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ORIGINAL ARTICLE – OPEN ACCESS

Evaluation of the Effect of Type 1 and Type 2 Diabetes Mellitus without Diabetic Retinopathy on Subfoveal Choroidal Thickness and Central Macular Thickness in Adolescents

Mustafa Hepokur[1], Hamdi Cihan Emeksiz[2], Merve Nur Hepokur[2], Ayşe Aşık[3], Halit Oğuz[1]

ABSTRACT

Objective: Evaluation of the effect of Type 1 and Type 2 diabetes mellitus (DM) without diabetic retinopathy on subfoveal choroidal thickness (SCT) and central macular thickness (CMT) in adolescents.

Materials and Methods: This prospective cohort study included a total of 70 eyes of 35 patients and 42 eyes of 21 age-matched healthy control individuals. SCT and CMT were measured in all participants using enhanced depth imaging-optical coherence tomography.

Results: Forty eyes of 20 patients with Type 1 DM, 30 eyes of 15 patients with Type 2 DM and 42 eyes of 21 healthy controls were examined. SCT was significantly lower in type 1 DM group than in type 2 DM group (p=0.008). CMT did not significantly differ among the three groups (p=0.412). SCT and CMT did not correlate with HbA1c, BMI, fasting blood glucose, HDL, LDL, total cholesterol and triglycerides levels and also duration of diabetes.

Conclusion: We revealed that the SCT was significantly thinner in Type 1 diabetic adolescents than type 2 DM. Larger series and further studies are needed to better demonstrate this different effect on choroidal layer.

Keywords: Adolescence, central macular thickness, diabetes mellitus, enhanced depth imaging-optical coherence tomography, subfoveal choroidal thickness

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[1]Department of Ophthalmology, İstanbul Medeniyet University Faculty of Medicine, Göztepe Prof. Dr. Süleyman Yalçın City Hospital, İstanbul, Turkey
[2]Department of Pediatric Endocrinology, İstanbul Medeniyet University Faculty of Medicine, Göztepe Prof. Dr. Süleyman Yalçın City Hospital, İstanbul, Turkey
[3]Department of Pediatry, İstanbul Medeniyet University Faculty of Medicine, Göztepe Prof. Dr. Süleyman Yalçın City Hospital, İstanbul, Turkey

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Correspondence
Mustafa Hepokur,
İstanbul Medeniyet University Faculty of Medicine, Göztepe Prof. Dr. Süleyman Yalçın City Hospital, Department of Ophthalmology, İstanbul, Turkey
Phone: +90 216 606 52 00
e-mail: hepokur34@gmail.com

INTRODUCTION

Diabetes mellitus (DM) is a chronic endocrine and metabolic disorder in which blood glucose level is elevated beyond normal. The disease has two major types. Type 1 DM is characterized by deficient insulin production as a result of autoimmune-mediated or idiopathic destruction of β-cells and type 2 DM is caused by reduced insulin sensitivity and relative insulin deficiency (1, 2). Both types of diabetes can cause significant morbidity and mortality in humans. Chronic hyperglycemia leads over time to serious damage to several tissues in the body, particularly by disrupting the structure and function of human vascular system.

Retinopathy is the most common microvascular complication of both types of diabetes and is one of the most important causes of blindness among adults (3). In diabetic retinopathy, retinal edema and ischemia occur as a result of increased vascular permeability due to disruption of blood-retinal barrier (4). In advanced stages, the development of proliferative retinopathy and clinically significant macular edema can lead to loss of vision in patients with diabetes (5, 6).

The choroid vessels are responsible for the oxygenation and nutrition of the outer third of the retina and metabolically active photoreceptor cells. Due to the lack of retinal vessels of the fovea, choroidal hypoperfusion may cause damage to the outer layers of the retina, especially in the fovea (7). Changes in retinal vessels observed in diabetic retinopathy may also occur in choroidal vessels in diabetic patients. These include choroidal microaneurysm, vascular dilatation and contraction, neovascularization, and obstruction of choriocapillaris (8).

There are many imaging methods for evaluating the choroidal layer such as indocyanine green angiography and B-scan ultrasonography. However, low image quality and invasive nature of these methods limit their use (9, 10). However, spectral-domain optical coherence tomography (SD-OCT) with enhanced depth imaging (EDI) software is a non-invasive, inexpensive, reproducible imaging method with high-resolution image quality that evaluates the choroidal layer (11).

Diabetes-related changes in subfoveal choroidal thickness (SCT) and central macular thickness (CMT) are highly investigated in adult diabetic patients, with conflicting results. However, it is not well known whether such ocular findings do already exist in pediatric patients with diabetes. To the best of our knowledge, there is no study in literature investigating the SCT in adolescents with Type 2 diabetes. Thus, the aim of this study was to compare

the SCT and CMT between Type 1 DM adolescents, Type 2 DM adolescents, and healthy controls and to evaluate the association of these ocular measurements with HbA1c, diabetes duration, body mass index, fasting blood sugar, and lipid profile.

MATERIALS and METHODS

This prospective cohort study was carried out in the department of ophthalmology at İstanbul Medeniyet University, Göztepe Prof. Dr. Süleyman Yalçın City Hospital. Written informed consent was obtained from all the patients, and an application was approved by the ethics committee of the İstanbul Medeniyet University Faculty of Medicine (Ethics Committee of the İstanbul Medeniyet University Faculty of Medicine, Date: 09.10.2019, Number: 2019-0393). The tenets of the Declaration of Helsinki were followed. In this study, 40 eyes of 20 type 1 DM patients (Type 1 DM group), 30 eyes of 15 type 2 DM patients (Type 2 DM group), and 42 eyes of 21 age-matched healthy controls (control group) were examined. SCT and CMT were measured in all participants using enhanced depth imaging-optical coherence tomography.

Inclusion Criteria

The inclusion criteria of the study were the absence of diabetic retinopathy and systemic disease other than diabetes and not using any medication other than anti-diabetic treatment.

Exclusion Criteria

Exclusion criteria were refractive errors more than 5 diopters, intraocular pressure outside normal limits or a diagnosis of glaucoma, chorioretinal disease, or laser treatment applied to the retina, uveitis, and the presence of media opacity that prevents the fundus image.

Study Procedures

Routine ophthalmologic examination was performed after fasting blood glucose, HbA1c, lipid profile, liver function tests, renal function tests, and blood pressure was measured in all patients. In routine ophthalmologic examination, visual acuity was evaluated with Snellen chart, intraocular pressure was measured and anterior segment was examined by biomicroscope. Fundus examination was performed after dilating the pupil with 1% tropicamide (Bilim Pharmaceuticals, İstanbul, Turkey) drop and CMT was evaluated with SD-OCT (Spectralis Heidelberg Engineering, Germany) and SCT was evaluated with EDI.

All OCT images were taken at 1 p.m. by a single experienced technician and choroidal thickness was evaluated in a masked manner by the diagnosis of patients by a single ophthalmologist and macular thickness was measured automatically by the device. The SD-OCT image was measured manually from the hyperreflective area to the hyporeflective area which represents the distance between the retinal pigment epithelium and the sclerochoroidal interface and evaluated as choroidal thickness (Fig. 1). CMT was evaluated by automatic measurement of the 1 mm central circular area of 9 Early Treatment Diabetic Retinopathy Study areas which is using a 6*6 mm circular pattern (Fig. 2).

Statistical Analysis

The statistical analyses were performed using SPSS Statistics for Windows version 22 (IBM Corp., Chicago, IL, USA). The normality distribution of the data in the groups was evaluated with the Kolmogorov–Smirnov test. An analysis of variance (ANOVA) test was used to compare the normal distribution parameters and the Kruskal–Wallis test was used to compare the parameters without a normal distribution in the three groups. A post hoc Tukey analysis was performed between two groups for the significant differences in ANOVA test. A Bonferroni adjustment was performed in the multiple comparisons between the groups in Kruskal–Wallis test.

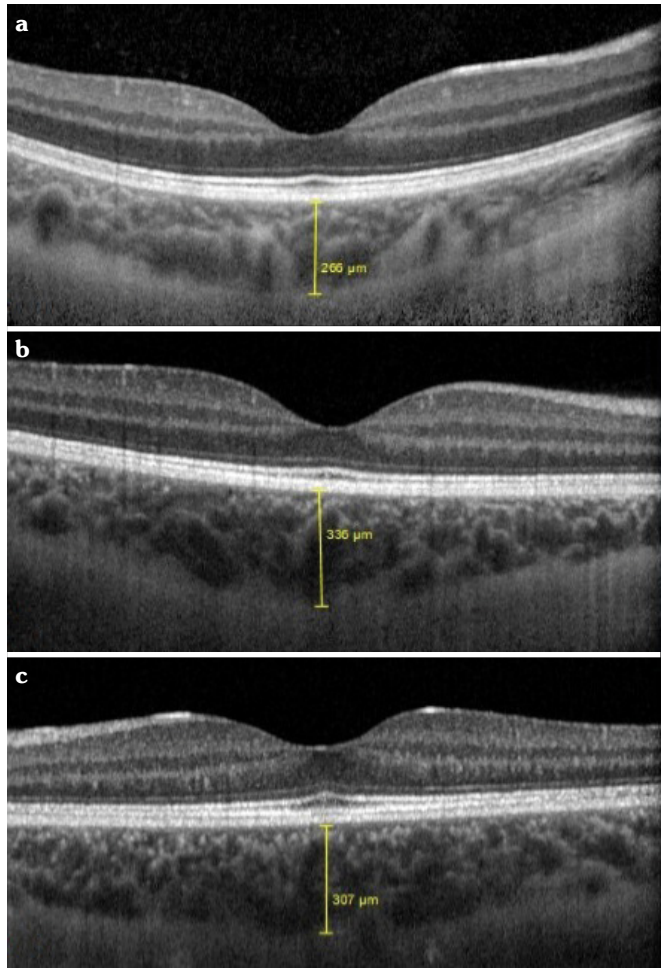

Figure 1. EDI-OCT images of choroidal thickness measurements for each group. (a) Type 1 DM group. (b) Type 2 DM group. (c) Control group

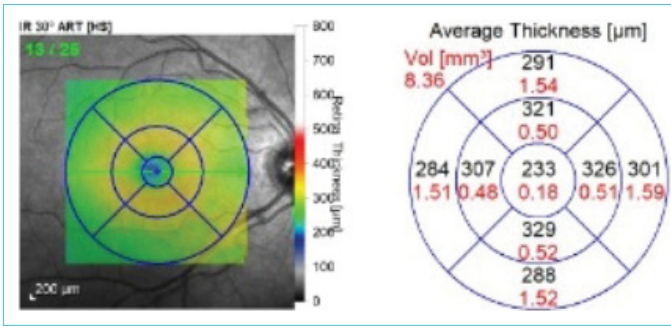

Figure 2. Schematic illustration of central macular thickness measurement

Table 1. Demographic characteristics of the study groups

	Type I DM	Type II DM	Control group	p
Patients	20	15	21	–
Eyes	40	30	42	–
Age	17.25 (2.50)* 16.85±1.53”	17.00 (2.50)* 16.53±1.83”	17.00 (2.00)* 16.66±1.06”	0.644[b]
Sex (M/F)	6/14	3/12	9/12	0.339[a]
Diabetes duration	5.25 (2.63)* 5.65±2.85”	4.00 (3.50)* 3.73±1.85”	–	0.037[b]

a: Chi-square test; b: Kruskal–Wallis test; DM: Diabetes mellitus; M: Male; F: Female; *: Median (interquartile range); ”: Mean±standard deviation

Table 2. Metabolic characteristics of the study groups

	Type I DM	Type II DM	Control group	p
HbA1c	10.40 (2.78)* 10.34±2.42”	9.10 (5.10)* 9.29±3.57”	5.60 (0.35)* 5.54±0.30”	<**0.001**[b]
HDL	48.50 (16.50)* 50.80±14.83”	45.00 (16.00)* 43.80±12.10”	43.00 (8.00)* 44.57±10.55”	0.230[b]
LDL	91.70±22.89”	119.73±35.38”	77.47±20.66”	<**0.001**[a]
T. cholesterol	161.60±24.12”	185.33±55.18”	138.57±26.89”	0.**001**[a]
Triglycerides	73.50 (40.25)* 98.00±62.66”	140.00 (107.00)* 147.00±70.20”	82.00 (47.50)* 82.76±27.68”	0.**008**[b]
BMI	22.47±3.13”	29.11±5.01”	24.47±4.35”	<**0.001**[a]
FBG	167.50 (119.75)* 171.25±83.01”	150.00 (135.00)* 190.60±112.77”	82.00 (12.00)* 82.71±11.10”	<**0.001**[b]

a: ANOVA test; b: Kruskal–Wallis test; DM: Diabetes mellitus; *: Median (interquartile range); ”: Mean±standard deviation; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; BMI: Body mass index; FBG: Fasting blood glucose; T. cholesterol: Total cholesterol

The correlations between the groups were analyzed using the Pearson and Spearman test. Values below p<0.05 were considered statistically significant.

RESULTS

This study included forty eyes of 20 patients with Type 1 DM (Type 1 DM group), 30 eyes of 15 patients with Type 2 DM (Type 2 DM group), and 42 eyes of 21 healthy controls (control group). Male percentages were 30%, 20%, and 42.8% in Type 1 DM, Type 2 DM, and control groups, respectively. Demographic and metabolic characteristics of the study groups are displayed in Tables 1 and 2.

The mean ages of the three groups included in the study were 16.85±1.53 years old in the type 1 DM group, 16.53±1.83 years old in the type 2 DM group, and 16.66±1.06 years old in the control group. There was no statistically significant difference between the three groups (p=0.644). Visual acuity was 20/20 in all patients and control group. Diabetes duration of the patient groups was 5.65±2.85 years in type 1 DM and 3.73±1.85 years in type 2 DM (p=0.037) (Table 1). Body mass index was significantly higher in the type 2 DM group as compared to the type 1 DM and control groups (p<0.001 and p=0.005, respectively).

SCT significantly differed among the three groups (p=0.008). It was significantly lower in the type 1 DM group (292.60±44.19 µm) than in the type 2 DM group (327.20±46.70 µm) (p=0.008). SCT was also lower in the type 1 DM group than in the control group (315.71±49.74 µm), but the difference was not statistically significant (p=0.071). Type 2 DM group was thicker than the control group, but this difference was not statistically significant (p=0.565) (Fig. 3).

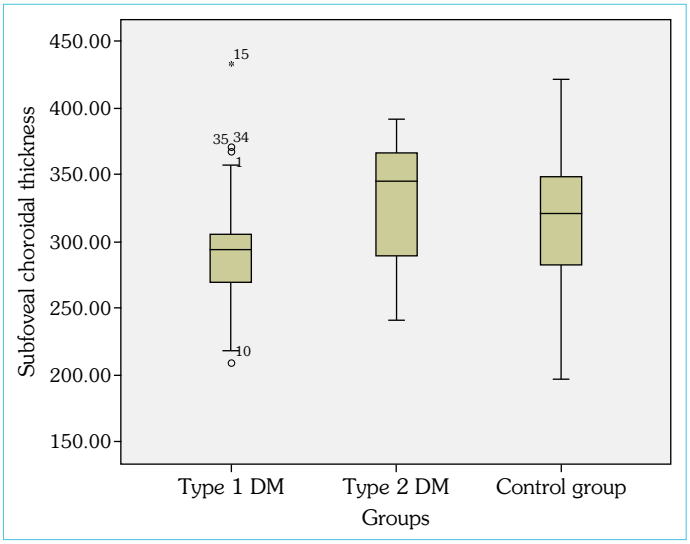

Figure 3. Comparison of subfoveal choroidal thickness among the groups

CMT was 262.32±20.38 µm in the type 1 DM group, 259.50±20.79 µm in the type 2 DM group, and 267.73±23.76 µm in the control group. There was no significant difference in CMT among the three groups (p=0.412) (Fig. 4 and Table 3).

SCT and CMT did not correlate with HbA1c, BMI, fasting blood glucose, HDL, LDL, total cholesterol, and triglycerides levels and also duration of diabetes (Table 4).

Table 3. Subfoveal choroidal thickness and central macular thickness of the study groups

	Type I DM	Type II DM	Control group	p
Subfoveal choroidal thickness	292.60±44.19”	327.20±46.70”	315.71±49.74”	**0.008**[a]
Central macular thickness	260.00 (34.50)* 262.32±20.38	258.00 (27.25)* 259.50±20.79	265.00 (32.00)* 267.73±23.76	0.412[b]

a: ANOVA test; b: Kruskal–Wallis test; DM: Diabetes mellitus; ”: Mean±standard deviation; *Median (interquartile range)

DISCUSSION

In our study, we demonstrated that SCT was thin in patients with Type 1 DM without diabetic retinopathy than age-matched Type 2 DM in adolescents. In addition, choroidal thickness was found to be thin in Type 1 DM patients compared to the control group. However, this difference did not reach statistical significance. At the same time, it was observed that the pediatric age group Type 2 DM patients without diabetic retinopathy were thicker than the control group but not statistically significant. There was no statistically significant difference between CMT in all groups. There are studies similar to this article in the adult age group previously published in the literature. To the best of our knowledge, this is the first study in the literature comparing choroidal thickness in pediatric age Type 2 DM without diabetic retinopathy with age-matched Type 1 DM and healthy control subjects.

Similar to our study, Esmaeelpour et al. (12) found that choroidal thickness was thin in patients with Type 1 DM with or without retinopathy compared to the control group. Parallel to our study, they demonstrated no significant correlation between HbA1c, body mass index, and duration of diabetes and choroidal thickness (12). Unlike our study, the mean age of patients was higher in their studies. It has been shown in the literature that choroidal thickness decreases with age (13). Ferreira et al. (14) showed that choroidal thickness decreases by an average of 2.1 µm and 3.2 µm/year. However, in our study, choroidal thickness was shown to be thin even in adolescents with Type 1 DM. In addition to these findings, they reported that retinal thickness did not differ between the groups as in our study (12). Querques et al. (15) found that choroidal thickness was thinner in diabetic patients with or without retinopathy in Type 2 DM patients than in the control group. They reported that the difference between the severity of retinopathy and choroidal thickness was not significant (15). The patient population in Querques et al.’s study was consisted of adults, while our study was consisted of adolescents. In our study, choroidal thickness was not significantly different between type 2 DM patients and control group. However, other concomitant metabolic disorders in type 2 DM patients may have led to this reduction over the years. Yılmaz et al. (16) found that choroidal thickness was thinner in obese patients than normal-weight healthy individuals in adults and they attributed this to the imbalance of vasoconstrictor and vasodilator molecules due to the obesity. In our study, BMI, LDL, and TG levels were significantly higher in Type 2 DM patients compared to the other two groups. We interpreted that such metabolic changes may not make changes in choroidal thickness in the early period while they may have an effect on choroidal thickness with a cumulative effect with age. Vujosevic et al. (17) reported that choroidal thickness of diabetic patients without retinopathy was thinner but not statistically significant compared to the control group. The authors found that diabetic patients with retinopathy were statistically thinner than the control group (17). Although this result is in parallel with our study, the diabetic group consisted of both Type 1 DM (25.5%) and Type 2 DM (74.5%). Two distinct subtypes of diabetes in the same group may have an effect on the results. Gupta et al. (18) showed that choroidal thickness was thinner in diabetic patients with or without retinopathy than in the control group in Indian adult humans. However, Tan et al. (19) showed no significant difference in choroidal

Table 4. Correlation between subfoveal choroidal thickness, central macular thickness, and metabolic parameters

	Subfoveal choroidal thickness	Central macular thickness
HbA1c	0.202”	0.441”
HDL	0.347”	0.644”
LDL	0.103*	0.158”
Total cholesterol	0.471*	0.448”
Triglycerides	0.512”	0.745”
BMI	0.065*	0.596”
FBG	0.599”	0.238”
Diabetes duration	0.169”	0.623”

”: Pearson correlation; *: Spearman correlation; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; BMI: Body mass index, FBG: Fasting blood glucose

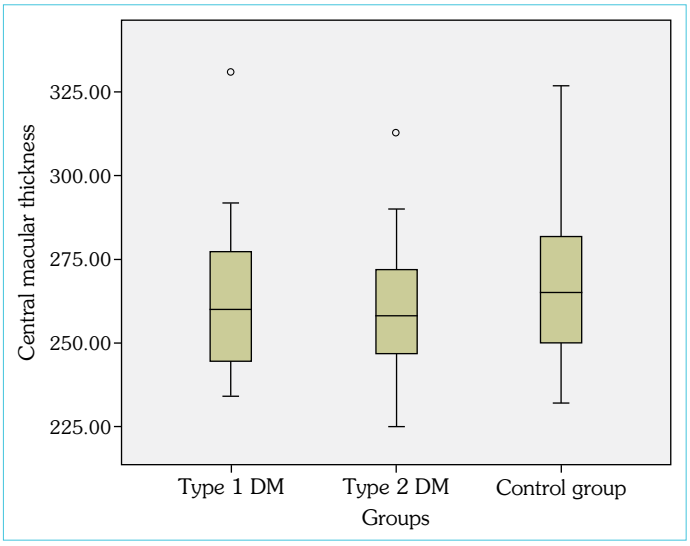

Figure 4. Comparison of central macular thickness among the groups

thickness between diabetic patients and control group. In these two studies, subtypes of diabetes were not identified. Similar to our study, Sayın et al. (20) demonstrated that there was no statistically significant difference between Type 1 DM patients without retinopathy and control group in adolescents. However, this study did not compare adolescents with type II DM. Yolcu et al. (21) reported that the choroidal thickness of Type 1 DM patients was thinner than the healthy individuals (21). The mean age of patients in their study was 23, and it was close to the adolescent age group, as in our study. Yolcu et al. (21) showed that there is a negative correlation between HbA1c/blood glucose level and choroidal thickness and stated that these findings may be effective in the tendency of choroidal thinning in Type 1 DM patients. There was no such difference found in terms of choroidal thickness in adolescents in the study of Sayin et al. (20). Yolcu et al. (21) attributed that the controversial result in these two studies might be the difference in diabetes duration of study groups. Ferreira et al.'s (14) study compares the choroidal thickness of type 2 DM patients without retinopathy with the control group in adults. Similar to our study, they showed that the choroidal thickness of Type 2 DM patients was thicker than the control group, but there was no statistically significant difference (14). They reported that the choroidal thickness increased in the 1st months, then decreased and eventually steady course, and stated that the increase in the 1st months may be the initial stage of choroidopathy (14). The authors explained the reduction up to 150 months with atrophy in the choroidal tissue and later stabilization interpreted as vascular resistance and vascular remodeling in large vessels (14). Since our study consists of pediatric Type 2 DM patients, the duration of diabetes follow-up is approximately 4 years and this value is within the first 77 months of the study of Ferreria et al. (14). In addition, they reported that choroidal thickness was not associated with diabetes duration, blood glucose level, HbA1c, and mean arterial pressure. Unlike our study, Torabi et al. (22) showed that the HbA1c level correlated with choroidal thickness in adults with Type 2 DM patients and stated that as the HbA1c level increased, the choroidal thickness decreased. Similar to our study, Ambiya et al. (23) could not see a significant difference between the choroidal thickness of DM patients without retinopathy and the control group. In addition, they showed that there was a negative correlation between the stage of diabetic retinopathy and choroidal thickness (23). However, unlike our study, they reported that choroidal thickness decreases with the increasing duration of diabetes (23). Besides that, Mohamed et al. (24) showed that in patients with diabetic retinopathy, choroidal thickness cannot be used in the monitoring and follow-up of diabetic macular edema.

The general structure of the choroid layer consists of blood vessels, melanocytes, fibroblasts, and connective tissue (25). Seppälä et al. (26) showed that catabolism is higher than anabolism in insulin-dependent diabetic patients due to changes in cellular, vascular, and connective tissue in gingiva. We also found the choroid thickness thinner in insulin-dependent diabetes in our study. Choroid vessels, especially choriocapillaris, provide nutrition and oxygenation of the outer retina, and metabolically active photoreceptor cells (27). Previous histological studies (7, 8) have demonstrated a reduction in choriocapillaris in eyes with diabetic retinopathy. Nagaoka et al. (28) reported that choroidal blood flow decreases before diabetic retinopathy development. The thickness of the choroidal layer may possibly be related to the width and number of choroidal vessels and connective tissue.

In this study, CMT was not significantly different among the three groups. As in our study, Esmaeelpour et al. and Yolcu et al. did not observe a difference in retinal thickness in DM patients without retinopathy compared to the control group, and Querques et al. and Vujosevic et al. also reported that there is no significant correlation between retinal thickness and choroidal thickness (12, 15, 17, 21).

Our study has several limitations. First one is the axial length of the patients not evaluated. However, patients with more than 5 diopter refractive errors were not included in our study. The second limitation is that the choroid layer is measured manually. Manual measurement increases the error rate more than automated measurement. The third limitation is the small sample size of the adolescents with Type 2 DM, due to the Type 2 DM is less common than Type 1 DM in pediatric age. The fourth limitation is that the difference in diabetes duration between the two subtypes of diabetes is significant in our study. However, we also showed that there was no correlation between choroidal thickness and duration of diabetes. Another limitation is the absence of patients with retinopathy in the study. Changes in choroidal thickness in patients with retinopathy may help us to better understand whether this finding is a precursor of retinopathy. Nevertheless, our study showed different choroid thicknesses in different diabetes subtypes without retinopathy, which contributed to the available information in the literature.

As a result, we demonstrated that the choroidal layer was thinner in Type 1 DM patients without retinopathy in the pediatric age group compared to age-matched Type 2 DM patients. Unlike type 2 DM, in Type 1 diabetic adolescents without retinopathy, the decreased SCT may be due to catabolic changes in vascular or connective tissue induced by insulin-dependent diabetes. In two separate diabetes subtypes, these findings in diabetics without retinopathy should be taken into account in investigating how the pathophysiological effect of choroidal function in retinopathy. CMT does not seem to be affected in the first decade of either type of diabetes in adolescence. Larger series and further studies are needed to better demonstrate this different effect on the choroidal layer.

Ethics Committee Approval: The İstanbul Medeniyet University Clinical Research Ethics Committee granted approval for this study (date: 09.10.2019, number: 2019-0393).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – MH, HCE, MNH, AA, HO; Design – MH, HCE, MNH, AA, HO; Supervision –MH, HCE, MNH, AA, HO; Data Collection and/or Processing – MH, MNH, AA; Analysis and/or Interpretation – MH, HCE, HO; Writing – MH, HCE; Critical Reviews – MH, HCE, MNH, AA, HO.

Conflict of Interest: The authors have no conflict of interest to declare.

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