COMPARISON OF RNFL THICKNESS AND VISUAL FIELD CHANGES BETWEEN DIABETIC WITHOUT RETINOPATHY AND NONDIABETIC CONTROLS- A CROSS-SECTIONAL STUDY

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ABSTRACT

BACKGROUND

Diabetes mellitus is one of the major component of metabolic syndrome and a leading cause of ocular morbidity in modern era and India will be considered to be the diabetes capital of the world. Before the onset of diabetic retinopathy, other structural and functional changes may predict the visual diminution of the individual.

MATERIALS AND METHODS

In this cross-sectional study in a tertiary care hospital, after inclusion and exclusion, the age-gender matched groups (diagnosed type 2 diabetes patients without diabetic retinopathy and controls without diabetes) were thoroughly examined clinically and by noninvasive and invasive examination (after proper counselling of the patient and informed consent). Then, they are tested for functional loss of retina by Humphrey FDT, GDx VCC. Comparison done between cases and controls as well as poorly-controlled and well-controlled diabetic groups.

RESULTS

It was found that the average RNFL thickness was significantly reduced in diabetics (mean 53.48, SD 2.69) compared to controls (mean 60.21, SD 1.87) ($p<0.05$). Also, in patients with uncontrolled diabetes (HbA1c >7%), the RNFL thickness was significantly reduced (mean 52.23, SD 1.31) compared to diabetics with good metabolic control (mean 56.38, SD 2.92) ($p<0.05$). In retinal functional testing, it was found that the Humphrey FDT mean deviation (FDT MD) and pattern standard deviation (FDT PSD) were significantly worse in diabetics (FDT MD- 1.478, SD 0.386), (FDT PSD- 3.485, SD 0.403) compared to normal controls (FDT MD- 0.442, SD 0.536), (FDT PSD- 1.438, SD 0.404). The parameters were also found to be significantly worse in uncontrolled diabetics ($p<0.05$).

CONCLUSION

To conclude, without diabetic retinopathy, functional and structural loss in retina in diabetes patients compared to age-sex matched individual and especially in poorly-controlled diabetes should be of concern as there are no detectable vasculopathy. So, early diagnosis and control of diabetes is advocated to control this functional loss.

KEYWORDS

Diabetes, Diabetic Retinopathy, Humphrey FDT, GDx VCC.

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BACKGROUND

Diabetic Retinopathy (DR) is one of the common complications of diabetes mellitus and one of the main causes of blindness in the world.[1] In two studies from South India, the prevalence rates of DR in NIDDM patients were 34.1% and 37%.[2,3] India has 31.7 million diabetic subjects at present as per the World Health Organization (WHO) estimates.[4] This figure is projected to reach 80 million by 2030. In the Andhra Pradesh Eye Disease Study (APEDS) of self-reported diabetics, the prevalence of DR was 22.4%.[5]

Although, all diabetics require ophthalmoscopic examination, there is a need for a test for early detection of retinal functional impairment before signs of retinopathy appear. The increase in oxidative stress that occurs during diabetes is likely to lead to Retinal Ganglion Cell (RGC) apoptosis and glial cell impairment and loss.[6] Results from several studies imply that neuronal dysfunction can occur prior to overt vasculopathy. Morphological changes of retinal nerve tissue have also been reported in patients with diabetes without retinopathy as evidenced by thinning of the retinal nerve fibre layer assessed by means of green filter photographs[7] and scanning laser polarimetry with fixed corneal compensator (GDx NFA).[7,8] Early functional impairment of the magnocellular component of ganglion cells has also been observed using screening test strategies

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of frequency doubling technology perimetry (Humphrey FDT).[9] In this study, we have studied the early functional and structural impairment in the eyes of diabetic subjects without any signs of retinal vasculopathy and compared it with control groups.

Aims and Objectives

To investigate the role of frequency doubling perimetry and GDx VCC in the detection of early functional and structural impairment in the eyes of diabetic subjects without any sign of retinal vasculopathy.

To detect an early reduction of retinal sensitivity in diabetics investigated by Humphrey FDT threshold testing and to investigate the early reduction in peripapillary RNFL thickness measured by GDx VCC and to compare both of them with age-matched individual.

MATERIALS AND METHODS

Study Population- 30 patients with established diagnosis of diabetes and 30 consecutive healthy subjects attending Outpatient's Department of RIO, Kolkata, were considered for the study.

Study Tools- Snellen's chart, slit-lamp (TRC-50X; TOPCON), binocular indirect ophthalmoscope (HEINE OMEGA 500), auto refractometer (Topcon RM-8800), Goldmann applanation tonometer, 78D/90D lens (Volk double aspheric lens), fundus photography (Topcon TRC-NW8), OCT and digital fundus angiography (SPECTRALIS, Heidelberg Engineering, Germany) Humphrey FDT, GDx VCC (Welch Allyn, Inc., Skaneateles Falls, NY; Carl Zeiss Meditec, Dublin, CA).

Study Techniques

Inclusion Criteria- Cases

- Age >30 yrs.
- Established diagnosis of diabetes.
- No evidence of diabetic retinopathy on slit-lamp biomicroscopy, indirect ophthalmoscopy or digital fluorescein angiography. OCT is used to rule out macular oedema.
- Best corrected visual acuity of 20/20.
- Clear media.
- No other ocular pathology.

Controls

- Age >30 yrs.
- Healthy subjects with BCVA of 20/20 and no other ocular pathology.

Exclusion Criteria

- Patients with spherical equivalent >± 6D.
- Patients with active or past retinal pathologies.
- Diagnosis of glaucoma, ocular hypertension (intraocular pressure >22 mmHg).
- Family history of POAG.
- Patients with hazy media.
- Evidence of diabetic retinopathy on slit-lamp biomicroscopy, indirect ophthalmoscopy or digital fluorescein angiography.
- Subjects with symptoms or signs of cardiovascular disease, vasculopathy, nephropathy peripheral and autonomic or motor neuropathy or any other metabolic or endocrine disease.

METHODS

A detailed medical history including duration of diabetes mellitus, any associated medical illness was taken and history of any treatment for diabetes was also taken.

All normal subjects and patients with diabetes mellitus underwent comprehensive ophthalmologic examinations that included best corrected visual acuity, applanation tonometry, slit-lamp examination, dilated funduscopic examination, high-quality fundus colour photography for evaluation of cup and disc size and automated perimetry with the Humphrey field analyser 30-2 SITA standard program. The IOP measurement was repeated on at least three occasions by Goldmann applanation tonometry. The vertical cup disc ratio was graded from the colour fundus photographs.

All subjects who were included had a best corrected visual acuity of 20/20 or better, an IOP of <22 mmHg, spherical equivalent refractive error within ±6.00 Dioptres, both vertical and horizontal cup-to-disk ratios within 0.6 and asymmetry within 0.2 and clear media without clinically relevant cataract. The glycosylated haemoglobin level (HbA1c) was assessed in the diabetic patients. Values between 4% and 6.9% were considered normal and 7% was chosen as the standard cut-off value for defining diabetic subjects with a good glycaemic control.[10]

In all subjects with diabetes mellitus, dilated slit-lamp and fundus examinations and high-quality fundus color photography were performed. In addition, slit-lamp biomicroscopy and fluorescein angiography (using TRC-50X; TOPCON) was performed to rule out diabetic retinopathy.

RNFL Thickness Measurements- The RNFL of all patients was imaged by SLP (GDx access with Variable Corneal Compensator (VCC) mode, software version 5.5.0: Zeiss-Humphrey Systems, Dublin, California, USA), an imaging method that measures the retardation of reflected light caused by the birefringence of the RNFL.

FDT Perimetry- All the patients underwent FDT perimetry with a commercially available instrument (Welch Allyn, Inc., Skaneateles Falls, NY; Carl Zeiss Meditec, Dublin, CA). The Mean Deviation (MD) and Pattern Standard Deviation (PSD) were noted. The right eye was arbitrarily chosen for statistical analysis.

Statistical Analysis- Statistical analyses were performed with the Statistical Package for Social Sciences Software (SPSS version 20). A probability value of $p < 0.05$ was considered statistically significant.

RESULTS AND ANALYSIS

The mean age of diabetic subjects was 59.07 years (±7.076).

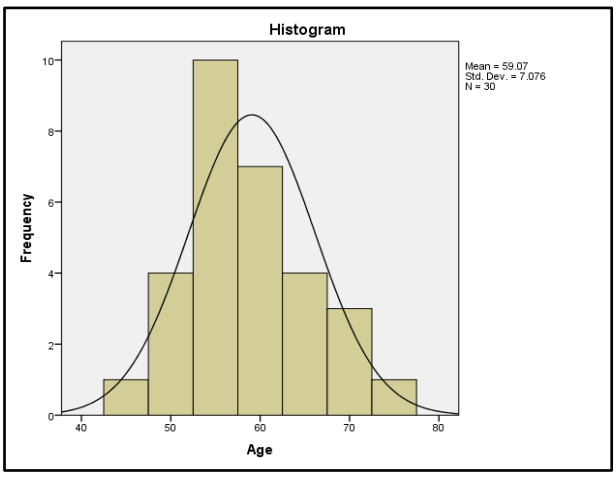

Figure 1. Histogram Showing Age Distribution of Diabetic Subjects

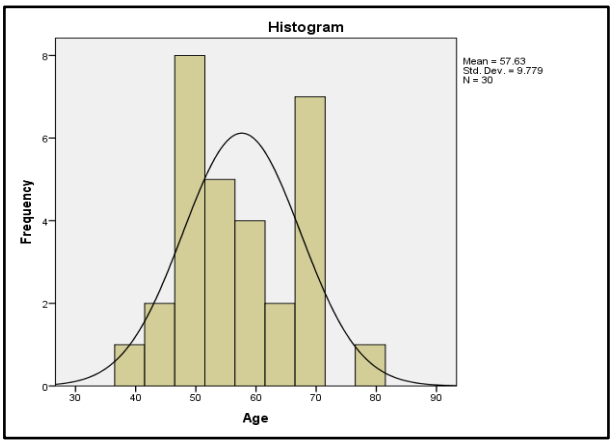

Figure 2. Histogram Showing Age Distribution of Healthy Controls

The mean age of healthy controls was 57.63 years (±9.779).

Group Statistics					
	Group	**N**	**Mean**	**Std. Deviation**	**Sig. (p)**
Age	DM	30	59.07	7.076	0.518
	No DM	30	57.63	9.779	

Table 1. Age Comparison between the Two Groups and Their Distribution (p=0.518)

Gender_Code * DM_Code Cross Tabulation					
		DM_Code		**Total**	**Sig.(p)**
		Diabetic	**Nondiabetic**		
Male	Count	16	17	33	
	% within gender_code	48.5%	51.5%	100.0%	
Female	Count	14	13	27	
	% within gender_code	51.9%	48.1%	100.0%	0.067
Total	**Count**	**30**	**30**	**60**	
	% within gender_code	**50%**	**50%**	**100%**	

Table 2. Gender Comparison between the Two Groups and Their Distribution (p=0.067)

It is evident from the assessment that groups are matched in respect to age and gender. So, both the groups are comparable.

The RNFL superior average, inferior average and the TSNIT average of diabetics was compared with controls. Using unpaired Student's t- test, values were found to be significantly reduced in diabetics.

	Number of Cases and Controls (n)	**RNFL (Savg) (Mean, SD)**	**RNFL Iavg (Mean, SD)**	**RNFL TSNIT (Mean, SD)**
Diabetic	30	61.62 , 3.23	61.58, 2.88	53.48, 2.69
Nondiabetic	30	65.64, 1.75	67.32, 2.21	60.21, 1.87
p value		0.000	0.000	0.000

Table 3. Comparison of RNFL Parameters between Subjects with Diabetes and Controls

	Number of Cases and Controls (n)	**RNFL Savg (Mean, SD)**	**RNFL Iavg (Mean, SD)**	**RNFL TSNIT (Mean, SD)**
HbA1c ≤7%	9	64.19, 3.39	62.71, 4.02	56.38, 2.92
HbA1c >7%	21	60.52, 2.50	61.10, 2.18	52.23, 1.31
p value		0.003	0.165	0.000

Table 4. Comparison of RNFL Parameters Between Subjects with Poorly-Controlled Diabetes and Subjects with Good Metabolic Control

The RNFL values of poorly-controlled diabetics were compared with diabetics with good metabolic control. The RNFL superior average and RNFL TSNIT average were found to be significantly reduced in the uncontrolled diabetic group. The RNFL inferior average was also found to be reduced, but it was not statistically significant.

	Number of Cases and Controls (n)	FDT-MD (Mean, SD)	FDT-PSD (Mean, SD)
Diabetic	30	-1.478, 0.386	3.485, 0.403
Nondiabetic	30	0.442, 0.536	1.438, 0.404
p value		0.000	0.000

Table 5. Comparison of Humphrey FDT Mean Deviation and Pattern Standard Deviation Between Diabetic Subjects and Controls

Functional testing of the retina was done using frequency doubling perimetry using Humphrey FDT (frequency doubling technology). Field defects which we have found were mainly paracentral scotoma, Seidel's scotoma, arcuate scotomas (corroborating with RNFL thinning) with few central scotomas though visual acuity after refraction and with Snellen's chart was 6/6. Vision was not affected in both the groups. Though vision was not compared, still refractive errors were the causes of dimness of vision and it was managed accordingly by refraction. The FDT mean deviation and pattern standard deviation was found to be significantly reduced in diabetics compared to controls.

	Number of Cases (n)	FDT-MD (Mean, SD)	FDT-PSD (Mean, SD)
HbA1c ≤7%	9	-1.06, 0.217	3.018, 0.151
HbA1c >7%	21	-1.657, 0.291	3.685, 0.294
p value		0.000	0.000

Table 6. Comparison of Humphrey FDT Mean Deviation and Pattern Standard Deviation Between Subjects with Poorly-Controlled Diabetes and Subjects with Good Metabolic Control

The FDT mean deviation and pattern standard deviation was found to be significantly reduced in subjects with poorly-controlled diabetes. Retinal sensitivity decreases as the RNFL decreases (varies as retinal sensitivity).

	Number of Cases (n)	RNFL Savg (Mean, SD)	RNFL Iavg (Mean, SD)	RNFL TSNIT (Mean, SD)
DM ≤5 yrs.	8	63.34, 2.42	62.79, 4.24	55.62, 3.89
DM >5 yrs.	22	60.99, 3.31	61.15, 2.17	52.69, 1.61
p value		0.079	0.172	0.006

Table 7. Comparison of RNFL Parameters Between Diabetics with Longer Duration of Disease (>5 yrs.) and Shorter Duration of Disease (<5 yrs.)

The diabetics with longer duration of disease were found to have significantly reduced average TSNIT RNFL irrespective of metabolic control. The superior and inferior average RNFL values were also found to be reduced, however, they were not statistically significant. This could be because RNFL thickness reduces with age and hence with longer duration of diabetes and consequently higher age groups, the RNFL differences tend to be smoothed out.

DISCUSSION

This study was done to find out any early retinal functional impairment associated with a reduction of retinal nerve fibre layer in diabetic subjects without any detectable sign of retinal vasculopathy. The functional and structural impairment of neural tissue may precede and may ultimately induce the earliest morphological and functional alterations of vascular tissue in patients.[6] In early DM without signs of retinopathy, functional and structural alterations of Muller cells with dysfunction and gliosis have been noted. This could explain the early neuronal functional loss and death and the late development of vascular abnormalities.[11]

In this study, diabetic subjects showed a decreased retinal sensitivity compared to nondiabetics as measured using Humphrey FDT (frequency doubling technology). However, the magnitude of difference was very small and hence it may be difficult to translate this into clinical practice.

The results of this study corroborate with a previous study by Parikh et al[9] where they found abnormalities in frequency doubling perimetry in diabetics using a screening strategy. This is also in agreement with a study by Paravanno et al[12] where functional and structural retinal impairment was noted in type 1 diabetics without retinopathy using Humphrey Matrix and scanning laser polarimetry. Other studies also reported significant reduction in contrast to sensitivity as measured by stationary gratings at different spatial frequencies in subjects with DM without any clinical sign of diabetic retinopathy.[13]

The subjects were also examined for retinal structural changes by measuring peripapillary RNFL thickness by GDx VCC (scanning laser polarimetry with variable corneal compensation). The average peripapillary RNFL thickness was found to be significantly thinner in diabetics, although the difference with regard to control subjects was of smaller magnitude.

Previous studies have suggested many potential causes of diabetes-associated RNFL loss. Morphologic studies that use terminal Deoxyuridine Triphosphate (dUTP) nick-end labelling (TUNEL) staining have reported that enhanced apoptosis of neuroglial elements might affect the early onset of diabetes-associated RNFL loss.[14,15,16] The apoptosis-promoting factors like Fas and Bax in retinal ganglion cells are enhanced in the sensory retina of diabetic patients and death of the retinal ganglion cells occurs early in diabetic eyes.[15] Another study demonstrated retrograde axonal transport impairment and reduction in the cross-sectional size of large optic nerve fibers in diabetic rats.[16] Thus, the nerve fibers maybe impaired easily by normal Intraocular Pressure (IOP) in early stage of retinopathy. The nerve fibre

loss in eyes with diabetes mellitus is a common finding, but is not associated with an enlarged cup[17] and thus can be differentiated from RNFL defects in normal tension glaucoma, in which the axons are impaired at the lamina cribrosa with accompanying glaucomatous excavation of the disc.

The effect of metabolic control of diabetes on optic nerve functions and RNFL seems positive. In a study on newly-diagnosed young diabetics, the P100 latency in visual evoked potentials was significantly delayed as compared with the control group, which was seen to be normalised following good metabolic control.[18] On the other hand, there are case reports reporting acute bilateral visual loss caused by diabetic ketoacidosis.[19] This implies that optic neural tissue is vulnerable to haemodynamic and metabolic complications of diabetes.

In the present study, structural parameters measured using GDx VCC were found to be significantly worse in diabetics with poor metabolic control (HbA1c >7%) compared to normal or diabetics with good metabolic control (HbA1c <7%). This finding compares favourably to the results of previous studies by Paravanno et al[12] and Ozdek et al.[20] However, in both the above-mentioned studies, FDT and RNFL abnormalities were found only in poorly-controlled diabetics (HbA1c >7%), a finding which was not replicated in this study.

In this study, it was also observed that in patients with longer duration of diabetes (>5 years) average RNFL thickness was significantly reduced compared to diabetics of shorter duration (<5 years). However, reduction noted in other parameters were not statistically significant.

This study shows that functional and structural retinal testing by frequency doubling perimetry and scanning laser polarimetry could be useful for the identification of early retinal impairment in diabetics without any sign of clinically-detectable retinal vasculopathy.

As RNFL thickness and mean deviation in FDT are the ultrastructural and functional indicator of retina, so we can easily conclude from the study that without microvascular complications of diabetes, statistically significant retinal thinning and functional damage progresses. These maybe due to ischaemia leading to RNFL damage (reflected as reduced RNFL thickness and mean deviation in FDT). Broader diagnostic studies with a larger sample size, a longer followup period and appropriately designed double masking techniques are required to assess their sensitivity and specificity accurately in clinical settings and for screening purposes.

SUMMARY AND CONCLUSION

In this cross-sectional study, 30 eyes of 30 patients (right eye of each patient) with diabetes mellitus with no sign of retinal vasculopathy and 30 eyes of 30 (right eye of each patient) age and gender-matched healthy controls without any history of ocular or systemic disease were enrolled. All normal subjects and patients with diabetes mellitus underwent comprehensive ophthalmologic examinations that included best-corrected visual acuity, applanation tonometry, slit-lamp examination, dilated funduscopic examination, high-quality fundus colour photography for evaluation of cup and disc size and automated perimetry with the Humphrey field analyser 30-2 SITA standard program. The Intraocular Pressure (IOP) measurement was repeated on at least three occasions by Goldmann applanation tonometry. The vertical cup-to-disc ratio was graded from the colour fundus photographs. Slit-lamp biomicroscopy and fluorescein angiography was performed in all subjects with diabetes mellitus to rule out diabetic retinopathic change. Baseline data including blood pressure measurement, HbA1c level were also recorded.

RNFL thickness in the enrolled subjects was measured using scanning laser polarimetry with Variable Corneal Compensation (GDx VCC), while retinal functional testing was done using frequency doubling perimetry (Humphrey FDT).

In our study, we have found that the average RNFL thickness was significantly reduced in diabetic patients compared to age-gender matched controls. In patients with uncontrolled diabetes, the RNFL thickness was significantly reduced compared to diabetics with good metabolic control. From the functional testing, we can conclude that the Humphrey FDT mean deviation and pattern standard deviation were significantly worse in diabetics compared to age-gender matched controls.

Hence, it may be concluded that functional and structural retinal testing by Humphrey FDT and GDx VCC is useful for the identification of early retinal impairment in people with diabetes with no sign of retinal vasculopathy. This can help us to initiate stricter metabolic control and prevent the devastating complications of diabetic retinopathy.

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