

Factors influencing foveal avascular zone size in healthy eyes

Sittikorn Laojaroenwanit¹, Adisai Varadisai^{1,2},
Pear Pongsachareonnont^{1,2},
Major Thanapong Somkijrungsroj^{1,2}, Kittisak Kulvichit^{1,2}

¹Department of Ophthalmology, Faculty of Medicine, Chulalongkorn University,
Bangkok, Thailand

²Vitreoretinal Research Unit, Department of Ophthalmology, Faculty of Medicine, Chulalongkorn
University and King Chulalongkorn memorial hospital, Bangkok, Thailand

Purpose: To evaluate factors influencing foveal avascular zone (FAZ) size in healthy eyes with swept-source OCT-A PLEX Elite 9000.

Methods: In this cross-sectional study, both eyes of healthy subjects were scanned with swept-source OCT-A PLEX Elite 9000 for superficial and deep capillary FAZ layers and foveal macular thickness (FMT). A multivariable analysis was conducted to determine the related factors influencing the FAZ size.

Results: In 224 eyes from 112 healthy subjects, mean $\pm$ standard deviation (SD) of superficial capillary plexus (SCP)-FAZ size was 0.31 ± 0.1 mm² and 0.30 ± 0.1 mm², and that of deep capillary plexus (DCP)-FAZ size was 0.56 ± 0.22 mm² and 0.56 ± 0.21 mm² in the right and left eyes, respectively. Age and sex were found significantly associated with SCP-FAZ and DCP-FAZ size in multivariable analysis. Age had associated with SCP-FAZ size (beta coefficient: 0.002 [95% CI of 0.001, 0.003], $P < 0.001$) and DCP-FAZ size (beta coefficient: 0.005 [95% CI of 0.002, 0.008], $P < 0.001$). SCP-FAZ size greater in women (beta coefficient: 0.035 [95% CI of 0.003, 0.070], $P = 0.047$) while DCP-FAZ smaller in women (beta coefficient: -0.071 [95% CI of -0.136, -0.007], $P = 0.029$).

Conclusion: Age and sex influence the size of normal superficial and deep FAZ of capillary network.

Conflicts of Interest: There are no conflicts of interest.

Keywords: Foveal avascular zone, foveal macular thickness.

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Introduction

The foveal avascular zone (FAZ) is a capillary-free area in the center of the macula

with a high density of photoreceptors. FAZ is a specialized area for high-accuracy vision of the human retina.¹ Many studies have focused on the size and shape of FAZ in normal human eyes.²⁻⁵ In healthy eyes, changing the size and shape of FAZ does not seem to affect visual function.^{4,6} However, in some retinal diseases, changes in the size and shape of FAZ can cause impaired vision.^{7,8}

Correspondence to:

Kittisak Kulvichit, Department of Ophthalmology, Faculty of Medicine, Chulalongkorn University, Thailand.

Email: KITTISAK.K@chula.ac.th

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Fluorescein angiography (FA) is an invasive and time-consuming method to perform retinal vascular mapping. The limitation of FA is a two-dimensional image and significant leakage. Optical coherence tomography angiography (OCT-A) imaging modality has recently emerged as a non-invasive method. OCT-A eliminated the limitations of FA and visualized the superficial and deep macular capillary plexuses.⁹

Recently, several studies have described FAZ sizes in normal healthy eyes using OCT-A.^{2, 4-8} Most studies focus on factors that affect FAZ size. The effect of sex on FAZ size has been inconclusive. Some studies reported that FAZ sizes were affected by sex¹⁰⁻¹², while others have reported no differences in FAZ size between men and women.⁴ The effect of age on FAZ size has been a focus area of study.^{10, 13}

Several studies have shown that factors such as sex and age affect FAZ size. However, the results are unclear. In this study, we aimed to determine the factors affecting FAZ size in the eyes of 112 healthy Thai individuals.

Methods

Study design and population

This cross-sectional study was conducted at King Chulalongkorn Memorial Hospital, Bangkok, Thailand. The Faculty of Medicine, Chulalongkorn University Institutional Review Board approved the study (IRB No. 492/60). Healthy volunteers were recruited from April 2019 to September 2019. The inclusion criteria were refractive error from -3.0 to +3.0 D of spherical equivalent, intraocular pressure < 21 mmHg, no media opacity, normal eye fundus, and normal macular OCT. The exclusion criteria were previous or current history of ophthalmic disease related to the posterior segment, previous ocular surgery, any systemic disease with ocular involvement, poor collaboration for complete

ophthalmic examination, and poor quality of angiography image to perform reliable measurements.

Informed consent was obtained from all subjects before enrollment in the study. The study was registered with the Thai Clinical Trial Registration before conducting the study [TCTR20200330003].

Demographic data including age, sex, and best corrected visual acuity (BCVA), and the results of autorefraction measurements and air-puff tonometry were recorded.

Visual acuity was measured using a modified numerical Early Treatment Diabetic Retinopathy Study chart 4 m away from the subject. Swept-source OCT-A imaging was performed with PLEX Elite 9000 swept-source OCTA (Carl Zeiss Meditec Inc., Dublin, California, USA) using a 1060-nm wavelength with a scanning speed of 100,000 A-scans/s, and the obtained images were processed using the OCT-microangiography complex algorithm.

Image protocol

OCT -A images were obtained by a trained single operator. Any image with poor quality was recaptured until a good-quality image was achieved. A good quality image is defined as signal strength greater than six. Only good-quality images were included in the analysis.

- A horizontal, high-definition, 16-mm line scan was obtained that included the fovea and optic nerve head area for analyzing the foveal macular thickness (FMT).

- OCT-A maps covering the central 3 × 3 mm macular area were obtained. All OCT-A images were carefully reviewed to check automatic segmentations of the superficial capillary plexus (SCP) and deep capillary plexus (DCP), and manual corrections were performed, when necessary, to ensure correct segmentation.

Parameter measurements

The SCP and DCP en face OCT-A scan images were exported to measure the FAZ area in each eye. These two en face images were then imported into ImageJ software version 1.52a (<http://imagej.nih.gov/ij/>; provided in the public domain by the National Institutes of Health, Bethesda, MD, USA) for image analysis. The borderline of the FAZ area was traced manually, and the surface area was calculated using ImageJ software.

FMT was measured at the foveal center, defined as the lowest point from the macular region, using the caliper of the ImageJ software from the internal limiting membrane to the top of the retinal pigment epithelium.

All the measurements were measured by trained physicians (S.L) who were masked. One of the parameters is repeatedly measured three times in one weeks apart.

Statistical analysis

Baseline characteristics of the subjects were analyzed using descriptive statistics. Categorical variables were presented as number of subjects and percentage, whereas continuous variables were summarized as mean $\pm$ standard deviation (SD) or median and range as appropriate.

FAZ size and FMT are summarized as mean $\pm$ SD and 95% confidence interval (CI) according to eye side and age group. Comparison between the right and left eyes was performed using the paired t-test.

Factors associated with SCP-FAZ, DCP-FAZ were explored using a univariable mixed-effect linear regression model. Factors which value ≤ 0.1 from a univariable analysis were considered in a multivariable analysis to determine the related factors influencing the FAZ size. FMT and smoking status were also considered in multivariable analysis due to

evidence from previous studie^{4, 14-15} showed association between these factors with FAZ size.

P value of less than 0.05 was considered statistically significant. All analyses were performed using Stata software version 15.1 (Stata Corp, College Station, Texas, USA).

Results

A total of 224 eyes from 112 healthy subjects were included in this study. Sixty-one (54.5%) subjects were women. The mean age of the subjects was 48.9 years. The demographic data of all subjects are shown in Table 1.

Foveal avascular zone areas and foveal macular thickness

The areas of SCP-FAZ and DCP-FAZ and the FMT are summarized in Table 2. The mean $\pm$ SD of SCP-FAZ were $0.31 \pm 0.1 \text{ mm}^2$ and $0.30 \pm 0.1 \text{ mm}^2$ in the right and left eyes, respectively. Mean $\pm$ SD of FAZ in DCP were $0.56 \pm 0.22 \text{ mm}^2$ and $0.56 \pm 0.21 \text{ mm}^2$ in the right and left eyes, respectively. The FMT was $379.48 \pm 37.66 \mu\text{m}$ and $382.04 \pm 36.61 \mu\text{m}$ in the right and left eyes, respectively. There was no statistically significant difference in SCP-FAZ, DCP-FAZ, and FMT between the two eyes.

Age grouping-based foveal avascular zone and foveal macular thickness

The summarized FAZ areas and FMT based on age categories are shown in Table 2. The data showed that FAZ areas in the SCP and DCP were greater in the older age group. In contrast, FMT decreased in the older age group.

Association of foveal avascular zone areas with other evaluated variables

The association of SCP-FAZ areas with other evaluated variables is summarized in Table 3. In univariable analysis, age was a significant predictive factor of SCP-FAZ with a beta

Table 1: Baseline demographic data from 112 subjects in this study

Characteristics (n, %)	Total (n = 112)
Sex	
Men	51 (45.5%)
Women	61 (54.5%)
Age (mean $\pm$ SD, yrs.)	48.9 $\pm$ 15.6
Age group (yrs.)	
20-40	38 (33.9%)
40-60	38 (33.9%)
≥ 61	36 (32.2%)
BCVA score	67.4 $\pm$ 7.1 (60-85)
Refractive error	
Myopia (SE -3.0 to < -0.5 D)	26 (23.2%)
Normal (SE -0.5 to +0.5 D)	53 (47.3%)
Hyperopia (SE $>+0.5$ to +3.0 D)	3 (29.5%)
Smoking status	
Yes	7 (6.3%)
No	105 (93.7%)
Alcohol drinking status	
Yes	17 (15.2%)
No	95 (84.8%)

Data are given as the number (%), mean $\pm$ SD, and/or range

BCVA best correct visual acuity, SE spherical equivalent

coefficient of 0.002 (95% CI of 0.001, 0.004, $P < 0.001$). After adjusting for age, sex, FMT, and smoking status in multivariable mixed-linear regression analysis, only age and sex were significant predictive factors associated with SCP-FAZ. The results showed that age was associated with the area of SCP-FAZ (beta coefficient: 0.002 [95% CI of 0.001, 0.003], $P < 0.001$). Women had a greater SCP-FAZ area than men, with a beta coefficient of 0.035 (95% CI of 0.003, 0.070, $P = 0.047$).

The association of DCP-FAZ areas with other evaluated variables is summarized in Table 4. Results from univariable analysis showed that age, sex, and refractive error

were significant predictive factors of DCP-FAZ (beta coefficient (95% CI) P -value; 0.007 (0.005, 0.009) $P < 0.001$; -0.081 (-0.157, -0.005) $P = 0.037$; and 0.167 (0.085, 0.248) $P < 0.001$, respectively). After adjusting for age, sex, FMT, refractive error, and smoking status in multivariable mixed-linear regression analysis, only age and sex were still significant predictive factors associated with DCP-FAZ. The results showed that age had associated with the area of DCP-FAZ with a beta coefficient of 0.005 (95% CI of 0.002, 0.008, $P < 0.001$). Women had a smaller DCP-FAZ area compared to men with a beta coefficient of -0.071 (95% CI of -0.136, -0.007, $P = 0.029$).

Table 2: Surface area of SCP-FAZ, DCP-FAZ and FMT

(mean ± SD)	Age group (yrs.)	Side		P value
		OD	OS	
SCP-FAZ (mm ²)	Overall	0.31 ± 0.10 (95% CI: 0.29, 0.32)	0.30 ± 0.10 (95% CI: 0.29, 0.33)	0.698
	20-40	0.26 ± 0.10	0.26 ± 0.09	
	41-60	0.31 ± 0.10	0.31 ± 0.10	
	≥ 61	0.35 ± 0.10	0.34 ± 0.11	
DCP-FAZ (mm ²)	Overall	0.56 ± 0.22 (95% CI: 0.52, 0.60)	0.56 ± 0.21 (95% CI: 0.52, 0.60)	0.936
	20-40	0.43 ± 0.16	0.43 ± 0.15	
	41-60	0.55 ± 0.22	0.55 ± 0.19	
	≥ 61	0.71 ± 0.17	0.71 ± 0.17	
FMT (μm)	Overall	379.48 ± 37.66 (95% CI: 372.43, 386.53)	382.04 ± 36.61 (95% CI: 375.19, 388.90)	0.389
	20-40	385.58 ± 31.28	380.89 ± 31.44	
	41-60	382.45 ± 40.99	390.63 ± 39.43	
	≥ 61	369.92 ± 39.27	374.19 ± 37.63	

SCP: superficial capillary plexus, DCP: deep capillary plexus, FAZ: foveal avascular zone, FMT: foveal macular thickness

Discussion

In our study, healthy eyes had larger SCP-FAZ areas than DCP-FAZ areas. The FAZ area varied with age and sex. Women had larger SCP-FAZ areas compared to men; whereas, men had larger DCP-FAZ areas than women. Both SCP-FAZ and DCP-FAZ areas were greater in the older age group. FMT was decreased in the older age group but did not associated with the FAZ area in multivariable analysis.

Table 5 shows the reports of FAZ areas from previous studies.^{10, 11, 13,16-27} In our study, the mean SCP-FAZ area was 0.31 ± 0.1 mm², which is similar to that of previous studies of SCP-FAZ areas using OCT-A. Data of normal SCP-FAZ from other studies, ranged from 0.240 mm²¹¹ to 0.373 mm².²³ For the DCP-FAZ area, the data from our study found that the mean DCP-FAZ was 0.56 ± 0.22 mm², which

was comparable with previously reported values, ranging from 0.298 mm²²⁶ to 0.641 mm².¹⁶ According to Table 5, various studies have reported differences in SCP-FAZ and DCP-FAZ areas in healthy individuals based on their studies. This discrepancy might be attributed to the ethical background, sample size, age of subjects, technique of measurement, and artifact removal technology used in the software. A consistent finding from previous studies was a larger DCP-FAZ size than SCP-FAZ. The larger size of DCP-FAZ can be explained by the unique relationship of capillary plexus at the fovea (i.e., the capillary plexuses intersect at the fovea). At DCP layers, the vessels move into the inner plexiform layers/ganglion cell layers, which are anatomic layers narrowing at the fovea. The segmentation may break down at the fovea because the capillaries in the DCP

Table 3: Association of SCP-FAZ with other evaluated variables

Predictive factors	Univariable analysis			Multivariable analysis		
	Beta Coefficient	95% CI	P value	Beta Coefficient	95% CI	P value
Age	0.002	0.001, 0.004	<0.001	0.002	0.001, 0.003	<0.001
Sex						
Men	Ref			Ref		
Women	0.033	-0.004, 0.071	0.084	0.035	0.003, 0.070	0.047
FMT	-0.0001	-0.00029, 0.000045	0.154	-0.001	-0.0002, 0.00004	0.157
Refractive error						
Myopia	-0.019	-0.065, 0.028	0.436			
Normal	Ref					
Hyperopia	0.042	-0.001, 0.085	0.057			
Smoking						
No	Ref			Ref		
Yes	-0.065	-0.143, 0.012	0.099	-0.129	-0.086, 0.060	0.73
Alcohol						
No	Ref					
Yes	-0.046	-0.098, 0.006	0.085			

layers are laminar and intersect only with vertical connecting vessels.¹³

Age was an important factor that could influence FAZ areas and foveal morphology. Age-related anatomical changes in the macular region should be considered with changes in vascular structure and hence in FAZ size. Several studies have found that retinal thickness declines with age.^{28, 29} Whereas other studies

have failed to find a relationship between age and macular thickness.^{30, 31} From previous studies, the association of FAZ area with age remains controversial. Some authors reported that age and FAZ area were not significantly associated.^{4, 11, 32} In contrast, some studies found that in advanced age, FAZ area increases, parafoveal blood flow decreases, and capillaries become occluded.^{12, 16, 33, 34} Similarly, the results

Table 4: Association of DCP-FAZ with other evaluated variables

Predictive factors	Univariable analysis			Multivariable analysis		
	Beta Coefficient	95% CI	P value	Beta Coefficient	95% CI	P value
Age	0.007	0.005, 0.009	<0.001	0.005	0.002, 0.008	<0.001
Sex						
Men	Ref			Ref		
Women	-0.081	-0.157, -0.005	0.037	-0.071	-0.136, -0.007	0.029
FMT	-0.0002	-0.0005, 0.000067	0.133	-0.0002	-0.0005, 0.00006	0.127
Refractive error						
Myopia	-0.068	-0.156, 0.021	0.134	-0.344	-0.115, 0.046	0.403
Normal	Ref			Ref		
Hyperopia	0.167	0.085, 0.248	<0.001	0.061	-0.025, 0.147	0.167
Smoking						
No	Ref			Ref		
Yes	-0.089	-0.247, 0.070	0.273	-0.100	-0.146, 0.126	0.885
Alcohol						
No	Ref					
Yes	-0.026	-0.133, 0.082	0.641			

of both the univariable and multivariable analyses in our study show a significant association between age and FAZ area in healthy eyes (Table 3 and Table 4).

The association between the FAZ area and sex has been documented in many studies.^{10-12, 14, 26} To our knowledge, macular structure is affected by sex. Adhi et al. and Song et al. reported that men had greater foveal and macular thicknesses than women.^{35, 36} Samara et al. and Coscas et al. failed to demonstrate an association between FAZ area and sex.^{4, 13} However, some studies have found that women have larger FAZ areas than men,^{10-12, 16, 37} as we know, estrogen, androgen, and progesterone receptors are present in eyes and that these steroid hormones are produced in ocular tissues. Sex hormones play a role in the retinal and ocular blood flow. Whereas Zhou et al. found that mean ganglion cell layer (GCL) thickness was

positively and significantly correlated with FAZ size in men, while women shown slightly negative correlation between mean GCL thickness and FAZ size.³⁸ In agreement with previous studies, our results also show that FAZ areas are influenced by sex and our study found that women had larger SCP-FAZ areas and smaller DCP-FAZ areas than men. The difference of SCP-FAZ and DCP-FAZ size in men and women needs further investigation.

Some studies have described the association of FAZ area with foveal thickness.^{4, 14, 37, 39-42} Samara et al. and Ghassemi et al. found that a lower FMT was associated with a larger FAZ area. Chui et al. studied the FAZ and retinal thickness and found that the outer retinal layer was associated with the FAZ area, while the inner retinal layer was not significantly associated with the FAZ area.⁴³ However, we did not find an association between the FMT and FAZ areas.

Table 5: Data of Foveal avascular zone areas from previous studies

Authors	Year	Eyes	Age	SCP-FAZ (mean±SD, mm ²)	DCP-FAZ (mean±SD, mm ²)	Device
Coscas et al. ¹³	2016	135	48.3 ± 17.5	0.28 ± 0.10	0.37 ± 0.12	AngioVue, Optovue
Iafe et al. ¹⁶	2016	113	48 ± 20	0.29 ± 0.11	0.61 ± 0.20	AngioVue, Optovue
Linderman et al. ¹⁰	2016	116	30.5 ± 14.5	0.26 ± 0.10		AngioVue, Optovue
Lupidi et al. ¹⁷	2016	47	39	0.28 ± 0.11	0.30 ± 0.10	Spectralis OCT2, Heidelberg
Shahlaee et al. ¹⁸	2016	34		0.27 ± 0.10	0.34 ± 0.12	SS-OCTA
Tan et al. ¹¹	2016	117	22.5	0.240	0.380	AngioVue, Optovue
Wang et al. ¹⁹	2016	105	35.9 ± 13.8	0.35 ± 0.12		AngioVue, Optovue
Choi et al. ²⁰	2017	52	52.1 ± 14.8	0.35 ± 0.11		Angioplex, Cirrus
Ghassemi et al. ¹⁴	2017	224	37.0 ± 11.3	0.27 ± 0.11	0.35 ± 0.12	AngioVue, Optovue
Goudot et al. ²²	2017	22	51 ± 17	0.29 ± 0.15	0.39 ± 0.14	AngioVue, Optovue
Guo et al. ²³	2017	25	55	0.37 ± 0.11		Angioplex, Cirrus
Mastropasqua et al. ²⁴	2017	64	34.4 ± 10.9	0.27 ± 0.09		DRI Triton, Topcon
Falavarjani et al. ²⁵	2018	70	42.8 ± 17.2	0.32 ± 0.11	0.50 ± 0.13	AngioVue, Optovue
Gomez-Ulla F et al. ²⁶	2019	240	39.2 ± 17.4	0.27 ± 0.11	0.29 ± 0.11	DRI Triton, Topcon
Yilmaz et al. ²⁷	2019	128	46	0.33 ± 0.12		RS-3000, Nidek
This study	2020	224	48.8 ± 15.6	0.31 ± 0.1	0.56 ± 0.22	Plex elite 9000, Zeiss

The use of OCT-A in ophthalmology practice is expanding very fast. OCT-A is a noninvasive, non-contact method of retinal vascular mapping. The FAZ size was closely related to vision. Many retinal and macular diseases altered the size and shape of FAZ. Our studies provided the normative data of SCP-FAZ, DCP-FAZ size, FMT thickness and factors influencing FAZ size in Thai healthy eyes. Our report may be helpful for diagnosis and follow-up of retinal and macular diseases.

There are some limitations to our study. First, only subjects with a small refractive error (-3 to +3) were included. Hence, the effects of higher levels of myopia or hyperopia on foveal microvasculature were not evaluated. Second, axial length, choroidal thickness, foveal morphology, foveal vascular density, and shape of FAZ were not included.

Conclusion

In this study, we demonstrated the size of FAZ at both the superficial and deep capillary levels in the eyes of healthy Thai individuals. It seems that DCP-FAZ is larger than SCP-FAZ. Age and sex influence the size of FAZ. OCT-A is non-invasive and widely available in clinical use. The data of normative FAZ size, FMT thickness and factors influencing FAZ size should be helpful for diagnosis and follow-up of retinal and macular diseases.

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