Alterations of Choroidal Thickness With Diabetic Neuropathy

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Submitted: August 20, 2015
Accepted: February 8, 2016

Citation: Yazici A, Sogutlu Sari E, Koc R, et al. Alterations of choroidal thickness with diabetic neuropathy. *Invest Ophthalmol Vis Sci*. 2016;57:1518–1522. DOI:10.1167/iovs.15-17966

Purpose. To evaluate the effect of diabetic polyneuropathy on choroidal thickness in type 2 diabetes patients.

Methods. Forty-one diabetic polyneuropathy (DPN) patients with no or mild retinopathy, 50 non-DPN diabetic patients with no or mild retinopathy, and 42 healthy controls without any retinal complaint were included in the study. All participants underwent detailed ophthalmic examinations. Choroidal thickness (CT) measurements were performed by the same independent technician in the morning between 9 and 11 AM to avoid diurnal variations. Perpendicular CT was measured from the outer edge of the hyperreflective retinal pigment epithelium to the inner sclera at seven locations: the fovea; and 500, 1000, and 1500 μm temporally and nasally to the fovea.

Results. The groups were age and sex matched ($P > 0.05$). The mean subfoveal CT values were significantly different in groups with a thickening trend from control to non-DPN and DPN ($P < 0.01$). The mean values for subfoveal CT in control, non-DPN, and DPN groups were 241.12 ± 52.71, 279.82 ± 51.42, and 304.71 ± 54.92 μm, respectively. The same thickening trend was also evident in all other six measurement points with statistical significance ($P < 0.01$).

Conclusions. Diabetic patients had increased CT compared to healthy controls. The presence of neuropathy in diabetes patients caused additional choroidal thickening, compared to nonneuropathic patients.

Keywords: choroid, diabetes, neuropathy, retinopathy, thickness

The retina is a highly functioning organ with increased metabolic demand, which explains why it attracts the highest blood flow rates like other vital organs in the body.[1] The choroid is one of two blood supplies of the retina and its primary role is to provide approximately 85% of the blood supply to the retina including all the photoreceptors and the entire retinal pigment epithelium (RPE).[2] Photoreceptors promptly degenerate if choroidal circulation or innervation to the choroid is disrupted.[3,4] To ensure a flawless oxygen supply to the retina, the choroidal blood supply must maintain a very high oxygen tension, which is achieved through high blood flow resulting in an arterial/venous oxygen tension difference of only 3%.[5] With the introduction of enhanced depth imaging (EDI) mode of optical coherence tomography (OCT), visualization of this important structure has become possible, which has increased our understanding of the choroidal changes in certain diseases such as central serous chorioretinopathy, age-related macular degeneration, polypoidal choroidal vasculopathy, choroidal neovascularization, and glaucoma.[6–9] The thickness of the choroid in some of these conditions represents a potential follow-up parameter in the course of the diseases.[10,11]

Diabetes mellitus (DM) might cause choriocapillaris loss, increased tortuosity, narrowing and dilation of vessels, and sinus-like structure formation between choroidal lobules.[10,11] The choroidal status in DM has recently gained attention after the role of the choroid in certain ocular diseases was assessed. However, the results are conflicting with thickening,[12] thinning,[13] and no change.[14] Choroid is a vascular structure that has rich neuronal innervation, thus neurogenic mechanisms might be strongly involved in choroidal blood flow regulation.[15] A recent study[16] has shown that the cornea, which resembles choroid with its rich nerve supply, is strongly involved in diabetic autonomic neuropathy (DAN). The authors[16] have even claimed that corneal confocal microscopy has the potential to demonstrate DAN, which is a challenge in diagnosis.

From this point of view, we hypothesized that neuropathy might cause choroidal thickness (CT) changes in diabetes mellitus patients. For this purpose, we tried to compare the CT values in controls and diabetes patients with or without neuropathy.

Materials and Methods

The study was conducted with adherence to the tenets of Helsinki declaration and under the approval of the institutional ethics committee. Informed consent from each participant was

Table 1. Demographic Characteristics of Groups

	Control	Non-DPN	DPN	*P**
Age, mean ± SD, y	62.1 ± 7.6	59.3 ± 10.5	59.3 ± 11.9	0.12
BCVA	0.84 ± 0.25	0.88 ± 0.24	0.82 ± 0.21	0.43
IOP, mm Hg	15.0 ± 2.9	14.8 ± 3.4	15.5 ± 2.0	0.53
Spherical error, diopter	−0.75 ± 0.54	−0.58 ± 0.59	−0.82 ± 0.49	0.25
HbA1c, %	5.33 ± 0.28	6.41 ± 1.20†	6.90 ± 1.31†	0.01
CMT, μm	245.4 ± 21.7	254.0 ± 20.5	252.2 ± 22.1	0.14
Sex, M/F	17/25	25/25	20/21	0.66
Hypertension, *n*	8/42	4/50	4/41	0.42
Coronary artery disease, *n*	1/42	3/50	2/41	0.29
Respiratory disease, *n*	1/42	1/50	1/41	0.98

* 1-way ANOVA for numerical data, χ^2 test for categorical variables.
† $P < 0.05$ for groups that differ when compared to the control group with post hoc LSD test.

also gathered. Patients admitted to the internal medicine department with new or previous diagnosis of type 2 DM, who were referred to the ophthalmology department for detailed ophthalmic examinations, and healthy controls who were admitted to daily ophthalmology visit without any retinal complaints between July 2013 and January 2015 were prospectively enrolled in the study. All subjects underwent detailed ophthalmologic examination including best-corrected visual acuity (BCVA), intraocular pressure measurement, slit-lamp biomicroscopy, and dilated fundus examination. Exclusion criteria were the presence of ametropia more than 3 diopters, axial length less than 22 mm or more than 25 mm, diagnosis of glaucoma, age-related macular degeneration, uncontrolled hypertension, previous intraocular surgery or intervention, macular diseases and media opacities, which limit the visualization of the fundus and choroid measurements. A total of 91 patients without retinopathy or with mild retinopathy without macular edema[17] and 42 controls who fulfilled the inclusion criteria were included. Patients were sent to the neurology department for neuropathy evaluation. Diabetic peripheral neuropathy (DPN) diagnosis was established with presence of clinical symptoms, Douleur Neuropathique 4 questionnaire (DN-4), neurological examination findings, and electroneurophysiological assessment after other possible causes of peripheral neuropathies were excluded (cancer related, side effect of immunosuppresive drugs, vitamin B12 deficiency, uremic and other metabolic causes, etc.). Finally, the study included 41 DPN patients, 50 non-DPN patients, and 42 controls. Age, sex, visual acuity, intraocular pressure, spherical refractive error, Hemoglobin A1c (HbA1c) levels, diabetes duration, and concomitant systemic diseases were noted for each participant.

The same independent technician performed central macular thickness (CMT) and CT measurements (Cirrus HD spectral domain-OCT Model 4000; Carl Zeiss Meditec, Inc., Dublin, CA, USA) in the morning between 9 and 11 AM to avoid diurnal variations. The CT scanning pattern used on Zeiss Cirrus HD 1-line raster is a 6-mm line consisting of 4096 A-scans. Images were taken with the vitreoretinal interface adjacent to the zero-delay and were not inverted to bring the choroid adjacent to zero-delay, as image inversion using the Cirrus software results in a low-quality image. The HD 1-line raster has 20 B-scans averaged together without tracking. Central macular thickness scanning with the Cirrus HD-OCT was performed with the 512 × 128 scan pattern where a 6×6-mm area on the retina is scanned with 128 horizontal lines, each consisting of 512 A-scans per line (total of 65,536 sampled points) within a scan time of 2.4 seconds. Participants were instructed not to consume caffeine or smoke cigarettes on the measurement day until the measurement time. Attention was given to have the signal strength of all measurements above 6/10. Two masked observers (ESS and GS) measured the perpendicular CT from the outer edge of the hyperreflective RPE to the inner sclera at seven locations: the fovea; 500, 1000, and 1500 μm temporally and nasally to the fovea. Three consecutive measurements from each location were obtained and the average value was recorded. The intraobserver and interobserver reliabilities of EDI-OCT measurements were assessed with intraclass correlation coefficient (ICC).

Normality distribution of the data was assessed with Shapiro-Wilk test; since the data were normally distributed, 1-way ANOVA and post hoc least significant difference (LSD) test at the 5% level of significance were used for comparison of the groups. Age and sex differences between patients and controls were analyzed with *t*-test and χ^2 test, respectively. Pearson correlation was used to assess the relationship of CT and diabetes duration. Power analysis post hoc was also performed for subfoveal CT measurements.

Results

The mean age was 59.28 ± 11.87 years for DPN patients, 59.29 ± 10.54 years for non-DPN patients, and 62.08 ± 7.57 years for controls. The male to female ratio in the same order was 20/21, 25/25, and 17/25, respectively. There was no significant difference between groups in terms of age and sex ($P = 0.12$ and 0.66, respectively). Intra- and interobserver ICC was 0.971 and 0.910, respectively, for EDI-OCT measurements and therefore the measurements of one observer (ESS) were used for analysis. Right and left eye CT values were compared within groups and there was no significant difference ($P > 0.05$). One eye of each participant, randomly chosen, was used for further analysis. Groups had similar spherical refractive error, HbA1c, intraocular pressure, BCVA, and CMT values ($P > 0.05$). Demographic characteristics of patients are listed in Table 1.

The mean subfoveal CT values were significantly different among groups, with gradually increasing readings from control to non-DPN and DPN groups ($P < 0.01$). The mean values for subfoveal CT in control, non-DPN patients, and DPN patients were 241.12 ± 52.71, 279.82 ± 51.42, and 304.71 ± 54.92 μm, respectively. Post hoc analysis confirmed that each group differed from the others with the exception of non-DPN and DPN comparison at CT-1500 N localization ($P < 0.05$ and $P = 0.09$, respectively). Figure 1 represents this thickening trend among groups. The same thickening trend was also evident in all other six measurement points with statistical significance ($P < 0.01$). The mean CT values subfoveally and at six points 500 μm apart from each other temporally and nasally are listed in Table 2. Diagrammatic representation of mean CT in all seven-measurement points is shown in Figure 2. The duration of the

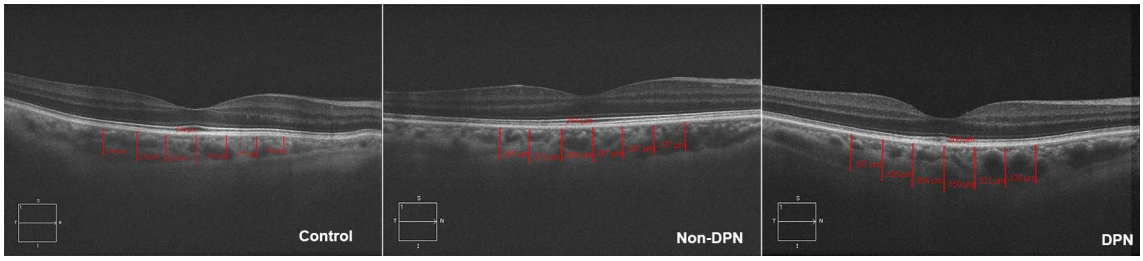

FIGURE 1. Example of manual segmentation of CT in control, non-DPN, and DPN groups. The perpendicular distance from the outer edge of the hyperreflective retinal pigment epithelium to the inner sclera is measured manually in each patient at seven locations: the fovea; 500, 1000, and 1500 μm temporally and nasally to the fovea.

DM diagnosis was higher in DPN group (8.8 ± 7.2 years) than non-DPN group (0.2 ± 0.9 years) ($P < 0.01$). However, DM duration was not correlated with any CT values in non-DPN and DPN group ($P > 0.05$).

The group sample sizes of 42 and 50 for control and non-DPN achieved 94% statistical study power for the detected difference of −39.0 μm in subfoveal CT measurements between groups with a significance level (α) of 0.05 with a two-sided two-sample *t*-test.

For sample sizes of 50 and 41 for non-DPN and DPN groups, the study power was 60% for the detected difference of −25.0 μm in subfoveal CT measurements between groups with a significance level (α) of 0.05 with a two-sided two-sample *t*-test.

DISCUSSION

The classical triad of involvement is nephropathy, neuropathy, and retinopathy; the latter one is the most familiar and troublesome for ophthalmologists. Neuropathy as an ocular involvement is mostly neglected and limited to the cornea and dry eye evaluations. Recent findings have also proposed that neuropathy is related to loss of retinal nerve fibers even without the presence of retinopathy findings.[18,19]

The choroidal changes in diabetic retinopathy have been studied and diverse results have been published. Regatieri et al.[13] have reported no difference in CT between nonproliferative retinopathy and healthy subjects with decrease in proliferative retinopathy and diabetic macular edema (DME). Similarly, in a multicenter trial, Gerendas et al.[20] have found thinner choroids in DME patients than in healthy volunteers. In contrast, Querques et al.[21] have stated that although the diabetic groups in their study (no retinopathy, nonproliferative retinopathy with and without macular edema) have significantly thinner choroids than the controls, there is no difference between the diabetic groups. Vujosevic et al.[22] have reported no difference between controls and diabetes patients, and DME does not influence the CT. In our study the diabetic patients with or without neuropathy had statistically thicker choroids in contrast to the results of the abovementioned studies. Our result is consistent with the results of the population-based Beijing Eye Study of Xu et al.[23] These authors have found that the subfoveal CT is thicker in diabetic patients but is not related to the severity of the retinopathy.

The literature search did not reach a conclusion about CT in diabetic patients or its relationship with the severity of the retinopathy. These controversial results might be attributed to several factors. First, most of the studies are retrospective in nature and include patients who have been treated with photocoagulation or anti–vascular endothelial growth factor (anti-VEGF) agents. Regatieri et al.[13] have pointed out this issue and stated that the presence of treated patients might be a limitation of their study. The same limitation might apply to the study of Gerendas et al.[20] as it includes treatment-naïve patients for a period of at least 3 months. Our study population had the advantage of being naïve and untreated, since it is known that photocoagulation or anti-VEGF treatment causes thinning of CT.[13,23] This issue has also been addressed by Xu et al.,[24] who have found thicker choroids in diabetic patients similar to our results. They emphasize that their results might be explained by the fact that their patients were treatment naive 'no or limited' retinopathy cases similar to our study population. A possible explanation for thicker choroids was proposed by Gerendas et al.[20] is that the choroid gets thicker as a result of systemic process and thinning is evident therein with the increasing severity of the disease as demonstrated by Vujosevic et al.[22] The second point is the time interval of the measurements. In retrospective studies one may not have the chance to pay attention to this issue and the results might be affected by the diurnal change of CT. Since our study was prospective, we had the opportunity to perform the measurements for all participants at the same time interval.

The main point of our study was the effect of the presence of neuropathy on the CT status of diabetic patients. The subfoveal CT in control, non-DPN, and DPN subjects was 242.33 ± 54.58, 270.45 ± 51.74, and 302.48 ± 51.71 μm, respectively, which demonstrated a statistically significant difference among groups. This difference was also significant

TABLE 2. Mean ± SD Values of CT in Seven Measurement Points Among Control, Non-DPN, and DPN Groups

	Control	Non-DPN	DPN	*P**
CT-1500 T	192.26 ± 54.75	229.51 ± 56.36	257.16 ± 48.03	<0.01
CT-1000 T	207.21 ± 53.77	243.20 ± 53.94	272.42 ± 52.56	<0.01
CT-500 T	216.91 ± 50.45	248.73 ± 50.26	286.61 ± 51.59	<0.01
CT-SF	241.12 ± 52.71	279.82 ± 51.42	304.71 ± 54.92	<0.01
CT-500 N	211.77 ± 55.77	236.24 ± 54.78	274.32 ± 55.33	<0.01
CT-1000 N	195.98 ± 60.34	227.57 ± 50.75	253.19 ± 54.31	<0.01
CT-1500 N	170.74 ± 61.38	212.73 ± 50.58	233.87 ± 51.77	<0.01

N, nasal; T, temporal.
* 1-way ANOVA.

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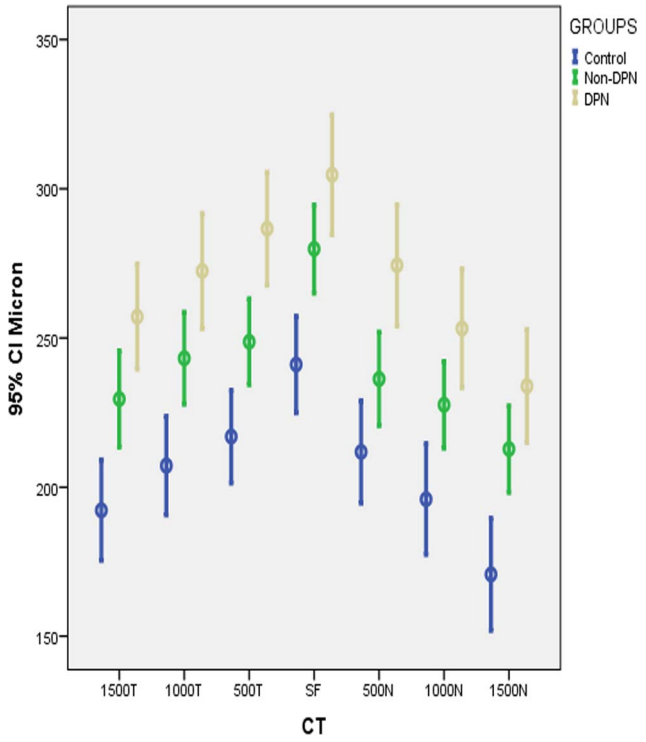

FIGURE 2. Distribution of choroidal thickness in seven measurement points. The diagram clearly shows that in each measurement point the DPN group had the highest CT readings followed by non-DPN and control groups.

in each measurement point but CT-1500 N. As seen, diabetes caused an increment in CT and the new finding was that neuropathy produced additional thickening in the choroid. We think that neuropathy might be the sole reason for this increment, since the patients in both diabetic groups had similar retinal involvement levels, HbA1c levels, and spherical errors. Previous studies have speculated that diabetic choroidopathy, first reported by Hidayat and Fine[25] in 1985, might be present before the onset of diabetic retinopathy and be involved in its development.[13,26] The current results of our study might propose the presence of diabetic neuropathy as a risk factor for diabetic choroidopathy. As we mentioned before, the choroid has an enormously rich neuronal innervation, probably necessary for a flawless retinal blood supply, so-called intrinsic choroidal neurons, which are mostly under the control of the autonomic nervous system. Our patients were DPN patients, and we know that DAN frequently accompanies DPN although most patients might be asymptomatic or have mild symptoms.[27,28] The sympathetic autonomic innervation of the choroid is mostly mediated through α1-adrenoreceptors,[29] and antagonistic treatment shows an increment in CT.[30] Zengin et al.[31] have studied oral nicotine and found that nicotine significantly decreases CT probably owing to vasoconstrictor effect. These two studies might be representative of the effect of sympathetic and parasympathetic receptor involvement in CT changes. Therefore, dysregulations of the choroidal blood flow in DPN patients, possibly related to autonomic involvement, might cause alterations in the CT. We might also speculate that this might be a warning sign for retinopathy or DAN. In a recent study, Tavakoli et al.[16] have demonstrated nerve damage in cornea, which is the other neuron-rich part of the eye, by confocal corneal microscopy and proposed that it is a rapid, noninvasive, highly sensitive and specific diagnostic test for DAN. Neurodegeneration has also been demonstrated with ganglion cell and retinal nerve fiber layer decrement in diabetic neuropathy patients with no or mild retinopathy.[18,19,32] The neurodegeneration of the inner retinal layers might not be related directly to increased CT or retinopathy, since the pathophysiology seems to be primary rather than secondary to microvascular complications.[18,32] Additionally, the inner layers atrophy and neurodegeneration might possibly be due to retinal circulation rather than the choroidal if vascular pathophysiology is suggested. Therefore, we think that neurodegeneration takes place in vaso nervosum of choroidal vessels, leading to loss of control of the autonomic nervous system rather than choroidal circulation, and the thickened choroid is an indirect presentation of this process. Although our results might be an indicator of autonomic involvement, we did not evaluate autonomic nervous system involvement specifically. This might be a limitation of our study. Another limitation of our study might be the relatively small sample size. However, with the current sample size of the groups, the power of the study was 94% and 60% for documented CT difference between control and non-DPN groups and between non-DPN and DPN groups, respectively. We used manual segmentation in CT measurements, which might cause intra- and interobserver measurement impact, but we tried to eliminate it by masking the clinicians who performed the measurements to subjects and diagnosis. The high ICC values are also important to show that our measurements were reliable. The HD 1-line raster measurements in our study might be suspected of not reflecting the whole macular change, and the absence of macular cube measurements might be accepted as a limitation. However, from a recently published study,[33] we know that single horizontal line scan measurements can represent the entire choroid successfully, and no significant difference was present when compared to macular cube measurements.

To our knowledge, this study is the first to evaluate the effect of DPN on CT. We found that diabetic patients had increased CT compared to healthy controls. The presence of neuropathy in diabetes patients caused additional choroidal thickening as compared to nonneuropathic patients. The status of the choroid is very critical for the evaluation of retinal diseases and deserves better understanding, as baseline CT has recently been speculated to be a predictor for anti-VEGF treatment response.[34] Further prospective, randomized, and large-scale studies are needed to evaluate the effect of neuropathy on choroidal vasculature.

Acknowledgments

The authors alone are responsible for the content and writing of the paper.

Disclosure: **A. Yazici**, None; **E. Sogutlu Sari**, None; **R. Koc**, None; **G. Sahin**, None; **H. Kurt**, None; **P.C. Ozdal**, None; **S.S. Ermis**, None

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