OCT angiography in optic disc drusen: comparison with structural and functional parameters

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ABSTRACT

Background Optic disc drusen (ODD) can cause retinal nerve fibre layer (RNFL) defects with progressive visual field (VF) loss. Microvascular changes are discussed as a cause. We measured the vessel density (VD) of the optic disc in ODD using optical coherence tomography angiography and compared it with a normal population. Another intent was to determine the sensitivity and correlations in comparison with functional (VF) and structural parameters (RNFL, minimum rim width (MRW), ganglion cell complex (GCC)).

Methods We analysed the VD of 25 patients with ODD and an age-matched control population including 25 healthy participants using AngioVue (Optovue, Fremont, CA, USA). We obtained data about RNFL, GCC, Bruch's membrane opening MRW (Spectralis HRA & OCT; Heidelberg Engineering, Germany) and VF (standard automated perimetry; SITA 24-2). Low image quality and pathologies interfering with the diagnostics were excluded. Parametric data were analysed using the t-test and non-parametric values using the Mann-Whitney U test. Linear regression analysis was used to determine correlations using the Bravais-Pearson test.

Results The VD was significantly reduced in the ODD group especially the peripapillary capillary VD (n=45 vs 50 eyes; mean 43.15% vs 51.70%). Peripapillary RNFL thickness correlated with the VD significantly (r=0.902 (n=44), 0.901 (n=44), 0.866 (n=45)). The RNFL analysis showed a reduction in ODD, especially the superior hemisphere (mean 107 µm, 129 µm; 49 vs 50 eyes). The GCC was significantly lower in the ODD group (n=38 vs 40; mean 87 µm vs 98 µm). Positive correlation between the VD and the GCC was significant (n=37, r=0.532). There is a significant negative correlation (n=19; r=−0.726) between the VD and the pattern standard deviation (PSD).

Conclusion This study reveals significant peripapillary microvascular changes in patients with ODD correlating with the RNFL and GCC reduction. There is a negative correlation between the PSD and the VD.

INTRODUCTION

Optic disc drusen (ODD) are acellular deposits located in the optic nerve head shown in postmortem studies in up to 2.4% of the population.[1] Different theories explain the reason for their formation. A narrow scleral canal and a genetical predisposition for these accumulations, which are believed to be a by-product of axoplasmic metabolism, are hypothesised.[2]

Initially symptom-free, these usually bilateral deposits can cause mechanical stress in the optic nerve head leading to progressive optic neuropathy with sometimes severe visual field (VF) loss.[3] Other complications such as a higher risk for vascular occlusions and anterior ischaemic optic neuropathy are associated.[3–5]

In childhood, these optic nerve head drusen are usually buried and uncalcified. In early adulthood, they become in the so-called transition phase increasingly calcified which makes them detectable in autofluorescence or ultrasound and often directly visible in funduscopy (figure 1).

Ultrasound remains the gold standard for diagnosing optic nerve head drusen but provides very little information about the exact location and progression of the deposits and can only detect drusen with a certain degree of calcification (figure 2).

ODD are autofluorescent and therefore detectable by autofluorescence imaging shown as round or oval hyperautofluorescent structures (figure 3) in the optic nerve head. Deeper lying ODDs are often not reliably detectable with this technique.[6]

With the invention of enhanced depth imaging optical coherence tomography (EDI-OCT, figure 4) a non-invasive diagnostic tool was introduced to the diagnosis of the optic nerve head drusen providing beneficial information about their localisation, morphological structure and the retinal nerve fibre layer (RNFL) of the optic nerve head.[7 8]

ODD, especially superficial drusen, cause thinning of the RNFL and VF defects.[9] Therefore, optical coherence tomography (OCT) measuring the RNFL and standard automated perimetry (SAP) is a common diagnostic tool for ODD management for screening and progression of the disease.

Based on the OCT technique using the split-spectrum-amplitude-decorrelation angiography algorithm, OCT angiography (OCTA) can visualise and quantify the microvascular structure of the optic nerve head (figure 5).

OCTA has found a significant reduction of the vessel density (VD) in other optic neuropathies such as glaucoma and Leber's hereditary optic neuropathy (LHON).[10 11] To date, only single case reports have described microvascular changes in patients with ODD.[12–14]

The purpose of this study was to measure the VD in patients diagnosed with ODD, to quantify microstructural changes and to compare them with a healthy control population. Relationships with other structural measurements such as the RNFL, macular ganglion cell complex (GCC) thickness and functional parameters such as VF defects are additionally analysed.

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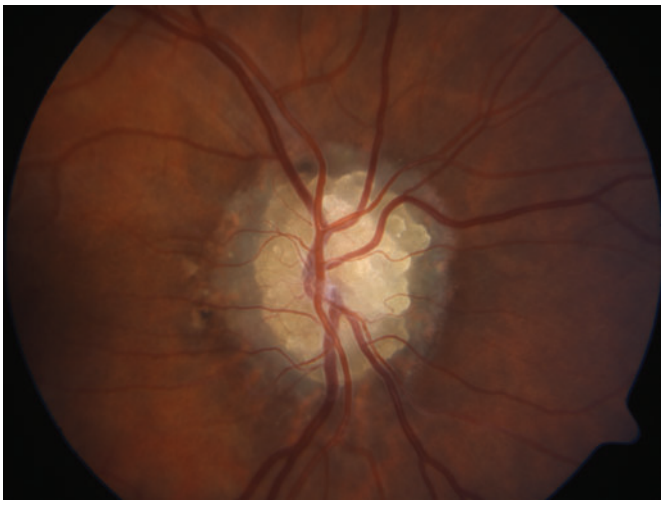

Figure 1 Optic disc drusen in funduscopy showing prominent drusen in the optic nerve head.

PATIENTS AND METHODS

This was a retrospective, single-centre, case–control study. The patients with ODD included were diagnosed with ODD by ultrasound (B-scan, reflectivity ≤20 dB, Aviso; Quantel Medical, Bozeman, USA) and autofluorescence (Spectralis HRA & OCT; Heidelberg Engineering, Heidelberg, Germany) and were evaluated between May 2015 and October 2018 at the Department of Ophthalmology, University Hospital, LMU Munich, Germany. A control group was recruited matching the patients with ODD in mean age and gender.

Each participant of the patients with ODD underwent full ophthalmological examination including funduscopy, Goldmann tonometry and SAP (24-2 SITA) measuring the mean deviation (MD) and pattern standard deviation (PSD). Peripapillary RNFL thickness was obtained by SD-OCT (Spectralis; Heidelberg Engineering) and AngioVue (Optovue, Fremont, CA, USA). GCC and VD were measured with the AngioVue Imaging System (Optovue). The Heidelberg SD-OCT was used to acquire the minimum rim width (MRW) and the RNFL in 3.5 mm, 4.1 mm and 4.7 mm radius distance around the optic disc centre.

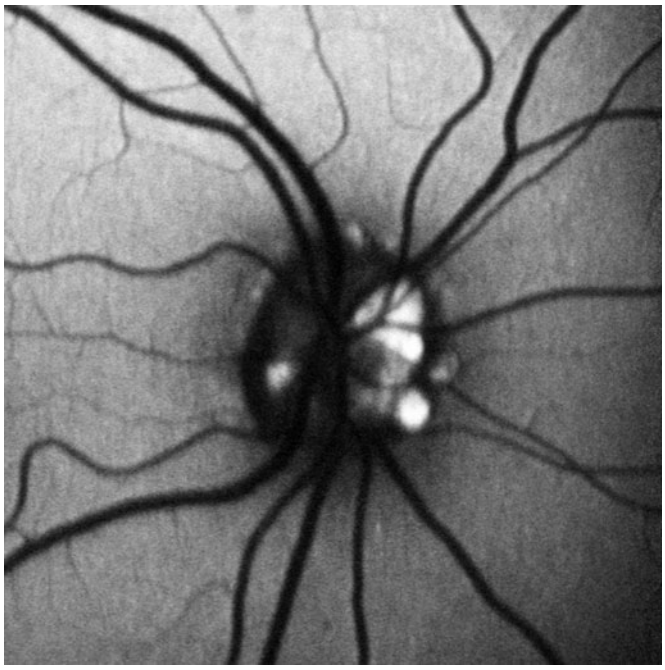

Figure 3 Optic disc drusen nasal being hyperautofluorescent in autofluorescence.

Exclusion criteria for ODD were the presence of any systemic or other ocular pathology such as other optic nerve diseases than optic nerve head drusen and disease of the macula which could interfere with the OCT measurement.

It is difficult to exclude glaucoma completely in patients with ODD. We excluded patients with an intraocular pressure (IOP) more than 21 mm Hg (Goldmann tonometry), a cup:disc ratio higher than 0.4 or more than 0.2 between the right and left eye as well as a positive history of glaucoma.

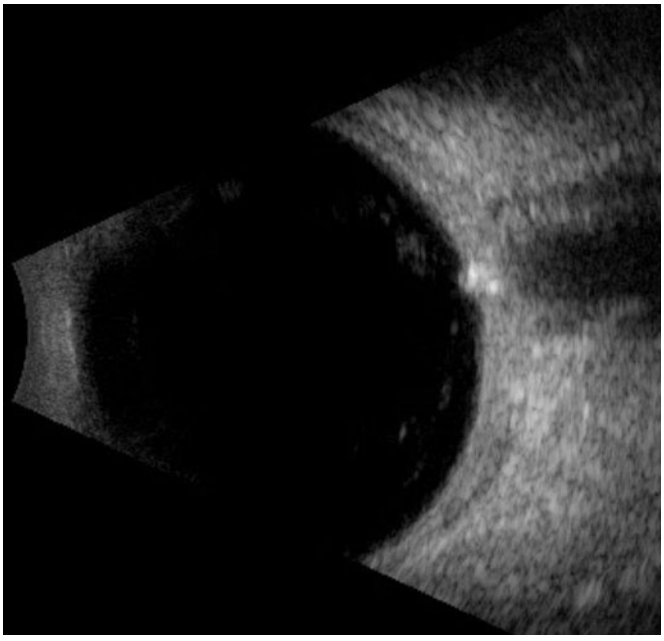

Figure 2 Hyper-reflective optic disc drusen in ultrasound.

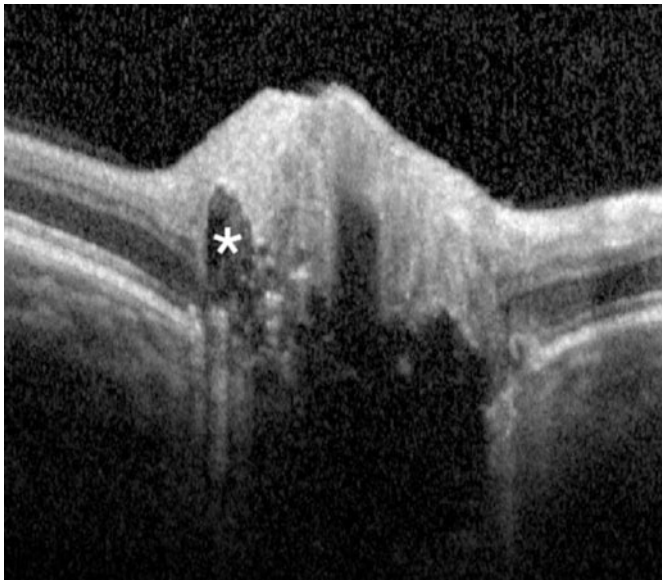

Figure 4 EDI-OCT of a patient with optic disc drusen.

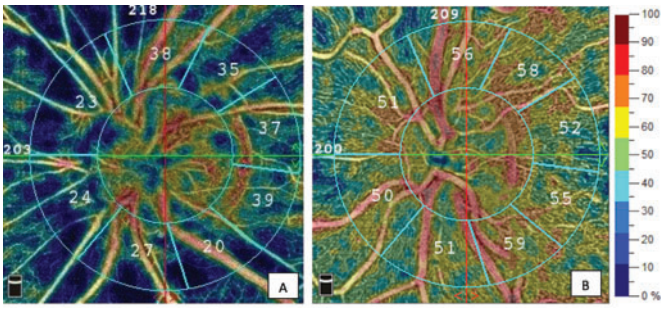

Figure 5 Vessel density in a patient with optic disc drusen (A) and control (B).

Exclusion criteria for the control group were the presence of any systemic or ocular pathology especially optic nerve disease, abnormal appearance of the optic nerve head and a cup:disc ratio higher than 0.5 as well as reduced RNFL thickness in any sector. Control group participants with any other pathology that could interfere with the OCTA examination and interpretation were excluded as well.

Low imaging quality or false segmentation was an exclusion criterion in both groups.

Values were statistically analysed using SPSS Statistics V.25 (2017). Data passing the normality test using the Kolmogorov-Smirnov test were analysed using the t-test. Otherwise, the Mann-Whitney U test was used. Correlations were analysed using the Bravais-Pearson test. A probability p value of less than 0.05 was considered significant. Data are presented as mean±SD. The left and right eyes of each patient were assumed to be independent.

RESULTS

Demographics

Comparing the groups of the ODD and the control group, there was no significant difference in age (mean 45.80±13.75 years vs 44.29±10.33 years). The gender was almost equal in both groups (male 52% vs female 48%) (table 1).

Since the patients with ODD regularly visited our institution, the IOP was measured several times (mean 4.88±SD 3.51), showing an overall average of 14.09 mm Hg (±SD 2.03 mm Hg). The highest overall measured IOP was 20 mmHg in one patient once. Three patients used eyedrops for neuroprotection off-label at least for 1 year from which two patients used brimonidine and one patient dorzolamide eye drops twice a day. The difference between the two groups just missed significance (eyedrop users: 13.90 mm Hg vs no eyedrops: 14.11 mm Hg; p=0.08).

Vessel density

VD was studied in 45 of 49 eyes with ODD and compared with 50 healthy eyes of the control group. Up to five eyes had to be excluded due to artefacts. The overall quality index for the OCTA, beginning with a score of 1 and reaching up to 10 for high quality, was not significantly different between the ODD and control group (8.16±1.0 vs 8.46±1.1; p<0.001).

The quality index is calculated by three major factors including focus, motion and signal:noise ratio (SNR). These scores are combined in a somewhat complex way, optimised to mimic human subjective grading of scan quality with a threshold at 6 for acceptable scans.

The region of interest can be chosen to all vessels or limited only to the capillary density in the area of the optic disc, peripapillary area or the whole picture (4.5 mm). We analysed all these regions both with all VD and only capillary VD and found all these regions to be highly significantly reduced in the ODD group compared with the control group (p<0.000).

Table 2 shows the significant reduction of the VD in each area and segment compared with the control group. We chose to focus mainly on the peripapillary capillary perfusion, a region defined as a 700 μm wide elliptical annulus around the disc when screening for significant correlations or differences to avoid bias through the ODD probably concealing underlying vessels. In addition, the peripapillary capillary VD showed the highest significant difference between the ODD and control group mean in all analysed VD areas (43.15% vs 51.70%).

Furthermore, the superior, nasal, inferior and temporal sector of the OCTA VD can be analysed separately: according to the previous results, a significantly reduced VD could be seen in each sector compared with the control group (p<0.0001) (table 3).

Table 1 Demographic parameters

	ODD	Control
Age (years; mean±SD; minimum, maximum)	45.0 (±13.75; 25–75)	44.29 (±10.33; 25–65)
Male (eyes n; %)	26 (52%)	24 (48%)
Female (eyes n; %)	24 (48%)	26 (52%)

ODD, optic disc drusen.

Table 2 Vessel density (VD) measurements including all vessels (all) or only capillary vessels (cap.) in the whole image, peripapillary area (peripap.), superior (Hemi sup.) and inferior hemisphere (Hemi inf.)

	ODD	Control	P value
VD whole image all (%, ±SD; eyes)	49.5 (±6.5; 49)	56.1 (±2.4; 50)	<0.0001
VD whole image cap. (%, ±SD; eyes)	42.9 (±6.4; 49)	49.2 (±2.4; 50)	<0.0001
VD peripap. all (%, ±SD; eyes)	50.1 (±8.1; 45)	58.4 (±2.3; 50)	<0.0001
VD peripap. cap. (%, ±SD; eyes)	43.2 (±8.3; 45)	51.7 (±2.7; 50)	<0.0001
VD Hemi sup. all (%, ±SD; eyes)	49.4 (±8.6; 45)	58.9 (±2.6; 50)	<0.0001
VD Hemi inf. all (%, ±SD; eyes)	50.7 (±7.8; 48)	57.8 (±2.7; 50)	<0.0001

ODD, optic disc drusen.

Retinal nerve fibre layer

The OCT obtains in vivo cross-sectional information from anatomical structures in the eye. Furthermore, the RNFL is often used as a follow-up tool to measure possible retinal thinning. The RNFL was measured with the Angiovue (Optovue) in 3.45 mm distance to the centre of the optic disc and, additionally, the Spectralis SD-OCT (Heidelberg) measuring the RNFL in 3.5 mm, 4.1 mm and 4.7 mm distance radius around the optic nerve head.

Comparing the ODD and control group, the RNFL showed no significant reduction in the overall RNFL compared with the control group (104 μm vs 111 μm, p=0.089) (table 4). When separately looked at the nasal, inferior, temporal and superior sector, only the superior sector showed significant reduction compared with the control group (110 μm vs 129 μm, p=0.001). The Bravais-Pearson test was used to assess correlations between each of the 3.5 mm, 4.1 mm and 4.7 mm radius RNFL thickness, and showed high significance in positive correlations with the peripapillary capillary VD (0.902, 0.901, 0.866, p>0.05).

Table 3 Vessel density (VD, % covering the image) of all vessels in the sectors nasal, inferior, temporal and superior in patients with optic disc drusen (ODD) and control group

	ODD	Control	P value
VD nasal all (%, ±SD; n)	39.35 (±10.1; 48)	48.9 (±4.04; 50)	<0.0001
VD inferior all (%, ±SD; n)	44.6 (±10.4; 49)	54.1 (±3.7; 50)	<0.0001
VD temporal all (%, ±SD; n)	49.1 (±5.7; 49)	52.5 (±3.9; 50)	0.003
VD superior all (%, ±SD; n)	40.7 (±10.9; 49)	52.4 (±3.5; 50)	<0.0001

Ganglion cell complex

The GCC thickness was significantly lower in the ODD group compared with the control group in the average and superior area (table 5). The inferior area did not pass the test for significant differences between the two groups.

A positive correlation between the VD and GCC was significant (0.532, p=0.001).

Minimum rim width

As expected, the overall Bruch's membrane opening MRW (BMO-MRW) compared with the reference table for Heidelberg-Spectralis was thicker due to the prominent optic nerve head (481.3 μm vs 336.1 μm). This underlines the optic nerve head is prominent in patients with ODD even in all sectors when analysed separately between ODD and reference (nasal 505.1 μm vs 374.2 μm; superior 500.1 μm vs 347.6 μm; temporal 429.1 vs 238.7 μm; inferior 523.9 vs 382.0 μm).

There was no significant correlation between the VD and the MRW comparing ODD and control group (r=0.17, p=0.23).

Visual field

No significant correlations were shown when analysing the VF data and structural diagnostics. Therefore, we made a subgroup analysis including only those VF measurements with no malfixation, no false positive or false negative failure (malfixation 0, false-positive 0, false-negative 0). Nineteen eyes with ODD were included in these subgroup analyses.

There was no significant correlation between the mean deviation (MD) and the VD but a quite strong negative correlation (−0.726, p<0.05) between the capillary VD and the PSD in the subgroup analysis.

DISCUSSION

Accurate diagnostic tests are essential for improved management of patients with ODD. Whether RNFL injury is caused directly by axonal compression by the drusen or indirect by vascular compression remains controversial.

The OCTA provides non-invasive and reliable data which allows us to measure microvascular changes and make them comparable with a control group.

Table 4 Retinal nerve fibre layer (RNFL) measured in microns in patients with optic disc drusen (ODD) and control

RNFL thickness	ODD	Control	P value
Nasal (mean µm, ±SD)*	106 (±36)	103 (±19)	0.87
Inferior (mean, ±SD)*	132 (±37)	142 (±18)	0.056
Temporal (mean, ±SD)	78 (±16)	72 (±10)	0.074
Superior (mean, ±SD)	110 (±35)	129 (±15)	0.001

*Parametric distribution.

Table 5 Ganglion cell thickness (GCC) average (av.), superior (sup.) and inf. (inf.) in patients with optic disc drusen (ODD) and control as well as the correlation concerning the GCC and the peripapillary capillary vessel density (VD peripap. cap.)

	ODD	Control	P value
GCC av. (mean (µm), ±SD) *	87.7 (±11.1)	98.1 (±4.9)	<0.0001
GCC sup. (mean (µm), ±SD)	88.0 (±10.7)	97.8 (±5.0)	<0.0001
GCC inf. (mean (µm), ±SD) *	86.8 (±12.3)	96.7 (±15.5)	<0.0001
GCC av. and VD peripap. cap. correlation (r)	0.532		0.001

*Parametric distribution.

Therefore, we evaluated the VD in patients with ODD by comparing 25 patients diagnosed with ODD using OCTA with age and gender considered comparable cohort of 25 healthy participants to analyse differences and correlations concerning OCT measurements such as RNFL, MRW and the perimetric functional parameters MD and PSD.

The significant reduction of the VD in the group of patients with ODD, especially the peripapillary area, underlines microvascular changes with a decrease of the VD in the disease. Furthermore, these findings go along with the results reported by colleagues concerning other optic nerve head pathologies as LHON and glaucoma which seem to be accompanied with a reduction of the VD as well.[10 11]

Analysing sectors separately the nasal, inferior and superior sectors, where ODD are most frequently found,[15] show the highest decrease of VD between the two groups suggesting a context between ODD localisation and microvascular network decrease.

Our findings of RNFL thinning go along with the results of numerous investigators who have concluded the RNFL measurement being a useful screening and follow-up monitoring tool for patients with ODD.[9 16 17]

A known problem in patients with ODD is to point out additional glaucoma since the optic nerve head is prominent due to the drusen. This makes it difficult for the ophthalmologist to detect additional glaucoma damage since the optic nerve head does not show the characteristic cupping of the optic nerve head seen in patients with glaucoma.[16 18]

Our patients with ODD showed an average IOP of 14.09 mm Hg and no measurement higher than 20 mm Hg. The off-label use of neuroprotective eyedrops such as brimonidine and dorzolamide was used in three patients. The neuroprotective effect shown in animal models still lacks proof of clinical data and is still controversially discussed in the literature.[19 20]

In addition, we were able to show a positive correlation between the RNFL and the VD suggesting an association of microvascular network attenuation and RNFL thinning. These findings are supported by the data of the GCC which as well were decreased in the ODD group and additionally showed a significant positive correlation with the VD. A thinning of RNFL and GCC in patients with ODD is described in other studies.[21] The RNFL measurement cannot precisely be located to the area of function in the VF since the origin of the axon originates from different regions. Furthermore, the temporal region underlies a high degree of variability which makes the interpretation difficult.[22]

Therefore, the GCC is a useful additional value to the RNFL.[21 23] It is highly comparable with the RNFL and also shows a high correlation to visual field defects in patients with glaucoma.[24] We were able to find similar findings in the patients with ODD: a significant reduction of the RNFL and the GCC in patients with ODD adding information for improved ODD management.

These findings go along with the results of the colleagues performing OCTA in ODD in case reports and small cohort studies.[12–14]

The minimum rim width (BMO-MRW) could not show any correlations concerning the VD in patients with ODD probably because of the prominent optic disc head measurements and therefore irregular MRW data. But the BMO-MRW being higher in any sector confirms that the optic nerve head of patients with ODD is prominent.

Authors of several studies have shown a relationship between RNFL thinning and perimetric parameters in patients with ODD.[4 9 25] Malmqvist and colleagues were able to show a positive correlation between the MD and the RNFL thinning in a larger cohort of 149 ODD eyes.[9] Inspired by these findings, we tried to find similar correlations in our study concerning the VD: we were able to show a quite strong negative correlation between the peripapillary capillary VD and the PSD ($r=-0.726$, $p<0.001$) in a subgroup analysis but no significant correlation concerning the MD. The results may be biased by an older population with a higher incidence of lens opacities and additionally a limited number of reliable VF data.

This study reveals significant peripapillary microvascular changes in patients with ODD compared with the control group within the optic disc, the peripapillary region and the whole picture and also the superior, nasal, inferior and temporal sectors. The peripapillary capillary vessel density shows a high correlation with other structural measurements such as the RNFL and GCC. Furthermore, the reduction of the VD was highly significant while other structural data showed a lack of significant differences between ODD and control, suggesting an earlier change concerning microvascular structure compared with other structural changes like the RNFL and GCC.

Comparison between structural and functional changes was limited by small subgroup analysis and remains difficult: we were able to show a significant negative correlation between the PSD and the VD but were also limited by a small number of participants with an evaluable VF.

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Contributors HE and MM contributed equally in planning and outlining the question of performing OCTA scans in patients with optic disc drusen. MM is an expert for glaucoma and we were both interested if according to glaucoma the OCTA scans would show a reduced vessel density in patients with optic disc drusen. In the following patient data and control group participants were collected by HE and OCT and OCTA scans were performed by HE, JR and NM. The analysis and interpretation of data were performed by HE and MS. SGP is the chief of medicine at our institution and was of helpful advice for processing the paper and a part of the institutional review board. The paper was written by HE and MM.

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Competing interests None declared.

Patient consent for publication Not required.

Ethics approval The study was performed according to the Declaration of Helsinki and was approved by the institutional review board and the expert ophthalmologists at my institution.

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