Optical coherence tomography angiography microvascular changes in diabetics without diabetic retinopathy

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Abstract:

PURPOSE: The purpose of this study was to analyze the retinal vasculature of diabetic eyes without clinical retinopathy in order to detect microvascular abnormalities, comparing them to that of healthy nondiabetic control eyes.

METHODS: This is a prospective, cross-sectional study including 40 patients (76 eyes). Twenty patients (40 eyes) were diabetics with no diabetic retinopathy group (NDRG). The twenty other patients (36 eyes) were nondiabetic and constituted the control group (CG). Images were obtained using the AngioVue optical coherence tomography angiography (OCTA) software of RTVue XR spectral-domain OCT device. We performed 3 mm × 3 mm and 6 mm × 6 mm scans to evaluate the foveolar avascular zone (foveal) size, a remodeling of the FAZ, microaneurysms, vessel tortuosity, and superficial vascular density. All statistics were performed using IBM SPSS statistics (version 21).

RESULTS: The average FAZ size was 314.6 ± 15.3 µm in the NDRG versus 291.5 ± 14.1 in the CG. The difference was not significant (P = 0.56). FAZ remodeling was noted in 40% of eyes in the NDRG and in 2.8% of eyes in the CG (P = 0.0001). Flow alteration zones (nonperfusion zones) were seen in 77.5% in the NDRG (P = 0.0001). Microaneurysms were present only in the NDRG (70% of eyes). Parafoveolar vascular density was 52.8% ± 0.7% in the NDRG and 54.1% ± 0.25% in the CG but without significant difference (P = 0.206), and vascular tortuosity was significantly present in the NDRG with 32.5% of eyes versus 11.1% of eyes in the CG (P = 0.003).

CONCLUSION: OCTA is a promising tool to identify microvascular changes in the diabetic retina before clinically visible retinopathy occurrence. It may identify in the future individuals at risk of developing retinopathy and therefore those needing a better balance of diabetes.

Keywords: Angiography, diabetic retinopathy, optical coherence tomography

INTRODUCTION

Optical coherence tomography (OCT) is currently an essential tool for the analysis of macular changes, especially during diabetes.

OCT angiography (OCTA) is one of the advances that marked its evolution. It offers a high-resolution analysis of the retinal and the choroidal microcirculation in different layers with no leakage or accumulation of contrast product. It also provides a quantitative and qualitative evaluation of several parameters such as foveal avascular zone (FAZ) and vascular density.

Recent publications demonstrated that OCTA depicts early diabetic vascular changes and may be promising in diabetic retinopathy (DR) screening compared to fundus examination (the current gold standard) and retinography which lack quantitative and qualitative informations.

Our aim is to analyze the retinal vasculature of diabetic eyes without clinical retinopathy in...
order to detect microvascular abnormalities, comparing them to that of healthy nondiabetic control eyes.

**Methods**

It is a prospective, cross-sectional study including 40 patients (76 eyes) who were recruited from the ophthalmology service of the FSI Hospital, La Marsa, Tunisia, between July and September 2017.

Twenty patients (40 eyes) were diabetics (no DR group [NDRG]) and did not have any DR on fundus examination and photography. The twenty other patients (36 eyes) were nondiabetic and constituted the control group (CG = control group).

In both diabetic patients and controls, the exclusion criteria were other diseases that may affect retinal microcirculation such as retinal vascular occlusive disease, hypertensive retinopathy, central serous chorioretinopathy, age-related macular degeneration, high myopia, vitreoretinal interface diseases, optic nerve diseases such as glaucoma and optic neuropathy, retinal photocoagulation, and surgery.

Images were obtained using the AngioVue OCTA software of RTVue XR spectral-domain OCT device.

It is a static technique with no contrast product injection, which through segmentation allows better localization of vascular structures. Thus, it allows individualizing a superficial and deep retinal vascular network and a choroidal network.

We performed 3 mm $\times$ 3 mm and 6 mm $\times$ 6 mm scans centered at the fovea and evaluated by the same reader. We do not have the software option to obtain a quantitative evaluation of the deep network; therefore, all of our data concerned the superficial vascular network.

Qualitative and quantitative analyses were made on 3 mm $\times$ 3 mm OCT angiograms of the superficial vascular network. Parameters considered were as follows:

The foveolar avascular zone (FAZ) size
- A remodeling of the FAZ within the 1 mm central zone defined as the presence of adjacent flow alteration zones (nonperfusion), vascular tortuosity, ruptures, and irregularity of the capillary border (spider web-like architecture)
- Microaneurysms defined as focal dilatations or loops along capillaries
- Vessel tortuosity
- Superficial vascular density with a flow mapping.

The 6 mm $\times$ 6 mm OCT angiograms provide an image with a wider field and a lower resolution, but it allows evaluating more distant abnormalities (nonperfusion area, vascular tortuosity, and microaneurysms) not always apparent within the limited 3 mm $\times$ 3 mm scanning.

Images of poor quality including those having a signal strength (SS) $<50$ or artifacts (double-vessel pattern and dark areas, media opacities, etc.) were excluded from the study.

All statistics were performed using IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0 Armonk, NY: IBM Corp. All quantitative data were expressed as mean ± standard deviation, and qualitative variables were expressed as effectives and percentages analyzed using Chi-squared test. Comparisons of means were made using the Student’s t-test.

A correlation between continuous variables was analyzed using Pearson’s correlation analyses. $P<0.05$ was considered to be statistically significant.

An oral informed consent was obtained from all of our patients, and the Ethics Committee of the FSI Hospital approved the study. We recorded our study in the Pan African Clinical Trials Registry (Trial registration number: PACTR20170900251116).

**Results**

There were no significant differences between the epidemiological features of the two groups [Table 1].

In NDRG, the mean duration of diabetes was of 3 years and the mean value of the glycated hemoglobin was 7.5%.

The average of the SS of the images was 68.

Concerning the studied parameters, the average FAZ size was 314.6 $\pm$ 15.3 $\mu$m in the NDRG versus 291.5 $\pm$ 14.1 in the CG. The difference was not significant ($P=0.56$) [Figure 1].

FAZ remodeling was noted in 40% of eyes in the NDRG and in 2.8% of eyes in the CG ($P=0.0001$), with an odds ratio of 23.3. Figure 2 shows FAZ remodeling in the OCTA in two diabetic patients with flow alteration

![Figure 1: FAZ size measurement with an optical coherence tomography angiography 3 x 3 angiogram in a diabetic patient](image)

| Table 1: Epidemiological features of the two groups |
|-------------------|--------|--------|---|
|                  | NDRG   | CG     | $P$ |
| Mean age (years) | 49.5 (33-60) | 47 (37-54) | 0.12 |
| Sex ratio        | 2.3    | 1.4    | 0.11 |

NDRG=No diabetic retinopathy group; CG=Control group
zones (nonperfusion) adjacent to the FAZ and ruptures of the capillary border. The correspondent fundus photos did not show FAZ changes.

Flow alteration zones (nonperfusion zones) were seen in 77.5% of eyes in the NDRG ($P = 0.0001$), with an odds ratio of 27.6 [Figure 3].

Microaneurysms were present only in the NDRG with 70% of eyes ($P = 0.0001$) [Figure 4].

Parafoveal vascular density was 52.8% ± 0.7% in the NDRG and 54.1% ± 0.25% in the CG but without significant difference ($P = 0.206$) [Figure 5].

Vascular tortuosity was significantly present in the NDRG with 32.5% of eyes versus 11.1% of eyes in the CG ($P = 0.003$), with an odds ratio of 3.9 [Figure 6].

**DISCUSSION**

OCTA is a promising tool for DR screening by detecting early retinal changes undetectable on biomicroscopic fundus examination, where the microaneurysm is the first sign of the disease.$^{[1-3]}$

Retinal fluorescein angiography is more sensitive, but it is an invasive investigation tool, hence not appropriate in DR screening.$^{[3,5]}$

Studies of OCTA in diabetic patients without clinically apparent DR suggest alterations in superficial and deep capillary retinal networks as well as choriocapillaris. These changes include enlargement and disintegrity of the vascular arcades of the foveal avascular zone (FAZ), visible areas of reduced capillary density, microaneurysms, venous beading, and tortuosity.$^{[1-3,6,7]}$

Our study demonstrated that FAZ remodeling, microaneurysms, nonperfusion zones, and vascular tortuosity were significantly present in the diabetic group.

We did not find a significant enlargement of the FAZ size or a decrease of the vascular density in diabetic eyes, as shown in previous studies.$^{[2,5]}$

In fact, Coscas et al. demonstrated that these parameters are variable from one person to another and depend on age.$^{[8,9]}$

Besides, Carnevali et al. and Simonett et al. found that a decreased vessel density is an early process in type 1 diabetes and initially occurs in the deep capillary plexus explaining why decrease of the vascular density was not significant in the superficial network.$^{[10,11]}$
Remodeling, however, was significantly present in DG, suggesting that it may precede FAZ enlargement installation. Further studies would be useful to prove these suggestions.

Vascular tortuosity is rather a subjective parameter. De Carlo et al. found this vascular abnormality in 25% of control eyes versus 21% of diabetic eyes, suggesting that some degree of vascular tortuosity may be a variant of normal and will probably not be useful as an OCTA-screening parameter for diabetic retinal vascular changes.[3]

Microvascular abnormalities are not restricted to the retina. Some studies described diabetic choroidopathy in the OCTA.[1,2] They showed choriocapillaris flow impairment and a pronounced inhomogeneity in the microvascular density that did not correlate with the presence or the severity of retinal microvascular changes.[2]

The major limitation of our study is the absence of the deep retinal capillary network study where microvascular changes could be more relevant.

In addition, the other limitation with OCTA is a limited field of view, movement artifacts, and learning curve for reading the images.

**Conclusion**

OCTA is a promising tool to identify microvascular changes in diabetic before retinopathy occurrence. It may identify in the future individuals at risk of developing retinopathy and therefore those needing a better balance and monitoring of diabetes. It may be useful to study possible correlations between these microvascular changes and other diabetic microangiopathies or markers of diabetes as the glycated hemoglobin and also improve the current disease classification.

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**Conflicts of interest**

There are no conflicts of interest.

**REFERENCES**

1. Choi W, Waheed NK, Moult EM, Adhi M, Lee B, De Carlo T, et al. Ultrahigh speed CT angiography in diabetes. Retina 2017;37:11-21.

2. Dimitrova G, Chihara E, Takahashi H, Amano H, Okazaki K. Quantitative retinal optical coherence tomography angiography in patients with diabetes without diabetic retinopathy. Invest Ophthalmol Vis Sci 2017;58:190-6.

3. De Carlo T, Chin AT, Bonini Filho MA, Mehreen Adhi AM, Adhi M, Branchini L, et al. Detection of microvascular changes in eyes of patients with diabetes but not clinical diabetic retinopathy using optical coherence tomography angiography. Retina 2015;35:2364-70.

4. Hwang TS, Jia Y, Gao SS, Bailey ST, Lauer AK, Flaxel CJ, et al. Optical coherence tomography angiography features of diabetic retinopathy. Retina 2015;35:2371-6.

5. Wiley HE, Ferris FL. Nonproliferative diabetic retinopathy and diabetic macular edema. In: Ryan SJ, Sadda SR, Hinton DR, editors. Retina. London, United Kingdom: Elsevier Saunders; 2013. p. 940-68.

6. Di G, Weihong Y, Xiao Z, Zhikun Y, Xuan Z, Yi Q, et al. A morphological study of the foveal avascular zone in patients with diabetes mellitus using optical coherence tomography angiography. Graefes Arch Clin Exp Ophthalmol 2016;254:873-9.

7. Freiberg FJ, Pfau M, Wons J, Wirth MA, Becker MD, Michels S. Optical coherence tomography angiography of the foveal avascular zone in diabetic retinopathy. Graefes Arch Clin Exp Ophthalmol 2016;254:1051-8.

8. Coscas F, Sellam A, Glacet-Bernard A, Jung C, Goudot M, Miere A, et al. Normative data for vascular density in superficial and deep capillary plexuses of healthy adults assessed by optical coherence tomography angiography. Invest Ophthalmol Vis Sci 2016;57:211-23.

9. Hasegawa N, Nozaki M, Takase N, Yoshida M, Ogura Y. New insights into microaneurysms in the deep capillary plexus detected by optical coherence tomography angiography in diabetic macular edema. Invest Ophthalmol Vis Sci 2016;57:348-55.

10. Carnevali A, Sacconi R, Corbelli E, Tomasso L, Querques L, Zerbini G, et al. Optical coherence tomography angiography analysis of retinal vascular plexuses and choriocapillaris in patients with type 1 diabetes without diabetic retinopathy. Acta Diabetol 2017;54:695-702.

11. Simonett JM, Scarinci F, Picconi F, Giorno P, De Geronimo D, Di Renzo A, et al. Early microvascular retinal changes in optical coherence tomography angiography in patients with type 1 diabetes mellitus. Acta Ophthalmol 2017;95:e751-5.