Original Article

Changes of Macular and Retinal Nerve Fiber Layer Thickness Measured by Optical Coherence Tomography in Diabetic Patients with and without Diabetic Retinopathy

Raghavendra Ramappa[1], Reji Koshy Thomas[2]

[1]Senior Resident, Department of Ophthalmology, Mysore Medical College and Research Institute, Mysore, Karnataka, India,
[2]Professor, Department of Ophthalmology, St. John's Medical College, Bengaluru, Karnataka, India

Abstract

Introduction: Diabetes mellitus (DM) is one of the leading causes of blindness. The long-term effects of DM on vascular tissues and its consequence on the retina are well-established, and this ranges from milder grades of non-proliferative diabetic retinopathy (NPDR) to advanced grades of proliferative retinopathy with or without clinically significant macular edema.

Materials and Methods: The retinal nerve fiber layer (RNFL) and macular thickness were measured in 100 patients (200 eyes) using spectral domain optical coherence tomography in the prospective observational study. The patients with DM over 40 years of age were included. Patients with a history of recent ocular surgery (1 month), pseudoexfoliation, pigment dispersion syndrome, thyroid dysfunction, long-term steroid users, high myopia, and media opacities such as cataract, other causes for secondary glaucoma, and DR with tractional retinal detachment, and post glaucoma and retinal surgery were excluded. The values of participants with DM were compared to controls. The participants were divided into 4 groups of containing 25 patients in each group: Controls (normal patients without diabetes), diabetics without retinopathy (NDR group), NPDR (NPDR group), and proliferative DR (PDR group).

Results: The average temporal RNFL thickness and average macular thickness are 65.02 μm and 278.46 μm, respectively. It is significant ($P < 0.01$) across the groups.

Conclusion: DR is associated with a decrease in RNFL thickness though this is not statistically significant in our study. However temporal RNFL shows a significant increase in thickness, which worsens with the stage of DR, this is due to the clinical significant macular edema which is associated with the retinopathy.

Key words: Diabetic retinopathy, Glaucoma, Macular thickness, Optical coherence tomography, Retinal nerve fiber layer thickness

INTRODUCTION

Diabetes mellitus (DM) is no longer an epidemic that can be ignored with over 80% of patients being concentrated in low and middle-income countries.[1] Currently, the number of cases of diabetes worldwide is estimated to be around 387 million.[1] This number is predicted to increase by additional 205 million by 2030. The World Health Organization reports indicate that India is second in the world after China with the largest number of diabetic subjects (65.1 million).[2]

DM is one of the leading causes of blindness.[3] Diabetic retinopathy (DR) is the most common ocular complication of diabetes with 5% of diabetics, progressing to severe visual loss of 5/200 or less.[4]

The long-term effects of DM on vascular tissues and its consequence on the retina are well-established, and this ranges from milder grades of non-proliferative DR

Corresponding Author: Dr. Raghavendra Ramappa, Department of Ophthalmology, Mysore Medical College and Research Institute, Mysore, Karnataka, India. Phone: +91-9686756750. E-mail: dr.raghuophthal@gmail.com

(NPDR) to advanced grades of proliferative retinopathy with or without clinically significant macular edema.

DR has been described as a type of optic neuropathy, which is different from glaucomatous optic nerve damage by that the cup of the disc was not enlarged in diabetic eyes in spite of discrete signs of retinal nerve fiber layer (RNFL) defects. The reduced visibility of the RNFL, the increased optic disc pallor and the unchanged size of the neuroretinal rim and parapapillary atrophy suggest that DM may be associated with non-glaucomatous optic nerve atrophy.[5]

The evolution of newer technologies such as the Heidelberg retina tomography, glaucoma diagnostics - variable corneal compensation, and optical coherence tomography (OCT) has made an evaluation of the optic nerve head (ONH), the peripapillary area, the macula and the RNFL revolutionary. The resolution and reproducibility of these technologies almost give us a near histological evaluation of the tissue or area we study in the retina.[6]

This study is intent to highlight the OCT characteristics of the RNFL in patients with DR. We plan to evaluate the association if any of RNFL thickness with DR and to evaluate the possibility of RNFL thickness (RNFLT) changes being a precursor to diabetic retinal changes. Early detecting of RNFL thinning, which seems to be a common factor in both diabetes and glaucoma, may be a useful tool in the understanding the progression of DR and may explain the probable higher incidence of glaucoma in diabetic patients.[7-10]

MATERIALS AND METHODS

This study was conducted on patients coming to the Department of Ophthalmology, St. John's Medical College Hospital during the period from September 2009 to August 2011. The study was approved by the Ethics Committee of St John's Medical College and adhered to the tenets of the declaration of Helsinki. We prospectively analyzed 100 patients (200 eyes). The study design was a prospective observational study.

Inclusion criteria were patients with DM (DM was diagnosed on the basis of the diabetes diagnostic criteria of the World Health Organization,[11] and the patients were under medical treatment by an experienced physician/endocrinologist) and age > 40 years of age.

Exclusion criteria were recent ocular surgery (1 month), patients < 40 years of age, patients with pseudoexfoliation and pigment dispersion syndrome, thyroid dysfunction, long-term steroid users, high myopia, media opacities such as cataract, other causes for secondary glaucoma, post glaucoma surgery, DR with tractional retinal detachment, and Post retinal surgery patients.

A detailed history which included demographics, information on past medical illness and drug intake (with special reference to DM and hypertension) and their duration was recorded. Ocular disease if any was noted. Family history of diabetic mellitus or glaucoma was recorded.

Ophthalmological examination was recorded in each eye individually which included visual acuity and best corrected visual acuity (BCVA), slit lamp examination, gonioscopy, fundus examination (cup to disc ratio [CDR] was measured with micrometer scale attached to eyepiece of slit lamp), applanation tonometry (with central corneal thickness - CCT correction), visual field testing with Humphrey field analyzer, RNFL analysis using Zeiss Cirrus™ HD-OCT. Blood sugars, glycosylated hemoglobin (HbA1c), serum cholesterol and serum creatinine was routinely done for all patients done.

In this study, the patients were divided into 4 groups: Controls (normal patients without diabetes) - 25 patients (50 eyes), diabetics without retinopathy (NDR group) - 25 patients (50 eyes), NPDR (NPDR group) - 25 patients (50 eyes) and proliferative DR (PDR group) - 25 patients (50 eyes).

Patients with DM were divided into three groups on the basis of the international clinical DR disease severity scale.[12] NDR was defined as the absence of all features of DR in diabetic eyes; NPDR was defined as the presence of micro aneurysms, hard exudates, dot and blot hemorrhages, cotton wool spots, venous beading and intraretinal microvascular abnormalities; and PDR was defined as the presence of neovascularization on optic disc or elsewhere, vitreous or preretinal hemorrhage, and fibrovascular proliferative tissue.

The statistical analysis was done as follows: First, the descriptive statistics were computed. Range, mean and standard deviation (SD) was estimated for quantitative variables and frequency counts with percentages for qualitative variables. Then, inferential statistical analysis was undertaken.

One-way ANOVA was done to evaluate the correlation of the diabetic groups and controls with the variables included in the study, such as nerve fiber layer thickness, macular thickness, BCVA, intraocular pressure (IOP) and CDR. Whenever there was statistical significance across groups, *post hoc* analysis (Bonferroni) was done to study any statistically significant difference between groups.

All tests were done using Statistical package for Social sciences version 10 software. Statistical significance was

considered whenever $P < 0.05$. There may be a fallacy while measuring temporal RNFL thickness, as anatomically the same fibers constitutes the macular nerve fibers also; an increase in macular thickness due to CSME may cause a fallacious increase in temporal RNFLT also. To differentiate an increase in temporal RNFL due to CSME from a true change in temporal RNFLT due to increasing severity of DR the study group was further divided into 3 different groups, i.e., no DM (NDM) group, DM without CSME (no CSME [NCSME]) group and DM with CSME (CSME), and data were analyzed.

OBSERVATIONS AND RESULTS

OCT was done in 100 patients. For analysis purpose, the data were taken as 200 eyes, which contain 50 eyes in the control group and 150 eyes in the DR group.

Demography
Age
The age of the patients in the study ranged from 40 to 77 years with a mean of 54.01 ± 7.94 (SD).

Sex
The study group had 65 males (65%) and 35 females (35%).

Duration of diabetes
It was increasing proportionately according to the severity of the retinopathy.

Family history
About 18 out of 75 (24%) diabetic patients had family history of diabetes in 1st and 2nd degree relatives.

BCVA
Since there was a statistically significant difference across the groups for the BCVA, between groups comparison of BCVA was analyzed.

IOP with CCT correction
1. The mean value is 14.10 ± 2.45 mm of Hg
2. There is no statistically significant of IOP with CCT across the groups.

CDR
The mean value is 0.30 ± 0.10.

RNFL defect
RNFL defect present in 78 eyes out of 150 (52%) eyes of diabetic group.

RNFLT
Average, Inferior, Superior, and nasal RNFLT were not statistically significant across the groups. Temporal RNFLT was statistically significant difference across the groups hence, between groups comparison was analyzed.

Macular thickness
Macular thickness was a statistically significant difference across the groups for the hence, between groups comparison was analyzed.

Macular thickness was significantly more ($P < 0.01$) in PDR group when compared to controls group, NPDR group to NDR group and PDR group to NDR group.

Blood Investigations
1. HbA1c was significantly more in PDR group compared to NDR group
2. Serum creatinine was minimally high in PDR group
3. Serum cholesterol is not statistically significant across the groups.

Analysis between NDM Groups, NCSME Group and CSME Group - Group 1
Since there was a statistically significant difference across the groups for the BCVA, temporal RNFLT and macular thickness, between groups comparison of the same were analyzed (Table 6).

BCVA
BCVA was significantly worse ($P < 0.01$) in CSME group when compared to NDM group, CSME to NCSME group.

Temporal RNFL Thickness
Temporal RNFLT was significantly more in CSME group when compared to NDM group and CSME to NCSME groups.

Macular Thickness
Macular thickness was significantly increased ($P < 0.01$) in CSME group when compared to NDM group and CSME group to NCSME group. It was not significant in NDM group versus NCSME group.

DISCUSSION

Demographic and Epidemiological Details
In the present study, most of the patients were in the age group of 40-60 years which accounted for 75% of the patients. Most of the patients were male patients accounting for 65% of the study group.

Duration of Diabetes and HbA1C Levels
As shown in Table 1, the stage of DR worsened with the duration of DM. Uncontrolled sugars trended towards worsening of DR as shown by Table 1 in which the HbA1c levels correlated well with severity of the DR.

BCVA

In our study, BCVA was a statistically significant ($P < 0.001$) across the groups for the (Table 2). Hence inter-group comparison of BCVA (Table 3) was analyzed, in which it was significantly worse ($P < 0.001$) in the NPDR group when compared to controls group, PDR group to controls group, NPDR to NDR group and PDR to NDR group. The BCVA is worse in PDR group. These differences in values may be due to the associated macular edema which often accompanies NPDR and PDR group. Hence to confirm this we divided the groups into three different groups, i.e. NDM group, NCSME, and CSME, and these data were analyzed. BCVA was significantly worse ($P < 0.01$) in CSME group when compared to NDM group, CSME to NCSME group as shown in Table 7.

These results are consistent with the study done by Sa´nchez-Tocino et al.,[13] in which they concluded that the retinal thickness at the foveal center correlated with BCVA in normal and diabetic eyes.

Otani et al.[14] reported a correlation between retinal thickness and visual acuity in eyes with diabetic macular edema, with or without cystoid macular edema.

Table 1: Duration of diabetes, RNFL defect, HbA$_1$C, serum cholesterol and serum creatinine across the groups

Parameters	Mean (SD**)		
	NDR[‡]	NPDR[§]	PDR[‖]
Duration of diabetes (in months)	73.04 (79.10)	136.24 (71.57)	140.64 (70.10)
RNFL* defect (%)	21/50 (42)	31/50 (62)	26/50 (52)
HbA$_1$C[†] (in %)	7.68 (1.65)	9.47 (1.60)	10.62 (1.09)
Serum cholesterol (in mg/dl)	192.32 (46.33)	191.04 (33.08)	182.96 (43.00)
Serum creatinine (in mg/dl)	1.22 (1.21)	1.34 (0.84)	1.58 (0.98)

*RNFL: Retinal nerve fiber layer, [†]HbA1C: glycosylated hemoglobin, [‡]NDR: No diabetic retinopathy, [§]NPDR: Non-proliferative diabetic retinopathy, [‖]PDR: Proliferative diabetic retinopathy, **SD: Standard deviation

IOP with CCT

The mean value of IOP with CCT of 200 eyes is 14.10 ± 2.45. There is no statistically significant variation of IOP across the groups (Table 2). Our study suggests that there is no association between increased IOP and diabetes.

Dielemans et al.[7] (The Rotterdam study) concluded that the newly diagnosed DM and high levels of blood glucose are associated with elevated IOP and high-tension glaucoma. Klein et al.[8] (The beaver dam eye study) concluded that the presence of open-angle glaucoma is increased in people with older-onset diabetes.

Tielsch et al. (the baltimore eye survey)[9] concluded that, there is no evidence from this population-based investigation that supports an association between diabetes and POAG. Ellis et al.[10] concluded that, their study failed to confirm an association between DM and primary open angle glaucoma and ocular hypertension.

CDR

The mean value in 200 eyes is 0.30 ± 0.10.

CDR showed statistical significance ($P = 0.036$) across the groups. CDR was increased ($P = 0.06$) in PDR group when compared to controls group though this was not statistically significant. Similarly, CDR was increased ($P = 0.08$) in PDR group when compared to NDR group, which was again not statistically significant (Table 2).

Klein et al.[15] analyzed change in optic disc cupping was evaluated in a 4 years follow-up of a well-defined cohort of people with DM. People who developed proliferative retinopathy by the follow-up examination were not more likely to have such an increase in the ratio at the follow-up. They concluded that clinically significant increases in CDR cannot be consistently predicted in people with diabetes from the risk factors evaluated with the grading system used in this study.

Table 2: BCVA, CDR, IOP, retinal nerve fiber layer and macular thickness across groups

Parameters	Mean (SD)				F value	Significance (P value)
	Controls	NDR	NPDR	PDR		
BCVA	0.84 (0.21)	0.83 (0.24)	0.62 (0.29)	0.48 (0.29)	22.474	<0.001
CDR	0.28 (0.12)	0.29 (0.15)	0.30 (0.11)	0.34 (0.13)	2.89	0.036
IOP	13.67 (2.14)	14.03 (2.77)	14.47 (2.63)	14.20 (2.20)	0.96	0.42
Average RNFLT* (µm)	93.26 (8.77)	91.80 (9.80)	94.24 (19.65)	96.36 (12.89)	1.54	0.205
Inferior RNFLT* (µm)	120.36 (13.38)	118.78 (14.16)	121.50 (22.03)	119.16 (21.26)	0.231	0.88
Superior RNFLT* (µm)	113.44 (13.79)	117.48 (16.01)	120.02 (16.9)	117.06 (21.56)	1.23	0.30
Nasal RNFLT* (µm)	71.38 (9.18)	69.46 (10.6)	72.66 (12.74)	73.96 (12.66)	1.41	0.24
Temporal RNFLT* (µm)	61.48 (8.33)	62.08 (9.67)	61.78 (10.84)	74.74 (21.43)	11.45	<0.001
Macular thickness (µm)	267.86 (17.39)	249.76 (28.94)	290.24 (42.69)	305.96 (40.49)	26.70	<0.001

*RNFLT: Retinal nerve fiber layer thickness, BCVA: Best corrected visual acuity, CDR: Cup disc ratio, IOP: Intraocular pressure

RNFL Defect

RNFL defect was detected by red free indirect ophthalmoscopy or red free slit lamp biomicroscopy and confirmed by OCT. In our study, RNFL defect (Table 1) was present in 78 eyes out of 150 (52%) eyes of the diabetic group. RNFL defect was present in 21/50 (42%) of NDR group, 31/50 (62%) of NPDR group and 26/50 (52%) of PDR group. RNFL defect was not found in any controls group.

Table 3: Between groups comparison of best corrected visual acuity

Groups	Comparison between the groups	Mean difference	P value
Control	NDR	1.3	1.00
	NPDR	0.22	<0.001
	PDR	0.36	<0.001
NDR	NPDR	0.21	<0.001
	PDR	0.35	<0.001
NPDR	PDR	0.13	0.05

NDR: No diabetic retinopathy, NPDR: Non-proliferative diabetic retinopathy, PDR: Proliferative diabetic retinopathy

Table 4: Between groups comparison of temporal retinal nerve fiber layer thickness

Groups	Comparison between the groups	Mean difference	P value
Controls	NDR	0.6	1.00
	NPDR	0.3	1.00
	PDR	13.26	<0.001
NDR	NPDR	0.3	1.00
	PDR	12.6	<0.001
NPDR	PDR	12.96	<0.001

NDR: No diabetic retinopathy, NPDR: Non-proliferative diabetic retinopathy, PDR: Proliferative diabetic retinopathy

Table 5: Between groups comparison of macular thickness

Groups	Comparison between the groups	Mean difference	P value
Controls	NDR	18.1	0.048
	NPDR	22.38	0.07
	PDR	38.10	<0.001
NDR	NPDR	40.48	<0.001
	PDR	56.20	<0.001
NPDR	PDR	15.72	0.127

NDR: No diabetic retinopathy, NPDR: Non-proliferative diabetic retinopathy, PDR: Proliferative diabetic retinopathy

This is inconsistent with the study done by Chihara et al.[16] They photographed the RNFL of the right eye of 137 patients with diabetes and 144 healthy control subjects. The level of DR[17] ranged from levels 1 (no microaneurysm) to 4 (eyes with localized intra-retinal microvascular abnormalities or venous beading). Defects of the RNFL were found in 6/30 (20%) eyes with level 1 retinopathy, 8/14 (57%) eyes with level 2 retinopathy, 24/47 (51%) eyes with level 3 retinopathy, and 36/46 (78%) eyes with level 4 retinopathy. These findings suggest that the RNFL abnormalities are common in patients with early DR. But in our study, nerve fiber layer defect was present more in NPDR group than PDR group.

RNFLT

In our study inferior RNFLT is thickest and temporal is thinnest in controls and NDR groups. The superior and inferior areas were thicker because of the superior and inferior arcuate bundling of nerve fibers. In our study The average, inferior, superior and nasal RNFLT in the study are 93.92 μm, 119.95 μm, 117.0 μm and 71.87 μm, respectively, and were not significant across the groups (Table 2). The average, nasal and inferior RNFL thicknesses were decreased in NDR group when compared to controls group, but it is not statistically significant.

The average temporal RNFLT in the study is 65.02 μm and it is significant ($P < 0.01$) across the groups (Table 2). Temporal RNFLT was significantly more ($P < 0.01$) in PDR group when compared with the controls group, PDR group versus NDR group and in PDR group versus NPDR group. Temporal RNFLT is increased in PDR group (74.74 ± 21.33) when compared to other groups (Table 4). This is due to associated CSME. The paired comparison of temporal RNFLT in NDM group and CSME group was statistically significant ($P < 0.001$), i.e. temporal RNFLT is increased in CSME group than in NDM group. Similarly, it was statistically significant ($P < 0.001$) between NCSME group and CSME group (Table 8).

Macular Thickness

The average macular thickness is 278.46 μm and it is statistically significant across the groups (Table 2). The paired comparison of macular thickness in controls group and PDR group was statistically significant ($P < 0.001$),

Table 6: BCVA, temporal RNFLT and macular thickness across the Group 1

Parameter	Mean (SD)			F value	Significance (P value)
	NDM*	NCSME†	CSME‡		
BCVA	0.85 (0.20)	0.76 (0.28)	0.45 (0.25)	37.34	<0.001
Temporal RNFLT	61.48 (8.33)	63.32 (15.22)	71.48 (16.16)	7.83	0.001
Macular thickness	267.86 (17.39)	262.61 (30.82)	317.45 (43.63)	53.14	<0.001

*NDM: No diabetes mellitus, †NCSME: No clinically significant macular edema, ‡CSME: Clinically significant macular edema, BCVA: Best corrected visual acuity

i.e. the macular thickness is increased in PDR group compared to NDM group. Similarly, it was statistically significant ($P < 0.001$) between NDR group and NPDR group, NDR group and PDR group (Table 5). The macular thickness is increased in both PDR group (305.96 ± 40.49 μm) and NPDR group (290.24 ± 2.69 μm). The increase in thickness is due to associated CSME. The paired comparison of macular thickness NDM group and CSME group was statistically significant ($P < 0.001$), i.e. the macular thickness is increased in CSME group than in NDM group. Similarly, it was statistically significant ($P < 0.001$) between NCSME group and CSME group (Table 9).

The increase in macular thickness corresponds to increase in temporal RNFLT in PDR group but not in NPDR group. This is again due to increased association of CSME with PDR group.

This result is consistent with the study done by Kim *et al.*,[18] in which RNFLT and ONH in diabetic patients with normal tension were analyzed using OCT. There was an increase in the temporal average thickness of RNFL in the PDR group. Diabetic changes should be considered when diabetes patients are diagnosed with glaucoma or glaucoma

progression. However, in subjects with very early glaucoma or in glaucoma suspects, the discriminating power of OCT might have been decreased because of thicker RNFL measurements affected by increased vascular permeability and changes in blood flow in DR.[19]

Since the association of glaucoma and DM is quite common, this issue should be taken into account while assessing RNFL in diabetic glaucomatous patients. When a decrease in RNFLT is detected in a diabetic glaucoma patient, one should consider the metabolic state of diabetes and the presence of retinopathy which may cause RNFL loss themselves before considering progression of glaucomatous damage in these patients.[20]

Sugimoto *et al.*[21] did a study to detect early diabetic damage in Type 2 DM patients with no DR using OCT and to evaluate OCT as a clinical test. The results of the study state that comparing the normal and NDR eyes, retinal thickness (which involves all the layers of the retina) significantly increased ($P = 0.03$), and RNFLT significantly decreased ($P = 0.02$) in the superior areas. There still remains a contrast with regard to the thickening of the retina that is seen in the macula compared to the thinning that is seen for the RNFL in the surrounding papilla. Because of the macular region has an abundance of Müller cells and it has no vasculature, it is more fragile with regard to diabetic damage than the peripapillary region. They concluded that OCT might be used to detect much earlier signs and structural changes of DR.

The results of our study are consistent with Sa´nchez-Tocino *et al.*,[13] study. They did a study to quantitatively assess retinal thickness by OCT in normal subjects and patients with diabetes. This study was intended to determine which retinal thickness value measured with OCT best discriminates between diabetic eyes, with and without macular edema. In this study, there were statistically significant differences in foveal thickness between control eyes and all the other eye groups ($P < 0.001$). Eyes with NPDR or PDR had a greater macular thickness in all regions than that in normal eyes. However, differences were not statistically significant in any of the areas. There were no significant differences in average thickness in any area between NPDR and PDR without CSME.

Hee *et al.*,[22] have reported similar results, finding differences in central foveal thickness between normal eyes and eyes with DR and no significant differences in average thickness between eyes with NPDR and PDR. Diabetic eyes with CSME had a statistically significant greater thickness in each of the areas compared with the other groups.

Table 7: Between Group 1 comparison of BCVA

Groups	Comparison between the groups	Mean difference	*P* value
NDM	NCSME	8.72	0.15
	CSME	0.40	<0.001
NCSME	CSME	0.32	<0.001

BCVA: Best corrected visual acuity, NCSME: No clinically significant macular edema, CSME: Clinically significant macular edema

Table 8: Between Group 1 comparison of temporal retinal nerve fiber layer thickness

Groups	Comparison between the groups	Mean difference	*P* value
NDM	NCSME	1.83	1.00
	CSME	9.99	0.001
NCSME	CSME	8.16	0.003

NCSME: No clinically significant macular edema, CSME: Clinically significant macular edema

Table 9: Between Group 1 comparison of macular thickness

Groups	Comparison between the groups	Mean difference	*P* value
NDM	NCSME	5.26	1.00
	CSME	49.60	<0.001
NCSME	CSME	54.85	<0.001

NCSME: No clinically significant macular edema, CSME: Clinically significant macular edema

CONCLUSION

DR is associated with a decrease in RNFL thickness though this is not statistically significant in our study. However temporal RNFL shows a significant increase in thickness, which worsens with the stage of DR, this is due to the CSME which is associated with the retinopathy.

As temporal RNFL shows a significant increase in thickness in some stages of DR, an early increase in this thickness could be an indicator of impending CSME. Similarly, while assessing a patient with glaucoma with diabetes, special care must be taken to evaluate the temporal RNFLT independently as this may be increased and should be excluded from analysis, as these values could in reality due to the diabetic changes in the retina and may skew the averages of the RNFLT while evaluating glaucoma.

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