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Original Article

Ophthalmology Section

Macular Thickness- An Early Predictor of Diabetic Macular Oedema

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ABSTRACT

Introduction: Diabetic Macular Oedema (DME) accounts for visual morbidity in about three-fourth of Diabetic Retinopathy (DR) patients. Traditional examination on 90D slit lamp or stereoscopic fundus photograph may not be able to identify early maculopathy. Optical Coherence Tomography (OCT) is a sensitive, non invasive modality which may detect early retinal thickness changes in DME.

Aim: To identify any increase in macular thickness in diabetic patients with early DR without any clinically detectable macular oedema.

Materials and Methods: This cross-sectional analytical study was conducted from September 2018 to July 2020 in the Ophthalmology Department at Bharati Vidyapeeth Medical College and Hospital, Pune, Maharashtra, India. A total of 277 eyes of 184 subjects were evaluated. Of these 182 eyes were of diabetic patients (124 patients) and 95 eyes belonged to controls (60 subjects). Amongst the diabetic eyes evaluated, group I consisted of 100 eyes with no evidence of DR and group II consisted of 82 eyes with mild Non Proliferative Diabetic Retinopathy (NPDR). Group III included 95 eyes of non diabetic age matched controls. Macular thickness was measured using the Topcon 3D OCT-1 Maestro System. The central 1 mm macular thickness of the three groups was analysed and compared using student's t-test.

Results: The mean Central Macular Thickness (CMT) showed no statistically significant difference (p-value <0.7) between group III (222.4±10.8) and group I (223.0±13.7 µm). However, a significant increase in CMT (p-value <0.0001 and p-value <0.0006) was noted in group II (230.7±15.6 µm) when compared with group III (222.4±10.7 µm) and group I (223.0±13.7 µm). Macular thickness amounting to Subclinical Macular Oedema (SCME) was seen in only in 6.09% of eyes in group II, five eyes of the total number of 82 eyes with mild NPDR.

Conclusion: Increased CMT was detected in mild NPDR patients on Optical Coherence Topography (OCT) even without any clinical evidence of macular oedema. Since eyes with SCME, diagnosed at base line assessment, are at a higher risk of developing clinical macular oedema subsequently, it is recommend that a base line OCT be performed in all patients detected to have mild NPDR irrespective of the absence of clinical findings suggestive of DME.

Keywords: Central macular thickness, Diabetic retinopathy, Optical coherence tomography

INTRODUCTION

The burden of diabetes mellitus is an increasing trend both worldwide and in India. According to the international diabetes federation, the total number of people affected by diabetes mellitus in 2019 was 463 million. It was estimated that by 2030 the number will be 578 million and by 2045 it will increase to 700 million. India stands second in rank with an estimated number of 77 million diabetics [1].

The DME accounts for visual morbidity in about three fourth of DR patients [2]. The global prevalence of Diabetic Macular Oedema (DME) was estimated to be 7.4% in 2012 [3]. Because of its special anatomical features like, loose intercellular adhesions and absence of Müller cells in the fovea, the macula is more susceptible for fluid and proteins accumulation leading to oedema, than other areas of the retina [2]. Traditional examination on slit lamp with 90D or stereoscopic fundus photographs may not be able to identify minimal changes in the retinal thickness. Optical Coherence Tomography (OCT) is a sensitive, non invasive modality for diagnosing and classifying DME [4,5].

Several studies have been conducted to assess macular thickness in patients with Diabetes Mellitus (DM) with and without Diabetic Retinopathy (DR). The results have been variable. A prospective observational study on mild Non Proliferative Diabetic Retinopathy (NPDR) patients compared macular central subfield and central point thickness in patients with mild NPDR to normative population database of Carl Zeiss and found that both are thicker in mild NPDR eyes (p-value<0.001) [6]. However, Srinivasan S et al., observed that the retinal thickness in both central and perifoveal zone of diabetes mellitus patients with no DR and mild NPDR did not show any significant difference when compared with the control group (p-value=0.27and p-value>0.41 respectively). Instead, a significant decrease in Parafoveal thickness was noted in diabetes mellitus patients with mild NPDR (p-value <0.02) [7]. Murgesan S et al., conducted a prospective case control study to compare Central Macular Thickness (CMT) between diabetes mellitus patients without DR and non diabetic controls and observed that the study group showed significantly thinner central macula (p-value<0.001) than the controls [8]. In view of these disparate findings, a study to analyse macular thickness in diabetics with and without DR was considered relevant.

It was also found that patients with sub clinical macular oedema in the central subfield at baseline showed a 12-fold risk of progression to Center Involving Macular Oedema (CIME) compared to patients without SCME at base line [9]. This study was undertaken to quantitatively measure the CMT in diabetics without DR and those with mild NPDR without any clinically detectable macular oedema, with the purpose of ascertaining if it could be considered as an early predictor of DME.

MATERIALS AND METHODS

This cross-sectional analytical study was conducted from September 2018 to July 2020 in the Ophthalmology Department of the Bharati Vidyapeeth Medical College and Hospital, Pune, Maharashtra, India, after approval from the college Ethics Committee (BVDUMC/IEC/64 dated 07/09/2018).

Sample size calculation: Sample size was calculated using Statulator online sample size calculator using two different means [7]. Assuming the mean central foveal thickness in control group as 253 and diabetic group as 246 and standard deviation of 25, alpha error of 5% and 80% power, the sample size was calculated to be 154 [7]. Hence, a total of 184 subjects were enrolled in the study.

After obtaining their informed consent, 124 Type II diabetics reporting to the Ophthalmology Department aged between 20-70 years were included in this study.

Inclusion criteria: Patients diagnosed with DM for more than 1 year and up to 20 year were included. Glycaemic control and treatment modalities were not considered during enrollment of the study subjects, since it was a single point assessment of macular thickness which was being evaluated. Sixty age and sex matched, healthy non diabetics were enrolled as controls.

Exclusion criteria: Patients with DM with moderate to severe NPDR, proliferative diabetic retinopathy or clinically significant macular oedema were not included in the study. Subjects with any other macular pathology, previous ocular surgeries or intravitreal injections, laser therapy and ocular infections were excluded. Patients with media opacities preventing good OCT evaluation were also excluded from the study.

Study Procedure

All the 124 diabetic study participants were subjected to a complete ophthalmic examination including-BCVA, anterior segment evaluation, fundus examination with 90 D lens and intra ocular pressure. Total 60 age and sex matched controls were similarly evaluated. Based on the clinical evaluation of the retina by 90D patients were further subdivided into three groups.

- Group I (n=60, 100 eyes)- Diabetic patients with no evidence of DR.
- Group II (n=64, 82 eyes)- Diabetics with mild NPDR Criterion for this grouping was according to the Early Treatment Diabetic Retinopathy Study (ETDRS) classification level 20-35 microaneurysms and microaneurysms with few retinal hemorrhages [10].
- Group III (n=60, 95 eyes)- Controls group.

Optical Coherence Tomography (OCT): The OCT was performed on all the subjects using Topcon 3D OCT-1 Maestro System (TOPCON, Japan) machine. This Spectral Domain-OCT (SD-OCT) has a scan speed of 50,000 A- scans per second, a scan depth of 2.3 µ, axial resolution of 5-6 µ and transverse resolution of 20 µ. The 3D- macula acquisition protocol consisting of 512 A-scans and 128 B-scans each (6.0×6.0 mm-512×128) was performed. Each scan was inspected for centration and image quality. Scans with signal strength less than 30 were discarded. The automated analysis report consists of the measurement of the macular thickness in different Early Treatment Diabetic Retinopathy Study (ETDRS) map locations, including the central area of 1 mm diameter, and 2 concentric rings around the fovea. These consist of an inner ring of 3 mm diameter and an outer ring of 6 mm diameter. Each ring is further divided into four subfields [Table/Fig-1]. The thickness value of the central 1 mm circular area was used for analysis. No manual measurements were made.

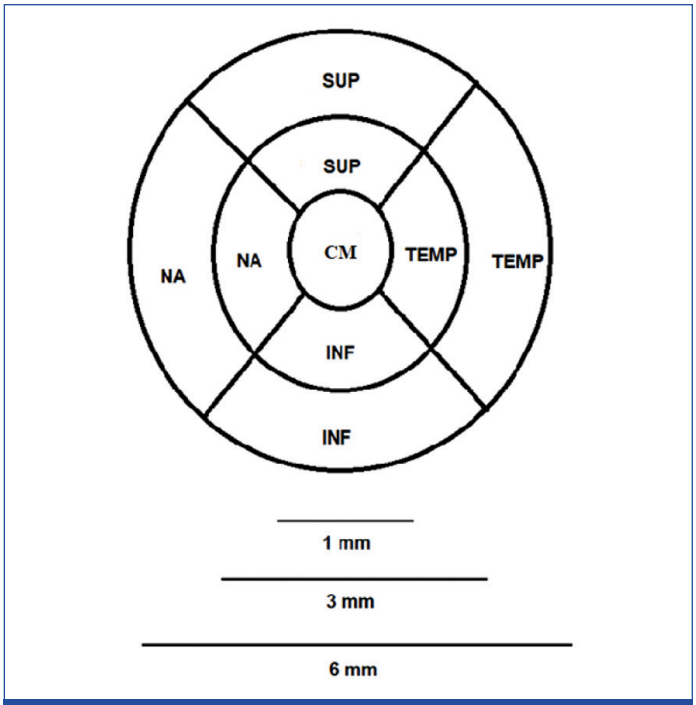
STATISTICAL ANALYSIS

The data was tabulated and analysed using the software Statistical Package for the Social Science (SPSS) version 22.0. Student's t-test was used to compare the mean CMT values between the groups. A p-value <0.05 was considered as significant.

RESULTS

Of the 184 subjects evaluated, 109 were males and 75 were females. Of 277 eyes included in the study, 100 eyes were in group I, 82 eyes in group II and 95 eyes formed the control group. The age of study subjects ranged from 20-70 years. Demographic details are as per [Table/Fig-2].

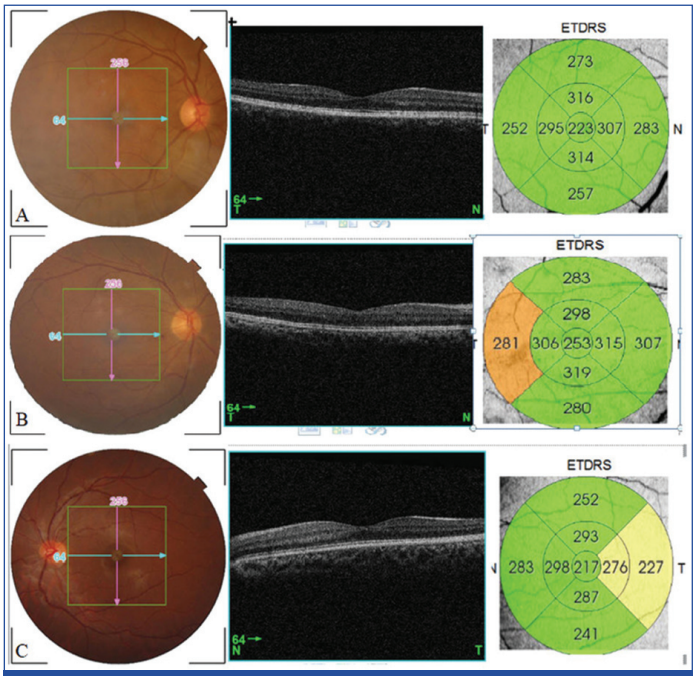
CMT in group I varied from 195-251 µm with a mean of 223.0±13.7 µm. In group II the values ranged from 202-270 µm with a mean value of 230.7±15.6 µm and in group III the range was from 195-244 µm with a mean of 222.4±10.7 µm [Table/Fig-3,4].



[Table/Fig-1]: Early Treatment Diabetic Retinopathy Study (ETDRS) map on macula showing central 1 mm ring.
CM: Central macula; SUP: Superior quadrant; TEMP: Temporal quadrant; INF: Inferior quadrant and NA: Nasal quadrant

Variables	Group I	Group II	Group III
Number of patients	60	64	60
Number of eyes (n)	100	82	95
Age (years)			
Minimum	20	37	25
Maximum	70	70	70
Average	52.6	54.1	50.3
Gender			
Male	34	38	37
Female	26	26	23

[Table/Fig-2]: Demographic data.



[Table/Fig-3]: OCT macula and ETDRS map in group I, group II and group III.
a) Group I (diabetics with no DR); b) Group II (diabetics with mild NPDR); c) Group III (controls)

SCME in the present study was seen only in 6.09% of eyes in group II (5 eyes of the total number of 82 eyes with mild NPDR).

CMT	Group I	Group II	Group III
Minimum (µm)	195	202	195
Maximum (µm)	251	270	244
Average (µm)	223.0±13.7	230.7±15.6	222.4±10.7

[Table/Fig-4]: Central Macular Thickness (CMT) in diabetics and controls.

Males were found to have a significantly thicker central macula when compared to females across all groups, with p-values of 0.002, 0.0001 and 0.005, respectively [Table/Fig-5].

Gender	Group I Mean CMT (µm)	Group II Mean CMT (µm)	Group III Mean CMT (µm)
Male	226.5±13.2	236.2±14.8	225.0±9.3
Female	218.1±13.1	223.1±13.5	218±11.8
p-value	0.002	0.0001	0.005

[Table/Fig-5]: Mean CMT in males and females.
*Students t-test Group I: Diabetics with no Diabetic retinopathy; Group II: Diabetics with mild Non proliferative diabetic retinopathy; Group III controls; p-value <0.05 was considered as statistically significant

The mean CMT in group I (223.0±13.7 µm) and group III (222.4±10.7 µm) was not found to be significantly different with a p-value of 0.7. However, a significant difference when mean CMT in group II was compared against group III (p-value=0.0001). A similar statistical significant difference was also noted between mean CMT values in group I and group II (p-value=0.0006) [Table/Fig-6].

Comparison	Macular thickness	p-value
Group I and III	223.0±13.7 µm, 222.4±10.7 µm	0.7
Group II and III	230.7± 15.6 µm, 222.4±10.7 µm	0.0001
Group I and II	223.0±13.7 µm, 230.7± 15.6 µm	0.0006

[Table/Fig-6]: Comparison of mean CMT between controls, group I and group II.
*Students t-test Group I: Diabetics with no Diabetic retinopathy; Group II: Diabetics with mild Non proliferative diabetic retinopathy; Group III controls; p-value <0.05 was considered as statistically significant

DISCUSSION

Diabetic Retinopathy (DR) remains high on the list of causes attributable for visual morbidity amongst individuals in the group of 50 years and above [11], DME being the primary pathology for the same in about 75% of patients with DR [12]. The ETDRS study has observed that central DME was responsible for the risk of moderate vision loss in 32%of patients [12]. Since, the visual loss is slow and progressive patients may be detected to have advanced retinal and macular changes even on initial presentation to the hospital resulting in a poor visual prognosis despite treatment.

For the DME to be clinically detected by conventional 90D examination, the macular thickness should be >299 µ [13]. OCT scanning of the macula enables increase in macular thickness to be assessed early to establish the presence of SCME. DRCR.net defined SCME as center point thickness between 225 to 299 µm on Stratus OCT [14]. Whereas on SD-OCT, SCME is considered as retinal thickness >260 µm to <290 µm in women and >275 µm to <305 µm in men [15].

Studies have established that patients with SCME have an increased risk of developing DME. Piers I et al., evaluated patients with mild NPDR for a period of two years and found the risk of developing DME was 3.6 times higher in those who had SCME at base line [16]. A similar study by Lobo C et al., at Portugal and LVPEI Hyderabad on diabetics with mild NPDR observed a 12 times higher risk of DME in patients diagnosed with SCME at initial examination [9].

The current study showed, the mean thickness of the central 1000 µ at the macula of 100 eyes of diabetics with no evidence of DR, 82 eyes of patients with early NPDR and compared these values with 95 eyes belonging to age matched controls. The mean CMT value was observed to be 223.0±13.7 µm in the eyes with no DR, 230.7±15.6 µ min eyes with mild DR and 222.4±10.7 µm in controls. The mean CMT in controls was similar to that observed by Adhi M et al., and Gautam M et al., (227.19±29.9.94 µm and 226.4±22.5 µm) in studies conducted on normal population in Pakistan and in India, respectively [17,18]. The mean CMT in group I and group II of the present study were also similar to the mean CMT in an Egyptian study on similar groups (221.2±24.2 µm and 231.3±29.3 µm, respectively) [19].

Higher values of mean CMT were seen in males as compared to females across all groups. A study of macular thickness using spectral domain OCT in healthy Indian population conducted by Gautam M et al., also found macular thickness to be more in males (229.8±21.4 µm) than in females (220.7±23.1 µm) [18]. Srinivasan S et al., in Australia, and Bressler NM et al., in United States of America who studied diabetic patients with and without DR also noted that males have a significantly thicker macula than females [7,20].

No significant difference (p-value=0.7) was noted in the mean CMT between group I and controls. Similar findings have been reported by Srinivasan S et al., and Demir M et al., [7,21]. Bressler NM et al., in their study on diabetics with and without DR also noted no difference between mean macular thickness in controls and diabetics with no retinal changes of DR [20]. This could suggest that central macular involvement may not precede the development of clinically evident retinopathy.

Authors observed a definitely thicker mean CMT in group II, i.e., eyes with mild NPDR (230.7±15.6 µm). The value was higher than that observed in studies conducted by Piers I et al., (219.2±25 µ) and lower than those by Srinivasan S et al., (245±25 µm) [6,7]. This may be due to variance in the populations studied (Caucasians) as well as different OCT machines used. Pires I et al., used a time domain Stratus OCT and Srinivasan S et al., used a RTVue-100 OCT [6,7]. There was a significant difference seen on comparison of the mean CMT of group II with controls and group I; p-value=0.0001 and p-value=0.0006 respectively. In eyes with mild NPDR, presence of vessel changes and microaneurysms suggest the onset of microangiopathy. The vasogenic oedema resulting from vascular damage and subsequent alteration of the blood-retinal barrier, which is mainly associated with an abnormal accumulation of extracellular fluid, can, explain the thickening observed in the central macula [22].

The SCME in the present study was seen in 5 eyes (6.09%) in group II (early NPDR). Piers I et al., reported an incidence of 9.3% in mild NPDR patients [16]. Ribiro L et al., studied a larger group (158 patients) of mild NPDR patients and reported an incidence as high as 30% [23].

Limitation(s)

This study was conducted on diabetic patients attending the Ophthalmology Outpatient Department of a tertiary care hospital. The number of eyes evaluated was hence limited and additional studies on larger numbers of patients may further confirm these findings. This was a single point observational study, so authors did not consider other factors like duration of DM or glycaemic control that can affect the CMT. Follow-up of patients with increased CMT to assess the development of CSME is ongoing and was not a part of this study.

CONCLUSION(S)

In this study we evaluated the mean CMT on OCT of diabetics with and without early NPDR and found a significantly increased macular thickness in patients with early NPDR. Though, SCME was seen in 6.09% of eyes in group II, the mean CMT was significantly more. This reveals that there can be minute changes at the macula in the early stages of DR, which are not evident on indirect ophthalmoscopy examination but can be detected on SDOCT. Thus, it can be concluded that there might be a subgroup of eyes

that may have an increase in CMT in the early stage of DR even if fundus examination reveals no signs of DME/Clinically-Significant Macular Oedema (CSME). Macular scans on OCT as a baseline evaluation of all eyes with early DR, irrespective of their glycaemic control, will need to be performed to diagnose such patients, so as to enable a closer follow-up and early treatment, if necessary, for preventing visual morbidity. However, there is a need for further studies with higher resolution OCT like swept source to confirm this finding in a large population.

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