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# Study of Retinal Nerve Fibre Layer Thickness in Type 2 Diabetes Mellitus by 3-Dimensional Optical Coherence Tomography from Eastern India

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**ABSTRACT**

Three dimensional optical coherence tomography (OCT) is a novel technique to diagnose retinal disorders. In diabetes, loss of retinal neurons is said to be an early event. We did a small pilot study from Eastern India to find the usefulness of OCT in detecting changes in retinal nerve fibre layer (RNFL) in diabetics. We selected adult type 2 diabetics without overt retinopathy. Patients aged more than 60 or with pre-existing problems like glaucoma or vasculitis were excluded. RNFL thickness was measured using HRA-OCT Spectralis analyser. A 12º area around optic nerve head was analysed and depth of each quadrant was separately measured. The patient values were compared with normative Indian data to detect aberrations. Also, the venous blood sugar levels were measured and correlation studies were done with the retinal thickness values. Standard statistical methods were used. We had 10 diabetic cases (20 eyes) and 11 controls (22 eyes). There was significant thinning of RNFL in 6 (60%) diabetic cases and none of the controls. Two of the diabetics had severe thinning around optic nerve head. 83% of the patients had thinning on temporal side and 50% on nasal side. Mean blood glucose levels were higher in those with RNFL thinning. Both FBS and PPBS showed significant negative correlation with retinal thickness measurements. This is probably the first study of its kind from India. 3-D OCT can be a valuable tool in screening diabetics for complications. However, more studies are needed to better elucidate the role of this novel technology.

## INTRODUCTION

Optical coherence tomography (OCT) is a newer method of determining nerve fibre layer thickness of retina (Jaffe et al, 2004). This method relies on the principal of Michelson interferometry where light reflected from a surface is processed to give an image (Jaffe et al, 2004). This method is reliable and reproducible in measuring retinal nerve fibre layer thickness (RNFLT) in different diseases. It can help in identifying retinal diseases in conditions where other conventional tests are ineffective. It correlates well with other retinal tests like fluoresce in angiography (Jaffe et al, 2004). Three dimensional (3-D) OCT is an improved version of this imaging technique. Here, slightly broader band of light sources are used and axial resolutions are better (Wojtkowski et al, 2005). This imaging modality makes possible the imaging of the topography of retina with minute details and microanatomy of papilla or macula in different layers is also obtained (Wojtkowski et al, 2005). High speed ultrahigh resolution OCT is a novel technique whereby quantitative maps of retina are obtained (figure 1). Diabetes is a disease with rapidly increasing prevalence in India. This multisystem metabolic disorder is associated with multiple complications, one of them being retinal damage. Retinal neural and glial element loss is an important feature of diabetic eye damage, even without overt retinopathic changes (Lopes de Faria et al., 2002).

Retinal nerve fibre layer thickness (RNFLT) measurement is an important way of evaluating neural damage in diabetes and estimating optic nerve health (Skarf, 2002). Changes in NFL are an early estimate of neurovisual damage. RFNLT measurement is a costly and sophisticated imaging technique and thus, not very accessible everywhere. But In India, a large number of diabetic patients develop retinopathy with morbidity and thus, early detection of retinal changes is important.

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This will help in early institution of preventive measures. When ophthalmoscopic changes appear, the damage is already advanced and thus, it is important to pick up neural changes in preclinical stage. For this, OCT can be a very valuable tool. However, studies on OCT findings in diabetic patients are very rare from India.

We therefore undertook this cross sectional study to measure RNFLT in diabetic patients by 3D OCT in a tertiary care setting. We wanted to compare the data of diabetic patients with normal matched controls. This was thus a short pilot study to check whether this new imaging technique is useful in our patients.

## MATERIALS AND METHODS

We selected adulttype 2 diabetic patients coming to the General Medicine outpatient department of a tertiary care medical college in Eastern India between 1st March 2013 and 30 June 2013. Patients were selected by random sampling. The patients who gave voluntary informed consent were included after proper screening. Patients with hypertension, glaucoma, any history of cerebral demyelination, ocular trauma, vasculitis, myopia, congenital ocular disorders or any other neurodegenerative disease were excluded from this study. The healthy controls were chosen from the relatives accompanying the patients, after excluding any dysglycemia. All patients and controls more than 60 years of age were excluded to avoid age related retinal thinning. All patients were examined by direct ophthalmoscopy after pupil dilatation to exclude any retinal or optic nerve pathologies like haemorrhage, exudate or neovascularisation. Anyone with these findings was excluded.

For the diabetic subjects, fasting and post prandial blood sugars (FBS, PPBS) were measured from venous blood by glucose oxidase method in our biochemistry department.

The RNFL thickness was measured using HRA-OCT Spectralis machine manufactured by Heidelberg Engineering, Germany (2011 Model) (Figure 2). It used the Heidelberg Eye Explorer software for analysis. The machine uses infrared rays of wavelength 830 nm and there was no need of artificially dilating the pupils before examination. The OCT lens used has a focus of 30—35 degrees. Each eye testing took on an average three minutes, including time for alignment. As shown in figure 1, high speed images are obtained with a resolution of upto 3 µm. A circular area of diameter 3.6 mm around optic nerve head (12 degrees) is analysed to a depth of 180± 50 µm, auto- adjusted by the analyser. Significant changes in corneal curvature caused change of this diameter; hence anyone found to have aberrant corneal curvature during testing was excluded. The area of analysis extended from internal limiting membrane to basement membrane. However, the depth of only RNFL is measured in this study. Normative Indian data were fed into the database before the study. Thus, the output measurements and diagnosis of thinning were based on this data only. We avoided the macular region because diabetics can also have macular edema which may give false high values.

All data were arranged in Microsoft Excel worksheet. For correlation studies, Pearson Correlation Coefficient (r) was calculated. Discreet data are expressed as number ± percentage. Continuous variables are expressed as mean± S.D. For comparing continuous variables, Mann-Whitney U Test was done. P value <0.05 was considered significant.

## RESULTS

We had ten diabetic patients and 11 normal controls. Initially 28 diabetic patients were selected but a lot of them were apprehensive about damage to the eye during testing and did not give consent. Altogether we tested 20 diabetic eyes and 22 normal eyes. The demographic characteristics are shown in table 1. It is seen that both the groups were matched with respect to baseline demographic variables. None of the patients had any visual problems.

**Table. 1**: Table showing the demographic characteristics of our study population

| Characteristics | | Case | Control |
|---|---|---|---|
| Age (Yrs.) | | 50±9.3 | 43±7.1 |
| Gender | Male | 7 | 8 |
| | Female | 3 | 3 |
| Smoker | | 4 | 6 |
| Residence | Rural | 2 | 1 |
| | Urban | 8 | 10 |

According to the machine readings, based on age and gender criteria, six (60%) of the diabetic subjects had significantly abnormal OCT values around the optic disc. Of them, four (67%) had borderline thinning according to age matched standards and only two had severe thinning. Of the six subjects with significant thinning, two patients had bilateral lesions and other four had unilateral lesions. 83% of the patients (n=5) had thinning on the temporal side and 50% (n=3) had thinning on the nasal side of the disc. None of the patients had superior lesions; however, three patients had minor inferior quadrant lesions. In comparison, none of the subjects in the healthy non diabetic control group had abnormal OCT readings. The absolute values of the readings are depicted in table 2. We did not find any thickening.

The average fasting blood glucose of the subjects with abnormal thinning of retina was 195.8 mg/dl as compared to 165.5 mg/dl in those with normal nerve fibre layer thickness. Similarly for the former group, average post prandial blood glucose (PPBS) was 313.4 mg/dl as compared to 281.5 mg/dl in diabetic subjects with normal thickness of retina. However, in both these cases, the sample size is too small to calculate p value. However, Pearson correlation analysis shows thatfasting blood glucose is negatively correlated with average retinal thickness (r=-0.75, figure 1). For PPBS, the corresponding correlation coefficient is -0.5. Thus, higher the blood glucose values lower the retinal NFL thickness.

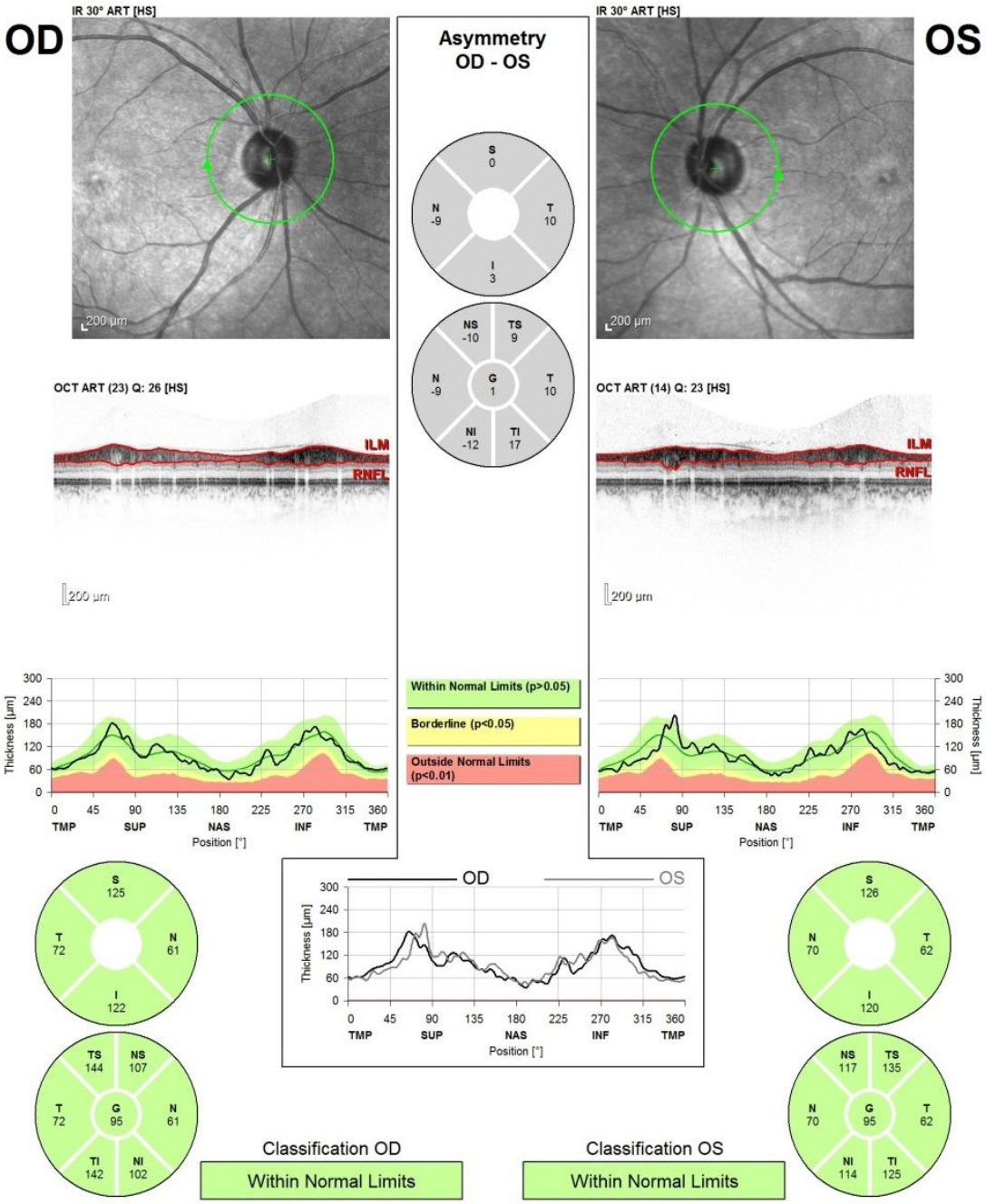


**Fig. 1:** Sample data sheet from the 3D OCT machine, RNFL measured around optic nerve head. A 3.6 mm diameter circular area around the optic nerve head (papilla) is measured (green circle). The output data sheet gives the thickness of each quadrant and also the comparison with normative standards (colour codes: green, yellow, and red) [ILM: internal limiting membrane; RNFL: retinal nerve fibre layer].

**Table. 2**: Table showing the OCT readings (in µm)in four quadrants in case and control eyes [R: right; L: left];*- denotes the abnormal values.

| Case number | Cases | | | | Controls | | | |
|---|---|---|---|---|---|---|---|---|
| | **Superior** | **inferior** | **Temporal** | **nasal** | **Superior** | **inferior** | **Temporal** | **Nasal** |
| 1. | R102 L164 | R126 L118 | R51* L83 | R97 L90 | R131 L141 | R147 L151 | R74 L63 | R78 L78 |
| 2. | R149 L122 | R106 L106 | R50* L92 | R69 L45* | R162 L139 | R145 L142 | R72 L63 | R80 L79 |
| 3. | R117 L102 | R118 L119 | R56 L74 | R55 L40* | R125 L126 | R122 L120 | R72 L62 | R61 L70 |
| 4. | R131 L145 | R128 L121 | R55 L76 | R104 L67 | R120 L124 | R105 L103 | R80 L69 | R50 L59 |
| 5. | R152 L132 | R120 L134 | R51* L85 | R76 L47* | R128 L120 | R119 L120 | R70 L73 | R82 L84 |
| 6. | R115 L139 | R137 L118 | R57 L73 | R103 L57 | R118 L106 | R141 L122 | R66 L80 | R95 L57 |
| 7. | R137 L118 | R137 L137 | R54* L81 | R100 L57 | R162 L139 | R145 L142 | R72 L63 | R80 L79 |
| 8. | R218 L108 | R86* L110 | R31* L62 | R169 L77 | R147 L152 | R146 L180 | R89 L75 | R81 L88 |
| 9. | R162 L156 | R134 L135 | R147 L99 | R107 L60 | R131 L141 | R147 L151 | R74 L63 | R78 L78 |
| 10. | R152 L173 | R163 L142 | R76 L114 | R130 L79 | R115 L115 | R115 L115 | R65 L60 | R61 L64 |
| 11. | n.a. | | | | R138 L140 | R148 L153 | R60 L70 | R77 L63 |

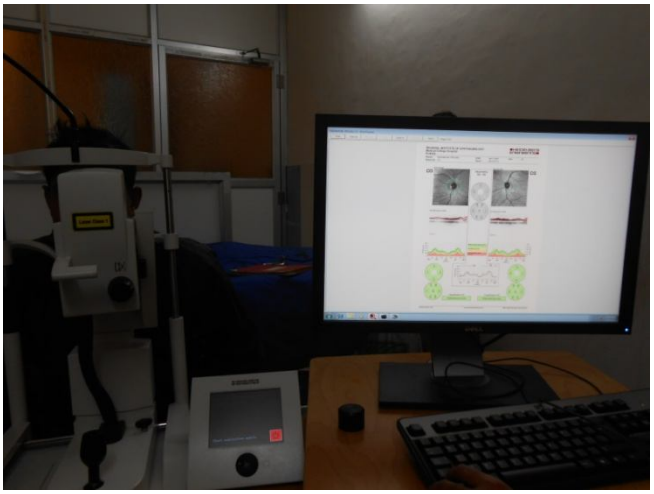

**Fig. 2:** The 3D OCT machine.

## DISCUSSION

In our small study, we found that 60% of the type 2 diabetic subjects had some degree of RNFL thinning. In a similar study from Amsterdam in 2007, significant levels of retinal thinning were documented in type 1 diabetics (Biallosterski et al., 2007). In that study, the authors used 2D stratus OCT around the fovea. We have used 3D OCT around the optic nerve head. In diabetes, early thinning of retina is an important comorbidity. It occurs due to neuroglial loss. Some authors opine that diabetes causes neural tissue apoptosis and thinning of retinal NFL is a manifestation of this neuro degeneration(Biallosterski et al., 2007). OCT is a useful tool in ophthalmologic examination in diabetes. Besides RNFLT, it can also detect incipient macular pathologies like macular edema (Goebel et al., 2006). The test is non-invasive and reproducible and thus can help in follow up of these patients. There is another method of measuring retinal thickness with retinal thickness analyser (RTA); but the OCT gives more reliable readings and is easier to us (Goebel et al., 2006).

In our study, we found that higher blood glucose levels were associated with thinner retina in OCT. Also, the fasting and post prandial glucose values were inversely correlated significantly with retinal thickness. In a 2003 study, similar observations were made(Loneville et al., 2003). Poor metabolic control was associated with lower average retinal thickness values. Also, the duration of diabetes has effect on retinal thickness (vanDijk et al., 2010). A 2010 study by vanDijk et al found that longer duration of diabetes was associated with thinner retinal layers. This change starts long before the vascular changes are visible. Although visual disturbances may be minimal, sensitive tests like electroretinogram, microperimetry or contrast sensitivity assay can detect the functional consequences of retinal nerve cell loss very early in the course. We could not do these tests due to logistic problems. Chronic hyperglycemia affects the central nervous system and similar to retinal NFL loss, neurons can also be lost from the brain, giving rise to cognitive dysfunctions.

Among our patients with RNFL thinning, most had temporal quadrant lesions. This is in accordance with other observations, where early diabetic temporal disease was preferentially found in superior temporal quadrant (Nor-Sharina et al., 2013). The exact reason for this is not known. However, some scientists are of the view that some parts of the retina lack the normal vasoconstrictor response to adverse stimuli like hypoxia (Kern and Engerman, 1995). Thus, these are more prone to develop oxidative damage and nerve cell loss. Although inferior quadrant is said to be the least affected in early retinopathy, we found one patient with significant inferior thinning (table 2).

In a study from Malaysia, the authors have found significantly increased retinal thickness in severe non proliferative retinopathy(Nor-Sharina et al., 2013). This may be due to the exudates and intraretinal edema. However, we excluded all cases with retinal exudate or haemorrhages. In this same study, the authors also showed a significant correlation of RNFLT with some blood lipid parameters(Nor-Sharina et al., 2013). Lipid molecules are said to be an important factor in pathogenesis of diabetic microvascular complications. Thus, there may be significant complications even if blood glucose is fairly controlled. More studies are needed to define the role of parameters other than blood glucose in diabetic retinopathy.

Studies concerning RNFL thickness in diabetes are very rare from Asia. One landmark study from Japan found significant RNFL thinning in diabetics (Oshitari et al., 2009). In that study, they also found significant differences of RNFL thickness according to gender. However, once proliferative changes developed, there was macular thickening (Oshitari et al., 2009). In another prospective study from Korea, the authors found significant peripapillary thickening in retina, correlating with the severity of diabetic retinopathy (Cho et al, 2010). However, our study was with patients in early stage of retinopathy or no overt retinopathy. Further studies are needed to find the changes in RNFL with time. Extensive literature search could not reveal any Indian study on RNFLT in diabetes. Our small pilot study is probably the first one of its kind from this country.

Our study is limited by small number of subjects, lack of HbA1C measurement and a prospective study would be better at characterising the retinal changes in diabetes. However this study shows the usefulness of OCT in detecting retinal pathology in the preclinical stage. Also, simple blood glucose measurement can predict retinal pathology in diabetes without the need for more sophisticated blood parameters. Although the initial cost of setting up the machine is very high by Indian standards, subsequently the cost decreases as more and more cases are analysed. This process is non-invasive, painless, needs no preparation and is also very quick. Thus, if proper infrastructure is there, it can be a very useful method of screening and follow up of patients with diabetes and a host of other disorders.

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