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Normative data assessment of age-related changes in macular and optic nerve head vessel density using optical coherence tomography angiography

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ABSTRACT

Objective: To investigate macular and optic nerve head vessel density in healthy individuals using optical coherence tomography angiography (OCTA), and determine their relationship with age.
Method: This retrospective study included 153 eyes of 153 individuals aged between 20 and 80 years, who had no systemic diseases, optic disk, or retinal pathologies. The retinal (6 × 6 mm) and optic disk (4.5 × 4.5 mm) OCTA images were evaluated for superficial capillary plexus (SCP), deep capillary plexus (DCP) and radial peripapillary capillary plexus (RPCP) vessel density, foveal avascular zone (FAZ) area, and choriocapillaris flow area and compared among 5 age groups.
Results: The SCP vessel density was significantly associated with age for the whole image ($P = 0.001$), parafovea ($P = 0.038$), and perifovea (P/ce:italic>= 0.001). The DCP vessel density significantly varied with age in the whole image ($P = 0.004$), parafovea ($P = 0.001$), and perifovea ($P = 0.002$). The SCP and DCP vessel densities were significantly lower in the older age groups, and more prominently so after 50 years of age. The FAZ area increased with age; however, this finding was not statistically significant ($P = 0.660$). The choriocapillaris flow area decreased with age ($P = 0.002$). The RPCP vessel density in the inside disk significantly decreased with age ($P = 0.038$).
Conclusion: Age should be taken into consideration when using OCTA in the diagnosis and follow-up of retinal and optic nerve diseases. It is believed that the results here in can be used as a reference baseline for future studies.

1. Introduction

Many ocular diseases are associated with vascular pathologies and examining the vascular system is very important in clinical practice [1]. Traditionally, posterior segment microvasculature has been visualized using fundus fluorescein angiography (FFA) and indocyanine green angiography (ICGA). These imaging methods require the intravenous administration of fluorescein or indocyanine green dyes [2].

Optical coherence tomography angiography (OCTA) is a novel imaging method that generates data on the microvascular structure of the eye by measuring and processing the motion contrast of intravascular erythrocytes by sequential optical coherence tomography (OCT) scans of a particular area of the retina [3]. Unlike FFA and ICGA, OCTA is non-contact, non-invasive, and easy to use, and provides a three-dimensional assessment of ocular microcirculation [4].

FFA displays the layers of the retinal vasculature as an overlapped image. On the other hand, OCTA allows the individual visualization of the radial peripapillary capillary network and the superficial and deep capillary plexus. The subsequent possibilities have opened the way for the description and quantification of retinochoroidal vascular diseases, their pathogeneses, and the development and assessment of new treatments [5].

Age is an important determinant of OCTA metrics. Therefore,we aimed to investigate aging-related changes in retinal and peripapillary microcirculation in healthy individuals. OCTA (RTVue XR AngioVue, Optovue, Inc. Fremont, CA) was used to assess the retinal, choroid, and optic nerve head vessel densities in different age groups, with the hypothesis that older age groups will be associated with lower vessel

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densities.

2. Method

2.1. Patient selection

The OCTA images of patients who presented at the NecmettinErbakan University Meram Medical Faculty Hospital Ophthalmology Clinic, between January and November 2019, were retrospectively evaluated.

A total of 250 Asian participants, between 20 and 80 years of age, who had no systemic diseases have enrolled in this study. The best-corrected visual acuity (BCVA), intraocular pressure, biomicroscopic and dilated fundoscopic examination, and OCTA measurements of the participants were reviewed. Of those, 153 participants with BCVA 20/20 and who had no optic disk or retinal pathologieswere included in this study.

The exclusion criteria included a spherical equivalent refractive error that was greater than +4.0D or less than −4.0D, systemic diseases that may affect the retina or visual pathways (diabetes mellitus, hypertension, etc.), any anterior or posterior segment pathology that may affect the OCTA images (advanced cataracts, corneal opacity, vitreous opacity, etc.) and signal strength index of the OCTA images < 7.

The study was granted ethical approval by the NecmettinErbakan University Meram Faculty of Medicine Ethics Committee (no: 2020/2277) and was performed in accordance with the principles of the Declaration of Helsinki.

2.2. Optical coherence tomography angiography

OCTA scans were performed using an RTVue-XR device (Angiovue; Optovue Inc., Fremont, CA, USA). This device uses the split-spectrum amplitude-decorrelation angiography (SSADA) algorithm and operates at a wavelength of 840 nm to acquire 70,000 A-scans per second. A volumetric A-scan image of 340 × 340 A-scan images can be acquired within approximately 3 s. The automated segmentation by the device software (Optovue, Version 2018.1.0.37) obtains en face images of 4 layers, namely the SPC, DPC, outer retinal layer, and choriocapillaris [2] (Fig. 1). Optovue's proprietary Motion Correction Technology (MCT™) reduces motion artifact, while 3D Projection Artifact Technology greatly improves OCTA image quality and ensures accurate measurement and interpretation of OCTA images.

OCTA images use the internal limiting membrane, the outer border of the inner plexiform layer, the outer border of the outer plexiform layer, and Bruch's membrane as reference [6]. Evaluated were 6 × 6 mm macular and 4.5 × 4.5 mm optic disk OCTA images obtained with AngioVue. According to the macular areas described in the Early Treatment Diabetic Retinopathy Study (ETDRS) grid, superficial capillary plexus (SCP) and deep capillary plexus (DCP) vessel densities of the fovea, parafovea, perifovea, and the whole image were measured using the device software. The foveal avascular zone (FAZ) area and choriocapillaris flow area for a fixed circle with a1-mm radius were also measured using the device software. Optic nerve head vessel density was calculated in the 750-μm-wide peripapillary region (Fig. 2). Only images with signal strength and quality of at least 7/10 were included.

2.3. Statistical analysis

Data were analyzed using IBM SPSS Statistics for Windows 20.0 (IBM Corp., Armonk, NY, USA). The demographic and clinical characteristics of the participants were analyzed using descriptive statistics (mean, standard deviation, percentage, etc.). The Kruskal Wallis h test was performed to compare clinical characteristics between the age groups. The independent samples *t*-test and the Mann Whitney U test were used

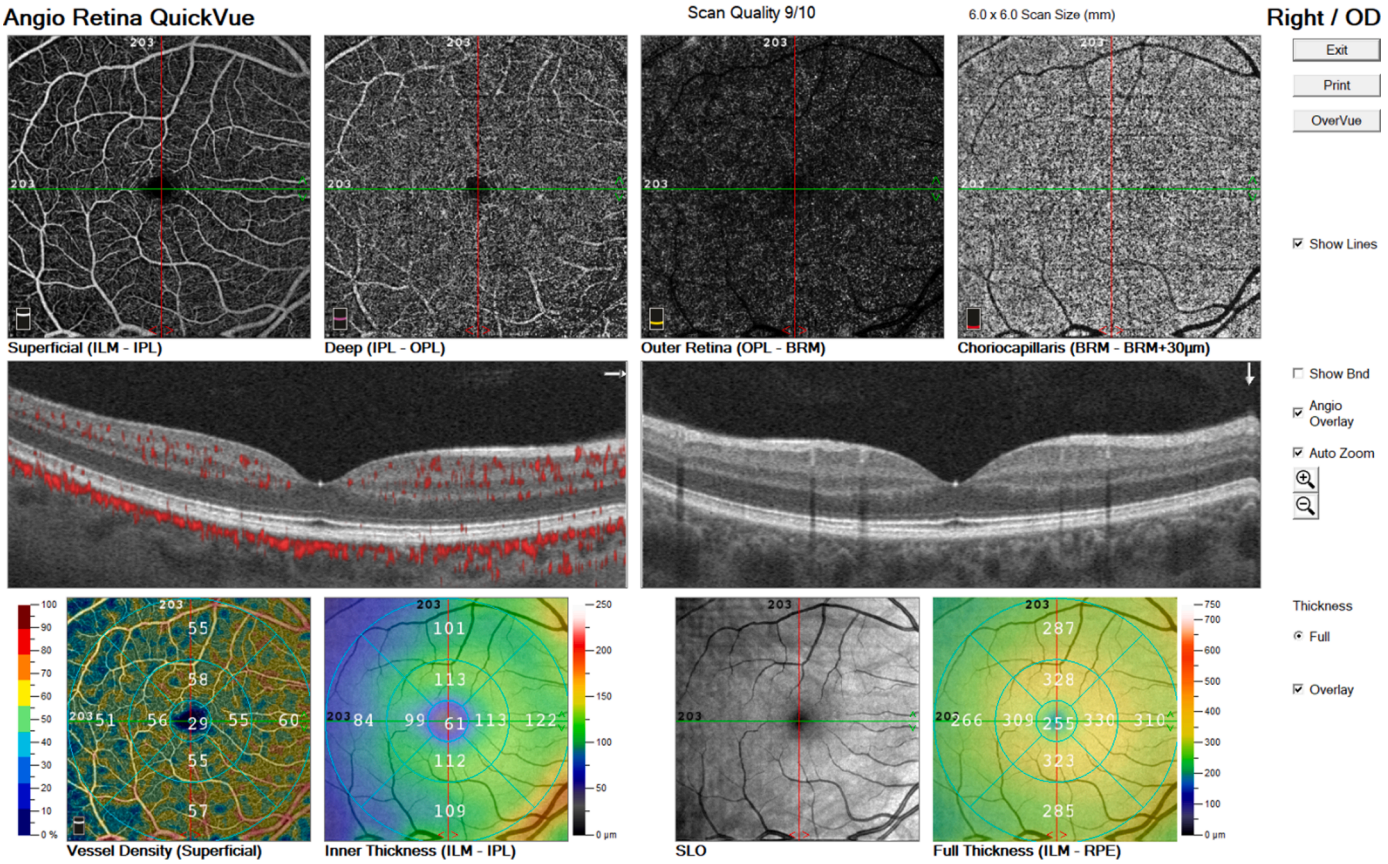

Fig. 1. OCTA images of the superficial and deep capillary plexus, outer retinaand choriocapillaris.

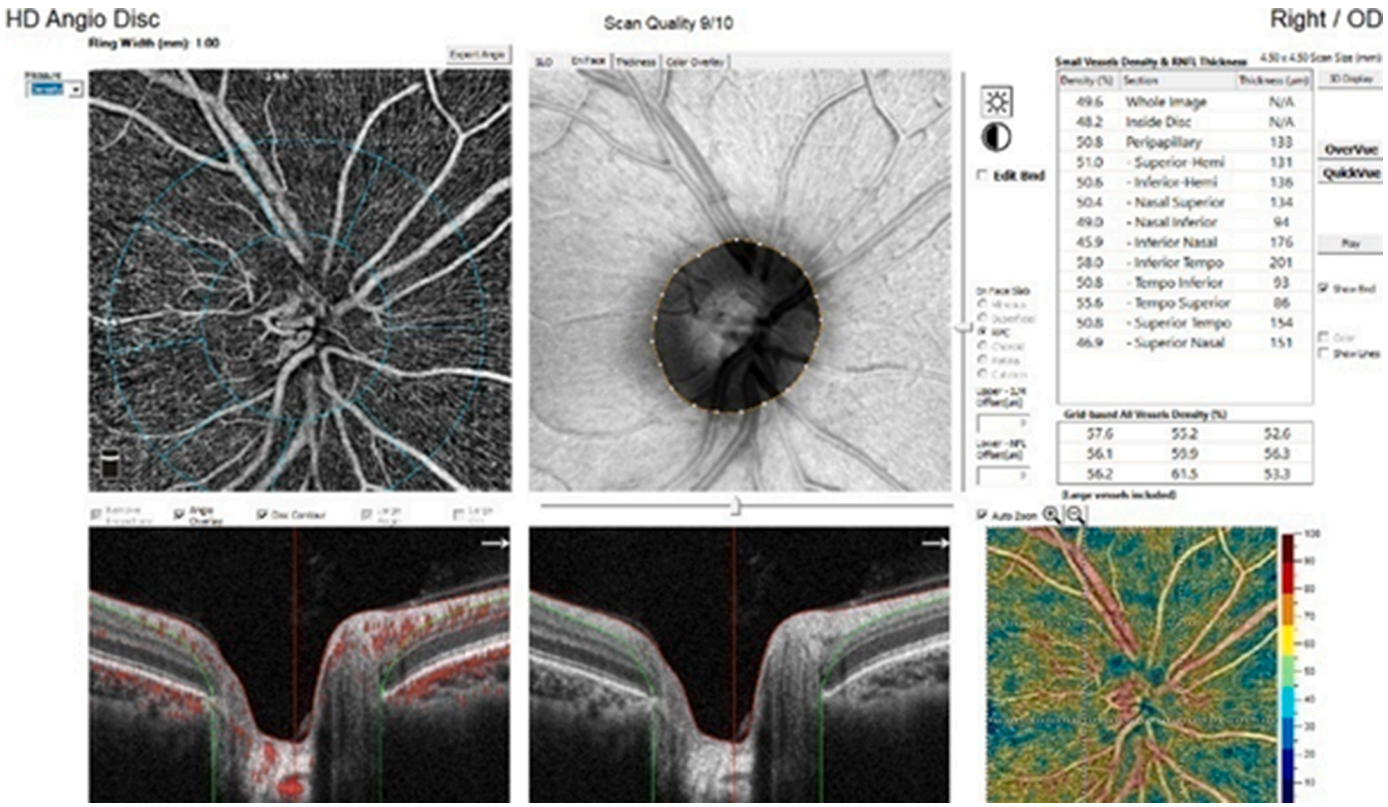

Fig. 2. OCTA images of peripapillary capillary plexus (RPCP).

for the pairwise comparison of the age groups. Chi-square analysis was used to compare the sex ratios between the age groups. $P < 0.05$ was accepted as statistically significant for all of the analyses.

3. Results

The mean age of the 153 participants was 45.14 (±14.11) (range 20–73) years. Moreover, 88 (57.5%) of the participants were female and 65 (42.5%) were male. The participants were divided into 5 groups according to age, comprising 20–29, 30–39, 40–49, 50–59, and 60–80. Table 1 shows the age distribution and gender ratios among different groups.

3.1. Superficial capillary plexus (SCP) vessel density

SCP vessel density increased with age in whole image ($P = 0.001$), superior hemi ($P = 0.005$), inferior hemi ($P < 0.001$), parafovea ($P = 0.038$), and perifovea ($P = 0.001$) readings, and decreased after the age of 50 (Table 2). Particularly, participants who were 60–80 years of age had a significantly lower whole-image and perifoveal SCP vessel densities when compared to those who were20–29, 30–39, 40–49 years of age, andsignificantly lower parafoveal SCP vessel densities when compared to those who were40–49 years of age (Table 2).When we compared the 20–29, 30–39, 40–49 age groups with each other, no statistically significant difference was observed in all areas.

3.2. Deep capillary plexus (DCP) vessel density

DCP vessel density significantly increased with age in whole image ($P = 0.004$), superior hemi ($P = 0.002$), inferior hemi ($P = 0.008$), parafovea ($P = 0.001$), and perifovea ($P = 0.002$) readings, and decreased after the age of 50 (Table 2). Patients who were 60–80years of age had a significantly lower whole-image, parafoveal, and perifoveal DCP vessel densities when compared to those who were 20–29, 40–49, 50–59 years of age (Table 2).When we compared 20–29, 30–39, 40–49 age groups with each other, only the 30–39 age group had significantly lower parafoveal DCP vessel density than the 40–49 age group ($p = 0.005$).

3.3. Foveal avascular zone (FAZ) area and choriocapillaris flow area

FAZ area (mm^2) and choriocapillaris flow area (mm^2) values of age groups were given in Table 4. The mean FAZ area was 0.27 (±0.10) mm^2. The FAZ area changed according to age; however,this finding was not statistically significant ($P = 0.660$). The FAZ area tended to increase with age but decreased in participants who were 60–80 years of age.

For all of the participants, the mean choriocapillaris flow area was measured as 2.08 (±0.13) mm^2. Intergroup comparison revealed that the choriocapillaris flow area significantly changed with age ($P = 0.002$) and decreased after the age of 30 (Table 3). Particularly, there was a significant difference between participants who were 20–29 years of age and the remaining age groups (Table 3).

3.4. Radial peripapillary capillary plexus (RPCP) vessel density

The radial peripapillary capillary plexus (RPCP) vessel density (%) values of age groups are given in Table 6. RPCP vessel density inside the disk significantly decreased with age ($P = 0.038$), starting at the age of 30 (Table 4). The RPCP vessel density in participants who were 60–80 years of age was significantly lower when compared to those who were 20–29 and 40–49 years of age (Table 4).

4. Discussion

OCTA provides high-resolution images of the foveal, parafoveal, and perifoveal microvasculature, including the SCP and DCP, the outer retinal layer, and layers of the choroid through segmentation [7]. OCTA has become widely accepted due to its ability to segment the obtained

Table 1
Average age and sex ratio by age group.

	All 20–80(n = 153)	Age Range 20–29(n = 29)	30–39(n = 28)	40–49(n = 35)	50–59(n = 25)	60–80(n = 36)	
	mean.±SD	mean.±SD	mean.±SD	mean.±SD	mean.±SD	mean.±SD	P
Age(years)	45.14±14.11	24.93±3.27	35.07±3.13	44.46±3.04	54.48±2.14	63.42±3.25	<0.001[a]
Gender (M:F)%	65:88 (42.5:57.5)	7:22 (24.1:75.9)	15:13 (53.6:46.4)	14:21 (40.0:60.0)	8:17 (32.0:68.0)	21:15 (58.3:41.7)	0.035[b]

SD=Standard Deviations, *M*=Male, *F*=Female, *a*=Kruskal Wallis-H Test, b=Chi-Square Analysis.

Table 2
Comparison of SCP and DCP vessel density(%) values among age groups.

		Participants20–80(n = 153)	Group 120–29 (n = 29)	Group 230–39 (n = 28)	Group 340–49 (n = 35)	Group 450–59 (n = 25)	Group 560–80(n = 36)	X2	P
Superficial Capillary Plexus Vessel Density (%)	Whole image	49.79±3.84	50.49±4.20[a]	50.50±2.55[b]	51.30±2.67[c,d]	49.56±3.51[c]	47.38±4.53[a,b,d]	18.24	0.001
	Superior hemi	49.72±3.85	50.45±4.17[a]	50.46±2.53[b]	50.99±2.68[d]	49.68±3.49	47.38±4.71[a,b,d]	14.76	0.005
	Inferior hemi	49.86±3.95	50.53±4.35[a]	50.55±2.67[b]	51.59±2.80[c,d]	49.45±3.66[c]	47.39±4.52[a,b,d]	21.03	<0.001
	Fovea	19.96±6.73	21.05±6.96	20.97±7.77	19.83±6.39	19.14±7.17	19.00±5.81	3.20	0.525
	Parafovea	52.05±4.62	52.38±5.22	52.61±3.00	53.60±3.48[c,d]	51.83±4.22[c]	50.01±5.76[d]	10.16	0.038
	Perifovea	50.48±3.99	51.18±4.30[a]	51.24±2.73[b]	52.03±2.89[d]	50.34±3.59	47.94±4.68[a,b,d]	17.73	0.001
Deep Capillary Plexus Vessel Density (%)	Whole image	50.56±5.52	51.54±5.92[a]	50.87±4.92[b]	52.54±4.76[d]	50.79±5.18[e]	47.44±5.55[a,b,e]	15.67	0.004
	Superior hemi	50.80±5.76	51.83±6.24[a]	51.09±5.24[b]	52.97±4.86[d]	50.98±5.30[e]	47.51±5.72[a,b,e]	16.85	0.002
	Inferior hemi	50.31±5.50	51.25±5.79[a]	50.62±4.83[b]	52.12±4.90[d]	50.58±5.20[e]	47.38±5.64[a,b,e]	13.93	0.008
	Fovea	37.21±7.52	38.68±7.05	38.23±8.41	37.37±7.54	36.19±9.09	35.83±5.86	4.59	0.332
	Parafovea	54.78±4.39	55.91±4.63[a]	53.98±3.96[b]	56.55±3.67[d]	55.23±3.83[e]	52.49±4.61[a,b,e]	18.75	0.001
	Perifovea	51.82±6.01	52.82±6.55[a]	52.19±5.38[b]	53.96±5.32[d]	52.18±5.35[e]	48.41±5.97[a,b,e]	16.92	0.002

[a] Group 1 vs 5 $p < 0.05$.
[b] Group 2 vs 5 $p < 0.05$.
[c] Group 3 vs 4 $p < 0.05$.
[d] Group 3 vs 5 $p < 0.05$.
[e] Group 4 vs 5 $p < 0.05$.
SD=Standard Deviations, X2=Kruskal Wallis-H Test
Pairwise comparisons were made with Independent Groups t-test and Mann Whitney U test.

Table 3
Comparison of FAZ area (mm^2) and choriocapillaris flow area (mm^2) values between age groups.

	Participants20–80(n = 153)	Group 120–29(n = 29)	Group 230–39(n = 28)	Group 340–49(n = 35)	Group 450–59(n = 25)	Group 560–80(n = 36)	X2	P
FAZ area (mm^2)	0.27±0.10	0.25±0.09	0.29±0.12	0.29±0.10	0.29±0.12	0.28±0.08	2.42	0.660
Choriocapillaris flow area (mm^2)	2.08±0.13	2.18±0.15[a,b,c,d]	2.10±0.14[a]	2.05±0.14[b]	2.05±0.12[c]	2.07±0.09[d]	19.95	0.002

[a] Group 1 vs 2 $p < 0.05$.
[b] Group 1 vs 3 $p < 0.05$.
[c] Group 1 vs 4 $p < 0.05$.
[d] Group 1 vs 5 $p < 0.05$.
SD=Standard Deviations, X2=Kruskal Wallis-H Test
Pairwise comparisons were made with Independent Groups t-test and Mann Whitney U test.

images and providethe layer-by-layer visualization of different retinal vascular structures [8]. OCTA was successfully used for the qualitative assessment of diabetic retinopathy, retinal venous or arterial occlusion, choroid neovascularization, and microvascular changes in glaucoma. The AngioVue system provides a quantitative assessment of these microvascular changes [9–12].

To the best of our knowledge, this study is one of the rare studies that assess macular and optic nerve vessels using OCTA in 5 age groups, between 20 and 80 years of age, to develop a normative database, and perform intergroup comparisons to improve retinal and optic nerve diagnostics.

In this study, we showed that the whole-image and perifoveal and parafoveal SCP and DCP vessel densities peaked in participants who were 40–49 years old and significantly decreased after the age of 50. There was a similar decrease in the foveal vessel densities; however, this finding was not statistically significant. Sato et al. examined the OCTA images (3 × 3 mm) of 145 healthy individuals who were 30–74 years of age and reported decreased whole-image and parafoveal SCP and DCP vessel densities after the age of 40 [13]. Coscas et al. analyzed OCTA images (3 × 3 mm) of 135 eyes of individuals who were grouped according to their age as 20–39, 40–59, and ≥60 years of age, and described a negative correlation between vessel density and age. Moreover, they reported decreased whole-image and parafoveal SCP and DCP vessel densities in participants who were 40 years of age or older [14].

In our study, although the vessel densities value peaked in the 40–49

Table 4
Comparison of RPCP vessel density (%) values between age groups.

		Participants20–80 (n = 153)	Group 120–29 (n = 29)	Group 230–39 (n = 28)	Group 340–49(n = 35)	Group 450–59 (n = 25)	Group 560–80 (n = 36)	X2	P
Radial	Whole image	49.87±2.40	50.26±1.98	49.95±1.67	50.62±2.53[d]	49.28±2.85	49.21±2.57[d]	7.13	0.129
Peripapillary	Inside disk	48.97±5.05	50.41±7.31[a]	49.56±4.47	49.46±4.81[d]	48.56±3.73	47.17±3.88[a,d]	10.13	0.038
Capillary	Peripapillary	53.00±2.75	53.01±2.27	53.08±2.12	53.79±2.67	52.54±3.24	52.52±3.21	3.34	0.503
Plexus	Superior hemi	53.18±2.79	52.74±2.46	53.13±2.30	53.91±2.78	53.11±3.05	52.92±3.22	3.48	0.480
Vessel	İnferior hemi	52.79±3.12	53.28±2.62	53.01±2.27	53.64±2.90[d]	51.89±3.84	52.05±3.54[d]	4.74	0.315
Density (%)	Nasalsuperior	50.57±3.61	50.94±3.06	50.07±2.62	51.17±4.19	50.16±3.52	50.41±4.21	5.68	0.224
	Nasalinferior	49.33±4.28	50.06±3.56	49.51±3.39	49.87±3.46	48.25±5.27	48.82±5.30	2.12	0.714
	Temporalinferior	53.01±4.65	53.59±4.20	52.41±3.92[b]	54.94±4.68[b,c,d]	52.18±5.05[c]	51.73±4.81[d]	8.64	0.071
	Temporalsuperior	55.88±3.94	55.37±3.91	56.20±3.26	55.79±3.58	56.48±3.40	55.74±5.12	1.83	0.767

[a] Group 1 vs 5 $p < 0.05$.
[b] Group 2 vs 3 $p < 0.05$.
[c] Group 3 vs 4 $p < 0.05$.
[d] Group 3 vs 5 $p < 0.05$.
SD=Standard Deviations, X2=Kruskal Wallis-H Test
Pairwise comparisons were made with Independent Groups t-test and Mann Whitney U test.

age group, no statistically significant difference was observed between the 20–29 and 30–39 age groups, except for one quadrant. This increased value was considered to be probably coincidental.The discrepancies between the different studies can be ascribed to differences in age and ethnicities across the study populations. These aging-related changes are thought to be the result of the occlusion and atrophy of retinal capillaries [15].

FAZ is a macular zone that features no capillary networks but is surrounded by interconnected capillary networks. The area of the FAZ reflects the status of the microcapillary circulation in the foveal area [16]. In a patient group with a mean age of 41.1 ± 16.46 (range 12–78) years, Shahlaee et al. reported the superficial FAZ area to be 0.27 mm^2 and the deep FAZ area to be 0.34 mm^2 [17].Göker et al. reported that among patients with a mean age of 40.85 ± 15.22 (range 18–68) years, the mean FAZ area in the entire retinal vasculature was 0.28 (±0.11) mm^2 [18]. In the current study, the mean FAZ area in the whole retina was 0.27 (±0.10) mm^2.

The literature presents controversial findings regarding the relationship between the FAZ area and age. Shahlaee et al. and Iafe et al. reported an increased FAZ area in the SCP and DCP with age [17,19]. Coscas et al. showed that the FAZ area in the SCP decreased significantly in people over 60 years of age, but that the change in the DCP was not statistically significant [14]. Falavarjani et al. reported that the FAZ area in the DCP increased with age [20]. On the other hand, Oh et al. did not find any correlation between age and the FAZ area [21]. Herein, likewise, no correlation was found between the FAZ area in the whole retina and age. The FAZ area tended to increase with age but decreased in participants who were 60–80 years ofage. In numerous studies, the measurement of the FAZ area has relied on manual data collection, and the segmentation of the retinal layers may have varied depending on the used devices. The software employed in this study allowed for an evaluation of the FAZ area in the complete retinal vasculature between the inner limiting membrane and the outer plexiform layer.

The choroid is a highly vascularized tissue that supplies oxygen and nutrients to the outer retina [22]. It is difficult to visualize the choriocapillaris using traditional methods. Fluorescein can leak from the choriocapillaris, thus affecting visualization quality. Choroid circulation can be assessed using ICGA; however, it can be difficult to distinguish the choriocapillaris from the large choroidal veins [23,24].

Multiple studies have reported that aging results in decreased choriocapillaris flow and choroid thickness [25,26]. Oh et al. demonstrated that choriocapillaris blood supply and vessel density decrease with aging [21]. In the current study, the mean choriocapillaris flow area was measured as 2.08 mm^2 for a fixed circle with a1-mm radius. It was found that the choriocapillaris flow area decreased after the age of 30. There was a significant difference between participants who were 20–29 years of age and the remaining age groups. Yun et al. demonstrated that choriocapillaris measurements vary depending on the OCTA device and the image adjustment method [27]; however, no other studies have reported similar results. Therefore, device-specific features and appropriate imaging settings should be taken into consideration in OCTA studies assessing the choriocapillaris.

RPCP vessel density is an important parameter in the early diagnosis and follow-up of glaucoma. Mammo et al. compared the glaucomatous with normal eyes and reported decreased RPCP vessel density in glaucoma, which was also strongly correlated with retinal nerve fiber layer thickness [28]. A study by Koca et al. found that the average RPCP vessel density in healthy individuals was 50.13 ± 2.26% [29]. Similarly, herein, it was found that the average RPCP vessel density was 49.87±2.40%. It was also determined that the RPCP vessel density in the inside disk significantly decreased with age. The RPCP vessel density in participants who were 60–80 years of age was significantly different when compared to those who were 20–29 and 40–49 years of age. The RPCP vessel density in other areas did not significantly change with age.

Despite the advances in OCTA technology, there were several limitations to this study. Since SSADA depends on detecting blood flow, any head or eye movement during measurement can negatively affect image quality. This is more common in older patients. For this reason, images with quality scores below 7 were excluded. Moreover, major SCP vessels can create projection artifacts and produce erroneously high DCP vessel densities. More advanced algorithms are needed to correct such artifacts. The strengths of thisstudy were the automated segmentation and data analysis of the device.The limitation of this study is retrospective data collection.

The interpretation of OCTA results can significantly improve the diagnosis, follow-up, and treatment of diseases affecting the optic disk and retina. Clinical applications should consider age groups. OCTA vessel density and flow measurements vary widely between healthy individuals. Larger prospectivestudies including healthy eyes of all ages and ethnicities and screening guidelines are needed to identify possible variations as early indicators of age-related secondary changes and macular and retinal vascular diseases that often affect elderly patients. We believe that theresults determined herein can be used as a reference baseline for future studies.

Declaration of Competing Interest

None.

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