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Original Article

Structural analysis of the choroid and the optic nerve in diabetes mellitus

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Abstract

Aim: The aim of this study was to determine the choroidal and peri-optic nerve head retinal nerve fiber layer (RNFL) changes in diabetes mellitus (DM) patients without retinopathy.

Material and Methods: Four groups of 70 eyes were defined: control group (healthy subjects); group 1 - DM patients with glycated hemoglobin (HbA1c) level of 6.5–7.9%; group 2 (DM patients, HbA1c 8–9.5%); and group 3 (DM patients, HbA1c > 9.5%). Optical coherence tomography measurements of choroidal thickness (CT) and RNFL changes and were compared within groups.

Results: CT was thinner in diabetic groups compared with control, but this decrease was not directly proportional to the HbA1c increase. CT loss in the subfovea was only seen in group 1. In temporal quadrant, all diabetic groups had RNFL loss compared with control, with no difference between them. RNFL in groups 2 and 3 had significant loss in the inferior temporal area compared with the control group, whereas in the inferior nasal quadrant, only group 3 had significant loss.

Conclusion: CT changes were consistently seen in the lower HbA1c group compared with healthy subjects. This could be the result of the combined effect of low blood flow - which leads to CT decrease- that is then rivaled by the choroidal thickening due to increased vessel rigidity that is observed because of diabetic inflammation and high glycation end-product accumulation. RNFL was affected in temporal quadrants regardless to glycemic control. However, inferior RNFL damage was correlated with higher HbA1c levels, showing that optic nerve changes differ by diabetic control.

Keywords: Choroid; diabetes mellitus; glycated hemoglobin; OCT; optic nerve; RNFL

INTRODUCTION

Diabetes mellitus (DM) is a common disease with major complications, one of which is diabetic retinopathy. An increase in glycation end-product accumulation and inflammatory cytokine and adhesion factors results in retinal ischemia, which is thought to be the pathogenesis of ocular disease (1,2). Choroidal circulation pathologies observed in DM also play a role in the pathogenesis, such as choriocapillaris obstruction, increased tortuosity, and narrowing of the choroidal vessels (3). In addition to choroid and retinal damage, human histological and immunohistochemical studies showed loss of retinal ganglion cells (4). Retinal neurodegeneration has been shown as the earliest pathology of diabetic due to early microvascular changes – like breakdown of the blood–retinal barrier- and impairments in neurovascular interactions, one of which is the thinning of peri-optic nerve head retinal nerve fiber layer (RNFL) (5,6). In type 1 DM studies, glucose fluctuations were shown to be related to RNFL loss (7). In type 2 DM patients, diminished RNFL were demonstrated to be one of the early signs of ocular diabetic damage (8).

Glycated hemoglobin (HbA1c) is used to monitor antihyperglycemic therapy. The HbA1c amount in the red blood cells is directly related to the amount of plasma glucose because it is glycated in a non-enzymatic reaction and it has the advantage of having less variability during acute illness (9). Lower HbA1c levels were found to be associated with the magnitude of vision improvement following treatment (10). Even in good glycemic control with low HbA1c levels, capillary dropouts were seen in healthy looking retinas (11).

Optical coherence tomography (OCT) is a non-invasive, non-contact technique that applies the principle of interferometry to determine the interface between different ocular tissues and by using automated segmentation algorithms based on reflectivity changes between adjacent retinal layers. As a result, the retina, choroid and RNFL thicknesses can be calculated (12,13). It has since

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become indispensable as a tool to RNFL thickness and diabetic retina follow ups.

The choroidal thickness (CT) and the RNFL changes of DM patients were evaluated in several studies using OCT with conflicting results (14,15). The aim of this study was to evaluate the effect of HbA1c on CT and RNFL in treatment-naïve eyes of diabetic subjects.

MATERIAL and METHODS

The study received approval from the study received approval Hitit University ethics committee (approval number: 2019-005, approval date: 05/01/2019) and adhered to the principles of the Declaration of Helsinki. Records and imagings of patients with for more than five years of DM who were sent by the Endocrinology Department for routine ophthalmological examination and normal subjects were studied retrospectively.

The right eyes of 280 subjects, comprising of 135 males and 145 females (mean age, 57.17 ± 7.9 years), without diabetic retinopathy or any other ocular pathologies were included in the study. Electronic blood test results were used to check for lipid profiles, liver and kidney function tests. Patients with abnormal results were not enrolled into the study. Patients had no other systemic diseases such as systemic hypertension and obesity. DM patients had measurements of serum glycosylated hemoglobin (HbA1c) level. Subjects with refractive errors greater than ±3 diopters, significant media opacities, intraocular pressure above 21 mmHg or glaucoma, uveitis, or retinal disease were excluded from the study. The control group included healthy subjects without ocular or systemic disease.

Four groups of 70 eyes were defined: a control group consisting of healthy subjects; group 1 (DM patients with HbA1c 6.5–7.9%); group 2 (DM patients with HbA1c 8–9.5%); and group 3 (DM patients with HbA1c > 9.5%). All patients had ophthalmological examination, RNFL and choroid imaging using Spectralis SD-OCT (Heidelberg Engineering, Heidelberg, Germany) records. Only good quality scans without overt misalignment, missing or blank areas, or artefacts with signal strength greater than 20 were used.

OCT software generated topographical macula, which is composed of nine sectorial thickness measurements in three concentric circles with diameters of 1, 3 and 6 mm - as defined by the Early Treatment of Diabetic Retinopathy Study (ETDRS) - were taken for retinal thickness measurements (16). RNFL measurements were given by automatic calculation in 7 quadrants (Figure 1).

Choroidal thickness was considered to be the distance between the retinal pigmented epithelium (RPE) outer border and the scleral interface. CT measurements were obtained manually at seven positions by a blinded technician as follows: subfoveal measurement, including three nasal and three temporal measurements to the fovea taken at 500-µm intervals.

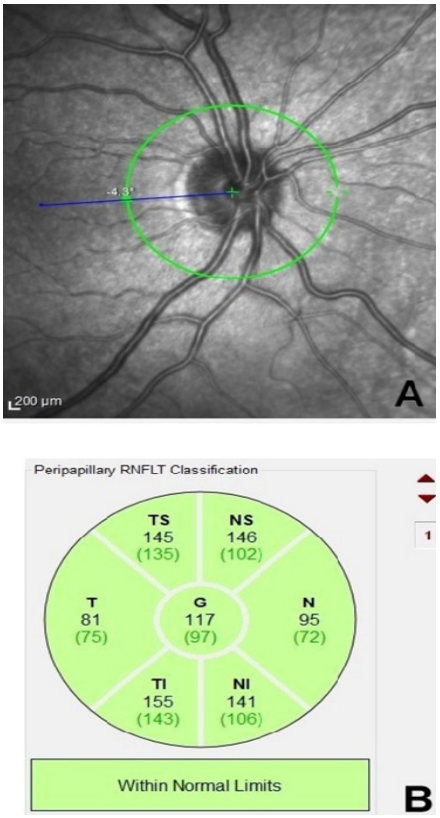

Figure 1. A) Optical coherence tomography image of the optic nerve head. B) 7 quadrants of the peri-optic nerve retinal nerve fiber layer, calculated automatically

A sample size calculation estimated that 64 eyes would be necessary for a type 1 error rate of 0.05 and a power of 80% to detect a mean difference of 30 microns, with a mean choroidal thickness 331.13±45 µm (calculated using GPower 3.1). Analysis of variance (ANOVA) (Tukey's post-hoc test for subgroups) was performed using Statistical Package for the Social Science (IBM SPSS Statistics for Windows, Version 24.0). A value of $P < 0.05$ was considered statistically significant.

RESULTS

There were no statistically significant differences in age or gender between the groups. Descriptive statistics are shown in Table 1.

Table 1. Mean age and gender distrubition between groups

Groups	Mean Age (years)	Gender (Female/Male)	Number of eyes
Control group	57.21±6.2	38/32	70
Group 1: HbA1c 6,5-7,9	55.89±6.9	35/35	70
Group 2: HbA1c 8-9,5	56.17±9.1	36/34	70
Group 3: HbA1c > 9,5	59.41±8.6	36/34	70
Total	57.17±7.9	145/135	280

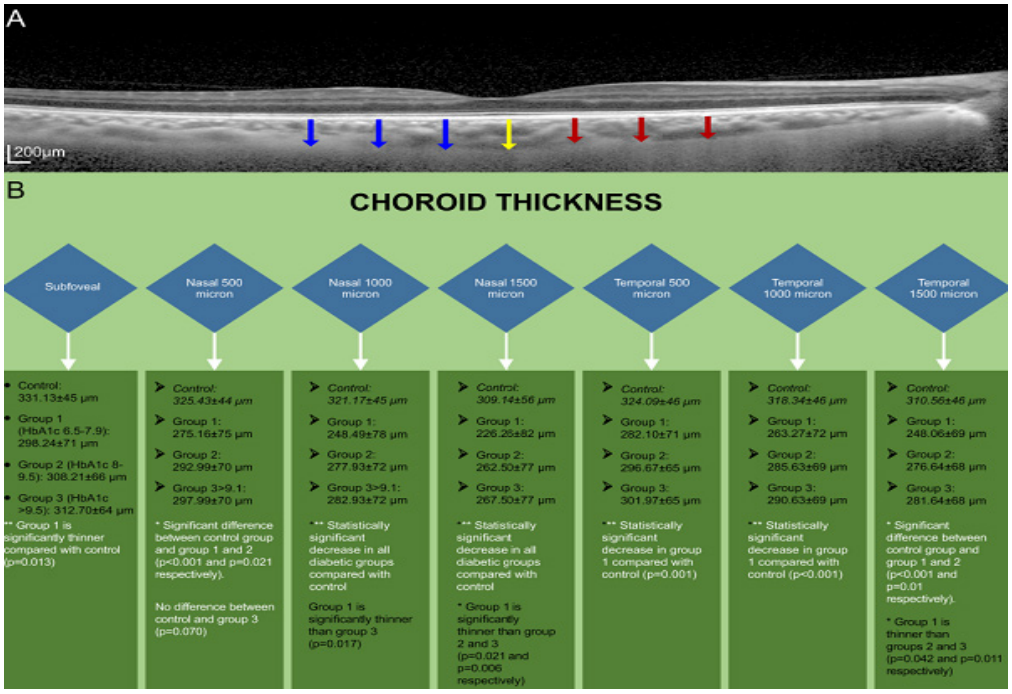

Figure 2. A) Choroidal thickness shown with Optical Coherence Tomography. Yellow arrow is subfoveal choroid. Red arrows are the nasal, and blue arrows are temporal choroid shown in 500 micron intevals. B) Mean choroidal thickness and inter-group comparison results

CT showed thinner results in diabetic groups compared with the control, but this decrease was not directly proportional to the HbA1c increase. Group 1 showed significantly thinner on CT measurement levels compared to the other groups. Group 3 showed no difference from the control 500-micron areas. Results are shown in Figure 2.

In temporal quadrant, RNFL loss was seen in all diabetic patients, without any statistical difference between diabetic subgroups. Groups 2 and 3 had RNFL loss compared with the control group in the inferior temporal area. And at the inferior quadrant, RNFL loss was seen in the highest HbA1c group, group 3. Results and p values are shown in Figure 3.

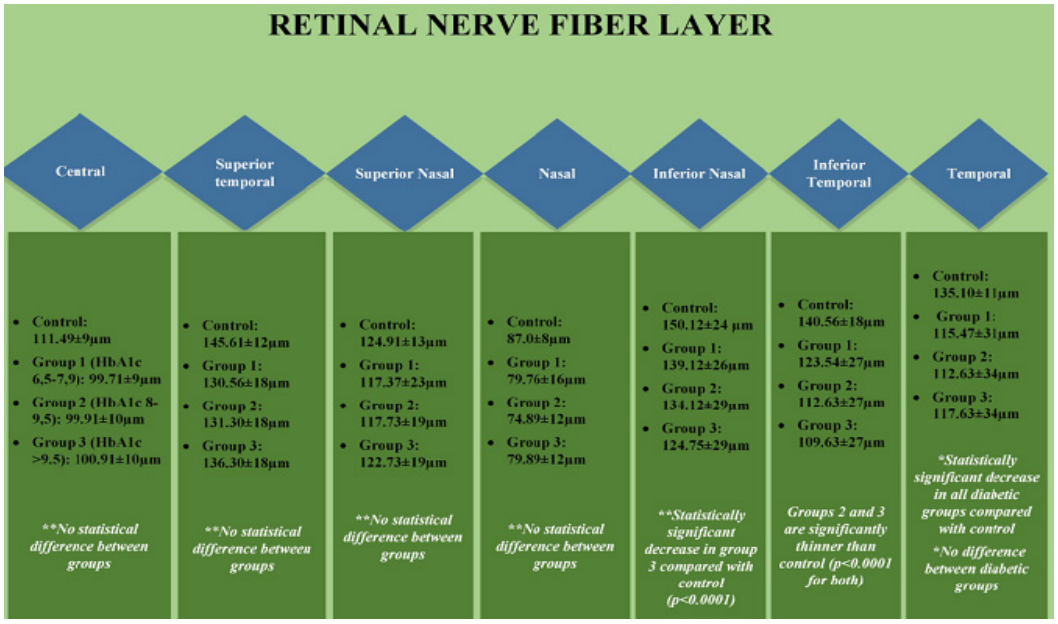

Figure 3. Peri-optic nerve head retinal nerve fiber layer measurements and inter-group comparison results

DISCUSSION

DM is a multifactorial disease, known to involve vessels and neurons (3,4). CT changes associated with DM were shown in many studies, which is consistent with capillary drop-out pathogenesis in diabetic retinopathy. Choroidal hypoperfusion might be the trigger to the development of DR resulting from retinal tissue hypoxia (17). Accumulation of advanced glycation end products in the choroidal tissues was shown using immunohistochemistry (18). Choroidal blood flow was reduction in DM, and it was shown in studies using laser Doppler blood flowmetry and indocyanine green angiography (19).

In OCT studies, CT seemed to change from study to study. Kase et al. showed that CT decreased in the presence of mild non-proliferative DR and postulated that a continuous high blood sugar state may facilitate vascular damage in the choroid (20). Gupta et al. found that DM subjects showed a significantly thinner choroid with fewer vascular areas and reduced vascularity, in contrast to DR subjects, who had a thicker choroid and significantly larger vascular areas (21). However, Vujosevic et al. reported that macular and peripapillary CT progressively and significantly decreased with an increasing level of DR. Kim et al. also reported that CT increased significantly as the severity worsened from mild/moderate non-proliferative DR to proliferative DR (22). Chen et al. found that the choroidal thickness was significantly decreased in patients with early-stage DM (23). Endo et al. found that the choroidal outer layer thickness was thinned in early DR (15). Yulek et al. found that foveal retinal thickness was decreased in patients with a longer duration of diabetes, but the foveal CT was not influenced by duration of systemic disease (24). Tavares Ferreira et al. showed that in diabetic patients without DR, there was evidence of overall thickening of the choroid compared with nondiabetic patients (25). They postulated that choroidal edema or vascular dilation with increased rigidity of the blood vessel may be responsible for this increase in CT (26).

In our study, CT reduction was consistently seen in HbA1c 6.5–7.9%. In 1500-micron measurements, this group's CT results were significantly thinner than groups with higher HbA1c. This is directly in contrast to Horváth et al.'s study, which found no significant correlation between HbA1c level and choroidal thickness (27). However, this change might be explained by the combined effect of low blood flow - which leads to CT decrease- that is then rivaled by the choroidal thickening due to increased vessel rigidity that is observed because of diabetic inflammation and high glycation end-product accumulation.

Optic nerve is shown to be affected by DM in a multitude of ways. For instance, Terai et al showed optic nerves in diabetic rats had a significant increase in stiffness compared to nondiabetic rats, which they explained by the effect of nonenzymatic collagen cross-linking mediated by advanced glycation end products due to high blood glucose levels in diabetes (28). Zhang et al showed retrograde axonal transport progressive damage and impairment of retinal ganglion cells which results in optic nerve involvement in DM (29). Apoptosis is also seen to be increased in retinal ganglion cells in DM (30).

In DM patients, RNFL thickness was shown to be changed in a multitude of studies, albeit in different segments (31).

For instance, Sugimoto at al found thinning to start in the superior area. They concluded that since micro aneurysms are seen in superior than in inferior areas in in vivo diabetic studies, this area was more likely to be susceptible to damage (32). They also suggested that RNFL thickness can be used as an indicator for glycemic control. This is similar to Oshitari et al's study, which had prominent loss in superior retina (33). In contrast, Vujosevic et al showed loss in the lower retina and postulated that due to the low blood flow per nerve fiber tissue in the inferior retina, this area was prone to RNFL loss in diabetic patients (34). Vujosevic et al found temporal-nasal RNFL loss in diabetic retinopathy patients (35).

As for the glycemic control, Lonneville et al found poor metabolic control of DM adversely affected the thickness of RNFL by using scanning laser polarimeter (36). On the other hand, Tekeli et al found that HbA1c values and duration of DM were not correlated with the optic nerve parameters (37). Verma et al. also postulated that the duration of diabetes and the glycemic control did not show any significant effect on RNFL thickness (38). In contrast to all, Demir et al, on the other hand, found no statistically significant difference between the RNFL thicknesses of DM and healthy groups (39).

In this study, we found RNFL changes had correlation with HbA1c levels. All diabetic patients showed temporal RNFL loss – similar to Vujosevic et al's study (35). We also observed that - in contrast to CT changes - RNFL loss were affected by higher HbA1c levels. Groups 2 and 3 showed RNFL loss in inferior temporal quadrant, and only the highest HbA1c group had inferior nasal RNFL damage. Therefore we postulate that, more prolonged the uncontrolled DM, more segmental damage to the optic nerve occurs.

This study had some limitations. First, there is no way of knowing the "real" onset of DM because of its insidious start. The OCT imagings are taken between 9AM and 3PM so it can be affected by circadian rhythm changes, but because the results in the subgroups were fairly consistent, we did not consider this to be a major limitation. Follow-up intervals are also necessary for these patients to observe the changes with increasing disease duration. Furthermore, in order to explain the paradoxical results see in the choroid segments, OCT – angiography can be added to future studies.

CONCLUSION

In conclusion, we found that CT changes gives a paradoxical result, first seen in lower HbA1c groups, possibly because of the complicated vascular effects of the disease. On the other hand, RNFL changes have direct

correlation with HbA1c levels, more segments getting affected as HbA1c increases. Depending on these results, we postulate that although diabetic control is effective against diabetic optic nerve damage, choroidal damage starts to occur no matter how low HbA1c is.

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