Original Article

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Relationship between Glycosylated Haemoglobin Levels and Macular Thickness on Optical Coherence Tomography in Type 2 Diabetic Patients: A Cross-sectional Study

Ophthalmology Section

VRUSHABH GHANSHYAM MALANI[1], T SANGEETHA[2], BO HANUMANTHAPPA[3], KK ATHISH[4], RAHEEL MOHAMED[5]

ABSTRACT

Introduction: Diabetic Macular Oedema (ME) is the main cause of poor visual acuity due to the breakdown of the inner and/or outer Blood Retinal Barrier (BRB). This can occur at any stage of Diabetic Retinopathy (DR) due to increased vascular permeability from retinal capillaries, as well as from microaneurysms and Intraretinal Microvascular Abnormalities (IRMAs). A high level of Glycosylated Haemoglobin (HbA1c) is a well known risk factor for diabetic ME.

Aim: To evaluate the relationship between glycosylated Haemoglobin (Hb) and macular thickness on Optical Coherence Tomography (OCT) in patients with Type 2 Diabetes Mellitus (T2DM).

Materials and Methods: A cross-sectional study was in the Department of Ophthalmology at RL Jalappa Hospital, Kolar, Karnataka, India. The study duration was one year and eight months, conducted from January 2021 to September 2022. A total of 162 eyes of 81 patients with Diabetes Mellitus (DM) were included. Patients were assessed for age, gender, duration of diabetes, subfield macular thickness, total macular volume as measured by Optical Coherence Tomography (OCT), and HbA1c levels. Pearson's correlation and paired t-test were used to identify the mean difference between paired data. A p-value <0.05 was considered statistically significant.

Results: Out of 81 patients, 52 (64.2%) were males and 29 (35.8%) were females, with a mean age of 59.36±8.98 years (range 40-81 years) and a duration of diabetes of 14.61±4.2 years. The mean HbA1c level was 8.18±1.47% (range 5.5-12.1). A significant positive correlation was observed between central subfield thickness and total macular volume with HbA1c among both eyes (p-value=0.001). This correlation was more prominent in patients with HbA1c values >8% compared to those with HbA1c values <8% (p-value=0.001). Additionally, a positive correlation was observed between duration of diabetes and right central macular thickness (p-value=0.046) and HbA1c levels (p-value=0.027). Age did not have a major influence on central subfield thickness and total macular volume, but it did show a positive Pearson's correlation with HbA1c levels (p-value=0.008).

Conclusion: A significant positive correlation was observed between central subfield thickness and total macular volume in both eyes with HbA1c levels. Patients with HbA1c levels >8% and a longer duration of diabetes exhibited increased macular thickness and total macular volume as measured by OCT, which was also observed in patients with severe non proliferative DR and proliferative DR.

Keywords: Diabetes mellitus, Oedema, Retinopathy

INTRODUCTION

Diabetes Mellitus (DM), a disease characterised by metabolic dysregulation, is estimated to have a global prevalence of 420 million and is expected to rise to 578 million by 2030 [1]. Complications of DM are progressive and result from long-term exposure to hyperglycemic levels, which affect insulin metabolism and biological macromolecules such as carbohydrates, lipids, proteins, and nucleic acids. These diabetic complications have a major impact on global morbidity and mortality [2,3]. Diabetic Macular Oedema (ME) is one of the main factors contributing to visual loss, affecting almost one in three patients with diabetes. OCT, using low coherence interferometry, is a non invasive and non contact imaging system that provides high-resolution cross-sectional images of the macula, which is impossible with slit lamp biomicroscopy [4]. HbA1c is a reliable indicator of blood sugar levels over the previous two to three months, with an ideal range of 5.6%-7%. Through therapeutic intervention, early diagnosis of ME can improve glycemic management and prevent visual damage [5-7]. One-third of the diabetic population develops some degree of Diabetic Retinopathy (DR), which has become the leading cause of vision loss. It is important to detect early signs of DR to facilitate timely monitoring and referral [8-10]. A newer investigative modality, OCT, enables detailed study of the macula and can even detect minimal changes in thickness. Subtle changes in retinal thickness have been attributed to occur even before the development of clinically significant ME, which could have an adverse effect on visual acuity [11].

Hence, the primary objective of the present study was to determine the relationship between HbA1c levels and macular thickness on OCT, and the secondary objective was to correlate the same with macular volume and grades of DR in patients with Type 2 Diabetes Mellitus (T2DM).

MATERIALS AND METHODS

A cross-sectional study was conducted on 81 patients with T2DM who fulfilled the inclusion criteria in the Department of Ophthalmology at RL Jalappa Hospital, Kolar, Karnataka, India. The study duration was one year and eight months, from January 2021 to September 2022. The study was conducted after obtaining approval from the Institutional Ethics Committee (IEC) (No.SDUMC/KLR/1EC/659/2020-21 dated 24/12/2020) and written informed consent and demographic data.

Inclusion criteria: All patients with T2DM aged 40-81 years, patients with a history of diabetes >10 years duration, and those referred for retinal examination from other specialties were included in the study.

Exclusion criteria: Patients with history of intraocular surgery, focal or panretinal photocoagulation, periocular or intravitreal injection of any medication, retinal pathologies such as age-related macular degeneration, macular hole, and central serous retinopathy, drugs such as oralglitazone, topical latanoprost, and pilocarpine and those with uncontrolled systemic hypertension, hyperlipidemia, and renal disease were excluded from the study.

Sample size calculation: The sample size was estimated based on a study by Yeung L et al., which reported a central subfield macular thickness of 27.64 µm. Considering an absolute precision of 6 µm around the mean, the estimated sample size was 81 Type 2 diabetic patients [12].

Sample size (n)=$Z^2(1-\alpha/2)\sigma^2/d^2$

Where σ: Standard Deviation, d: Precision, α/2: desired confidence level.

Study Procedure

All subjects underwent slit lamp examination to evaluate the anterior segment and indirect ophthalmoscopy to assess the posterior segment. The subjects were graded according to the early treatment for Early Treatment for Diabetic Retinopathy Study (ETDRS) study classification [Table/Fig-1] [13].

Category	Description
Mild NPDR	Microaneurysms
Moderate NPDR	Retinal haemorrhages in 1-3 quadrants or mild IRMA, Significant venous beading <1 quadrant, cotton-wool spots commonly present
Severe NPDR	Severe haemorrhages in all four quadrants, significant venous beading > 2 quadrants, moderate IRMA >1 quadrants
Very severe NPDR	Two or more of the criteria for severe NPDR
Mild-moderate PDR	New vessels on the disc (NVD) or elsewhere (NVE)
High-risk PDR	NVD about 1/3 disc area, any NVD with vitreous haemorrhage, NVE greater than 1/2 disc area with vitreous haemorrhage
Advanced diabetic eye disease	Preretinal haemorrhage, tractional retinal detachment and rubeosis iridis

[Table/Fig-1]: Early treatment diabetic retinopathy study classification of diabetic retinopathy.
NPDR: Non proliferative diabetic retinopathy; PDR: Proliferative diabetic retinopathy; IRMA: Intraretinal microvascular abnormalities

Further assessment was conducted using OCT to measure the central subfield macular thickness (the average thickness within the central 1 mm diameter zone of the foveola from six different radial scans) and total macular volume (the volume in cubic millimeters of the central 6 mm macula in retinal map analysis). Additionally, glycated haemoglobin levels were estimated. Based on the severity of HbA1c levels, the subjects were classified into the following groups: Group 1 with HbA1c levels <7% (17 patients, 21%), Group 2 with HbA1c levels between 7% and 8% (28 patients, 34.56%), and Group 3 with HbA1c levels >8% (36 patients, 44.44%) [14].

STATISTICAL ANALYSIS

The data was entered into a Microsoft Excel data sheet and analysed using Stastistical Packages for Social Sciences (SPSS) version 22.0. Categorical data was presented as frequencies and proportions, while continuous data was presented as mean and standard deviation. Pearson's correlation and paired t-test were used as tests of significance to identify mean differences between paired data. A p-value <0.05 was considered statistically significant.

RESULTS

The study included 162 eyes of 81 patients, with 52 (64.2%) males and 29 (35.8%) females, and a mean age of 59.36±8.98 SD years (range 40-81 years). The duration of diabetes was 14.61±4.2 years. The mean HbA1c level was 8.18±1.47% (range 5.5-12.1).

The mean central, nasal, and temporal subfield thickness in the right and left eye were 249.05±49.09 µm, 299.49±53.29 µm, 298.42±46.55 µm, and 242.54±64.21 µm, 300.88±64.81 µm, and 300.76±52.09 µm, respectively, as shown in [Table/Fig-2]. There was no statistical difference in the comparison of mean subfield thickness and total macular volume between the right and left eye (p=0.317, 0.820, 0.609).

Subfield thickness (µm)	Right eye	Left eye	p-value
Central	249.05±49.09	242.54±64.21	0.317
Nasal	299.49±53.29	300.88±64.81	0.820
Temporal	298.42±46.55	300.76±52.09	0.609
Total macular volume (μm^3)	9.65± 1.55	9.85±1.62	0.130

[Table/Fig-2]: Comparison of subfield thickness and total macular volume between the right and left eye.
Paired t-test

A significant positive correlation was found between the central subfield thickness and total macular volume of both eyes with HbA1c level (p=0.001) [Table/Fig-3].

Subfield thickness (µm)	HbA1c	Correlation coefficient	p-value
Right eye	Central	0.635	0.001*
	Nasal	0.567	0.001*
	Temporal	0.428	0.001*
Left eye	Central	0.309	0.005*
	Nasal	0.472	0.001*
	Temporal	0.538	0.001*
Total macular volume (μm^3)	Right eye	0.463	0.001*
	Left eye	0.462	0.001*

[Table/Fig-3]: Correlation of HbA1c with subfield thickness and total macular volume.
HbA1c: glycated Haemoglobin; (Pearson Correlation) *Statistically significant (p<0.05) r value: (0.462, 0.463)

The relationship between subfield thickness and macular volume with HbA1c was significantly higher among patients with HbA1c >8% (36) compared to patients with HbA1c <8% (45) [Table/Fig-4].

Variables		HbA1c			p-value
		<7 (N=17)	7-8 (N=28)	>8 (N=36)	
Subfield thickness right eye (µm)	Central	187.94±33.16	239.78±30.93	285.11±32.38	0.001*
	Nasal	240.94±37.05	284.75±28.89	338.61±42.50	0.001*
	Temporal	252.29±29.57	296.25±31.34	321.88±46.82	0.001*
Subfield thickness left eye (µm)	Central	197.41±21.95	235.61±35.70	269.25±80.36	0.001*
	Nasal	249.23±23.61	290.11±30.07	333.67±78.44	0.001*
	Temporal	265.41±38.50	283.07±30.28	331.22±54.83	0.001*
Total macular volume (μm^3)	Right eye	7.97±1.11	9.66±0.84	10.42±1.54	0.001*
	Left eye	8.65±1.21	9.66±1.02	10.57±1.81	0.001*

[Table/Fig-4]: Comparison of subfield thickness and Total macular volume based on HbA1c.
HbA1c: Glycated heamoglobin; (Analysis of Variance) *Statistically significant (p <0.05)

The association of grades of DR with subfield thickness and total macular volume showed higher values in the Severe non proliferative DR and proliferative DR group [Table/Fig-5]. A significant positive correlation was observed between the duration of diabetes and the right central macular thickness (p=0.046*) as well as HbA1c (p=0.027) [Table/Fig-6]. The stratification of patients based on the grade of DR is shown in [Table/Fig-7]. Moderate NPDR was the most common finding in 38 (46.9%) right eyes and 35 (43.2%) left eyes, followed by severe NPDR in 10 (12.3%) right eyes and 11 (13.6%) left eyes. PDR was noted in 1 (1.2%) right eye and 4 (4.9%) left eyes.

Variables		Retinopathy changes (Mean±SD)				
		No DR	Mild NPDR	Moderate NPDR	Severe NPDR	PDR
Central subfield thickness (μm)	RE	213.06±36.62	194.50±38.89	265.82±37.58	306.10±36.19	230.0
	LE	216.62±40.52	206.50±24.74	233.28±61.35	296.82±42.51	380.25±35.54
Total macular volume (μm^3)	RE	8.69±1.21	8.50±1.97	9.89±1.24	11.65±1.36	10.80
	LE	9.03±1.43	8.50±1.69	9.88±0.99	10.70±1.23	14.0±0.88

[Table/Fig-5]: Association of Diabetic Retinopathy (DR) with subfield thickness and total macular volume.
DR: Diabetic retinopathy; NPDR: Non proliferative diabetic retinopathy; PDR: Proliferative diabetic retinopathy

Variables	Duration	Correlation coefficient	p-value
Central macular thickness (μm)	Right	0.223	0.046*
	Left	0.066	0.561
Glycated haemoglobin (%)		0.246	0.027

[Table/Fig-6]: Correlation between duration of diabetes with macular thickness and HbA1c.
(Pearson's Correlation). *Statistically significant (p <0.05)

Grades	Right eye		Left eye		p-value
	Number (n)	Percentage (%)	Number (n)	Percentage (%)	
No DR	30	37.03	29	35.8	0.736
Mild NPDR	2	2.5	2	2.5	
Moderate NPDR	38	46.9	35	43.2	
Severe NPDR	10	12.34	11	13.6	
PDR	1	1.23	4	4.9	
Total	81	100	81	100	

[Table/Fig-7]: Grading of Diabetic Retinopathy (DR).
DR: Diabetic retinopathy; NPDR: Non proliferative diabetic retinopathy; PDR: Proliferative diabetic retinopathy

DISCUSSION

The OCT is a sophisticated non invasive objective method for quantitatively assessing retinal diseases, providing high-resolution and cross-sectional images accurately. While fluorescein angiography can qualitatively assess vascular leakage associated with DME, macular thickness is the primary factor in evaluating best-corrected visual acuity in patients. The data from the right and left eyes of all 81 participants were considered separately due to anatomical differences between the eyes.

There was no significant difference in the mean central, nasal, and temporal subfield thickness between the eyes, consistent with a study by Jiang J et al., which showed higher mean subfield thickness at the central, nasal, and temporal regions in the right eye compared to the left eye [15]. Increased macular thickness may affect visual acuity, but significant vision loss was not observed when the central subfield macular thickness was <300 μm [16].

As the newer investigative modality OCT detects mild changes in the macula without clinical evidence of DME, present study showed a higher mean total macular volume in both eyes, which could possibly increase the severity of DR. These values are much higher than the observations in a study by El-Deen AMBS et al., which reported a mean total macular volume of 7.33±0.68 μm SD in 100 diabetics (p<0.004) [17]. It has been postulated that hyperglycemia causes macular hydration due to osmosis and increased thickness [11].

Glycated haemoglobin (HbA1c) is an important modifiable risk factor that can influence the progression of DR and vision loss. A positive correlation was observed between HbA1c and macular thickness and volume. These observations are consistent with other researchers who have also observed an increased retinal thickness in individuals with advanced DR [18-20].

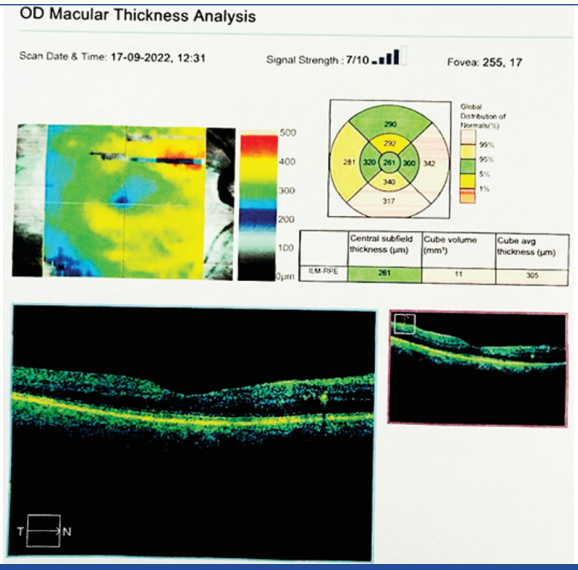
When comparing macular thickness and total macular volume with different categories of HbA1c, patients with HbA1c >8% had higher subfield thickness and total macular volume compared to patients with HbA1c <8%. It has been observed that a change in the OCT measurements >10% of the baseline thickness is likely to represent a true change in macular thickness and Glycosylated haemoglobin is an effective parameter used to monitor long term hyperglycemia [21,22]. This suggests that good glycemic control has a major impact on macular thickness and function. Uncontrolled HbA1c levels can lead to breakdown of the inner Blood Retinal Barrier (BRB) due to microvascular damage, resulting in macular thickening. An evaluation of 124 patients showed that HbA1c values were inversely associated with central macular thickness in patients with ME (r=-0.374, p=0.005), which remained statistically significant after adjusting for age, sex, DR severity, and other metabolic factors (p=0.002) [23].

Cho A et al., reported that progression from no DR to NPDR stage in diabetic patients was associated with higher HbA1c levels [24]. In the present study, higher values of subfield thickness and total macular volume were noted in the Severe NPDR and PDR group. Similarly, a statistically significant association was found between central subfield thickness and HbA1c level in the NPDR group [25]. However, Jiang J et al., documented that only the temporal perifoveal thickness exhibited a negative correlation with HbA1c level, indicating that increased HbA1c levels contributed to decreased retinal thickness [15].

It is well known that a longer duration of diabetes is a risk factor for the development of DR and DME. This was evident as a positive correlation between the duration of diabetes and right central macular thickness. While age did not have a major influence on central subfield thickness and total macular volume, it did have a positive correlation with HbA1c levels. In contrast, a study showed a decreased macular thickness with a longer duration of diabetes, which was attributed to alterations in ganglion cell or glial cell structure [26].

Hence, regardless of age, early screening can detect such changes, and good glycemic control can decrease the risk of diabetic ME and its complications. It has been found that patients with subclinical ME ultimately progress to clinically significant ME compared to controls, with a 15% increase in the odds of progression with each 10 μm increase in central subfield macular thickness. Therefore, it is important to monitor diabetic individuals to detect early vision-threatening ME for prompt management [27].

In this study 11 patients or Eleven patients (five PDR and six severe NPDR) were treated with three doses of intravitreal ranibizumab at one month intervals (Oceva 10 mg/mL, Sun Pharmaceutical Industries Ltd., Mumbai). Nine patients with severe NPDR were treated with panretinal photocoagulation, five with focal laser, and three with grid laser. Others were regularly observed with strict glycemic control. Patients with high HbA1c levels had increased macular thickness as measured by OCT, and there was a statistically significant correlation. As actual macular thickness is the greatest contributing factor to best-corrected visual acuity, strict glycemic control could decrease the risk of diabetic ME. Thus, OCT could be an excellent detector of early diabetic ME and its impact on visual acuity. An OCT image showing increased macular thickness and volume in a 45-year-old male with mild non proliferative DR is shown in [Table/Fig-8].



[Table/Fig-8]: The OCT showing increased macular thickness and volume in 45-year-old male with mild non proliferative DR.

Limitation(s)

The observations from the present study suggest that high HbA1c values might increase the risk of DME. However, the limitation was that other risk factors, such as lipid dysfunction, increased diastolic blood pressure, insulin use, and nephropathy, were not analysed in present study.

CONCLUSION(S)

A significant positive correlation was observed between central subfield thickness and total macular volume of both eyes with HbA1c levels. Patients with HbA1c > 8% and a longer duration of diabetes had increased macular thickness and total macular volume, which was also observed in severe non proliferative DR and proliferative DR patients. There is evidence that an increase in macular thickness and volume is noted even in the absence of diabetic ME. Hence, strict glycemic control and regular follow-up of diabetic patients are mandatory to prevent deterioration in macular function even before ME is clinically detected. This also calls for more research studies to understand the haemodynamic changes at the macula.

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PARTICULARS OF CONTRIBUTORS:
1. Senior Resident, Department of Ophthalmology, Sri Devaraj Urs Academy of Higher Education and Research, Kolar, Karnataka, India.
2. Professor, Department of Ophthalmology, Sri Devaraj Urs Academy of Higher Education and Research, Kolar, Karnataka, India.
3. Professor, Department of Ophthalmology, Sri Devaraj Urs Academy of Higher Education and Research, Kolar, Karnataka, India.
4. Intern (MBBS), Department of Ophthalmology, Sri Devaraj Urs Academy of Higher Education and Research, Kolar, Karnataka, India.
5. Intern (MBBS), Department of Ophthalmology, Sri Devaraj Urs Academy of Higher Education and Research, Kolar, Karnataka, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. T Sangeetha,
Associate Professor, Department of Ophthalmology, Sri Devaraj Urs Academy of Higher Education and Research, Kolar-563101, Karnataka, India.
E-mail: sangeetha31jayakumar@gmail.com

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