Original Article

Evaluation of Retinal and Choroidal Thicknesses in Patients with Diabetes Mellitus Without Diabetic Retinopathy: A Comparative Study

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Received: 25-Nov-2021;
Revision: 04-Apr-2022;
Accepted: 17-May-2022;
Published: 22-Sep-2022

ABSTRACT

Background: One of the most important complications of diabetes mellitus (DM) is vision loss due to diabetic retinopathy (DR). Optical coherence tomography (OCT) provides visualization of early structural abnormalities of the retina and choroid. **Aim:** To compare retinal thickness (RT) and choroidal thickness (CT) between patients with DM without DR and healthy controls. **Patients and Methods:** Diabetic patients without DR were divided into two groups according to serum glycosylated hemoglobin (HbA1c) levels. Group 1: HbA1c ≤7.5 (n = 25) and group 2: HbA1c >7.5 (n = 23). The 3rd group was the healthy control group (n = 25). CT and RT measured by OCT were compared between the three groups. **Results:** CT in the subfoveal, temporal, and nasal quadrants was significantly higher in the healthy control group than in groups 1 and 2. Subfoveal and temporal quadrant CT in group 2 were significantly thinner than those in group 1. The average RT (ART) was thinner in group 1 than in the other groups, but there was no difference between the control group and group 2. **Conclusions:** This study showed that CT and ART decreased in diabetic patients without DR.

Keywords: *Choroidal thickness, diabetes mellitus, diabetic retinopathy, HbA1c, optical coherence tomography, retinal thickness*

Introduction

The increasing incidence of diabetes mellitus (DM) and vision loss due to diabetic retinopathy (DR), one of the most important complications of DM, has led experimental studies to focus on the early diagnosis and treatment of DR. Studies show that some structural changes can be detected in the retina and choroid before the onset of retinal vascular problems and vision loss due to DM.[1-5] Optical coherence tomography (OCT) is a noninvasive imaging technique that allows for a detailed examination of retinal neurovascular structures and the detection of preclinical disorders. Furthermore, enhanced depth imaging (EDI) demonstrates choroidal thickness (CT) and structural abnormalities.[6,7]

The choroid is an important vascularized structure that supplies the outer third of the retina with nutrients and oxygen. Therefore, choroidal vasculopathy may play a role in the deterioration of the blood–retina barrier as well as retinal vascular integrity and may be associated with hemodynamic abnormalities, all of which are involved in the pathogenesis of DR.[8] Studies comparing patients with DM with healthy control groups have shown that there may be significant changes in the CT in patients with DM even in the absence of DR.[1,3,9] Similarly, histopathological studies in diabetic eyes have shown various choroidal abnormalities, such as aneurysms, neovascularization, choriocapillaris obstruction, and vascular degeneration.[10,11]

It has been reported that chronic hyperglycemia in DM causes oxidative stress, inflammation, and hypoxia, leading to changes in retinal neurons, glial cells, endothelial cells, and pericytes. Even in the absence

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Quick Response Code:

Website: www.njcponline.com

DOI: 10.4103/njcp.njcp_1960_21

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How to cite this article: Kaptı HB, Şahin AK, Özdemir Ö. Evaluation of retinal and choroidal thicknesses in patients with diabetes mellitus without diabetic retinopathy: A comparative study. Niger J Clin Pract 2022;25:1495-500.

of DR, a decrease in retinal nerve fiber layer (NFL) and ganglion cell layer (GCL) thickness has been demonstrated in diabetic patients.[12] In some studies, changes in the inner retinal layers have been demonstrated using OCT in diabetic patients with minimal findings or without diabetic retinopathy, suggesting that the symptoms of diabetic neuroretinopathy can be detected before microvascular damage.[13-15]

Detection of preclinical biomarkers of retinal microvascular and neuroglial abnormalities in patients with DM is critical as early treatment is associated with improved outcomes. This study aimed to compare retinal thickness (RT) and CT between patients with DM without DR and healthy controls. The secondary aim was to investigate the changes in CT and RT, as well as the relationship between CT/RT and demographic/clinical characteristics in the group with DM.

Materials and Methods

This prospective observational study, which included 73 patients, was conducted between January 2015 and January 2018. This study was approved by the local ethics committee (approval number: 2018/154) and was performed in accordance with the ethical guidelines of the Declaration of Helsinki. Informed consent was obtained from all patients.

The inclusion criteria were as follows:[1] age ≥ 8 years;[2] group 1: patients with hemoglobin A1c (HbA1c) ≤7.5, good diabetic control, and no DR; group 2: patients with HbA1c >7.5, poor diabetic control, and no diabetic retinopathy; group 3: age-matched healthy controls without DM. The exclusion criteria were as follows:[1] DR and any vitreoretinal disorder,[2] history of intraocular surgery in the last 3 months,[3] ocular disorders such as glaucoma, uveitis, or amblyopia,[4] refractive error, spherical equivalent ≥±3 D,[5] history of serious systemic diseases such as uncontrolled hypertension and cardiovascular or cerebrovascular disease other than DM[6], and a signal strength on OCT <6/10.

Age, sex, duration of DM, and other systemic diseases were documented. Blood samples were obtained from patients with DM, and fasting blood glucose (FBG) and HbA1c levels were determined using standard methods. Body-mass index (BMI) values were calculated using the standard formula (weight in kg/height in m^2). In addition to OCT measurements, a comprehensive ophthalmological examination including visual acuity, refractive error, axial length measurement, intraocular pressure measurement, slit-lamp examination, and dilated fundus examination was performed for each patient.

OCT measurements were performed using a Cirrus HD 500 spectral OCT platform (Carl Zeiss Meditec, Dublin, CA, USA). Measurements were taken without pupil dilation on the same day as blood sampling. All OCT scans were performed by the same experienced technician between 10:00 and 11:00 am to prevent possible changes in the circadian rhythm. CT was measured in 3 mm-long horizontal sections using the EDI-OCT mode at 500 μm intervals from the subfoveal, nasal, and temporal regions. Measurements were taken by a single observer blinded to the identity of the patients and study groups. Measurements were based on the distance between the outer hyperreflective border of the retinal pigment epithelium and the inner scleral surface. In addition, the central RT (CRT) and average RT (ART) were measured for each eye.

Statistical analysis

To summarize the data obtained from the study, descriptive statistics for continuous (numerical) variables are shown in a table [Table 1] using mean ± standard deviation or median, minimum, and maximum depending on the distribution of data. Categorical variables were summarized as numbers and percentages. The normality of numerical variables was checked using Shapiro–Wilk, Kolmogorov–Smirnov, and Anderson–Darling tests. To compare two independent groups, an independent sample t-test was used when numerical variables showed normal distribution, and the Mann–Whitney U test was used when numerical variables did not show normal distribution. To compare differences between categorical variables in different groups, Pearson's Chi-square test was used. To compare more than two independent groups, one-way analysis of variance was used for normally distributed numerical variables, and the Kruskal–Wallis H test was used for non-normally distributed numerical variables. Tukey's post-hoc test was used to analyze multiple comparisons in parametric tests, and the Dwass–Steel–Critchlow–Fligner test was used in non-parametric testing to evaluate differences between groups.

To analyze the relationships between CT and RT and HbA1c, FBG, and disease duration, Pearson's correlation coefficient was used when the data showed normal distribution, and Spearman's rho correlation coefficient was used when the data did not show normal distribution.

Statistical analyses were performed using the Jamovi project (2020), Jamovi (version 1.6.13.0) (Computer Software) (retrieved from https://www.jamovi.org), and JASP (version 0.14.1.0) (retrieved from https://jasp-stats.org) software. In all analyses, $P < 0.05$ was accepted as the level of statistical significance.

Results

The demographic and clinical characteristics of diabetic patients are shown in Table 1. A total of 48 diabetic patients were included in the study; of these, 21 were male (43.8%) and 27 were female (56.2%), and the control group consisted of 25 people. Based on the right and left eye measurements of each patient, 50 eyes were included in the HbA1c ≤7.5% group, 46 were included in the HbA1c >7.5% group, and 50 were included in the control group and evaluated in the study. There were 25 patients in the HbA1c ≤7.5% group and 23 patients in the HbA1c >7.5% group. The mean HbA1c value was 7.1 ± 0.3 in the ≤7.5% group and 10.6 ± 1.5 in the >7.5% group. The groups were similar in terms of age, sex distribution, BMI, disease duration, and FBG level (P > 0.05). There was no significant difference between the HbA1c ≤7.5% and HbA1c >7.5% groups in terms of spherical equivalent and axial length (P = 0.796 and P = 0.438, respectively).

Table 1: Demographic and clinical characteristics of the patients

	Groups		*P*
	HbA1c ≤ %7.5 (*n*=25)	HbA1c > %7.5 (*n*=23)	
Age (year) †	59.0±7.9	59.0±9.4	0.974
Sex ‡			
Male	11 (44.0)	10 (43.5)	0.999
Female	14 (56.0)	13 (56.5)	
BMI (kg/m²) †	31.3±5.5	31.0±4.9	0.885
Disease duration (year) Ω	15.0 [10.0-20.0]	15.0 [12.0-18.0]	0.860
Fasting blood glucose (g/dL) †	97.0±14.8	100.4±15.7	0.451
Spherical equivalent (diopter) Ω	−0.5 [−1.8-0.8]	−0.2 [−1.1-0.4]	0.796
Axial length (mm) †	23.3±1.2	23.1±0.7	0.438

†: mean±standard deviation, ‡: frequency (percentage), Ω: median [min-max]

Table 2: Distribution of the choroidal and retinal thickness of patients

	Groups		*P*
	HbA1c ≤ %7.5 (*n*=25)	HbA1c > %7.5 (*n*=23)	
Choroidal thickness (µ) †			
Subfoveal	292.8±53.2	250.0±61.2	0.014
Temporal-1	284.7±44.8	244.1±63.4	0.015
Temporal-2	273.3±43.1	234.3±59.4	0.013
Temporal-3	254.4±45.4	222.6±54.0	0.034
Nasal-1	266.6±50.2	237.0±59.4	0.070
Nasal-2	253.7±49.7	223.4±58.3	0.060
Nasal-3	226.1±48.4	206.0±60.2	0.212
Retinal thickness (µ)			
Central †	250.3±27.2	246.4±23.0	0.599
Average Ω	274.0 [272.0-281.0]	282.0 [276.0-286.5]	0.017

†: mean±standard deviation, Ω: median [min-max]

The distribution of CT and RT measurements in the quadrants determined in the OCT images of the patients is summarized in Table 2. It was observed that the CT in the subfoveal quadrant was higher compared to those in the other quadrants in both patient groups. There were significant differences between the patient groups in terms of subfoveal, temporal-1 (500 µ), temporal-2 (1000 µ), and temporal-3 (1500 µ) quadrant measurements (P < 0.005). The measurement values in the HbA1c >7.5% group were significantly lower compared to the values in the HbA1c ≤7.5% group [Table 2]. The CTs in the nasal-1 (500 µ), nasal-2 (1000 µ), and nasal-3 (1500 µ) quadrants as well as CRT were similar between the groups (P > 0.05). The ART in the HbA1c ≤7.5% group was 274.0 mµ, which was significantly lower than the median value (282.0 µ) in the HbA1c >7.5% group (P = 0.017).

There was no significant difference between the patient groups and the control group in terms of age, sex, BMI, spherical equivalent, and axial length [Table 3]. However, there were significant differences between the groups in terms of CT and RT. The subfoveal, temporal-1 (500 µ), temporal-2 (1000 µ), temporal-3 (1500 µ), nasal-1 (500 µ), nasal-2 (1000 µ), and nasal-3 (1500 µ) quadrant CTs in the control group were significantly higher than those in the HbA1c ≤7.5% and HbA1c >7.5% groups (P < 0.05) [Table 3 and Figure 1]. The median RT was similar between the HbA1c >7.5% group and the control group (P = 0.883). However, the median RT in the control group was significantly higher than that in the HbA1c ≤7.5% group (283 µ vs. 274 µ, P = 0.012).

There was a significant negative correlation between the spherical equivalent diopter value and disease duration (r = −0.308, P = 0.033). There was no

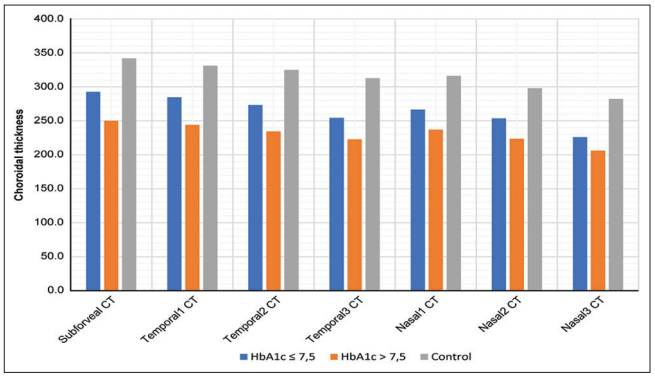

Figure 1: Graphical representation of the group and quadrant-based choroidal thickness (T: temporal, N: nasal)

Table 3: Comparison of patient groups and the control group in terms of demographic and clinical characteristics and choroidal and retinal thickness

	Groups			*P*	*P* (between groups)*		
	HbA1c ≤ %7.5 (*n*=25)	HbA1c > %7.5 (*n*=23)	Control (*n*=25)		1 vs 2	1 vs 3	2 vs 3
Age (year) †	59.0±7.9	59.0±9.4	55.1±5.8	0.085			
Sex ‡							
Male	11 (44.0)	10 (43.5)	9 (36.0)	0.815			
Female	14 (56.0)	13 (56.5)	16 (64.0)				
BMI (kg/m^2) †	31.3±5.5	31.0±4.9	29.7±4.4	0.476			
Spherical equivalent (diopter) Ω	−0.5 [−1.8-0.8]	−0.2 [−1.1-0.4]	−0.8 [−1.2-−0.1]	0.433			
Axial length (mm) †	23.3±1.2	23.1±0.7	23.0±0.7	0.589			
Choroidal thickness (µ) †							
Subfoveal	292.8±53.2	250.0±61.2	341.9±54.1	<0.001	0.028	0.008	<0.001
Temporal-1	284.7±44.8	244.1±63.4	331.0±51.6	<0.001	0.028	0.009	<0.001
Temporal-2	273.3±43.1	234.3±59.4	324.8±53.9	<0.001	0.032	0.003	<0.001
Temporal-3	254.4±45.4	222.6±54.0	312.8±56.1	<0.001	0.094	<0.001	<0.001
Nasal-1	266.6±50.2	237.0±59.4	316.2±48.3	<0.001	0.134	0.004	<0.001
Nasal-2	253.7±49.7	223.4±58.3	298.2±48.9	<0.001	0.119	0.01	<0.001
Nasal-3	226.1±48.4	206.0±60.2	282.1±51.1	<0.001	0.397	0.001	<0.001
Retinal thickness (µ)							
Central †	250.3±27.2	246.4±23.0	249.2±18.6	0.854			
Average Ω	274.0 [272.0-281.0]	282.0 [276.0-286.5]	283.0 [277.0-291.0]	0.009	0.045	0.012	0.883

†: mean±standard deviation, ‡: frequency (percentage), Ω: median [min-max], 1. HbA1c ≤ %7.5, 2. HbA1c > %7.5, 3. Control

Table 4: Correlation of choroidal and retinal thickness with HbA1c, fasting blood glucose, and disease duration

	HbA1c		Fasting blood glucose		Disease duration	
	r	*P*	*r*	*P*	*r*	*P*
Spherical equivalent	−0.056	0.704**	0.006	0.968**	−0.308	0.033**
Axial length	0.003	0.985*	0.070	0.639*	0.001	0.993**
Choroidal thickness						
Subfoveal	−0.314	0.030*	0.078	0.600*	−0.191	0.194**
Temporal-1	−0.36	0.012*	0.005	0.974*	−0.262	0.072**
Temporal-2	−0.372	0.009*	−0.035	0.811*	−0.184	0.210**
Temporal-3	−0.337	0.019*	−0.023	0.876*	−0.143	0.331
Nasal-1	−0.227	0.121*	0.097	0.514*	−0.191	0.193**
Nasal-2	−0.26	0.074*	0.126	0.395*	−0.227	0.120**
Nasal-3	−0.174	0.237*	0.128	0.385*	−0.21	0.152**
Retinal thickness						
Central	−0.012	0.935*	0.27	0.064*	−0.144	0.330**
Average	0.374	0.009**	0.092	0.534**	−0.012	0.934**

*: Pearson correlation coefficient, **: Spearman's rho correlation coefficient

significant correlation between disease duration and other measurements. Negative correlations between the HbA1c value and subfoveal and temporal quadrant CTs were observed [Table 4]. There was a positive correlation between ART and HbA1c values (r = 0.374, P = 0.009). No significant correlation was found between FBG levels and OCT measurements.

Discussion

Studies show that it may be possible to identify preclinical DR using OCT before clinically evident DR occurs. Recent studies using OCT imaging showed that neuroretinal degeneration begins before microvascular damage.[3,4,6,16] In a study comparing patients with DM without DR with healthy controls, significant thinning of the GCL and retinal NFL was found in patients with DM.[17] In a study by Li *et al*.,[5] parafoveal vessel density and temporal retinal NFL thickness were found to be lower in diabetic patients without DR symptoms compared to those in the healthy control group.

In the present study, patients with good glycemic control (HbA1c ≤7.5%), patients with poor glycemic control (HbA1c >7.5%), and healthy controls without DR symptoms were compared and no significant difference was found in the CRT between the three groups. When

the ART was compared, no significant difference was found between the control group and the patient group with poor glycemic control (HbA1c >7.5%), whereas the ART in the patient group with good glycemic control (HbA1c ≤7.5%) was significantly lower than that in the control group. These results show that despite good glycemic control, there is a decrease in macular thickness due to retinal neurodegeneration in patients with DM. These findings do not imply that there is no change in RT in diabetic patients with poor glycemic control. As the HbA1c level increases, poor glycemic control may lead to an increase in vascular permeability in the retina and a subsequent increase in RT. Therefore, the reduction in RT due to neurodegeneration may be masked. The positive correlation between ART values and HbA1c levels supports this theory (r = 0.374, P = 0.009). The progression of DR accelerates with an increase in the HbA1c level.[18] Another study showed that the pericentral macular area is thinner in patients with mild DR and thicker in patients with pre-proliferative DR supporting our findings.[7] In contrast to the findings of the present study, when the findings in patients with type 1 DM without DR were compared with those in the healthy control group, the ART and CRT values were found to be similar between the groups.[3] This difference may be associated with parameters such as DM type and disease duration.

In the present study, there was no significant difference in the CRT between the three groups; however, the ART values indicated significant differences. Based on these findings, it can be hypothesized that the central retinal region is not affected in the early period or before the signs of DR appear. In a study supporting this hypothesis, central and perifoveal RT were compared in patients with non-proliferative DR, patients with DM without DR, and healthy controls, and no significant difference was found between the three groups. The central foveal and perifoveal areas have fewer neural layers as they predominantly contain the outer retinal layers. It is possible that the outer retinal layers are not affected before the onset of DR or during the early stages of the condition.[19]

Despite the absence of significant changes in macular vessel parameters, Dai *et al*.[20] found that choriocapillaris perfusion decreased significantly in their study comparing 16 patients with DM without DR and 16 healthy controls. Similarly, in the present study, CT was compared between patients with type II DM and healthy controls, and subfoveal and temporal 1 (500 μ), temporal 2 (1000 μ), temporal 3 (1500 μ), nasal 1 (500 μ), nasal 2 (1000 μ), and nasal 3 (1500 μ) quadrants were found to be significantly thinner in the patient group. Comparable results were found in a study by Yolcu *et al*.[3] on patients with type 1 DM. In the present study, a comparison between the patient groups showed that the CT in the subfoveal, temporal 1, temporal 2, and temporal 3 quadrants was significantly thinner in the patient group with poor glycemic control (HbA1c >7.5%) compared to those in the patient group with good glycemic control (HbA1c ≤7.5%). Similar to the present study, Torabi *et al*.[21] showed that the CT in patients with poor glycemic control (HbA1c >7%) was significantly thinner compared to that of the group with HbA1c ≤7%. These results show that there is a decrease in CT as the HbA1c level increases. We found a negative correlation between the HbA1c level and subfoveal and temporal CT. Impaired glycemic control and high HbA1c levels are associated with more severe stages of DR. High blood glucose concentration can result in lower choroidal blood flow, leading to choroidal thinning.

Many factors, such as the BMI, spherical equivalent (SE), and axial length, affect the CT.[22,23] In the present study, there was no significant difference between the three groups in terms of BMI, SE, and axial length. On the other hand, no significant correlation was found between CT and RT and DM-related parameters, such as FBG and disease duration. There are similar results in the literature.[8,24,25] In contrast to these studies, Yolcu *et al*.[3] reported a negative significant correlation between FBG and average CT. The difference in results may be due to the different inclusion criteria used in the study.

There are certain limitations of the present study. These include manual measurements and possible measurement errors as the measurements were made by a single observer. Averaging the CT measurements taken by two independent observers and analyzing the interobserver correlation may provide stronger evidence.

Conclusion

The present study showed that despite good glycemic control, a decrease in CT can be observed in patients with DM, and the CT may decrease further with deterioration of glycemic control. In addition, it was demonstrated that a decrease in ART may be observed in patients with DM, despite good glycemic control, and an increase in ART may be observed with deterioration of glycemic control. It is possible to demonstrate retinal and choroidal abnormalities using OCT before clinical signs of DR appear in patients with DM. These abnormal findings obtained with OCT can serve as a warning and guide for more strict regulation of blood glucose levels.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the

patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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