Progression of Diabetic Microaneurysms According to the Internal Reflectivity on Structural Optical Coherence Tomography and

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Corresponding Author: Professor Giuseppe Querques, MD, PhD

Corresponding Author's Institution: Department of Ophthalmology, University Vita-Salute, IRCCS San Raffaele, Milan, Italy

First Author: Mariacristina Parravano, MD

Order of Authors: Mariacristina Parravano, MD; Daniele De Geronimo, MD; Fabio Scarinci, MD; Lea Querques, MD; Gianni Virgili, MD; Joseph M Simonett, MD; Monica Varano, MD; Francesco Bandello, MD, FEBO; Giuseppe Querques, MD, PhD

ABSTRACT

Purpose: To correlate the appearance of Microaneurysms (MAs) on structural spectral-domain optical coherence tomography (SD-OCT) with their detection on OCT angiography (OCTA) in patients with non-proliferative diabetic retinopathy (NPDR).
Design: Inter-instrument reliability study.
Methods: Sixteen patients with NPDR without macular edema underwent SD-OCT and OCTA. To compare MAs seen on OCTA to those on SD-OCT, we superimposed the OCTA superficial capillary plexus (SCP) vascular landmarks onto those of the near infrared. Two observers blinded to patient groupings evaluated reflectivity of MAs on SD-OCT scans, graded as hypo-, moderate, or hyper-reflective, and their visualization at the level of SCP and deep capillary plexus (DCP) on OCTA.
Results: Among 145 MAs imaged with SD-OCT, 47 (32.4%) appeared as hyperreflective, 71 (49%) as moderately reflective, and 27 (18.6%) as hyporeflective. After excluding 3 eyes (10 MAs) because of poor quality OCTA scans, 135 MAs were evaluated on OCTA; 76 (56.3%) were visible only in the DCP, 9 (6.7%) only in the SCP, 29 (21.5%) were visible in both SCP and DCP; 21 (15.6%) were not visible on OCTA. Compared to MAs with hyper or moderate reflectivity, MAs with hypo reflectivity on structural SD-OCT were significantly less likely to be detected on OCTA (OR: 4.6; 95% CI: 1.5-14.0, p = 0.008; and OR: 4.2, 95% CI 1.2-14.2, p = 0.022, respectively).
Conclusions: MAs that appear hyporeflective on structural SD-OCT have a lower detection rate on OCTA. The results of this study may help further understand the different blood flow dynamics pattern in MAs.

Relationship between internal reflectivity of diabetic microaneurysms on SD-OCT and detection on OCT Angiography

Mariacristina Parravano[1], Daniele De Geronimo[1], Fabio Scarinci[1], Lea Querques[2], Gianni Virgili[3], Joseph Michael Simonett[4], Monica Varano[1], Francesco Bandello[2], Giuseppe Querques[2]

Authors affiliations:

1 Fondazione G.B.Bietti-IRCCS, Rome, Italy

2 Department of Ophthalmology, University Vita-Salute, IRCCS San Raffaele, Milan, Italy

3 Azienda Ospedaliero-Universitaria Careggi - Largo Brambilla 3, Firenze 50134

4 Department of Ophthalmology, Feinberg School of Medicine, Northwestern University, Chicago, IL, USA

Corresponding author:

Giuseppe Querques
Department of Ophthalmology, IRCCS San Raffaele Scientific Institute, University Vita-Salute San Raffaele, Via Olgettina 60, 20132, Milan, Italy;
E-mail: giuseppe.querques@hotmail.it;
Tel: +390226432648; Fax: +390226433643

Short Title: Microaneurysms reflectivity on SD-OCT and OCT Angiography

INTRODUCTION

Diabetic retinopathy (DR) is the leading cause of blindness among working aged individuals in the developed world and its prevalence increases with increasing duration of the disease. Loss of pericyte cells and proliferation of endothelial cells are early pathologic changes in DR, which lead to weakened vascular walls and the formation of microaneurysms (MAs).[1-3] Macular edema, which often arises from leaking MAs, is a common cause of DR related vision loss.[4, 5]

In the past, most knowledge regarding diabetic MA features was obtained from histological and pathological studies.[6-8] These studies have shown that diabetic MAs are vascular outpunchings of the retinal capillary bed, primarily arising from the deep part of the inner retinal capillary plexus located in the inner nuclear layer.

Fluorescein angiography (FA) has been widely used to detect early signs of DR[9, 10] including MAs. However, this examination is invasive, costly and time consuming. Recent advances in imaging techniques, such as spectral-domain optical coherence tomography (SD-OCT), have improved image resolution and reduced speckle noise, clearly delineating the individual retinal layers and several lesions of the retinal parenchyma and vasculature.

More recently, optical coherence tomography angiography (OCTA), a fast, noninvasive imaging technique, has allowed for three-dimensional vascular mapping of macular vasculature and differentiation of the superficial and deep vascular plexus.[11-14] Several studies have reported new findings of vascular changes in diabetic patients using OCTA such as foveal avascular zone shape changes, retinal non-perfusion, and microaneurysms.[15-18]

The purpose of this study was to correlate the appearance of MAs on SD-OCT with their detection on OCTA in patients with non-proliferative DR.

MATERIAL AND METHODS

In this inter-instrument reliability study, MAs from eyes of type 2 diabetic patients with mild, moderate or severe non-proliferative DR were randomly selected and analyzed at the Department of Ophthalmology, G.B. Bietti Eye Foundation–IRCCS, Rome, between March 15, 2016 and July 15, 2016. This study was approved by the Institutional Review Board of the G.B.Bietti Eye Foundation-IRCCS, and followed the tenets of the Declaration of Helsinki. Written informed consent was obtained from all participants.

Inclusion criteria were: Patients with type 2 diabetes mellitus, age > 18 years old, and clinical evidence of DR on ophthalmologic exam, ranging from mild to severe non-proliferative DR.

Exclusion criteria were: MAs secondary to diseases other than DR (e.g. retinal vascular occlusive diseases), diagnosis of age related macular degeneration, central serous chorioretinopathy, or vitreoretinal interface diseases, diabetic macular edema, diagnosed either clinically or with SD-OCT, that could disrupt the contour of the

segmentation on OCTA, or diffuse edema that could obscure the presence of MAs. We also excluded patients with evidence of significant cataract, graded above NO3 or NC3, in order to avoid optical artifacts that may compromise SD-OCT and OCTA image quality.

All patients underwent color fundus photograph, SD-OCT, FA and OCTA imaging. For each patient, all analyzed images were obtained on the same day.

After acquisition of 45° color fundus photographs (Topcon TRC 50DX, Topcon Corporation, Tokyo, Japan), where the MAs appear as whitish, reddish, or mixed dots[6], simultaneous FA and SD-OCT (Spectralis HRA+OCT, Heidelberg Engineering, Heidelberg, Germany, version 6.4.7.0) were performed. To match the MAs seen on color fundus photographs to those that appeared as hyperfluorescent dots in the early phase of FA imaging, we superimposed the vascular landmarks of both images; additionally the FA images were overlaid with the near infrared images of the Heidelberg Spectralis HRA+OCT. Color fundus photograph, FA and near infrared were used to verify the identification of MAs detected on SD-OCT. The SD-OCT protocol used included 49 horizontal B-scans per volume scan spanning 20°x20° of the macula volume with either the vertical or horizontal bisecting the center of each microaneurysm (each B-scan including an average of 16 frames).

To exclude from the selection MAs with fast turnover,[4, 19] SD-OCT imaging was repeated in all patients, a second time 7 days after the first imaging session. Only MAs present on both dates were included in the analysis. Low-quality SD-OCT images were defined by signal strength below 25 decibels. The internal reflectivity within the lumen of each MA was graded as hypo-, moderate, or hyper-reflective as described previously.[20] Briefly, the lumen was considered hyperreflective if reflectivity was similar to that of the MA wall, hyporeflective if it was similar to that of cystic intraretinal fluid and moderate if the reflectivity was intermediate.

Finally, to explore the OCTA characteristics of MAs, we used the XR Avanti Optical Coherence Tomography Angiography instrument (Optovue Inc., Fremont, California, USA) with split-spectrum amplitude-decorrelation angiography (SSADA) software.[12] This instrument has an A-scan rate of 70,000 scans per second and uses a light source centered on 840 nm and a bandwidth of 45 nm. A 6 X 6-mm scanning area, centered on the fovea was obtained. Two consecutive B-scans (M-B frames), each containing 304 A scans were captured at each sampling location and SSADA software was used to extract OCTA information. En face OCT angiograms were segmented to define the superficial capillary plexus (SCP) and deep capillary plexus (DCP), using the segmentation algorithm by the built-in software.

Customized settings were also used to produce thinner slabs that were moved progressively from the outer retina to the inner plexiform layer to look for undetected MAs.

MAs were identified as focally dilated saccular or fusiform capillaries in the 6x6 mm area of the en face OCT angiograms. Low-quality OCTA images defined as OCT angiograms with signal strength below 72 or with motion artifacts, were excluded.

To compare the MAs seen on OCTA to those seen on Spectralis SD-OCT B-scan, we superimposed the OCTA SCP vascular landmarks onto the vascular landmarks of the near infrared. This allowed point-by-point correlations between both the SCP and DCP and corresponding Spectralis B-scan.

After the characterization of the MA features using OCTA and SD-OCT, the goal of the study was to evaluate if the reflectivity of MAs on SD-OCT scans could influence their visualization at the level either of SCP or DCP on the corresponding OCTA images. With regard to this, the observers determined whether the MAs were visible in the SCP and in the DCP images, both of them or not visible in any scan.

Two masked examiners (D.D.G, F.S) evaluated all SD-OCT scans and OCTA images independently, and in case of disagreement there was open adjudication until a consensus was established.

Statistical analysis

Continuous data were described as mean ± standard deviation and categorical data as frequencies. The association of categorical variables with the groups was calculated using logistic and ordinal logistic regression. Specifically, we investigated the association of increasing reflectivity with MA visibility and position according to OCTA.

We assessed the inter-grader reliability of the grading of MA reflectivity with SD-OCT using Cohen's weighted kappa for ordered categories. Since MA assessment with OCTA yielded partly unordered categories (MAs non-visible or localized in the superficial layer, deep layer or in both layers) we used an asymptotic symmetry and marginal homogeneity tests.

Analyses were adjusted for within-subject correlation using mixed models with individuals as a random effect. All statistical analysis was performed using Stata 14.2 software (College Station, TX, USA). A $p<0.05$ was considered statistically significant.

RESULTS

One hundred and forty-five randomly selected MAs, identified on color fundus photography, FA, near infrared and B-scan SD-OCT, from 30 eyes of 16 type 2 diabetic patients with mild, moderate or severe non-proliferative DR were analyzed in the study. All 145 MAs selected and analyzed were detectable in the aforementioned techniques. The quality of images was considered as sufficient for qualitative analysis in 100% (30/30) of eyes on SD-OCT and in 90% (27/30) of eyes on OCTA; 10 % (3/30) of eyes imaged with OCTA were not included due to low quality of images. Patients demographics are shown in Table 1.

Among all 145 diabetic MAs imaged with SD-OCT, 47 (32.4%) was classified as hyperreflective, 71 (49%) as moderate internal reflectivity, and 27 (18.6%) as hyporeflective. After excluding 3 eyes with poor quality OCTA scans, of 135 MAs remained, 114 (84.4%) were visible on OCTA, 76 (56.3%) were visible only in the DCP, 9 (6.7%) only in the SCP, 29 (21.5%) were visible in both SCP and DCP and 21 (15.6%) were not visible on any OCTA images.

Considering MAs that appeared hyperreflective on SD-OCT, 40 (88.9%) were visible on OCTA, 28 (62.2%) were visible only in the DCP (Figure 1), 2 (4.4%) only in the SCP, 10 (22.2%) in both the SCP and DCP, and 5 (11.1%) were not visible on any OCTA images.

Among MAs that appeared moderately reflective on SD-OCT 56 (88.9%) were visible on OCTA, 39 (61.9%) were visible only in the DCP, 5 (7.9%) only in the SCP, 12 (19%) in both the SCP and DCP, and 7 (11.1%) were not visible on any OCTA images.

Finally, 18 (66.7%) of MAs that appeared hyporeflective on SD-OCT were visible on OCTA, 9 (33.3%) were visible only in the DCP, 2 (7.4%) only in the SCP, 7 (25.9%) were visible in both the SCP and DCP, and 9 (33.3%) were not visible on any OCTA images (Figure 2) (Table 2). Compared to MAs with hyper reflectivity or moderate reflectivity, MAs with hypo reflectivity on SD-OCT were significantly less likely to be detected on OCTA (OR: 4.6; 95%CI: 1.5-14.0, p = 0.008; and OR: 4.2, 95%CI 1.2-14.2, p = 0.022, respectively).

Compared to non-visible MAs, superficial (OR:1.7, 95%CI: 0.4 – 8.4), mixed (OR: 2.5; 95%CI: 0.8-7.8) and deep (OR: 3.6; 95%CI: 1.3-9.7) MAs were increasingly more likely to be more reflective (test for trend p=0.011), though only the OR of deep MAs reached significance when position was a categorical variable (p=0.013).

Grading of MA hyperreflectivity proved to be highly reliable, since Cohen's kappa was 0.90 between graders. There was also good agreement on retinal layer location of each MA in the symmetry test since only 7 out ouf 135 ratings disagreed, 4 of which regarded the 'non-visible MA' category (p=0.960).

DISCUSSION

In this study we imaged diabetic MAs in a heterogeneous group of diabetic patients with SD-OCT and OCTA. We assessed the internal reflectivity of MAs on SD-OCT B-scans and evaluated the relationship between this finding and MA visualization on the OCTA images. Interestingly, MAs with internal hyporeflectivity on SD-OCT B-scan had a significantly lower detection rate on OCTA (66.7%) compared to MAs with internal hyperreflectivity (88.9%) or moderate reflectivity (88.9%).

One possible explanation for this result could be that MAs that appear hyporeflective on SD-OCT are more likely to have a blood flow rate below the threshold necessary to register as flow in the OCTA system. It has previously been reported that the SSDA algorithm does not allow detecting retinal capillary flow less than 0.3 mm per second.[21] Other authors have also hypothesized that the blood flow inside MAs is turbulent and may not be shown using OCTA.[16] Another possible explanation that has been previously suggested[17] is that the MAs appear hyporeflective because they contain only plasma without erythrocytes. Previous histologic studies have demonstrated that some microaneuryms are not perfused and have extensive luminal fibrosis and lipid infiltration[7]; it is possible that some of the hyporeflective MAs represent these scleroses, poorly perfused MAs.

Supporting our data, recently Seidel et al.[22] reported that a low retinal blood flow velocity reflects in a visually distinct contrast reduction of the intraluminal pattern of retinal vessels on SD-OCT and that an absent pattern highly correlated with a severely diminished blood flow velocity.

A previous study[17] has evaluated diabetic MAs using OCTA and FA, but to the best of our knowledge this is the first study to compare SD-OCT reflectivity and OCTA features of MAs. Ishibazawa et al.[16] compared FA and OCTA features of 47 eyes of 25

patients with DR and reported that OCTA can clearly visualize MAs, most of which were located in the DCP, and retinal non perfusion areas. Couturier et al.[17] recently analyzed the clinical features of 20 eyes of 14 patients with DR and demonstrated that FA is more sensitive than OCTA in detecting MAs, while OCTA is more accurate compared to FA in assessing capillary non perfusion. The authors also reported that the number of MAs was significantly higher in the DCP than in the SCP. Similarly, looking at the data regarding MAs localization, we found that the majority of MAs visible on the OCTA (56.3%) were isolated to the DCP. Furthermore, we found a significant correlation (p 0.011) between the location of selected MAs (SCP or DCP) and the characteristics of internal reflectivity of the lumen on SD-OCT. In particular, the hypereflective MAs were significantly more likely to be detected on DCP in comparison either with the moderate or the hyporeflective MAs (p 0.013). Because the MA formation rate and MA turnover, showed positive correlations with increases in retinal thickness[23], we can speculate that the hyperreflective MAs, characterized by an high blood flow rate, might problably be associated with the extracellular fluid accumulation resulting from alteration of the blood-retinal barrier in the DCP. Further studies are necessary to confirm the associations between the Mas reflectivity and alterations of the inner retinal thickness and DCP in diabetic patients. A recent study[24] showed that eyes with diabetic macular edema that are poor responder to anti-vascular endothelial growth factor showed a larger number of MAs along with a significantly lower flow density as well as larger area of the foveal avascular zone in the DCP. With regard to this, we believe that our findings in term of MA characteristics and localization could add some information, which in turn would mean improving the identification of a possible biomarker to the diabetic macular edema treatment response.

Taken together, OCTA and SD-OCT MAs findings provide not only static but also dynamic information allowing for a better understanding of the pathogenetic mechanisms of DR. In addition, this study also demonstrate that OCTA is a very useful device to image and study the MA features in diabetic patients, although it may underestimate the presence of MAs that appear hyporeflective on SD-OCT.

There are some limitations of this study mainly related to the inclusion of patients with different disease stages and duration, and to the relatively small numbers of MAs evaluated.

In conclusion, we demonstrated that MAs that appear hyporeflective on SD-OCT have a lower detection rate on OCTA images. This relationship between the internal reflectivity of MAs on SD-OCT and their visualization on the OCTA images may help further understand the different pattern of blood flow dynamics in MAs, and improve our interpretation of MA detection on OCTA.

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Figure Captions

Figure 1

The Spectralis B-scan showing an hypereflective microaneurysms (yellow arrow) (Top left) and the infrared image (Top right) with the green line with arrow passing through the microaneurysm. This exactly corresponds to the focally dilated microanerysm highlighted by red circle at the level of DCP in the OCTA imaging (6x6 scanning area) (Bottom right); the inset shows the characteristics of hypereflective microaneurysms in details. *En face* imaging with red and green lines indicating the location of B-scans (Optovue). The DCP segmentation boundaries (green lines) passing through the microanerisysm are visible (Bottom left).

Figure 2

The Spectralis B-scan showing an hyporeflective microaneurysms (yellow arrow) (Top right) and the infrared image (Top left) with the green line with arrow passing through the microaneurysm. The microanerysm (red circle) cannot be detected at the level of the deep capillary plexus (DCP) by means OCT Angiography (OCTA) imaging (6x6 scanning area) (Bottom left); the inset (green box) shows the area of interest with more details. *En face* imaging with red and green lines indicating the location of B-scans (Optovue). The DCP segmentation boundaries (green lines) passing through the microanerisysm are visible (Bottom right).

TABLE 1 - Demographics and characteristics of patients

Patients/Eyes, n	16/30
Male/Female, n	9/7
Age,Years Mean **Mean±SD**	64.3±8.16
Range	52-77
Duration of diabetes, years **Mean±SD**	9.3±5.2
Range	4-20
HbA1c (%) Mean ± SD	8.1±1.6
Range	6.4-11.4
DR stage, n eyes (%)	
Mild nonproliferative	8 (26.7)
Moderate nonproliferative	12 (40)
Severe nonproliferative	10 (33.3)

n, number; SD, standard deviation; DR, diabetic retinopathy; HbA1c, glycated hemoglobin;

Table 2 – SD-OCT internal reflectivity and OCTA visualization of diabetic microaneurysms

Internal reflectivity		All MAs (N=145) N (%)	OCTA Visualization				
			SCP N (%)	**DCP** N (%)	**SCP+DCP** N (%)	**Total Not Visible** N (%)	**N/A**
SD-OCT	**Hyper**	47 (32.4)	**Total visible** N (%) 40 (88.9)				
			2 (4.4)	28 (62.2)	10 (22.2)	5 (11.1)	2
	Moderate	71 (49)	**Total visible** N (%) 56 (88.9)				
			5 (7.9)	39 (61.9)	12 (19)	7 (11.1)	8
	Hypo	27 (18.6)	**Total visible** N (%) 18 (66.7)				
			2 (7.4)	9 (33.3)	7 (25.9)	9 (33.3)	-

N, number; MAs, Microaneurysms; SCP, Superficial capillary plexus; DCP, Deep capillary plexus; N/A, Not Applicable

*The OCTA percentages are considered in relation to the total of evaluable MAs

Figure 1

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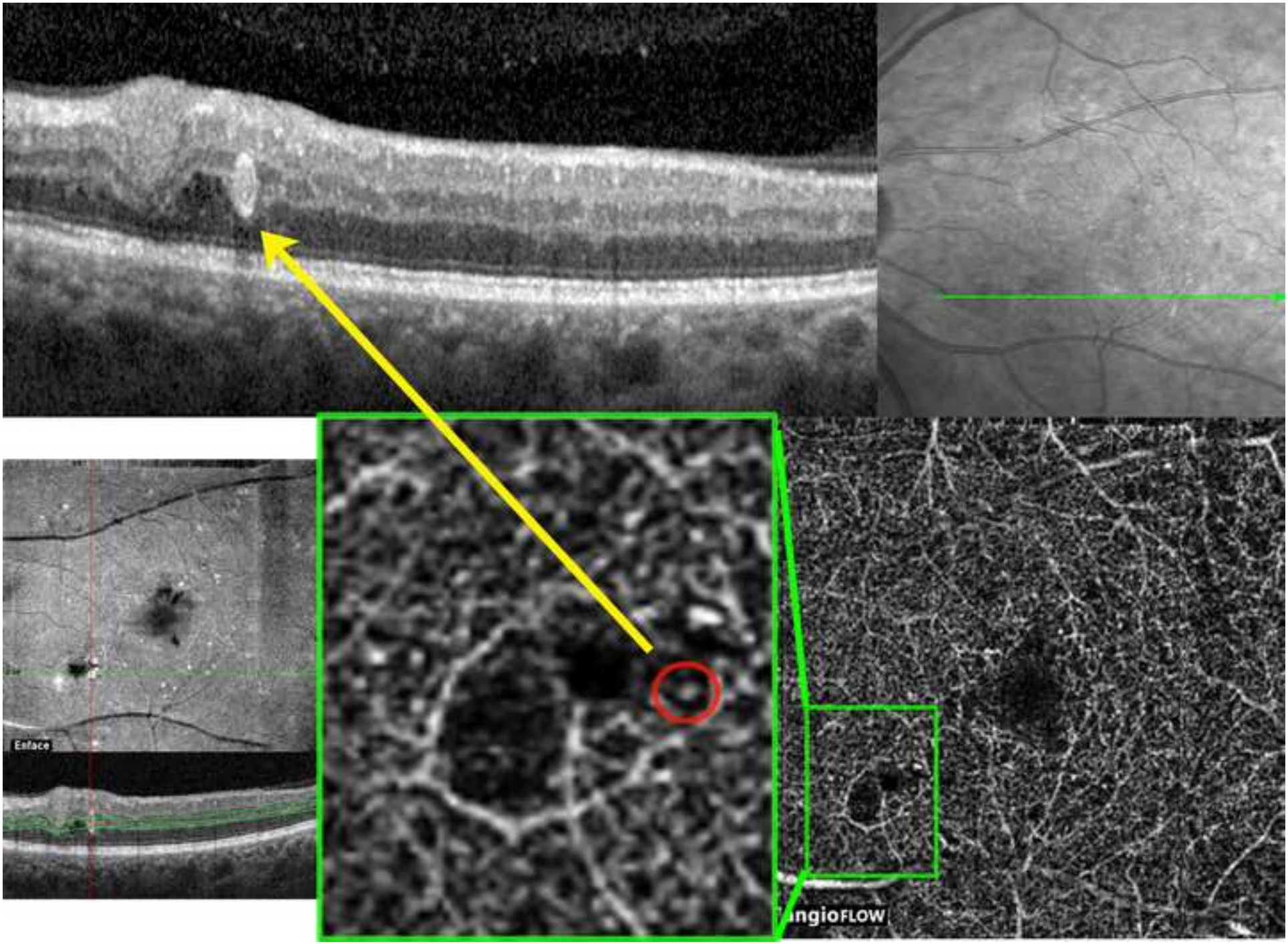

Figure 2

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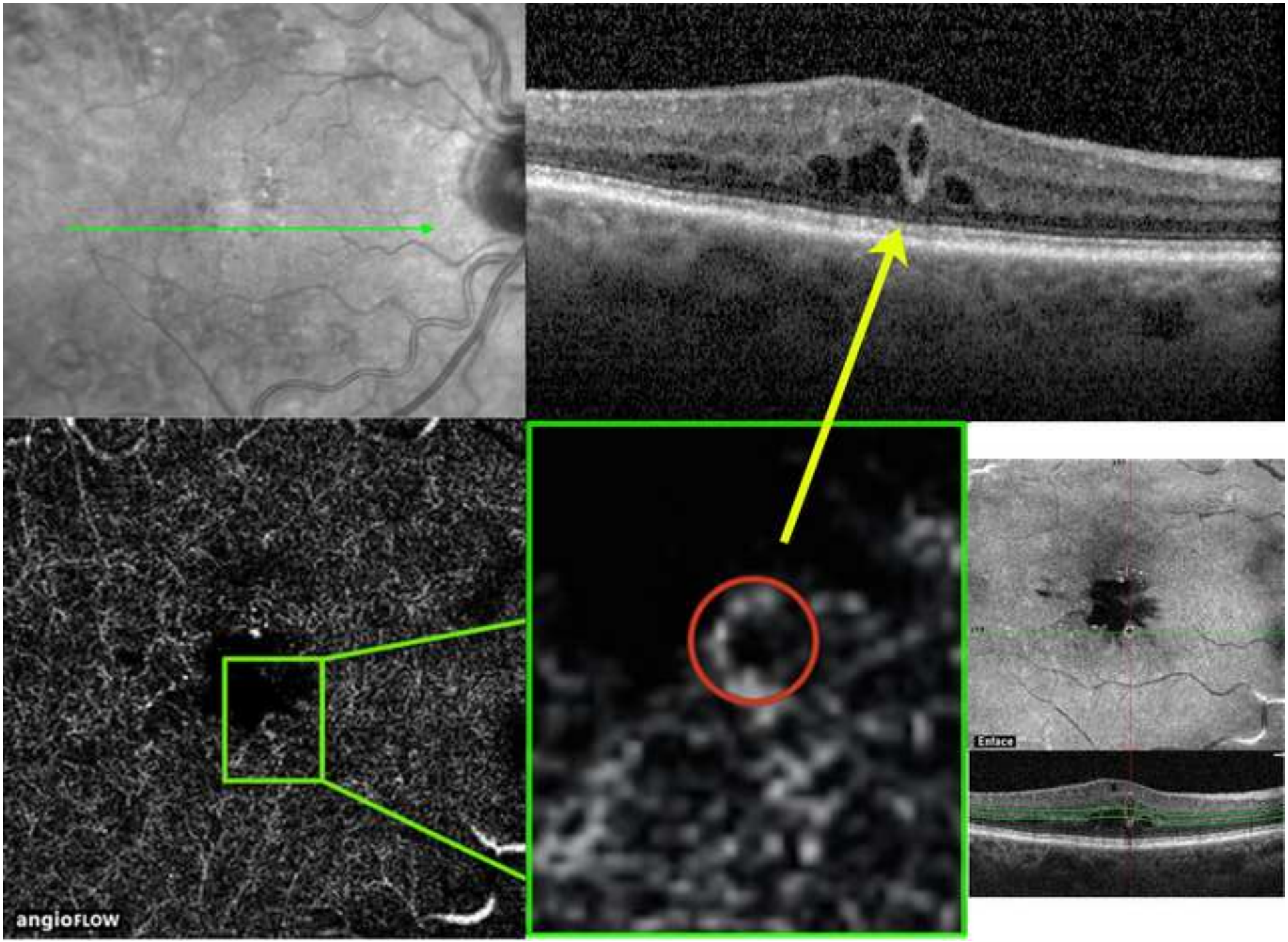

*Table of Contents Statement (Original Articles and Perspectives only)

Relationship between internal reflectivity of diabetic microaneurysms on SD-OCT and detection on OCT Angiography

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This study shows a lower detection rate on optical coherence tomography angiography of microaneurysms that appear hyporeflective on spectral domain optical coherence tomography. On the contrary, the majorities of hypereflective microaneurysms are visible on the optical coherence tomography angiography and are isolated at the level of the deep capillary plexus. Because hyperreflective microaneurysms are characterized by a high blood flow rate, this finding could suggest an important role in the pathophysiology of diabetic macular edema.

Biosketch Dr. Parravano

Mariacristina Parravano is the Head of the Medical Retina Unit of Fondazione G.B.Bietti-IRCCS in Rome. She received her degree in Medicine and Surgery at the University Campus Bio-Medico in Rome in 2000 and the residency in Ophthalmology at the University of Rome “Tor Vergata” in 2004. She is elected member of the Club Jules Gonin and fellow of the ARVO. He has authored over 65 peer-reviewed papers.

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