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Macular thickness in diabetic retinopathy without clinically significant macular edema: a prospective study

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Abstract

Aim: *To measure macular thickness by optical coherence tomography (OCT) in various grades of diabetic retinopathy with no clinically significant macular edema (CSME) and its comparison with non-diabetics.*

Design: *Prospective cross–sectional study.*

Methods: *Macular thickness was measured by OCT in 72 healthy volunteers (107 control eyes), 45 patients with mild and moderate non-proliferative diabetic retinopathy (NPDR) (78 eyes), and 37 patients with severe NPDR and proliferative diabetic retinopathy (PDR) (66 eyes). Patients with diabetic macular edema (DME) as assessed by stereoscopic evaluation or photographs were excluded. One-way ANOVA test to compare the mean thickness and Tukey's test for multiple comparison between groups were used.*

Results: *Central subfield thickness (CST) was 238.57 ± 25.077 µm, 251.22 ± 24.649 µm, and 270.45 ± 28.956 µm in the three groups respectively. As the severity of retinopathy increased, the macular thickness significantly increased ($p = < 0.001$) in all the nine zones on OCT. There was a significant increase in CST noted in all the grades of retinopathy when compared with non-diabetics ($p = 0.004$, $p = < 0.0001$). No significant difference in macular thickness was noted between genders, irrespective of their groups ($p = 0.72$), or between the three groups in all the nine zones ($p = 0.609$).*

Conclusion: *There is a significant increase in CST in all grades of retinopathy, as well as with increasing severity of retinopathy when compared to non-diabetics. This warrants the need to obtain OCT measurements even in patients with moderate NPDR without CSME to rule out subclinical DME.*

Keywords*: central subfield thickness, diabetic retinopathy, macular thickness, optical coherence tomography, subclinical diabetic macular edema*

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Introduction

The most common cause of visual loss in patients suffering from diabetic retinopathy is macular edema. This is a preventable cause of blindness and treatments that reduce diabetic macular edema (DME) can improve or stabilize visual acuity. The Early Treatment Diabetic Retinopathy Study (ETDRS) has demonstrated that focal (direct/grid) laser photocoagulation can reduce moderate vision loss from DME by 50% or more.[1] Hence, the quantitative and objective assessment of macular thickness is important.

Macular edema is routinely detected clinically by fundus examination using a contact lens through a biomicroscope. However, this is dependent on observer skill, patient co-operation, degree of pupillary dilatation, amount of media opacity, and the pattern of retinal edema.[2] Therefore, optical coherence tomography (OCT) has emerged as the ideal imaging modality in the evaluation and management of DME.

On comparing OCT with contact lens biomicroscopy for the detection of macular edema, Brown *et al.*[2] found excellent agreement between the two for the absence or presence of foveal edema when OCT thickness was normal (≤ 200 μm) or increased (> 300 μm). However, the agreement was poor when foveal thickness was only mildly increased (201-300 μm). This meant that contact lens biomicroscopy is relatively insensitive for the detection of mild foveal thickening, apparent on OCT.

This thickening, which cannot be detected clinically, but is present on quantitative indices of the centre point obtained from OCT, is termed as subclinical DME. This finding is of increasing clinical importance because it may be a forerunner for the development of clinically significant macular edema (CSME)[3,4] and finally lead to irreversible visual loss. The management has to be altered in such patients, and a shorter follow-up may be recommended in order to attain a better visual outcome.

Thus, the objectives of our study included the following:

1. To examine the relationship of OCT measured macular thickness to retinopathy severity in patients with diabetes, but without clinically detectable macular edema and its comparison with non-diabetics.
2. To verify the need for a change in protocol for follow-up in patients with diabetic retinopathy without CSME based on OCT measurements.

Methods

This was a prospective cross–sectional comparative study performed over a period of two years. The inclusion criteria for the group of cases were:

1. Patients with type 2 diabetes, with all grades of diabetic retinopathy as per ETDRS classification.[5]

2. Absence of DME, where DME was defined as retinal thickening, assessed by stereoscopic evaluation of the fundus by slit-lamp biomicroscopy or assessment of photographs.[6]

The control group was age- and sex-matched to the cases and did not have diabetes. The exclusion criteria were all those conditions that may affect macular thickness, such as prior treatment for DME and/or diabetic retinopathy, age-related macular degeneration, macular hole, post-cataract surgery of < 4 weeks duration, central serous retinopathy, renal failure, drug-induced like HCQ, and an OCT scan signal strength ≤ 4/10.

Ethical Committee clearance from the institution was obtained.

The subjects were divided into three groups: Group 1 included controls, *i.e.*, subjects without diabetes; Group 2 included patients with mild and moderate non-proliferative diabetic retinopathy (NPDR); and Group 3 included patients with severe NPDR and proliferative diabetic retinopathy (PDR).

All subjects underwent the following examination: best-corrected visual acuity with Snellen's chart, slit-lamp biomicroscopy with a 90-diopter lens, indirect ophthalmoscopy, fundus photography, and OCT. The OCT scans were acquired by centring at the fovea through a dilated pupil by a single examiner who was masked to the diagnosis of the patients. OCT imaging was performed with the Spectral domain (SD); Cirrus HD-OCT; Model 4000; Software version 4.0.

Macular Cube 512 x 128 scan protocol was obtained where a 6 × 6 mm area on the retina was scanned with 128 horizontal lines, each consisting of 512 A-scans per line within a scan time of 2.4 seconds. Scans with a signal strength > 5 that exhibited correct delineation of the retinal layers as detected automatically by the software and were without image artefacts were accepted. Central subfield thickness (CST), quantitative measurements within the four inner subfields, four outer subfields, and macular volume were taken directly from the automated analysis. CST was defined as the circular area of diameter 1 mm centred around the centre point; 128 thickness measurements were made in this circular area.[7]

CST values of ≥ 320 µm for males and 305 µm for females was considered as the cut-off value in diagnosing DME.8 Subclinical DME was considered present if this thickness was found to be ≥ 225 and ≤ 299 µm, according to the definition of the Diabetic Retinopathy Clinical Research Network (DRCR.net).[4]

Statistical analysis

Results were expressed as mean ± standard deviation. One-way ANOVA was used to compare if there was a significant difference in mean thickness between the three groups. Multiple comparison between groups was performed using Tukey's post-hoc test. An independent samples T test was performed to compare the mean thickness between groups having diabetes of various durations. Two-way

ANOVA was used to compare the relationship of mean thickness between males and females in the groups and in each of the zones. A p value of < 0.05 was considered statistically significant.

Results

A total of 251 eyes from 154 patients were included in the study. Group 1 had 107 eyes from 72 patients, Group 2 had 78 eyes from 45 patients, and Group 3 had 66 eyes from 37 patients. Of the 251 eyes, a total of 154 (61.3%) were males and 97 (38.6%) were females. Group 1 had 56 (52%) males and 51 (48%) females, Group 2 had 49 (63%) males and 29 (37%) females, and Group 3 had 49 (74%) males and 17 (26%) females.

The mean age in Group 1 was found to be 54.37 years, while in Group 2 it was 59.81 years, and in Group 3 it was 56.67 years. The mean age of the males was 56.47 years and that of females was 56.97 years.

The mean and standard deviation of OCT measurements of the nine zones in the three groups is highlighted in Table 1.

The one-way ANOVA test compared the means of the three groups and found that, as the severity of retinopathy increased, the macular thickness significantly increased (p = < 0.001) in all the nine zones. Similarly, the mean cube volume measurements also showed that there was a significant increase (p = < 0.001) in mean cube volume as the severity of retinopathy increased.

Table 1. Analysis of the mean macular thickness in the three groups using the one-way ANOVA test

Subfield zones	Controls Mean ± SD [µm]	Mild and moderate NPDR Mean ± SD [µm]	Severe NPDR and PDR Mean ± SD [µm]	p
Central	238.57 ± 25.077	251.22 ± 24.649	270.45 ± 28.956	< 0.001
Innernasal	308.91 ± 17.163	317.55 ± 16.382	322.83 ± 19.266	< 0.001
Outernasal	281.78 ± 18.044	291.19 ± 19.177	301.64 ± 22.665	< 0.001
Innertemporal	300.24 ± 21.264	309.18 ± 19.435	317.15 ± 19.129	< 0.001
Outertemporal	259.77 ± 20.602	270.88 ± 21.378	282.68 ± 28.062	< 0.001
Innersuperior	305.89 ± 21.739	319.86 ± 19.819	321.71 ± 20.770	< 0.001
Outersuperior	270.86 ± 18.206	280.50 ± 16.206	294.32 ± 28.477	< 0.001
Innerinferior	306.38 ± 21.263	314.38 ± 17.254	320.53 ± 18.623	< 0.001
Outerinferior	258.96 ± 18.295	274.28 ± 19.962	276.92 ± 20.612	< 0.001
Cube volume	9.764 ± 0.5253	10.105 ± 0.4509	10.462 ± 0.5317	< 0.001

On comparing the mean macular thickness between Group 1 eyes with the other two groups, we found that there was a statistically significant difference in all the nine zones, as shown in Table 2. This meant that there was a significant increase in macular thickness in all grades of diabetic retinopathy when compared with non-diabetics. A similar significant increase in mean macular thickness was also noted as the severity of diabetic retinopathy increased. Table 2 shows the comparison between Groups 2 and 3, where it was seen that most of the zones showed a statistically significant difference in the mean macular thickness excepting the inner nasal, inner superior, inner inferior, and outer inferior zones.

Table 2. Inter group comparison of mean macular thickness using Tukey's post-hoc test

Subfield zones	Groups	P
Central	Mild-Moderate NPDR vs Controls	0.004
	Severe NPDR & PDR vs Controls	< 0.0001
	Mild-Moderate NPDR vs Severe NPDR & PDR	< 0.0001
Innernasal	Mild-Moderate NPDR vs Controls	0.003
	Severe NPDR & PDR vs Controls	< 0.0001
	Mild-Moderate NPDR vs Severe NPDR & PDR	0.17
Outernasal	Mild-Moderate NPDR vs Controls	0.004
	Severe NPDR & PDR vs Controls	< 0.0001
	Mild-Moderate NPDR vs Severe NPDR & PDR	0.003
Innertemporal	Mild-Moderate NPDR vs Controls	0.006
	Severe NPDR and PDR vs Controls	< 0.0001
	Mild-Moderate NPDR vs Severe NPDR & PDR	0.049
Outertemporal	Mild-Moderate NPDR vs Controls	0.004
	Severe NPDR & PDR vs Controls	< 0.0001
	Mild-Moderate NPDR vs Severe NPDR & PDR	0.007
Innersuperior	Mild-Moderate NPDR vs Controls	< 0.0001
	SevereNPDR & PDR vs Controls	< 0.0001
	Mild-Moderate NPDR vs Severe NPDR & PDR	0.857
Outersuperior	Mild-Moderate NPDR vs Controls	0.004
	Severe NPDR and PDR vs Controls	< 0.0001
	Mild-Moderate NPDR vs Severe NPDR & PDR	< 0.0001

Subfield zones	Groups	P
Innerinferior	Mild-Moderate NPDR vs Controls	0.017
	Severe NPDR and PDR vs Controls	< 0.0001
	Mild-Moderate NPDR vs Severe NPDR & PDR	0.143
Outerinferior	Mild-Moderate NPDR vs Controls	< 0.0001
	Severe NPDR & PDR vs Controls	< 0.0001
	Mild-Moderate NPDR vs Severe NPDR & PDR	0.696

Table 3 and Figure 1 show the analysis of mean macular thickness when sorted by gender. In all the zones, there was no statistically significant difference between male and female eyes when compared, irrespective of their groups ($p = 0.720$). Likewise, the two-way ANOVA test, which was used to compare the thickness between the two genders in the three groups and in all the zones, did not find any statistically significant difference ($p = 0.609$).

An independent samples T test was performed to compare the mean macular thickness in relation to the duration of diabetes. In Group 2, there were 67 patients with diabetes of < 5 years duration and 11 patients with > 5 years duration. Table 4 and Figure 2 show that no statistically significant difference was found in the mean macular thickness in this group in any of the zones, although the mean macular thickness in most of the zones except in the outer temporal, inner superior, and outer superior zones was found to be higher in patients with > 5 years duration of diabetes.

Table 5 and Figure 3 highlight the mean macular thickness in relation to the duration of diabetes in Group 3. There were 52 patients with diabetes of < 5 years duration and 14 patients with > 5 years duration. The mean macular thickness in four zones, *i.e.*, the central, outer nasal, outer temporal, and outer superior zones, was higher in patients with diabetes of > 5 years duration. However, it was not statistically significant in any zone excepting the inner temporal zone.

Table 6 and Figure 4 show the comparison of the mean macular thickness in relation to a longer duration of diabetes. In Group 2, there were 75 patients with diabetes of < 10 years duration and 3 patients with > 10 years duration. The thickness in all nine zones was higher in patients with > 10 years duration of diabetes. However, it was statistically significant in only three zones, *i.e.*, inner nasal, outer nasal, and outer inferior.

Table 7 and Figure 5 show that in Group 3, consisting of 58 patients with diabetes of < 10 years duration and 8 patients with > 10 years duration, the mean macular thickness in eight zones, except in the inner temporal zone, was higher in patients with >10 years duration of diabetes, but not statistically significant in any zone.

Table 3. Analysis of the mean macular thickness sorted by gender

Subfield zones	Males Mean ± SD [µm]	Females Mean ± SD [µm]
Central	252.21 ± 30.50	248.77 ± 26.31
Innernasal	316.25 ± 19.22	313.68 ± 16.96
Outernasal	292.49 ± 21.51	285.85 ± 20.19
Innertemporal	309.14 ± 21.25	304.81 ± 21.06
Outertemporal	271.47 ± 25.96	265.71 ± 22.37
Innersuperior	314.79 ± 20.87	313.75 ± 24.00
Outersuperior	282.75 ± 24.63	275.70 ± 19.04
Innerinferior	314.35 ± 20.90	309.79 ± 18.78
Outerinferior	268.50 ± 22.86	268.36 ± 17.94
Cube volume	10.079 ± 0.602	10.013 ± 0.538

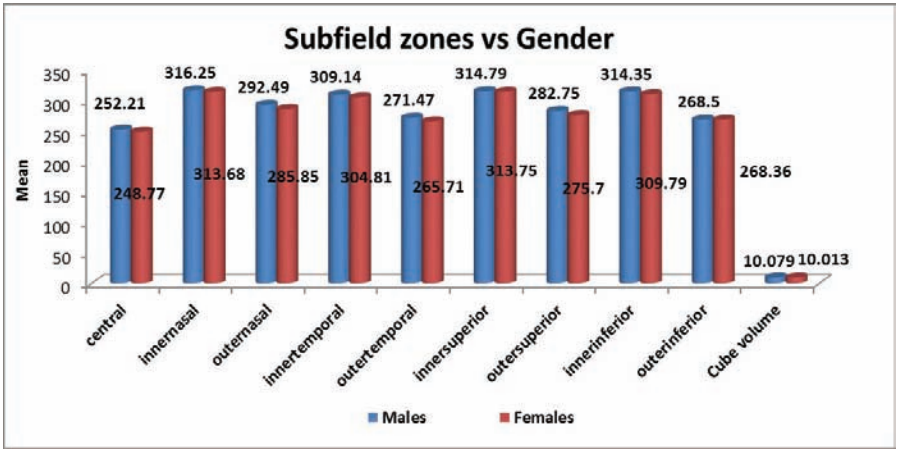


Table 4. Comparison of mean macular thickness in relation to the duration of diabetes in Group 2 (< 5 years vs > 5 years)

Subfield zones	Diabetes duration	Mean ± SD	p
Central	1	251.21 ± 24.93	0.994
	2	251.27 ± 23.99	
Innernasal	1	316.12 ± 15.89	0.56
	2	326.27 ± 17.38	
Outernasal	1	290.12 ± 19.24	0.225
	2	297.73 ± 18.29	
Innertemporal	1	308.84 ± 19.93	0.703
	2	311.27 ± 16.76	
Outertemporal	1	272.19 ± 21.98	0.184
	2	262.91 ± 15.75	
Innersuperior	1	319.90 ± 20.34	0.968
	2	319.64 ± 17.13	
Outersuperior	1	281.93 ± 16.18	0.55
	2	271.82 ± 14.06	
Innerinferior	1	313.73 ± 16.85	0.413
	2	318.36 ± 19.93	
Outerinferior	1	274.27 ± 19.65	0.988
	2	274.36 ± 22.77	

Duration of diabetes: 1 = < 5 years duration; 2 = > 5 years duration

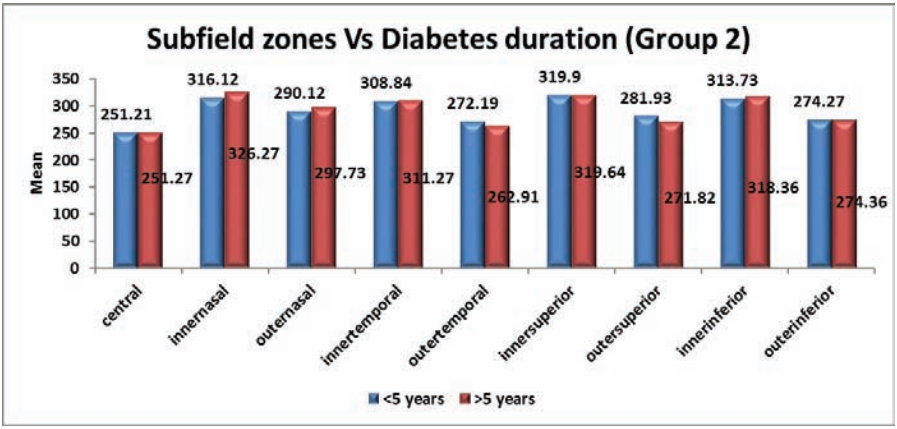


Table 5. Comparison of mean macular thickness in relation to the duration of diabetes in Group 3 (< 5 years vs > 5 years)

Subfield zones	Diabetes duration	Mean ± SD	P
Central	1	269.96 ± 28.94	0.792
	2	272.29 ± 30.04	
Innernasal	1	323.87 ± 16.67	0.534
	2	319.00 ± 27.32	
Outernasal	1	301.37 ± 23.28	0.853
	2	302.64 ± 20.10	
Innertemporal	1	320.23 ± 14.12	0.011
	2	305.71 ± 29.50	
Outertemporal	1	282.46 ± 29.14	0.903
	2	283.50 ± 24.67	
Innersuperior	1	322.21 ± 18.19	0.778
	2	319.86 ± 29.24	
Outersuperior	1	293.06 ± 29.69	0.493
	2	299.00 ± 23.78	
Innerinferior	1	321.48 ± 16.02	0.428
	2	317.00 ± 26.64	
Outerinferior	1	277.46 ± 21.11	0.686
	2	274.93 ± 19.26	

Duration of diabetes: 1 = < 5 years duration; 2 = > 5 years duration

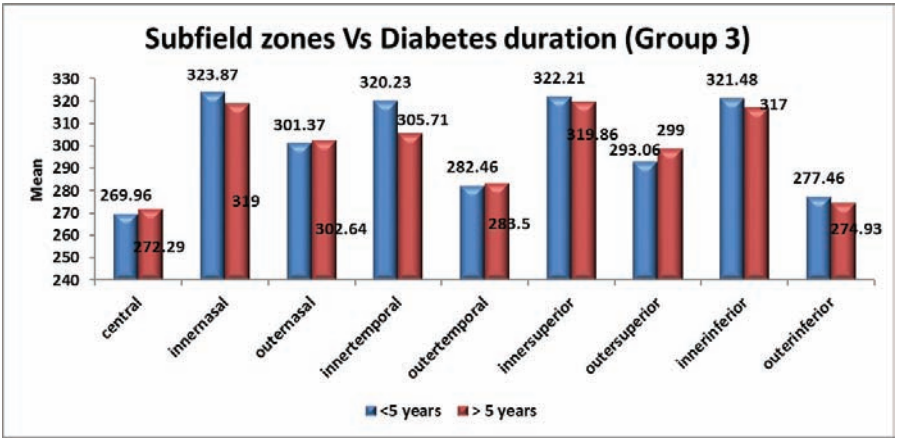


Table 6. Comparison of mean macular thickness in relation to the duration of diabetes in Group 2 (< 10 years vs > 10 years)

Subfield zones	Diabetes duration	Mean ± SD	P
Central	1	316.75 ± 16.04	0.029
	3	337.67 ± 13.61	
Innernasal	1	290.15 ± 18.48	0.015
	3	317.33 ± 21.22	
Outernasal	1	308.40 ± 19.26	0.076
	3	328.67 ± 14.98	
Innertemporal	1	270.45 ± 21.67	0.376
	3	281.67 ± 6.66	
Outertemporal	1	319.03 ± 19.62	0.063
	3	340.67 ± 14.50	
Innersuperior	1	280.17 ± 16.40	0.377
	3	288.67 ± 7.57	
Outersuperior	1	314.15 ± 16.81	0.546
	3	320.33 ± 30.90	
Innerinferior	1	273.20 ± 19.11	0.016
	3	301.33 ± 26.10	

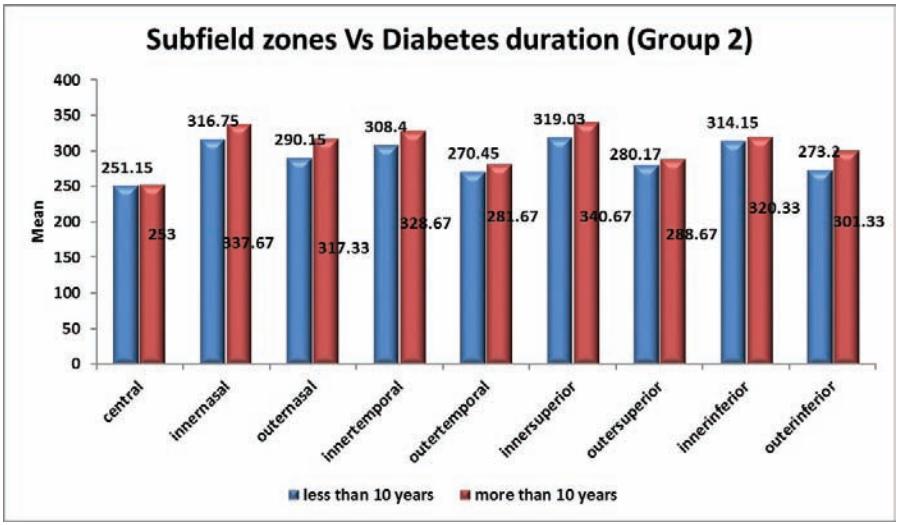


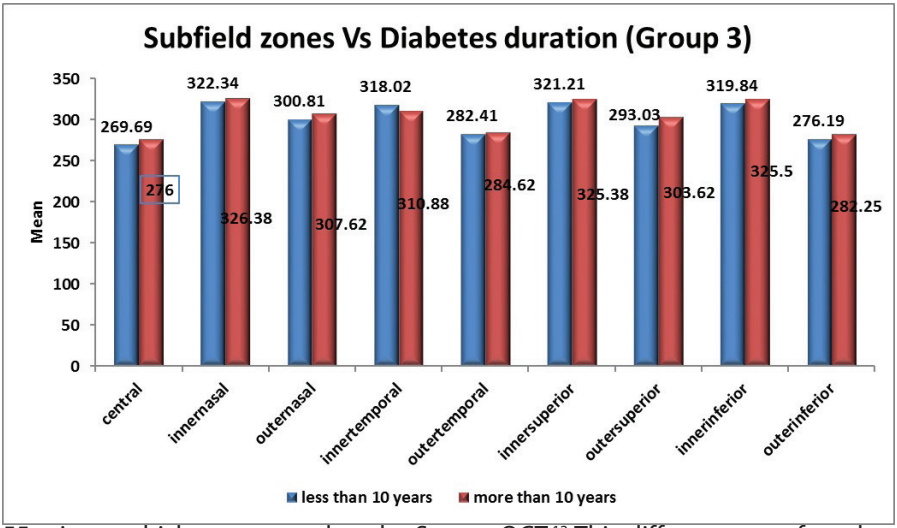
Table 7. Comparison of mean macular thickness in relation to the duration of diabetes in Group 3 (< 10 years vs > 10 years)

Subfield zones	Diabetes duration	Mean ± SD	P
Central	1	269.69 ± 28.52	0.567
	3	276.00 ± 33.53	
Innernasal	1	322.34 ± 18.03	0.583
	3	326.38 ± 27.97	
Outernasal	1	300.81 ± 22.57	0.430
	3	307.62 ± 23.96	
Innertemporal	1	318.02 ± 18.58	0.326
	3	310.88 ± 23.17	
Outertemporal	1	282.41 ± 28.80	0.836
	3	284.62 ± 23.51	
Innersuperior	1	321.21 ± 19.72	0.599
	3	325.38 ± 28.64	
Outersuperior	1	293.03 ± 29.53	0.328
	3	303.62 ± 17.78	
Innerinferior	1	319.84 ± 17.89	0.425
	3	325.50 ± 24.13	
Outerinferior	1	276.19 ± 21.26	0.440
	3	282.25 ± 15.06	

Duration of diabetes: 1 = < 10 years duration; 3 = > 10 years duration

Discussion

The DRCR.net had primarily used the TD-OCT in its studies related to measurements of DME up until 2011.[9] They have established a mean CST of 250 µm as the cut-off value to represent the upper limit of normal macular thickness. However, with the advent of Fourier domain (SD) OCTs, most studies have started using these devices due to better resolution. With the Spectralis SD-OCT, Grover *et al.*[10] found the mean CST in normal eyes to be 270.2 ± 22.5 µm. In contrast, the corresponding values on the TD-OCT (Stratus) were 212 ± 20 µm. Jean-Antoine *et al.*[11] noted a 50 µm increase in CST in favour of the Cirrus OCT as compared to the Stratus OCT. Similarly, other studies that have compared data obtained using the Stratus OCT and the Cirrus HD-OCT in both normals and patients with DME, have demonstrated that the median difference between Stratus and Cirrus CST was 43 µm,[9] *i.e.*, that Cirrus OCT measured retinal thickening was between 30 to



55 microns thicker compared to the Stratus OCT.[12] This difference was found to be based on the fact that the boundaries of the retina used to demarcate the macular thickness in TD-OCT are the internal limiting membrane and the junction between the inner and outer segments of the photoreceptors as opposed to the SD-OCT, which measures the distance between the retinal pigment epithelium and the inner limiting membrane. Thus, Grover *et al.*[10] have proposed 315 µm as the upper limit and 225 µm as the lower limit of normal CST.

Appukuttan *et al.*[13] have suggested a lower range, *i.e.*, 220-300 µm, be taken as the normal for central foveal thickness in Indian eyes using SD-OCT, with men having a greater central foveal thickness than women.

The major hurdle in our study has been to integrate the data from the Stratus OCT, used in our reference studies, into the Cirrus OCT, used in our study, so as to formulate normative values that will enable our measurements to be both accurately assessed and clinically applicable.

Taking the aforementioned normative values into consideration, our study found that there was a significant increase in macular thickness in all grades of retinopathy when compared with non-diabetics. When non-diabetic eyes were compared with eyes of mild and moderate NPDR, the highest increase in mean macular thickness was noted in the parafoveal zones followed by the central zone, but when such a comparison was done with eyes of more severe grades of retinopathy, the highest increase was in the CST. This phenomenon may probably be due to fluid leaking from retinal vessels into the parafoveal zones, with relative sparing of the foveal region in milder grades of retinopathy as well as due to the breakdown of the outer blood retinal barrier affecting the Müller cells that are

more abundant in the foveal floor than in the retinal edges14 in severe grades of diabetic retinopathy.

In contrast, Goebel *et al.*[15], in their study of diabetic patients of unspecified grade of retinopathy without CSME and unspecified gender, found that foveal and average retinal thickness did not differ from normal eyes. This could be because they pooled both genders and all grades of retinopathy, unlike our study.

In a study similar to ours, Browning *et al.*[16] had stratified the eyes of patients with diabetes based on gender and retinopathy severity, finding that there was a significant difference between the CST in the normal and the severe NPDR/PDR groups, as well as between the mild/moderate NPDR vs severe NPDR/PDR groups. The mean thicknesses of paracentral subfields did not show differences for normals or for any group.

In both females and males, they found a significant difference between CST in the severe NPDR/PDR groups, but no significant differences in other pairwise comparisons by retinopathy severity. Our study, however, did not find any statistically significant difference in the mean macular thickness between male and female eyes in any of the nine zones nor across the three groups compared. The importance of gender differences in macular thickness is limited to comparisons of groups in clinical studies. There is no clinical significance, as management remains the same, irrespective of gender.

When duration of diabetes was taken into account, we found that although the mean macular thickness was greater in eyes with diabetes of > 5 years duration in most zones, it was statistically significant in only one zone. Similar results were found when a longer 10-year duration was taken into consideration. Likewise, Goebel *et al.*[15] did not find any association between retinal thickness and duration of diabetes. However, Browning *et al.*[16] found statistically significant differences in duration of diabetes among groups of diabetics and varying levels of retinopathy severity.

Sanchez-Tocino *et al.*[17] found significant differences in foveal thickness between eyes in the control group and eyes in all the other groups, which were similar to our study. However, contrary to our study, they did not find significant differences in thickness in any zone in eyes with NPDR without CSME and PDR without CSME. They suggested that a foveal thickness greater than 180 µm may be useful for the early detection of macular thickening. Hee *et al.*[18] found similar results and reported 216 µm as the maximum value observed in normal eyes. However, the shortcomings of these studies were the manual measurements of TD-OCT readings, lack of gender stratification, and inclusion of eyes with CSME.

The fact that eyes with CSME were excluded from our study means that, as the severity of retinopathy increases, subclinical DME becomes more prevalent, which is in concordance with the Browning *et al.*[16] study.

Bressler *et al.*[4] suggested that approximately one-quarter to one-half of eyes with subclinical DME will progress to more definite thickening or will need treatment for DME within two years of its identification. Progression to CSME has been found to occur over a median period of 14 months by Browning *et al.*[16] Therefore, earlier detection of subclinical DME is preferred with the aim of preserving photoreceptors at early disease stages and retaining central visual acuity.

At this juncture, the question arises: at what level of CST and of severity of diabetic retinopathy without CSME should we begin obtaining OCT scans? Although it would be ideal to perform the OCT scans at the mild NPDR level itself, it is not always financially and practically feasible to obtain an OCT for every such patient in the Indian scenario. Earlier and more frequent follow-up would be more beneficial in these cases.

Hence, we suggest that it is more useful to perform an OCT scan in all patients with moderate NPDR levels of retinopathy, even in the absence of CSME, in order to monitor for increased CST and allow timely intervention to be decided upon. A CST of 251.22 ± 24.65 μm could be considered the cut-off point.

However, the decision to treat cannot be based entirely on OCT values and should be individualized depending on the level of visual acuity, patient compliance, and systemic factors such as hypertension and renal disease.[19]

In conclusion, our study is the first to provide information relating to retinopathy severity and macular thickness as measured by SD-OCT in a large cross-section of Indian eyes without DME. Unlike previous studies, our study was a prospective one, employed gender stratification, and considered the duration of diabetes. Patients with moderate NPDR without CSME would benefit from OCT measurements at each visit, so that upon detection of subclinical DME, a decision to frequently follow-up or initiate treatment may be recommended, thus preventing the visual loss that would occur by pursuing a normal follow-up regimen.

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