Evaluation of Choroidal Thickness in Patients with Diabetic Macular Edema and Relationship Between Choroidal Thickness and Treatment and Diabetic Complications

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ABSTRACT

Purpose: Firstly, to compare the choroidal thickness using optical coherence tomography (OCT) between diabetic macular edema (DME) patients who received intravitreal bevacizumab, ranibizumab and dexamethasone implant injection and a age-matched healthy group. Secondly, to investigate the relationship between diabetic choroidopathy and diabetic nephropathy, neuropathy, HbA1c levels and metabolic conditions in these patients undergoing intravitreal injection therapy.

Materials and Methods: Total 72 (52 males, 20 females) DME patients and 60 (44 males, 16 females) healthy control participants were included in this retrospective, cross-sectional, and comparative study.

Results: The baseline choroidal thickness (ChT) in patients with DME was thinner than in the control group. When the relationship between changes in central macular thickness and mean macular thickness values and age, gender, disease duration, mean arterial pressure, body mass index (BMI), LDL level, and HbA1c values were examined, no significant relationship was observed (p>0.05 for all). There was a significant inverse correlation between BMI and initial average ChT (p:0.027). There was also a positive correlation between LDL levels and choroidal thickness (0.007). In the comparison between ChTs according to the presence of microalbuminuria, last subfoveal ChT was observed to be thinner in presence of microalbuminuria (p: 0.038). In the comparison between ChTs of patients with and without neuropathy, the average last nasal ChT was higher in patients with diabetic neuropathy (p: 0.025). There was no significant relationship between HbA1c levels and choroid thicknesses.

Conclusions: The choroidal thinning in this study may be a sign of diabetic choroidopathy-induced choroid ischemia.

Keywords: Choroidal thickness, Diabetic macular edema, Intravitreal injection.

INTRODUCTION

In the pathogenesis of diabetic macular edema (DME), there is retinal vascular hyperpermeability associated with focal leakage from microaneurysms or diffuse leakage from capillaries. The choroid takes 95% of the entire ocular blood flow and supplies oxygen and nutrients to the retina, therefore diabetic patients may have changes in choroidal vascular structures. However, histopathological studies have shown that choriocapillaris loss, increased tortuosity, narrowing and dilation of vessels, and sinus-like structure formation between the choroid lobes are found in diabetic retinopathy (DRP).[1, 2] In addition, the association of DRP and diabetic choroidopathy has also been demonstrated in clinical studies.[3]

By using non-invasive imaging techniques, it is easier for clinicians to evaluate posterior structures such as choroid and retina. Detailed, high resolution, cross-sectional view of microscopic retinal and choroidal structures can be obtained with spectral domain optical coherence tomography (SD-OCT), which is one of the mentioned non-invasive imaging methods.[4] The relationship between diabetic choroidopathy and diabetic retinopathy (DRP) has also been demonstrated by clinical findings, however the results are controversial.[5-12] In addition, the relationship between diabetic complications (such as microalbuminuria) and HbA1c levels and choroidal thickness (ChT) is controversial.[5, 6, 13-15] Also, the effects of intravitreal (such as anti-vascular endothelial growth factors (VEGF) and

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steroid) injections on the ChT are another controversial issue.[16-20]

Our first aim in this study was to compare the ChT using SD-OCT between DME patients who received intravitreal bevacizumab (IVB), ranibizumab (IVR) and dexamethasone implant (IVD) injection and a non-diabetic group. Our second aim is to investigate the relationship between diabetic choroidopathy and diabetic nephropathy, neuropathy, and HbA1c levels in these patients undergoing intravitreal injection therapy.

MATERIALS AND METHODS

In this retrospective, cross-sectional, and comparative study, total 72 (mean age 66.0 ± 4.1 years) DME patients and 60 (mean age 66.1 ± 4.0 years) healthy control participants were included. The worst eyes of the patients and only right eyes of the healthy participants were evaluated for study. All subjects were informed about the study procedure, and written consent was obtained. The study followed the tenets of the Helsinki Declaration and was approved by the institutional ethics committee.

This study was composed of five groups as follows:

Group 1: Healthy participants

Group 2: Who received iv bevacizumab injection only

Group 3: Who received iv bevacizumab + ranibizumab injection

Group 4: Who received iv bevacizumab + dexamethasone implant injection

Group 5: Who received bevacizumab + ranibizumab + dexamethasone implant

In the presence of diabetic macular edema, as the health system obliges in our country, the first 3 doses should be bevacizumab if intravitreal injection will be performed. In cases responding to 3 doses of IVB treatment, IVB treatment was continued when necessary (group 2). In case of unresponsiveness to IVB, a switch was made from bevacizumab to ranibizumab (group 3). In patients with an increase in macular thickness despite 3 doses of IVB, a switch was made from bevacizumab to dexamethasone (group 4). In patients with an increase in macular thickness despite IVR after 3 doses of bevacizumab unresponsive to treatment, a switch was made from ranibizumab to dexamethasone (group 5).

The patients included in the study consisted of patients diagnosed with DME with persistent central involvement defined as central macular thickness (CMT) >300 µm after 3 or more consecutive 1.25 mg IVBs. In the eyes undergoing IVR treatment, changes in CMT between the visits before and after the last IVB were below 10% in all eyes. A decrease of >50 µm in dry macula and/or CMT after the first IVR was considered an anatomical response. IVD treatment was initiated in those without anatomical response. In eyes that switched to IVD treatment after IVB, an increase of >50 µm after the last IVB was the criterion for switching to IVD treatment.

Participants who had no intraocular disease other than non-proliferative diabetic retinopathy, who received at least 3 doses of intravitreal injections due to DME, and were followed for at least 1 year after the first injection were included in the patient group. Patients whose body mass index (BMI), mean arterial pressure (MAP), low density lipoprotein (LDL), and HbA1c levels were noted at the end of 1-year follow-up were included. Healthy individuals without any ophthalmic or systemic disease were included for the control group. All participants underwent a detailed ophthalmic examination by the same ophthalmologist. All individuals with <21mm or >24 mm axial length, significant refractive errors (>3 diopters of spherical equivalent refraction), intraocular pressure ≥21 mmHg, retinal vascular diseases other than non-proliferative DRP (such as proliferative DRP, retinal artery/vein occlusion, macroaneurysm, etc.), uveitis, glaucoma, pseudo-exfoliation, patients who had previous ocular surgery, presence of any macular degeneration type, and smokers or ex-smokers were excluded from the analysis.

Choroidal thickness and central foveal thickness (CFT) were measured by spectral domain optic coherence tomography (SD-OCT) (RS-3000, NIDEK, Japan) by the same experienced operator. OCT measurements before and 1 year after treatment were statistically evaluated. For ChT values, five lines at nasal and temporal were drawn at 500 microns intervals, centering the subfoveal sclero-choroidal junction. For nasal ChT, the average of 2 measurements at 500 µm intervals at the nasal, the average of 2 measurements at the temporal interval at 500 µm interval for the temporal ChT, and for the average ChT, the average of the nasal, the average of the temporal, and subfoveal ChT were evaluated. In addition, it was noted whether the patient had systemic diabetic complications such as microalbuminuria and neuropathy and whether panretinal photocoagulation (PRP) was performed.

Statistical analysis

Analysis were performed using the SPSS statistical software for Windows, version 21, released in 2012 (IBM, Armonk, NY, USA). The descriptive statistics are expressed as means ± standard deviations for variables with normal distributions, medians (interquartile range for non-normal distributions), and the number of cases and

percentages (%) for nominal variables. The Kolmogorov-Smirnov distribution test was used to examine the normal distribution. Pearson Chi-square test and Fisher's Exact test were used for comparison of descriptive statistics, as well as qualitative data. Mann-Whitney U test was performed for comparison of non-normally distributed quantitative data of two groups; Student's t test was used for normal distributed data. Kruskal-Wallis test was performed for comparison among more than two groups of non-normally distributed quantitative data, and Mann-Whitney U test was performed to analyze the group causing the difference. For comparison among more than two groups of normally distributed quantitative data, ANOVA test was performed and the group causing the difference is defined with post hoc Tukey test. Repeated measures ANOVA test was used for the analysis of repeated measurements. When the relationship between parameters were investigated, Pearson's correlation test was used for normally distributed data, and Spearman's correlation test was used for nonparametric distributed data. The results were evaluated at 95% confidence interval, p <0.05 significance level.

RESULTS

The demographic and clinical features of the patients are shown in table 1. Initial and final CMT and mean macular thickness (MMT) values of the groups and intra-group comparisons are demonstrated in table 2. When the relationship between changes in CMT and MMT values and age, gender, disease duration, MAP, BMI, LDL level, and HbA1c values were examined, no significant relationship was observed (p>0.05 for all). In addition, there was no significant correlation between the presence

Table 1. *Demographic and clinical features of the patient and control groups.*

	Group 1 (n:60)	Group 2 (n:40)	Group 3 (n:6)	Group 4 (n:16)	Group 5 (n:10)	p value*
Age (years)	66.1±4.0	66.2±4.5	66.6±1.0	66.0±2.9	65.2±5.0	0.644
Gender (male/female)	44/16	26/14	6/0	12/4	8/2	0.438
Disease duration (years)	N/A	20.3±5.9	16.3±3.6	19.2±4.1	19.8±4.8	0.549
BMI		23.3±2.4	24.4±1.3	26.2±3.5[a]	27.0±1.3[a]	<0.001
MAP (mm/Hg)		96.2±20.0	87.0±20.1	96.6±20.9	115.6±15.3[a, b]	<0.001
LDL		141.7±21.5	141.3±9.8	189.7±54.3[a, b]	234.4±41.6[a, b, c]	<0.001
HbA1c (mg/dl)		7.3±0.9	9.0±0.5[a]	8.6±2.1[a]	11.1±1.2[a, b, c]	<0.001
Microalbuminuria (n)		16	2	10	10	0.004
Neuropathy (n)		4	0	6	10	<0.001
PRP		4	0	6	10	
Bevacizumab (n)		6.2±1.1	3.0±0.0	3.3±0.5	3.7±1.3	
Ranibizumab (n)		N/A	5.6±0.5	N/A	4.1±1.6	
Dexamethasone (n)		N/A	N/A	1.6±0.5	1.4±0.5	

BMI: Body mass index, MAP: Mean arterial pressure, PRP: Panretinal photocoagulation
[a]: there was a significant difference compared to group 2, [b]: there was a significant difference compared to group 3
[c]: there was a significant difference compared to group 4, *: belong to comparisons among groups 2, 3, 4, and 5

Table 2. *Initial and final central macular thickness (CMT) and mean macular thickness (MMT) values of groups. and comparisons within groups.*

	Initial CMT	Final CMT	Initial MMT	Final MMT
	Mean ± Standard Deviation; µm			
Group 1	259.2±21.4		316.5±57.0	
Group 2	390.0±87.8	281.1±35.6*	366.1±57.7	348.7±66.8*
Group 3	391.4±95.2	296.1±21.1*	381.0±74.7	344.2±19.9*
Group 4	400.0±60.9	287.7±13.2*	378.9±38.5	335.7±16.7*
Group 5	394.8±112.3	277.8±11.2*	422.6±100.1	353.4±70.4[+]

*: Significantly different from the initial value. p<0.05 for all, [+]: p:0.070

of microalbuminuria, and neuropathy and response to treatment (p>0.05 for all).

Choroidal thickness values, intra-group and inter-group comparisons are summarized in table 3. In the patient group, there was a significant inverse correlation between body mass index (BMI) and initial average ChT in the regression analysis by adding age, gender, disease duration, mean arterial pressure, BMI, LDL, and HbA1c levels, and presence of microalbuminuria and neuropathy into the model (p:0.027). There was also a positive correlation between LDL levels and choroidal thickness (0.007). Apart from these, the presence of neuropathy was close to being significant with choroid thickness, although it was not significant (p:0.054).

Microalbuminuria was present in 38 patients. In the comparison between ChTs according to the presence of microalbuminuria, last subfoveal ChT was observed to be thinner in presence of microalbuminuria (p: 0.038). In the repeated measurement analysis between microalbuminuria groups, changes in ChT were similar in each region. Twenty patients had diabetic neuropathy. In the comparison between ChTs of patients with and without neuropathy, the average last nasal ChT was higher in patients with diabetic neuropathy (p: 0.025). In the repeated measurement analysis between neuropathy groups, changes in ChT were similar in each region.

Patients were also classified into 3 groups according to their HbA1c levels: those with good glycemic control in group 1 (HbA1c <7%), those with moderate glycemic control in group 2 (HbA1c between 7% and 8%), and those with poor glycemic control (HbA1c >8%) in group 3.[8] In the analysis, which was divided into 3 groups according to HbA1c levels, the mean temporal ChT was different between group 1 and group 2 (p: 0.016). In the repeated measurement analysis between HbA1c groups, changes in ChT were similar in each region. As well, there was no significant relationship between HbA1c levels and choroid thicknesses (p>0.1).

DISCUSSION

The structural and functional integrity of the choroid is essential for the normal function of the retina, as the choroid contributes to the metabolic support of the retinal pigment epithelium and the external retina.[21, 22] The recent imaging studies have focused on choroidal thickness, a feature of diabetic choroidopathy or atrophy, and the relationship between clinical findings and treatment modalities and ChT has been investigated. However, results regarding changes in ChT in diabetics vary.

In diabetic patients without DRP, the consensus regarding choroid thickness has not been reached due to different results. In some studies, there are results reporting that the choroid has become thinner,[5, 8] in others it has become thicker, [6, 7, 9] and even in prediabetic patients.[10] However, in diabetic patients with macular edema, the issue of thinning or thickening of the choroid thickness is controversial.[12, 23-25] In this study, it was observed that the choroid thickness

Table 3. *Comparison of choroid thicknesses within and between groups.*

	Temporal		Subfoveal		Nasal		Average	
	first	last	first	last	first	last	first	last
	Median (Interquartile range); µm Mean ± Standard Deviation; µm							
Group 1 (n:60)	201(184;244) 210±33		217 (204;257) 226±33		214 (195;243) 216±32		210 (191;249) 218±31	
Group 2	156(138;199)[1] 169±41	152(132;163)[1] 172±48[a]	161(130;212)[1] 172±41	150(115;185) 170±39[a]	169(129;192)[1] 149±32	141(119;167)[1] 154±51[a]	169(136;200)[1] 143±28	145(126;170)[1] 149±33[a]
Group 3	173(132;269) 191±62	151(134;228) 161±27	151(138;196)[1] 167±28	147(126;245) 173±28	159(140;202)[1] 171±44	155(136;249) 172±56	190(136;193) 180±54	151(132;240) 174±51
Group 4	194(153;222) 189±32	170(138;219)[1] 192±25	195(178;213)[1] 193±25	165(132;234)[1,2] 192±26	193(167;220) 176±40	163(140;230)[1] 177±47	195(167;214) 180±45	165(136;228)[1] 178±44
Group 5	161(143;188)[1] 165±27	159(146;169)[1] 169±32	163(144;200)[1] 162±20	159(145;190)[2] 165±26	159(149;182)[1] 156±12	165(139;172)[1] 165±26	161(145;191)[1] 156±20	157(143;178)[1] 129±17
p value*	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
p value**	0.908		0.459		0.103		0.453	
Total (n:72)	172(139;203)[1] 175±40	156(135;176)[1] 158±34[a]	177(139;210)[1] 175±41	159(126;190)[1] 162±48[a]	173(144;199)[1] 174±36	148(132;174)[1] 156±37[a]	179(139;201)[1] 174±35	153(131;179)[1] 159±37[a]

[a]: In the analysis made with repeated measures ANOVA test, there was a difference between the last measurement and the first measurement. (intra-group analysis)
*: Evaluation between groups by Kruskal-Wallis test analysis
**: Evaluation of the difference between the first and last measurement between the groups performed with repeated measures ANOVA test
[1]: There was a significant difference compared to group 1 (inter-groups analysis)
[2]: There was a significant difference compared to group 2 (inter-groups analysis)

was thinner in the patients with untreated diabetic macular edema compared to the healthy population.

VEGF concentrations increase in eyes with DME.[26] VEGF, by penetrating all retinal layers and reaching the choroid, induces vasodilation through a mechanism involving increased nitric oxide production, and may increase ocular blood flow. Therefore, intravitreal anti-VEGF treatments cause choroid thinning, leading to narrowing of choroid vessels and decreased choriocapillaris endothelial cell fenestration.[27-29] Indeed, clinical studies with anti-VEGF, such as bevacizumab and ranibizumab, have also shown thinning of the choroid thickness.[18, 20] However, there are also studies that are not in line with our results, indicating no significant change in choroidal thickness with anti-VEGF treatment. However, there are publications that are not in line with the results of these studies, indicating that there is no significant change in ChT with anti-VEGF treatment.[16, 17] Also, corticosteroids block the production of inflammatory cytokines and VEGF, improve the barrier function of vascular endothelial cell tight connections, inhibit endothelial nitric oxide synthase, reduce tissue edema. IVD, therefore, can exert its therapeutic effect on the choroid, by reducing VEGF production.[30-32] Clinical studies have been conducted in which IVD application also has a thinning effect on choroidal thickness.[19] The current study also showed the thinning of the choroid thickness after iv anti-VEGF and dexamethasone administration in line with previous studies. In addition, in this study, it has been shown that whether or not anti-VEGF treatment was continued, the ChT was thinned and there was no difference between the treatment groups.

A study on healthy populations demonstrated the relationship between BMI increase and thinning in ChT.[33] It has been previously reported that high BMI increases the risk of retinopathy in diabetic patients.[34] In this study, the thinning of the ChT with increased BMI was also seen in diabetic patients. In the study examining the effect of fenofibrate for the treatment of dyslipidemia, it was shown that the risk of DME progression decreased by 31% in the group using fenofibrate[35] Also, an increase in ChT has been reported in patients with hypercholesterolaemia.[36] The positive correlation of serum LDL levels and ChT in this study is consistent with the results of previous studies. The relationship between HbA1c levels and ChT is also controversial. There are publications stating that there is a positive, negative relationship, or no relationship between them.[5, 6, 14] In the current study, there was no significant relationship between HbA1c levels and/or groups and ChT (except temporal choroid).

In this study, subfovel ChT was thinner in patients with microalbuminuria, possibly after treatment with choroidal edema regressed. There are also publications reporting decreased ChT in patients with microalbuminuria.[13,15] In another study, in evaluation before and after hemodialysis in diabetic patients with renal failure, DME eyes had a significant reduction in ChT.[37] However, there are also studies reporting an increase in choroid thickness in patients with microalbuminuria.[6, 14] Increased ChT in microalbuminuric patients may be associated with increased vascular permeability and/or vasodilation, autonomic irregularity or increased oncotic pressure due to endothelial damage and impaired regulation of extracellular matrix remodeling.[22, 38] However, since this may also represent generalized vascular dysfunction, it can also be interpreted as the cause of choroidal ischemia due to microvascular choroid damage in patients with DME. In addition, none or some of the patients included in the studies indicating an increase in ChT did not have DME.

Although the pathogenesis of the disruption in the blood-nerve barrier (BNB), which is the basis of diabetic neuropathy, has not been fully elucidated, it is thought that glycosylated albumin causes damage to the BNB in recent studies.[39] In addition, metabolic changes such as excess glucose and increased fatty acid influx can damage endoneurial endothelial cells and thus BNB. In this context, endothelial cells in the choroidal vessels are likely to undergo a similar effect.[40, 41] In the current study, there was an increase in choroidal thickness in the neuropathy group compared to the non-neuropathy group, though it was not significant before treatment. Although there was a decrease in choroidal thickness after treatment, nasal choroidal thickness was higher in the neuropathy group. Moreover, a greater thinning was observed in the non-neuropathy group compared to the neuropathy group with more inflammation. From this, we infer that the inflammation in the choroid is relatively reduced with intravitreal treatment, but it is less effective in the neuropathy group, where inflammation is probably higher. Therefore, we can attribute the significantly thicker nasal choroid after treatment to this situation.

There are some limitations of the present study;

- Because it is a cross-sectional study, it does not provide data about the change over time.
- The effect of the presence of the disease on different age groups is not known, as the duration of the disease may have an effect on the outcome.
- Due to the obligation to use bevacizumab initially in intravitreal therapies, a single drug-created group (IVR or IVD only) could not be created.

Considering all these results, the differences in ChT between studies, the metabolic status of patients (such

as disease duration, BMI, microalbuminuria/presence of neuropathy, serum lipid/HbA1c levels, etc.), retinopathy severity, differences in the treatments (iv anti-VEGF/dexamethasone) may be caused by such factors. Despite choroidal thickening, which can be seen by increased intraocular VEGF and increased serum lipids, we think that choroidal thinning in this study may be a sign of diabetic choroidopathy-induced choroid ischemia. Indeed, we speculate that the lower subfoveal ChT after treatment in patients with microalbuminuria was likely to be a supportive finding of that speculation, possibly due to regression of choroidal edema. In addition, thinning of the choroid after treatment in DME patients can be explained by an increase in VEGF levels, vasodilation of the choroid, increased choroidal blood flow and/or vascular hyperpermeability. Although the thinning of the ChT and diabetic complications are associated, there is no difference in response to treatment in patients with and without metabolic complications.

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Disclosure of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the article.

Ethical approval

All procedures involving human participants were in accordance with the ethical standards of our institution's research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Informed consent

Informed consent was obtained from all individuals included in the study.

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