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Quantitative assessment and determinants of foveal avascular zone in healthy volunteers

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Abstract

Objectives: To evaluate the foveal avascular zone (FAZ) area in healthy volunteers using optical coherence tomography angiography (OCTA) and identify factors that influence the FAZ.

Methods: This single-center cross-sectional study included 526 eyes of 263 healthy volunteers who underwent macular scanning by Zeiss OCTA. A linear mixed model was used to investigate the effects of systemic factors (age, sex, blood pressure, height, and weight) and ocular factors (intraocular pressure, biometric parameters, and central macular thickness) on FAZ.

Results: In total, 520 eyes of 262 healthy volunteers were included in the analysis. The mean volunteer age was 38.59 ± 22.03 years (range, 5–84 years); 124 volunteers were male (47.33%) and 138 volunteers were female (52.67%). The mean FAZ area was 0.30 ± 0.03 mm^2 (95% confidence interval [CI], 0.29–0.31 mm^2). Univariate analysis showed that FAZ area was associated with age ($\beta = 0.0011$), anterior chamber depth ($\beta = -0.0513$), and axial length ($\beta = -0.0202$). Multivariate analysis showed that FAZ area was negatively correlated with axial length ($\beta = -0.0181$).

Conclusions: The mean FAZ area in healthy volunteers, measured using Zeiss OCTA, was 0.30 ± 0.03 mm^2. Furthermore, FAZ area was negatively associated with axial length; this relationship should be considered in clinical practice.

Keywords

Optical coherence tomography angiography, foveal avascular zone, axial length, cross-sectional study, healthy volunteer, macula

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Introduction

The foveal avascular zone (FAZ)—a ring-shaped, capillary-free area in the macular center—is essential for maintenance of normal visual function.[1] In 1985, Wu et al.[2] evaluated the FAZ area in 45 healthy individuals using the fundus fluorescein angiography and found that the mean FAZ area was 0.42 mm^2 in the superficial retina. In an analysis of 31 healthy adults, John et al.[3] determined that the mean FAZ area was 0.27 mm^2. However, fundus fluorescein angiography is an invasive and time-consuming method; moreover, it is unsuitable for some patients, especially individuals who are allergic to fluorescein sodium.

In recent years, optical coherence tomography angiography (OCTA) has been shown to provide rapid FAZ examinations involving high-resolution three-dimensional maps,[4] without the limitations of fundus fluorescein angiography. OCTA is currently used in the assessment of macular diseases, retinovascular diseases, and neurodegenerative diseases (e.g., Alzheimer's disease).[5–7] Notably, FAZ changes can serve as a potential macular biomarker, which is important for clinical diagnosis and treatment.[8–10] There is a critical need to acquire FAZ data from healthy individuals and analyze factors that may influence FAZ changes. To the best of our knowledge, few studies have focused on these influencing factors.[11,12] In this study, we used OCTA to measure the FAZ and identify potential influencing factors from among ocular and systemic parameters.

Materials and methods

Study design

This prospective single-center cross-sectional study was conducted at the Department of Ophthalmology, Affiliated Foshan Hospital, Southern Medical University, between May 2019 and April 2020. The study protocol was approved by the Institutional Review Committee of Affiliated Foshan Hospital (KJ20190012) and registered in the Chinese Clinical Trial Registration Center (ChiCTR1900024921; http://www.chictr.org.cn). All volunteers provided written informed consent before participating in the study.

Study population

Healthy Chinese volunteers, with decimal best-corrected visual acuity better than 0.8, were recruited from the ophthalmology clinic and routine community screening sessions. The inclusion criteria were intraocular pressure <21 mmHg, normal slit lamp findings, and normal fundus examination findings. Exclusion criteria were any history of intraocular diseases or intraocular surgery, any history of systemic diseases (e.g., hypertension and/or diabetes), and media opacity that could hinder high-quality fundus OCTA imaging.

General ophthalmic examinations

All volunteers underwent comprehensive ophthalmic examinations, including best-corrected visual acuity, slit-lamp examination, spherical equivalent, intraocular pressure (via non-contact tonometry), fundus evaluation, and OCTA examination. Ocular biometric parameters (e.g., central corneal thickness, axial length, anterior chamber depth, and lens thickness) were obtained using optical low-coherence reflectometry (LenStar LS 900, Haag-Streit, Inc., Koeniz, Switzerland). Furthermore, arterial blood pressure, body weight, and body height were recorded; body mass index was calculated using the weight and height data.

OCTA examination

Both eyes of all volunteers were subjected to OCTA examinations using the Zeiss Cirrus 5000 HD-OCT with Angioplex

(Carl Zeiss Meditec, Inc, Dublin, CA, USA); all OCTA examinations were completed by the same skilled clinical staff members. To determine the FAZ area of the superficial capillary plexus, a 6×6-mm scanning model was used with a real-time eye-tracking system (Figure 1a). The OCTA software automatically calculated the FAZ area (Figure 1b). The superficial capillary plexus was defined as the distance from the inner limiting membrane to the inner plexiform layer (Figure 1c). Furthermore, all volunteers underwent macular scanning with a 512×128 scan model (128 horizontal B-scans, at 512 A-scans per B-scan) to assess the central macular thickness (center 1 mm). OCTA images with a quality signal strength of ≥ 7 were included in the data analysis. Furthermore, all images were manually checked to identify errors that may arise due to automatic analysis.[13]

Statistical analysis

Continuous variables are presented as means $\pm$ standard deviations, and categorical variables are presented as frequencies (%). The Kolmogorov–Smirnov test was used to determine whether a normal distribution was present for systemic factors regarded as continuous variables (e.g., age, height, weight, blood pressure, and body mass index). Comparisons of systemic factors between female and male volunteers were performed using an independent sample t-test for variables with normal

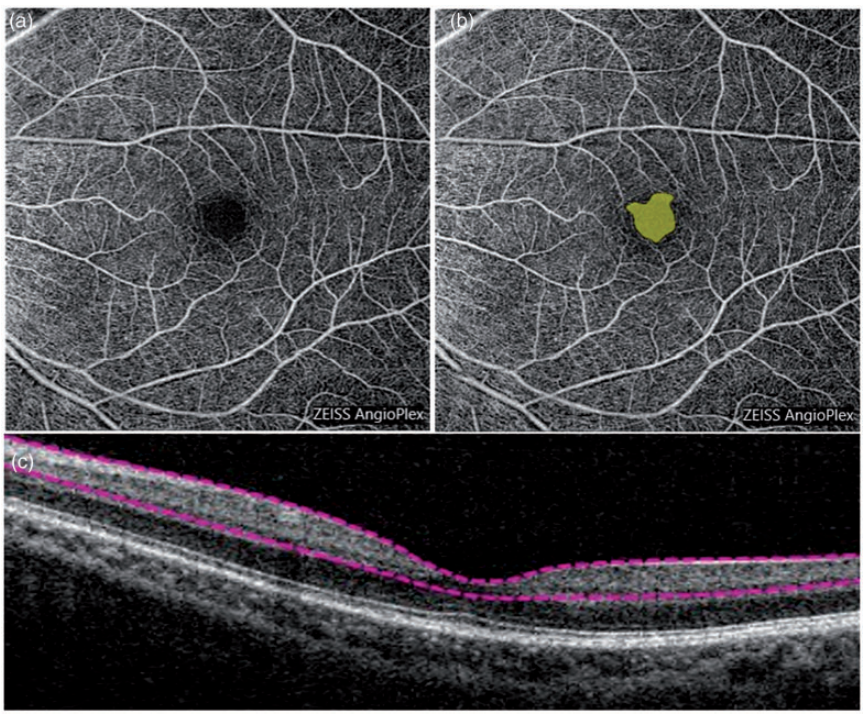

Figure 1. Optical coherence tomography angiography (OCTA) images of superficial capillary plexus in the macula. (a) OCTA image showing 6 x 6-mm scanning model in the superficial capillary plexus of the macula. (b) OCTA image showing foveal avascular zone area (in yellow) obtained automatically by OCTA software. (c) OCTA image showing superficial capillary plexus from the inner limiting membrane to the inner plexiform layer (between red dotted lines).

distributions. For variables with skewed distributions, comparisons were performed using the Mann–Whitney U test. To correct for intra-eye correlations, a linear mixed model was used to compare ocular parameters. Subsequently, analysis was performed to identify factors potentially affecting the FAZ area. First, a linear mixed model was used for univariate analysis regarding the influences of ocular and systemic parameters on FAZ area. Then, variables with $P < 0.20$ in univariate analysis were included in the multivariate model; adjustments were made for potential confounders (i.e., age and sex). Regression coefficients with 95% confidence intervals (CIs) were calculated. SAS statistical software, version 9.4 (SAS Institute Inc., Cary, NC, USA) was used for statistical analyses. *P*-values < 0.05 were considered statistically significant.

Results

In this study, 526 eyes of 263 volunteers underwent full assessments as described in the Methods section. Six eyes were excluded because of low image quality and incomplete data. Finally, 520 eyes of 262 volunteers were included in the analysis. The mean volunteer age was 38.59 ± 22.03 years (range, 5–84 years); 124 volunteers were male (47.33%) and 138 volunteers were female (52.67%). Systemic and ocular factors are described in detail in Table 1 and Table 2, respectively.

The mean FAZ area in all eyes was $0.30 \pm 0.03\,mm^2$ (95% CI, 0.29–0.31 mm^2). The mean FAZ areas were $0.28 \pm 0.11\,mm^2$

Table 1. Demographic and clinical characteristics of systemic factors in study volunteers.

Variables	Total (n = 262)	Male volunteers (n = 124)	Female volunteers (n = 138)	Unadjusted P-value
Age (years)	38.59 ± 22.03 (range, 5–84)	37.53± 22.56	39.54 ± 21.59	0.3561†
Weight (kg)	52.67 ± 14.11 (range, 17–95)	56.45 ± 16.39	49.28 ± 10.64	<0.001†
Height (cm)	158.28 ± 11.58 (range, 110–183)	162.40 ± 13.14	154.57 ± 8.45	<0.001†
BMI (kg/m^2)	20.66 ± 3.89 (range, 8.89–32.85)	20.93 ± 4.27	20.42 ± 3.51	0.3004‡
SBP (mmHg)	114.42 ± 15.97 (range, 64–140)	115.81 ± 16.38	113.16 ± 15.54	0.1085†
DBP (mmHg)	72.44 ± 10.11 (range, 45–90)	73.23 ± 10.23	71.74 ± 9.95	0.2101†

Data are shown as mean ± SD unless otherwise indicated. †by Mann–Whitney U test, ‡by independent-samples t-test.
SD: standard deviation, BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure.

Table 2. Demographic and clinical characteristics of ocular factors in study volunteers.

Variables	Total (n = 520)	Male volunteers (n = 246)	Female volunteers (n = 274)	Unadjusted P-value‡
SE (diopters)	−1.60 ± 2.51 (range, −11.75 to 4.00)	−1.64 ± 2.37	−1.59 ± 2.63	0.8794
IOP (mmHg)	14.80 ± 2.71 (range, 8.60–21.00)	14.75 ± 2.68	14.85 ± 2.74	0.7401
LT (mm)	4.01 ± 0.57 (range, 3.10–5.36)	4.00 ± 0.59	4.02 ± 0.55	0.6795
CCT (μm)	537.77 ± 31.71 (range, 447.00–630.00)	544.53 ± 30.25	531.70 ± 31.82	0.0010
ACD (mm)	3.40 ± 0.43 (range, 2.04–5.33)	3.50 ± 0.41	3.31 ± 0.43	0.0002
AL (mm)	24.10 ± 1.21 (range, 21.43–28.08)	24.35 ± 1.14	23.87 ± 1.22	0.0008
CMT (μm)	279.85 ± 13.93 (range, 152.00–317.00)	280.21 ± 13.55	279.52 ± 14.27	0.6102

Data are shown as mean ± SD unless otherwise indicated. ‡by linear mixed model analysis.
SD: standard deviation, SE: spherical equivalent, IOP: intraocular pressure, CCT: central corneal thickness, ACD: anterior chamber depth, AL: axial length, CMT: central macular thickness.

(95% CI, 0.27–0.30 mm^2) in male volunteers and $0.31 \pm 0.10\,mm^2$ (95% CI, 0.30–0.32 mm^2) in female volunteers; there was no significant sex-related difference. Univariate regression analysis showed that the FAZ area was significantly associated with age ($\beta = 0.0011$, $P < 0.001$), anterior chamber depth ($\beta = -0.0513$, $P < 0.001$), and axial length ($\beta = -0.0202$, $P < 0.001$) (Table 3). Multivariate analysis showed that axial length was significantly negatively associated with FAZ area ($\beta = -0.0181$, $P = 0.0076$) (Table 4). There were no significant associations of FAZ area with age, sex, or anterior chamber depth.

Discussion

There is a critical need to measure the FAZ area and determine important factors that influence clinically relevant changes in this parameter, thus providing insights regarding macular diseases. In the present study, we used Zeiss OCT with Angioplex to

Table 3. Univariate analysis of factors associated with FAZ area.

Variables	β (95% CI)	Standard error	P-value
Age (years)	0.0011 (0.0006–0.0016)	0.0003	<0.0001
Sex (male vs. female)	−0.0237 (−0.0474 to 0.0001)	0.0121	0.0504
Weight (kg)	0.0003 (−0.0005 to 0.0011)	0.0004	0.4918
Height (cm)	0.0000 (−0.0010 to 0.0010)	0.0005	0.9835
BMI (kg/m^2)	0.0017 (−0.0013 to 0.0048)	0.0016	0.2645
SBP (mmHg)	0.0007 (0.0000–0.0015)	0.0004	0.0586
DBP (mmHg)	0.0006 (−0.0006 to 0.0017)	0.0006	0.3535
SE (diopters)	0.0056 (0.0016–0.0095)	0.0020	0.0059
IOP (mmHg)	−0.0011 (−0.0042 to 0.0021)	0.0015	0.4978
CCT (μm)	−0.0003 (−0.0007 to 0.0000)	0.0002	0.0623
ACD (mm)	−0.0513 (−0.0771 to 0.0255)	0.0131	0.0001
LT (mm)	0.0396 (0.0198–0.2190)	0.0101	0.0594
AL (mm)	−0.0202 (−0.0289 to −0.0115)	0.0044	<0.0001
CMT (μm)	−0.0004 (−0.0010 to 0.0003)	0.0003	0.2929

CI: confidence interval, BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure, SE: spherical equivalent, IOP: intraocular pressure, CCT: central corneal thickness, ACD: anterior chamber depth, LT: lens thickness, AL: axial length, CMT: central macular thickness.

Table 4. Multivariate analysis of factors associated with FAZ area.

Variables	β (95% CI)	Standard error	P-value
Age (years)	0.0010 (−0.0001 to 0.0022)	0.0006	0.0855
Sex (male vs. female)	−0.0108 (−0.0356 to 0.0140)	0.0126	0.3928
SBP (mmHg)	−0.0002 (−0.0011 to 0.0008)	0.0005	0.7426
SE (diopters)	−0.0029 (−0.0085 to 0.0028)	0.0029	0.3233
CCT (μm)	−0.0001 (−0.0005 to 0.0003)	0.0002	0.5880
ACD (mm)	−0.0032 (−0.0443 to 0.0378)	0.0209	0.8771
LT (mm)	−0.0052 (−0.0498 to 0.0394)	0.0226	0.8191
AL (mm)	−0.0181 (−0.0314 to −0.0049)	0.0067	**0.0076**

CI: confidence interval, SBP: systolic blood pressure, SE: spherical equivalent, CCT: central corneal thickness, ACD: anterior chamber depth, LT: lens thickness, AL: axial length.

examine 520 eyes in a healthy population, and the results showed that the mean FAZ area was $0.30 \pm 0.03\,mm^2$. After adjustments for systemic and ocular factors, the FAZ area was significantly negatively correlated with axial length.

Several studies have investigated the FAZ area in healthy populations using various types of OCTA equipment. In a study of 67 healthy adults using the Optovue RTVue XR OCTA, Samara et al.[14] found that the mean FAZ area was $0.27 \pm 0.10\,mm^2$. In a swept source OCTA study of 224 eyes in 112 healthy volunteers aged 12 to 67 years, Ghassemi et al.[15] determined that the mean FAZ area was $0.27 \pm 0.11\,mm^2$. Tan et al.[16] reported a mean FAZ area of $0.24\,mm^2$ in 117 volunteers. Finally, using the Optovue RTVue XR OCTA, Wang et al.[17] found that the mean FAZ area was $0.35 \pm 0.12\,mm^2$ in 105 healthy Chinese volunteers. Notably, compared with the above results, the mean FAZ area in our study was generally slightly greater, although it was smaller than the mean value reported by Wang et al.[17] There are many possible reasons for the discrepancies in FAZ area among these studies, including the use of various OCTA instruments with different algorithms. Other reasons may involve differences regarding inclusion criteria and ethnic backgrounds.[18]

Axial length, a readily accessible ocular parameter, is an essential factor that affects the FAZ area. Previous studies showed that the FAZ area was negatively correlated with the axial length.[11,17,19] After adjusting for systemic and ocular factors, our study also demonstrated that the axial length was significantly negatively associated with FAZ area. For every 1-mm increase in the axial length, the FAZ area decreased by 0.0181 mm. However, some contradictory findings have been published. Fujiwara et al.[20] found no significant association between FAZ area and axial length in a multivariate analysis. Zhou and colleagues[12] also reported no significant association between FAZ area and axial length; they suggested that the lack of association may have been related to differences in experimental designs, compared with previous studies. Additionally, the specific range of axial length among enrolled volunteers might influence the association with FAZ area.

With respect to systemic factors, clinicians tend to focus more on age and sex. However, there remains no consensus regarding the relationship of FAZ area with age. In theory, capillaries on the macular surface may gradually decrease with increasing age, and the avascular area may become larger within the macular fovea. Iafe et al.[21] demonstrated that the FAZ area was positively associated with age: the FAZ area increased by 0.0014 mm for every 1-year increase in age, consistent with the findings by Rommel et al.[22] and Fujiwara et al.[20] However, some studies have shown dissimilar results. Ghassemi et al.[15] evaluated the FAZ area by swept source OCTA, but found no correlations between FAZ area and specific age groups. Our study showed that the FAZ area was positively associated with age in univariate analysis; in particular, the FAZ area increased by 0.0011 mm for every 1-year increase in age. However, after adjustments for systemic and ocular factors, the FAZ area was no longer associated with age.

In the present study, we found no sex-related difference in FAZ area. Samara et al.[14] showed that the mean FAZ areas were $0.26\,mm^2$ in men and $0.27\,mm^2$ in women; they concluded that no significant correlation was present between FAZ area and sex. However, another study showed that FAZ area may differ according to sex: Tan et al.[16] reported that FAZ area was larger in women than in men. Larger sample sizes are needed to further evaluate this relationship, following adjustments for confounding factors.

Our study's principal strengths included the comparatively large sample size of

volunteers aged 5 to 84 years, which helped to improve the accuracy of the regression models. Additionally, a linear mixed model approach was used to correct for intra-eye correlations. Nonetheless, there were some limitations. First, children younger than 5 years of age were not included because they could not complete the OCTA examination with sufficient image quality. Second, some personal habits that may impact the FAZ area (e.g., sedentary lifestyle, daily exercise, drinking, and smoking) were not considered in the present study. Third, volunteers in our study were Chinese; the generalizability of our results may be limited because previous studies have demonstrated that ethnic background can influence FAZ area.[18,23] Finally, we did not correct for the magnification effect of axial length, especially high myopia, on FAZ area; this might have led to underestimation of the FAZ area.[24]

In conclusion, OCTA is a rapid and non-invasive FAZ detection method. In the present study, we found that the mean FAZ area in healthy volunteers was $0.30 \pm 0.03\,mm^2$ (95% CI, $0.29–0.31\,mm^2$); moreover, axial length was significantly negatively associated with FAZ area. Thus, there is a need to consider the influence of axial length on FAZ area in clinical practice.

Author contributions

Lijun Zhou: Methodology, Data curation, Writing-Original draft; **Fengqun Wang:** Formal analysis; **Ling Wang:** Visualization; **Peiyang Shen:** Supervision; **Yi Cao:** Supervision; **Yushen He:** Writing-Review & Editing; **Shigang Yan:** Project administration; **Xiangbin Kong:** Conceptualization, Methodology; **Xiaohe Lu:** Conceptualization, Writing–Review & Editing. All authors approved the final manuscript.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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