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The Relationship between Macular Pigment and Vessel Density in Patients with Type 1 Diabetes Mellitus

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Keywords
Macular pigment · Optical coherence tomography angiography · Diabetic retinopathy · Macular pigment optical density

Abstract
Aim: Macular pigment density and microvascular density on optical coherence tomography angiography (OCTA) were measured in a cohort of type 1 diabetes mellitus (T1DM) patients with retinopathy in the attempt to shed light on the pathophysiology of this condition. ***Methods:*** Eighty-two consecutive eyes of 59 patients with diabetic retinopathy examined at the Eye Clinic of the University of Naples Federico II from November 2016 to April 2017 were enrolled in this prospective study. Eighty normal eyes of 40 age-matched subjects without diabetes mellitus, without a history of glaucoma or evidence of intraocular surgery, and without retinal pathologic features constituted the control group. All patients and controls underwent a complete ophthalmic examination, best corrected visual acuity evaluation according to the ETDRS visual logMAR scale, measurement of intraocular pressure, OCTA, and evaluation of macular pigment. ***Results:*** There were no significant age differences between patients and controls. Both macular pigment measurements and vessel density measured by OCTA were significantly lower in patients than in controls. A moderate correlation was found between vessel density in all ETDRS sectors and macular pigment parameters. ***Conclusions:*** There was a reduction in macular pigment and in OCTA vessel density in T1DM patients with retinopathy, which may have prognostic value in determining disease progression.

Introduction

Diabetic retinopathy is the leading cause of visual impairment and blindness in industrial countries, with a high prevalence in patients with type 1 diabetes mellitus (T1DM) [1, 2]. It is a microangiopathy that causes capillary occlusion, vascular hyperpermeability, and reti-

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nal neovascularization [3]. Histopathologic studies have demonstrated that diabetic retinopathy results from microvascular changes, i.e., capillary remodeling and regression, and decreased capillary density [4]. These alterations suggest that the microvascular retinal network is impaired in early-stage diabetic retinopathy, even in patients with no evidence of retinopathy [5]. Early detection and treatment can prevent severe vision loss in patients affected by diabetic retinopathy. Therefore, there is a pressing need to identify accurate easy-to-use techniques with which to evaluate the status of the retinal microvasculature.

Optical coherence tomography angiography (OCTA) is a noninvasive method with which to analyze both the superficial and the deep capillary plexus [6]. It also provides information about blood flow and vessel density, which, as mentioned above, can be altered in diabetic patients even at an early stage of the disease [7].

Oxidative stress has been implicated in the pathogenesis of diabetic retinopathy [8–10]. Macular pigment is constituted of lutein and zeaxanthin, which absorb maximally at wavelengths of 460 and 440 nm, respectively [11]. Blue wavelengths are hazardous because they can generate reactive oxygen species from endogenous photosensitizers. Lutein and zeaxanthin provide antioxidant protection to the human retina by inhibiting the peroxidation of polyunsaturated fatty acids [12]. Consequently, high levels of macular pigment may protect against damage caused by blue light.

Reduced levels of macular pigment have been identified in diabetic patients affected by retinopathy [13, 14]. The aim of this study was to measure macular pigment optical density (MPOD) and vessel density assessed by OCTA and to assess the correlation between the parameters obtained in a cohort of T1DM patients in an attempt to shed light on the pathophysiology of diabetic retinopathy.

Materials and Methods

Eighty-two consecutive eyes of 59 patients with diabetic retinopathy examined at the Eye Clinic of the University of Naples Federico II from November 2016 to April 2017 were enrolled in this prospective study. All patients with T1DM were characterized by the classic retinal microvascular signs of nonproliferative diabetic retinopathy: microaneurysms, hemorrhages, hard exudates, cotton-wool spots, venous dilation and beading, and intraretinal microvascular abnormalities [15]. Exclusion criteria were clinically relevant opacities of the optic media and low-quality OCTA images, congenital eye disorders, pre-existing macular diseases (e.g., age-related macular degeneration, severe macular scarring, or severe subfoveal exudates), pathologic myopia, history of ocular surgery, previous diagnosis of glaucoma, optic disk anomaly, and other ocular pathologic features (e.g., combined retinal vein and artery occlusive disease). Patients with a history of vitreous hemorrhage or cataract were not included. Eighty normal eyes of 40 controls without diabetes mellitus, without a history of glaucoma or evidence of intraocular surgery, and without retinal pathologic features constituted the control group. Normal eyes had a best corrected visual acuity (BCVA) of 0.1 logMAR or better, with a refractive error between +2.00 and –3.00 diopters.

All patients and controls underwent a complete ophthalmic examination, BCVA evaluation according to the ETDRS visual logMAR scale, measurement of intraocular pressure, OCTA, and evaluation of MPOD. Neither patients nor controls had previously used nutritional supplements containing lutein or zeaxanthin.

Optical Coherence Tomography Angiography

We obtained OCTA images with the Optovue Angiovue System (software ReVue version 2014.2.0.93; Optovue Inc., Fremont, CA, USA) using the split-spectrum amplitude decorrelation algorithm. The instrument has an A-scan rate of 70,000 scans/s with a tissue axial resolution of 5 μm and a 15-μm beam width. Each B-scan contained 304 A-scans. Two consecutive B-scans were captured at a fixed position before proceeding to the next sampling location. Blood flowing through vessels causes a change in reflectance over time and results in localized areas of flow decorrelation between frames. The spectrum of the light source was split into multiple component parts to decrease the noise present in the image; each part was used to perform the decorrelation step, and the results of all split spectra were averaged. In any given region of tissue, the projection image can be viewed to obtain an image of the contained blood flow. Cross-sectional registered reflectance intensity images and flow images were summarized and viewed as an en face maximum flow projection from the inner limiting layer to the retinal epithelial pigment.

Vessel density was defined as the percentage area occupied by the large vessels and microvasculature in the region analyzed. The OCTA software, according to the ETDRS classification of diabetic retinopathy, applied to all angiograms, a grid centered on the fovea that divides the macular region into a foveal and a parafoveal area, and further divides the parafovea into the superior and inferior hemispheres, the temporal section, nasal section, inferior section, and superior section. For each eye analyzed, the software automatically calculates vessel density in the entire scanned area and in all sections of the applied grid. Poor quality images with a signal strength index <40 and image sets with residual motion artefacts were excluded from the analysis.

Assessment and Analysis of Macular Pigment

We used the one-wavelength fundus reflectance method to evaluate macular pigment density (Visucam 200; Zeiss Meditec, Jena, Germany) [16, 17]. The Visucam is a fundus camera that uses narrow-band wavelength reflectance to measure macular pigment density. Retinal areas containing macular pigment absorb more blue light than the rest of the retina. In the blue reflectance image, the degree of darkening is a measure of MPOD.

The patients' pupils were dilated with one drop of 1% tropicamide, and fundus color photographs at 45° were obtained 30 min after pupil dilation. Head alignment was maintained with chin-head straps, and an internal fixation target with a central position

Table 1. Characteristics of the study population

	Patients	Controls	*p* value
Eyes, *n*	82	80	–
Females, *n*	26	22	–
Age, years	38.21±13.40	31.63±7.47	0.465
BCVA, logMAR	0.38±0.28	0.02±0.05	0.001
Whole image[1]	45.68±4.86	52.84±2.74	0.001
Fovea[1]	30.83±7.01	31.30±5.55	0.058
Parafovea[1]	47.16±5.60	54.89±2.74	0.001
Superior hemisphere[1]	47.22±5.85	55.04±2.59	0.001
Inferior hemisphere[1]	47.17±5.89	54.73±3.24	0.001
Temporal sector[1]	47.18±5.86	53.69±3.68	0.001
Superior sector[1]	47.36±6.32	55.63±2.74	0.001
Nasal sector[1]	47.49±6.22	54.86±3.20	0.001
Inferior sector[1]	46.04±6.41	55.46±3.31	0.001
MP volume	8,279.95±3,466.35	14,338.3±2,822.11	0.001
MP area	64,696.32±15,451.24	77,628.9±8,282.65	0.001
Maximum MP	0.32±0.09	0.47±0.06	0.001
Mean MP	0.12±0.03	0.18±0.02	0.001

Values are presented as mean ± SD or *n*. BCVA, best corrected visual acuity; MP, macular pigment. [1] Data are expressed as vessel density percentage.

was used for image alignment. The retina was illuminated with blue light, and only the blue channel of the capture sensor was used for the MPOD image; this suppresses unwanted autofluorescence signals in the green wavelength range. The MPOD was measured in a 30° field of the fundus photograph with the flash level set on automatic and flash intensity set at 12. Autofocus function was enabled. The MPOD signal was calculated in a range of 4–7° of eccentricity around the fovea, spanning the region where the majority of xanthophylls are concentrated. This was separated from the background signal of the normal reflection of the retina beyond 7° of eccentricity, where it is assumed that no macular pigment is present. The optical density and distribution of macular pigment were calculated using a dedicated software algorithm, and the following fundus reflectometry measurements within each image were recorded: mean MPOD and reproducibility, maximum MPOD value, MPOD area (the area within which the macular pigment was detected and defined on the background), and MPOD volume (the sum of all optical densities within the MPOD area). Mean MPOD is the ratio of volume to area and referred to the mean MPOD xanthophylls in relation to the surface area. Maximum MPOD refers to the maximum MPOD xanthophylls (usually in the fovea). MPOD is measured in density units [18, 19].

Statistical Analysis

Statistical analysis was performed with the Statistical Package for Social Sciences (version 20.0 for Windows; SPSS Inc., Chicago, IL, USA). The Mann-Whitney U test was used to evaluate differences in BCVA, OCTA vessel density, and macular pigment measurements between controls and patients with diabetic retinopathy. Spearman correlation was used to assess the correlation between parameters obtained with the two techniques. A p value <0.05 was considered statistically significant.

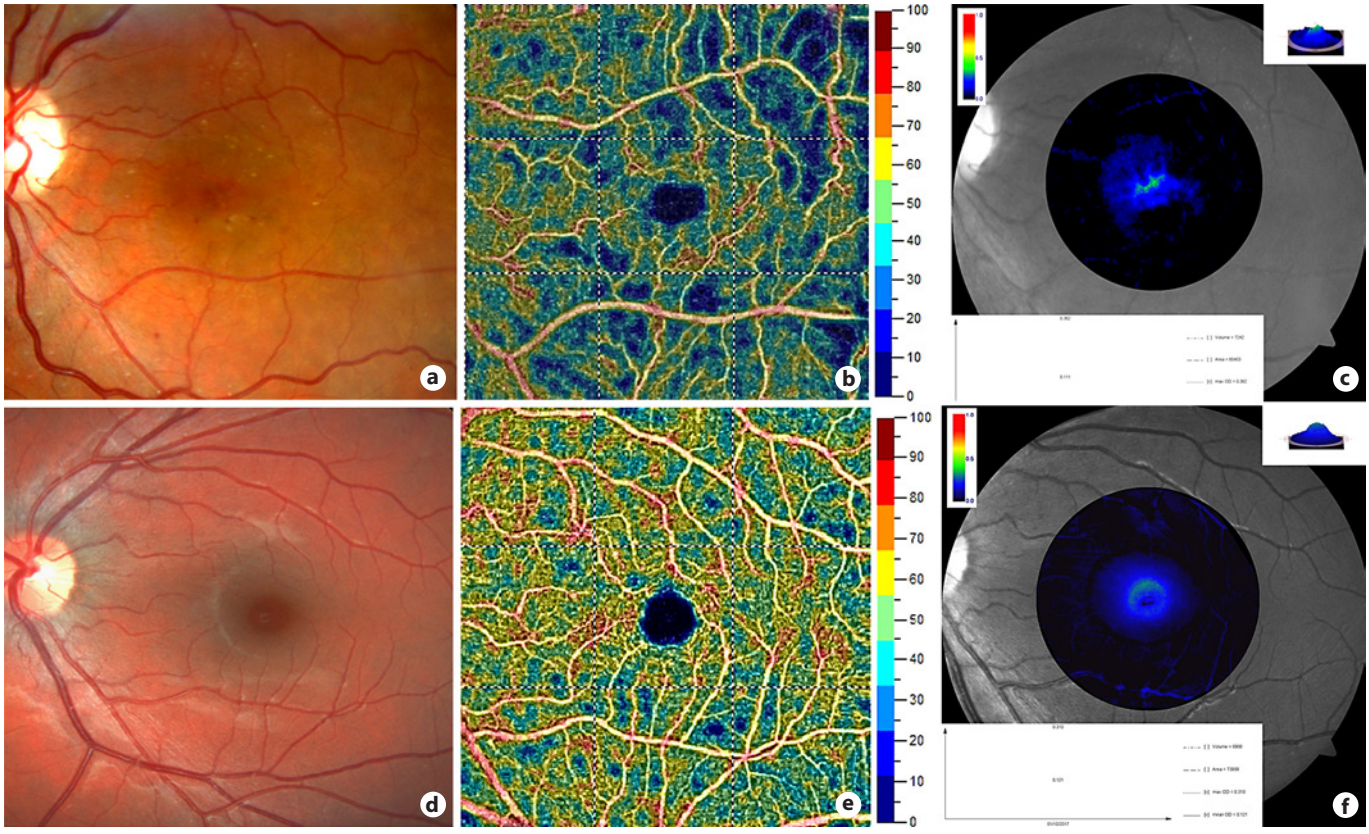
Results

Fifty-nine patients (26 females, 33 males, mean age 38.21 ± 13.40 years) for a total of 82 eyes examined were included in this prospective study. Mean BCVA was 0.38 ± 0.28 logMAR. The control group was constituted of 40 individuals (22 females, 18 males, mean age 31.63 ± 7.47 years) for a total of 80 eyes examined. There were no significant age differences between patients and controls. Both macular pigment measurements and OCTA vessel density were significantly lower in patients than in controls (Table 1; Fig. 1, 2). Similarly, Spearman coefficient revealed a strong correlation between vessel density in all ETDRS sectors and macular pigment parameters (Table 2).

Discussion

This is the first study to measure MPOD and vessel density, assessed by OCTA, in a cohort of T1DM patients in the attempt to shed light on the pathophysiology of diabetic retinopathy.

Changes in T1DM patients could precede detectable damage induced by diabetic neuroretinopathy [20]. In fact, OCTA revealed early vascular alterations in T1DM patients [21]. Vasoregression is probably the first event in diabetic retinopathy [22, 23]. Although the exact se-



Color version available online

Fig. 1. a–c Color fundus photography, vessel density, and macular pigment in a 50-year-old male with type 1 diabetes mellitus. Note the reduced vessel density and macular pigment. **d–f** Color fundus photography, vessel density, and macular pigment in a 45-year-old healthy male. Note the normal vessel density and macular pigment.

quence of events has not been identified in humans, animal studies have shown that pericytes are the first cells to disappear, followed by endothelial cells, thereby resulting in acellular capillaries and capillary closure [22, 23].

Diabetic patients have a significant decrease in vessel density in all retinal layers [24]. In addition, there is evidence that capillary rarefaction starts in the deep capillary plexus [20, 25]. Moreover, Agemy et al. [24] reported that the loss of capillary density was greater in the superficial capillary plexus than in the deep capillary plexus. Notably, in all the abovementioned studies, a decrease in capillary density was found in the superficial capillary plexus and deep capillary plexus [26, 27]. In one study, the decrease in perfusion index became more pronounced as the disease progressed [28].

In our study, vessel density was significantly lower in eyes with diabetic retinopathy than in normal eyes, which is in accordance with the concept that oxidative stress plays an important role in the development of vascular damages in diabetic patients [29, 30]. Local acidosis can promote vascular endothelial growth factor upregulation and increase leukostasis in small retinal capillaries [25] and so result in microvascular complications in the retina. Distance from the larger arterioles, proximity to the high metabolic demand of the outer retina, and the complex vascular anatomical architecture may increase the susceptibility of the deep capillary plexus to diabetic damage [31]. Retinal acidosis was most prominent in the outer nuclear layer in the early stages of a diabetic retinopathy mouse model [32]. None of these mechanisms are mutually exclusive, and more than one may be operating in T1DM patients.

Macular pigment consists of three dietary carotenoids (lutein, zeaxanthin, and meso-zeaxanthin) that act as an optical filter for wavelengths <550 nm and provide antioxidant protection to the human retina by inhibiting the peroxidation of long-chain polyunsaturated fatty acids [33, 34]. MPOD has a slow biological turnover that probably results from the local balance between pro-oxidant stress and antioxidant defenses in the retina [35]. Levels of MPOD

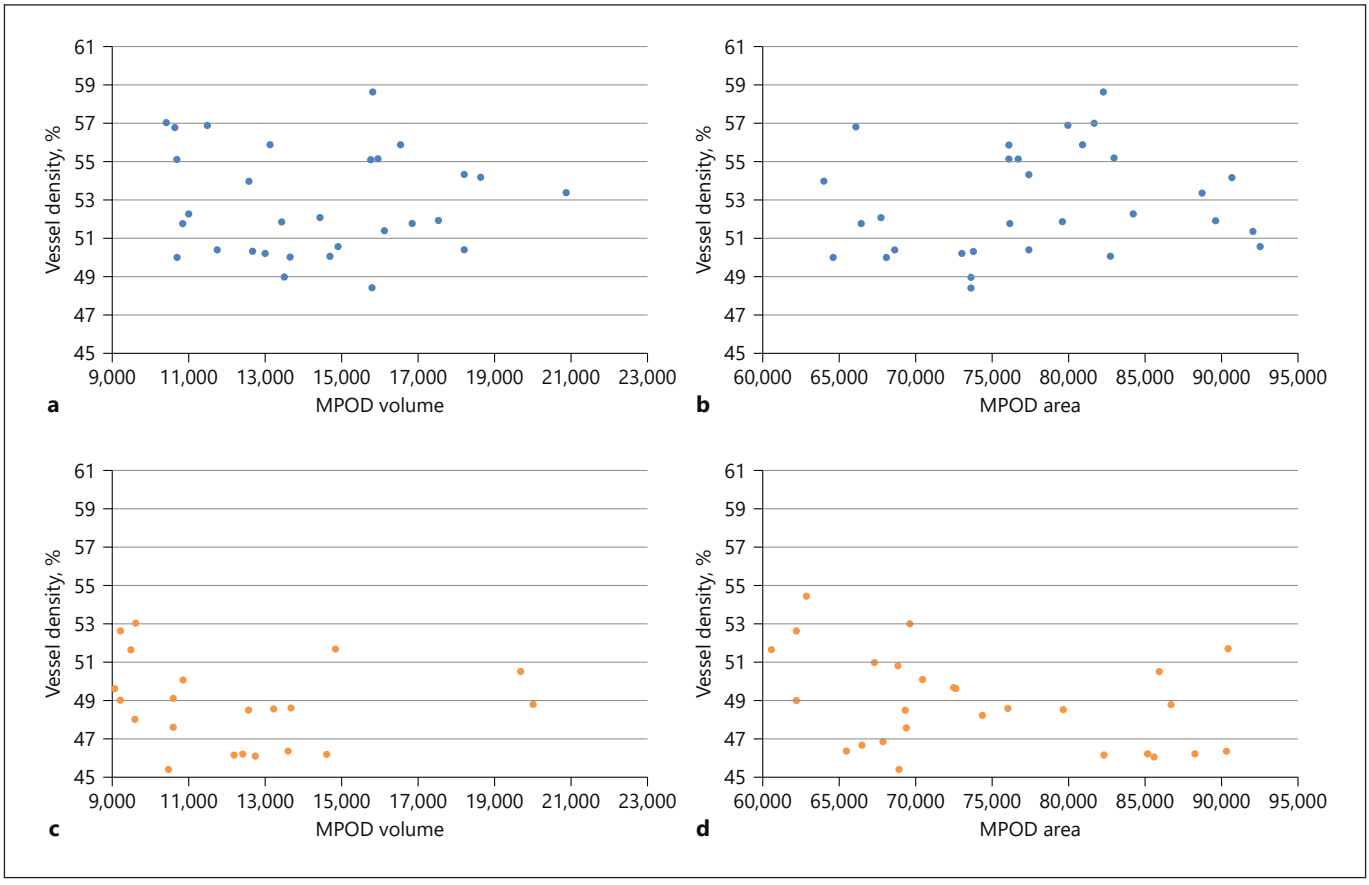


Fig. 2. **a** Scatterplot of the correlation between MPOD volume (*x* axis) and vessel density (*y* axis) in whole OCTA scan in the control group. **b** Scatterplot of the correlation between MPOD area (*x* axis) and vessel density (*y* axis) in whole OCTA scan in the control group. **c** Scatterplot of the correlation between MPOD volume (*x* axis) and vessel density (*y* axis) in whole OCTA scan in the patient group. **d** Scatterplot of the correlation between MPOD area (*x* axis) and vessel density (*y* axis) in whole OCTA scan in the patient group. MPOD, macular pigment optical density; OCTA, optical coherence tomography angiography.

Table 2. Correlation between vessel density and macular pigment measurements

	Volume		Area		Maximum		Mean	
	r value	*p* value	*r* value	*p* value	*r* value	*p* value	*r* value	*p* value
Whole image	–0.421	0.001	–0.320	0.003	–0.354	0.001	–0.367	0.001
Fovea	–0.466	0.001	–0.322	0.003	–0.318	0.004	–0.379	0.001
Parafovea	–0.389	0.001	–0.311	0.004	–0.320	0.003	–0.342	0.002
Superior hemisphere	–0.370	0.001	–0.270	0.014	–0.296	0.007	–0.324	0.003
Inferior hemisphere	–0.443	0.001	–0.347	0.001	–0.387	0.001	–0.397	0.001
Temporal sector	–0.357	0.001	–0.276	0.012	–0.310	0.005	–0.348	0.001
Superior sector	–0.344	0.001	–0.264	0.016	–0.260	0.018	–0.283	0.010
Nasal sector	–0.372	0.001	–0.377	0.001	–0.268	0.015	–0.254	0.021
Inferior sector	–0.415	0.001	–0.290	0.008	–0.395	0.001	–0.406	0.001

in the human body are highest in Henle's fibers at the fovea and in the inner nuclear layer of the perifoveal area [16, 36].

Lutein, zeaxanthin, epilutein, and 3'-oxolutein are the main dietary sources of xanthophylls in the human retina [37]. Although the human body cannot synthesize these carotenoids, they are involved in maintaining eye health [38]. Diabetic patients with or without retinopathy were found to have significantly reduced MPOD when compared with nondiabetic patients [14]. Our cohort of T1DM patients had decreased MPOD on Visucam fundus images. The relationship between reduced macular pigment levels and increasing severity of maculopathy may implicate oxidative stress as a causative factor in T1DM retinopathy [39]. Moreover, lutein and zeaxanthin are versatile antioxidants that neutralize reactive oxygen species in both the low-pO_2 inner retina and the high-pO_2 photoreceptor-retinal pigment epithelium complex. This oxygen-rich outer retina is particularly vulnerable to oxidative damage because of the high concentrations of polyunsaturated fatty acids, which, in turn, are susceptible to photo-oxidation and exposure to high-energy blue light [38].

Various mechanisms may underlie reduced MPOD in diabetic patients, i.e., a genetic mechanism [40], a dietary deficit of lutein and zeaxanthin or reduced absorption from the gut [41, 42], a reduced rate of lutein and zeaxanthin incorporation into the retinal tissue, or an increased rate of removal from the retina. Lutein and zeaxanthin protect the macula against photo-oxidative stress [37] by absorbing harmful shortwave length blue light [43]. Consequently, reduced macular pigment density may result from increased oxidative stress in the diabetic macula [39]. Sustained hyperglycemia triggers the disruption of normal cellular metabolism that leads to the development of retinopathy [44]. It increases oxidative stress, which appears to be one of the key regulators in the development of diabetic complications [45, 46]. There is strong evidence that chronic hyperglycemia causes oxidative stress, which plays an important role in the development of diabetic retinopathy. In particular, oxidative stress results in microvascular complications at the retina level [47] and in reduced macular pigment density [39]. Vascular alterations in patients with diabetic retinopathy can result from continuous oxidative stress caused by thickening of the basement membranes of the retinal capillaries, increased the affinity of oxygen for glycosylated hemoglobin, a redox shift due to the effects of hyperglycemia on glycolysis and on sorbitol metabolism, and an abnormal vasculature in parafoveal capillaries [48].

The fact that projection artifacts may confound image quality could also be considered a limitation. Moreover, it is possible that duration of diabetes mellitus, compliance to treatment, type of medication, and lifestyle could affect the relationship between macular pigment density and OCTA measurements in patients with T1DM. The strength of this study is the analysis of both MPOD and vessel density in a large number of T1DM patients with diabetic retinopathy.

In conclusion, a reduction in MPOD and in vessel density in T1DM seems to be associated with hyperglycemia, which causes oxidative stress. Hyperglycemia and oxidative stress are major factors in the pathophysiology of diabetic retinopathy, therefore vessel density and MPOD could be prognostic factors of disease progression. However, further studies are needed to understand the correlation between macular pigment, vessel density, and diabetic retinopathy progression.

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Statement of Ethics

The study was approved by our Institutional Review Board and informed consent was obtained from all subjects before enrollment. All investigations adhered to the tenets of the Declaration of Helsinki (64th WMA General Assembly, Fortaleza, Brazil, October 2013).

Disclosure Statement

The authors declare that there are no conflicts of interest. No financial support was received for this submission.

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