Relationships between Vascular Structure and Neural Function of Macula in Patients with Diabetes Mellitus

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Running title: Focal macular ERG vs OCTA in diabetes

Figures: 8

Tables: 1

Words: 3,574

Acknowledgements

We thank Professor Emeritus Duco Hamasaki of the Bascom Palmer Eye Institute for discussions and for editing the manuscript.

ABSTRCT

Purpose: To determine the significance of the correlation between the vascular structure and the neural function of the macula in patients with diabetes mellitus.

Methods: Ninety eyes of 90 diabetic patients with an average age of 63.5±13.8 years were studied. There were 50 eyes without clinically apparent diabetic retinopathy (non-DR) and 40 eyes with mild to moderate non-proliferative DR (NPDR). Thirty age-matched normal subjects were also studied in the same way. Swept source optical coherence tomography angiography (OCTA) was performed to obtain 3x3 mm enface images of the posterior pole of the eye. The vascular density (VD) of the superficial capillary plexus (SCP) and the deep capillary plexus (DCP) was determined. The focal macular ERGs elicited by a 15° circular stimulus were recorded. The amplitudes of the a- and b-waves, sum of the oscillatory potentials (ΣOPs), and photopic negative response (PhNR), and the implicit times of the OPs (from OP1 to OP3) were measured.

Results: The VDs of the SCP and DCP were reduced in eyes with advanced DR (P<0.01 for the SCP). The implicit times of OP1-OP3 were significantly prolonged in eyes with a lower VD of the SCP and DCP in the non-DR group (P<0.05). The amplitudes of the ΣOPs were significantly smaller in eyes with a reduced VD of the SCP and DCP in the NPDR group (P<0.05). The correlation coefficients were higher

for the OPs implicit times than for the ΣOPs amplitudes in the non-DR group.

Conclusions: The OPs of the focal macular ERG are smaller with prolonged implicit times in association with capillary loss in the macula of diabetic patients. The implicit times are the most sensitive functional parameter that reflects the early changes of the microvasculature in the macula caused by diabetes.

INTRODUCTION

Diabetic retinopathy (DR) is a leading cause of blindness in many countries (Wong et al, 2016). The initial signs of DR include microaneurysms, hemorrhages, and exudation which are related to abnormalities of the retinal vasculatures. It has been reported that the functional changes of the retina preceded these structural changes in the early stage of DR (Yonemura et al, 1962; Shirao and Kawasaki, 1998).

The oscillatory potentials (OPs) of the full-field electroretinograms (ERGs) elicited by bright flashes are small wavelets that appear on the ascending limb of the b-wave of the ERGs (Yonemura et al, 1962). The OPs are believed to originate from the activity of the neurons in the inner retina (Wachtmeister, 1998), and these neurons include the amacrine cells which are vulnerable to retinal ischemia (Shirao and Kawasaki, 1998). Yonemura et al and his co-workers reported a selective loss of the OPs in diabetic patients without apparent clinical signs of DR (Yonemura et al, 1962; Kawasaki, 1998; Shirao and Kawasaki, 1998). Shirao and Kawasaki reported that prolonged implicit times of the OPs were present earlier than the decrease in the amplitudes of the OPs (Shirao and Kawasaki, 1998). They also showed that the prolongation of the implicit times of the OPs was significantly correlated with motion contrast even in diabetic patients without apparent DR. This indicated that

disturbance of the visual function can precede the retinal vascular impairments.

Recent advances of optical coherence tomography (OCT) has allowed clinicians to evaluate the microvasculature of the retina noninvasively and in greater detail. The vascular structures of the retina are clearly visible by OCT angiography (OCTA) which has been applied to various retinal diseases for diagnosis and understanding the pathophysiology (Spaide et al, 2018). The foveal avascular zone (FAZ) has been reported to increase in size in eyes with advance of diabetic retinopathy (Takase et al, 2015). The vascular density (VD) of the retinal capillaries has been demonstrated to be reduced in patients with diabetic retinopathy (Ishibazawa et al, 2015; Salz et al, 2016). Thus, the vascular structure of the retina can be quantitatively analyzed by OCTA. It has been reported that ultra-widefield OCTA is more useful in detecting avascular areas than fluorescein angiography in patients with DR (Couturier et al, 2019). This then raises the question of whether abnormalities of the retinal vasculature may be missed by examining only fluorescein angiograms.

Analysis of the focal macular ERGs is one method to assess the function of the macula objectively (Miyake et al, 1981). Its use has enabled clinicians to analyze the retinal function in the macula layer-by-layer (Miyake, 1988). Miyake et al have

extensively studied characteristics of the OPs of the focal macular ERG (Miyake et al, 1989; 1990), and they reported that the function of the inner retina in the macular area can be assessed by evaluating the OPs of the focal macular ERG. Yoon et al (Yoon et al, 1990) demonstrated that the amplitudes of the OPs of the focal macular ERGs were selectively affected in patients with early DR.

The purpose of this study was to determine whether there is a significant correlation between the microvascular structure and the function in the macular area. To accomplish this, we determined the VD of the macular area by OCTA and the function in the same area by recording the focal macular ERGs in diabetic patients.

METHODS

Subjects

Ninety patients with diabetic mellitus received a comprehensive ophthalmological examination including measurements of their Snellen visual acuity, slit-lamp biomicroscopy, and indirect ophthalmoscopy. Only the data from a randomly selected eye of each patient was used for the statistical analyses.

The stage of retinopathy was determined by the ophthalmoscopic findings, and they

were based on International Clinical Diabetic Retinopathy Disease Severity Scales (Wilkinson et al., 2003). This classification system consisted of five scales with increasing risks of retinopathy. The first level is “no apparent diabetic retinopathy” (non-DR), and the second level is “mild non-proliferative diabetic retinopathy (NPDR)” in which only microaneurysms are seen. The third level, “moderate NPDR”, includes eyes with more than just microaneurysms but less severe than NPDR. The fourth level, “severe NPDR”, includes any of the following ocular findings; more than 20 intraretinal hemorrhages in each of the quadrants, definitive venous beading in 2 quadrants, prominent intraretinal microvascular abnormalities, and no signs of proliferative diabetic retinopathy (PDR). The fifth level, “PDR”, includes eyes with definite neovascularizations.

The patients consisted of 59 men and 31 women with a mean age of 63.5 ± 13.8 (standard deviation) years. There were 50 eyes of 50 patients with non-DR. Patients with “mild NPDR” or “moderate NPDR” were combined and classified as NPDR and there were 40 eyes of 40 patients in this group.

Thirty eyes from 30 normal volunteers (normal subjects) with a mean age of 65.4 ± 12.8 years were studied with the same protocol for the ERG and OCTA recordings.

No significant difference was found in the age between the normal subjects and diabetic patients.

This research was conducted in accordance with the Institutional Guidelines of Dokkyo Medical University, and the procedures conformed to the tenets of the Declaration of Helsinki. An informed consent was obtained from all subjects after a full explanation of the nature of the experiments.

Focal macular ERG recordings

The pupils were dilated to approximately 8 mm by topical 0.5% tropicamide and 0.5% phenylephrine hydrochloride. The focal macular ERGs were recorded from the macular area by the methods developed by Miyake et al (1988, 1989). The stimulus system was integrated into an infrared fundus camera (ER-80, Kowa Company, Ltd., Aichi, Japan), and the stimulus was a circular with a diameter of 15-degrees. The stimulus was centered on the fovea, and the position was confirmed by viewing the ocular fundus on the monitor of the fundus camera. The luminance of the white stimulus was 30 cd/m^2 and that of the background was 1.5 cd/m^2. The stimulus duration was 16.6 msec. During the ERG recordings, all subjects were instructed to gaze at a fixation point in the central visual field, and the position of the stimulus on

the retina was monitored through the infrared fundus camera.

The ERG signals were picked-up by a Burian-Allen bipolar contact lens electrode (Hansen Ophthalmic Laboratories, Iowa City, IA), and a chlorided silver electrode was placed on the left ear lobe as the ground electrode. The responses were digitally band-passed from 5 to 200 Hz for the a- and b-waves and the PhNR, and from 50 to 500 Hz for the OPs (PuREC, Mayo Corporation, Inazawa, Aichi, Japan). Approximately 300 responses were summed at a stimulation frequency of 5 Hz for the fmERGs.

The a-wave amplitudes were measured from the baseline to the trough of the first negative response, and the b-wave amplitudes were measured from the first trough to the peak of the following positive wave (Figure 1B). The PhNR amplitudes were measured from the baseline to the negative trough. The amplitudes of the OP1, OP2, and OP3 were measured and summed and were designated as the ΣOPs. The implicit times of the OP1, OP2 and OP3 were also measured.

Optical Coherence Tomography Angiography (OCTA)

OCTA images were 3 × 3 mm enface images and were recorded with a swept-source

OCT instrument (SS-OCT, PLEX® Elite 9000, ZEISS, Oberkochen, Germany). The OCTA images were automatically segmented to evaluate the superficial capillary plexus (SCP) or the deep capillary plexus (DCP). The SCP is defined as a slab that extended from the internal limiting membrane (ILM) to the outer border of the inner plexiform layer (IPL). The DCP is located between the outer border of the IPL to the outer border of the outer plexiform layer (OPL). The size of the FAZ was measured in the SCP images by the embedded software in the Advanced Retinal Imaging (ARI) network. The VD of the retinal capillaries was determined by using a binary thresholding method embedded in ARI network. The focal macular ERGs were elicited by a 15-degree stimulus spot and the OCTA images were recorded from the essentially the same area (Figure 1A).

Spectral-domain optical coherence tomography (SD-OCT)

The thickness of the ganglion cell complex (GCC) that extend from the ILM to the outer border of the IPL was measured at 512 x 128 points in the posterior pole of the eye by a spectral-domain OCT instrument (SD-OCT, RS-3000 Advance, Nidek Co. LTD., Gamagori, Aichi, Japan). We used the GCC charts for the analysis (Figure 1). The mean GCC thickness was determined for each half of an annulus with an outer diameter of 4.5 mm corresponding to 15 degree on the retina (enclosed by squares in

Figure 1A) except for the foveal area within 1.5 mm. These values were averaged for the comparisons. The tracking system of the OCT system allowed the averaging of the images of the same areas.

Statistical analyses

Kruskal-Wallis tests were used to determine the significance of the differences in the pre-treatment and post-treatment values of affected eyes and the values of corresponding areas of the unaffected eyes. Dunn's post hoc tests were used for multiple comparisons among the groups. The statistical analyses were performed with Graph Pad PRISM 7. A P <0.05 was taken to be statistically significant.

RESULTS

Representative waveforms and OCTA images

Representative focal macular ERGs and digitally band-passed OPs recorded from normal subjects and diabetic patients from the non-DR and the NPDR groups along with the binary thresholding OCTA images of SCP and DCP are shown in Figure 2. In the non-DR patient, the amplitudes of the a- and b-waves and the PhNR were comparable to those of the normal subject. However, the implicit times of the OPs were prolonged and the amplitudes were reduced. In the patient from the NPDR

group, the b-wave amplitude was reduced with a greater reduction of the OPs amplitudes. The OCTA images showed a clear loss of the capillaries in the SCP and DCP in the patients from the non-DR and NPDR groups.

Comparisons of size and vascular density of foveal avascular zone (FAZ)

The average size of the FAZ area and the VD of the SCP and DCP for normal subjects and diabetic patients from the non-DR and NPDR groups are shown in Figure 3. Although a significant enlargement of the FAZ size was not seen in the diabetic patients compared with normal subjects, the FAZ size was larger in the NPDR (Figure 3A). The VDs of SCP and DCP were more reduced in eyes with more advanced DR (Figures 3B and 3C), and the difference in the VD of the SCP between normal subjects and patients in the NPDR group was significant (P <0.01).

Correlation between focal macular ERGs and OCTA

Each ERG parameter is plotted against the VD of SCP for normal subjects and diabetic patients in Figure 4. Although the a- and b-waves and PhNR amplitudes were not significantly correlated with the VD of SCP (Figure 4A-C), the ΣOPs amplitudes were significantly smaller in eyes with a decrease in the VD of the SCP (P<0.0001, Figure 4D). The implicit times of the OP1-OP3 were significantly prolonged in eyes

with a decrease in the VD of the SCP (P <0.0001).

Each ERG parameter is plotted against the VD of the DCP for normal subjects and diabetic patients. Although the amplitudes of the a- and b-waves and the PhNR were not significantly correlate with the VD of the DCP (Figure 5A-C), the amplitudes of the ΣOPs were significantly smaller in eyes with a loss of the FAZ of the SCP (P <0.005, Figure 5D). The implicit times of the OP1-OP3 were significantly delayed with a decrease in the VD of the DCP (P <0.01 to 0.0001).

Correlation between OPs and OCTA in diabetic patients with subtypes of DR

Because the implicit times and amplitudes of the OPs were significantly depressed in eyes with more severe DR, we plotted the OPs parameters against the VD of SCP and DCP for diabetic patients from the non-DR and NPDR groups separately.

The amplitudes of the ΣOPs were more reduced in eyes with a greater decrease in the VD of the SCP and DCP in patients from the non-DR group (Figures 6A and 6C) and the NPDR group (Figures 6B and 6D). Significant correlations were found only between the ΣOPs amplitudes and the VD in the NPDR group (P <0.005 for SCP and P <0.05 for DCP).

The implicit times of the OP1-OP3 were significantly prolonged with a decrease in the VD of the SCP (P <0.05-0.01, Figures 7A, 7C, and 7E) and the DCP (P<0.01-0.001, Figures 8A, 8C. and 8E) in patients from the non-DR group. Significant correlations were found only between the VD of the SCP and the implicit time of OP2 (P = 0.01, Figure 7D) and the implicit time of OP3 (P <0.05, Figure F) in the NPDR group.

Correlation coefficients and P-values are presented in Table 1. Higher correlation coefficients were obtained for the implicit times of the OPs than for the amplitudes of the ΣOPs in the non-DR group. In contrast, the amplitudes of the ΣOPs had higher correlation coefficients than the implicit times of the OPs which failed to show significant correlation with the VD of DCP in the NPDR group.

Correlation between inner retinal structure and OCTA and OPs

The GCC thickness was averaged and compared among the normal subjects and diabetic patients from the non-DR and NPDR groups. The GCC thickness was 110 ± 7.94 in the normal subjects, 107 ± 12.6 in the non-DR patients, and 113 ± 17.6 μm in the NPDR patients. None of the differences was significant. No significant correlations were found between the GCC thickness and the OPs parameters or the

VD of the SCP.

DISCUSSION

Our results demonstrated that the implicit times and amplitudes of the OPs of the focal macular ERG were significantly correlated with the density of the microvasculature of the macula even in patients in the non-DR group. This indicates that the functional and mircrovascular abnormalities are present even while the fundus appears normal ophthalmoscopically.

Is early DR neuropathy or vasculopathy?

It has been documented that the implicit times of the OPs are prolonged even at the very early stage of DR without any visible signs of DR ophthalmoscopically (Shirao and Kawasaki, 1998). Accumulated evidence based on animal studies has shown that a decrease in the level of dopamine in the retina plays an important role in the OPs abnormalities in diabetes (Shirao and Kawasaki, 1998). Thus, it was suggested that the prolongation of the OP implicit times at the early stage of DR may not be due to diabetic vasculopathy but rather to neural alterations involving the neurotransmitters.

The degree of diabetic vasculopathy has been evaluated by fluorescein angiography which was the most sensitive method to detect and quantify the degree of retinal vasculopathy at that time. However, recent studies have shown that OCTA is a more exact method to detect non-perfused areas in diabetic retinas (Couturier et al, 2019; Salz et al, 2016; Sawada et al, 2018; Hirano et al, 2018). Therefore, microvascular abnormalities could be overlooked at the very early stage of DR in the conventional fluorescein angiography. Our results showed that an increase in the OP implicit times was well correlated with the vascular densities even in the non-DR group which suggests that the early functional abnormalities of the retina depend on the microvascular changes.

Differences between amplitudes and implicit times of OPs

In diabetic patients with more advanced DR, the NPDR group, the amplitudes of the OPs were reduced along with a decrease in the VD of the SCP and DCP. However, the OP implicit times were not significantly correlated with the VD. The implicit times are believed to be related to the physiological status of the retinal cells. On the other hand, the amplitudes may be related to the number of functioning retinal cells. Based on this concept, the amacrine cells which are the most likely generator of the OPs may be affected physiologically while maintaining the same number of surviving cells

at the early stage of DR. However, at the advanced stage, the number of surviving cells may decrease along with impairments of the retinal vasculature. This would then lead to the reduction of the OPs amplitudes.

Recently, similar findings were observed in the full-field flicker ERGs. Zeng et al (Zeng et al, 2019; 2020) reported that the amplitudes of the full-field flicker ERGs were significantly reduced with a loss of retinal capillaries in patients with NPDR (Zeng et al, 2020). They also stated that the implicit time represented the reduction in the capillary density in patients with non-DR (Zeng et al, 2019).

OPs of full-field flicker ERGs and focal macular ERGs

Zeng et al (2019) reported that the VD of the parafoveal SCP obtained by OCTA was correlated with the implicit times of the full-field flicker ERGs in diabetic patients with non-DR. This indicated that the retinal dysfunction coincided with the microvascular changes at an early stage of DR which is consistent with our results. However, the full-field flicker ERGs are responses that are derived from the entire retina while the OCTA are images from the macula. We used the focal macular ERG recorded from the corresponding retinal area where the OCTA images were obtained.

The full-field flicker ERGs represent responses consist mainly of the interaction of the ON- and OFF-bipolar cells (Kondo and Sieving, 2001). The inner retinal responses contributed less to shaping the flicker ERGs (Kondo and Sieving, 2002). On the other hand, the OPs originate from the inner retina, possibly the amacrine cells, which may be a better parameter being directly correlated with the structure of the microvasculature in the inner retina such as the VD of the SCP. As mentioned, the OPs of the focal macular ERGs seem a better measure than the full-field flicker ERGs in investigating the retinal vasculature-function correlation in the macula. However, the correlation coefficients were generally comparable to those obtained using the flicker ERGs. This indicates that studies are needed to determine the best functional indicator for detecting early functional abnormalities in diabetic patients using same recording area and patients.

Discrepancy between inner retinal function and thickness

Although the VD of the SCP was significantly reduced in eyes with advanced DR, the GCC thickness was not decreased but may have even been increased in patients with NPDR. The significance of the reduction of the GCC thickness and the peripapillary retinal nerve fiber layer (pRNFL) thickness are contradictory at the early stage of DR. It has been reported that the inner retina and pRNFL thickness were

significantly reduced even in patients with non-DR (Park et al, 2020; Vujosevic et al, 2018). However, the earlier and present studies did not find a significant reduction in the thickness of the GCC (Zheng et al, 2019). This does not necessarily indicate that the retinal cells in the inner retina remained intact because the abnormalities of the retinal vasculature could lead to retinal edema. In addition, the GCC thickness was not significantly correlated with the macular function and vascular structure. This would then suggest that an analysis of the retinal thickness may not be an adequate way to detect early vascular and functional changes in the retina of diabetic patients.

PhNR was not significantly correlated with vascular structure

The PhNRs of the full-field cone and focal macular ERGs have been reported to represent the functions of the retinal ganglion cells (RGCs) (Viswanathan et al, 1999; Viswanathan et al, 2000; Machida, 2012; Machida et al, 2008; Kondo et al, 2008). We have reported that the PhNR of the focal macular ERG can be used to assess the function of patients with open angle glaucoma and optic nerve atrophy which mainly affects the RGCs (Machida et al, 2008; Machida et al, 2010; Tamada et al, 2009; Tamada et al, 2010). We did not find any significant correlations between the PhNR amplitude and macular vascular structure.

In our earlier study in which we recorded the full-field ERGs from diabetic patients with early retinopathy, we found that the implicit times and amplitudes of the OPs were better functional measures than the PhNR amplitude to detect earlier functional abnormalities (Kizawa et al, 2006). The present results indicate that this is also the case in the macular region.

Limitations

There are limitations in this study. The area of OCTA images did not correspond exactly with the stimulus areas for the focal macular ERG recordings (see Figure 1). This could be one factor that reduced the correlation between the macular function and vascular structure. Analyses of the full-field ERGs may be a better way to detect early functional abnormalities in diabetic patients because diabetic lesions take place throughout the retina. Ultra-widefield OCTA can obtain OCTA images over a large area of the retina. It would be interesting to determine the correlation of the VD of the whole retina and the OPs of the full-field ERGs.

In patients with NPDR the OPs amplitudes were so small that it was difficult in measuring the implicit time of the OPs accurately. This could then lead to unreliable evaluations and failure to find significant correlation between some OPs implicit times

and macular vascular structure in the NPDR group.

It has been reported that the rod-driven ERGs are more susceptible to diabetic mellitus than the cone-driven ERG (Luu et al, 2010). Among the rod-driven ERG components, the OP4 is the most sensitive in detecting DR (Li et al, 1991) and retinal arteriolar dilation associated with DR (Luu et al, 2010). The focal macular ERG is a cone-driven ERG and does not have a recordable OP4 (See Figure 1). More detailed studies are needed to determine the most sensitive ERG component that is significantly correlated with vascular abnormalities in diabetic patients.

Conclusions

The OPs of the focal macular ERG are reduced with prolonged implicit times which are significantly correlated with a decrease in the VD of the SCP and OCP in eyes with non-DR and with NPDR. The implicit times of the OPs are the most sensitive functional parameter that reflects the early changes of microvasculature in the macula caused by diabetes.

Figure legends

Figure 1: Retinal area where the optical coherence tomography angiography (OCTA), focal macular ERGs (ERGs), and ganglion cell complex (GCC) were recorded (A). The length of 4.5 mm is approximately equivalent to 15 degrees on the ocular fundus. In the GCC chart, the values enclosed by squares were averaged to obtain the mean GCC thickness. Each parameter was evaluated in the original and digitally band-passed waveforms of the focal macular ERG (B).

OCTA: OCT angiography, ERG: electroretinogram, GCC: ganglion cell complex; PhNR: photopic negative response; OP: oscillatory potential.

Figure 2: Representative focal macular ERGs (A) and OCTA binary threshold images (B). The original and digitally band-passed waveforms of the focal macular ERGs are shown for a normal subject and diabetic patients from the non-DR and NPDR groups. The normal waveforms shown by the gray traces are superimposed on the individual waveform obtained from patients from the non-DR and NPDR groups. The implicit times of the OPs are prolonged even in the patient from the non-DR group compared to those in the normal subject. In the patient from the NPDR group, the OPs amplitudes were severely depressed. In the OCTA images of the SCP and DCP, the vessel density is reduced even in the eyes from the non-DR group.

ERG: electroretinogram, OCTA: OCT angiography, non-DR: no apparent diabetic retinopathy, NPDR: non-proliferative diabetic retinopathy, OP: oscillatory potential, SCP: superficial capillary plexus, DCP: deep capillary plexus.

Figure 3: Averaged size of the FAZ (A) and VD of SCP (B) and DCP (C). There was no significant change in average size of the FAZ among the normal subjects and patients from the non-DR and NPDR groups. The VD of SCP and DCP is lower in eyes with more advanced DR. A significant reduction of the VD is present in the patients from the NPDR group compared to that in normal subjects. Error bars: standard deviation. Asterisk indicates $P<0.01$.

FAZ: foveal avascular zone; VD: vessel density, SCP: superficial capillary plexus, DCP: deep capillary plexus, non-DR: no apparent diabetic retinopathy, NPDR: non-proliferative diabetic retinopathy.

Figure 4: Correlation between the ERG parameters and VD of SCP including normal subjects (open circles), and patients from the non-DR (filled circles) and NPDR groups (open squares). The amplitudes of the a-wave (A) and PhNR amplitudes (C) are not significantly correlated with the VD of the SCP. The b-wave (B) and ΣOPs (D) amplitudes are smaller in eyes with reduced VD. The implicit times of the OP1 (E),

OP2 (F) and OP3 (G) are significantly prolonged and the degree of prolongation is significantly correlated with the degree of decrease of the VD.

ERG: electroretinogram, VD: vessel density, SCP: superficial capillary plexus, non-DR: no apparent diabetic retinopathy, NPDR: non-proliferative diabetic retinopathy, PhNR: photopic negative response, OP: oscillatory potential.

Figure 5: Correlation between ERG parameters and VD of the DCP of normal subjects (open circles), and patients from non-DR (filled circles) and from the NPDR groups (open squares). The amplitudes of the a-wave (A) and PhNR (C) are not significantly correlated with the VD of the DCP. The amplitudes of the b-wave (B) and ΣOPs (D) are smaller in eyes with a lower VD. The implicit times of the OP1 (E), OP2 (F), and OP3 (G) are significantly prolonged in eyes with a lower VD.

ERG: electroretinogram, VD: vessel density, DCP: deep capillary plexus, non-DR: no apparent diabetic retinopathy, NPDR: non-proliferative diabetic retinopathy, PhNR: photopic negative response, OP: oscillatory potential.

Figure 6: Correlations between the amplitude of the ΣOPs and the VD of SCP and DCP of diabetic patients from the non-DR (filled circles, A and C) and NPDR (open squares, B and D). The ΣOPs amplitudes are significantly and proportionally reduced

with a reduction of the VD of the SCP and DCP in diabetic patients from the NPDR group.

OP: oscillatory potential, VD: vessel density, SCP: superficial capillary plexus, DCP: deep capillary plexus, non-DR: no apparent diabetic retinopathy, NPDR: non-proliferative diabetic retinopathy.

Figure 7: Correlation between the implicit times of the OPs (OP1, OP2 and OP3) and the VD of SCP for diabetic patients from the non-DR (filled circles, A, C and E) and NPDR groups (open squares, B, D and F). The implicit times of the OP1, OP2 and OP3 are significantly and proportionally reduced with a decrease in the VD of the SCP even in the non-DR group.

OP: oscillatory potential, VD: vessel density, SCP: superficial capillary plexus, non-DR: no apparent diabetic retinopathy, NPDR: non-proliferative diabetic retinopathy.

Figure 8: Correlation between the implicit times of the OPs (OP1, OP2 and OP3) and the VD of DCP for diabetic patients from the non-DR (filled circles, A, C and E) and NPDR groups (open squares, B, D and F). The implicit times of the OP1, OP2 and

OP3 are significantly and proportionally decreased in eyes with a reduction of the VD of DCP in the non-DR group.

OP: oscillatory potential, VD: vessel density, DCP: deep capillary plexus, non-DR: no apparent diabetic retinopathy, NPDR: non-proliferative diabetic retinopathy.

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