ORIGINAL PAPER

Optical Coherence Tomography Angiography Contributions in Classification of Nonproliferative Diabetic Retinopathy

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doi: 10.5455/aim.2020.28.103-107

ACTA INFORM MED. 2020 JUN 28(2): 103-1077

Received: Dec 28, 2019
Accepted: Mar 12, 2020

ABSTRACT

Introduction: To show the importance of optical coherence tomography (OCT) angiography imaging of superficial and deep capillary network in patients with non-proliferative diabetic retinopathy (NPDR), and to show the correlation between blood glucose level and changes in the foveal microvasculature. Methods: A cross-sectional study was performed on eyes with NPDR and healthy subjects using a highspeed 840-nm-wavelength spectral-domain optical coherence tomography instrument (RTVue XR Avanti; Optovue, Inc, Fremont, California, USA). Blood flow was detected using the split-spectrum amplitude-decorrelation angiography algorithm. A fully automated microstructural analysis of the foveal avascular zone (FAZ) and avascular surfaces was performed. Quantitative values from diabetic patients were compared with those of healthy subjects. Data about blood status in diabetic patients and healthy subjects were taken from patients' medical history. Results: Size of both, FAZ and vascular dropout are significantly different between healthy patients and patients with NPDR. OCT angiography detected enlargement and distortion of the foveal avascular zone, retinal capillary dropout, and a higher number of vascular loops and microaneurysms. Sizes of FAZ and vascular dropout increase with the duration of disease. Central macular thickness (CMT) is not significantly different between healthy patients and patients with NPDR. A study has proven a positive correlation between the size of FAZ and the size of vascular dropout in superficial vascular plexus in patients that have DM over 10 years. Conclusion: A qualitative and quantitative OCT angiography approach to retinal vascular status can offer objective data on monitoring patients with non-proliferative diabetic retinopathy as well as indicate the progression of the disease.

Keywords: Optical Coherence Tomography Angiography, diabetes, diabetic retinopathy, non-proliferative diabetic retinopathy, foveal avascular zone, vascular drop-out..

1. INTRODUCTION

Optical coherence tomography angiography (OCT-A) is a useful diagnostic tool for assessing eyes\' health in patients with chronic diseases, such as diabetes, hypertension, Parkinson\'s disease and chronic kidney disease (1). In diabetic patients without diabetic retinopathy signs, changes in capillary network have been detected using OCT-A2 (2). Several studies have reported a connection between retinopathy (microaneurysms and retinal hemorrhages) and systemic disorders, as well as changes in the caliber of retinal vessels (3,4). It is possible to examine the smallest vessels by OCT-A (5). Diabetic retinopathy (DR) is one of the well-known long-term complications of diabetes, and it is a common cause of visual loss in middle-aged people. There are two main types of DR: non-proliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR). Increased permeability of blood vessels, microaneurysms, hemorrhages, hard exudates, as well as capillary occlusion are the main characteristics of NPDR (6). Macular nonperfusion is a risk factor for disease progression, but patients are usually asymptomatic until advanced stages of disease (7). It is estimated that 38% of diabetics suffer from diabetic retinopathy (8).

2. AIM

To evaluate how optical coherence tomography (OCT) angiography contributes to the distinction of early stages of diabetic retinopathy and which parameters are specific and sensitive for NPDR.

3. METHODS

The study was performed in Eye polyclinic „Dr. Sefić“ during May 2017. 180 patients were enrolled in this cross-sectional study. Patients were divided into three groups: patients with diabetes mellitus (DM) disease duration less than ten years, patients with DM duration more than ten years and control group of healthy individuals, without signs and symptoms of DM. Each of these groups counted 60 people in total.

Variables		DM < 10 years (n=60)	DM > 10 years (n=60)	Control group (n=60)
Age (years)		65 (55-69)	67 (57-73)	44.5 (40-54)*♦
Type of DM	DM type 1	4 eyes	10 eyes	
	DM type 2	56 eyes	50 eyes	
Therapy type	Oral antidiabetic therapy	50 eyes	21 eyes	
	Insulin	10 eyes•	39 eyes•	
Glycated hemoglobin HbA1c (%)		6,90 (6,40-7,20)	7,0 (7,0-8,42)¥	
Fasting blood sugar in the morning (mmol/L)		7,2 (6,62-8,22)	7,2 (6,5-9,0)	
BMI		27,10 (25,40-30,79)	26,93 (25,09-29,86)	22,85 (22,0-24,3)*♦
Systolic blood pressure		130 (122,5-140,0)	137,5 (130,0-140,0)	120 (120-130)*♦
Diastolic blood pressure		80 (80-90)	80 (80-90)	80 (80-80)#

Table 1. Characteristics of patients with DM < 10 years, patients with DM > 10 years and control group. Data are presented as median (25th and 75th percentiles), n-number of eyes; DM – diabetes mellitus; BMI - body mass index. *p < 0.0005 compared to DM < 10 years, •p < 0.0005 compared to DM > 10 years, # p = 0.01 compared to DM < 10 years, •p <0.0005 compared to the oral antidiabetic therapy, ¥p=0.006 compared to DM < 10 years

All patient's eyes were scanned in Eye polyclinic „Dr. Sefić“ by a high-speed 840-nm-wavelength spectral-domain optical coherence tomography instrument (RTVue XR Avanti; Optovue, Inc, Fremont, California, USA). Blood flow was detected using a split-spectrum amplitude-decorrelation angiography algorithm. A fully automated microstructural analysis of the foveal avascular zone (FAZ) in superficial vascular plexus, vascular drop-out (VOD) in superficial vascular plexus, central macular thickness (CMT) was performed.

Blood analyses, blood pressure, and anthropometric values were taken in the competent health center.

Inclusion criteria for the study were: patients with diagnosed type 1 or type 2 diabetes mellitus for less or over ten years, on oral or insulin therapy and without any other ocular pathology except diabetic retinopathy.

Exclusion criteria for the study were: pregnancy, any other ocular pathology except diabetic retinopathy, previous ocular surgeries, high myopia, patients younger than 18 and older than 75 years of age.

Statistical analysis: The results were analyzed using standard statistical methods, using the SPSS computer program for statistical analysis (SPSS Statistical Package for Social Sciences) version 13.0. Results are presented as the median and interquartile range (25-75 percentile), as mean ± SEM, and a percentage value (%). Values of $p<0.05$ are considered as statistically significant, and values of $p<0.001$ as statistically highly significant.

4. RESULTS

Individuals in the first group were 65 years of age in on average (55-69 years of age), in the second group 67 (57-73) years of age and 44.5 (40-54) years of age in the control group. In the first group of diabetes duration less than ten years, there were 4 eyes of people with type 1 DM and 56 with type 2 DM. The second group counted 60 eyes, 10 of which were of people with type 1 DM, and 50 of which with type 2 DM. Observing all patients' therapy,

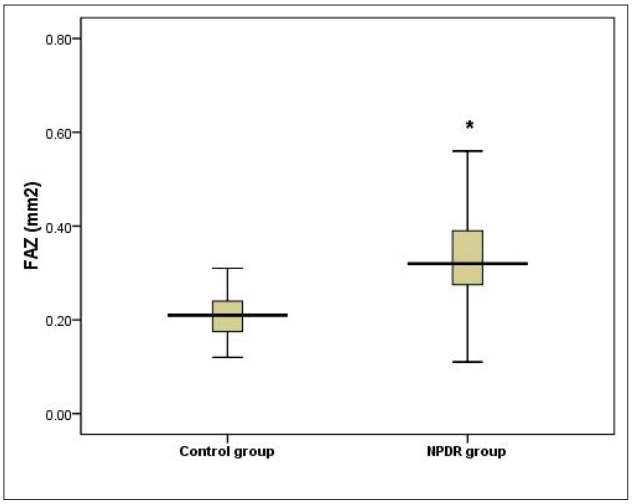

Figure 1. Box-and-whisker plots of FAZ size (mm2) in superficial vascular plexus in patients with non-proliferative diabetic retinopathy (NPDR) and control group. Solid horizontal lines denote the median value, the box represents the 25% and 75% interquartile ranges and whiskers represent the minimum and maximum values. *p< 0.0005 compared to control group

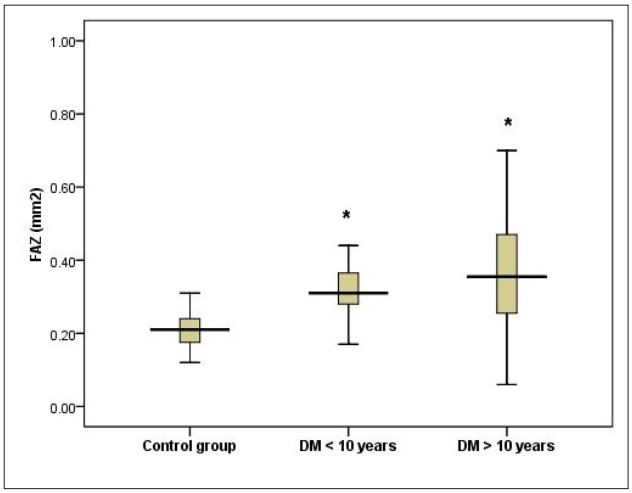

Figure 2. Box-and-whisker plots of FAZ size (mm2) in superficial vascular plexus in patients with DM<10 years, patients with DM>10 years and control group of patients. Solid horizontal lines denote the median value, the box represents the 25% and 75% interquartile ranges and whiskers represent the minimum and maximum values. *p<0.0005 compared to control group

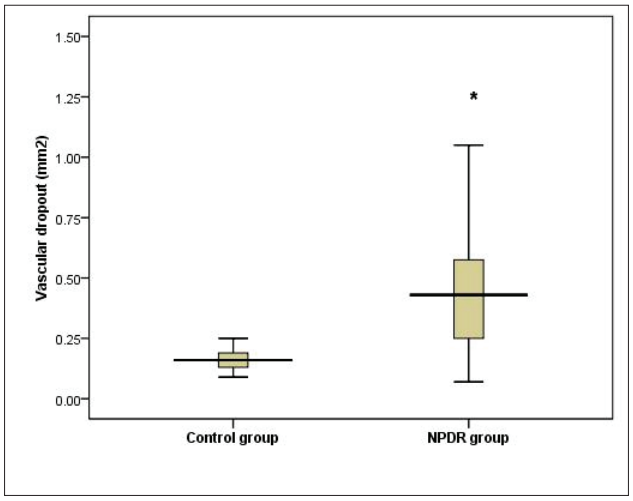

Figure 3. Box-and-whisker plots of Vascular dropout size (mm2) in superficial vascular plexus in patients with non-proliferative diabetic retinopathy (NPDR) and control group. Solid horizontal lines denote the median value, the box represents the 25% and 75% interquartile ranges and whiskers represent the minimum and maximum values. *p<0.0005 compared to control group

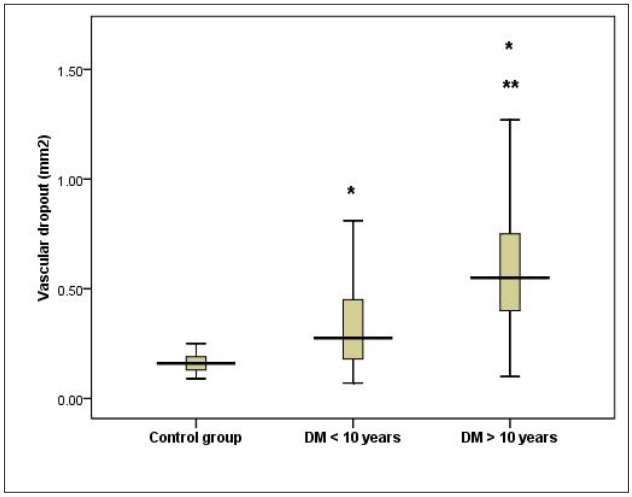

Figure 4. Box-and-whisker plots of Vascular dropout size (mm2) in superficial vascular plexus in patients with DM<10 years, patients with DM>10 years and control group. Solid horizontal lines denote the median value, the box represents the 25% and 75% interquartile ranges and whiskers represent the minimum and maximum values. *p<0.0005 compared to control group. **p<0.0005 compared to DM<10 years

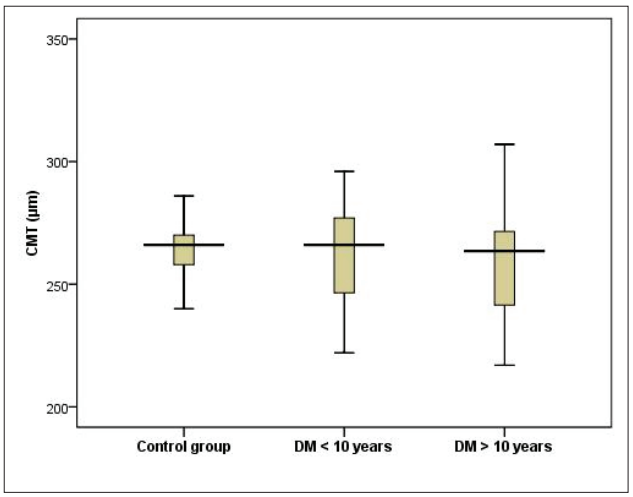

Figure 5. Box-and-whisker plots of Central macular thickness (µm) in patients with DM<10 years, patients with DM>10 years and control group. Solid horizontal lines denote the median value, the box represents the 25% and 75% interquartile ranges and whiskers represent the minimum and maximum values.

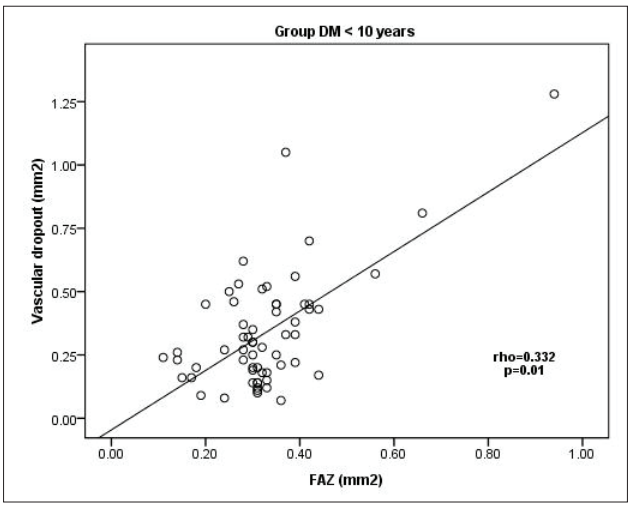

Figure 6. Correlation between the size of FAZ (mm2) and the size of vascular dropout (mm2) in superficial vascular plexus in patients with DM <10 years.

71 patients were on oral antidiabetic therapy, and 49 on insulin therapy. Glycated hemoglobin HbA1c (%) values were measured for every patient, and in a group of DM, less than ten years average value was 6.90% (6.40-7.20) compared to 7.00% (7.00–8.42) in the second group of patients with DM more than ten years. Fasting blood sugar in the morning was measured for each patient and average values were equal for both groups of examiners: 7.2 mmol/l. Median data were 6.62-8.22 mmol/l for the first group and 6.50-9.00 mmol/l for the second group. Body mass index (BMI) values were significantly higher for patients of both groups compared to healthy individuals in a control group. Diastolic blood pressure was almost the same in all three groups.

The average size of FAZ in the control group of patients was 0.21mm2 (0.17-0.24) and in the diabetic group of patients 0.32 mm2 (0.28-0.40). Statistical analysis shows a significant increase of FAZ in the NPDR group, with a very high statistic variation (p<0.0005 compared to the control group).

The average size of FAZ in the control group of patients was 0.21 mm2 (0.17-0.24 mm2), in DM<10 years it was 0.31 mm2 (0.28-0.36 mm2) and in DM>10 years it was 0.35 mm2 (0.25-0.47 mm2). When comparing FAZ in all three groups of patients, there were significant variations between the sizes of FAZ (done with the Kruskal-Wallis test, p<0.0005). But, while comparing the sizes of FAZ between two diabetic groups, there was no significant variation (p=0.1 - not significant), which means that the duration of diabetic disease doesn\'t influence on the enlargement of FAZ, although in the group above 10 years of disease, there were sizes of FAZ above 0.40 mm2. Of course, both diabetic groups showed a significant variation when compared to the FAZ in the control group of patients (p<0.0005).

The average size of Vascular dropout around the FAZ in superficial vascular plexus in the control group of pa-

tients was 0.16 mm2 (0.13-0.19 mm2) and in the diabetic group of patients 0.43 mv2 (0.25-0.57 mm2). Statistical analysis shows a very significant increase in vascular dropout areas (areas without any flow) in the NPDR group of patients no matter of duration of disease, with a very high statistical variation ($p<0.0005$ compared to the control group).

The average size of Vascular dropout around the FAZ, measured in superficial vascular plexus, in the control group of patients, was 0.16 mm2 (0.13-0.19 mm2), in DM<10 years it was 0.27 mm2 (0.18-0.45 mm2) and in DM>10 years it was 0.55 mm2 (0.40-0.75 mm2). When comparing Vascular dropout in all three groups of patients, there was a significant variation between the sizes of those nonflow areas around FAZ (done with the Kruskal-Wallis test, $p<0.0005$). Also, when we did an individual comparison, we acquired very significant variation in vascular dropout size between both NPDR groups and control group, as well as between diabetic patients who have the disease under 10 years and the ones who have disease over 10 years (in all three comparisons p was<0.0005). Sufficient fact is that the average VDO in diabetic patients under 10 years was 0.27 mm2, and in diabetic patients over 10 years 0-55 mm2.

The average size of Central macular thickness (μm) in the control group of patients was 266 microns (258-270 microns); in DM<10 years it was also 266 microns (246-277), and in DM>10 years it was 263 microns (241-271 microns). When comparing CMT in all three groups of patients, there was no significant variation between those values (done with the Kruskal-Wallis test, $p=0.5$). Also, when we did an individual comparison, there was no significant variation in CMT between both NPDR groups and control group, nor between diabetic patients who have the disease under 10 years and the ones who have disease over 10 years ($p=0.5$ between DM<10 years and DM>10 years; $p=0.7$ between DM<10 years and control group; $p=0.2$ between DM>10 years and control group).

In the group of patients with diabetes under 10 years a significant positive correlation between the size of FAZ (mm2) and the size of vascular dropout (mm2) in superficial vascular plexus is proven ($rho=0.332$, $p=0.01$). This means that by the development of non-proliferative diabetic retinopathy, both FAZ and vascular dropout increase at the same time.

Figure 7. Correlation between the size of FAZ (mm2) and the size of vascular dropout (mm2) in superficial vascular plexus in patients with DM >10 years.

In the group of patients with diabetes over 10 years there was a very significant positive correlation between the size of FAZ (mm2) and the size of vascular dropout (mm2) in superficial vascular plexus ($rho=0.556$, $p<0.0005$). This means that the more diabetes progresses and lasts longer, the FAZ and vascular dropout expand more and involve a larger region.

5. DISCUSSION

Using fluorescein angiography, Bresnick et al. (9) were the first to show the enlargement of the FAZ in diabetic retinopathy. Later, other reports have confirmed that FAZ enlargement reflects diabetic retinopathy advancement, which enables FAZ area to be one of the markers for staging diabetic retinopathy (10-16).

In 2015, authors from Nagoya City University Graduate School of Medical Sciences in Japan (17) showed statistically significant FAZ area enlargement in superficial plexus, as well as in deep plexus, in 44 diabetic eyes compared to 19 healthy eyes ($p<0.01$). According to this study, there is impairment in retinal microcirculation even before diabetic retinopathy develops and OCTA is a useful non-invasive tool for diabetic retina screening. Our study confirmed these statements with high significance ($p<0.005$), where average FAZ in patients with diabetes was 0.32 mm2, compared to 0.21 mm2 in a control group.

Talisa E. de Carlo et al. (18) found that FAZ and capillary nonperfusion had a higher prevalence in diabetic eyes concerning healthy eyes. They presented results of 0.348 mm2 FAZ size in diabetic eyes and 0.288 mm2 in control eyes ($p=0.04$).

In 2017, authors from Ancona and Pescara, Italy presented results of study (19) with 80 eyes enrolled, 60 of which diabetic patients with diabetic retinopathy and 20 healthy subjects. They underwent OCTA scans followed by analyses of the FAZ area and parafoveal vessel densities (PRVD). The authors concluded that the FAZ area increased and PRVD decreased in both superficial and deep plexus layers compared to measurements in the control group. These results were also in correlation with the ones from our study.

Rodrigues TM et al. (20) confirmed in 2019. that parafoveal vessel density is a significant predictor of NPDR. The study enrolled 101 eyes from 56 subjects age 62.64 years.

In 2018, Shen C. et al. (21) presented a study „Assessment of capillary dropout in the superficial retinal capillary plexus by OCTA in the early stage of diabetic retinopathy“ in which they concluded that in the early stage of NPDR, vascular dropout changes can be easily and analyzed by non-invasive OCTA, which was also correlated to our results.

6. CONCLUSION

We have to emphasize that FAZ and VDO are both enlarged in patients with NPDR. FAZ doesn't differ statistically between NPDR patients, although it was larger in patients who had disease over 10 years. VDO is significantly larger in patients with NPDR, and it enlarges as the disease lasts longer. CMT doesn't differ in size when comparing healthy patients and patients with NPDR. FAZ and vascular drop-out have shown a positive correlation in diabetes less than 10 years group, which means that both FAZ and vascular drop-out increase at the same time. FAZ and VDO have shown a high positive correlation in diabetes over 10 years group, which means that the more diabetes progresses and lasts longer, both FAZ and vascular drop-out expand more and involve larger regions. Both VDO and FAZ have shown good diagnostic accuracy in differentiating healthy patients and patients with NPDR, but fair diagnostic accuracy for estimating the duration and stage of the disease. A qualitative and

quantitative OCT angiography approach to retinal vascular status can offer objective data on monitoring patients with non-proliferative diabetic retinopathy as well as indicate the progression of the disease. Further study with larger sample size is may be of interest.

- **Author's Contribution:** A.K, I.M and N.A gave substantial contributions to the conception or design of the work in acquisition, analysis, or interpretation of data for the work. T.H, B.V and L.M had a part in article preparing for drafting or revising it critically for important intellectual content, and S.C.D and I.S gave final approval of the version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.
- **Financial support and sponsorship:** None.
- **Conflicts of interest:** There are no conflicts of interest.

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