Fovea Plana on Optical Coherence Tomography Angiography: New perspectives

Short title: Foveal Plana on OCT Angiography

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Presented in a meeting:
43rd Annual Macula Society Meeting, February 19-22, 2020

Disclosure of funding:
No funding was received for this work.

Acknowledgments:
Xavier Bays, Swiss Statistical Design & Innovation, Switzerland
**Summary statement**

Optical coherence tomography angiography is a valuable tool in diagnosing fovea plana, which presents with significantly different vascular characteristics when compared to healthy subjects and may have no impact on visual acuity.

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**Abstract**

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 (SD-OCT), and superficial (SCP) and deep capillary plexus (DCP) foveal vascularization confirmed by OCTA. A healthy control group was selected. Best-corrected visual acuity (BCVA) was obtained.

SD-OCT was used for measuring the outer nuclear layer thickness and OCTA determined the foveal avascular zone (FAZ), SCP and DCP vascular density (VD).

Results: OCTA reliability, based on all parameters, reached 97%, while based only on SCP VD 91%. The plana group (n=57) differed significantly from the control group (n=28) in terms of FAZ, SCP and DCP foveal VD (p<0.005). Subjects with SCP foveal VD >30% or FAZ <0.1 mm² had fovea plana. The BCVA of the plana group had no correlation with OCTA quantitative parameters (Pearson |r|<0.18, Spearman |r|<0.44).
Conclusion: OCTA has a high accuracy in diagnosing fovea plana, as its characteristics differ significantly from the normal population. The lack of correlation between BCVA and OCTA parameters implies that reduced BCVA is likely to result from co-existent diseases rather than from the foveal structure.

**Key words:** Fovea plana, Foveal avascular zone, Foveal hypoplasia, Foveal pit, Inner retinal layers, OCT, OCTA, Optical coherence tomography angiography, SDOCT, Spectral domain optical coherence tomography

**Introduction**

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. 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. In detail, Thomas et al 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, 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 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 to 45th month post-birth. 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.\textsuperscript{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.\textsuperscript{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 visual acuity if possible, to determine any
functional implications thereof.

\textbf{Methods}

\textit{Subjects \& Measurements}

A retrospective, cross-sectional and case-control study was conducted at the 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, outer plexiform layer) in the FAZ, confirmed with the “gold” standard SD-OCT
(Spectralis OCT, Heidelberg Inc\textsuperscript{®}), were included in the study. (Figure 1) 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\textsuperscript{®},
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 x 3.0
mm images on the same day were required. 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.

SD-OCT imaging at 30° and OCTA 3.0 x 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 (ONL) at the fovea (1 mm diameter, Early Treatment Diabetic Retinopathy Study (ETDRS)) in µm. OCTA images were assessed for the existence of vascularization in the FAZ, following software directed segmentation of the SCP and DCP. Furthermore, the FAZ was automatically measured in mm² based on the full retinal vasculature from the internal limiting membrane to the outer plexiform layer. The SCP and DCP vascular density 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 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 ETDRS letter chart.

Statistical analysis
For all tests, p < 0.05 was considered significant. Fovea plana was diagnosed in OCTA using depth 2 and 3 classification trees and logistic regression. Both depth 2 and 3 classification trees were fitted in order 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 1000 times in order to compute the mean accuracy and standard deviation on both the training and the test set. The relative importance of mean variables was also generated in order to measure the influence of each OCTA parameter on the model. Mean accuracy for 1000 10-fold cross-validations was also conducted for logistic regression. Logistic regression was further used in order 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 vascular density, SCP foveal vascular density, DCP whole image vascular density, DCP foveal vascular density) were compared between the study and control groups in order 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 in order to quantify the relationship between the BCVA, ONL, SCP FAZ, SCP and DCP whole image vascular density and SCP and DCP foveal vascular density.

**Results**

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

Depth 2 and depth 3 classification trees provided similar results with mean accuracy 0.99 on the 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 vascular density, SCP foveal vascular density, DCP whole image vascular density, DCP
foveal vascular density) OCTA mean accuracy is 97%, while when taking only quantitative parameters (SCP FAZ, SCP whole image vascular density, SCP foveal vascular density, DCP whole image vascular density, DCP foveal vascular density) it reaches 90%. (Table 2) The best quantitative parameter combination includes the SCP foveal vascular density and SCP whole image vascular density with mean accuracy of 91%. (Table 3)

Further analysis was performed in order 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 vascular density, SCP foveal vascular density and DCP foveal vascular density (p<0.001 for all comparisons) while DCP whole image vascular density did not present a significant difference (p=0.055). (Table 4) An important linear division of FAZ and SCP foveal vascular density was also identified between the two groups. When FAZ was smaller than 0.1 mm² and/or SCP foveal vascular density was higher than 30%, subjects belonged in the plana group. (Figure 3, Figure 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**

Even though 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 with controversial effects on 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 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, following our study, the qualitative parameters could be considered of lesser importance, therefore, we underline the use of two quantitative parameters, SCP foveal vascular density and SCP whole image vascular density to be included when evaluating features/characteristics of fovea plana, with which OCTA accuracy reaches 91%.

Additionally, when comparing fovea plana to the fovea of healthy participants, the FAZ was found to be significantly smaller in subjects with fovea plana, while vascular density was significantly higher in both plexuses at the central fovea, but lower at the whole OCTA image, thus agreeing with Le et al14. Interestingly, in our study the DCP vascular density of the whole image was lower in the plana group; however found to be not significantly different. The higher vascular density at the fovea of the plana group can be explained by the lack of a FAZ, while 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 al11 who showed a different vascular arrangement in patients with a fovea plana, however this is in contrast with Dolz-Marco et al13 who presented a case-series of fovea plana subjects without any FAZ reduction. In detail, our results show an important linear division of FAZ and SCP foveal vascular density 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 mm² and/or a SCP foveal vascular density of higher than 30%, it could create suspicion in support of fovea plana. (Figure 3, Figure 4)
Finally, our analysis shows 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 co-existent 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 have already highlighted the insignificance of the foveal pit in determining visual acuity, a theory that aligns with our results. However, Thomas et al as well as some other small case-reports 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 parameters. It is strongly implied when the SCP FAZ is smaller than 0.1 mm² and/or SCP foveal vascular density 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 vascular density, when compared to healthy subjects and finally, it implies that visual acuity is not necessarily affected by the abnormal foveal development. Further comparative studies should be conducted in order to identify the actual effect of fovea plana, with and
without known concomitant ocular co-morbidities on the visual acuity as well as on retinal vasculature.

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Legends

Figure 1: Spectral domain optical coherence tomography – Fovea plana defined as the persistence of inner retinal layers – A) Partial fovea plana, B) Complete fovea plana
Figure 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 hyalose, B) a patient with fovea plana and vitreous opacities, C) and D) subjects from the control group

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

Figure 4: Superficial capillary plexus foveal vascular density in fovea plana and in control group
| Parameters                                    | Fovea plana group | Control group |
|----------------------------------------------|-------------------|---------------|
| **Subjects (number)**                        | 57                | 28            |
| **Age (median ± IQR, years)**                | 69 ± 24           | 66 ± 19       |
| **Sex (Males / Females)**                    | 12 / 16           | 29 / 28       |
| **BCVA (median ± IQR, logMAR)**              | 0.10 ± 0.20       | 0.00 ± 0.10   |
| **Vitreomacular and inner retinal conditions** | 36                | 0             |
| **Outer retinal and choroidal conditions**   | 6                 | 0             |
| **Retinal syndromes and dystrophies**        | 15                | 0             |

Table 1: Baseline characteristics of the two groups – IQR: Interquartile range, BCVA: Best-corrected visual acuity; Vitreomacular and inner retinal conditions: Epiiretinal membrane, vitreous opacities, asteroid hyalosis, diabetic retinopathy, hypertensive retinopathy; Outer retinal and choroid conditions: drusen, epitheliopathy; Retinal syndromes and dystrophies: Best syndrome, Alport syndrome, Enhanced S-cone syndrome
| Parameters                                | Mean accuracy ± Standard deviation |
|-------------------------------------------|-----------------------------------|
| 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 vascular density          | 0.79 ± 0.04                       |
| SCP foveal vascular density               | 0.78 ± 0.05                       |
| DCP whole image vascular density          | 0.74 ± 0.05                       |
| DCP foveal vascular density               | 0.77 ± 0.05                       |

Table 2: Mean accuracy ± standard deviation of OCTA based on each parameter – SCP: Superficial capillary plexus, DCP: Deep capillary plexus, SCP FAZ: Superficial capillary plexus foveal avascular zone
| 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                     | 0.87 ± 0.04                 | 0.86 ± 0.04                     |
| SCP whole image vascular density | 0.09 ± 0.04 | —                               | 0.91 ± 0.03                 | 0.86 ± 0.04                     |
| SCP foveal vascular density    | 0.08 ± 0.04 | 0.91 ± 0.03                     | —                           | 0.77 ± 0.05                     |
| DCP whole image vascular density | 0.08 ± 0.04 | 0.08 ± 0.04                     | 0.85 ± 0.04                 | —                               |
| DCP foveal vascular density    | 0.08 ± 0.04 | 0.86 ± 0.04                     | 0.77 ± 0.05                 | 0.83 ± 0.04                     |

Table 3: Mean accuracy ± standard deviation for OCTA quantitative parameter combinations. SCP FAZ: Superficial capillary plexus foveal avascular zone, SCP: Superficial capillary plexus, DCP: Deep capillary plexus
| Parameters                             | Fovea plana group | Control group |
|---------------------------------------|-------------------|---------------|
| SCP FAZ*                              | 0.06 ± 0.04       | 0.21 ± 0.14   |
| SCP whole image vascular density*     | 42.1 ± 6.1        | 46.8 ± 2.1    |
| SCP foveal vascular density*          | 29.1 ± 9.8        | 22.5 ± 9.6    |
| DCP whole image vascular density      | 48.8 ± 7.4        | 52.2 ± 6.4    |
| DCP foveal vascularization*           | 44.3 ± 9.6        | 38 ± 9.15     |

Table 4: Median ± interquartile range (IQR) for age and for OCTA parameters per group – SCP FAZ: Superficial capillary plexus foveal avascular zone, SCP: Superficial capillary plexus, DCP: Deep capillary plexus, *p<0.001
