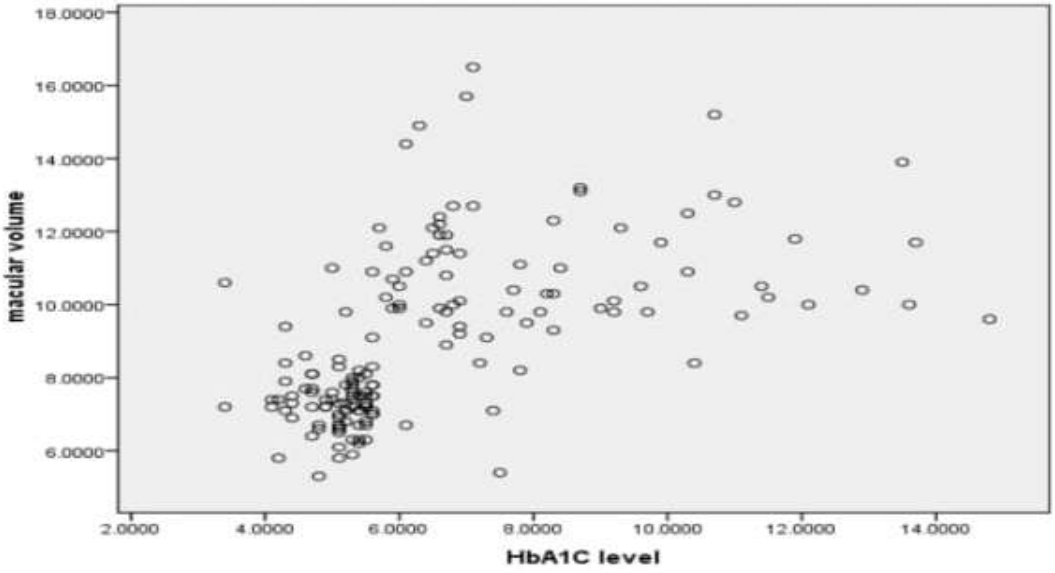

Figure 2b: Scatter plot showing Correlation of HbA1C level with Total macular volume among cases

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DISCUSSION

Our study delves into the intricate relationship between diabetes mellitus (DM), specifically diabetic retinopathy (DR), and the importance of glycemic control. It emphasizes the role of glycosylated hemoglobin (HbA1c) as a marker for long-term glycemic control and discusses the significance of optical coherence tomography (OCT) in detecting subclinical diabetic macular edema (DME).

The study comprised 80 cases and controls, with mean ages of 64.925±10.674 SD [47 to 97 years] and 64.6625±9.932 SD [47 to 92 years] respectively. In both groups, over 60% of patients fell within the 50 to 70-year age bracket (table 3).

Age in years	Cases	Control
41-50	6	5
51-60	27	25
61-70	23	28
71-80	19	16
81-90	5	5
>90	1	1

Table 3a: Age distribution in cases and controls.

Subclinical central macular thickness		
<200	00	11
201-250	45	62
251-300	24	07
>300	11	00
Total macular volume		
<7	01	26
7.1-8.0	02	45
8.1-9.0	04	09
9.1-10.0	24	00
10.1-11.0	19	00
11.1-12.0	11	00
12.1-13.0	11	00
>13.0	8	00

Table 3b: Subclinical CMT and MVT among cases and controls.

Males accounted for 60% (48) of cases and 58.75% (47) of controls, possibly due to higher male visitation rates in ophthalmology OPDs.

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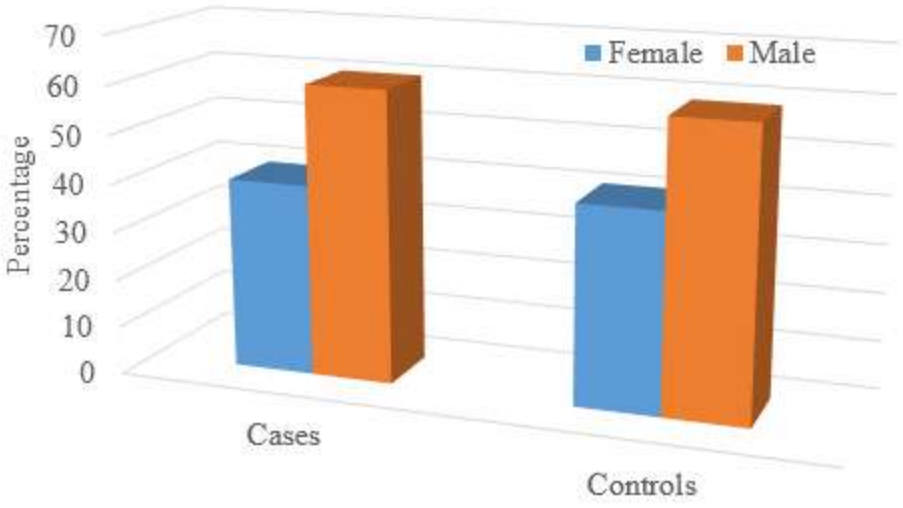

Figure 3: Graph showing Distribution of subjects according to sex among cases and controls

The mean subclinical central macular thickness (CMT) in cases was 248.4±38.31 SD [202 to 337], compared to 228.37±15.10 SD [174-265] in controls, with a notable increase in CMT observed in cases.

Total macular volume (TMV) was also higher in cases, with a mean of 10.83±1.88 SD [5.4 to 16.5], compared to 8.33±0.72 SD [5.3-8.6] in controls, indicating a significant difference between the two groups.

The elevated CMT and TMV in diabetic patients, even in the absence of diabetic retinopathy symptoms, suggest a need for stricter glycemic control and closer monitoring due to the heightened risk of developing macular edema.

Spectral Domain OCT provides high-resolution, cross-sectional images of the retinal structure, enabling objective assessments of central macular thickness (CMT) and total macular volume (TMV). In diabetic individuals without apparent retinopathy, the application of SD-OCT has proven instrumental in detecting subclinical changes, showcasing alterations in macular health that may precede clinically detectable DR.

The nuanced interplay between SD-OCT measurements and glycemic control status underscores the intricate relationship between systemic glucose regulation and early macular alterations. Our study's findings, as well as those from related research, propose a temporal sequence of ocular changes associated with diabetes, emphasizing the potential for early intervention strategies.

The exceptional capabilities of Spectral Domain Optical Coherence Tomography (SD-OCT) in precisely quantifying retinal thickness have been vividly illustrated in a seminal study conducted by Goebel et al. The investigation, focused on retinal thickness in diabetic retinopathy, attests to the technology's unparalleled reproducibility.[9] This aligns seamlessly with the core objective of our own study, which seeks to assess macular health in diabetic individuals devoid of overt diabetic retinopathy.

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Furthermore, the reliability of SD-OCT in detecting early retinal damage is substantiated by the findings of another influential study led by Masahiko Sugimoto, Mikio Sasoh, and Masashi Ido, among others. This particular investigation delves into the detection of early diabetic changes using optical coherence tomography in type 2 diabetes mellitus patients without retinopathy.[10] The resonance between these results and our emphasis on subclinical changes underscores the imperative nature of proactive diabetic eye care.

Collectively, these studies highlight the transformative role of Spectral Domain OCT in early diabetic retinopathy assessment, paving the way for a comprehensive approach to diabetes management. The evolving recognition of SD-OCT as a key diagnostic tool in diabetic eye care reinforces the need for continued research and clinical integration to improve patient outcomes through timely interventions.

The average levels of glycosylated hemoglobin (HbA1C) among the cases were 7.99±2.35 SD, with a range from 3.4 to 14.8. Specifically, there were 8 cases with HbA1C levels below 5.7%, 13 cases between 5.7% and 6.4%, 18 cases between 6.5% and 7.0%, 11 cases between 7.1% and 8.0%, 9 cases between 8.1% and 9.0%, 6 cases between 9.1% and 10.0%, 6 cases between 10.1% and 11.0%, 4 cases between 11.1% and 12.0%, 2 cases between 12.1% and 13.0%, 3 cases between 13.1% and 14.0%, and 1 case above 14%. The mean HbA1C level in the control group was 5.06±0.41 SD, ranging from 3.4 to 5.6. A significant positive correlation was observed between HbA1C levels and Central macular thickness across all subjects. Additionally, a statistically significant moderate positive correlation was found between HbA1C levels and Total macular volume among all subjects.

A study by Ling Yeung, Chi Chin Sun, et al. indicate a positive correlation between chronic HbA1c levels and macular volume as well as macular thickness in individuals with diabetes mellitus (DM) lasting 10 years or more without diabetic macular edema (DMO).[11] These results suggest that macular hemodynamic alterations may precede the clinical manifestation of DMO. Furthermore, the observed macular changes in these patients are likely attributable to the long-term impact of hyperglycemia.

CONCLUSION

Our analysis leads us to a conclusion – subclinical changes in central macular thickness (CMT) and total macular volume (TMV) may precede overt diabetic retinopathy (DR) alterations. The pronounced elevation of CMT, TMV, and HbA1C levels in the study group suggests a potential link between subclinical macular changes and glycemic control status. This correlation emphasizes the intricate interplay between glycemic control and early macular alterations.

Furthermore, our findings propose a pivotal insight into the temporal sequence of ocular changes associated with diabetes. The suggestion that subclinical CMT and CMV changes precede clinically detectable DR changes underscores the potential for early intervention strategies. Tight glycemic control, implemented before the onset of diabetic retinopathy, emerges as a crucial factor in preventing the deterioration of macular function. The alteration of macular

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hemodynamics through early glycemic control could serve as a pivotal preventive measure against the cascading effects of diabetic retinopathy on macular health.

In essence, our study contributes valuable evidence to the growing body of knowledge surrounding the nuanced relationship between glycemic control, subclinical macular changes, and the prevention of diabetic retinopathy. The implications of our findings extend beyond the confines of ophthalmology, advocating for a comprehensive approach to diabetes management that recognizes the early ocular manifestations as crucial indicators for proactive intervention.

The study's limitations include a small sample size and a lack of follow-up, resulting in a lack of data on the development of diabetic retinopathy over time and the effectiveness of stricter glycemic control in managing its progression among these patients.

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