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Comparison of Retinal Nerve Fibre Layer Thickness in Diabetic Patient with and Without Diabetic Retinopathy

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ABSTRACT
Purpose: To evaluate the RNFL thickness in diabetic patients with and without Diabetic retinopathy without macular edema. Study design: A cross sectional, non interventional observation study. A total of 124 subjects were consecutively recruited for the study. Thus, a total of 124 eyes of 124 subjects were included in the analysis and were classified into two groups. The association if any of Retinal nerve fibre layer (RNFL) thickness with diabetic retinopathy and the also the possibility of RNFL thickness changes being a precursor to diabetic retinal changes was evaluated in this study. Peripapillary RNFL thickness was measured using spectral domain OCT Optovue (U.S.A) (software version 11.1;) and reported as an overall mean and by quadrants, Macular scan was performed, to exclude macular edema. On comparison between DM with retinopathy and DM without retinopathy, the global RNFL thickness showed significant difference with mean±SD of 94.15±10.1and 98.5±16.9 respectively with p value of 0.06. The superior quadrant RNFL thickness showed significant difference with mean±SD of 115.19±13.9 and 124.77± 8.1 respectively with p value of 0.001 and the temporal RNFL thickness showed highly significant difference with mean±SD of 66.71±13.52and 71.56±11.85 respectively with p value of 0.14. There was significant reduction in RNFL thickness in especially in superior and temporal quadrant in patients with diabetic retinopathy as compared to diabetic patients without retinopathy.

INTRODUCTION

Diabetes mellitus (DM) has become an epidemic too big to be ignored, with over 80% of patients being concentrated in low and middle income countries. Diabetes mellitus is a leading cause of morbidity in the world as well as in the Indian subcontinent[1]. India has the highest number of diabetes subjects in the world. Diabetes is higher in income states compared to low income states[2]. Diabetic retinopathy is a common micro vascular complication of diabetes and is expected to affect around 10% of diabetic individuals during a five-year period, whereas retinopathy affects virtually all diabetic patients over a 30-year period[5]. Diabetes retinopathy is the leading cause of new incidents of blindness in persons aged 20-74 years. During the first two decades of the illness, virtually all type 1 diabetics and >60% of type 2 diabetics develop retinopathy. In the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR), 3.6% of younger-onset (type 1 diabetes) patients and 1.6 percent of older-onset (type 2 diabetes) patients were legally blind[7].

Depending on various risk factors, diabetics may have varying degrees of diabetic retinopathy. These grades of diabetic retinopathy (ophthalmoscopic findings) are internationally accepted for documentation, evaluation, plan of treatment and prognosis. Where facilities exist, fundus photographs are used for documentation. Studies with scanning laser polarimetry and optical coherence tomography (OCT) demonstrated thinning of the retinal nerve fibre layer in patients with diabetic retinopathy. The association if any of Retinal nerve fibre layer (RNFL) thickness with diabetic retinopathy and the also the possibility of RNFL thickness changes being a precursor to diabetic retinal changes was evaluated in this study.

Aim and objectives: To evaluate the RNFL thickness in diabetic patients with and without Diabetic retinopathy without macular edema.

MATERIALS AND METHODS

This study was a cross sectional, non interventional observation study conducted over a period of 24 months in a tertiary eye care hospital from November 2019 to October 2021. A total of 124 subjects were consecutively recruited for the study. Thus, a total of 124 eyes of 124 subjects were included in the analysis and were classified into two groups. **Group I** consisted of 62 eyes of 62 diabetic patients without any ophthalmological sign of diabetic retinopathy.

Group II consisted of 62 eyes of 62 diabetic patients with ophthalmological sign of diabetic retinopathy. All participants were subjected to detailed history regarding age, duration of diabetes, drugs used for treatment, hypertension, previous ocular surgery. Complete ophthalmological examination was performed along with best corrected visual acuity, Anterior segment was then examined by slit-lamp biomicroscopy along with IOP measurement by goldman applanation tonometer, gonioscopy was done by four mirror gonioprism, after this dilated fundus examination by direct ophthalmoscope, indirect ophthalmoscope and slit lamp bio microscope using+90D lens was done Grading of diabetic retinopathy done according to ETDRS classification. Hba1c levels, Sr cholesterol levels, fasting and postmeal blood sugar levels and OCT imaging using spectral domain OCT Optovue (U.S.A) (software version 11.1).

Peripapillary RNFL thickness was measured and reported as an overall mean and by quadrants, Macular scan was performed, to exclude macular edema.

Inclusion criteria: Patient attending ophthalmology OPD, diagnosed with type 2 diabetes (Diabetes mellitus. In diabetic retinopathy group only Diabetic patients with mild to moderate non proliferative diabetic retinopathy are included and those who are willing to give written informed consent.

Exclusion criteria:

- Diagnosed cases of glaucoma and those with intraocular pressure (IOP) >21 mm Hg in either eye
- Eyes with media opacity in which oct had poor signal strength
- Diabetic patients with severe NPRD and PDR, macular edema and CSME
- History of previous intraocular surgery in the past 6 months
- Diabetics on insulin, uncontroled diabetics or hbA1c values >8%.
- Any type of previous retinal treatment (laser photocoagulation, vitrectomy, intravitreal steroids and /or antiangiogenic drugs)
- H/o consumption of Anti tubercular medication
- H/o steroid consumption, tobacco consumption of any form
- H/o any cardiovascular condition or known hypertensive patients on medication
- High myopic patients
- Ocular diseases like macular degeneration, diabetic papillopathy, retinal vein occlusion, hypertensive retinopathy, anemic retinopathy, uveitis
- Diagnosed cases of Neurodegenerative disease such as Alzheimer's, Parkinson's and dementia
- Associated anterior and posterior segment pathology
- Intolerance to topical anesthetics or mydriatics
- Inability to maintain fixation without movement for the duration of the scan

Sample size: Consecutive sample of 124 subjects(eyes) were selected from the various wards and/or OPD by convenience sampling method.

RESULTS AND DISCUSSIONS

As shown in (Table 1), out of 124 subjects 70 were female and 54 were male, most of the subjects were in the age group of 50-60 years. As shown in (Table 2), 62 subjects were allotted in case (DM with retinopathy) and control (DM without retinopathy) The mean duration of diabetes was 7.67±3.31 years in Diabetic retinopathy group and 5.25±2.64 years in diabetics without retinopathy.

As shown in (Table 4), on comparison between DM with retinopathy and DM without retinopathy, the macular thickness showed no significant difference with mean±SD of 261.55±23.51 and 259.84±28.1 respectively with p value of 0.06. As shown in (Table 5), on comparison between DM with retinopathy and DM without retinopathy, the superior quadrant rnfl thickness showed significance difference with mean±SD of 115.19± 13.9and 124.77±18.1 respectively with p value of 0.001. As shown in (Table 6), on comparison between DM with retinopathy and DM without retinopathy, the temporal RNFL thickness showed highly significant difference with mean ± SD of 66.71±13.52 and 71.56±11.85 respectively with p value of 0.14.

As shown in (Table 7), on comparison between DM with retinopathy and DM without retinopathy, the nasal rnfl thickness showed no significance difference with mean±SD of 77.19±12.09 and 82.61±19.12 respectively with p value of 0.08. As shown in table 8, on comparison between DM with retinopathy and DM without retinopathy, the nasal rnfl thickness showed no significance difference with mean±SD of 127.16± 13.81and 131.11±19.42 respectively with p value of 0.09. As shown in table 9, on comparison between DM with retinopathy and DM without retinopathy, the global rnfl thickness showed significant difference with mean ± SD of 94.15± 10.1and 98.5 ± 16.9 respectively with p value of 0.06.

As shown in (Table 1), Distribution of subjects according to age and group As shown in (Table 2), distribution of subjects according to age and gender.The mean age of the subjects in diabetic without retinopathy group is 50.13 ± 9.82 years and in diabetic with retinopathy group is 54.89 ± 11.47 years. An average reduction of 2.7 micro meter in thickness of global RNFL per 10 years with increase in age is been shown in study by Hougaard Jesper Leth *et al*.[8]. Similarly Nazli Demirkaya *et al*.[9] analysis showed that, in healthy population over a period of 20 years, an individual will lose approximately 2.66 micrometer of peripapillary RNFL, Sohn *et al*.[10], 2016 found that in 45 people with DM and no or minimal clinical DR there was a significant, progressive loss of NFL thickness (0.25 micrometer/year) and GCL+IPL thickness (0.29 micrometer/year) over a 4- year period As in table no 3 Duration of diabetes.

In this study we have included the patients having controlled blood sugar level on oral hypoglycemics alone and patients needed insulin are excluded from study As insulin upregulates and enchances vascular permeability and insulin itself plays an important role in neovascularization or BRB breakdown and may be one of the causes of several complications like macular edema during glycemic control as shown by the study done by Aiello *et al*.[11]. The concept of early worsening of diabetic retinopathy on intensification of glycemic control is been explained by Masahiko sugimoto *et al*.[12] he expressed that on intensification of glycemic control apperence of fresh hard exudates and macular edema appeares. In study by Bain *et al*.[13] eyes with no DR showed a linear correlation between mean HbA1c and mean RNFL thickness.while Oshitari *et al*. 84, showed a weak negative correlation between the two A prospective study conducted by Takis *et al*.[14] over a period of 3 years also confirmed there is progressive thining in rnfl layer with the increase in duration of diabetes.

As we have already excluded the diabetic patients with clinically significant macular edema as well the patient of cystoids macular edema on OCT we have removed patients with abnormal macular thickness from our study on macular scan. There is no significant difference in macular thickness in both the groups. But still there is increase in central macular thickness in diabetic group owing to the fact that an increase in vascular permeability of diabetic retinas and longer duration of DM in the DR group has been implicated as a cause for increasing central macular thickness.

In the NPDR group, macular edema was not apparent clinically or on OCT. However, upon analyzing the OCT scans while processing the images, we observed either a discrete diffuse thickening or small cysts in the OPL or INL layers. These findings led us to the conclusion that the increased macular volume in NPDR may be attributed to incipient macular edema. This could be a reason of increased macular thickness. Ischemia and other factors that might disrupt Müller cell function were implicated as a predisposing factor for the development of cystic macular edema as explained by Neelakshi bhagat *et al*.[15] Thus, because of the abundance of Müller cells, the macular region is more fragile with regard to diabetic damage than the peripapillary region. this correlates with our study showing a increased central macular thickness although not significant The fluctuation in peripappilary RNFL measurement is mainly due to peripappilary retinal edema which is correlated with diabetic macular edema (Hyun seung yang *et al*.[16]). Similarly Hwang *et al*.[17] Showed that the peripappilary RNFL decrease after intravetireal injections in short

Table 1: Distribution of subjects according to age and gender

		Gender		
		Female	Male	Total
Age	40-44	5	4	9
	45-49	7	8	15
	50-54	17	13	30
	55-59	13	17	30
	60-64	15	7	22
	65-70	13	5	14
Total		70	54	124

Table 2: Distribution of subjects according to age and group

		Group		
		with diabetic retinopathy	without diabetic retinopathy	Total
Age	40-44	4	5	9
	45-49	7	8	15
	50-54	15	15	30
	55-59	20	10	30
	60-64	9	13	22
	65 -70	4	10	14
Total		62	62	124

Table 3: distribution according duration of diabetes (in years)

	Duration of diabetes	
Group	Mean	Standard deviation
DM without retinopathy	7.67	3.31
DM with retinopathy	5.25	2.64

Table 4: Comparison of macular thickness between diabetes mellitus with Retinopathy and Diabetes Mellitus without Diabetic retinopathy

	Macular thickness			
Group	Mean	Standard deviation	t value	p-value
DM without retinopathy	259.84	28.1	1.86	0.06
DM with retinopathy	261.55	23.51		

Table 5: Comparison of Superior quadrant peripappillary RNFL thickness between diabetes mellitus with Retinopathy and Diabetes Mellitus without Diabetic retinopathy

	Superior quadrant RNFL thickness			
Group	Mean	Standard deviation	t value	p-value
DM without retinopathy	124.77	18.1	1.7	0.03
DM with retinopathy	118.19	13.9		

Table 6: Comparison of temporal quadrant peripappilary RNFL thickness between diabetes mellitus with Retinopathy and Diabetes Mellitus without Diabetic retinopathy

	Temporal rnfl thickness			
Group	Mean	Standard deviation	t value	p-value
DM without retinopathy	71.56	11.85	1.11	0.14
DM with retinopathy	66.71	13.52		

Table 7: Comparison of nasal rnfl thickness between diabetes mellitus with Retinopathy and Diabetes Mellitus without Diabetic retinopathy

	Nasal rnfl thickness			
Group	Mean	Standard deviation	t value	p-value
DM without retinopathy	82.61	19.12	1.3	0.08
DM with retinopathy	77.19	12.09		

Table 8: Comparison of inferior rnfl thickness between diabetes mellitus with Retinopathy and Diabetes Mellitus without Diabetic retinopathy

	Inferior rnfl thickness			
Group	Mean	Standard deviation	t value	p-value
DM without retinopathy	131.11	19.42	1.25	0.09
DM with retinopathy	127.16	13.81		

term after decrease in retinal edema and corresponding rnfl edema. Demir *et al*.[18] detected no

Table 9: Comparison of global rnfl thickness between diabetes mellitus with Retinopathy and Diabetes Mellitus without Diabetic retinopathy

	Global rnfl thickness			
Group	Mean	Standard deviation	t value	p-value
DM without retinopathy	98.5	16.9	1.6	0.06
DM with retinopathy	94.15	10.1		

statistically significant relationship among central macular thickness, HbA1c and fasting plasma glucose levels in diabetic patients.

As in table no 5 there is no significant difference is noticed in best corrected visual acuity of both the group. (p = 0.25) which correlates with the macular thickness. Otani reported a correlation between retinal thickness and visual acuity in eyes with diabetic macular edema, with or without cystoid macular edema (correlation coefficients r = -0.64 and r = -0.61, respectively). Winfried Goebel conducted a controlled study to quantify macular retinal thickness in diabetic retinopathy using optical coherence tomography (OCT). In their study, lower levels of visual acuity (<20/30 Snellen equivalent) were significantly associated with a marked increase in retinal thickness an overall inverse relation was found but this may be caused because of macular odema.

Demir detected no statistically significant relationship among central macular thickness, HbA1c and fasting plasma glucose levels in diabetic patients As shown in table 6, on comparison between DM with retinopathy and DM without retinopathy, the superior rnfl thickness. The findings of the present study corroborate with an experimental study conducted by Kern and Engerman[19] in two animal models of DR, showing that the early events of diabetic retinal disease (micro aneurysms) were not uniformly distributed across the retina and both lesions were significantly more prevalent in the superior and temporal retina rather than in inferior and nasal areas. Among other studies, an experimental study was conducted by Chung *et al*.[20] to evaluate the blood flow response to hyperoxia and hypercapnia in peripapillary retinal tissue superior and inferior to the optic nerve head using confocal scanning laser Doppler flowmetry. Their results revealed that the superior temporal regions were more responsive to vasoconstriction and less responsive to vasodilatation and thus more prone to develop oxidative damage and nerve cell loss.

As shown in table 7, on comparison between DM with retinopathy and DM without retinopathy, the temporal RNFL thickness, the differences were not statistically significant. This could be due to the dual presence of neurodegeneration that induces thinning and sub OCT and sub clinical macular edema. Oshitari *et al*.[21] OCT findings demonstrated that the macula in the diabetic patients was significantly thinner than that of the healthy age matched controls we did not find significant difference in other than superior quadrant of peripapillary RNFL thickness

between the diabetic groups without DR and with NPDR. This is probably due to the fact that all the patients with diabetes were at a very early stage of DR and in fairly good and comparable metabolic control. It is coherence with the OCT findings of meta analysis study by Xiofen chen *et al*.[22] where he didn't found statistically significant reduction in temporal quadrant while there was reduction in superior, inferior and nasal quadrant, in diabetic patients without clinical diabetic retinopathy. As shown in table 8, on comparison between DM with retinopathy and DM without retinopathy, the nasal rnfl thickness in left eye showed no significance difference with mean±SD of 77.19±12.09and 82.61±19.12 respectively with p value of 0.08.

As shown in table 8, on comparison between DM with retinopathy and DM without retinopathy, the inferior rnfl thickness. Contrary to our study Aleksandra Araszkiewicz *et al*.[23] found significant thinning in inferior quadrant in diabetics with retinopathy and without retinopathy in type 1 diabetic patients. but this could be because of different in the insulin levels in between type 1 and type 2 diabetes. As shown in table 9, on comparison between DM with retinopathy and DM without retinopathy, the global rnfl thickness in right eye showed insignificance difference with mean±SD of 94.15±10.1 and 98.05±16.9 respectively with p value of 0.14. But when compared to the average rnfl thickness in and normal adult. Of age between 40-60 having no other ocular co morbidity as shown by the following studies showed thinning.

CONCLUSION

There was significant reduction in RNFL thickness in especially in superior and temporal quadrant in patients with diabetic retinopathy as compared to diabetic patients without retinopathy.

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