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RETINAL MICROCIRCULATION INVESTIGATION IN TYPE I AND II DIABETIC PATIENTS WITHOUT RETINOPATHY USING AN ADAPTIVE OPTICS RETINAL CAMERA

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Abstract

Context. State of art imaging techniques might be a useful tool to early detect the retinal vessels lesions in diabetes.

Objective and design. This analytical observational study investigates the retinal microcirculation changes in type I and II diabetic patients without retinopathy using adaptive optics ophthalmoscopy (AOO) and optical coherence ophthalmoscopy angiography (OCTA).

Subjects and methods. Fifty-five subjects were included in this study and were divided in three groups: type I diabetic group (n=16), type II diabetic group (n=19) and control group (n=20). An adaptive optics retinal camera was used to assess the parameters of the temporal superior retinal arterioles. Moreover, vessel density of the superficial capillary plexus across the parafoveal area was measured with OCT-A. All cases were investigated once, in a cross-sectional design.

Results. Diabetic patients from both groups had a higher wall-to-lumen-ratio compared to the controls (p=0.01 and 0.01, respectively). Interestingly, no significant differences were found between the two diabetic groups (p=0.69). Moreover, the vessel density was smaller in the type I diabetic group than in the control group (p=0.001)

Conclusion. AOO might be a useful tool to detect early retinal vascular changes in diabetes before any clinical signs and together with OCTA it might bring important information on the prognostic and pathophysiology of the disease.

Key words: adaptive optics ophthalmoscopy, optical coherence ophthalmoscopy angiography, diabetic retinopathy, retinal vessels.

INTRODUCTION

The eye is the only organ that allows the direct inspection of the vascular system with relatively simple methods, such as a slit lamp or an ophthalmoscope. The retinal vessels can provide important information on the vascular functional and morphological changes in diabetes (1), hypertension, cardiovascular disease (2). The retinal needs in terms of energy are exceeding the ones of the brain (3). Nevertheless, retina is a direct extension of the brain and their vessels share anatomical, pathophysiological, embryological features.

In order to better assess the structural and functional features of the microvascular network, both topology and geometric abnormalities that affect the hemodynamic network should be taken into consideration (4). The topological structure of the vascular networks has been firstly achieved using the Horton-Strahler and generation nomenclature (5). Further studies have demonstrated the cellular structure and distribution heterogeneity in the macular vasculature (4). Moreover, the branching model of the retinal vascular systems has the features of a fractal. A fractal is a pattern of expanding symmetry, whose each part has the same statistical character as the whole. It has been discussed that the normal retinal and venous branching patterns have a fractal dimension similar to the one measured for different physical phenomena (6). Nevertheless, in diabetes the fractal dimension decreases, possibly associated with impairments of the retinal circulation (7). In addition to this, network geometry is dealing with the length and diameters of the vessels, length-to diameter ratio. A considerable number of reports have emphasised the potentiality to use the changes of major retinal vessel's caliber as biomarkers for inceptive vascular abnormalities in diabetes. Diabetic patients were proved to present changes of the retinal arteriolar and venular calibers (8, 9). Moreover, the increased venular diameter has been significantly correlated to the severity of the diabetic retinopathy (DR) (9). The relationship between the blood flow and vessel diameter depicted by Poiseuille's law underlines the significance of accurate measurements of the retinal vessels diameters.

Adaptive optics ophthalmoscopy (AOO) allows the noninvasive visualisation and quantification with high precision of the microvessels. Recently it has

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been proved that adaptive optics retinal imaging can be a useful tool to assess retinal arterioles parameters *in vivo* (10).

Structural abnormalities of microvessels are associated to a worse outcome in hypertension and diabetes (11). The media thickness to internal lumen ratio (MLR) of small resistance arteries measured by micromyographic approaches is considered to be the gold standard for the morphological evaluation of the small arteries in human beings. More recently, *in vivo* non-invasive measurement methods of the wall to lumen ratio (WLR) of arterioles have been compared, proving the superiority of the adaptive optics camera over the scanning laser Doppler flowmetry (11,12).

Using AO retinal camera, blood vessels consist of a central dark line surrounded by two peripheral darker lines (13-15).

In addition to this, according to the ETDRS (Early Treatment Diabetic Retinopathy Study) guidelines, the hallmark of DR is the vascular lesions in the retinal layers (16). Using optical coherence tomography angiography (OCTA) it is also possible to analyse noninvasively the anatomical, morphological, vascular features of the retinal layers.

In this work, we studied the retinal arterioles parameters near the emergence from the optic disk in adult patients with a history of type I and II diabetes, respectively, and in adult healthy volunteers using the rtx1 AO retinal camera. Moreover, vascular density measurements in the parafoveal region were obtained employing OCTA. Comparative analysis of these imaging biomarkers has been performed between the three studied groups.

MATERIALS AND METHODS

The study protocol was created in line with the Declaration of Helsinki and received the approval of the local ethics commission. Retinal investigations were conducted during the screening of DR in the Retina Clinic in Bucharest and informed consent was obtained from all subjects.

Study participants

Fifty-five participants were included in this observational study (Table 1). The study groups were divided into type I and type II diabetic patients and healthy controls. The type I DM group contained 16 subjects (6 females and 10 males), the type II DM, 19 subjects (8 females and 11 males), whereas the control group included 20 subjects (11 females and 9 males). The best corrected visual acuity was 20/20 or better among all three study groups. The duration of diabetes in the first group (17.38 ± 6.94 years) was significantly longer than in the second group (7.47 ± 4.27 years), $p<0.001$. In the type II DM group all subjects required oral hypoglycaemic agents, with one exception, in which diet and exercise were enough to lower the blood sugar level. The subjects met the eligibility criteria, namely, adult age (>18 years old, Caucasians), confirmed diagnosis of type I and type II, respectively, in compliance with the American Diabetes Association (17), with no lesions of DR (after the ETDRS guidelines (18)), 20/20 or better best corrected visual acuity (BCVA). Subjects with positive diagnosis of any ophthalmological disorder (including any eye intraocular surgery, intravitreal injections, laser treatment, macular edema, media opacities, refractive error greater than 3 spherical diopters or 2.5 cylindrical diopters) or other systemic pathology were excluded. The control group included healthy subjects without any past ophthalmological or systemic medical history. All cases were investigated once, in a cross-sectional design.

Examination

All subjects were thoroughly investigated with the assessment of the best corrected visual acuity on ETDRS optotypes, of the intraocular pressure and of the slit lamp eye exam (of both anterior and posterior segment). Subjects whose pupils diameters were less than 4.5 mm received Phenylephrine 10% and Tropicamide 1% in order to obtain the pharmacological dilation of the pupils. The rtx1TM AO flood illumination retinal camera (Imagine Eyes, Orsay, France) was used to obtain images of the superior temporal retinal

Table 1. Characteristics of groups included in the study (mean ± standard deviation 95%CI)

	DM I group	DM II group	Control group
N	16	19	20
Sex (female/ male)	6/ 10	8/11	11/ 9
OD/ OS	7/ 9	12/7	11/ 9
Age (years)	38.06 ± 6.87	54.42 ± 9.47	39.60 ± 5.64
Axial length (mm)	23.87 ± 0.81	23.34 ± 0.52	24.16 ± 0.82
Duration of DM (years)	17.38 ± 6.94	7.47 ± 4.27	-

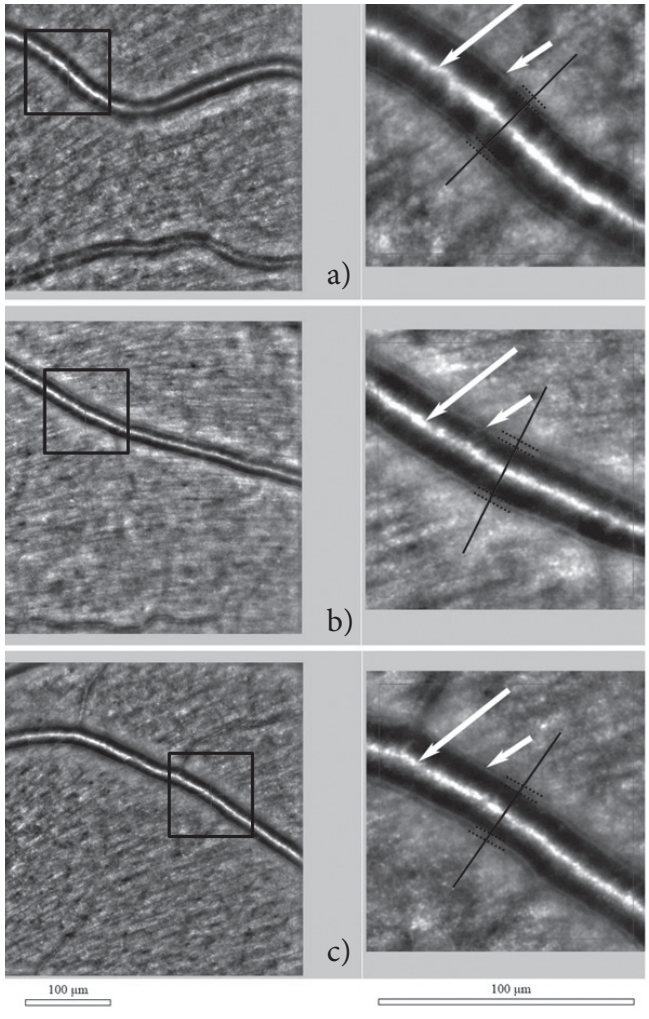

Figure 1. Image of the retinal artery of a patient from the control group (a), from the type I diabetes mellitus group (b) and from the type II diabetes mellitus group (c), with visualization of the walls (short arrows) and lumen (long arrows), employing AOdetect artery software.

arteriolar branches, close to the optic disc. During the acquisition, the subjects were instructed to track the yellow cross of the instrument whose position was decided by the investigator. An extensive depiction of this camera and its practicability are already available (19). The comprehensive retinal imaging included also SS OCT (DRI OCT Triton, Topcon), OCTA (SS OCT Angio, Topcon), colour fundus and red free photography (DRI OCT Triton, Topcon). Axial length measurements were obtained with optical biometry (Aladdin, Topcon). For further analysis, we have included the parameters obtained from one eye of each subject.

Image processing

The analysis of the retinal vessels was acquired automatically from the software offered by the manufacturer (AO detect artery, Imagine Eyes, France) (Fig.1) for each analyzed region of interest, selected by the investigator. The measured parameters are the vessel diameter (VD), the lumen diameter (LD), the mean wall thickness (WT), the wall to lumen ratio (WLR) and the cross sectional area of the vascular wall (WCSA). Vessel diameter is expressed as the algebraic sum of the arterioles walls and the vessel lumen. WLR is the ratio between the wall thickness and the lumen diameter, whereas the WCSA is determined based on the lumen diameter and vessel diameter values. Vascular density is defined as the percentage of a given area represented by vessels (20). The vascular densities along the superficial retinal plexus in the parafoveal area were obtained calculating the mean of the values provided by the proprietary software in a 3x3mm angiocube. The deeper plexuses vessel densities were

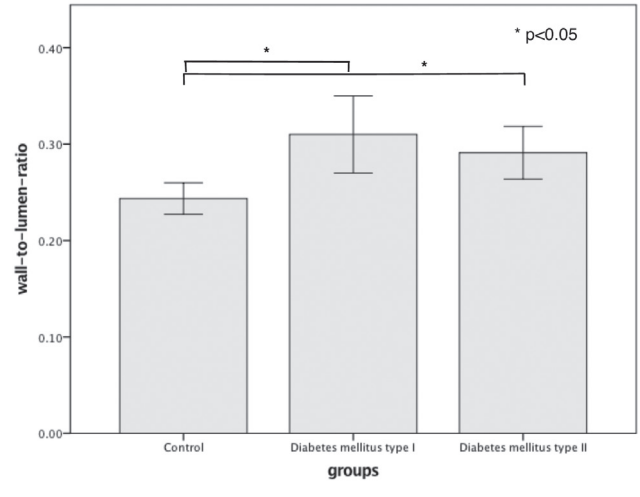

Figure 2. Bar-graph of the wall-to-lumen-ratio values in the three groups included in the study. The error bars represent the standard error of the mean.

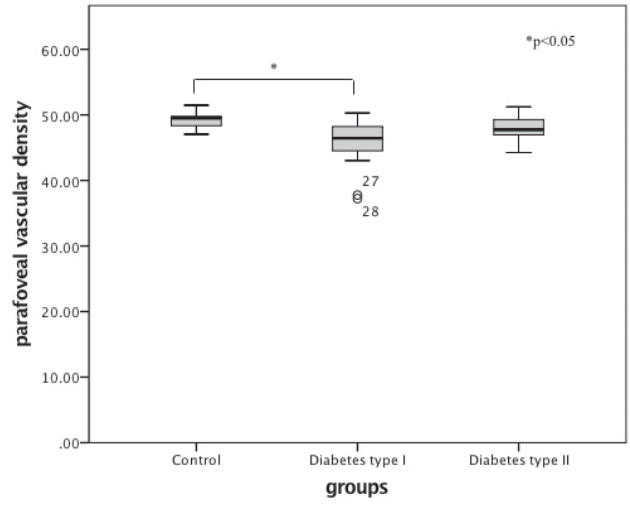

Figure 3. Box-plot of the values of vascular density, with significant outliers plotted on the graph as points out-side the box-plots.

not included in the analysis as the current software of the SS-OCTA does not provide them.

Statistical analysis

For all variables descriptive statistics was achieved. Shapiro-Wilk's test assessed the normality of the studied variables (p>0.05) in all the three groups. Vessels parameters were compared between groups using one-way ANOVA with Tukey post-hoc analysis. When variances were unequal, one-way Welch ANOVA with Games-Howell post-hoc analysis was conducted. For non-linear data or not normally distributed, non-parametric tests were applied (Kruskall-Wallis, with standard post-hoc analysis). The results are depicted as mean ± standard deviation, unless otherwise mentioned. P-values <0.05 were considered statistically significant. IBM SPSS Statistics software (version 23; Armonk, NY: IBM Corp) was used.

RESULTS

Retinal arterioles metrics (Tables 2, 3). The values of VD did not vary between the groups (F(2, 53)=1.714, p=0.19) and neither did those of LD (F(2, 53)=-0.468, p=0.629), walls (F(2, 53)=1.057, p=0.355) or WCSA (F(2, 53)=0.251, p=0.779).

For the mean wall to lumen ratio (WLR) a one-way Welch ANOVA was conducted and assessed the statistically significant variation of this parameter between groups (Fig. 2) (F(2, 53)=6.685, p=0.003). Post-hoc Games-Howell analysis revealed that WLR was significantly less in the control group (0.24 ± 0.035) when compared to the diabetic groups (for the DM I group mean WLR=0.31 ± 0.75, mean difference=-0.067, 95% CI= -0.113, -0.020; p=0.01 and for the DM II group mean WLR=0.29 ± 0.58, mean difference= -0.047, 95% CI=-0.091,-0.004; p=0.01, respectively). Interestingly, between the diabetic groups no statistically significant difference was found with respect to the WLR (p=0.69).

Vascular density

To check whether there are differences in the vascular densities of the superficial capillary plexus, a Kruskal-Wallis H test was used. Distributions of the vascular densities values were not similar in the three groups included in the study, as assessed by the visual inspection of the box-plots of the data. Significant variations between the three groups (H(2)=13.236, p=0.001) (Fig. 3) were found. Pairwise comparisons were assessed using Dunn's procedure with a Bonferroni correction for multiple comparisons (21). Values are mean ranks unless otherwise stated. This post-hoc analysis revealed statistically significant differences in vascular density values between controls (37.37) and type I diabetic patients (17.63) (p=0.001), but not between the controls and the type II diabetic patients (27.40) (p=0.156) and between the two groups of diabetics (p=0.207).

DISCUSSION

Adaptive optics ophthalmoscopy is a new imaging tool that allows the visualisation of photo-receptors (22) and vessels in the human living retina, at a histological resolution. In this research, an AO fundus camera was used to appreciate the differences of retinal arterioles parameters in type I and II diabetic patients

Table 2. Mean ± standard deviation of the retinal arterioles parameters measured in the two diabetic and the control groups

Group	VD (μm)	LD (μm)	Mean wall thickness (μm)	WLR	WCSA
Control	94.87 ± 18.73	76.27 ± 15.36	9.29 ± 2.10	0.24 ± 0.035	2585.1 ± 1057.46
DM I	83.12 ± 22.5	71.31 ± 22.44	9.97 ± 2.19	0.31 ± 0.75	2501.06 ± 1178.34
DM II	92.49 ± 18.18	71.82 ± 14.50	10.33 ± 2.52	0.29 ± 0.58	2758.25 ± 1138.26

Legend: VD=vessel diameter, LD=lumen diameter, WLR=wall to lumen ratio, WCSA=cross sectional area of the vascular wall, DM I= type I diabetes mellitus, DM II= type II diabetes mellitus.

Table 3. Results of the post-hoc analysis between the three groups included in the study

Groups	VD (Tukey)	LD (Tukey)	Mean wall thickness (Tukey)	WLR (Games-Howell)	WCSA (Tukey)
Control *vs.* DM I (p value)	0.19	0.67	0.66	**0.01**	0.97
Control *vs.* DM II (p value)	0.92	0.70	0.33	**0.01**	0.88
DM I *vs.* DM II (p value)	0.34	0.99	0.88	0.69	0.77

Legend: VD=vessel diameter, LD=lumen diameter, WLR=wall to lumen ratio, WCSA=cross sectional area of the vascular wall, DM I= type I diabetes mellitus, DM II= type II diabetes mellitus

with no DR and in healthy volunteers. Moreover, vascular densities were measured. Our results suggest that diabetic patients without retinopathy present signs of early dysfunction of retinal arterioles, as depicted by WLR. Subjects with hypertension or any other vascular disorders were excluded in order to avoid any interaction between the retinal vessel parameters and these conditions. Interestingly, no statistically significant difference was found between the two diabetic groups with respect to the studied parameters. To our knowledge, this is the first study in the literature to compare the retinal arterioles parameters between type I and type II diabetic patients using an AO retinal camera. The results of this study are confirmed by the literature that describes as well arterial remodelling signs in diabetic patients with no retinopathy (23-25). Lombardo *et al.* (15) studied the lumen of parafoveal retinal capillaries in eyes with nonproliferative DR and healthy controls with an AO retina camera. The vessels were found to be narrower in diabetic subjects than in healthy ones. Also, Zaleska *et al.* (25, 26) compared the arteriolar parameters in type I diabetic patients and controls and noticed similar results, using the AOO. An increased WLR depicts very well the arterial remodelling process in diabetes mellitus, that may encompass the thickening of the wall, the narrowing of the lumen or both. In diabetic patients, retinal arterioles narrow their lumen because of fibrosis and the growth of smooth muscle cells (27, 28). These changes represent an early stage of the diabetes associated vascular impairments. Nevertheless, although the significant difference of duration of diabetes and subjects' age between the two diabetic groups included in this study, the retinal arterioles parameters assessed by the AO retinal camera did not differ much between the two groups.

Furthermore, another result of this study proved a lower vascular density in the superficial capillary plexus in the parafoveal area in type I diabetic patients compared to controls, using OCTA. In diabetes, the lesions in the microcirculation appear before any clinical sign of retinopathy and OCTA angiography is enabling early detection of these retinal vascular changes (29). Vascular density is a biomarker that allows the quantitative assessment of vascular disorders. In diabetic retinopathy, vascular density decreases in both superficial and deep plexuses (30). Yet, some studies showed a lower vascular density in the deep capillary plexus only (but not superficial capillary plexus or choriocapillaris) in diabetic subjects without DR (30-32). The significant lower vessel density found in the type I diabetic group, but not in the type II diabetic group, when compared to controls, might be connected to the longer duration of the disease in the first group. Lacking OCTA data from the deep capillary layers, no conclusion can be made with respect to the extent of microvascular lesions induced by diabetes in the two study groups. However, the vascular density and the foveal avascular zone are the most common OCTA parameters used for the early detection of DR. Its severity, the visual function and the response to treatment are correlated to these biomarkers (33, 34).

Adaptive optics ophthalmoscopy proved to be a valuable instrument to quantify the retinal microvascular changes associated to diabetes mellitus in patients with no DR (35). Thus, prognostic information might be obtained with respect to the incidence and progression of DR (36). In this study, AO retinal camera was able to reveal retinal microvascular lesions in the type II diabetic patients group, whereas OCTA found no differences when comparing to the control group.

The small sample sizes might represent a source of bias. Besides larger study groups, future studies should analyse the superficial, deep capillary and choriocapillaris layers with OCTA, include correlations of the vessels data with the blood parameters, the diabetes duration.

In conclusion, an increased WLR significantly shows the microvascular disease in DM. The investigation of the retinal vessels with these state of art imaging techniques (AOO and OCTA) might help to better understand the pathophysiological mechanisms of DR (in DM I and DM II), the chronology of the retinal vasculature lesions and their connection to risk factors and blood parameters. They both give valuable information on the topological and geometrical changes of the retinal vessels in diabetes before any clinical sign of DR.

Conflict of interest

The authors declare that they have no conflict of interest.

References

1. Aioanei CS, Ilies RF, Bala C, Petrisor MF, Porojan MD, Popp RA, Catana A. The role of adiponectin and toll-like receptor 4 gene polymorphisms on non-proliferative retinopathy in type 2 diabetes mellitus patients. A case-control study in Romanian and Caucasian patients. Acta Endocrinol (Buc). 2019; 15(1):32-38.

2. Stanca HT, Petrović Z, Munteanu M. Transluminal Nd:YAG laser embolysis-a reasonable method to reperfuse occluded branch retinal arteries. Vojnosanit Pregl. 2014;71(11):1072-1077.
3. Yu DY, Cringle SJ. Oxygen distribution and consumption within the retina in vascularised and avascular retinas and in animal models of retinal disease. Prog Retin Eye Res. 2001; 20(2):175-208.
4. Yu PK, Balaratnasingam C, Cringle SJ, McAllister IL, Provis J, Yu D-Y. Microstructure and Network Organization of the Microvasculature in the Human Macula. Investig Ophthalmology Vis Sci. 2010;51(12):6735.
5. Pries AR, Secomb TW. Blood Flow in Microvascular Networks. In: Tuma RF, Ronald F, Durán WN, Ley K. Microcirculation. Elsevier Academic Press; 2008:18.
6. Mainster MA. The fractal properties of retinal vessels: Embryological and clinical implications. Eye 1990; 4(1):235-241.
7. Gutterman DD, Chabowski DS, Kadlec AO, Durand MJ, Freed JK, Ait-Aissa K, Beyer AM. The Human Microcirculation: Regulation of Flow and Beyond. Circ Res. 2016; 118(1):157-172.
8. Klein R, Klein BEK, Moss SE, Wong TY. Retinal Vessel Caliber and Microvascular and Macrovascular Disease in Type 2 Diabetes. Ophthalmology. 2007; 114(10):1884-1892.
9. Klein R, Knudtson MD, Klein BEK, Zinman B, Gardiner R, Suissa S, Sinaiko AR, Donnelly SM, Goodyer P, Strand T, Mauer M. The relationship of retinal vessel diameter to changes in diabetic nephropathy structural variables in patients with type 1 diabetes. Diabetologia. 2010; 53(8):1638-1646.
10. Koch E, Rosenbaum D, Brolly A, Sahel J-A, Chaumet-Riffaud P, Girerd X, Rossant F, Paques M. Morphometric analysis of small arteries in the human retina using adaptive optics imaging. J Hypertens. 2014;32(4):890-898.
11. Rizzoni D, Agabiti Rosei C, De Ciuceis C, Semeraro F, Rizzoni M, Docchio F. New Methods to Study the Microcirculation. Am J Hypertens. 2018;31(3):265-273.
12. De Ciuceis C, Agabiti Rosei C, Caletti S, Trapletti V, Coschignano MA, Tiberio GAM, Duse S, Docchio F, Pasinetti S, Zambonardi F, Semeraro F, Porteri E, Solaini L, Sansoni G, Pileri P, Rossini C, Mittempergher F, Portolani N, Ministrini S, Agabiti-Rosei E, Riz-zoni D. Comparison between invasive and noninvasive techniques of evaluation of microvascular structural alterations. J Hypertens. 2018;36(5):1154-1163.
13. Paques M, Meimon S, Rossant F, Rosenbaum D, Mrejen S, Sennlaub F, Grieve K. Adaptive optics ophthalmoscopy: Application to age-related macular degeneration and vascular diseases. Prog Retin Eye Res. 2018;66:1-16.
14. Tam J, Dhamdhere KP, Tiruveedhula P, Manzanera S, Barez S, Bearse MAJr, Adams AJ, Roorda A. Disruption of the Retinal Parafoveal Capillary Network in Type 2 Diabetes before the Onset of Diabetic Retinopathy. Investig Ophthalmology Vis Sci. 2011;52(12):9257-9266.
15. Lombardo M, Parravano M, Serrao S, Ducoli P, Stirpe M, Lombardo G. Analysis of retinal capillaries in patients with type 1 diabetes and nonproliferative diabetic retinopathy using adaptive optics imaging. Retina. 2013; 33(8):1630-1639.
16. Early Treatment Diabetic Retinopathy Study design and baseline patient characteristics. ETDRS report number 7. Ophthalmology. 1991; 98(5 Suppl):741-756.
17. American Diabetes Association. 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes-2018. Diabetes Care. 2018; 41(Supplement 1):13-27.
18. Grading diabetic retinopathy from stereoscopic color fundus photographs-an extension of the modified Airlie House classification. ETDRS report number 10. Early Treatment Diabetic Retinopathy Study Research Group. Ophthalmology. 1991; 98(5 Suppl):786-806.
19. Godara P, Dubis AM, Roorda A, Duncan JL, Carroll J. Adaptive optics retinal imaging: emerging clinical applications. Optom Vis Sci. 2010; 87(12):930-941.
20. Coscas F, Sellam A, Glacet-Bernard A, Jung C, Goudot M, Miere A, Souied EH. Normative data for vascular density in superficial and deep capillary plexuses of healthy adults assessed by optical coherence tomography angiography. Investig Ophthalmol Vis Sci. 2016; 57(9):211-223.
21. Kruskal-Wallis H test in SPSS Statistics. Laerd Statistics Premium. (Accessed January 06, 2020, at site <https://statistics.laerd.com/premium/spss/kwht/kruskal-wallis-test-in-spss-16.php>)
22. Cristescu I-E, Baltă F, Zăgrean L. Cone photoreceptor density in type I diabetic patients measured with an adaptive optics retinal camera. Rom J Ophthalmol. 2019;63(2):153-160.
23. Gardiner TA, Archer DB, Curtis TM, Stitt AW. Arteriolar Involvement in the Micro-vascular Lesions of Diabetic Retinopathy: Implications for Pathogenesis. Microcirculation. 2007; 14(1):25-38.
24. Bursell SE, Clermont AC, Kinsley BT, Simonson DC, Aiello LM, Wolpert HA. Retinal blood flow changes in patients with insulin-dependent diabetes mellitus and no diabetic retinopathy. Investig Ophthalmol Vis Sci. 1996; 37(5):886-897.
25. Zaleska-Żmijewska A, Wawrzyniak ZM, Dąbrowska A, Szaflik JP. Adaptive Optics (rtx1) High-Resolution Imaging of Photoreceptors and Retinal Arteries in Patients with Diabetic Retinopathy. J Diabetes Res. 2019;2019:1-12.
26. Zaleska A, Barbara Ś, Soko A, Wawrzyniak ZM, Romaniuk D, Szaflik J, Szaflik JP. Retinal Photoreceptors and Microvascular Changes in Prediabetes Measured with Adaptive Optics (rtx1 TM): A Case-Control Study. J Diabetes Res. 2017;2017:8.
27. Ritt M, Schmieder RE. Wall-to-lumen ratio of retinal arterioles as a tool to assess vascular changes. Hypertension. 2009; 54(2):384-387.
28. Trost A, Lange S, Schroedl F, Bruckner D, Motloch KA, Bogner B, Kaser-Eichberger A, Strohmaier C, Runge C, Aigner L, Rivera FJ, Reitsamer HA. Brain and Retinal Pericytes: Origin, Function and Role. Front Cell Neurosci. 2016;10:20.
29. De Carlo TE, Chin AT, Bonini Filho MA, Adhi M, Branchini L, Salz DA, Baumal CR, Crawford C, Reichel E, Witkin AJ, Duker JS, Waheed NK. Detection of microvascular changes in eyes of patients with diabetes but not clinical diabetic retinopathy using optical coherence tomography angiography. Retina. 2015; 35(11):2364-2370.
30. Khadamy J, Abri Aghdam K, Falavarjani K. An update on optical coherence tomography angiography in diabetic retinopathy. Journal of Ophthalmic and Vision Research. 2018; 13(4): 487-497.
31. Kim M, Choi SY, Park YH. Quantitative analysis of retinal and choroidal microvascular changes in patients with diabetes. Sci Rep. 2018;8(1):4-6.
32. Vujosevic S, Toma C, Villani E, Gatti V, Brambilla M, Muraca A, Ponziani MC, Aimaretti G, Nuzzo A, Nucci P, De Cilla' S. Early Detection of Microvascular Changes in Patients with Diabetes Mellitus without and with Diabetic Retinopathy: Comparison between Different Swept-Source OCTA Instruments. J Diabetes Res. 2019; 2019:4-9.
33. de Barros Garcia JMB, Isaac DLC, Avila M. Diabetic retinopathy and OCT angiography: clinical findings and future perspectives. Int J Retin Vitr. 2017;3(1):14.
34. Mastropasqua R, Toto L, Mastropasqua A, Aloia R, De Nicola C, Mattei PA, Di Marzio G, Di Nicola M, Di Antonio L. Foveal avascular zone area and parafoveal vessel density measurements in different stages of diabetic retinopathy by optical coherence tomography angiography. Int J Ophthalmol. 2017;10(10):1545-1551.
35. Gallo A, Girerd X, Rosenbaum D, Dietenbeck T, Kachenoura N, Paques M. Adaptive optics camera enables to describe different patterns of retinal vasculature in hypertension and type 2 diabetes. J Hypertens. 2018;36:223.
36. Ding J, Ikram MK, Cheung CY, Wong TY. Retinal vascular calibre as a predictor of incidence and progression of diabetic retinopathy. Clin Exp Optom. 2012; 95(3):290-296.