ORIGINAL ARTICLE

Foveal Avascular Zone Change in Idiopathic Macular Hole Patients

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ABSTRACT

Purpose: The macular hole(MH) is a retinal defect that involves all layers. We aimed to assess the preoperative and postoperative foveal avascular zone (FAZ) changes by using optical coherence tomography angiography(OCTA).

Material and Methods: This is a retrospective study including eyes with MH. The study included 25 eyes operated and 18 healthy fellow eyes of 25 patients. The FAZ values were evaluated in the OCTA images obtained at baseline and on postoperative months 1, 3 and 6.

Results: In the patients, the mean FAZ value was 0.30±0.08 mm² at baseline whereas 0.22±0.11 mm² on postoperative month 1, 3rd month FAZ value was 0, 20±0, 11 mm² on postoperative month 3 and 0.20±0.10 mm². There were significant decrease in mean FAZ value from baseline to postoperative month 3 and 6 (p=0.030, p=0.049, respectively). The mean FAZ value on postoperative month 6 was 0.17±0.02 mm² in eyes with MH of the cases in which health fellow eyes with no exclusion criteria were included. The mean FAZ value was significantly higher in fellow eyes than eyes with MH on postoperative month 6 (p<0.0001).

Conclusion: In our study, it was found that the reduction in the postoperative FAZ value when compared to baseline persisted until month 6 after successful surgery. We consider that retinal orientation to the macula center , filling the spaces with neuroglial cells, micro-vascular damage and retinal remodeling play a role in this decrease in FAZ measurements after successful surgery.

Keywords: Macular hole, optical coherence tomography angiography, foveal avascular zone, pars plana vitrectomy, retina

INTRODUCTION

Macular hole (MH) is a retinal defect that involves all layers[1]. It was first described by Knapp in 1869[2]. In MH, the symptoms include decreased visual acuity, metamorphopsia and central scotoma. The incidence has been reported as 1: 3300 after 55 years of age[3]. More than one-half of patients are older than 65 years. It is 2-3 folds more common among women. The incidence of bilateral MH is 20%[5].

MH is idiopathic in most cases. The vitreal adhesions, tangential traction, abnormal posterior vitreous detachment and partial dehiscence at posterior vitreous cortex play role in the pathogenesis[5, 6].

Fundus examination, optical coherence tomography (OCT) and, recently, OCT angiography (OCTA) are used for diagnosis and staging in MH. In previous studies, it was found that there were alterations in retinal vascular blood flow between preoperative and postoperative OCTA in MH patients[7, 8]. It was proposed that a rearrangement developed in retina and foveal avascular zone (FAZ) value after closure of MH after successful surgery[9, 10].

Currently, the treatment is surgery in macular hole. The most effective method is internal limiting membrane peeling plus chromovitrectomy plus intraocular tamponade (gas or air)[11].

We believe that retinal vascularity can be involved in the development of MH and that retinal vascular remodeling can occur with successful surgery. In addition, we think that the clarification of differences between eyes with MH and contralateral health eyes in the same patient will contribute elucidating etiopathogenesis of MH disease. Thus, we

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Received: 05.04.2022
Accepted: 28.06.2022
J Ret-Vit 2023; 32: 83-90
DOİ: 10.37845/ret.vit.2023.32.15

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aimed to investigate preoperative and postoperative FAZ changes and role of FAZ in the pathogenesis of MH disease.

MATERIAL AND METHODS

Patient Selection

This retrospective study included 60 eyes of 30 patients who presented to Retina Unit in Ophthalmology Department of Antalya Teaching and Research Hospital, Health Sciences University and underwent surgery due to macular hole. Three patients were excluded due to incomplete data. Two patient underwent re-operation as the macular hole failed to close after first surgery. ILM peeling plus free flap technique was used and macular hole was closed during follow-up in these patients. However, the patients were excluded du to need for second surgery.

The surgery for macular hole was performed in the single eyes of 25 patients without exclusion criteria; thus, study included 25 eyes underwent surgery. In addition, 18 of the healthy fellow eyes were also included to the study. Of the 7 healthy fellow eyes excluded, there was history of previous MD surgery in 2 eyes, history of epiretinal membrane in one eye, lamellar hole in one eye, vitreomacular traction in one eye and history of pars plana vitrectomy for retinal detachment in one eye. All patients had idiopathic MH.

Exclusion criteria: Pathologies other than macular hole (e.g. glaucoma, uveitis, diabetic retinopathy, amblyopia, epiretinal membrane); myopia >-6 diopters; axial length>26 mm, previous history of ocular surgery other than uncomplicated cataract surgery; and systemic diseases.

In all patients, data regarding demographic characteristics (age, gender, systemic diseases etc.) and finding of ocular examination were extracted from patient files. In addition, the best corrected visual acuity was measured at presentation and after treatment using ETDRS (Early Treatment Diabetic Retinopathy Scale). The decimal system was used to analyze visual acuity data. Fundus examination was performed in all patients. The OCTA images were obtained at baseline and on month 1, 3 and 6 after surgery. The OCTA images were captured using "Spectral-domain OCTA" (AngioVue; Optovue, Inc, Fremont, CA).

OCTA analysis

OCTA measurements were performed at 6x6 mm HD angiography retina scale. The images with poor quality due to motion artifacts and other artifacts were excluded. The images with signal quality poorer than 6/110 were excluded from analyses.

The patients included were classified into two groups: minimum macular hole size (MMHS) < 400 µm or >400 µm (Figure 1).

FAZ: FAZ measurement was defined as FAZ area (mm^2) estimated by automated mode (Figure 2, 3).

Surgical technique

All surgical procedures were performed using Leica F19 model surgical microscope and Constellation Vitrectomy System (Alcon, Fort Worth, TX, USA). All surgeries were performed under retrobulbar anesthesia by a single surgeon. In all eyes, standard pars plana chromovitrectomy. Again, core vitrectomy was performed in all eyes and posterior hyaloid peeling was performed in all eyes. After identification of ILM using ILM dye (OCUBLUE I.L.M. BLUE 1.0 ml Miray Medikal Bursa/Turkey) injected via intravitreal route, ILM was grasped at a point 2 disc diameter distant from foveal and peeled around fovea in a circular manner. Fluid-air and air-gas tamponade

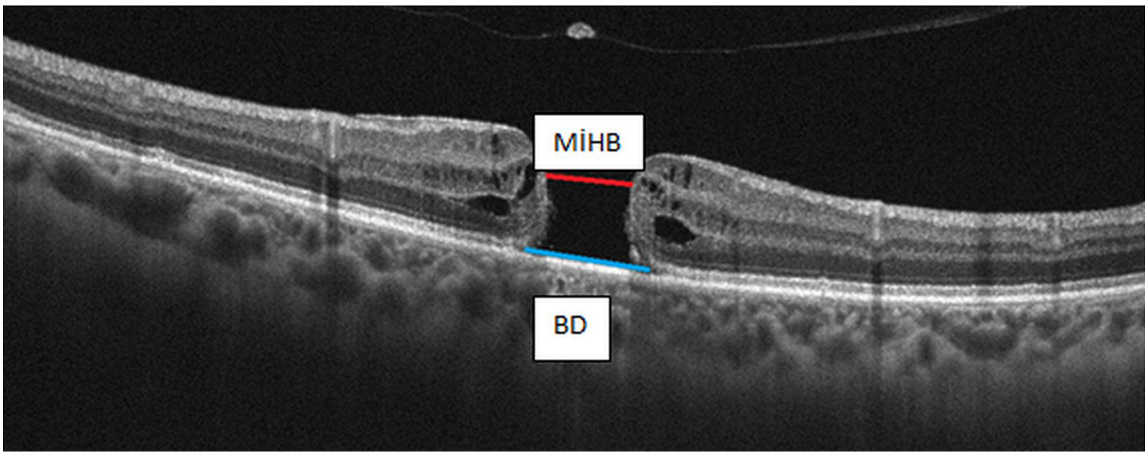

Figure 1: *Minimal macular hole size (MMHS) and BD (baseline diameter) on preoperative OCTA in a patient with macular hole*

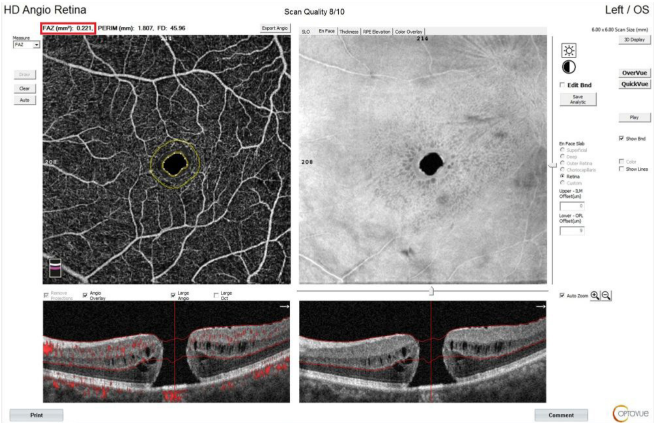

Figure 2: *Foveal avascular zone value on preoperative OCTA in a patient with a macular hole*

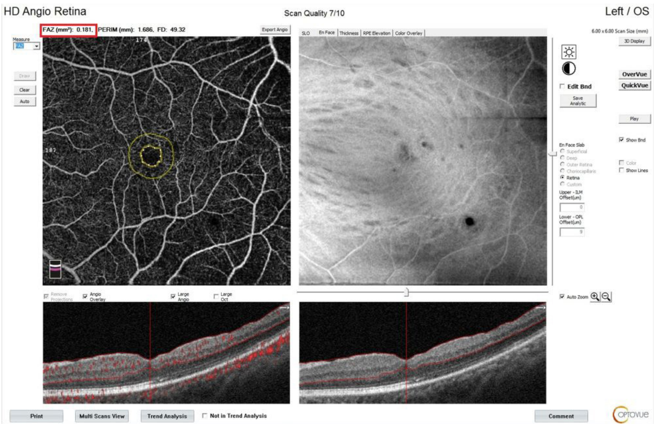

Figure 3: *Foveal avascular zone value on postoperative month in the patient presented in Figure 2*

changes were performed. Then, the surgery was completed following antibiotic administration. SF6 gas was preferred for the surgery.

Pars plan vitrectomy plus phacoemulsification plus posterior IOL implantation was performed In 13 eyes where cataract was detected at baseline ocular examination.

At postoperative period, patients were instructed to maintain prone position for minimum one week. All patients were prescribed antibiotic, steroid and non-steroid anti-inflammatory eye drops for 4 weeks.

Statistical analysis

The descriptive statistics are presented as frequency, percent, mean, standard deviation and minimum-maximum. Normality was tested using Shapiro-Wilk test. For variables with normal distribution, The time- and surgery-dependent changes was analyzed using ANOVA in repeated measurements. Binary comparisons were performed using Bonferroni correction. For variables with skewed distribution, the time-dependent changes was analyzed using Friedman test and Wilcoxon test. Binary comparisons were performed using Bonferroni-Dunn procedure. The relationship between numerical data were analyzed using non-parametric Spearman's correlation test or parametric Pearson's correlation test where appropriate. All statistical analyses were performed using SPSS version 23.0. A p value<0.05 was considered as statistically significant.

FINDINGS

The study included 25 patients with a mean age was 66.40 ± 6.08. Of the patients, 13 were women with a mean age of 65.38±5.14 years and 12 were men with a mean age of 67.50 ± 7.03. The surgery was performed in right eye in 13 patients and in left eye in 12 patients. The minimum macular hole size was <400 µm in 12 patients and >400 µm in 13 patients. Table 1 presents demographic characteristics.

The best-corrected visual acuity (BCVA) was found as 0.13 ± 0.07 at baseline and 0.49±0.23 on postoperative month 6, indicating a significant improvement (p=0.002). No significant correlation was detected between BCVA on postoperative month 6 and FAZ value at baseline or on postoperative month 6 (p=0.765 and p=0.697, respectively.

Mean FAZ value was 0.30 ± 0.08 mm² at baseline, 0.22 ± 0.11 mm² on postoperative month 1, 0.20 ± 0.11 mm² on postoperative month 3 and 0.20 ± 0.10 mm² on postoperative month 6 (Table 2). In the group with MMHS ≤400 µm, there was a decrease in the FAZ until postoperative month 3, which was, then, increased until postoperative month 6. In the group with MMHS >400 µm, there was a decrease in the FAZ until postoperative month 1, which was, then, increased until postoperative month 6. It was found that the decrease from baseline to postoperative month 1, the change between postoperative month 1 or the decrease from postoperative month 3 to postoperative month 6 were

Table 1: *Demographic characteristic of the patients*

Patient	**Mean ± SD**
Age	66.40 ± 6.08
Female/Male	13/12
Female age/Male age	65, 38 ± 5, 14 / 67, 50 ± 7, 03
Right eye/Left eye	13/12
MMHS <400 (µm)	12
MMHS >400 (µm)	13
Mean MMHS (µm)	417, 84 ± 172, 97
Mean baseline distance (µm)	1006, 40 ± 288, 08

MMHS : Minimal macular hole size; SD: Standard deviation

Table 2: *Foveal avascular zone values according to time and groups*

	Minimum macular hole size		
	≤400	**>400**	**Control**
Foveal Avascular Zone	Mean±SD	Mean±SD	Mean±SD
(mm²)	Min-Max	Min-Max	Min-Max
	n=12	n=13	n=18
Baseline	0.27 ± 0.11	0.31 ± 0.06	0.30 ± 0.08
	0.13-0.47	0.22-0.40	0.13-0.47
Month 1	0.20 ± 0.10	0.23 ± 0.12	0.22 ± 0.11
	0.08-0.34	0.08-0.50	0.08-0.50
Month 3	0.21 ± 0.19	0.19 ± 0.11	0.20 ± 0.11
	0.15-0.40	0.07-0.49	0.07-0.49
Month 6	0.22 ± 0.12	0.19 ± 0.09	0.20 ± 0.10
	0.02-0.40	0.07-0.43	0.02-0.43
SD: Standard deviation; Min: Min-max: minimum-maximum			

insignificant ($p=0.082$, $p=0.99$ and $p=0.99$, respectively). However, it was found that the decrease from baseline to postoperative month 6 and the decrease from baseline to postoperative month 3 were statistically significant ($p=0.030$ and $p=0.049$, respectively). In addition, no significant difference was found between groups ($p=0.928$).

Figure 4 presents comparison of FAZ values according to the group and time.

In patients with macular hole in one eye and no ocular pathology in the fellow eye (18 patients), mean FAZ value was 0.26 ± 0.09 mm² at baseline and 0.17 ± 0.02 mm² on postoperative month 6 in eyes with MH while it was 0.36 ± 0.07 mm² at baseline. The baseline FAZ value in healthy fellow eyes was higher than FAZ values measured at baseline and on postoperative month 6 in eyes with MH, indicating a significant difference ($p=0.001$ and $p<0.0001$, respectively) (Table 3).

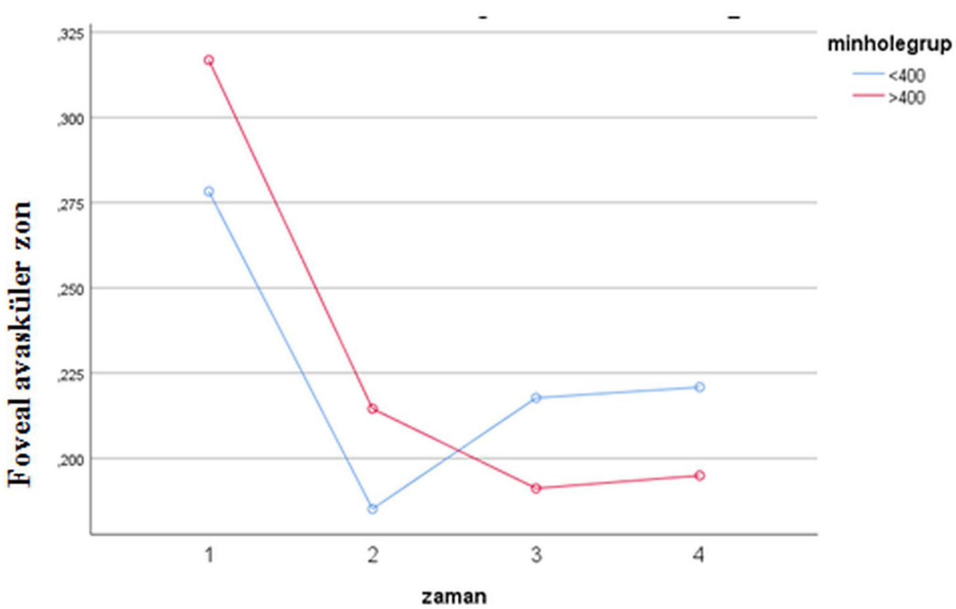

Figure 4: *Comparison of foveal avascular zone measurements obtained at 4 time points (baseline, postoperative month 1, postoperative month 3 and postoperative month 6) according to groups*

Table 3: *Comparison of baseline foveal avascular zone value of healthy fellow eye with foveal avascular zone value of eyes with MH at baseline and on postoperative month 6*

	Group	N	Ort.	S.S.	Min.	Max.	P
Foveal avascular zone baseline (mm²)	Control	18	0.36	0.07	0.27	0.53	
Foveal avascular zone baseline (mm²)	Patient	18	0.26	0.09	0.13	0.40	0.001
Foveal avascular zone month 6 (mm²)	Patient	18	0.17	0.08	0.02	0.32	<0.0001

SD: Standard deviation; Min: Min-max: minimum-maximum

No significant correlation was found between FAZ measurements on postoperative month 6 and baseline FAZ measurement in eyes with MH (p=0.106). There was a significant, negative correlation between FAZ measurement on postoperative month 6 and central foveal thickness (CFT) on postoperative month 6 (r=-0.65, p=0.001) (Figure 5). No significant correlation was found between FAZ measurement on month 6 and baseline CFT in healthy fellow eye (p=0.675).

There were significant negative correlations between baseline FAZ and superficial capillary plexus (SCP) total retinal vascular density (TRVD) at baseline, SCP foveal vascular density (FVD) at baseline, SCP parafoveal vascular density (PEFVD) at baseline and deep capillary plexus (DCP FVD at baseline (r=0.54 p=0.005; r=0.57 p=0.003; r=0.41 p=0.041; r=0.43 p=0.03; r=0.71 p<0.0001, respectively) (Table 4).

DISCUSSION

In this study, we evaluated changes in preoperative and postoperative FAZ values in patients with idiopathic MH.

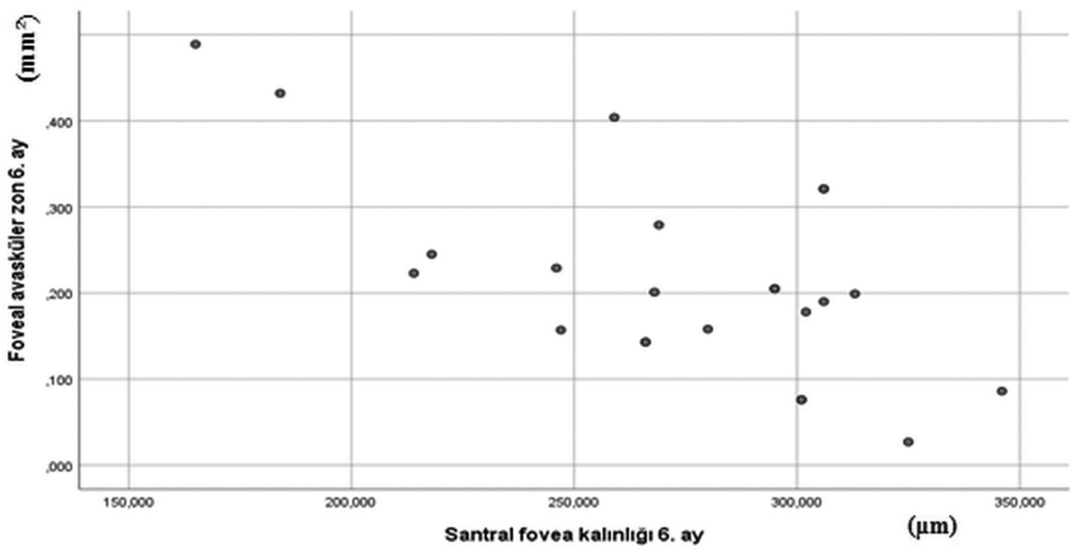

Figure 5: *Correlation between foveal avascular zone measurement and central foveal thickness on postoperative month 6*

Table 4: *Correlation between baseline foveal avascular zone value and baseline OCTA parameters*

	r	p
Superficial capillary plexus, total vascular density (%)	0.54	0.005
Superficial capillary plexus, foveal vascular density (%)	0.57	0.003
Superficial capillary plexus, parafoveal vascular density (%)	0.41	0.041
Superficial capillary plexus, perifoveal vascular density (%)	0.43	0.03
Deep capillary plexus, foveal vascular density (%)	0.71	<0.0001

Spearman's correlation test

In addition, we compared FAZ value between eyes with MD and healthy fellow eye.

In a study by Tomasz t al., mean FAZ value was found as 0.39 ± 0.07 mm² at baseline and 0.24 ± 0.07 mm² on postoperative month in patients underwent surgery for macular hole. In a study by Kita et al., mean FAZ value was measured 0.42 ± 0.12 mm² at baseline and 0.23 ± 0.12 mm² on month 6 in 25 patients diagnosed as MH. Again, in a study by Baba et al., mean FAZ value was found as 0.45 ± 0.14 mm² at baseline and 0.25 ± 0.08 mm² on month 6 in 16 patients diagnosed as MH. The decreases were found as significant in these studies (p<0.0001, p<0.0001, p<0.0001)[3, 12, 13].

In a study by Tsuboi t al., surgery was performed in 51 patients with macular hole and OCTA measurements were performed at baseline and on postoperative month 1 and 6. It was found that mean FAZ value was 0.42 ± 0.11 mm² at baseline, 0.25 ± 0.09 mm² on postoperative month 1 and 0.31 ± 0.11 mm² on postoperative month 6. Authors found that there was a decrease in FAZ value from baseline to postoperative month 1 and from baseline to postoperative month 6 (p<0.0001)[14].

There was a decrease in FAZ value on postoperative month 3 when compared to baseline, indicating a significant difference (p=0.049) in agreement with above-mentioned studies. Again, there was a significant decrease in FAZ value on postoperative month 6 when compared to baseline (p=0.030).

In a study by Cho et al., surgery was performed in 18 patients with MH and OCTA measurements were performed on postoperative month 12. In eyes with macular hole, mean SCP FAZ value was 0.29 ± 0.11 mm² whereas mean DCP FAZ value was 0.39 ± 0.14 mm² at postoperative period. In the fellow eyes, mean SCP FAZ value was 0.45 ± 0.14 mm² whereas mean DCP FAZ value was 0.62 ± 0.22 mm² at baseline, indicating a significant difference (p=0.0001 and p <0.001, respectively)[1].

In a study by Kim et al., surgery was performed in 18 patients with macular hole and OCTA measurements were performed on postoperative month 6. In eyes with macular hole, mean SCP FAZ value was 0.27 ± 0.13 mm² whereas mean DCP FAZ value was 0.37 ± 0.13 mm² at postoperative period. In the fellow eyes, mean SCP FAZ value was 0.43 ± 0.09 mm² whereas mean DCP FAZ value was 0.56 ± 0.09 mm² at baseline, indicating a significant difference (p<0.001 and p <0.001, respectively)[10].

In a study by Baba et al., surgery was performed in 16 patients with macular hole and OCTA measurements were performed on postoperative month 3. In eyes with macular hole, mean FAZ value was 0.25 ± 0.08 mm² at postoperative period whereas baseline preoperative FAZ value was 0.36 ± 0.12 mm² in the fellow eyes, indicating a significant difference (p=0.003)[13].

In agreement with above-mentioned studies, baseline FAZ value in fellow eyes was higher than FAZ value at baseline and postoperative month 6 in eyes with MH, indicating a significant difference (p=0.001, p<0.0001).

It has been proposed that there is a central movement in retina as a result of MH closure following successful surgery. Thereby, MD-related central gap is filled, explaining decrease in FAZ. It is also proposed that FAZ values are decreased due to micro-vascular damage occurred during ILM peeling in MH surgery. After surgery, retina undergoes vascular remodeling when MH is closed and choriocapillaris blood flow is improved. Concurrently, glial proliferation occurs together with vascular remodeling and the gap is filled by neuroglial cells. It is thought that FAZ value is decreased as a result of vascular remodeling and MH formation[3, 13, 14].

In a study by Kim et al., it was found that postoperative SCP FAZ and DCP FAZ values were negatively correlated with postoperative BCVA; in addition, it was found that postoperative BCVA was negatively correlated with CFT and FAZ values in patients underwent MH surgery (r=0.561; p=0.038, r=0.602; p=0.025, r=0.47; p=0.05, r=0.6; p=0.01, r=0.59, p=0.01, respectively)[3, 10].

No significant correlation was detected between postoperative BCVA and postoperative or baseline FAZ values in patients underwent MH surgery in the studies by Yun et al.[7], Baba et al.[13] and Tsubo et al.[14].

In our study, no significant correlation was found between postoperative FAZ value and postoperative BCVA or postoperative CFT measurements.

In previous studies, postoperative FAZ and CFT values were compared in patients underwent MH surgery. A significant, negative correlation was detected between postoperative FAZ and CFT values in the studies by Kim et al.[10], Kita et al.[12], Baba et al.[13] and Tsubo et al[14] (r=0.703, p<0.001, r = 0.515, p = 0.012, r=0.30, p=0, 0337, r = 0.589, p= 0.016, respectively). However, there was no significant correlation between postoperative FAZ value and CFT value of the fellow eye[12].

In our study, a significant, negative correlation was detected between FAZ value measured on postoperative month 6 and CFT measured on postoperative month 6 while there was no significant correlation between postoperative FAZ value and baseline CFT measurement in the healthy fellow eye.

In previous studies, it was found that CFT was thicker in eyes with lower FAZ value. It is thought that this is due to MD closure mechanism after surgery. It is thought that the mechanism retinal remodeling towards foveal centre[12, 14]. In a study by Takamura et al., a positive correlation was detected between postoperative BCVA and CFT[15]. Thus, postoperative FAZ and CFT values are important in predicting visual acuity gain.

In our study, a negative correlation was detected between baseline FAZ value, SCP vascular density and DCP FVD with lower FAZ value by higher vascular density. By formation of macular hole, parafoveal cysts are formed, disrupting retinal vascularity. After closure of MH by successful surgery, vascular remodeling is developed in retina and choriocapillaris blood flow is increased while FAZ is decreased at postoperative period[16-18].

This study has some limitations including limited sample size and shorter follow-up. This study shows role of FAZ in MH pathogenesis. Further studies with larger scale will contribute elucidating MD pathogenesis.

CONCLUSION

In our study, it was found that the reduction in the postoperative FAZ value when compared to baseline persisted until month 6 after successful surgery. We consider that retinal orientation to the macula center , filling the spaces with neuroglial cells, micro-vascular damage and retinal remodeling play a role in this decrease in FAZ measurements after successful surgery. In addition, we think that FAZ is decreased as a result of disrupted vascular anatomy due to parafoveal cyst formation.

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