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FOVEA PLANA ON OPTICAL COHERENCE TOMOGRAPHY ANGIOGRAPHY

New Perspectives

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Purpose: To report on the reliability of optical coherence tomography angiography (OCTA) to diagnose fovea plana.

Methods: A retrospective, cross-sectional, case–control study included patients with foveal persistence of the inner retinal layers, confirmed by spectral domain OCT, and superficial capillary plexus (SCP) and deep capillary plexus foveal vascularization confirmed by OCTA. A healthy control group was selected. The best-corrected visual acuity was obtained. Spectral-domain OCT was used for measuring the outer nuclear layer thickness, and OCTA determined the foveal avascular zone, SCP, and deep capillary plexus vascular density.

Results: Optical coherence tomography angiography reliability, based on all parameters, reached 97%, whereas based only on SCP vascular density 91%. The plana group (n = 57) differed significantly from the control group (n = 28) in terms of foveal avascular zone, SCP, and deep capillary plexus foveal vascular density ($P < 0.005$). Subjects with SCP foveal vascular density >30% or foveal avascular zone <0.1 mm^2 had fovea plana. The best-corrected visual acuity of the plana group had no correlation with OCTA quantitative parameters (Pearson $|r|<0.18$, Spearman $|r|<0.44$).

Conclusion: Optical coherence tomography angiography has a high accuracy in diagnosing fovea plana, as its characteristics differ significantly from the normal population. The lack of correlation between the best-corrected visual acuity and OCTA parameters implies that reduced the best-corrected visual acuity is likely to result from coexistent diseases rather than from the foveal structure.

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Fovea plana and foveal hypoplasia definitions have generated debates among specialists. Within this framework, it has been suggested that the foveal pit has no actual visual significance; thus, "fovea plana" bears no inference to the visual function but only to the anatomic lack of the foveal pit.[1] In parallel, foveal hypoplasia has been described as the disruption of the normal foveal development and has been widely associated with conditions such as albinism, PAX6 mutations, achromatopsia, aniridia or isolated cases with consequent restricted visual acuity.[2–8] In detail, Thomas et al[8] defined foveal hypoplasia as the persistence of the inner retinal layers at the fovea and developed a grading system based on optical coherence tomography (OCT) features according to which, fovea plana, as described by Marmor et al,[1] corresponds to Grade 2, 3, and 4 of foveal hypoplasia.

In all the above cases, an irregular persistence of the inner retinal layers, including the ganglion cell layer, inner plexiform layer, inner nuclear layer, and outer

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plexiform layer has been observed at the fovea. The continuation or incursion of these layers could be as a result of the disruption of the normal process of foveal development, a contouring that starts from week 25 post gestation and lasts until the 15th month to 45th month after birth.[9] Studies have suggested that foveal pit formation is associated with the absence of foveal vascularization, referencing to the integrity of the foveal avascular zone (FAZ); thus, remaining vasculature could result in an incomplete structural development of the fovea.[10]

A recent case-report study has managed to identify different vascular layers with optical coherence tomography angiography (OCTA) in patients with incomplete development of the fovea and has suggested a future use of OCTA in assessing the grade of this condition.[11] In this study, we aim to report the reliability of OCTA to diagnose foveal plana, defined as the persistence of inner retinal layers at the fovea, confirmed by spectral-domain optical coherence tomography (SD-OCT) and relate this to the visual acuity if possible, to determine any functional implications thereof.

Methods

Subjects and Measurements

A retrospective, cross-sectional and case–control study was conducted at RétinElysée Centre, Lausanne, Switzerland with subjects examined between April 2017 and April 2019. The study adhered to the tenets of the Declaration of Helsinki and was authorized by the Swiss Ethics Committees (Reference number: 2019-01972). Subjects who had a persistence of at least two inner retinal layers (ganglion cell layer, inner plexiform layer, inner nuclear layer, and outer plexiform layer) in the FAZ, confirmed with the ¨gold¨ standard SD-OCT (Spectralis OCT; Heidelberg Inc, Heidelberg, Germany), were included in the study (Figure 1). The inclusion criteria for the study group consisted of vascularization of the FAZ either in the superficial capillary (SCP) or the deep capillary plexus (DCP) confirmed with OCTA (Optovue, Angiovue, RTVue XrPAR, Version 2017.1.0.150 with phase 7 software) (Figure 2). Moreover, acquisition of the best-corrected visual acuity (BCVA), SD-OCT scans, and OCTA 3.0 mm × 3.0 mm images on the same day were required. The inclusion criteria for the control group consisted of the absence of all inner retinal layers in the FAZ, the absence of any known ocular disease, and the acquisition of BCVA, SD-OCT scans, and OCTA images on the same day. Subjects were excluded in case of ocular comorbidities severely affecting the foveal architecture and/or vasculature and in case of coexisting albinism, PAX6 mutations, achromatopsia, aniridia, retinopathy of prematurity, or infantile nystagmus. Subjects with low-quality SD-OCT images that did not allow the segmentation of retinal layers or OCTA images with a quality index of less than six were also excluded.

Spectral-domain OCT imaging at 30° and OCTA 3.0 mm × 3.0 mm scan size images were captured by an experienced optometrist, who centered on the fovea. Segmentation of the layers was performed automatically by the software available. Image assessment was performed by two different investigators and in cases of dissensus a third investigator contributed. Apart from the identification of the inner retinal layers, SD-OCT images were used for the automatic measurement of the outer nuclear layer at the fovea (1 mm diameter, Early Treatment Diabetic Retinopathy Study) in μm. Optical coherence tomography angiography images were assessed for the existence of vascularization in the FAZ, after software directed segmentation of the SCP and DCP. Furthermore, the FAZ was automatically measured in mm^2 based on the full-retinal vasculature from the internal limiting membrane to the outer plexiform layer. The SCP and DCP vascular density (VD) of the whole image and of the fovea were also measured in percentage points by the same software. The device segmented the SCP from the internal limiting membrane to the inner plexiform

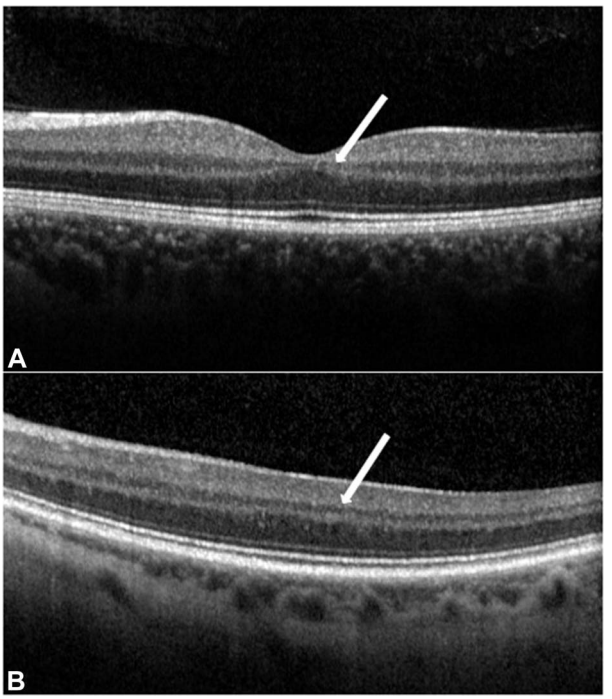

Fig. 1. Spectral-domain optical coherence tomography—fovea plana defined as the persistence of inner retinal layers—(**A**) partial fovea plana, (**B**) complete fovea plana.

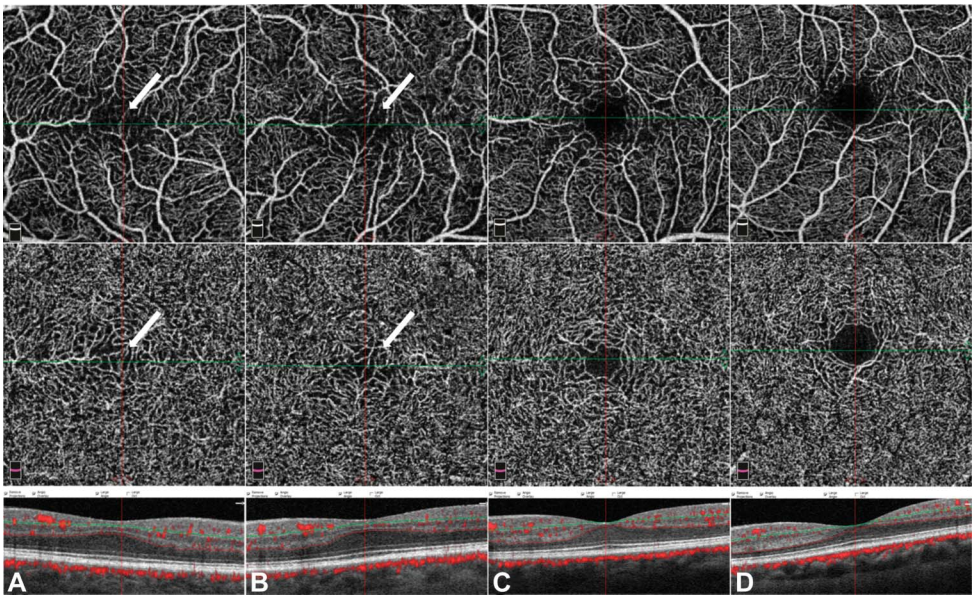

Fig. 2. Optical coherence tomography angiography—foveal vascularization of the superficial (upper arrows) and deep (lower arrows) capillary plexus and corresponding b-scan of (**A**) a patient with fovea plana and asteroid hyalosis, (**B**) a patient with fovea plana and vitreous opacities, (**C** and **D**) subjects from the control group.

layer minus 10 μm, and the DCP from the inner plexiform layer minus 10 μm to the outer plexiform layer plus 10 μm. Finally, the BCVA was measured in all subjects with a standard Early Treatment Diabetic Retinopathy Study letter chart.

Statistical Analysis

For all tests, $P < 0.05$ was considered significant. Fovea plana was diagnosed in OCTA using depth two and three classification trees and logistic regression. Both depth two and three classification trees were fitted to avoid overfitting. Cross-validation was performed for each classification tree, by randomly splitting the population into a training set (90% of observations) and a test set (10% of observations) and by calculating the accuracies. This was repeated 1,000 times to compute the mean accuracy and the SD on both the training and the test set. The relative importance of mean variables was also generated to measure the influence of each OCTA parameter on the model. Mean accuracy for 1,000 10-fold cross-validations was also conducted for logistic regression. Logistic regression was further used to test the model based on the use of only quantitative parameters, only quantitative parameters in pairs, and only single quantitative or qualitative parameters.

Quantitative parameters (SCP FAZ, SCP whole image VD, SCP foveal VD, DCP whole image VD, and DCP foveal VD) were compared between the study and control group to identify potential differences, with the Mann–Whitney *U* test, as according to the Shapiro–Wilk test no parameter was normally distributed.

Finally, the Pearson and Spearman correlations were computed to quantify the relationship between the BCVA, outer nuclear layer, SCP FAZ, SCP, and DCP whole image VD and SCP and DCP foveal VD.

Results

The study group consisted of 57 eyes and the control group of 28 (Table 1).

Depth two and depth three classification trees provided similar results with mean accuracy 0.99 on the

Table 1. Baseline Characteristics of the Two Groups

Parameters	Fovea Plana Group	Control Group
Subjects (number)	57	28
Age (median ± IQR, years)	69 ± 24	66 ± 19
Sex (males/females)	29/28	12/16
BCVA (median ± IQR, log MAR)	0.10 ± 0.20	0.00 ± 0.10
Vitreomacular and inner retinal conditions (no. of subjects)	36	0
Outer retinal and choroidal conditions (no. of subjects)	6	0
Retinal syndromes and dystrophies (no. of subjects)	15	0

Vitreomacular and inner retinal conditions: epiretinal membrane, vitreous opacities, asteroid hyalosis, diabetic retinopathy, hypertensive retinopathy; outer retinal and choroidal conditions: drusen, epitheliopathy; retinal syndromes and dystrophies: Best disease, Alport syndrome, enhanced S-cone syndrome.

IQR, interquartile range.

Table 2. Mean Accuracy ± SD of OCTA Based on Each Parameter

Parameters	Mean Accuracy ± SD
All OCTA parameters	0.97 ± 0.02
All quantitative parameters	0.9 ± 0.03
DCP foveal vascularization	0.96 ± 0.02
SCP foveal vascularization	0.86 ± 0.06
SCP FAZ	0.81 ± 0.04
SCP whole image VD	0.79 ± 0.04
SCP foveal VD	0.78 ± 0.05
DCP whole image VD	0.74 ± 0.05
DCP foveal VD	0.77 ± 0.05

training set (SD = 0.005 and SD = 0.004, respectively) and 0.97 (SD = 0.06) on the test set. The relative importance analysis showed that DCP foveal vascularization contains almost all diagnostic information in both trees (0.88 and 0.87, respectively). Logistic regression provided similar results to classification trees with mean accuracy 0.97 (SD = 0.01) and DCP foveal vascularization a relative importance of 0.76. When taking into consideration all variables (DCP foveal vascularization, SCP foveal vascularization, SCP FAZ, SCP whole image VD, SCP foveal VD, DCP whole image VD, and DCP foveal VD), OCTA mean accuracy is 97%, whereas when taking only quantitative parameters (SCP FAZ, SCP whole image VD, SCP foveal VD, DCP whole image VD, and DCP foveal VD) it reaches 90% (Table 2). The best quantitative parameter combination includes the SCP foveal VD and SCP whole image VD with 91% mean accuracy (Table 3).

Further analysis was performed to compare quantitative OCTA parameters between the fovea plana and control group. Strong evidence of a significant difference between the groups was identified in FAZ, SCP whole image VD, SCP foveal VD, and DCP foveal VD ($P < 0.001$ for all comparisons), whereas DCP whole image VD did not present a significant difference ($P = 0.055$) (Table 4). An important linear division of FAZ and SCP foveal VD was also identified between the two groups. When FAZ was smaller than 0.1 mm^2 and/or SCP foveal VD was higher than 30%, subjects belonged in the plana group (Figures 3 and 4).

Finally, both Pearson and Spearman test showed no correlation between BCVA and OCTA quantitative parameters ($|r|<0.18$ and $|r|<0.44$, respectively).

Discussion

Although SD-OCT has been widely used for the imaging of retinal structure, OCTA in addition, can provide high-resolution images of the retinal vasculature in the SCP and DCP, which can be really valuable in the diagnosis and classification of various retinal diseases.[12] Fovea plana is a condition that affects both the retinal layer structure and the vasculature in the fovea[9–11] with controversial effects on the visual acuity.[1,8,11,13] Thus, OCTA could provide useful additional information on the diagnosis of fovea plana, as well as on the evaluation of the retinal vasculature in patients with an abnormal foveal pit, probably caused by a potential delay or arrest during macular development. To the best of our knowledge, this is the first report to study the reliability of OCTA in detecting fovea plana.

Our results showed that the presence or absence of vascularization at the fovea in the DCP has the highest diagnostic accuracy. Thus, the evaluation of both qualitative and quantitative OCTA variables can reach an accuracy of 97%, probably not replacing but enhancing the SD-OCT diagnosis, which focuses on the integrity of the cellular foveal structure, underlying the emerging benefits that OCTA can offer to retinal imaging. Provided the possibility of subjective misinterpretation is taken into account, after our study, the qualitative parameters could be considered of lesser importance; therefore, we underline the use of two quantitative parameters, SCP foveal VD, and SCP whole image VD to be included when evaluating features/

Table 3. Mean Accuracy ± SD for OCTA Quantitative Parameter Combinations

Parameters	SCP FAZ	SCP Whole Image Vascular Density	SCP Foveal Vascular Density	DCP Whole Image Vascular Density	DCP Foveal Vascular Density
SCP FAZ	—	0.09 ± 0.04	0.08 ± 0.04	0.87 ± 0.04	0.08 ± 0.04
SCP whole image VD	0.09 ± 0.04	—	0.91 ± 0.03	0.08 ± 0.04	0.86 ± 0.04
SCP foveal VD	0.08 ± 0.04	0.91 ± 0.03	—	0.85 ± 0.04	0.77 ± 0.05
DCP whole image VD	0.08 ± 0.04	0.08 ± 0.04	0.85 ± 0.04	—	0.83 ± 0.04
DCP foveal VD	0.08 ± 0.04	0.86 ± 0.04	0.77 ± 0.05	0.83 ± 0.04	—

Table 4. Median ± Interquartile Range (IQR) for Age and for OCTA Parameters per Group

Parameters	Fovea Plana Group	Control Group
SCP FAZ*	0.06 ± 0.04	0.21 ± 0.14
SCP whole image VD*	42.1 ± 6.1	46.8 ± 2.1
SCP foveal VD*	29.1 ± 9.8	22.5 ± 9.6
DCP whole image VD	48.8 ± 7.4	52.2 ± 6.4
DCP foveal vascularization*	44.3 ± 9.6	38 ± 9.15

*$P < 0.001$.

characteristics of fovea plana, with which OCTA accuracy reaches 91%.

In addition, when comparing fovea plana with the fovea of healthy participants, the FAZ was found to be significantly smaller in subjects with fovea plana, whereas VD was significantly higher in both plexuses at the central fovea, but lower at the whole OCTA image, thus agreeing with Le et al.[14] Interestingly, in our study, the DCP VD of the whole image was lower in the plana group, however found to be not significantly different. The higher VD at the fovea of the plana group can be explained by the lack of a FAZ, whereas the lower values of the whole image could possibly be attributed to the disruption of the normal process of foveal development and to the incomplete displacement of the inner retinal layers during infancy.[9] This theory is also supported by Kaidonis et al[11] who showed a different vascular arrangement in patients with a fovea plana; however, this is in contrast with Dolz-Marco et al[13] who presented a case series of fovea plana subjects without any FAZ reduction. In detail, our results showed an important linear division of FAZ and SCP foveal VD between the two groups, potentially providing a cut-off value in making the diagnosis of fovea plana with OCTA. Our findings suggest, if the FAZ is smaller than 0.1 mm^2 and/or the SCP foveal VD is higher than 30%, it could create suspicion in support of fovea plana (Figures 3 and 4).

Finally, our analysis showed no relationship between the visual acuity and SD-OCT or OCTA quantitative parameters of the study group, implying that reduced visual acuity was most likely to result rather from coexistent ocular diseases, than from the apparent changed foveal anatomic architecture, highlighting that the term ¨fovea plana¨ is more appropriate to describe the foveal appearance than ¨foveal hypoplasia¨, as it does not imply a necessary association with visual loss. Marmor et al[1] have already highlighted the insignificance of the foveal pit in determining the visual acuity, a theory that aligns with our results. However, Thomas et al[8] and some other small case reports[5,11,15] present patients with abnormal foveal contour manifesting with unexplained loss of vision. Taking into consideration the results of ours and previous studies, we suggest that the term ¨fovea plana¨ be used to describe the incomplete development of the fovea in evolving to form a pit, which can be categorized into partial or complete fovea plana based on the pit contour (Figure 1).

Our study has a limitation, as patients with mild ocular conditions known to affect retinal vasculature, such as diabetic retinopathy and early age-related macular degeneration, have been included in the study group, which could possibly confound the actual effect of fovea plana on the vascular structure and density.

In summary, our study suggests that OCTA has a high accuracy in diagnosing fovea plana using quantitative

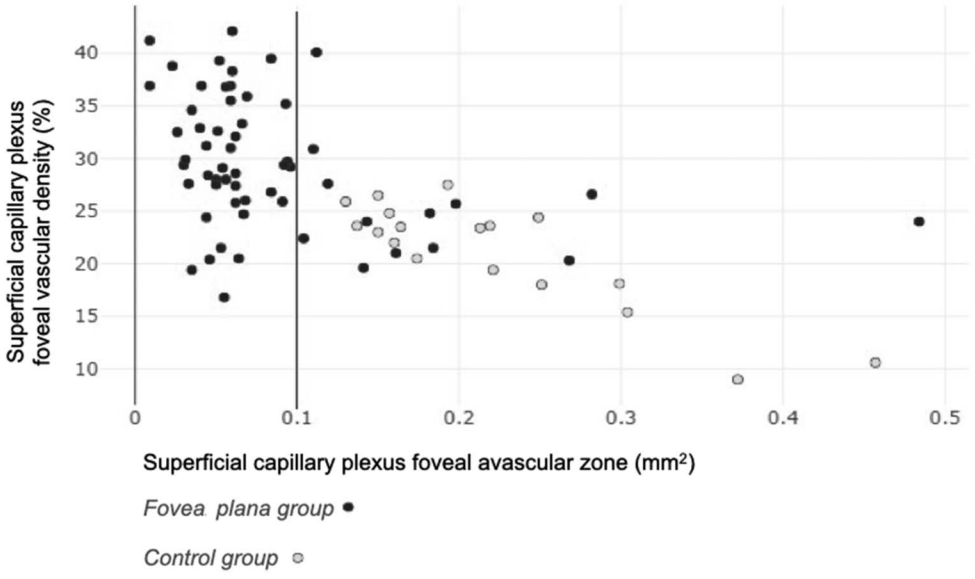

Fig. 3. Superficial capillary plexus foveal avascular zone (SCP FAZ) in fovea plana and in control group.

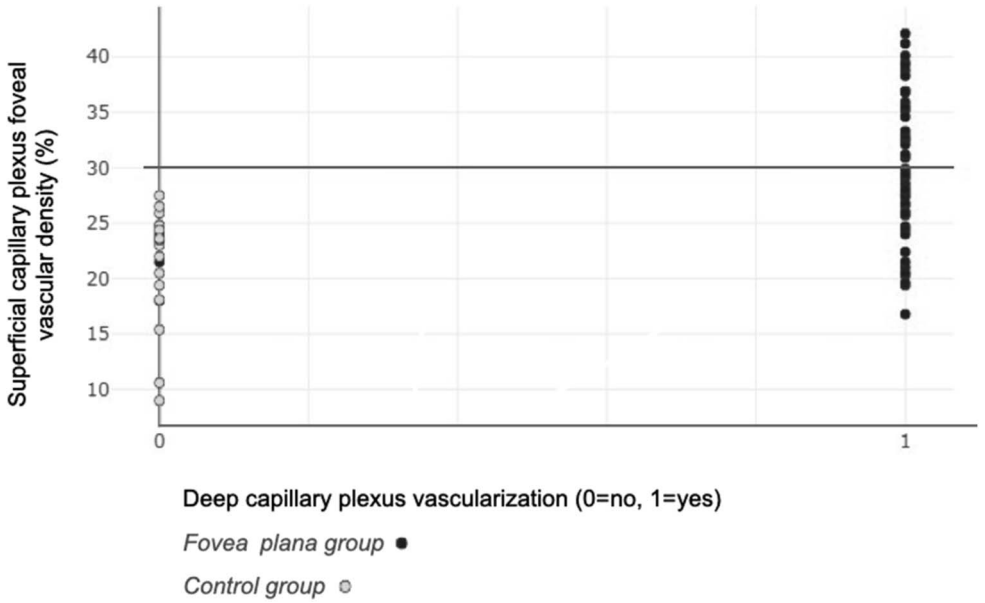

Fig. 4. Superficial capillary plexus foveal VD in fovea plana and in control group.

parameters. It is strongly implied when the SCP FAZ is smaller than 0.1 mm^2 and/or the SCP foveal VD is higher than 30%. Thus, OCTA can be a useful tool in further analyzing the retinal architecture in patients with abnormal macular development. Moreover, it suggests that patients with a fovea plana have a significantly altered FAZ and retinal VD, when compared with healthy subjects, and finally, it implies that the visual acuity is not necessarily affected by the abnormal foveal development. Further comparative studies should be conducted to identify the actual effect of fovea plana, with and without known concomitant ocular comorbidities on the visual acuity as well as on retinal vasculature.

Key words: fovea plana, foveal avascular zone, foveal hypoplasia, foveal pit, inner retinal layers, OCT, OCTA, SDOCT.

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