(01)

Evaluation of macular and choroidal thickness in diabetic patients without diabetic retinopathy

Ocena grubości plamki i naczyniówki u chorych na cukrzycę bez retinopatii cukrzycowej

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Abstract: Purpose: To compare macular and choroidal thickness in diabetic and healthy eyes using optical coherence tomography angiography.
Material and methods: Sixty-five eyes of 33 patients with type 2 diabetes, without clinically evident diabetic retinopathy and without diabetic macular edema and 34 eyes of 32 healthy volunteers were enrolled in the prospective study.
Optical coherence tomography angiography of the retina was performed in all subjects. Retinal thickness in the foveal and parafoveal region was determined based on Retina Map scans. Choroidal thickness was measured manually on horizontal spectral optical coherence tomography scans acquired with AngioVue SOCT in Enhanced HD line mode. Measurements were performed at the foveola, as well as 1.5 mm nasally and 1.5 mm temporally from the site of the first measurement.
Results: There was no difference in the foveal retinal thickness, foveal retinal volume, parafoveal retinal thickness and parafoveal retinal volume between diabetic subjects and healthy controls. In diabetic patients, the mean choroidal thickness at the fovea and at the nasal and temporal parafoveal areas were significantly lower as compared to healthy volunteers.
Conclusions: Diabetic patients without clinically manifest diabetic retinopathy have a significantly thinner choroid at the fovea and parafoveal area than healthy volunteers. There is no difference in the mean retinal thickness at the fovea and parafovea, as well as in the mean retinal volume both at the fovea and parafovea between diabetic and healthy eyes. Enhanced depth optical coherence tomography is a useful tool which can be used for non-invasive evaluation of the retinal and choroidal structure, thickness and volume.

Key words: AngioVue SOCT, OptoVue, macular thickness, choroidal thickness.

Abstrakt: Cel: porównanie grubości plamki i naczyniówki u chorych na cukrzycę oraz u osób zdrowych za pomocą angiografii optycznej koherentnej tomografii.
Materiał i metody: do badania prospektywnego włączono 65 oczu (33 pacjentów) z cukrzycą typu 2., bez klinicznie widocznych cech retinopatii cukrzycowej oraz bez cukrzycowego obrzęku plamki, i 64 oczu (32 osób) zdrowych ochotników.
U wszystkich badanych wykonano badanie angiografii optycznej koherentnej tomografii siatkówki. Aby ocenić grubość siatkówki w dołku oraz okołodołkowo, wykonano skany „Retina Map". Grubość naczyniówki została zmierzona za pomocą poziomych skanów „Enhanced HD" spektralnej optycznej koherentnej tomografii aparatem AngioVue. Grubość naczyniówki mierzono ręcznie. Pomiary były wykonywane zarówno w dołku, 1,5 mm donosowo, oraz 1,5 mm doskroniowo od dołka.
Wyniki: nie uwidoczniono różnic w grubości siatkówki w dołku, objętości siatkówki w dołku, okołodołkowej grubości siatkówki oraz okołodołkowej objętości siatkówki u chorych na cukrzycę oraz u osób zdrowych. U chorych na cukrzycę średnia grubość naczyniówki w dołku oraz nosowo i skroniowo od dołka była znacząco niższa niż u osób zdrowych.
Wnioski: u chorych na cukrzycę bez klinicznie widocznych cech retinopatii cukrzycowej grubość naczyniówki w dołku oraz okolicy okołodołkowej jest znacząco niższa niż u osób zdrowych. Nie ma różnic zarówno w średniej grubości siatkówki w dołku oraz okolicy okołodołkowej, jak i w średniej objętości siatkówki w dołku oraz okolicy okołodołkowej u chorych na cukrzycę i u osób zdrowych. Optyczna koherentna tomografia jest użytecznym narzędziem, które może być używane do nieinwazyjnej oceny grubości i objętości siatkówki i naczyniówki.

Słowa kluczowe: AngioVue SOCT, OptoVue, grubość plamki, grubość naczyniówki.

The authors declare no conflict of interest/ Autorzy zgłaszają brak konfliktu interesów w związku z publikowaną pracą

Introduction

As retinal vasculature is absent within the fovea, normal choroidal structure and function are crucial for the proper retinal function. In diabetes, systemic vascular changes may affect the choroid, as well (1). Obstruction of the choriocapillaris, vascular remodeling and choroidal neovascularization can result in outer retinal dysfunction (2–5).

Diabetic retinopathy (DR) and diabetic macular edema (DME) are the result of microvascular retinal changes. During the first two decades of the disease, nearly all patients

with type 1 diabetes and more than 60% of patients with type 2 diabetes develop some form of retinopathy (6). Visual acuity of diabetic patients often depends on the central foveal involvement, perifoveal capillary blood flow velocity, severity of perifoveal capillary occlusion and foveal retinal thickness (7–9).

Therefore, we decided to evaluate macular and choroidal thickness in diabetic patients without clinically evident DR and without DME and compare these values to those of healthy subjects without diabetes.

Aim

The aim of this study was to assess foveal and parafoveal macular thickness, as well as subfoveal and subparafoveal choroidal thickness using spectral domain optical coherence tomography (SD-OCT), in patients with diabetes, without clinically evident DR, and to compare these values with healthy non-diabetic subjects.

Material and methods

The analyzed data was gathered prospectively from a non-randomized consecutive series of patients in an observational study. All patients gave an informed consent to participate in the study. All tenets of the Declaration of Helsinki were followed for all study protocols. The study was approved by the Bioethics Committee of the Medical University of Lodz (approval no. RNN/313/17/KE).

Group 1 consisted of 65 eyes of 35 patients (19 men [58%] and 14 women [42%]) aged from 31 to 71 years old (mean age of 59 ± 10 years) with diabetes type 2, without clinically evident DR and without DME. Thirty-three right and 32 left eyes were enrolled.

Group 2 consisted of 64 eyes of 32 healthy individuals (29 women [91%] and 3 men [9%]) aged from 39 to 83 years old (mean age of 56 ± 11 years) without diabetes. Thirty-two right and 32 left eyes were enrolled

There was no difference in the mean age between the two groups ($p<.05$).

The exclusion criteria were any previous ocular surgery or laser procedure and any present or previous ocular disease.

All patients underwent ophthalmic examination, including refraction, best corrected distance visual acuity (BCDVA), intraocular pressure (IOP), anterior segment and fundus evaluation with a slit lamp and indirect ophthalmoscopy, as well as optical coherence tomography angiography (OCT-A) of the retina.

Retinal thickness

Retina Map scans with automated measurement function were used in order to determine retinal thickness in the foveal and parafoveal region (Fig. 1).

Choroidal thickness

Choroidal thickness was measured on horizontal optical coherence tomography (SOCT) scans acquired with Angio-Vue SOCT (OptoVue) in Enhanced HD line mode. Angiovue OCT-A is a non-invasive imaging technique, which makes it possible to obtain a high resolution, three-dimensional visualization of the retinal and choroidal morphology, as well as the vascular structure (10). It provides precise visualization

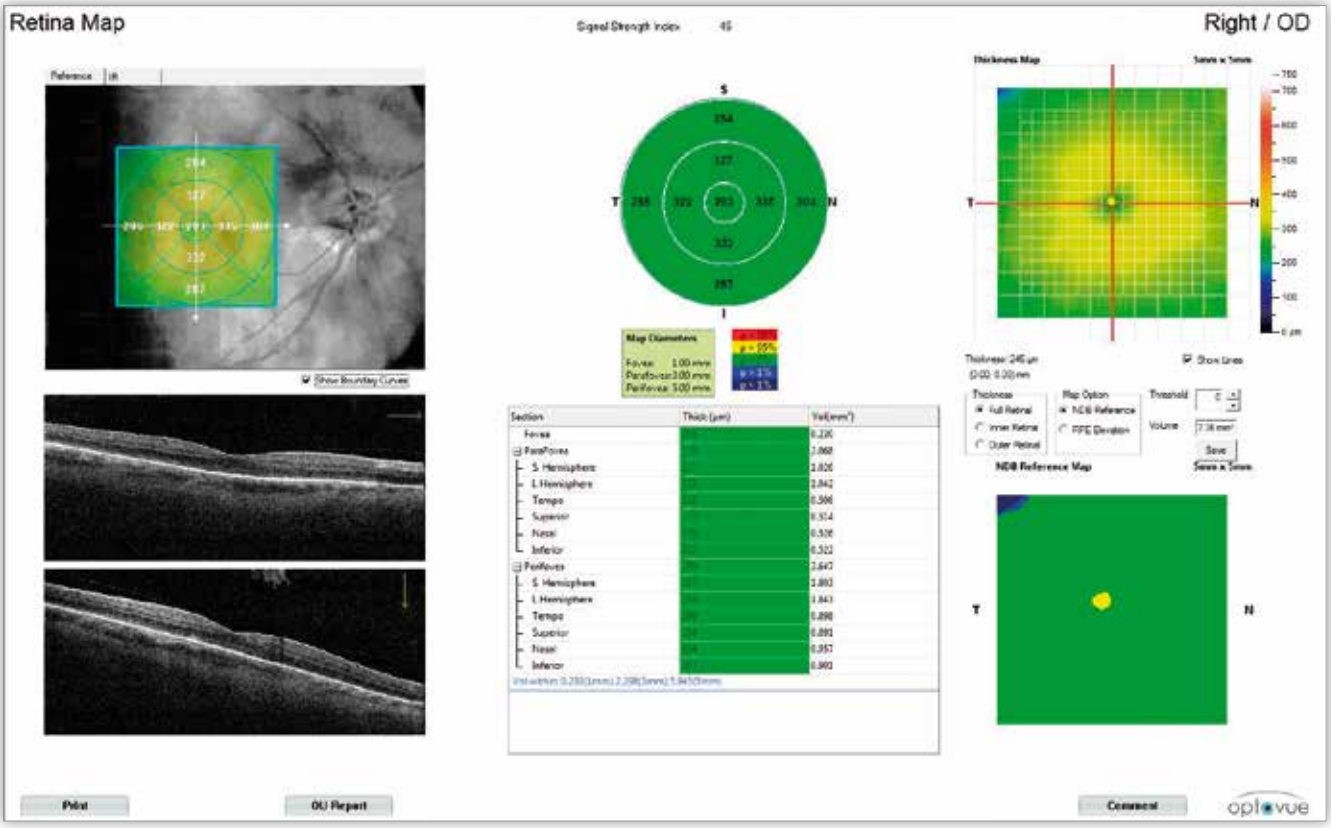

Fig. 1. Retina map scan.
Ryc. 1. Skan "Mapa siatkówki"

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of the specific layers of retinal vasculature by detecting blood flow in vessels without the use of dye to enable personalized management of disease progression (11). The analysis reports present side-by-side OCT-A and OCT (en-face) tomograms derived from the same data.

Choroidal thickness was measured manually using manual calipers in ImageJ graphical analysis software. Enhanced HD line OCT scans contain a 250 μm line, which was used to calibrate the calipers used to perform measurements (Fig. 2). The choroidal thickness was measured from the outer portion of the hyperreflective line corresponding to the base of retinal pigment epithelium (RPE) to the margin or hyperreflective line corresponding to chorioscleral interface.

The measurements were performed at the foveola, as well as 1.5 mm nasally and 1.5 mm temporally from the site of the first measurement and the mean of 2 measurements was included in the analyses. The images were analyzed by 1 ophthalmologist (W. M.). The results were repeatable.

Fig. 2. Enhanced HD line scan.
Ryc. 2. Skan liniowy wysokiej rozdzielczości.

Statistical analysis

Parametric tests were used. The between-group differences were determined using the two-tailed independent samples student T-test. All calculations were performed for the significance level $\alpha = .05$ using Microsoft Excel and Addinsoft XL Stat 2008 software. A *p* value below .05 was considered statistically significant.

Results

The mean retinal foveal thickness was 266 $\pm$ 29 μm and 259 $\pm$ 23 μm in groups 1 and 2, respectively. There was no difference in the foveal thickness between diabetic and healthy subjects ($p > .05$). The mean retinal foveal volume was 0.21 $\pm$ 0.02 mm^3 and 0.20 $\pm$ 0.01 mm^3 in groups 1 and 2, respectively. There was no difference in the foveal volume between diabetic and healthy subjects ($p > .05$). The mean retinal parafoveal thickness was 317 $\pm$ 18 μm and 320 $\pm$ 15 μm in groups 1 and 2, respectively. There was no difference in the parafoveal thickness between diabetic and healthy subjects ($p > .05$). The mean retinal parafoveal volume was 1.99 $\pm$ 0.14 mm^3 and 2.01 $\pm$ 0.09 mm^3 in groups 1 and 2, respectively. There was no difference in the parafoveal volume between diabetic and healthy subjects ($p > .05$). The mean choroidal foveal thickness was 150 $\pm$ 68 μm and 236 $\pm$ 86 μm in groups 1 and 2, respectively (Fig. 3). Diabetic patients had significantly lower choroidal foveal thickness than healthy subjects ($p < .0001$).

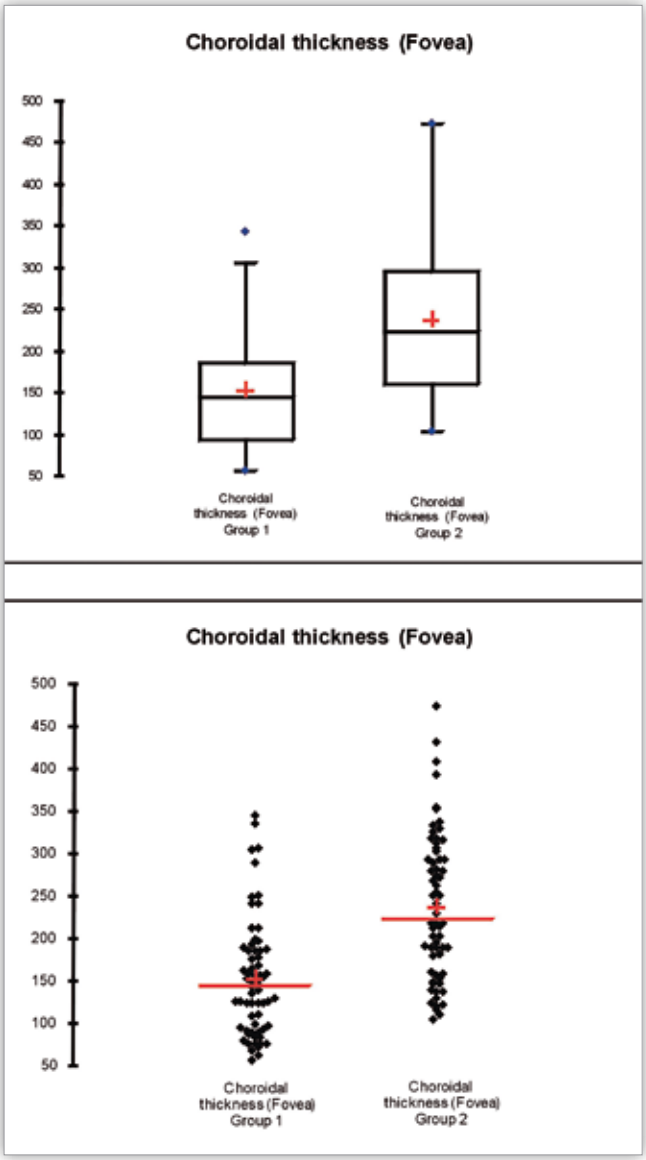

Fig. 3. Choroidal thickness in the fovea.
Ryc. 3. Grubość naczyniówki w dołku.

The mean choroidal thickness at the nasal parafovea was 132 $\pm$ 66 μm and 220 $\pm$ 82 μm in groups 1 and 2, respectively. Diabetic patients had significantly lower choroidal thickness at the nasal parafovea than healthy subjects ($p < .0001$). The mean choroidal thickness at the temporal parafovea was 148 $\pm$ 68 μm and 222 $\pm$ 80 μm in groups 1 and 2, respectively. Diabetic patients had significantly lower choroidal thickness at the temporal parafovea than healthy subjects ($p < .0001$).

Discussion

Manjunath et al. (12) examined choroidal thickness and area in healthy eyes using SD-OCT. Just as in the current study, they noted that the choroidal thickness was the lowest in the nasal parafoveal region and only slightly higher in the temporal parafoveal region to further increase in the subfoveal region. They also suggested that retinal thickness may not directly cor-

relate with choroidal thickness in healthy eyes. Similarly, Margolis and Spaide (13, 14) evaluated macular choroidal thickness in normal eyes using enhanced depth imaging OCT and noted that the choroid was the thickest in the subfoveal region, thinning nasally.

Kim et al. (15) assessed choroidal and central macular thickness in patients with DR using SD-OCT. They reported that choroidal thickness increased significantly as the severity worsened from mild/ moderate/ severe non-proliferative DR (NPDR) to proliferative DR (PDR). The subfoveal choroid was thicker in eyes with DME than those without DME.

Unsal et al. (16) also examined choroidal and central macular thickness in patients with DR using OCT. They found that the choroidal thickness decreased as the disease progressed from mild–moderate NPDR to PDR. Just as in the current study, the choroid was the thickest in the subfoveal area, thinning nasally (where it was the thinnest) and temporally. However, unlike the current study, they observed a significantly higher central macular thickness in patients with DR as compared to healthy controls.

Regaieri et al. (17) examined the choroidal thickness in patients with diabetes using SD-OCT. They compared subjects with NPDR, PDR, and DR with DME with healthy controls using Cirrus™ HD-OCT and found no significant difference between the NPDR and control groups, however the choroidal thickness was reduced in patients with DME and treated PDR. Their study also confirmed that the choroidal thickness was the highest in the subfoveal area further decreasing nasally and temporally.

Xu et al. (18) examined the subfoveal choroidal thickness in patients with diabetes with and without DR, as well as healthy controls, using OCT. They found that patients with diabetes had a slightly yet significantly thicker subfoveal choroid, whereas presence of DR was not associated additionally with an abnormal subfoveal choroidal thickness.

Vujosevic et al. (19) examined macular and peripapillary choroidal thickness in diabetic patients with and without DR. The mean macular and peripapillary choroidal thickness decreased progressively and significantly from NPDR to PDR. Contrary to our study, they found no significant difference in the choroidal thickness between healthy controls and diabetic patients without DR. They also suggested that DME did not influence choroidal thickness.

Demir et al. (9) measured the central macular thickness in patients with type 2 diabetes mellitus without clinical retinopathy and found it not to be significantly higher than in healthy controls, which is consistent with our findings.

Lattanzio et al. (20) found that macular thickness was higher in diabetic patients than in controls, tending to increase with the increasing severity of DR and DME.

Sanches-Tocino et al. (21) found that diabetic patients with DME had a significantly higher thickness in each area compared with all the other diabetic and control groups and confirmed significant differences in central foveal thickness between the controls and other diabetic groups.

The literature review yields varying reports of choroidal thickness measurements in diabetic patients. There are also many factors which influence choroidal thickness. Some authors found choroidal thickness to decrease in diabetic patients (16, 19), whereas others observed its increase (15, 18) and yet others found no difference between patients with diabetes and healthy individuals (9, 17). These unequivocal results found in the literature may result from different study methodology, different devices and study protocols used, as well as different vascular status of the populations examined by various authors.

Conclusions

Diabetic patients without clinically manifest DR have significantly thinner choroid at the fovea and parafovea than healthy individuals. There is no difference in the mean retinal thickness at the fovea and parafovea, as well as in the mean retinal volume both at the fovea and parafovea between diabetic subjects and healthy controls. Enhanced depth OCT is a useful tool which can be used for non-invasive evaluation of the retinal and choroidal structure, thickness and volume.

References:

1. Weinberger D, Kramer M, Priel E, Gaton D, Axer-siegel R, Yassur Y: *Indocyanine green angiographic findings in non-proliferative diabetic retinopathy*. Am J Ophthalmol. 1998; 126: 238–247.
2. Cao J, McLeod S, Merges CA, Lutty GA: *Choriocapillaris degeneration and related pathologic changes in human diabetic eyes*. Arch Ophthalmol. 1998; 116: 589–597.
3. McLeod DS, Lutty GA: *High-resolution histologic analysis of the human choroidal vasculature*. Invest Ophthalmol Vis Sci. 1994; 35: 3799–3811.
4. Hidayat AA, Fine BS: *Diabetic choroidopathy. Light and electron microscopic observation of seven cases*. Ophthalmology. 1985; 92: 512–522.
5. Lutty GA, Cao J, McLeod DS: *Relationship polymorphonuclear leukocytes to capillary dropout in the human diabetic choroid*. Am J Pathol. 1997; 151: 707–714.
6. Fong DS, Aiello L, Gardner TW, King GL, Blankenship G, Cavallerano JD, et al.: *Diabetic retinopathy.* Diabetes Care. 2003; 26: 226–229.
7. Gardner TW, Larsen M, Girach A, Zhi X: *Protein Kinase C Diabetic Retinopathy Study (PKC-DRS2) Study Group. Diabetic macular oedema and visual loss: relationship to location, severity and duration*. Acta Ophthalmol. 2009; 87: 709–713.
8. Sakata K, Funatsu H, Harino S, Noma H, Hori S**:** *Relationship of macular microcirculation and retinal thickness with visual acuity in diabetic macular edema*. Ophthalmology. 2007; 114: 2061––2069.
9. Demir M, Dirim B, Acar Z, Yilmaz M, Sendul Y: *Central macular thickness in patients with type 2 diabetes mellitus without clinical retinopathy*. J Ophthalmol, 2013, 2013, 767931, doi: 10.1155/2013/767931.
10. On day 05.01.2016, 16:00, http://www.optovue.com/products/angiovue
11. On day 05.01.2016, 18:00, http://www.haagstreituk.com/products/optovue.html
12. Manjunath V, Taha M, Fujimoto JG, Duker JS: *Choroidal thickness in normal eyes measured using Cirrus HD optical coherence tomography*. Am J Ophthalmol. 2010; 150: 325–329.
13. Margolis R, Spaide RF: *A pilot study of enhanced depth imaging optical coherence tomography of the choroid in normal eyes*. Am J Ophthalmol. 2009; 147: 811–815.

ISSN 0023-2157 Index 362646

14. Spaide RF,Koizumi H, Pozzoni MC: *Enhanced depth imaging spectral-domain optical coherence tomography*. Am J Ophthalmol. 2008; 14: 496–500.
15. Kim JT, Lee DH, Joe SG, Kim JG, Yoon YH: *Changes in choroidal thickness in relation to the severity of retinopathy and macular edema in type 2 diabetic patients*. Invest Ophthalmol Vis Sci. 2013; 54: 3378–3384.
16. Unsal E, Eltutar K, Zirtiloglu S, Dincer N, Erkul S, Gungel H: *Choroidal thickness in patients with diabetic retinopathy*. Clin Ophthalmol. 2014; 8: 637–642.
17. Regatieri CV, Branchini L, Carmody J, Fujimoto JG, Duker JS: *Choroidal thickness in patients with diabetic retinopathy analyzed by spectral-domain optical coherence tomography*. Retina. 2012; 32: 563–568.
18. Xu J, Xu L, Fang K, Shao L, Chen Ch, Zhou J: *Subfoveal choroidal thickness in diabetes and diabetic retinopathy*. Ophthalmology. 2013, doi:10.1016.
19. Vujosevic S, Martini F, Cavarzeran F, Pilotto E, Midena E: *Macular and peripapillary choroidal thickness in diabetic patients*. Retina. 2012; 32: 1781–1790.
20. Lattanzio R, Brancato R, Pierro L, Bandello F, Iaccher B, Fiore T, et al.: *Macular thickness measured by optical coherence tomography (OCT) in diabetic patients*. Eur J Ophthalmol. 2002; 12: 482–487.
21. Sanchez-Tocino H, Alvarez-Vidal A, Maldonaldo MJ, Moreno-Montanes J, Garcia-Layana A: *Retinal thickness study with optical coherence tomography in patients with diabetes*. Invest Ophthalmol Vis Sci. 2002; 43: 1588–1594.

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