Research Article

Relation of retinal nerve fiber layer thickness with blood glycemic parameters in diabetic subjects: a study from Eastern India

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Abstract

Background: Diabetes affects the retina in various ways. The microvascular changes may be detected clinically by direct ophthalmoscopy. But the early neurodegenerative retinal changes are not clinically detectable. Optical coherence tomography (OCT) is a quick, reproducible, and noninvasive method of detecting retinal nerve fiber layer thickness (RNFLT). Changes in this thickness correlate with neurodegenerative retinal changes.

Objectives: This study aims to generate data on RNFLT in diabetes in an Indian population. It aims to study any correlation of RNFLT with blood glucose parameters.

Materials and Methods: This was a cross-sectional study on adult diabetic patients in a tertiary care medical college. RNFLT was measured by OCT in a circular area of diameter 3.6 mm around the optic nerve head. Pearson correlation study was done between the retinal thickness and blood glucose parameters: fasting (FBS) and postprandial glucose (PPBS) levels and glycated hemoglobin (HbA1C).

Results: We had a total of 250 patients, which means 500 eyes. Average age of the participants was 51.6 ± 8.1 years. Out of 500 eyes, retinal thickness was low in 10.6% (95% C.I. 7.9%–13.3%). The average HbA1C level in those with low RNFLT was significantly higher than others ($p < 0.001$). Average RNFLT around optic nerve head was significantly correlated with blood glucose parameters. For FBS, correlation coefficient (r) was -0.5, for PPBS, it was –0.46, and for HbA1C it was –0.58.

Conclusion: The RNFLT showed significant negative correlation with blood glucose parameters. Especially for HbA1C, this correlation was high in all quadrants around optic nerve head. Further studies will be needed to elucidate the relation of other blood parameters such as cholesterol with retinal thickness in diabetes.

KEY WORDS: Diabetes, HbA1C, retinal nerve fiber layer, optical coherence tomography

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Introduction

Ocular involvement is very common in diabetes and leads to significant morbidity.[1] The commonest is retinopathy. Various grades of diabetic retinopathy affect vision. Along with retinal involvement, eyelids, cornea, lens, and optic nerve are also affected in diabetes.[1]

Retinal nerve fiber layer (RNFL) is an important layer in the retina formed by continuation of the optic nerve and changes

in its thickness correlate directly with structural changes in the retina. Retinal nerve fiber layer thickness (RNFLT) is therefore, thought to be an important parameter for depicting retinal damage.[2] This thickness is affected in various ocular and systemic disorders. Changes in RNFLT occur much before overt clinical signs of retinopathy appear. More importantly, RNFLT is found to correlate with optic nerve involvement and visual acuity.[3] Hence, measurement of RNFLT is not only a descriptive entity, but also has potential as a predictive parameter.[4]

Traditionally, physicians have used ophthalmologic examination for various signs of retinopathy to detect diabetic affection of the retina. However, by the time clinical changes of retinopathy appear, the damage is already advanced and often irreversible. The visible changes of diabetic retinopathy are mostly of microvascular origin.[5] Neurodegenerative changes are difficult to detect clinically. But studies have shown that neurodegenerative changes in retina precede microvascular changes.[5] RNFLT measurement can detect this neurodegenerative change at an early stage.

Three-dimensional (3-D) optical coherence tomography (OCT) is a quick and noninvasive method of measurement of RNFLT. The modern machines are accurate with easy handling, high reproducibility, and low inter-observer variation.[2] Hence, measurement of RNFLT is now no longer a sophisticated research technique but a simple clinical procedure.

In India, various studies have documented an ominous increasing trend in the prevalence of diabetes.[6] A large part of this patient group is of relatively young adult age group. Hence, retinopathy and the consequent visual impairment will have a significant impact on their lives and economic productivity. Thus, from a public health point of view, early detection of diabetic retinal changes and institution of suitable treatment is an important aspect of holistic diabetes management. Measurement of RNFLT by 3-D OCT is a feasible and acceptable way of detecting these changes at an early stage.

However, there are very few studies on RNFLT by OCT in Indian diabetic population. A recent small pilot study from Eastern India showed significant RNFL thinning in diabetics compared to controls.[7] But still there is a large gap in the literature in this aspect. This study aims to fill this gap and examines the relation between RNFLT and blood glycemic parameters in a sample Indian diabetic population.

Materials and Methods

This cross-sectional study was done in a tertiary care medical college of Eastern India. The study was done over a period of one and half years from May 2014 to September 2015. Adult diabetic patients (both type 1 and type 2) coming to the general medicine department were chosen for the study. Thus, this was a purposive sampling technique. The institutional ethical committee gave full permission.

The patients were at first clinically examined for any overt retinopathy. Those with overt retinopathy, cataract, or any opacity in the cornea or vitreous were excluded. Also, patients with any local ocular disease such as glaucoma, lenticonus, or retinitis or anyone with demyelinating conditions such as multiple sclerosis were excluded. After exclusion of all these cases, the remaining diabetic patients were provisionally recruited.

The patients were at first explained about the procedure in local language and proper informed consent was obtained. The ongoing treatment for diabetes was not changed or withheld. The blood parameters for glycemic status (fasting blood glucose [FBS], post prandial blood glucose [PPBS] and glycosylated hemoglobin [HbA1C]) were done at the central biochemical laboratory of the hospital. All analyses were done in the same machine using kits from the same manufacturer. RNFLT was measured by HRA-OCT Spectralis machine (Heidelberg Engineering, Germany 2011). The testing was done in undilated eyes and average time for testing each eye was 3 min. A circular area of diameter 3.6 mm around the optic nerve head was measured for retinal thickness with infrared rays of wavelength 830 nm and resolution of 3 μm. All readings were taken by the same operator. Each reading was an average of three consecutive readings. If any image was found to be distorted, it was rejected and a new set of readings was taken.

Output data from the machine were both qualitative and quantitative. Actual RNFLT (in microns) in the four quadrants (temporal, nasal, superior, and inferior) of the circle was given, along with a color-coded grading of each quadrant based on the normative Indian data for age and sex. Thus, each quadrant of the circular area around the optic nerve head was given a color code (green, normal; yellow, borderline; red, thin). This grading was given by the Heidelberg eye explorer software® inbuilt in the machine.

The data were entered in Microsoft Excel worksheet and later transferred to SPSS version 19. Age of the patients was recorded as whole numbers and not fractions. Thus, age was recorded according to the nearest birthday. Continuous variables are expressed as mean ± S.D. and discrete variables are expressed as number/percentage. Pearson correlation coefficient (r) was used to find the relation between continuous variables. Ninety-five percent confidence interval was calculated for the coefficients. A p value <0.05 was considered statistically significant.

Results

In this study, we had a total of 250 patients, that is, 500 eyes. The male:female ratio was 123:127. The age range was 34–74 years with average of 51.6 ± 8.1 years. Table 1 shows the total number and also the gender distribution in different age groups. It is seen that the maximum number of patients (44%) was in the age group of 41–50 years.

Fasting blood glucose (FBS) varied from 79 to 267 mg/dL with an average of 101.6 ± 26.3 mg/dL. Postprandial blood glucose (PPBS) varied from 87 to 384 mg/dL with an average of 149.5 ± 36.1 mg/dL. HbA1c levels of the patients are shown in Figure 1. As seen in the figure, the majority (74%) of the

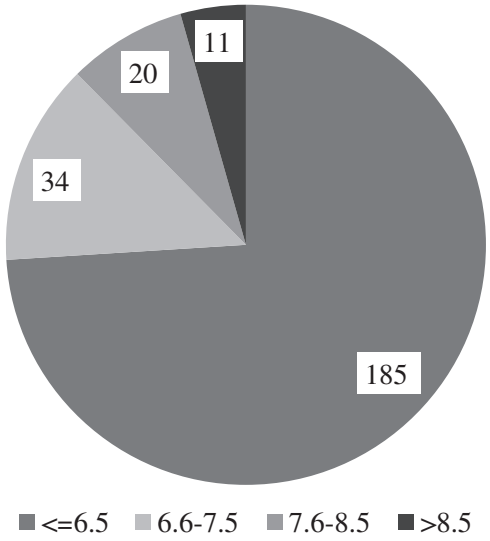

Figure 1: Pie chart showing HbA1C distributions in the subjects.

patients had HbA1C level below or equal to 6.5% (good control of blood sugar).

As the reading from the OCT apparatus showed, out of the 500 eyes examined, average thickness was low in 53 eyes (10.6%; 95% C.I. 7.9%–13.3%). Thickness was borderline in 117 eyes (23.4%; 95% C.I.: 19.7%–27.1%). The rest was normal. The average HbA1C in persons with low RNFLT (7.4 ± 0.65%) was significantly higher than those with normal RNFLT (6.3 ± 0.17%); *p* value was found to be <0.001 by Student's t test.

Table 1: Age and gender distribution of study subjects

Age group (years)	Gender		Total
	Male	Female	
≤40	3	8	11
41–50	50	60	110
51–60	48	39	87
61–70	20	18	38
>70	2	2	4
Total	123	127	250

Pearson correlation coefficient analysis showed that average RNFLT had significant correlation with FBS, PPBS, and HbA1C. Correlation coefficients for average RNFLT was –0.5 (95% C.I. –0.43 to –0.56; $p < 0.001$) for FBS, –0.46 (95% C.I. –0.39 to –0.52; $p < 0.001$) for PPBS, and –0.58 (95% C.I. –0.52 to –0.63; $p < 0.001$) for HbA1C. Thus, with increasing blood glucose parameter values, the RNFLT showed a statistically significant decrease. The HbA1C values also showed significant negative correlation with RNFLT in each quadrant separately (Figure 2).

Discussion

This cross-sectional study shows that a large number of diabetic patients had thinned out RNFL, and the blood

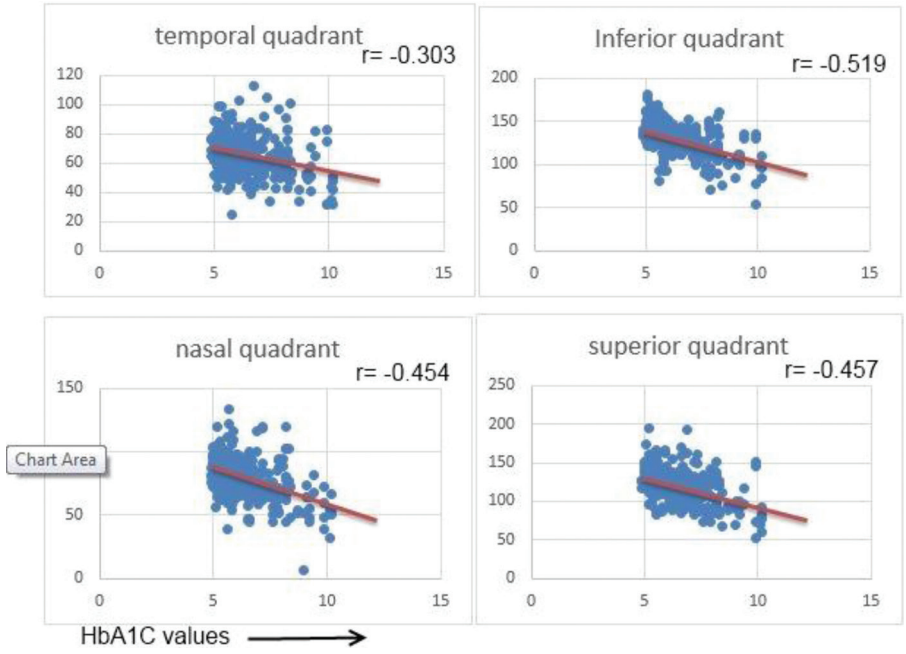

Figure 2 : X–Y scatter diagram of HbA1C with RNFLT (in microns; Y axis) in each quadrant with trend line.

glucose parameters had significant negative correlation with RNFLT.

RNFL thinning is a common finding in diabetes. It has been earlier documented in both type 1 and type 2 diabetes in Europe and the United States.[8,9] A recent pilot study by the present authors from India also showed thinning of RNFLT in type 2 diabetes compared with controls.[7] In this study also, 34% of the diabetic subjects had some degree of RNFL thinning. A recent meta-analysis has documented significant thinning of peripapillary RNFL in diabetics (both type 1 and type 2), measured by both OCT and scanning laser polarimeter—based studies.[10] In a recent study from Amsterdam, the duration of diabetes was the most important predicting factor in diagnosing retinal thinning.[11]

The retinal thinning, as measured by RNFLT, is not uniform. The aforementioned meta-analysis shows that superior, inferior, and nasal quadrants are more affected by thinning compared to the temporal areas. Another study from China also documented thinning of the superior quadrant RNFL in diabetics.[12] However, in this study, thinning of all quadrants was documented.

The pathophysiology behind RNFL thinning is multifactorial. The exact mechanism is still debated. But probable theories include ganglion cell dysfunction and apoptosis.[13] Chronic hyperglycemia is also said to affect neurons.[11] Chronic hyperglycemia activates a lot of metabolic pathways that ultimately lead to activation of nuclear factor kappa B.[14] This leads to oxidative stress in the retina and damage to neuronal tissue. Metabolites of the renin–angiotensin system, especially angiotensin II, activates AT1R receptor in retina and leads to the formation of reactive oxygen species. This also damages the RNFL.[15] Dysregulation of neurotrophic factor such as BDNF (brain-derived neurotrophic factor) is also a contributory factor in diabetic retinal neurodegeneration.[16] Reduced levels of BDNF affects cell growth and differentiation in retina. Thus, there are multiple pathways leading to neurodegeneration and hence thinning of RNFL in diabetes.

In our study, significant negative correlation was found between RNFLT and blood glucose parameters, especially HbA1C. A study from China showed a weak correlation between RNFLT and FBS in diabetes.[12] However, the study from Amsterdam did not find any correlation between HbA1C and ganglion cell layer thickness.[11] In another study, negative correlation was found between superior, inferior, and average RNFLT and HbA1C levels.[17] The other parameters correlated with RNFLT in that study were uric acid levels, carotid intima-media thickness, and presence of carotid plaque. In our study, although HbA1C levels showed negative correlation with RNFLT in all quadrants, the correlation was the strongest for superior and inferior quadrants and weakest for the temporal side (Figure 2).

However, control of blood glucose does not always lead to reversal of the changes. As a study from Japan showed, even after glycemic control, the RNFLT continued to decrease in diabetics.[18] In other words, the neurodegenerative changes are mostly irreversible. Thus, early initiation of blood glucose control is the key to retard the progression of neurodegeneration.

Also, studies have shown that there are some associated factors besides blood glucose affecting the retinal thickness in diabetes. One example is blood pressure.[19]. Other potential confounding variables are level of oxidized low-density lipoprotein and vitamin D levels.[2,20] Hence, management of associated metabolic conditions such as hypertension is also essential.

The study is limited by lack of measurement of other parameters besides blood glucose. Also, a prospective study is better to document the change in RNFLT over time with change in other variables.

Conclusion

The RNFLT, as measured by OCT, is significantly decreased in diabetes and this thinning correlates with blood glucose parameters. OCT may be a viable technique to detect early neurodegenerative changes in the retina in a resource-limited setting.

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