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Choroidal thickness in Malaysian eyes with full-thickness macular holes

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患单侧特发性全层黄斑裂孔的马来西亚患者脉络膜厚度研究

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摘要

目的:比较患单侧特发性全层黄斑裂孔(FTMH)眼、对侧眼以及正常对照组黄斑脉络膜厚度。

方法:横断面研究。选取30例单侧特发性全层黄斑裂孔马来西亚患者,以及年龄、性别、种族相匹配的正常对照组。用激光干涉法测量研究对象眼轴长度。利用谱域光学相干层析成像技术获取增强深度成像光学相干断层成像。在黄斑中心凹处,距中心凹1 mm和2 mm鼻侧、颞侧、上方、下方测量脉络膜厚度。采用独立统计分析法、配对样本*t*-tests、chi-square tests和Pearson相关性检验进行数据分析。

结果:全层黄斑裂孔组平均中心凹脉络膜厚度为201.0±44.0 μm,对侧眼平均为225.3±51.4 μm,对照组为262.3±70.3 μm。相较于对照组,全层黄斑裂孔各部位脉络膜较薄($P<0.05$)。对侧眼组除了鼻侧1 mm和2 mm处,其余地方脉络膜厚度较对照组薄($P<0.05$)。全层黄斑裂孔组脉络膜厚度低于对侧眼组,但两组间差异无统计学意义($P>0.05$)。脉络膜厚度通常在中心凹处最高,在鼻侧最低。黄斑中心凹脉络膜厚度与年龄($r=-0.278$, $P=0.032$)和眼轴长度($r=-0.328$, $P=0.011$)呈负相关。

结论:单侧全层黄斑裂孔患眼与对侧眼和健康对照组相比,脉络膜厚度较低。

关键词:脉络膜厚度;黄斑裂孔;光学相干断层扫描;谱域;增强深度成像;海德尔堡

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Abstract

• AIM: To compare choroidal thickness at the macula in eyes with unilateral idiopathic full-thickness macular holes (FTMH) with that of unaffected fellow eyes, and eyes of normal control patients.

• METHODS: Cross-sectional study. Thirty patients with unilateral idiopathic FTMH and thirty age, sex, and race-matched controls were recruited. Axial lengths were measured using laser interferometry. Enhanced depth imaging optical coherence tomography images were obtained using Heidelberg spectral-domain optical coherence tomography. Choroidal thickness was measured at the fovea, and at 1 mm and 2 mm nasally, temporally, superiorly and inferiorly from the center of the fovea. Statistical analysis was performed using independent and paired *t*-tests, chi-square tests, and Pearson correlation tests ($P<0.05$).

• RESULTS: The mean subfoveal choroidal thickness was 201.0±44.0 μm in the FTMH group, 225.3±51.4 μm in the fellow eye group and 262.3±70.3 μm in the control group. The choroid was thinner in FTMH eyes at all locations when compared to control eyes ($P<0.05$). The fellow eye group also had thinner choroids than the control group at all locations except at 1 mm and 2 mm nasal to the fovea ($P<0.05$). Choroidal thickness in the FTMH group was lower than in the fellow eye group, but the differences were not statistically significant ($P>0.05$). Choroidal thickness was generally highest subfoveally and lowest nasally. Subfoveal choroidal thickness was negatively correlated with age ($r=-0.278$, $P=0.032$), and axial length ($r=-0.328$, $P=0.011$).

• CONCLUSION: Choroidal thickness is lower in both eyes of patients with unilateral FTMH compared to healthy control eyes.

• KEYWORDS: choroidal thickness; macular holes; optical coherence tomography; spectral-domain; enhanced depth imaging; Heidelberg
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INTRODUCTION

A full-thickness macular hole (FTMH) is a defect in the retinal tissue in the foveal region which affects central

vision[1]. The pathogenesis of idiopathic FTMH has been extensively studied, and it is currently widely accepted to be caused by tangential vitreofoveal traction. However, macular holes also have been reported in eyes which have undergone previous vitreous surgery, and in eyes with pre-existing complete posterior vitreous detachment where there is absence of vitreofoveal traction[1-5]. These findings imply that other factors may play a role in the formation of macular holes, such as foveal cystic degeneration and local vascular alterations.

The choroid may also have a role in the pathogenesis of macular hole formation. This highly vascularized layer supplies oxygen and nutrients to the outer retina and photoreceptors, and has been implicated in the pathophysiology of various eye conditions including central serous retinopathy, Vogt-Koyanagi-Harada disease, age-related macular degeneration, and polypoidal choroidal vasculopathy[6-7]. In particular, reduced choroidal blood flow has been observed in eyes with macular holes, suggesting that choroidal hypoperfusion may be a predisposing factor in the development of macular holes[8].

Advancements in optical coherence tomography (OCT) have enabled the measurement of choroidal thickness by using the enhanced depth imaging (EDI) technique[9]. Studies have shown that choroidal thickness may be used as an indirect measurement of choroidal blood flow and ocular perfusion[10-11]. As the fovea depends on the choroidal vasculature for nourishment and removal of metabolic waste, thinning of the underlying choroid may indicate a decrease in oxygen and nutrient supply to the highly metabolically active region, resulting in an increased susceptibility to damaging factors and subsequent dysfunction[8,12-13]. Recent studies have showed that choroidal thickness is reduced in eyes with macular holes compared to normal healthy eyes, demonstrating a relationship between choroidal thinning and macular holes which further supports the theory of choroidal abnormalities in the formation of macular holes[1-5].

This study was conducted to determine choroidal thickness in the macular area in predominantly Malay race eyes with idiopathic FTMH, comparing it with the unaffected fellow eyes, and healthy control eyes. The intended outcome was to observe if patients with thinner choroids should be monitored closely for the development of macular holes.

SUBJECTS AND METHODS

This cross-sectional study was approved by the Malaysian Medical Research and Ethics Committee (MREC), and followed the tenets of the Declaration of Helsinki. It was conducted at the Department of Ophthalmology in Selayang Hospital from June 2016 to December 2016. All participants were informed regarding the purpose of the study and tests that were being performed on them. Written informed consent was obtained prior to recruitment of participants.

All patients above 18 years of age with unilateral idiopathic FTMH (Stages 2-4) and an unaffected fellow eye were recruited. The staging of the macular holes was based on the Gass classification. Exclusion criteria included presence of macular pathologies such as age-related macular degeneration, polypoidal choroidal vasculopathy, myopic maculopathy, diabetic retinopathy with or without maculopathy, macular edema or macular scar, previous retinal laser or surgery, axial length more than 26 mm, amblyopia, glaucoma, previous history of uveitis, central serous chorioretinopathy, ocular trauma or tumor, significant media opacities that may interfere with optical coherence tomography, using of systemic steroids or any intravitreal medications, systemic conditions that may affect the eyes such as systemic lupus erythematosus, rheumatoid arthritis, uncontrolled diabetes mellitus and uncontrolled hypertension, and a history of smoking. For each recruited patient with unilateral FTMH, an age, sex, and race-matched control was recruited. The exclusion criteria for controls were similar to those of the patients with FTMH. In the control group, one randomly selected eye was included in the study.

The eyes were divided into three groups, Group A (eyes with FTMH), Group B (unaffected fellow eyes), and Group C (control eyes). All participants had a full medical history taken to obtain information such as duration of symptoms, past ocular history and co-morbidities. A full slit-lamp examination of the anterior segment and fundus was performed on all participants. Axial length was measured using an IOL Master 500 (Carl Zeiss Meditec AG, Jena, Germany) by a trained optometrist. Choroidal images were then captured using a Heidelberg Spectralis OCT (Heidelberg Engineering, Heidelberg, Germany) with the EDI technique. Seven sections, each comprising 100 averaged scans, were obtained in a 5×15 degree rectangle encompassing the macula. The horizontal and vertical sections going directly through the center of the fovea were selected. In eyes with idiopathic FTMH, the horizontal and vertical scans passing through the center of the hole were taken. Acquisition of scan images was done between 11 a.m. to 1 p.m., to take into account the diurnal variation of choroidal thickness. OCT imaging of the choroid, and subsequent choroidal thickness measurement was performed by a single operator to reduce inter-observer bias. The thickness of the choroid was measured from the outer portion of the retinal pigment epithelium (RPE) to the inner surface of the sclera. The outer portion of the RPE and the inner surface of the sclera were identified, and red lines were placed on them manually (Figure 1). The OCT software automatically displayed the thickness between the 2 red lines. Measurements were taken at the fovea, and at 1 mm and 2 mm nasally, temporally, superiorly and inferiorly from the center of the fovea.

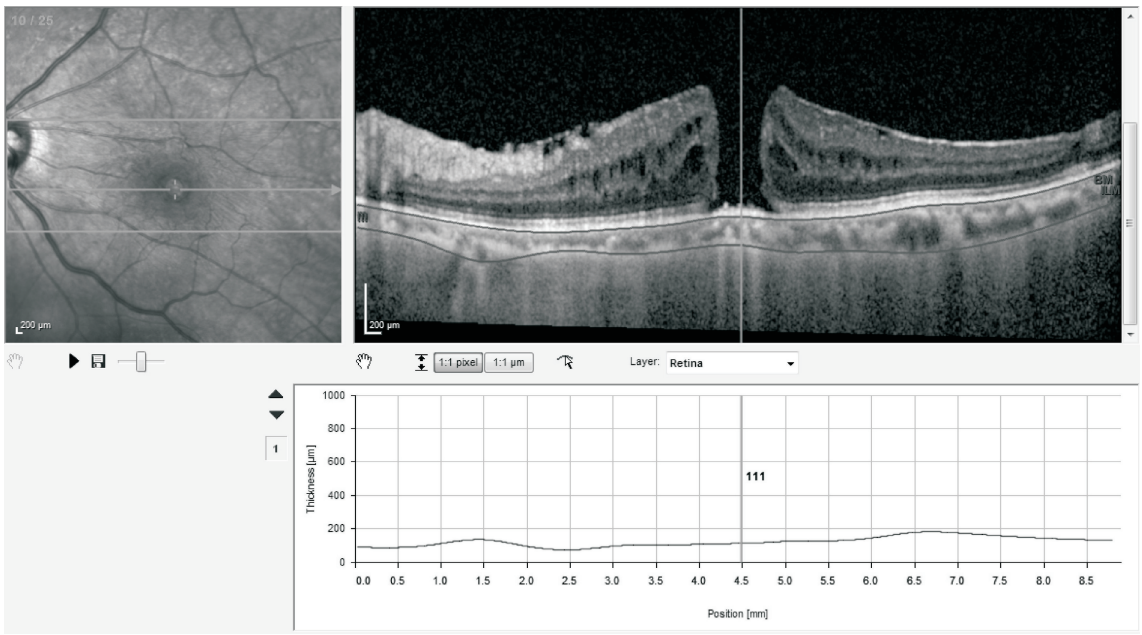

Figure 1 Enhanced depth imaging OCT horizontal scan of an eye with a macular hole Measurement of the subfoveal choroidal thickness was taken from the outer portion of the retinal pigmented epithelium to the inner surface of the sclera.

Table 1 Demographic data and clinical characteristics of patients and controls

Parameters	Data of patients(n=30)	Data of control(n=30)	P
Age (y)			
Mean±SD	66.2±6.1	65.9±6.0	0.848[a]
Range	54-78	52-77	
Gender, n (%)			
M	8(26.7)	8(26.7)	>0.995[b]
F	22(73.3)	22(73.3)	
Ethnic group, n (%)			
Malay	15(50)	15(50)	>0.995[b]
Chinese	10(33.3)	10(33.3)	
Indian	5(16.7)	5(16.7)	
Comorbidity, n (%)			
Diabetes mellitus	6(20)	8(26.7)	0.542[b]
Hypertension	13(43.3)	17(56.7)	0.302[b]

[a]Independent t-test (Group A *vs* Group C; Group B not taken into consideration as Group A and Group B consist of the same patient);
[b]Chi-square test (Group A *vs* Group C; Group B not taken into consideration as Group A and Group B consist of the same patient).

Statistical analysis was performed using Statistical Package for Social Science, version 20.0 (SPSS, Inc., Chicago, Ill., USA). All results were expressed as mean±SD if the variables were continuous and as percentage if categorical. Independent t-tests were used to compare the FTMH and fellow eyes with control eyes, while paired t-tests were used to compare between FTMH and fellow eyes. Chi-square tests were used to compare categorical data. Finally, Pearson correlation analysis was performed to look at the correlations between choroidal thickness and age, and axial length (P<0.05).

RESULTS

Thirty eight patients with unilateral idiopathic full-thickness macular holes were initially evaluated. Eight were excluded because they did not fulfill the eligibility criteria: 2 had glaucoma, 3 had diabetic retinopathy, 1 had previous ocular trauma, and 2 had eyes with poor delineation of the choroidal-scleral junctions on the scans. The demographic data and clinical characteristics of all groups are summarized in Table 1. The duration of those patients with a macular hole was 12.2±9.9 (range: 1-48) mo, the lacular hole diameter was 1075.5±40.5 (range: 495-1840) μm, the number of eyes in different stages of macular hole was 7(23.3%) in Stage 2, 19(63.3%) in Stage 3, 4(13.3%) in Stage 4. The axlial length in Group A, Group B and Group C was 23.60±0.98, 23.59 ± 0.97, 23.27 ± 0.69 mm, respectively and the differences between either two of the groups were not significant (Independent t-tests to compare Group A with Group C, and Group B with Group C; Paired t-test to compare Group A with Group B). There were no statistically significant differences in age, gender, ethnic group, comorbidities between the groups.

The mean subfoveal choroidal thicknesses were 201.0±

Table 2 Choroidal thickness at various locations in macular holes, fellow eyes, and control groups

Location	Mean±SD (μm)			*P*		
	Group A	Group B	Group C	Group A *vs* C[a]	Group B *vs* C[a]	Group A *vs* B[b]
SFCT	201.0±44.0	225.3±51.4	262.3±70.3	<0.001	0.024	0.055
S 1 mm	200.7±55.7	219.0±57.4	265.0±69.2	<0.001	0.006	0.214
S 2 mm	192.5±54.6	218.3±47.9	265.0±72.1	<0.001	0.004	0.056
I 1 mm	190.2±39.0	202.6±54.8	255.0±76.0	<0.001	0.003	0.318
I 2 mm	179.6±44.7	190.8±51.7	240.0±68.0	<0.001	0.002	0.376
N 1 mm	184.4±43.9	206.1±49.8	233.3±74.0	0.003	0.096	0.078
N 2 mm	157.2±42.3	168.1±51.3	199.3±72.1	0.007	0.056	0.374
T 1 mm	195.9±50.0	219.7±50.8	258.3±64.2	<0.001	0.013	0.072
T 2 mm	191.9±52.0	205.3±43.9	247.5±61.9	<0.001	0.003	0.285

SFCT: Subfoveal choroidal thickness; S: Superior; I: Inferior; N: Nasal; T: Temporal; [a]Independent *t*-test; [b]Paired *t*-test.

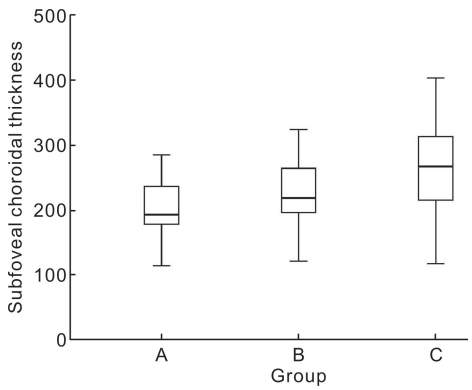

Figure 2 Boxplot showing subfoveal choroidal thickness in the three groups A: FTMH eyes; B: fellow eyes; C: control eyes; The differences between Groups A and C, and between Groups B and C were statistically significant ($P<0.05$).

44.0 μm in the FTMH group, 225.3±51.4 μm in the fellow eye group and 262.3±70.3 μm in the control group (Figure 2). Choroidal thicknesses at other locations in the macular region for the same groups are listed in Table 2. The choroid was thinner in FTMH eyes at all locations when compared to control eyes ($P<0.05$). The fellow eye group also had thinner choroids than the control group at all locations except at 1 mm and 2 mm nasal to the fovea ($P<0.05$). Choroidal thickness in the FTMH group was lower than in the fellow eye group, but the differences were not statistically significant ($P>0.05$). Choroidal thickness was generally highest subfoveally and lowest nasally. When we looked at the fellow eye and control groups together *i.e.* eyes without macular holes, there were negative correlations between subfoveal choroidal thickness and age ($r=-0.278$, $P=0.032$), and axial length ($r=-0.328$, $P=0.011$).

DISCUSSION

In this study, patients with idiopathic FTMH were found to have thinner choroids in the affected eye as well as in the unaffected fellow eye, in comparison with normal control eyes. The FTMH group had thinner choroids than their fellow eyes but the differences were not statistically significant. Our results were similar to those reported by Zhang *et al*[1-3]. However, our study is different from these mentioned as it includes a majority of patients from the Malay race, which has not been reported before; previous studies have investigated either Caucasian or Chinese patients[1]. The use of separate independent and paired *t*-tests in our study is also more appropriate than comparing the affected eye, its unaffected fellow eye, and control eyes together using ANOVA or Kruskal-Wallis tests[2-3]. Finally, Zeng *et al*[4-5] also reported that their macular hole eyes had thinner choroids than the unaffected fellow eyes, but the former study measured slightly different areas of the macula and the latter study involved patients with unilateral FTMH and contralateral vitreomacular adhesion.

Considering the results of this study and others previously, there is strong evidence linking choroidal thinning and macular holes. We believe that choroidal thinning is associated with the formation of macular holes through choroidal hypoperfusion[1-5,8]. Heidelberg retinal flowmetry has shown that mean blood flow and velocity are reduced in eyes with FTMH as compared to normal eyes[8]. The authors proposed that choroidal hypoperfusion could be a factor for FTMH formation by reducing perfusion to the foveal avascular zone, thus leading to decreased nutrient transport. While this choroidal thinning could be a consequence rather than a result of the macular holes, we believe that this is less likely as the unaffected fellow eyes also have thinner choroids. Furthermore, other studies have also shown no difference in choroidal thickness three to six months after successful surgical closure of macular holes[3,14-15].

We found that choroidal thickness was generally highest subfoveally and lowest nasally. We also found negative correlations between choroidal thickness and age, and axial length. The thickness of the choroid is affected by several factors, including age, axial length and diurnal fluctuations[12-13,16]. These factors were taken into consideration in this study. The patients were age-matched, the SD-OCT images of the choroid were obtained at a specific time of the day, and the mean axial lengths between the groups were similar. In addition, systemic diseases, most notably diabetes mellitus and hypertension may also affect choroidal thickness[17-20]. The relationship between diabetes mellitus and choroidal thickness is controversial. In the

Beijing Eye Study, it was reported that patients with diabetes mellitus had thicker choroids than normal controls, and the stage of diabetic retinopathy did not have an additional effect on choroidal thickness[17]. In a study from India, the authors found that patients with diabetes mellitus regardless of their diabetic retinopathy status had thinner choroids compared to normal controls, and the thinning increased with increasing severity of diabetic retinopathy[18]. For systemic hypertension, one study found the choroid to be thinner in hypertensive patients[19]. However, a more recent study found no association between systemic hypertension and choroidal thickness[20]. In our study, patients with diabetic retinopathy were excluded. The numbers of patients with diabetes mellitus and hypertension were slightly more in the control group but the differences were not statistically significant.

We acknowledged some limitations of this study. First was the method of measurement of choroidal thickness. From the OCT scans, the choroidal-scleral junctions had to be identified and delineated manually by the operator, thus introducing potential measurement bias. Some images we obtained were of inferior quality and the choroidal-scleral junction could not be identified properly. Additionally, this method also prevents blinding of the operator to the diagnosis, as the macular holes are readily seen on the OCT scans. We also did not take into account any possible effect of lateral magnification on the choroidal thickness measurements. However, as there were no statistically significant differences in axial lengths between the groups, we anticipated any effect to be minimal. Finally, as a suggestion for future studies, choroidal thickness in eyes with macular holes could perhaps be correlated with choroidal blood flow. Newer technologies such as optical coherence tomography angiography (OCTA) offer a non-invasive way to measure choroidal blood flow and choroidal thickness at the same time. Longitudinal cohort studies too may determine the exact relationship between choroidal thickness and the development of macular holes.

Choroidal thickness is reduced in patients with unilateral idiopathic FTMH and the fellow unaffected eye. This may indicate choroidal hypoperfusion and therefore, patients with thinner choroids should be monitored closely for the development of the macular disorder.

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