VIA MEDICA
RESEARCH PAPER
ISSN 2450–7458
e-ISSN 2450–8187

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Subfoveal Choroidal and Macular Thickness Assessed with Optical Coherence Tomography in Indonesian Subjects with Type 2 Diabetes: A Cross-Sectional Study

ABSTRACT

Objective: The present study aims to assess the difference in choroidal and macular thickness in type 2 diabetes (T2D) patients with and without diabetic retinopathy (DR).

Materials and methods: This cross-sectional analytic study included 84 eyes from 56 subjects by consecutive sampling which were divided into control, T2D without DR/non-diabetic retinopathy (NDR), and T2D with DR/ /diabetic retinopathy (DR) group. The subjects were patients with T2D aged 40–60 years with or without DR, with normal intraocular pressure, and never received any DR therapy. The data collected were age, gender, mean arterial pressure, glycemic control, choroidal thickness (CT), and macular thickness (MT).

Results: Mean age of the NDR group was 51.67 ± ± 4.64 years, the DR group was 52.45 ± 4.46 years, and the control group was 51.31 ± 5.72 years. Subjects in DR group (247.57 ± 57.95 microns) had significantly thinner choroids when compared to the NDR group (266.68 ± 51.76 microns), they both also had significantly thinner choroids when compared to the control group (283.07 ± 69.98; p = 0.042). On the contrary, subjects in DR group (263.79 ± 45.17 microns) had thicker macula compared to the NDR (236.11 ± 26.49 microns) and control group (239.82 ± 17.42 microns; p = 0.015).

Conclusions: Subjects with type 2 diabetes and retinopathy had significantly thinner choroid and thicker macula when compared to non-diabetic retinopathy group. The thinning of choroid and thickening of macula develops as the disease progresses to diabetic retinopathy. (Clin Diabetol 2023; 12; 2: 80–86)

Keywords: choroid, choroidal thickness, macular thickness, type 2 diabetes mellitus, diabetic retinopathy

Introduction

Diabetic retinopathy (DR) is the most prevalent and distinct consequence of DM which is also one of the major risk factors for avoidable blindness in productive-age adults. Annual number of blindness and visual impairments caused by DR is gradually increased [1–3]. Visual impairments which occur before the clinical signs of DR might involve photoreceptor cells which metabolism was regulated by choroid. The function and structure of choroid is crucial in the pathophysiology of many retinal disease, such as DR. Abnormality affecting choriocapillaris may cause severe damage to retina functionalities, especially the macula fovea [4–6].

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Clinical Diabetology 2023, 12; 2: 80–86
DOI: 10.5603/DK.a2022.0064
Received: 18.08.2022 Accepted: 24.10.2022
Early publication date: 27.01.2023

Loss of blood-retina barrier (BRB) contributes to the pathogenesis of DR, especially the inner BRB which has been well studied due to the apparent relevance to diabetic retinopathy. Disturbance of choroid, such as choroidal inflammation and ischemia may also lead to breakdown of the BRB and choroidal thickness (CT) thinning [7–9]. Number of previous pathological studies found choroid vasculature abnormalities, including vascular degeneration, aneurysms of the choroid, choriocapillaris obstruction, and neovascularization in the choroid in patients with diabetes. Limitations of effective examinations made the changes in the choroid structure and how they affected the retinal tissue difficult to be detected [4, 10].

Several factors, including hyperglycemia, the duration of diabetes, and HbA1c have a role in the development of DR [11, 12]. Huang et al. [13] found that CT decline was in fact strongly related to DR after controlling these factors. These factors might also be risk factors or even predictors of diabetic macular edema (DME), as well as contributing to changes in macular thickness (MT) in patients with diabetes [14]. The early diagnosis of the emergence of DR and a subsequent management may result from measuring MT in patients [15].

CT and MT visualization and measurement in DR cases could be done using optical coherence tomography (OCT) [16, 17]. The limited and sparse data on the CT of patients with diabetes with each stage of DR showed varied and contradictive results. The results of choroid thickness investigations in diabetes were mixed; they showed that choroidal thickening [18–20], thinning [21–23], or no change [21, 24] occurred in eyes with diabetic retinopathy. Numerous studies also have been done to assess macular thickness in patients with diabetes. They showed inconsistent results which were macular thickening [14, 25], thinning [26], or no changes at all [27]. The purpose of this study is to assess the difference in choroidal and macular thickness in patients with diabetes with and without DR.

Materials and methods

Study design

This study is a cross-sectional analytic study which was conducted in December 2018–April 2019 at Cicendo National Eye Center Hospital in Bandung. The aim of this study was to assess the difference in choroidal and macular thickness in type 2 diabetes (T2D) patients with and without diabetic retinopathy (DR).

Study population

The patients included in this study were patients with T2D aged 40–60 years with or without DR whose intraocular pressure (IOP) ≤ 21 mmHg and who never received any ocular therapy, such as panretinal laser photocoagulation or macular laser, anti-VEGF injection, and pars plana vitrectomy surgery. We excluded pregnant subjects, subjects with optic media opacity (e.g., opacification of cornea, lens or vitreous), macular degeneration or edema, severe myopia ≥ 6 diopters, history of ocular trauma, surgery as well as corticosteroid use, or other neuropathies besides DR.

Variables collected

The sampling technique used was consecutive sampling. The subjects were matched by age categories (40–45, 46–50, 51–55, and 56–60 years old) and sex, then divided into 3 groups (control, T2D without DR, and T2D with DR groups). HbA1c, presenting visual acuity, anterior segment examination, intraocular pressure, fundus photography (Zeiss VISUCAM Pro NM, Carl Zeiss, Germany), choroidal thickness, and macular thickness data (Zeiss Cirrus HD OCT, Carl Zeiss Meditec, Dublin, CA) were collected.

Choroidal thickness was measured by SD-OCT with EDI software using manual caliper tool on perpendicular horizontal line across central fovea, from the superior margin of hyperreflective line of Bruch membrane until the inferior margin of outer hyperreflective line of sclera (Fig. 1). Signal strength value ≥ 6 in OCT results were considered reliable. Macular thickness was measured by SD-OCT using macular cube 512 x 128 protocol and was automatically analyzed. CT and MT examinations were done by one trained personnel at a similar time of the day.

Statistical methods used for data analysis

The data were analyzed using SPSS 24.0 version for windows. The analytic test used was ANOVA test between the characteristics of 3 groups, if the data was normally distributed. If the data was not normally distributed, Kruskal-Wallis test was used. Post hoc analysis was done using Mann-Whitney test. P value ≤ 0.05 were considered significant.

Results

Fifty-six patients with type 2 diabetes whose age and sex were matched were enlisted in the study including 41 females (73.2%) and 15 males (26.8%). The characteristics of the study subjects were shown in Table 1. Of the 56 subjects, 16 were enrolled in the control group, 18 were enrolled in non-diabetic retinopathy (NDR) group, and 22 were in diabetic retinopathy (DR) group.

The baseline features among 3 groups were comparable in terms of the average age (control group

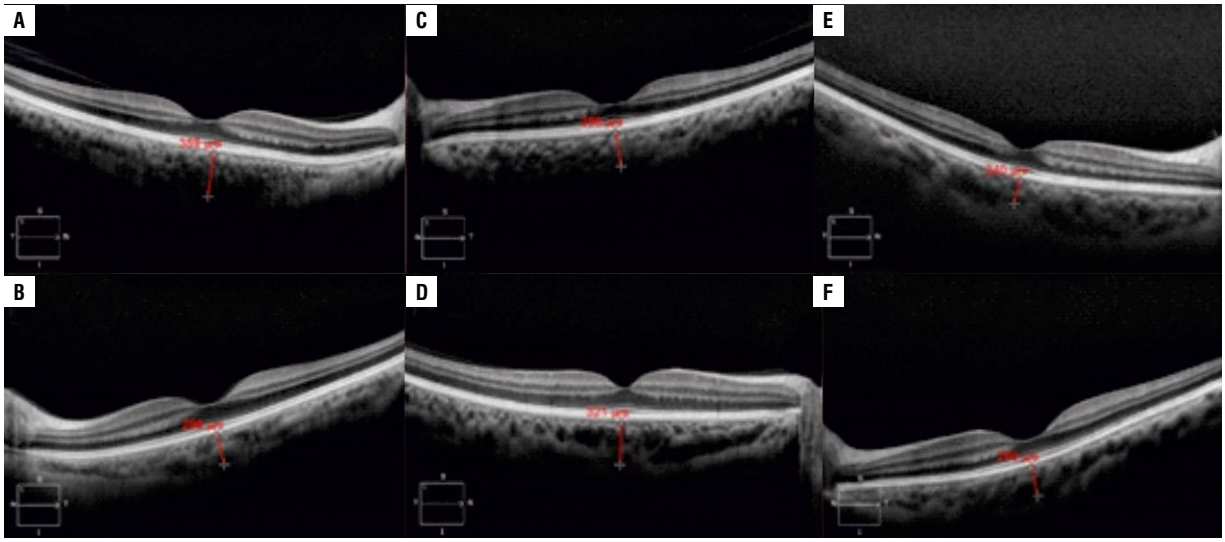

Figure 1. Representative Cases of Enhanced depth imaging spectral-domain optical coherence tomography (EDI-OCT) images in control group (A and B); NDR group (C and D); and DR group (E and F)
DR — diabetic retinopathy; NDR — non-diabetic retinopathy

Table 1. Characteristics of the Study Subjects in Control, NDR, and DR Group

Variables	Groups			P-value
	Control	NDR	DR	
	N = 16	N = 18	N = 22	
Age [years]	51.31 ± 5.72	51.67 ± 4.64	52.45 ± 4.46	**0.761**
Mean ± SD				
Sex				**0.981**
Male	4 (25.0%)	5 (27.8%)	6 (27.3%)	
Female	12 (75.0%)	13 (72.2%)	16 (72.7%)	
MAP [mmHg]	95.41 ± 11.36	95.83 ± 6.91	99.55 ± 8.12	**0.276**
Mean ± SD				
HbA1c [%]	5.44 ± 0.32	8.99 ± 1.96	9.01 ± 1.82	**0.0001***
Mean ± SD				
IOP [mmHg]				**0.29**
Mean ± SD	15.13 ± 2.84	16.28 ± 2.24	14.86 ± 3.38	
T2D duration [years]				
Mean ± SD	—	3.44 ± 2.85	9.48 ± 5.13	**0.0001***

The analytic test used was ANOVA test among the characteristics of 3 groups, if the data was normally distributed. If the data was not normally distributed, Kruskal-Wallis test was used. Post hoc analysis was done using Mann-Whitney test. P value ≤ 0.05 was considered significant
DR — diabetic retinopathy; HbA1c — glycated hemoglobin; IOP — intraocular pressure; MAP — mean arterial pressure; NDR — non-diabetic retinopathy; SD — standard deviation; T2D — type 2 diabetes

51.31 ± 5.72 years; NDR group 51.67 ± 4.64; and DR group 52.45 ± 4.46). The glycemic control shown by HbA1c in DR and NDR group were significantly higher (p = 0.0001) than the control group and there was also a significant difference in duration of DM between DR and NDR group which was longer in the DR group with the median of 3.5 years in the NDR group and 10 years in the DR group.

Table 2 demonstrates a significant difference in choroidal thickness measurement (p = 0.042) among 3 groups which are control (283.07 ± 69.98), NDR (266.68 ± 51.76), and DR group (247.57 ± 57.95). DR group has the lowest choroidal thickness compared to NDR and control group. Our study found significant difference in choroidal thickness measurement (p = = 0.037) between NDR group (266.68 ± 51.76) and DR

Table 2. Comparison of Choroidal Thickness in 3 Groups

Variable	Group			P-value
	Control	NDR	DR	
	N = 28	N = 28	N = 28	
Choroidal thickness (CT)				**0.042***
Mean ± SD	283.07 ± 69.978	266.68 ± 51.764	247.57 ± 57.947	

For numerical data, the p value was tested by One Way ANOVA test if the data were normally distributed with alternative Kruskal-Wallis test if the data were not normally distributed. For categorical data, the p value was tested with the Chi Square test. The significance is based on the p value < 0.05. The * sign indicates the p value < 0.05, which means that it is statistically significant or significant.
DR — diabetic retinopathy; NDR — non-diabetic retinopathy; SD — standard deviation

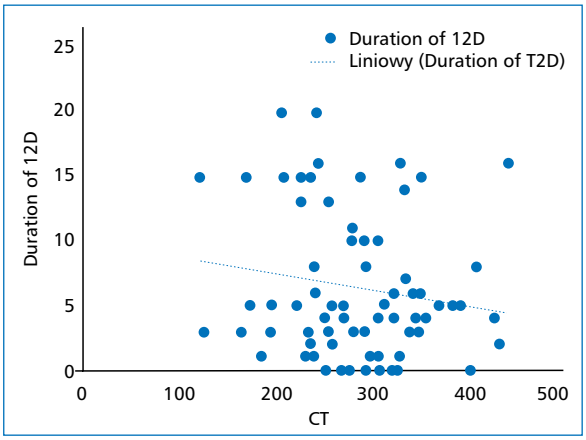

Figure 2. Scatter Dot Plot, Correlation between Choroidal Thickness and Duration of T2D

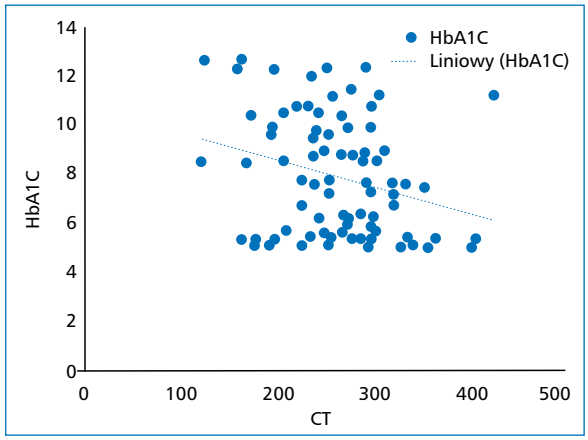

Figure 3. Scatter Dot Plot, Correlation between Choroidal Thickness and HbA1c

Table 3. Comparison of Macular Thickness (MT) in 3 Groups

Variable	Groups			P-value
	Control	NDR	DR	
	N = 28	N = 28	N = 28	
Macular thickness (MT)				
Mean ± SD	239.82 ± 17.419	236.11 ± 26.494	263.79 ± 45.169	**0.015***

For numerical data, the p value was tested by One Way ANOVA test if the data were normally distributed with alternative Kruskal-Wallis test if the data were not normally distributed. For categorical data, the p value was tested with the Chi Square test. The significance is based on the p value < 0.05. The sign * indicates the value of p < 0.05, which means that it is statistically significant or significant
DR — diabetic retinopathy; NDR — non-diabetic retinopathy; SD — standard deviation

group (247.57 ± 57.95) and between control (283.07 ± 69.97) and DR group (p = 0.032).

Statistical analysis results of Spearman's correlation test between choroidal thickness and duration of T2D showed p value of 0.145 which is more than 0.05 (p value > 0.05). This result shows no significant or statistically meaningless correlation between these variables. It can be concluded that there is no correlation between the choroidal thickness and the duration of DM (Fig. 2). The same result can be seen between choroidal thickness and HbA1c which shows p value of 0.168 (p value > 0.05). It can also be concluded that there is no correlation between the choroidal thickness and HbA1c (Fig. 3).

Table 3 also demonstrates a significant difference in macular thickness measurement (p = 0.015) among 3 groups which are control (239.82 ± 17.42), NDR (236.11 ± 26.49), and DR group (263.79 ± 45.17). On the other hand, the highest macular thickness was seen in DR group. Significant difference in macular thickness measurement (p = 0.027) between control (239.82 ± 17.419) and DR group (263.79 ± 45.169)

and between NDR group (236.11 ± 26.494) and DR group ($p = 0.009$) was found in our study.

Discussion

In this study, we aimed to compare the choroidal thickness (CT) and macular thickness (MT) of Indonesian DM patients with DR (DR) and without DR (NDR). We found that there is a significant difference in choroidal thickness among control, NDR, and DR group. The lowest CT was found in the DR group. On the other hand, we found that DM patients with DR had the highest MT compared with those without DR. We also found that CT was not correlated with HbA1c and duration of DM.

The lowest CT was observed in the group of patients with diabetes and DR in the current study. This suggests that thinner choroid may contribute to the latter stages of retinopathy or may cause retinopathy by itself. Studies of CT in patients with diabetes showed various findings in eyes with DR. Kim et al. [18] found that as DR progressed from mild to PDR, CT grew noticeably. In contrast, Temel et al. [23] found that mean subfoveal, nasal, and temporal CT were decreased in treatment-naïve patients with NPDR in comparison with controls. The subfoveal CT were also significantly reduced in patients with PDR in a study by Adhi et al. [20] and thinner in patients with DME compared with normal subjects in a study by Regatieri et al. [21]. This suggests that our study supports previous studies on the decrease in CT as DR progressed.

Our study, which found that the CT decreased from the NDR to the DR group, also supports earlier studies on the reduction in choroidal flow during DR [21, 28]. Earlier studies with laser Doppler flowmetry in DR patients have shown a reduction in choroidal blood flow and selective filling of the choriocapillaris during indocyanine green angiography [29–31]. The outer layers of retina and the retinal pigment epithelium (RPE) may receive less oxygen, which may cause alterations in the diabetic choroid resulting in DR. CT reduction may be related to hypoxia of the retinal tissue, although it is unclear whether underlying ischemia of the retina is primary or secondary to another process.

Several systemic variables, including, HbA1c level and duration of diabetes have already been linked to CT. [18, 32, 33]. It is still unclear how HbA1c affects CT. HbA1c may be a confounding factor since Unsal et al. [32] and Kim et al. [18] reported a strong connection between HbA1c and CT. On the other hand, recent study by Temel et al. [23] found a moderate negative correlation between the duration of diabetes and HbA1c level and choroidal vasculature index. This was in line with Sahinoglu-Keskek et al. [34] who found HbA1c and subfoveal CT were not correlated at all. Similarly, after accounting for other variables, Wang et al. [35] found that HbA1c levels had no effect on the average CT. In line with previous studies, our study found no direct correlation between CT and HbA1c.

Duration of diabetes was also included in our study, but we did not find a significant correlation between duration of DM and CT. In contrast, Ambiya et al. [36] found that choroidal thickness decreases with longer diabetes duration, significantly after the onset of severe DR. On the other hand, Abadia et al. [33] found a marginally negative correlation between CT and duration of diabetes throughout the whole research population. These findings were in line with Shen et al. [28], Torabi et al. [31], and Sahinoglu-Keskek et al. [34] study which found no significant correlation between these two variables.

Our study also provided data on the macular thickness measurements in patients with diabetes with and without DR, which showed that the macular thickness was lower in patients without DR when compared with the DR group. These results were similar to recent study by Wei et al. [14] which found that MT in the NDR group was much lower than that in the NPDR group, demonstrating that OCT can detect MT that gradually deteriorates with the development of DR. Similar to our findings, Murugesan et al. [27] found that MT in patients with T2DM without DR was thinner than the general population. This data supports the theory that neuronal damage may occur before clinical DR. Our findings were also in line with Fernández-Espinosa et al. [37] who found higher retinal thickness in patients with DR compared to controls and Lattanzio et al. [38] who found thicker MT as DR advances.

The strength of this study is that it included samples from Southeast Asian population, specifically Indonesian. One of the limitations of the study is that we did not evaluate DR severity profile in a finer manner. As this study used a cross-sectional analysis, findings from this study cannot ascertain the actual causal relationship between retinal layer thickness changes and DR. Hence, future longitudinal follow-up studies are required to further validate our findings. Our study found that patients with diabetes generally had thinner choroid and thicker macula with the progression of diabetes. These findings may provide new insights in understanding the pathogenesis of DR.

Conclusions

In conclusion, Indonesian subjects with type 2 diabetes with retinopathy had significantly thinner choroid and thicker macula when compared to diabetes without retinopathy group. The thinning of choroid and thickening of macula develops as the disease progresses to diabetic retinopathy

Funding

No funding was received for this study.

Acknowledgements

The authors appreciate the patients enrolled in this study, Department of Ophthalmology and Internal Medicine, Faculty of Medicine, Universitas Padjadjaran, National Eye Center Cicendo, Hasan Sadikin General Hospital, Bandung, Indonesia for their cooperation and involvement in this study.

Conflict of interests

None declared.

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