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Research Paper

Optical coherence tomography angiography characteristics of the retinal and optic disc morphology in prolactinoma

Muberra Akdogan [a], Mustafa Dogan [a], Selvihan Beysel [b], Hamidu Hamisi Gobeka [a,*], Mehmet Cem Sabaner [a], Merve Oran [a]

[a] Afyonkarahisar Health Sciences University, Faculty of Medicine, Department of Ophthalmology, Afyonkarahisar, Turkey
[b] Afyonkarahisar Health Sciences University, Faculty of Medicine, Department of Endocrinology and Metabolism, Afyonkarahisar, Turkey

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ABSTRACT

Purpose: To investigate changes in the retinal and optic disc (OD) morphology in prolactinoma patients without optical chiasmal compression and/or visual field defects using optical coherence tomography angiography (OCTA).

Methods: In this cross-sectional imaging study, 16 consecutive prolactinoma patients (group 1, 32 eyes) and 15 age- and gender-matched healthy subjects (group 2, 30 eyes) underwent a thorough neuro-ophthalmological examination, which included testing for the presence of any intracranial compressive lesion that could cause optic neuropathy. Retinal morphological parameters, outer retinal and choriocapillaris flow areas, as well as OD vessel density (VD) and retinal nerve fiber layer (RNFL) thickness in for quadrants were then measured using OCTA.

Results: Mean age ($p = 0.537$) and gender ($p = 0.385$) of participants in groups 1 and 2 did not differ significantly. The mean BCVA for both groups was 0.00 ± 0.00 logMAR. Microadenomas made up the majority of prolactinomas (87.1 %). All retinal morphological parameters in deep capillary plexus (excluding foveal VD) differed significantly between groups 1 and 2 (whole: $p < 0.001$, parafoveal: $p = 0.021$, and perifoveal: $p < 0.001$). Peripapillary RNFL thickness in temporal ($p < 0.001$), nasal ($p = 0.010$), and inferior ($p = 0.007$) quadrants also differed significantly between the two groups. Foveal deep ($r = -0.304$, $p = 0.035$) and choriocapillaris flow ($r = -0.511$, $p = 0.008$) were negatively correlated with tumor size at diagnosis.

Conclusions: Significant microvascular morphological changes, particularly in the deep retinal layer, as well as in the peripapillary RNFL thickness, were observed in prolactinoma patients. OCTA appears to be capable of detecting non-manifest circumpapillary and even intra-retinal microvascular changes even when there are no obvious signs of prolactinoma-related ocular complications caused by chiasmal compression.

1. Introduction

Prolactinomas are categorized by size as being either microprolactinomas (<10 mm) or macroprolactinomas (≥10 mm), and are by far the most frequent source of hyperprolactinemia, resulting in a number of endocrine-related symptoms [1]. They are thought to be caused by lesions secondary to dopamine metabolism disorders that trigger an uncontrolled increased prolactin secretion and functional hyperplasia [2].

Prolactinomas affecting sellar area are associated with typical visual symptoms [3,4]. Compression of the retinal ganglion cell axons due to a growing tumor may cause visual field defects (VFDs) and decreased visual acuity (VA) [5]. Sometimes these tumors don't have signs until associated with mass effect. Chiasmal tumors with temporal hemianopsia may also cause ganglion cell layer (GCL) and retinal nerve fiber layer (RNFL) thinning as a result of neuronal injury [4,5]. Thus, prolactinoma patients need a comprehensive intervention due to a frequently existing combination of systemic and ocular complications [6].

Optical coherence tomography (OCT) has been used to detect morphological changes in peripapillary RNFL and GCL in compressive optic neuropathies (ONs) [6–9] Development of OCT angiography (OCTA), [10,11] has further led to the detection of microvascular morphological changes in ONs, including glaucoma [12] ischemic ONs

* Corresponding author.
E-mail address: hgobeka@gmail.com (H.H. Gobeka).

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[13] and inflammatory ONs [14]. A strong association between OCTA microvascular morphological changes and visual functions [13–15], as well as between vascular and structural damages, both in normal eyes [16] and in diabetic retinopathy [17] has been reported in previous OCTA studies. Higashiyama et al., [18] evaluated microvascular changes in eyes with chiasmal compression using OCTA.

A recent case report of a prolactinoma patient showed a significantly reduced capillary in OCTA and its apparent association with RNFL thinning in OCT [19] To our knowledge, no prior studies have used OCTA to investigate morphological changes in the retina and optic disc (OD), especially in several prolactinoma patients. We therefore intended to investigate retinal and OD morphological changes in several prolactinoma patients without optical chiasmal compression and/or VFDs using OCTA, and to compare the results with healthy subjects.

2. Methods

2.1. Study design

This comparative single-centered cross-sectional study involving 16 consecutive patients with prolactinoma (group 1) and 15 age- and gender-matched healthy subjects (group 2) was performed at Afyonkarahisar Health Sciences Faculty of Medicine, Department of Ophthalmology. The study protocol complied with the ethical principles of the Declaration of Helsinki and received full approval from the institutional review boards of Afyonkarahisar Health Sciences University Ethics Committee. Written informed consent was obtained from all participants.

2.2. Study participants

Patients with a magnetic resonance imaging (MRI)-confirmed prolactinoma, age $>$ 18 years, absence of any other central nervous system or cerebrovascular disorder, and who successfully completed all necessary tests with high quality images were included in this study. Patients with any prior pituitary adenoma (PA) treatment, presence of congenital ocular disorders, myopia $>$2 diopters, a history of ocular surgery, an involvement of any other ophthalmological conditions such as significant lens opacities or any macular disease, a prior diagnosis of glaucoma and any OD anomaly, and systemic diseases, including diabetes and systemic hypertension, which could impair visual functions or cause vascular modifications were not included in the study. The healthy volunteers from the out-patient ophthalmology clinics served as the control group. Those suffering from systemic disorders such as diabetes or hypertension or from ocular diseases such as glaucoma, maculopathy or a history of prior surgery were not included.

2.3. Initial patient assessment and cranial MRI

Each patient's tumor size at the time of evaluation, prior treatments including surgery and dopamine agonist, disease duration, and hormonal levels were all recorded. Prolactin normalization was indicated in a complete biochemical response when serum prolactin levels were $\leq$ 20 ng/ml. And, a complete structural response was demonstrated after MRI imaging failed to show a detectable tumor.

Before referral to the ophthalmology clinic, all patients were evaluated for prolactinoma by an endocrinologist with cranial MRI and hematological examination. The cranial MRI with high-resolution coronal T2-weighted and fat-suppressed T1-weighted gadolinium injection sequences was performed while concentrating on the pituitary zone. Additionally, manual tumor segmentation was conducted by a qualified neuroradiologist. Oral cabergoline therapy was prescribed to patients diagnosed with prolactinoma.

2.4. Neuro-ophthalmological examination and OCTA acquisition

All patients underwent a neuro-ophthalmological examination to assess the existence of potential ON secondary to any intracranial compressive lesion. Measurement of best-corrected VA (BCVA) in LogMAR and intraocular pressure by Goldmann applanation tonometry, as well as slit-lamp biomicroscopy and color fundus photography was performed by the same physician under standard physiological conditions.

Optical coherence tomography angiograms were obtained using RTVue XR Avanti in the Angio Retina mode (6 $\times$ 6 mm). The AngioVue software (version 2018.0.0.18; Optovue, Inc) automatically generated vessel density (VD) parameters corresponding to proportion of the scanned area covered by large vessels and capillaries identified as pixels with decorrelation values, achieved by a split-spectrum amplitude-decorrelation angiography algorithm, just above threshold level. Ocular movement artefacts were minimized by an eye-tracking mode and eliminated by a motion correction technology. All scans were checked to ensure appropriate segmentation and image quality. Poor quality scans (defined as Quality Index $<$7/10, or saccade or blinking artefacts) were not included in the analysis.

Automated segmentation of superficial and deep capillary plexuses (SCP and DCP) was used to determine VD in the macular region by using predetermined boundaries established by Optovue: SCP was between internal limiting membrane (ILM) and 10 μm above the intersection between inner plexiform layer (IPL) and inner nuclear layer (INL) (IPL-INL), while DCP was between 10 μm above the IPL-INL intersection and 9 μm underneath the outer plexiform layer (OPL) and outer nuclear layer (ONL) intersection; there was no connection between the two segments. Retinal morphological parameters including foveal, parafoveal, and perifoveal macular SCP and DCP VDs, as well as foveal avascular zone (FAZ) parameters, including FAZ area, FAZ perimeter, and foveal VD in 300 μm-wide region around FAZ (FD-300) were then recorded. The maximum circular area that could be captured by the fovea-centered image section with a radius of 2.98 mm was manually created in the outer retinal and choriocapillaris layers. The device software automatically quantified capillary flows, which were then recorded as outer retinal and choriocapillaris flows.

Moreover, the angio disc function automatically generated papillary VD for the whole en face area (wVD, whole en face image VD) and peripapillary VD. Peripapillary area was defined by a 0.75 mm-wide elliptical annulus projecting from the OD boundary (inner elliptical contour) and also was used to calculate peripapillary VD. The OD was divided into four quadrants: superior, temporal, inferior, and nasal, with VD generated for each. The RNFL thickness was determined in the peripapillary region, as well as in superior, temporal, nasal, and inferior quadrants.

2.5. Statistical analysis

Statistical analysis was carried out using the SPSS 22.0 program (IBM, Armonk, NY, USA). Data were evaluated using descriptive statistical methods (mean and standard deviation). The Shapiro–Wilk test was used to examine the data distribution. The independent *t*-test was used to perform intergroup analyses. Data assessments were made at 95 % confidence intervals (CI). The Spearman's rho test was used to perform a correlation analysis of OCTA parameters. Odds ratio (OR) for the independent predictors was determined using logistic regression analysis. Sensitivity and specificity were determined using a receiver operating characteristics (ROC) curve analysis. $P < 0.05$ was considered statistically significant.

3. Results

3.1. Patients' demographic characteristics

A total of 32 and 30 eyes were studied in groups 1 and 2, respectively. Mean age and gender of participants in groups 1 and 2 did not vary statistically significantly ($p = 0.537$; and $p = 0.385$, respectively). Both groups had an average BCVA of 0.00 ± 0.00 logMAR. The majority of prolactinomas were microadenomas (87.1 %). None of the prolactinoma patients displayed VFDs. All patients were treated with only cabergoline as a dopamine agonist. There was no history of prior surgery or radiation therapy in any patient. Demographic characteristics of the participants in the respective groups are displayed in Table 1. While not all prolactinoma patients experienced a complete structural response, 71.0 % of patients had a complete biochemical response.

3.2. OCTA analyses

3.2.1. Macular VDs, FAZ and Capillary Flow Parameters

Groups 1 and 2 did not differ statistically significantly in terms of whole, foveal, parafoveal, or perifoveal SCP VDs ($p > 0.05$). Except for foveal DCP VD ($p = 0.215$), the differences in whole ($p < 0.001$), parafoveal ($p = 0.021$), and perifoveal ($p < 0.001$) DCP VDs between groups 1 and 2 were statistically significant [Fig. 1(a, b, c, d) and (a*, b*, c*, d*)]. The FAZ and capillary flow parameters did not differ significantly between the two groups ($p > 0.05$) (Table 2, Fig. 2).

3.2.2. The OD VDs and RNFL thickness

The nasal quadrant OD VDs differed statistically significantly between the two groups ($p = 0.006$); however, other quadrants, as well as whole and peripapillary superficial and deep OD VDs, did not ($p > 0.05$). Except for the superior quadrant ($p = 0.533$), peripapillary RNFL thickness differed statistically significantly between the two groups in the temporal ($p < 0.001$), nasal ($p = 0.010$), and inferior ($p = 0.007$) quadrants [Table 3, Fig. 3(a, b, c, d) and (a*, b*, c*, d*)].

3.3. Correlation analyses

- *DCP VD parameters:* Whole deep was positively correlated with disease duration ($r = 0.329$, $p = 0.045$). Fovea deep was negatively correlated with tumor size at diagnosis ($r = -0.304$, $p = 0.035$).
- *SCP VD parameters:* Serum prolactin level before treatment was negatively correlated with superficial whole ($r = -0.390$, $p = 0.036$), superficial parafoveal ($r = -0.396$, $p = 0.035$), and superficial perifoveal ($r = -0.390$, $p = 0.040$).
- *Flow parameters:* Choriocapillaris flow was positively correlated with patient age ($r = 0.310$, $p = 0.18$) and negative correlated with tumor size at diagnosis ($r = -0.511$, $p = 0.008$). Duration of drug usage was positively correlated with FD-300 ($r = 0.396$, $p = 0.045$) and choriocapillaris flow area ($r = 0.396$, $p = 0.045$).
- *OD RNFL thickness:* The global OD RNFL thickness had a statistically significant positive correlation with peripapillary superficial VDs ($r = 0.721$, $p < 0.001$) but not with deep VDs ($r = 0.030$, $p = 0.856$). Also, duration of drug usage was positively correlated with temporal quadrant OD RNFL thickness ($r = 0.449$, $p = 0.011$). The OD RNFL thickness in global ($r = -0.401$, $p = 0.025$), as well as superior ($r = -0.437$, $p = 0.014$), and nasal quadrants ($r = -0.372$, $p = 0.040$), on the other hand, were all found to be negatively related to tumor size at diagnosis.

In logistic regression analysis, tumor size was found to be an independent predictor of deep foveal ($B = 1.6$, 95 % CI = 1.21–2.45, $p = 0.043$) (model independent variable: deep foveal below 50.05, dependent variables: gender, age, tumor size, duration of drug usage, dose).

4. Discussion

In this study, changes in the retinal and OD morphology in prolactinoma patients without chiasmal compression were investigated using OCTA, and the findings were compared to healthy subjects. Microadenomas made up the vast majority of MRI-detected prolactinomas (87.1 %) based on the pituitary tumor classification reported in the Yu et al., [1] study. In all patients, there were no apparent prolactinoma tumor compressive effects on the optic nerve and associated structures, which could be accompanied by optic nerve inflammation and/or OD atrophy, potentially leading to a relative afferent pupil defect, scotoma, decreased VA, or color desaturation. Cabergoline therapy had no effect on the BCVA or intraocular pressure measurements in any of the patients. Besides, no other notable ophthalmological findings were discovered. Cabergoline's inhibition of dopamine synthesis could have indirectly suppressed tumor enlargement, preventing subsequent ophthalmological complications.

Optical coherence tomography angiography studies have revealed morphological changes in the ocular posterior segment in PA patients, especially when compressive effects are present. Dallorto et al., [20] published a recent OCTA study that examined retinal vascular changes in peripapillary and macular areas in 17 PA patients with ON. As per the RNFL and ganglion cell complex (GCC) thinning, there was a significantly reduced peripapillary and superficial macular VDs in these patients compared to healthy eyes. Moreover, the RNFL and GCC thicknesses have previously been assessed in PA patients using OCT [8,21,22]. The mean RNFL and GCC thicknesses were lower in PA patients than normal subjects in many of these reports, and also most PA patients showed anterior visual pathway compression. Nonetheless, systemic OCTA studies have not been performed, particularly in prolactinoma patients without chiasmal compression, where early clinical findings may have merited an ophthalmological and neuroendocrinological therapeutic intervention.

Optical coherence tomography angiography is a novel non-invasive imaging technique that allows for simultaneous in vivo imaging of both ocular morphology and microvasculature [10,23,24]. The use of OCTA in diagnosis and monitoring of the retinal and OD diseases has been reported in several studies, involving patients with multiple sclerosis, [25] OD edema, pseudo-edema, and optic atrophy, [26] as well as peripapillary nerve fiber myelination [27]. Kim et al., [19] recorded reduced peripapillary RNFL corresponding to VFDs in a 32-year-old man with a pituitary tumor who had bitemporal hemianopsia on presentation. They also registered a capillary decrease in OCTA that was highly associated with RNFL loss in OCT. Cennamo et al., [28] on the other hand, reported RNFL damage in PA patients who did not have VFD or optic chiasmal compression.

To our knowledge, this could be the first OCTA-based study to demonstrate potential association between retinal and OD morphological changes and pituitary tumors, particularly prolactinomas in several

Table 1
Demographic characteristics of the study population.

Parameter	Group 1 (N = 16)	Group 2 (N = 15)	p Value
Age (Years)	42.81 ± 11.11	41.06 ± 9.83	0.537
Female:male	9:7	8:7	0.385

	Mean ± SD (range)
Mean tumor size at diagnosis (mm)	9.23 ± 5.46 (4.5–27.0)
Mean treatment duration (months)	6.67 ± 3.76 (3–14)
Mean cabergoline dosage (mg/week)	0.81 ± 0.54 (0.50–2.0)
Serum prolactin before treatment (ng/ml)	71.93 ± 14.81 (55.0–100.0)
Serum prolactin after treatment (ng/ml)	17.12 ± 7.36 (10.0–35.0)

N: Number of participants; *SD:* Standard deviation; $p < 0.05$ was considered statistically significant.

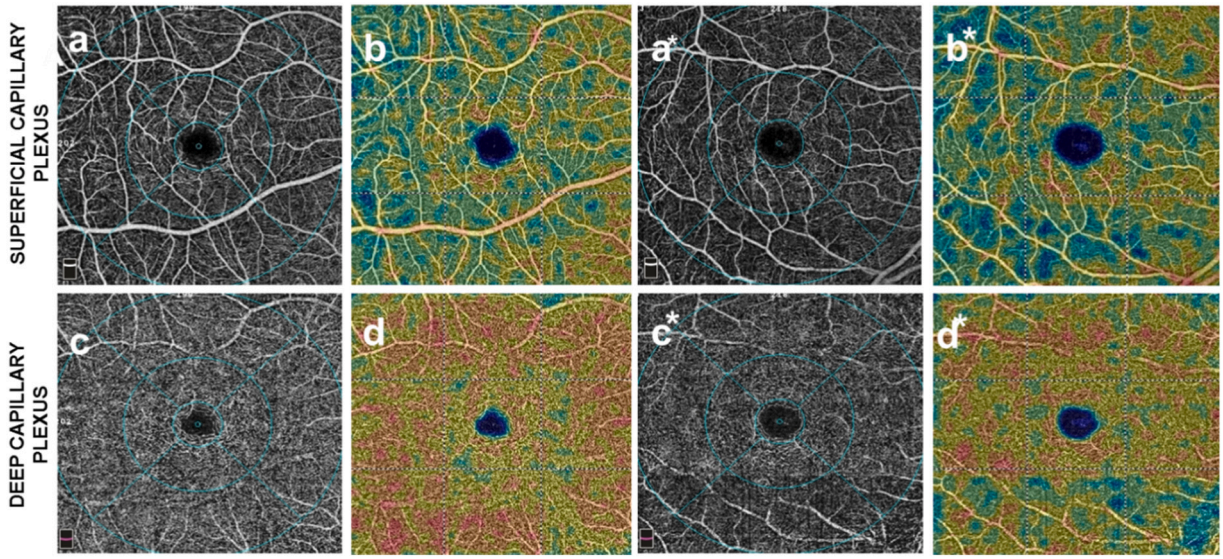

Fig. 1. En face OCTA 6 × 6-mm macular VD scans of the right eye of a prolactinoma patient without chiasmal compression, compressive ON and/or VFDs (SCP row: a, b; DCP row: c, d), and a healthy individual (SCP row: å, ƀ; DCP: č, đ). Although there was no discernible difference between the two groups in terms of SCP VDs, almost all retinal morphological parameters in DCP VDs were significantly different, with prolactinoma patients having markedly increased VDs. The Quality Index for all images was 9/10.

Table 2
The OCTA results for each study group in terms of macular plexus vessel density, foveal avascular zone and capillary flow parameters.

Parameters		Group 1 (N = 32) (mean ± SD)	Group 2 (N = 30) (mean ± SD)	p value[†]
VD parameters (%)				
Superficial	Whole	52.87 ± 3.25	51.23 ± 4.29	0.118
	Foveal	22.70 ± 6.81	22.24 ± 8.19	0.816
	Parafoveal	54.90 ± 3.60	53.55 ± 5.18	0.255
	Perifoveal	53.29 ± 3.40	51.49 ± 4.35	0.085
Deep	Whole	60.59 ± 3.80	54.46 ± 7.74	**0.001**
	Foveal	42.11 ± 7.31	39.35 ± 9.24	0.215
	Parafoveal	60.69 ± 4.49	57.37 ± 5.98	**0.021**
	Perifoveal	62.25 ± 3.90	56.20 ± 7.81	**0.001**
FAZ parameters				
FAZ area (mm^2)		0.27 ± 0.90	0.28 ± 0.11	0.715
FAZ perimeter (mm)		1.99 ± 0.36	2.05 ± 0.43	0.638
FD-300 (%)		57.21 ± 3.72	55.50 ± 6.62	0.234
Capillary flow parameters				
Outer retinal flow		27.77 ± 0.23	27.71 ± 0.60	0.224
Outer retinal flow area (mm^2)		8.66 ± 1.01	9.33 ± 2.51	0.192
Choriocapillaris flow		27.74 ± 0.24	27.71 ± 0.60	0.567
Choriocapillaris flow area (mm^2)		19.67 ± 0.68	19.28 ± 1.01	0.091

Group 1: Prolactinoma patients; *Group 2:* Healthy subjects; *SD:* Standard deviation; *VD:* Vessel density; *SCP:* Superficial capillary plexus; *DCP:* Deep capillary plexus; *FAZ:* Foveal avascular zone; *FD-300:* Foveal VD in 300 μm-wide region around FAZ; [†]Independent t-test results; Bold values are statistically significant values ($p < 0.05$); *N:* Number of participants.

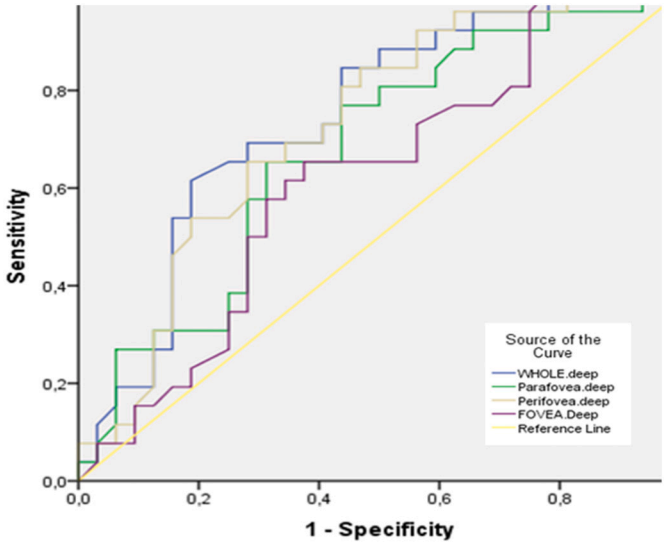

Fig. 2. ROC analysis of the OCTA deep retinal layer, including whole, parafoveal, perifoveal, and foveal regions (P = 0.001, P = 0.021, P = 0.003, and p = 0.125) respectively.

patients without chiasmal compression, compressive ON and/or VFDs. Despite the fact that the two groups were of approximately similar age (p = 0.537) and gender distribution (p = 0.385), our study found statistically significant differences in VDs, especially in DCP, including deep whole (p = 0.001), parafoveal (p = 0.021), and perifoveal (p = 0.001) regions, as well as in OD nasal quadrant (p = 0.006). Overall, we found that prolactinoma patients had increased VDs in almost all parameters as compared to healthy subjects. We also found that peripapillary RNFL of prolactinoma patients in superior and temporal quadrants was thicker than that of healthy subjects, although the difference was not significant (Table 3). Only peripapillary RNFL thickness in nasal and inferior quadrants was statistically significantly thinner in prolactinoma patients relative to healthy subjects (p = 0.010 and 0.007, respectively). Furthermore, while FAZ and flow parameters differed between prolactinoma patients and healthy subjects, the differences were not statistically significant. These outcomes suggest, generally, that anterior visual pathway injury may occur well before clinically observable ocular findings. Even if there is no compressive impact on the MRI chiasma, the presence of pituitary tumor such as prolactinoma may induce severe structural changes in GCC and circumpapillary RNFL thicknesses [28]. In this regard, OCTA offers new knowledge, including the ability to quantify OD RNFL thickness and retinal VD status. Even in prolactinoma patients without chiasmal compression, as seen in our study, this technique may reveal variations in the thicknesses of both retinal and OD microvasculature, which may suggest flow variation due to ganglion cell dysfunction or loss. Our results revealed a wide range of

Table 3
The OCTA results for each study group in terms of optic disc parameters.

Parameters			Group 1 (N = 32) (mean ± SD)	Group 2 (N = 30) (mean ± SD)	p value†
Vessel density (%)	Whole		49.28 ± 3.27	47.80 ± 3.36	0.263
	Peripapillary	Superficial	51.40 ± 3.38	50.23 ± 3.23	0.383
		Deep	51.74 ± 4.39	54.70 ± 9.11	0.190
	Quadrants	Superior	51.48 ± 4.55	50.56 ± 4.09	0.383
		Temporal	52.61 ± 5.21	51.72 ± 13.70	0.418
		Nasal	46.06 ± 3.27	48.31 ± 3.21	**0.006**
		Inferior	52.58 ± 3.60	51.61 ± 3.43	0.264
Retinal nerve fiber layer thickness (μm)	Global		111.61 ± 15.08	110.06 ± 6.87	0.699
	Peripapillary quadrants	Superior	129.79 ± 19.76	126.64 ± 15.65	0.533
		Temporal	81.41 ± 6.55	74.31 ± 8.96	**0.001**
		Nasal	92.21 ± 4.15	99.15 ± 15.92	**0.010**
		Inferior	133.79 ± 20.06	148 ± 82 ± 18.76	**0.007**

Group 1: Prolactinoma patients; *Group 2:* Healthy subjects; *SD:* Standard deviation; †Independent t-test results; Bold values are statistically significant values ($p < 0.05$); *N:* Number of participants.

microvascular changes in prolactinoma patients without chiasmal compression, which could be clarified by a wide variation in tumor size at diagnosis (4.5–27.0 mm).

Pituitary macroadenomas, unlike microadenomas, are often associated with VFDs. Bitemporal hemianopsia is caused by chiasmal compression, which affects crossed nerve fibers that serve the nasal hemiretina. Damage induced by visual pathway lesions to the axons of retinal ganglion cells, which form RNFL, is apparent on fundus ophthalmoscopy but can also be determined by OCT via RNFL thickness. Axonal damage and dysfunction, as well as ganglion cell apoptosis, may appear once the optic chiasm is directly compressed, which was not the case in our study, or an inherent change in the microcirculatory system caused by sellar tumors like prolactinoma, [6,29,30] leading to changes in RNFL and GCC thicknesses [31–33]. One study found that a PA without VFD did not cause RNFL changes [33]. On the other hand, improvements in retinal microstructures have been related to visual function recovery in PA with chiasmal compression [32]. Other studies have reported thinner RNFL in patients with chiasmal compression than healthy subjects [4,5]. Acromegaly with macroadenomas has also been linked to a reduced RNFL thickness in the OD inferior quadrant, [34] possibly due to chiasmal compression [4,5]. Additionally, RNFL, GCL, IPL, INL, ONL, and retinal pigment epithelium were all thinner in prolactinoma patients without VFD, based on the Ogmen et al., study [29]. The discrepancy between our findings and those of earlier studies could be ascribed to the fact that our study focused at only prolactinoma patients without chiasmal compression, and was conducted in a cross-sectional design. Due to the fact that OCTA measures capillary flow, one aspect of VD change in the retinal vascular plexuses may be transient, owing to transient neuronal dysfunction [35]. It appears that changes in VD are related to changes in cellular activity, which happen preceding cellular death, emphasizing the significance of OCTA analysis.

Biochemically, prolactinoma patients exhibit thrombotic and pro-inflammatory plasma alterations, along with microvascular dysfunction, denoting a proatherothrombotic condition [36]. Furthermore, prolactin may induce vasoconstriction by blocking a vasodilatory beta-2 adrenergic receptor-mediated effect. Elevated prolactin levels have been shown to be harmful to the endothelial cell wall, which contains prolactin receptors. In addition to facilitating both angiogenesis and vasoconstriction [37], prolactin has been shown to induce an inflammatory reaction in vitro. Indeed, all of these actions, as well as microcirculatory disturbances, contribute to the development of atherothrombosis [38]. Prolactin exposure over time may also alter the vascular smooth muscle cell layer by facilitating smooth muscle cell proliferation [39]. Contractile activation in vascular smooth muscle cells is a major determinant of changes in arteriole vascular diameter. Given the potential connection between decreased microcirculatory flow and endothelial dysfunction, prolactin-induced vasoconstriction could result in significant changes in vessel density as well as microvascular flow parameters,

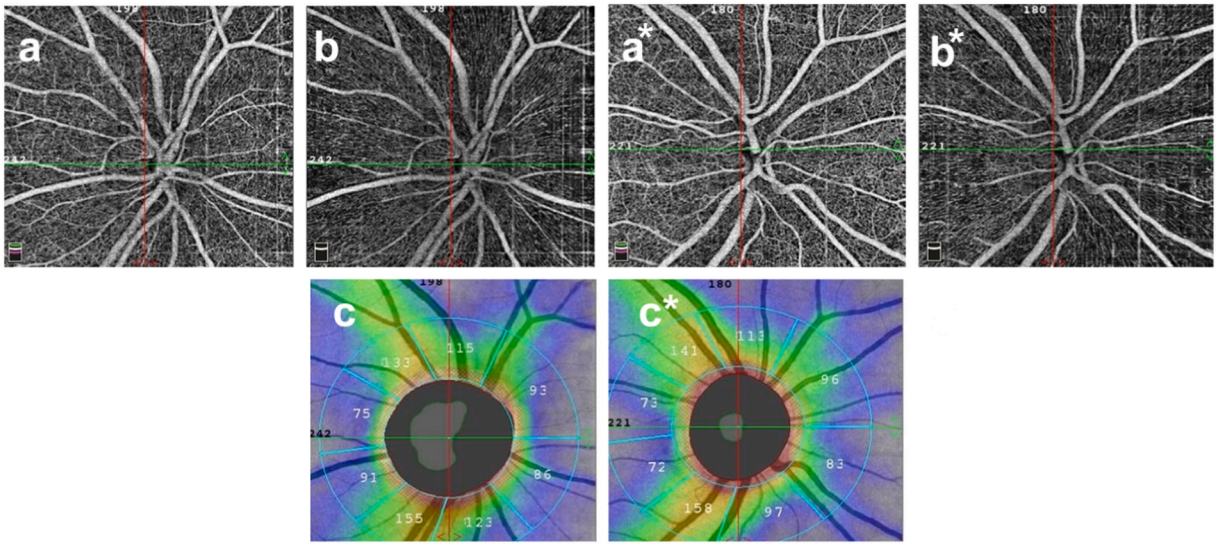

Fig. 3. The OD OCTA images of the right eye of a prolactinoma patient without chiasmal compression, compressive ON and/or VFDs (a, b, c, d) and a healthy individual (a*, b*, c*, d*) displaying a vitreous/retina segmentation (above OPL) (a, a*), a radial peripapillary capillaries segmentation (b, b*) as well as the corresponding RNFL thickness map (c, c*) Warmer colors denote greater thickness. There are apparent differences between the two groups in terms of peripapillary RNFL thickness, particularly in the temporal, and nasal quadrants, where a prolactinoma patient appears to have thicker RNFL. The Quality Index for all images was 9/10.

as revealed in our OCTA study.

Moreover, the retina may be affected by dopamine. Reduced retinal dopamine levels and impairment of retinal dopaminergic functions have been associated with Parkinson's disease [40]. When patients with Parkinson's disease were given a dopamine agonist, their RNFL was found to be lower than when they were given levodopa, which has a protective effect on RNFL [41]. Secondary delayed VFD has been identified after beginning prolactinoma therapy with cabergoline. This may be due to the dopamine agent's toxic impacts, which contributes to a reversible fibrosis or ischemia [42,43]. Our cross-sectional OCTA study, however, showed different findings in most of the retinal and OD morphological parameters, with a propensity of increased thickness in most of these parameters relative to healthy subjects. We used OCTA to measure retinal and OD morphological changes only once, during which the average tumor size at diagnosis was 9.235.46 mm. Over the course of 6.67 ± 3.76 months, an average cabergoline dosage of 0.81 ± 0.54 mg/week was related to a substantial reduction in serum prolactin, which fell from 71.93 ± 14.81 ng/ml to 17.12 ± 7.36 ng/ml. Long-term prospective studies with a larger study population may be necessary to fully comprehend the effects of cabergoline therapy in prolactinoma, especially on the fate of the ocular posterior segment microvascular system.

We also conducted correlation analyses between different OCTA parameters and patient demographics. Tumor size was significantly negatively correlated to DCP VD parameters, particularly in the foveal region ($r = -0.304$, $p = 0.035$). Serum prolactin levels were found to be negatively correlated with a number of SCP VD parameters before therapy, including whole ($r = -0.390$, $p = 0.036$), parafoveal ($r = -0.396$, $p = 0.035$), and perifoveal ($r = -0.390$, $p = 0.040$) regions. Tumor size was negatively correlated with choriocapillaris flow ($r = -0.511$, $p = 0.008$). Furthermore, peripapillary RNFL thickness in the superior ($r = -0.437$, $p = 0.014$) and nasal ($r = -0.372$, $p = 0.040$) quadrants was negatively correlated with tumor size. While global OD RNFL thickness was significantly positively correlated with peripapillary superficial VDs ($r = 0.721$, $p < 0.001$), global OD RNFL thickness ($r = -0.401$, $p = 0.025$), as well as superior ($r = -0.437$, $p = 0.014$), and nasal quadrants ($r = -0.372$, $p = 0.040$), were all found to be negatively related to tumor size at diagnosis. Overall, these findings suggest that prolactinoma could have an impact on not only the optic nerve and peripapillary area, but also the ocular deep capillary blood microcirculation. This condition may occur even if there is no obvious tumor compression, which is frequently characterized by prominent visual symptoms as a result of optic chiasm, optic nerve, or optic tract compression. As a result, measuring microvascular VDs with OCTA may aid in better understanding the pathological processes underlying prolactinoma-related morphological changes in the ocular microvasculature.

We acknowledge the drawbacks of our study. This study's cross-sectional design has restricted our ability to explore processes related to potential long-term interaction between prolactinoma and morphological changes of the ocular microvasculature, including retina as well as optic nerve head and peripapillary area. All patients had no manifestations of tumor compression as verified by crania MRI prior to study inclusion. We were unable to elaborate on the predictive value of VD in disease progression. Prolactinoma patients who did not receive cabergoline therapy and/or those with ON were not also analyzed. A limited sample size of participants in our study prevented further subgroup analysis, including for patients with compressive ON diagnosed with different disease severity. Since our study data came from a single center and only included participants of Turkish ethnicity, some of our findings may not be applicable to other ethnic groups. Further prospective and systematic OCTA studies are needed to better understand the pathophysiology and long-term effects of prolactinoma on microvascular changes, particular in the ocular posterior segment before and after therapy.

Nonetheless, we fervently believe that our study offers the first quantitative description of microvascular changes in prolactinoma patients without noticeable optical chiasmal compression compared to healthy subjects using OCTA automated software. An ophthalmologist's pretreatment evaluation of prolactinoma patients is recommended not only to determine patients with asymptomatic VFDs. Also, to offer knowledge on the recovery of clinical characteristics such as RNFL thickness reduction or retinal ganglion cell loss [44].

5. Conclusions

Prolactinoma patients had significant microvascular morphological changes, particularly in the deep retinal layer and OD RNFL thickness. Non-manifested circumpapillary and even intra-retinal microvascular changes could be detected with OCTA even if there were no obvious signs of prolactinoma-related ocular complications induced by chiasmal compression. Our results may not be sufficient enough to clearly indicate that OCTA be used in the routine diagnosis and follow-up of prolactinoma patients. They may, however, aid in understanding of the ocular posterior segment's microvasculature status by demonstrating substantial morphological changes in retinal and peripapillary VDs, as well as OD RNFL thickness. As structural OCT and OCTA data are combined, it may be possible to gain a better understanding of the prolactinoma patient's condition, and as a result, a more reliable and comprehensive approach for early detection of prolactinoma-related ocular complications. Despite this, prospective comparative studies with greater population and a longer follow-up period would be necessary to demonstrate the value of integrating OCTA into clinical practice of these particular endocrinology patients.

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Financial interest

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Ethics approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Consent to participate

Informed consent was obtained from all individual participants included in the study.

Consent for publication

The authors note that human study participants have given informed consent to the release of the images.

CRediT authorship contribution statement

Muberra AKDOGAN: Conceptualization, Methodology, Formal analysis, Investigation, Writing-Original Draft, Writing-Review & Editing, Visualization, Project administrator; **Mustafa DOGAN:** Conceptualization, Methodology, Writing-Review & Editing, Project administrator; **Selvihan BEYSEL**: Methodology, Formal analysis, Visualization; **Hamidu Hamisi GOBEKA:** Conceptualization, Methodology,

Formal analysis, Investigation, Writing-Original Draft, Writing-Review & Editing, Visualization; Project administrator; **Mehmet Cem SABANER**: Methodology, Investigation, Formal analysis, Visualization; **Merve ORAN**: Methodology, Investigation, Formal analysis, Visualization.

Declaration of competing interest

The authors claim no conflict of interest.

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