

## Assessing OCTA changes in morphology and structure of retinal microvascular bed in patients with exudative AMD

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**Background:** Optical coherence tomography angiography (OCTA) enables measuring characteristics of the retinal microvascular bed such as vascular plexus density and foveal avascular zone (FAZ) area.

**Purpose:** To assess the OCTA changes in morphology and structural characteristics of the retinal microvascular bed in patients with exudative age-related macular degeneration (AMD).

**Materials and Methods:** Forty seven patients with exudative AMD (51 eyes) and 13 healthy controls (22 eyes) were included in the study. OCTA was used to measure superficial plexus FAZ area (SPFA), deep plexus FAZ area (DPFA), vessel density and retinal thickness. Patients were divided into three groups based on the ratio of SPFA to DPFA: Group 1 (SPFA/DPFA < 0.6; 15 eyes), Group 2 (0.6 ≤ SPFA/DPFA < 0.8; 17 eyes), and Group 3 (SPFA/DPFA ≥ 0.8; 19 eyes).

**Results:** Deep plexus FAZ area in all groups of patients was increased and superficial plexus FAZ area in Group 3 was significantly increased compared to controls. Patients in Group 1 exhibited mostly apparent signs of retinal edema and minimal alterations in the retinal microvascular bed. Patients in Group 2 had greater retinal thickness, but moderately lower plexus vessel density compared to controls. Patients in Group 3 had substantially lower superficial plexus vessel density and insubstantially altered retinal thickness compared to controls.

**Conclusion:** OCTA enables assessing the changes in morphology and structure of the retinal microvascular bed, measuring FAZ area and vessel density in patients with exudative AMD.

### Keywords:

optical coherence tomography angiography, age-related macular degeneration, foveal avascular zone, vessel density

### Introduction

Age-related macular degeneration (AMD) complicated by choroidal neovascularization is a major cause of central vision loss in the elderly [1]. Fluorescence angiography (FA), indocyanine green angiography and optical coherence tomography (OCT) are the most common imaging techniques used in multimodal imaging of this disorder [2]. The advent of OCT and, in particular, OCT angiography (OCTA), has created new opportunities for investigating pathological retinal changes in posterior eye disorders, in particular, wet AMD. OCTA is a relatively new non invasive, dyeless technology that is now routinely and very widely used by ophthalmologists for 3D imaging of the retina and choroidal microcirculation [3]. The method uses variations in the phase and intensity of backscattered light to detect moving red blood cells in the retinal tissue [4]. OCT angiograms are co-registered with OCT B scans that are obtained concurrently, which allows for comprehensive assessment of functional as well as morphological changes in the retina [5]. OCTA studies have confirmed the complex structure of the retinal capillary bed which incorporates both superficial and deep vascular plexuses [6, 7]. Because each plexus has a specific

function, performing separate analyses of each plexus will contribute to knowledge on the pathophysiology of retinal disease [8]. OCTA enables not only detailed visualization of the retinal microvascular bed, but also allows obtaining measurements of characteristics of this bed. The most practically significant and commonly used characteristics are retinal plexus density and area of the foveal avascular zone (FAZ) [6, 9]. To the best of our knowledge, there have been no reports on studies of the changes in FAZ area and retinal plexus density in wet AMD.

The FAZ is an avascular zone located in the central macula (also known as fovea), and its dimensions vary among healthy individuals [10, 11]. In addition, in a retinal disease, the FAZ may undergo changes or deformation, which may be associated with visual acuity loss [12, 13, 14, 15]. Although increased FAZ area has been found in diabetic retinopathy and central retinal vein occlusion, a wide variation in FAZ area among normal eyes is still a substantial barrier for using this characteristic in a routine

clinical practice as diagnostic criterion for retinal disease [16]. In a particular patient, the FAZ area, therefore, not always can be categorized as definitely normal or pathologically increased. Given the above and reports that in eyes of healthy individuals, FAZ area was significantly larger in the deep plexus ( $P < 0.0001$ ) compared with superficial plexus [10], we decided to determine ratio of superficial plexus FAZ area to deep plexus FAZ area, and to investigate the morphometrics and retinal microvascular bed structure characteristics in wet AMD patients with various ratio values.

**The purpose** of this study was to assess the OCTA changes in morphology and characteristics of the retinal microvascular bed in patients with exudative AMD.

### Materials and Methods

Forty seven patients (27 women and 20 men; 51 eyes) with a first-diagnosed exudative AMD accompanied by active choroidal neovascularization were included in the study. Patient mean age was  $71.3 \pm 10.05$  years (range, 43 – 91). Inclusion criteria were untreated subretinal neovascularization in the presence of wet AMD. Exclusion criteria were other retinal disease that may influence the significance of study results, retinal angiomatous proliferation (type 3) or polypoidal choroidal vasculopathy. The study group included patients with subfoveal choroidal neovascularization (CNV) lesions (classical CNV, type 1, 22 eyes; subclinical CNV, type 2, 16 eyes, and mixed CNV, type 4, 16 eyes).

OCT- and OCTA-based morphologic criteria of lesion activity in neovascular AMD [17] were used. Cystoid macular edema, serous neuroepithelial and/or RPE detachment, and subretinal hemorrhage, in the presence of signs of subretinal neovascular membrane (SNM; presence of a focus of increased reflectivity above or below the RPE and/or dome-shaped RPE detachment with a region of non-uniform reflectivity underneath the RPE) were considered OCT evidence of active SNM. Presence of secondary vascular branching, numerous thin dense capillaries with frequent anastomoses, vessel loops and peripheral arcades were considered angiographic evidence of active SNM [17]. The control group involved 13 age- and gender-matched controls (22 eyes; 9 women and 7 men; mean age,  $66.1 \pm 7.6$  years (range, 55 – 77)). Inclusion criteria for the controls were age older than 55 years, best-corrected visual acuity  $\geq 1.0$  and absence of ocular disease. Informed consent was obtained from all participants. The study protocol was approved by the local ethics committee. Each patient underwent eye examination including visual acuity, perimetry, tonometry, biomicroscopy and ophthalmoscopy. In addition, the AngioVue OCT-A system (RTVue XR OCT Avanti, Optovue, Inc., Fremont, CA) was used for split-spectrum amplitude-decorrelation angiography (SSADA) measurements with OCT. Eyes were examined with dilated pupils (tropicamide 1%) to enhance readability of scanned images. Poor OCTA images, which were defined as those with a signal strength index (SSI) less than 50

due to motion artifacts or media opacity were excluded from the analysis [18]. Quantitative analysis of retinal microvascular bed characteristics (vascular plexus density and FAZ area) was performed using AngioRetina mode ( $6 \times 6$ -mm scans), software AngioAnalytics (Optovue). OCTA-based assessment of morphometric characteristics and characteristics of the retinal microvascular bed state (superficial plexus FAZ area (SPFA), and deep plexus FAZ area (DPFA), vessel density and retinal thickness) was performed. Calculation of FAZ area was performed on the superficial retinal OCTA slab (or the deep retina slab) and using the non-flow function of the imaging software. Calculation of vessel density and retinal thickness within a  $300\mu\text{m}$  width perimeter surrounding the FAZ was performed using the density option. The parafoveal zone was divided into four sectors (temporal, superior, nasal and inferior). Patients were divided into three groups based on the ratio of SPFA to DPFA: Group 1 (SPFA/DPFA  $< 0.6$ ; 15 eyes), Group 2 ( $0.6 \leq \text{SPFA/DPFA} < 0.8$ ; 17 eyes), and Group 3 (SPFA/DPFA  $\geq 0.8$ ; 19 eyes). The ratio among the 22 control eyes varied from 0.7 to 1.0.

Statistical analyses were conducted using Statistica 10.0 (StatSoft, Tulsa, OK, USA) software. The Student t test was used to assess statistical significance. The level of significance  $p \leq 0.05$  was assumed. Data are presented as mean  $\pm$  standard deviation (SD).

### Results

We investigated changes in BCVA, superficial plexus FAZ area, deep plexus FAZ area, superficial plexus vessel density and retinal thickness with changes in the ratio of superficial plexus FAZ area to deep plexus FAZ area. We found no significant difference ( $p > 0.05$ ) in any of the parameters studied among eyes with different types of CNV.

The mean BCVA in groups 1, 2 and 3 was  $0.37 \pm 0.26$ ,  $0.29 \pm 0.28$  and  $0.27 \pm 0.21$ , respectively, with no significant difference among the groups. The superficial plexus FAZ area was found to be significantly larger only in Group 3 compared to controls ( $0.661 \pm 0.43 \text{ mm}^2$  vs  $0.318 \pm 0.105 \text{ mm}^2$ , respectively,  $p < 0.01$ ), whereas the deep plexus FAZ area was found to be significantly larger in Groups 1, 2 and 3 ( $0.723 \pm 0.46 \text{ mm}^2$ ,  $0.527 \pm 0.139 \text{ mm}^2$ , and  $0.649 \pm 0.375 \text{ mm}^2$ , respectively) compared to controls ( $0.373 \pm 0.118 \text{ mm}^2$ ,  $p < 0.01$  for each comparison). There was no significant difference in superficial plexus FAZ area in Groups 1 and 2 compared to controls ( $0.295 \pm 0.125 \text{ mm}^2$ ,  $0.374 \pm 0.104 \text{ mm}^2$  and  $0.291 \pm 0.105 \text{ mm}^2$ , respectively,  $p > 0.05$ ) (Fig. 1). Therefore, in Group 1, only the deep plexus FAZ area was larger than in controls. In addition, in Group 2, the superficial plexus FAZ area was moderately larger and the deep plexus FAZ area was larger than in controls. Moreover, in Group 3, both the superficial plexus FAZ area and deep plexus FAZ area were substantially larger than in controls (Figs. 2, 3, 4).

Our findings with regard to superficial plexus vessel density are presented in Table 1.

No significant difference ( $p > 0.05$ ) in foveal vessel density was seen between any group of patients and controls. The mean parafoveal vessel density in groups 1, 2 and 3 was  $50.2 \pm 4.3\%$ ,  $48.5 \pm 4.8\%$ , and  $45.4 \pm 5.3\%$ , respectively, which was 5.4% ( $p < 0.05$ ), 8.6% and 14.4% (both  $p < 0.01$ ), respectively, less compared to controls ( $53.04 \pm 2.37\%$ ). In groups 2 and 3, the mean parafoveal vessel density in each of the four sectors was significantly less than in controls ( $p < 0.05$  and  $p < 0.01$ , respectively).

In group 1, the mean parafoveal vessel density in the temporal and inferior sectors (up to  $50.19 \pm 4.98\%$  and  $49.32 \pm 4.93\%$ , respectively), but not in the nasal and superior sectors, was significantly less than in controls ( $53.58 \pm 3.86\%$  and  $52.61 \pm 4.26\%$ , respectively,  $p < 0.05$ ), indicating insubstantial retinal microvascular bed alterations in this group, likely due to the age of patients.

Our findings with regard to retinal morphometric changes in study groups are presented in Table 2.

Retinal thickness was significantly ( $p < 0.05$ ) increased in Groups 1 and 2 in all thickness measurement zones compared to controls, but there was no significant difference ( $p > 0.05$ ) in retinal thickness for any thickness measurement zone in Group 3 compared to controls. In Groups 1, 2 and 3, total foveal thickness was 52.7%, 39.2%, and 24.8%, respectively, increased, and total parafoveal thickness was 12.9%, 15.9%, and 7.3%, respectively, increased, compared to controls.

It can be concluded from the above that patients in Group 1 exhibited mostly apparent signs of retinal edema and minimal alterations in the retinal microvascular bed. Patients in Group 2 had greater retinal thickness, but moderately lower plexus vessel density compared to controls. Patients in Group 3, as opposed to those in Groups 1 and 2, had substantially lower superficial plexus vessel density and insubstantially altered retinal thickness compared to controls, which should be taken in account when selecting the treatment strategy for these patients.

## Discussion

FA has been traditionally considered the gold standard for diagnosing vascular changes in AMD [1, 2]. FA, but not OCTA, uses dye to assess the permeability of walls of normal or newly formed vessels. However, with the help of OCTA, vascular abnormalities can be identified using an approach based on the assessment of vessel depth and imaging the vessels above or below the RPE. OCTA images are not obscured by leakage from damaged vessels, enabling a more accurate assessment of the borders and area of capillary obstruction and neovascular network. OCT angiograms are co-registered with OCT B scans that are obtained concurrently, which enables visualization of subretinal fluid accumulation at the neovascular membrane, allowing for obtaining the information that is similar to the information on leakage in retinal FA. Another benefit of OCTA is that it enables a separate assessment of abnormalities of different retinal and choroidal plexuses [19]. In addition, OCTA allows for quantitative assessment of retinal blood flow, and measurements of the vessel

density using OCTA showed relatively good repeatability for various retinal diseases [20].

Therefore, OCTA is a dyeless technique that enables accurate software-based assessment and quantification of FAZ area and retinal microvascular bed structure at various levels. The FAZ is an anatomic area of a special interest for clinicians since changes in the metrics related to this area may mirror the onset and progression of retinal disease. It has been reported [10, 21] that, in normal eyes, the superficial plexus FAZ area varied from 0.25 to 0.34 mm<sup>2</sup>, whereas the deep plexus FAZ area varied from 0.37 to 0.48 mm<sup>2</sup>, which is in line with our findings for healthy controls. FAZ area and vessel density have been investigated in various pathological conditions. Thus, increased OCTA measures of FAZ area and decreased OCTA measures of retinal vascular plexus density may reflect retinal pathologies such as diabetic retinopathy or retinal vessel occlusion [13, 14, 22, 23]. In a study by Stavrev et al [24], patients with different stages of dry AMD demonstrated no significant changes in FAZ area compared to healthy controls.

To the best of our knowledge, there have been no studies on the changes in FAZ area and retinal microvascular bed structure in exudative AMD. The results of the current study evidence an increased deep plexus FAZ area in all patients with wet AMD irrespective of changes in the retinal microvascular bed and retinal thickness. In addition, there was a group of patients with a normal superficial plexus FAZ area, marked retinal edema and no decreased plexus density, and a group with an increased superficial plexus FAZ area, decreased microvascular bed capacity and insubstantial retinal edema.

There have been reports on negative correlation between superficial plexus FAZ area and central retinal thickness in normal eyes [10, 20], which was also observed in the control group of the current study ( $r = -0.62$ ;  $p < 0.05$ ). However, no statistically significant correlation was found between FAZ area and retinal thickness in patients with exudative AMD.

## Conclusion

First, OCTA is a contactless and non-invasive technique for examination of retinal microvascular bed structure which enables us to perform quantitative measurements related to the retinal vascular plexus (retinal plexus density and FAZ area).

Second, deep plexus FAZ area was 1.5 to 1.9 times increased compared to controls ( $p < 0.01$ ) in all groups of patients with exudative AMD.

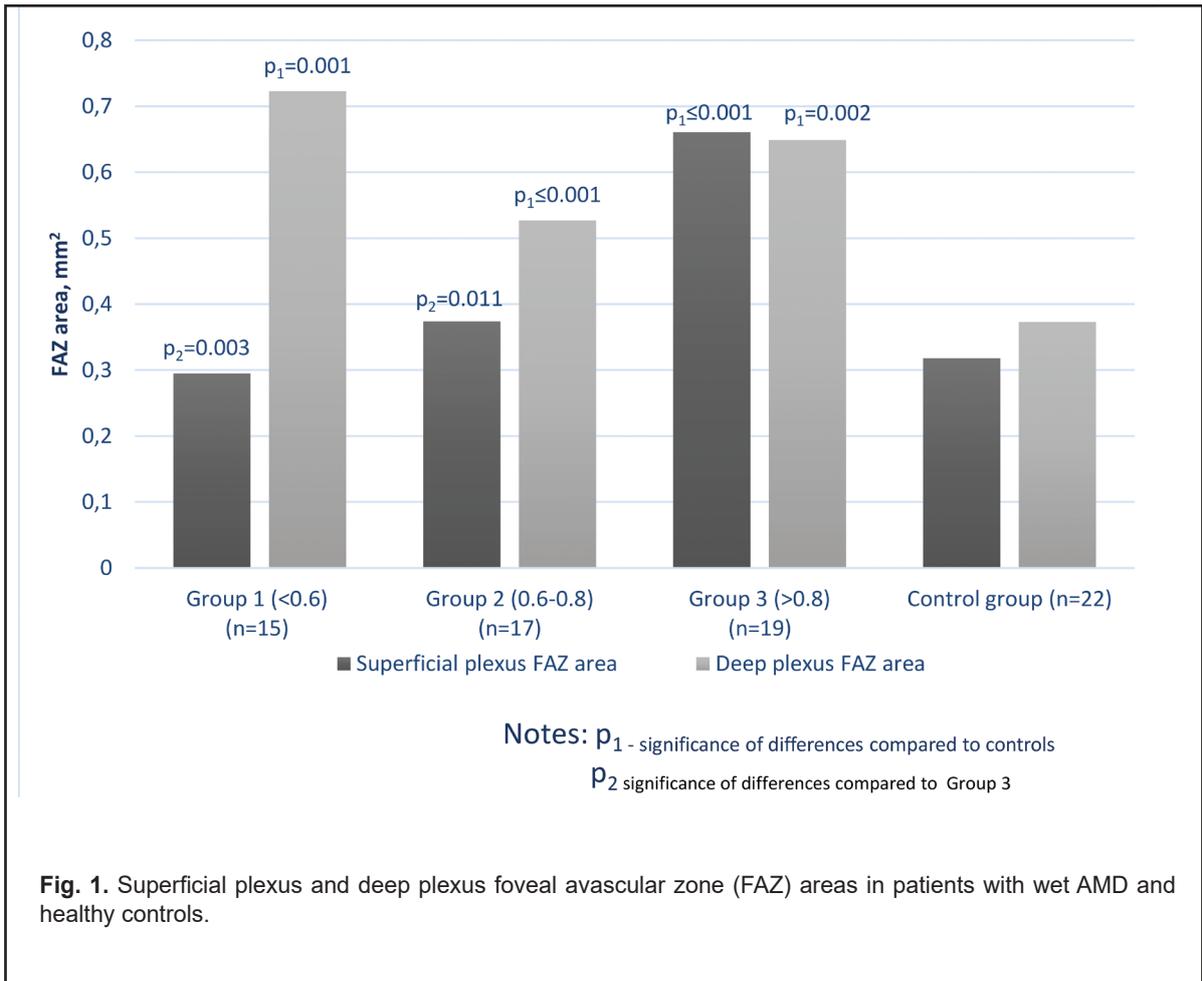
Third, superficial plexus parafoveal vessel density in Group 3 of exudative AMD patients ( $45.4 \pm 5.3\%$ ) was statistically significantly lower than in Group 1 ( $50.2 \pm 4.3\%$ ) and controls ( $53.04 \pm 2.37\%$ ).

Finally, retinal morphological changes in eyes with exudative AMD do not reflect changes in the vascular bed of retinal plexuses. In eyes with the ratio of superficial plexus FAZ area to deep plexus FAZ area (SPFA/DPFA)  $< 0.6$ , retinal thickness was increased, and there were no

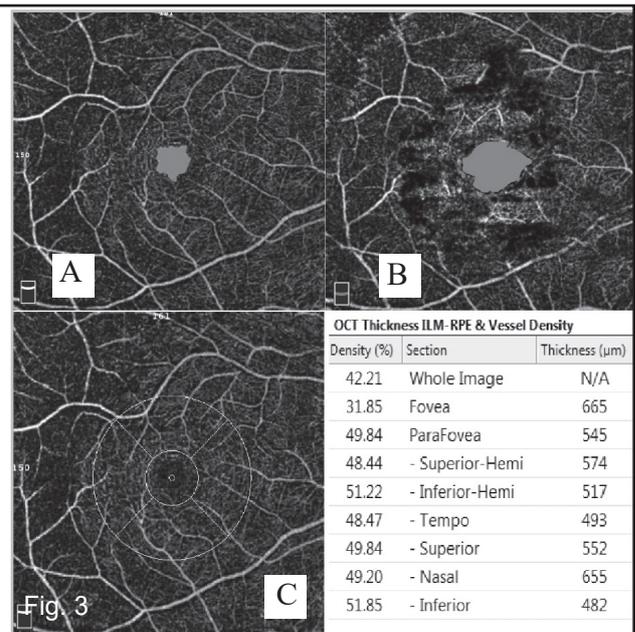
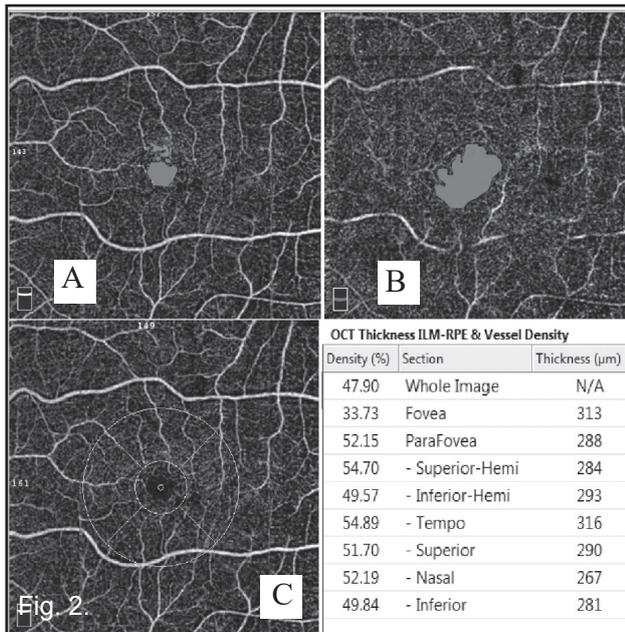
substantial changes in vessel density compared to controls. In eyes with the ratio  $> 0.8$ , there was no significant change in parafoveal thickness ( $343.68 \pm 93.08 \mu\text{m}$ ), but vessel density was decreased compared to controls.

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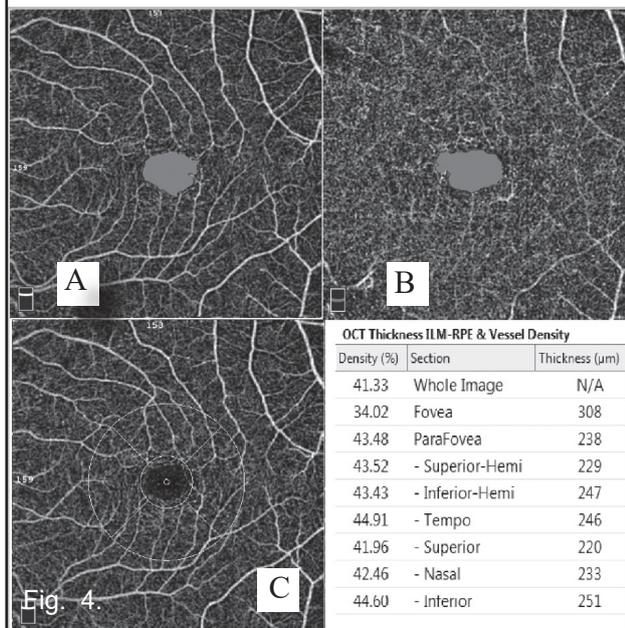


**Fig. 1.** Superficial plexus and deep plexus foveal avascular zone (FAZ) areas in patients with wet AMD and healthy controls.



**Fig. 2.** Group 1 patient N with a BCVA of 0.3. Note normal superficial plexus FAZ area (0.283 mm<sup>2</sup>) (A) and increased deep plexus FAZ area (0.690 mm<sup>2</sup>) (B) (the ratio of these areas is 0.41). The vessel density is within the normal range, whereas the retinal thickness is increased compared to controls (C).

**Fig. 3.** Group 2 patient K with a BCVA of 0.1. Note insubstantially increased superficial plexus FAZ area (0.340 mm<sup>2</sup>) (A) and increased deep plexus FAZ area (0.480 mm<sup>2</sup>) (B) (the ratio of these areas is 0.71). The parafoveal vessel density is decreased, whereas the retinal thickness is significantly increased compared to controls (C).



**Fig. 4.** Group 3 patient P with a BCVA of 0.1. Note increased superficial plexus FAZ area (0.656 mm<sup>2</sup>) (A) and deep plexus FAZ area (0.781 mm<sup>2</sup>) (B) (the ratio of these areas is 0.84). The parafoveal vessel density is decreased in all sectors, whereas the retinal thickness is insubstantially increased compared to controls (C).

**Table 1.** Superficial plexus vessel density in patients with wet AMD and healthy controls

Vessel density (M±SD), (%)	Group 1 (<0.6) (n=15)	Group 2 (0.6-0.8) (n=17)	Group 3 (>0.8) (n=19)	Control group (n=22)
All images	47.02±4.18 p <sub>1</sub> =0.013	45.72±4.28 p <sub>1</sub> ≤0.001	44.56±4.8 p <sub>1</sub> ≤0.001	50.18±3.16
Fovea	33.98±7.3 p <sub>2</sub> =0.031	34.7±17.9	27.7±8.5	31.25±5.45
Parafovea	50.2±4.3 p <sub>1</sub> =0.03 p <sub>2</sub> =0.009	48.5±4.8 p <sub>1</sub> =0.001	45.4±5.3 p <sub>1</sub> ≤0.001	53.04±3.27
Temporal sector	50.19±4.98 p <sub>1</sub> =0.026	49.84±5.01 p <sub>1</sub> =0.012	46.16±6.35 p <sub>1</sub> ≤0.001	53.58±3.86
Superior sector	50.69±3.70 p <sub>2</sub> =0.004	48.08±5.45 p <sub>1</sub> =0.001	45.19±6.08 p <sub>1</sub> ≤0.001	53.3±4.0
Nasal sector	50.46±5.10 p <sub>2</sub> =0.002	47.81±5.93 p <sub>1</sub> =0.003 p <sub>2</sub> =0.049	43.64±6.30 p <sub>1</sub> ≤0.001	52.59±3.6
Inferior sector	49.32±4.93 p <sub>1</sub> =0.037	48.43±6.23 p <sub>1</sub> =0.017	46.82±5.97 p <sub>1</sub> ≤0.001	52.61±4.26

Note. p<sub>1</sub>, significance of differences compared to controls; p<sub>2</sub>, significance of differences compared to Group 3.

**Table 2.** Retinal thickness in patients with wet AMD and healthy controls

Retinal thickness (M±SD), (μm)	Group 1 (<0.6) (n=15)	Group 2 (0.6-0.8) (n=17)	Group 3 (>0.8) (n=19)	Control group (n=22)
Fovea	391.9±135.5 p≤0.001	357.17±134.88 p=0.001	320.36±162.77	256.6±15.66
Parafovea	361.86±81.86 p=0.024	371.41±80.05 p=0.005	343.68±93.08	320.41±10.91
Temporal sector	365.66±108.83 p=0.029	357.29±90.05 p=0.027	336.44±101.36	312.95±9.64
Superior sector	367.53±99.68 p=0.04	361.76±76.33 p=0.021	327.21±116.25	322.09±11.49
Nasal sector	378.33±73.10 p=0.002	384.41±88.58 p=0.004	360.0±114.32	326.55±12.82
Inferior sector	363.06±87.16 p=0.028	382.17±123.95 p=0.025	337.73±88.61	320.27±11.25

Note. p, significance of differences compared to controls.

*The authors certify that they have no conflicts of interest in the subject matter or materials discussed in this manuscript.*