

## A COMPARATIVE STUDY OF CENTRAL MACULAR THICKNESS IN DIABETICS WITH DIFFERENT STAGES OF DIABETIC RETINOPATHY

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### ABSTRACT

#### BACKGROUND

Macular oedema is one of the important causes of vision impairment in patients with diabetic retinopathy. In diabetic retinopathy, single measurements of central foveal thickness using OCT correlate with visual acuity. The purpose of the study is to assess Central Macular Thickness (CMT) in diabetics with and without diabetic retinopathy and to compare CMT within different stages of retinopathy.

#### MATERIALS AND METHODS

A total of 500 eyes of 250 diabetic subjects and 150 eyes of 75 age and gender matched controls were included. Complete ophthalmological examination was done and they were divided into 5 subgroups according to the diabetic retinopathy grading. OCT scanning was performed using Nidek RS-3000 Lite OCT, which generated a topographical map of the macula. Central macular thickness was defined as the average thickness in the central 1 mm diameter. Other parameters like body mass index, duration of diabetes and glycated haemoglobin levels of last 3 months were also assessed.

#### RESULTS

A statistically significant difference was observed in the mean central macular thickness between the study and control group ( $p < 0.001$ ). Among the subgroups, subjects in the CSME group showed maximum CMT ( $394.0 \pm 105.3 \mu\text{m}$ ) while minimum CMT was seen in no diabetic retinopathy group ( $248.3 \pm 21.8 \mu\text{m}$ ). Central macular thickness was seen to increase progressively with increasing stages of diabetic retinopathy. CMT in no DR and mild NPDR differed significantly with each of the other subgroups ( $p < 0.001$ ). The difference in central macular thickness between moderate NPDR subgroup and severe NPDR ( $p = 0.431$ ) and PDR subgroup ( $p = 0.106$ ) was not statistically significant. On regression analysis, increased duration of diabetes and glycated haemoglobin correlated with higher CMT.

#### CONCLUSION

Subclinical macular thickening was observed in diabetics, which increased with increasing stages of diabetic retinopathy without evidence of any clinically significant macular oedema.

#### KEYWORDS

Diabetic Retinopathy, Central Macular Thickness, Optical Coherence Tomography.

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#### BACKGROUND

Diabetic retinopathy is responsible for a majority of cases of blindness in adults, especially those in the working age group.<sup>1</sup> Macular oedema is one of the important causes of vision impairment in patients with diabetic retinopathy. Therefore, early diagnosis and metabolic control are of critical significance for prevention or at least postponement of potential visual compromise. Macular oedema has been

reported in 10% of diabetics and occurs more frequently in type 2 diabetes mellitus.<sup>2</sup> Their visual acuity is often dependent on the central foveal involvement, perifoveal capillary blood flow velocity, severity of perifoveal capillary occlusion and retinal thickness at the central fovea.<sup>3</sup> Optical Coherence Tomography (OCT) a noninvasive imaging modality has been applied in the diagnosis of a variety of macular diseases and in evaluation of treatment effects. In patients with diabetes and diabetic retinopathy, single measurements of central foveal thickness using OCT correlate with visual acuity.<sup>4</sup>

Despite its widespread clinical use, there are only few studies on the distribution and correlations of OCT measured retinal thickness mostly in white ethnic groups. Normative data in general populations is essential to allow pathological changes to be compared, identified and characterised. It is

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particularly important to establish normative values in persons with diabetes with nearly 400 million such individuals worldwide by 2030.<sup>5</sup> Previous studies on macular thickness measurements in persons with diabetes obtained using OCT and other instruments such as the retinal thickness analyser have reported variable findings. Biallosterki et al reported significantly thinner pericentral macular thickness in patients with minimal Diabetic Retinopathy (DR) and hypothesised that this was due to neuronal loss in the earliest stage of DR.<sup>6</sup> In contrast, Lattanzio et al found that the macula in subjects with diabetes without DR was thicker (by more than 40  $\mu\text{m}$ ) than that in nondiabetic controls.<sup>7</sup> Kashani et al have reported no difference in macular thickness between subjects with diabetes with minimal or no DR and nondiabetic controls.<sup>8</sup> The Singapore Indian Eye Study of Indian population residing in Singapore, it was found that macular thickness did not differ significantly between diabetics with no or mild diabetic retinopathy and nondiabetics.<sup>9</sup>

Due to few studies in the Indian population, we conducted this study in our set up to assess central macular thickness in diabetics with different stages of retinopathy and in nondiabetic controls.

## MATERIALS AND METHODS

This study was conducted in the Department of Ophthalmology of Christian Medical College and Hospital, Ludhiana. It was conducted on 500 eyes of 250 diabetics and 150 eyes of 75 age and gender matched controls. Diabetes mellitus was identified from non-fasting plasma glucose  $\geq 200$  mg/dL, self-reported use of diabetic medication or physician-diagnosed diabetes.<sup>10</sup> Subjects were divided into five groups according to the International Clinical Diabetic Retinopathy Disease Severity Scale.<sup>11</sup>

1. Diabetics with no apparent Retinopathy.
2. Diabetics with Mild Nonproliferative Diabetic Retinopathy.
3. Diabetics with Moderate Nonproliferative Diabetic Retinopathy.
4. Diabetics with Severe Nonproliferative Diabetic Retinopathy.
5. Diabetics with Proliferative Diabetic Retinopathy.

For each group, macula was evaluated for the presence or absence of Clinically Significant Macular Oedema (CSME).<sup>12</sup> A total of 150 eyes of no diabetic age and gender matched volunteers with no ophthalmological complaints were taken as controls. Subjects with any coexisting macular pathology or history of retinal laser or intraocular surgery were excluded. Informed consent was obtained from all subjects. Demographic data was recorded for each subject as per protocol. All cases underwent complete ophthalmological examination including best corrected visual acuity, anterior segment examination and posterior segment examination was performed using a +90 dioptre lens. OCT scanning was performed using Nidek RS-3000 Lite OCT. Macular thickness measurements were obtained after pupil dilatation using tropicamide 1% and phenylephrine

hydrochloride 2.5%. The OCT software generated a topographical map of the macula as defined by the Early Treatment of Diabetic Retinopathy Study (ETDRS). Foveal or central macular thickness is defined as the average thickness in the central 1 mm diameter. The fovea was measured 3 times. The report of glycosylated haemoglobin (HbA1C) test done in last 3 months was recorded for the study group. If not done, then nonfasting venous blood sample was analysed at the hospital laboratory for biochemical testing of HbA1C.

## STATISTICAL ANALYSIS

The data was entered in Microsoft Excel and analysed using SPSS (Statistical Package for Social Sciences) software version 16. Statistical analysis was done using the chi-square test, Student's t-test and one-way analysis of variance (ANOVA). The correlation between central macular thickness and best corrected visual acuity was determined by Pearson's correlation coefficients. Significance level was set at  $p < 0.05$ .

## RESULTS

In the demographic profile, no statistical difference was seen in the mean age ( $p = 0.054$ ) or gender distribution ( $p = 0.051$ ) between the study and control group as shown in Table 1. The mean Central Macular Thickness (CMT) in the study group was  $283.0 \pm 73.0$  microns and the mean CMT in the control group was  $226.5 \pm 13.7$  microns. A statistically significant difference was observed in the mean central macular thickness between the two groups ( $p < 0.001$ ) using unpaired Student's t-test as shown in Figure 1. On comparing CMT among the various study subgroups, subjects in the CSME group showed maximum CMT ( $394.0 \pm 105.3$   $\mu\text{m}$ ) while minimum CMT was seen in no diabetic retinopathy group ( $248.3 \pm 21.8$   $\mu\text{m}$ ). Central macular thickness was seen to increase progressively with increasing stages of diabetic retinopathy. It was observed that there was a statistically significant difference of CMT between these groups ( $p$  value  $< 0.001$ ) as depicted in Table 2.

To look for the probability of difference in CMT in each subgroup when compared independently with other subgroups, a statistically significant difference in mean CMT of controls when compared with each of the diabetic subgroups independently was observed as shown in Table 3 ( $p < 0.001$ ). Central macular thickness in no DR and mild NPDR also differed significantly with each of the other subgroups ( $p < 0.001$ ). The difference in central macular thickness between moderate NPDR subgroup and severe NPDR ( $p = 0.431$ ) and PDR subgroup ( $p = 0.106$ ) was not statistically significant. CMT was significantly higher in successive stages from no DR to mild and moderate NPDR, respectively. The progression of CMT from moderate-to-severe NPDR and then PDR was not significant.

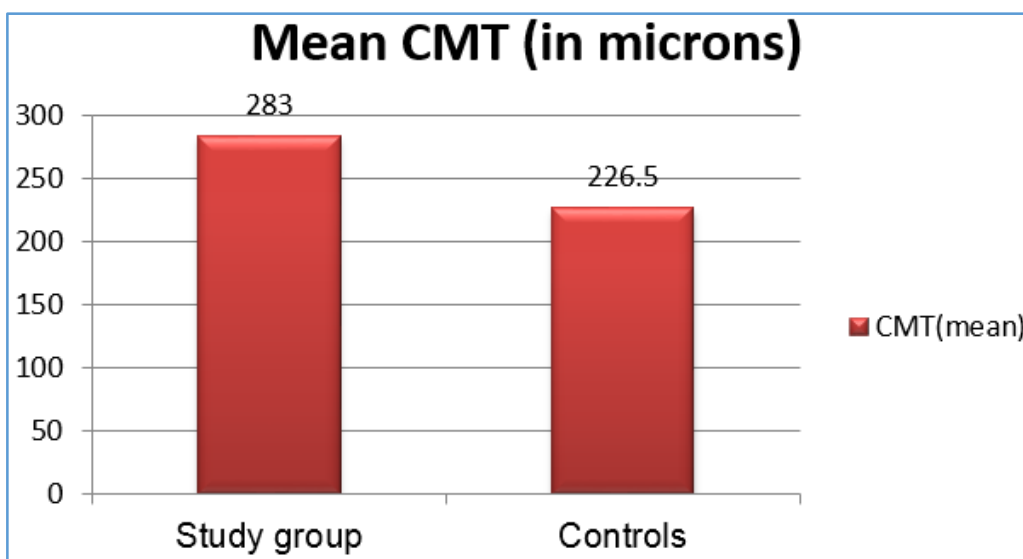
On comparing mean BMI in different subgroups of the study subjects, no statistically significant difference was found ( $p = 0.368$ ). There was a statistically significant difference in duration of diabetes within the subgroups ( $p < 0.001$ ).

On comparing BMI with CMT, a weakly positive correlation was observed using Pearson’s correlation coefficient ( $r=0.052$ ). On doing regression analysis, it showed a statistically insignificant result ( $p=0.237$ ). A statistically significant and positive correlation was observed between CMT and duration of diabetes in the study group (Pearson’s correlation coefficient,  $r=0.19$ ;  $p<0.001$ ). Statistically significant differences were observed when

comparing HbA1C in no DR with NPDR subgroups ( $p<0.001$ ) and on comparing NPDR subgroup with PDR ( $p=0.001$ ). Thus, the control of diabetes correlated with the severity of retinopathy. There was a statistically significant correlation between mean CMT and mean HbA1C values in the study group (Pearson’s correlation coefficient  $r=0.325$ ,  $p<0.001$ ). Higher values of HbA1C were associated with higher CMT.

Demographics		Control	No DR	Mild NPDR	Moderate NPDR	Severe NPDR	PDR	CSME
		(n= 150)	(n=197)	(n=151)	(n=41)	(n=10)	(n=11)	(n=90)
Age (Years) (Mean±SD)		55±8	56±12	59±9	60±8	57±8	51±6	57±7
Gender	Male	68 (45.3%)	99 (50.3%)	79 (52.3%)	20 (48.8%)	9 (90%)	10 (90.9%)	55 (61.1%)
	Female	82 (54.7%)	98 (49.7%)	72 (47.7%)	21 (51.2%)	1 (10%)	1 (0.01%)	35 (38.9%)

**Table 1. Demographic Profile of Study and Control Group**



**Figure 1. Difference in Mean Central Macular Thickness in Study and Control Group**

Subgroups	No. DR (n=197)	Mild NPDR (n=151)	Moderate NPDR (n=41)	Severe NPDR (n=10)	PDR (n=11)	CSME (n=90)
CMT (microns) (Mean±SD)	248.3±21.8	259.1±21.5	284.5±40.4	294.9±14.9	305.5±22.9	394.0±105.3

**Table 2. Central Macular Thickness in Different Subgroups**

$P<0.001$  by ANOVA test.

Groups	Control	No. DR	Mild NPDR	Moderate NPDR	Severe NPDR	PDR	CSME
Control	-	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
No. DR	-	-	<0.001	<0.001	<0.001	<0.001	<0.001
Mild NPDR	-	-	-	<0.001	<0.001	<0.001	<0.001
Moderate NPDR	-	-	-	-	0.431	0.106	<0.001
Severe NPDR	-	-	-	-	-	0.229	0.007
PDR	-	-	-	-	-	-	0.006
CSME	-	-	-	-	-	-	-

**Table 3. Probability of Group Differences in Central Macular Thickness**

## DISCUSSION

Central macula is the most sensitive retinal area responsible for changes in visual acuity. In diabetics, breakdown of inner blood retinal barrier leads to haemorrhages, leakage and collection of lipid exudates within the retinal layers leading to macular oedema.<sup>13</sup> This is a major cause of decreased vision in DR.<sup>2</sup> Hence, assessment of thickness of central macula is important. OCT is used to quantitatively measure macular thickness for diagnosis and management of macular oedema and also to detect subclinical macular thickening in DR.<sup>14,15,16</sup>

It was found that the mean CMT in diabetics was more than that in controls and the difference was statistically significant ( $p < 0.001$ ). Our results are similar to those observed in previous studies done by Schaudig et al in 2000, Sanchez-Tocino et al in Milan, Italy in 2002 and Singapore Indian Eye Study conducted by Sng et al in Singapore in 2012.<sup>9,15,17</sup> The increase in macular thickness in diabetics as compared to nondiabetic controls can be explained by looking at the pathophysiology of DR. Changes in glucose metabolism lead to alterations in the capillary walls of retinal vessels. This leads to breakdown of blood retinal barrier resulting in haemorrhages and leakage of exudates, which in turn present as detectable retinal thickening in OCT.<sup>18</sup> In contrast, Massin et al reported early macular thickening in 12 out of 60 diabetic eyes, however, the difference was not statistically significant.<sup>19</sup> We also observed significantly higher macular thickness in diabetics without clinical retinopathy when compared with controls. This was similar to the study done by Lattanzio et al, which stated that macular thickness in diabetics without DR was more as compared to the controls and the difference was statistically significant ( $p < 0.001$ ).<sup>7</sup> Certain studies published in the past show varying results. In a study conducted by Oshitari et al in Japan in 2009, it was seen that central macula in early stages of DR was significantly thinner than controls ( $p = 0.0229$ ).<sup>20</sup> This was explained by the neuronal abnormalities due to diabetes including retinal ganglion cell death and axonal degeneration. These neuronal alterations were hypothesised to precede the vascular abnormalities in diabetic subjects with early diabetes and thus were responsible for thinner macula in diabetic patients. In contrast, the Singapore Indian Eye Disease Study also showed no statistically significant difference in macular thickness in diabetics with no or mild DR and in nondiabetics.<sup>9</sup>

On comparing mean CMT in different DR subgroups, it was found to be progressively increasing with increasing stage of DR. The mean CMT values in different subgroups of our subjects are comparable with previous studies.<sup>7,9</sup> This increased macular thickness with progressively increasing retinopathy can be explained by alterations in vascular permeability of perifoveal and macular capillaries in diabetics eyes.<sup>9</sup> In our study, there was a statistically significant difference in mean CMT when comparing no DR with mild NPDR and mild NPDR with moderate NPDR. But, no significant difference in mean CMT between moderate NPDR and severe NPDR was observed. This could be because of

small number of cases in severe NPDR subgroup. In the study conducted by Sanchez-Tocino et al, statistically significant differences were found between the control group and no DR ( $p = 0.043$ ), NPDR ( $p = 0.001$ ), PDR ( $p = 0.018$ ) and CSME subgroups ( $p = 0.001$ ).<sup>17</sup> In a similar study conducted in Singapore on diabetics, diabetic participants with moderate or severe DR had greater foveal thickness compared with those with mild DR and no DR ( $p = 0.003$  and  $P = 0.045$ ).<sup>9</sup> They had grouped moderate and severe NPDR in a single subgroup. Another possible mechanism for increased foveal thickness in moderate or severe DR is interstitial oedema secondary to perifoveal capillary loss, which has been found to occur in the course of DR.<sup>21</sup>

Our study showed statistically significant difference in mean CMT in CSME group as compared with other groups as shown in previous studies.<sup>4,14,17</sup> This difference can be because of leaking microaneurysms or diffusion from capillary incompetent areas lead to the collection of intraretinal fluid in the macular area.

A statistically significant difference was observed in the duration of diabetes in various study subgroups ( $p < 0.001$ ). Similar findings were seen in the study done by Sng et al ( $p < 0.001$ ).<sup>9</sup> Therefore, increasing stages of diabetic retinopathy were associated with more duration of diabetes. A positive correlation was observed between central macular thickness and duration of diabetes in the subjects in our study on linear regression analysis ( $r = 0.19$ ). Oshitari et al also concluded that central macula is thicker in eyes with longer duration of diabetes because of increased vascular permeability.<sup>20</sup>

On comparing HbA1C among the various groups, significant difference was seen between diabetics with no DR and NPDR ( $p < 0.001$ ) and between NPDR and PDR ( $p < 0.001$ ). Higher HbA1C was associated with higher CMT. Yeung et al conducted a study on 97 eyes of diabetics without macular oedema and concluded that HbA1C level positively correlates with macular thickness in diabetes.<sup>22</sup> Chou et al showed that a HbA1C level of 8% or above was associated with an increase in macular thickness in diabetic patients without diabetic retinopathy.<sup>23</sup> Thus, meticulous diabetic control may slow the progression of early diabetic retinopathy and may play an important role in preventing macular dysfunction.

Our study suggested correlation between best corrected visual acuity and foveal thickness as measured by OCT ( $r = 0.718$ ). This was also seen in a study done by Sng et al ( $r = 0.78$ ).<sup>9</sup> These findings confirm the findings of Neussenblatt et al that actual macular thickness is better correlated with visual loss in patients with diabetic retinopathy.<sup>24</sup> The correlation was also consistent with the results of previous studies using OCT measured macular thickness by Hee et al and Otani et al.<sup>25</sup>

Thus, our study suggests that changes in macular thickness can be detected by OCT despite normal findings in slit lamp biomicroscopy. These patients are candidates for more frequent and more detailed follow up as they are likely to develop CSME.

**CONCLUSION**

In conclusion, subclinical macular thickening was observed in diabetics, which increased with increasing stages of diabetic retinopathy without evidence of any clinically significant macular oedema. It may therefore be important to monitor such diabetic individuals more closely so that potential vision-threatening macular oedema can be detected earlier.

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