

Factors affecting choroidal thickness

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影响脉络膜厚度的因素

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摘要

本文详细描述了脉络膜厚度的影响因素,眼科疾病中脉络膜厚度的变化以及血流与脉络膜厚度之间的关系。脉络膜厚度受许多因素影响,例如年龄,性别,眼压,屈光不正,轴长,收缩压,每日节律,身体位置,吸烟史等,脉络膜厚度异常与许多眼科疾病也显著相关。脉络膜厚度在眼科疾病的诊断和治疗中非常重要。

关键词: 脉络膜厚度;血流;光学相干断层扫描血管造影

Abstract

• This article summarized the choroidal thickness systematically and followed by relevant findings which describes the influencing factors of the choroidal thickness, the changes of the choroidal thickness in ophthalmic diseases and the relationship between the blood flow and the choroidal thickness detailedly. Choroidal thickness is affected by many factors, such as age, gender, intraocular pressure, refractive error, axial length, systolic blood pressure, daily rhythm, body position, smoking history, etc. And choroid is significantly correlated with many ophthalmic diseases. Choroidal thickness is of great importance in the diagnosis and treatment of ophthalmic diseases.

• **KEYWORDS:** choroidal thickness; blood flow; optical coherence tomography angiography

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INTRODUCTION

The choroidal thickness (CT) refers to the thickness from the retinal pigment epithelial layer to the junction of the choroid and the sclera^[1]. Histologically, the choroid is often been divided into five layers; Bruch's membrane starting from the inner side, the choriocapillaris, the two vascular layers (Haller's and Sattler's), and the suprachoroidea. The thickening of the choroid may be related to the homeostatic control of eye growth^[2]. The morphology and structure of the choroid could not be observed in the past due to the limitations of medical technology and equipment. The invention of optical coherence tomography (OCT) realized the observation of choroid *in vivo*. It makes three-dimensional imaging possible. Measuring the thickness of the choroid is of great significance for the analysis of the pathogenesis and treatment of ophthalmic diseases using OCT. Moreover, the newly emerging optical coherence tomography angiography (OCTA) not only can measure choroidal thickness, but also the blood flow in the choroid layer, providing a better basis for the diagnosis, prevention and treatment of choroid-related diseases. OCTA is a potential novel tool to evaluate the choroid so that we can use this technique to assess the relationship between choroidal thickness and choroidal blood flow.

Variation in Choroidal Thickness in Physiological Conditions

The measurement of choroidal thickness can be divided into para papillary choroidal thickness and macular choroidal thickness. The posterior polar choroidal thickness varies with topography and differs in different locations. The thickness of choroid becomes thinner with age, increased degree of myopia and axial length (AL), and thicker with increased degree of hyperopia. There is an asymmetry in the choroidal thickness between the two eyes in a few people^[3]. Choroidal thickness can be measured in the majority of eyes using OCT and more clear with OCTA^[4]. The studies have showed that the temporal, superotemporal, superior, superonasal, and nasal thickness were significantly thicker than the inferonasal, inferior, and inferotemporal peripapillary choroidal thickness in healthy subjects. At birth, the choroid is approximately 200 μm thick and decreases to about 80 μm by age 90^[2]. Mean subfoveal choroidal thickness in healthy adults is approximately 300 μm ^[2]. Studies have found that subfoveal choroidal thickness (SFCT) under the age of 60 is not related to age, and the choroidal thickness decreases by

about 5.40 μm per year with age over 60 years old^[5-6]. According to Li *et al*^[6], for every one year of age and 1 mm increase in the axial length, the choroidal thickness is reduced by about 3 μm and 79 μm respectively. The study also showed that men's choroidal thickness is 99 μm thicker than women's. Another study showed that excluding the effects of age and AL, the choroidal thickness of healthy young participants is 18% higher in men than in women. This study explains the effect of sex in diseases related to choroidal thickness like myopia, central serous chorioretinopathy (CSC), and age-related macular degeneration (AMD). However, another study showed that choroidal thickness thins as the axis of the eye grows and is not related to gender. What's more, studies have found that the choroidal thickness has circadian rhythm, the choroidal thickness gradually thickens from 12:00 to 24:00 in the day, and the choroidal thickness gradually becomes thinner from 24:00 to 12:00 the next day^[7-8].

It has been known that choroidal thickness is related to age, gender, intraocular pressure, refractive error, AL, and systolic blood pressure^[9]. In addition, choroidal thickness is also related to many factors such as daily rhythm, body position, smoking history, *etc.* Some of these factors have been confirmed, and some have yet to be confirmed by further research^[9].

The Changes of Choroid Thickness in Ophthalmic Diseases

Diabetic retinopathy Control eyes had greater SFCT compared to subjects with diabetes, with and without retinopathy. The thinning progressed with increasing severity of diabetic retinopathy (DR). Choroidal thinning may contribute to DR pathogenesis^[10]. Choroidal thickness may be related to the degree of severity of the retinopathy. A significant decrease in the CT presents in patients with diabetic macular edema. With the occurrence and exacerbation of DR, SFCT thickened at the beginning and then thinned. SFCT was thicker in eyes with DME than in those without^[11]. Spectral-domain OCT is a noninvasive technology to assess the choroid and OCTA is an emerging technology in the evaluation of the vascular changes in proliferative diabetic retinopathy (PDR). The macular choroidal thickness of patients with DR is significantly thicker within 1wk after panretinal photocoagulation (PRP) treatment. With the time prolonging the choroidal thickness gradually decreases, and becomes even thinner than untreated. It is speculated that the measurement of choroidal thickness can be used as a new index to evaluate the therapeutic effect of sugar nets, which provides a new method for clinical guidance on whether to continue drug injection therapy and predict the therapeutic effect^[12].

Compared with the control group, the macular blood flow density of superficial retinal layer, deep retinal layer and choroidal capillary layer in the patients with diabetic retinopathy decreased significantly^[13]. By quantitatively measurement of the macular blood flow, OCTA may be used

for monitoring the progression of diabetes, and early detection of diabetic retinopathy.

Refractive error The measurement of choroidal thickness values at each measurement point of the myopia study group was significantly lower than that of the reference group^[14]. The choroidal thickness of the macular fovea in patients with moderate and high myopia is thinner with the equivalent mirror, eye axis, and intraocular pressure^[15]. Kaderli *et al*^[16] showed that as the degree of hyperopia increases in all quadrants, the choroid is significantly thickened, and the choroid thickens as the AL becomes shorter. Macular choroid thickens as the hyperopic error increases as well as axial length decreases in short eyes^[16]. The thickest part of the choroid varies with the degree of myopia. Low myopia is in the fovea, moderate myopia is on the temporal side, high myopia is below, and super-high myopia greater than -10.00 D is above. It can be inferred that the change in choroidal thickness of the hyperopic eye is opposite to that of myopia. Studies have shown that the higher the diopter, the thinner the choroidal thickness, and there is a significant positive correlation between the two^[17-18].

The choroid is the only source of five layers of oxygen and nutrients outside the retina including the foveal avascular zone (FAZ). The changes in vascular structure, blood vessel density and blood flow directly affect the metabolism and function of the retinal visual cell layer. The choriocapillaris layer acts as a structure directly involved in the metabolic process, and the density of the capillaries is a key parameter representing its function. Studies have found that the choroidal capillaries in high myopia are thinner^[19-21]. OCT angiography (OCTA) will help to discover choroidal involvement by exploring the distribution of choroidal capillary density in children at critical stage of myopia and its correlation with choroidal thickness, axial length and diopter, providing a new perspective and entry point for the study of myopia mechanisms^[22]. Another study showed that the development of high myopia may be associated with the choroid perfusion. The reduced choroid perfusion lead to thinning choroidal thickness, which may play a role in the pathological process of choroidal neovascularization^[23].

Age-related macular degeneration The average choroidal thickness in dry age-related macular degeneration (AMD) patients was thinner than the normal subjects. Wet AMD is bot different from dry AMD patients^[24]. Indocyanine green angiography (ICGA) is an important imaging modality to prognosticate treatment outcome of polypoidal choroidal vasculopathy (PCV). The presence of choroidal vascular hyperpermeability (CVH) is related to best-corrected visual acuity (BCVA) in eyes with PCV^[25]. Increased choroidal thickness and choroidal vascular hyper permeability represent different functional disturbances and anatomical changes in PCV. A large number of recent studies have shown that intravitreal injection of anti-VEGF drugs treating wet AMD can significantly improve the patient's vision, and reduce choroidal thickness and blood flow resistance, and increase

choroidal perfusion^[26]. Intravitreal injection of ranibizumab (IVR) is one of the most effective therapies for neovascular age-related macular degeneration (nAMD). OCTA could evaluate the effect of intravitreal injection of conbercept for nAMD more safely, objectively and conveniently, suggesting a possible linkage of retinal thinning with vascular alterations^[27-28]. IVR for nAMD can lead to subfoveal choroid atrophy instead of RPE atrophy. IVR does not accelerate the atrophy progression of both RPE and choroid^[29-30].

Idiopathic macular holes Studies have shown that the choroid has thinned before the appearance of the macular hole^[31]. The pathogenesis of idiopathic macular hole may be related to the significant decrease of choroidal thickness. The choroidal thickness of the fellow eye is also significantly thinner than that of the normal controls, suggesting that the decrease of choroidal vascular metabolism may be the causative factor of idiopathic macular hole^[32]. They observed that the SFCT and choriocapillary blood flow area (CBFA) in the patients with idiopathic macular hole (IMH) are both reduced^[33].

Idiopathic macular epiretinal membrane There is a positive correlation between postoperative choroidal thickness and BCVA in patients with idiopathic macular epiretinal membrane^[34]. The choroidal thickness may be affected by the presence of idiopathic macular epiretinal membrane. A study showed that choroidal thickness has a tendency to decrease 3mo after vitrectomy with both epiretinal and internal limiting membrane (ILM) peeling^[35].

Central retinal artery occlusion Ahn *et al.*^[36] also found that SFCT of most severe CRAO was lower than the control group and the difference was statistically significant. Choroidal thinning suggests choroidal ischemia, further leading to destruction and atrophy of the outer retina. There is inner and outer retinal thickening in the acute stages of CRAO. Subsequently, it results atrophic changes in the inner and outer retina. These results support the use of OCT examination, in particular the measurement of baseline central macular thickness (CMT), in eyes with CRAO for accurately documenting the disease severity, staging, and predicting visual outcome^[36].

Traditionally, the blood supply to the retina comes from two different circulatory systems. The central retinal artery system supplies the inner lining of the retina, and the choroidal vasculature supplies the outer layer of the retina. However, in the acute CRAO macular area, the photoreceptor cell layer is also thickened, and the thickness is statistically different from the normal eye. OCTA can observe the blood flow of different levels of retina and choroid. In En Face mode, we observed that the blood of the outer retina and choroid also changed in the eyes of acute CRAO. Studies have shown that CRAO has reduced blood flow in the outer layer of the retina, and some patients have normal choroidal blood flow, but most patients have reduced choroidal blood flow. However, no matter whether the choroidal blood flow is normal or not, the retinal photoreceptor cell layer has dark areas. The phenomenon of

broadening suggests that the nutrient supply of photoreceptor cells may be accompanied by the simultaneous supply of retinal vessels and choroidal vessels^[37].

There exists a positive correlation between visual outcome and center retinal thickness (CRT) before receiving treatments. This study showed that BCVA was positively correlated with CRT after CRAO treatment. Chen *et al.*^[38] also found a positive correlation between visual acuity and CRT after CRAO eye treatment. Therefore, the initial CRT of CRAO can be used as a reference for assessing the final prognosis. Recently, some scholars have used OCTA to observe CRAO eyes, which can clearly show the reduction of superficial and deep capillary perfusion and abnormal blood flow distribution, and can more intuitively and accurately analyze the development of CRAO^[36].

Acute Vogt-Koyanagi Harada disease The choroid of Vogt-Koyanagi Harada disease (VKH) is significantly thickened, which may be related not only to inflammatory cell infiltration but also to increased exudation. The choroid was significantly thickened in the acute phase of VKH, and it was significantly thinner after glucocorticoid treatment, and the height of serous retinal detachment also decreased. After one month of corticosteroid treatment, choroidal thickness and serous retinal detachment returned to normal^[39].

OCTA can be used for quantitative evaluation of vascular densities of retinal and choroidal capillary layers in VKH. There is a significant increase in BCVA and vascular densities of all retinal and choroidal layers while a sharp thinning of SFCT through the systematic anti-inflammatory treatment of the acute VKH. In acute VKH, correlation test revealed a negative correlation between vascular density of the superficial capillary plexus (SCP), deep capillary plexus (DCP), choriocapillaris (CC) and BCVA, vascular density of the CC and SFCT, respectively. While no significant associations were found between BCVA and SFCT. Vascular densities of retinal and choroidal layers may become alternative imaging indicators apart from SFCT for surveillance of VKH^[40].

Central serous chorioretinopathy Studies showed that increased choroidal thickness and reduced retinal blood flow in patients with central serous chorioretinopathy (CSC)^[41]. Compared with controls, the choroid of acute idiopathic unilateral CSC and fellow eyes were diffusely thickened in the macular and peripapillary area. The choroid is thicker in CSC eyes than in the fellow ones. A study showed that there may be a threshold for SFCT, and when the threshold is exceeded, the accumulation of subretinal fluid is more likely to occur, leading to clinical symptoms of CSC^[42]. It is unclear whether OCT findings, distribution of the pachyvessels in the Haller's layer and attenuation of the inner choroid (choriocapillaris and Sattler's layer), indicate that choroidal thickening represents only the activity of the cytoplasm. The choroidal thickness of patients with CSC is significantly thicker than that of normal controls, and is often bilateral. The measurement of choroidal thickness by enhanced depth imaging-optical coherence tomography (EDI-OCT) technique has important

clinical significance for the diagnosis and treatment of CSC, and it is worthy of popularization and application^[43].

CSC seems to be a bilateral eye disease with choroidal focal ischemia followed by vessels congestion and hyperpermeability. OCT is a useful tool for monitoring choroidal thickness changes caused by choroidal vascular hyperpermeability. The degree of choroidal telangiectasia and subfoveal choroidal thickness in patients with central serous chorioretinopathy are significantly increased with the severity of the disease, and there is a positive correlation between them^[44].

Pachychoroid pigment epitheliopathy Pachychoroid pigment epitheliopathy (PPE)^[45] may have retinal pigment epithelial (RPE) abnormalities that correspond to the choroid that is abnormally hypertrophic. Clinically, there are no obvious symptoms, and vision is often normal. PPE can be regarded as a precancerous lesion of CSC. We cannot observe the blood flow signal of neovascularization in the lesion area using OCTA^[46]. It is characterized by abnormalities in RPE which correspond to the subchoroidal thickening. This disease may be associated with focal choroidal hyperpermeability and choroidal hypertrophy, and the choroidal capillaries become thinner, while the ratio of choroidal capillary layer thickness to total choroidal thickness would decrease.

Pachychoroid neovascuopathy Pachychoroid neovascuopathy (PNV)^[47] refers to a type of disease in which type I CNV accompanied by retinal pigment epithelium abnormalities or CSC. Often with a long history of chronic CSC, they are younger than AMD patients. OCT showed that type I CNV was located above the hypertrophic retina, and shallow irregular RPE detached. OCTA can be expressed as a neovascular blood flow signal tangled between RPE and Bruch's membrane^[46]. The disease progresses on the basis of PPE or CSC. The thinning of the choroidal capillaries produces ischemia-promoting expression of VEGF, which is a chronic inflammation of choroidal capillaries. It needs treatment when accompanied by macular exudation. The therapeutic effect of anti-VEGF alone is obtained. Affirmation, when the effect of treatment alone is poor, it is necessary to combine photodynamic therapy (PDT).

Focal choroidal excavation Focal choroidal excavation (FCE)^[48], without posterior scleral staphyloma and scleral bulging. Clinical manifestations are asymptomatic or mild visual blur, visual distortion, etc. They are often associated with CSC, PCV, PNV and other diseases^[49]. The fundus appears as a normal or non-specific pigment disorder or a punctate yellow-white lesion. OCT can be seen in two manifestations: 1) uniform depression; no separation between photoreceptor and RPE; 2) non-uniform depression; separation between photoreceptor and RPE, with reflective dark areas in the middle. OCTA showed no abnormal blood flow signal in the lesion area. Such diseases may be associated with congenital choroidal developmental defects, or local scarring of choroidal connective tissue during inflammatory processes leading to RPE contraction, reverse compression of

the choroidal capillary layer aggravating ischemia, and easy formation of CSC and choroidal neovascularization^[50]. If choroidal neovascularization is secondary, anti-VEGF therapy is required.

Peripapillary pachychoroid syndrome Peripapillary pachychoroid syndrome (PPS)^[51] refers to the place where the maximum thickness of the choroid is located next to the optic disc, rather than under the fovea. Clinically, hyperopia is more common, and male eyes are more common, often accompanied by crowded optic discs and choroidal folds. OCT showed intranasal or subretinal effusion of the macula, and the nasal choroid thickness of the macula was greater than that of the temporal RPE and the outer membrane of the retina (ELM). OCTA showed no abnormal blood flow signal in the lesion area. This type of disease is the ventricular syndrome effect caused by increased hydrostatic pressure caused by choroidal congestion under the optic disc. The cause of optic collateral congestion under the optic disc and the source of subretinal fluid under the optic disc are still unclear.

CONCLUSION

With the development of science and technology, the appearance of OCTA can measure the choroidal thickness of most people and the blood flow density of various layers of the retina. The software for measuring choroidal thickness and volume has a good application prospect for the follow-up of choroidal diseases. It has been documented that choroidal blood flow can affect choroidal thickness^[52]. A growing body of research suggests a possible link between choroidal thickness and vascular changes. OCTA is rapidly evolving, introducing faster and deeper scanning source devices, a wider scanning range, and artificial intelligence-guided segmentation and image analysis methods^[53]. In the future, OCTA is likely to become indispensable in clinical practice. The tools are critical for accurate assessment of the retina and choroidal microcirculation.

This article summarizes many ophthalmic diseases associated with choroidal thickness. The importance of choroidal thickness in the diagnosis and treatment of ophthalmic diseases can be seen. Thickening and thinning can reflect the progression of certain ophthalmic diseases. More importantly, there is a link between choroidal thickness and vascular changes, which can be monitored by OCTA. This article also describes a special type of choroidal thickening disease, pachy-choroid diseases, which is characterized by a diffuse or focal increase in choroidal thickness, the pathogenesis of Haller's layer vasodilatation (hypertrophic blood vessels) and the choroidal capillary layer and the Sattler's layer are thinned, with or without abnormalities in the retinal pigment epithelial layer covered by hypertrophic blood vessels. Whether choroidal vasodilation is venous congestion is not clear, and more imaging studies are needed in the future to determine the direction and velocity of blood flow in the body. These diseases have thickening of the choroidal thickness, and the measurement of choroidal thickness is very helpful for the diagnosis and prognosis of these diseases.

In conclusion, choroidal thickness is influenced by many factors, and is also significantly associated with many ophthalmic diseases, and is closely related to changes in the blood circulation of the eye. It is of great significance in the past, present and future.

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