A Meta-Analysis of Alterations in the Retina and Choroid in High Myopia Assessed by Optical Coherence Tomography Angiography

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Keywords

High myopia · Microvasculature · Optical coherence tomography angiography · Meta-analysis

Abstract

Background: High myopia (HM) is a risk factor for several pathological structural changes in retinal and choroidal thickness or vessel. To date, changes in retinal and choroidal microvasculature circulations in HM have yielded inconsistent results. **Objectives:** The objective of this article was to evaluate alterations in retinal and choroidal thickness, and capillary microvasculature using optical coherence tomography angiography (OCTA) in HM. **Methods:** PubMed, Embase, and the Cochrane Library databases were searched for relevant published studies. Primary outcomes were foveal avascular zone, vessel density, retinal nerve fiber layer (RNFL) thickness, foveal thickness, sub-foveal choroidal thickness, and chorio-capillary density. Alterations in outcomes were evaluated by standardized mean difference with a 95% confidence interval. **Results:** Eleven eligible articles were included for the meta-analysis. The whole superficial and deep vessel densities of macular and parapapillary superficial vessel density were lower in HM than in control eyes. The thickness of parafoveal RNFL, parapapillary RNFL, and sub-foveal choroid was significantly lower in HM eyes. Also, chorio-capillary

density was shown to be lower in HM eyes. **Conclusions:** The retinal and choroidal vessel network change may be related to the axial elongation in the progression of myopia. Furthermore, OCTA is an effective and noninvasive technology for monitoring the progress of myopia eyes.

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Introduction

High myopia (HM) is defined as a refractive error with a spherical equivalent (SE) of more than -6.0 diopters (D) and/or an axial length (AL) exceeding 26 mm. The prevalence of HM continues to rise across the world, particularly in younger populations [1, 2]. HM is always a risk factor for several pathological structural changes, including chorio-retinal atrophy, lacquer crack formation, myopic maculopathy, posterior scleral staphyloma, choroidal neovascularization, and other vision-threatening conditions. These changes are commonly associated with alterations in retinal and choroidal thickness or vascular alterations [3–5]. Benavente et al. [6] and Azemin et al. [7] reported that decreased retinal vessel density and choroidal blood flow in myopia are features that can be detected by fundus photography or color Doppler imaging. These changes lead to poor retinal or choroidal capillary perfu-

Fig. 1. Flowchart of study selection.

sion, ischemia and hypoxia, which may be possible indications for the development of refractive errors or AL.

Optical coherence tomography angiography (OCTA) is an advanced imaging technology that is used to noninvasively visualize the vasculature and can provide 3-dimensional detail of the retinal microvasculature but also the chorio-capillaries [8]. It can also be used to quantitatively assess retinal nerve fiber layer (RNFL) thickness, choroidal thickness, foveal avascular zone (FAZ), and vessel density. These measurements can provide new insights into the pathogenic mechanisms of retinal and choroidal diseases [9, 10]. Yang et al. [11] and Su et al. [12] demonstrated various changes in the retinal microcirculation chorio-capillaries of HM eyes. Li et al. [13] found that the superficial and deep vascular densities were decreased in HM eyes, while no statistically significant difference in the retinal microvessel blood flow velocity was

reported. He et al. [14] reported reductions in the peripapillary capillary and deep parafoveal vessel density along with an enlarged size of the FAZ in HM, but did not find any change in superficial parafoveal vessel density.

To date, changes in retinal and choroidal microvasculature circulations in HM have yielded inconsistent results underlying the need for a comprehensive meta-analysis. The primary aim of this study was to perform a meta-analysis study to evaluate alterations in retinal and choroidal thickness and capillary microvasculature in HM.

Methods

Search Strategy and Selection Criteria

This meta-analysis was performed based on PRISMA guidelines (online suppl. material 1; for all online suppl. material, see www.karger.com/doi/10.1159/000517096) [15]. PubMed, Em-

Table 1. Characteristics of 11 studies included in the meta-analysis

Study	Area	Device	Eyes HM/ control, <i>n</i>	Mean age, HM/ control, years	AL, HM/control, mm	Refractive error, HM/control, D	NOS score
Ucak et al. [18]	Turkey	Nidek	92 70	35.19±14.29 36.22±11.42	26.97±0.79 23.09±0.78	−8.13±1.71 0.53±0.27	7
Leng et al. [19]	USA	Carl Zeiss	14 64	NA	NA	< −6.0 −1.0 to +1.0	7
Guo et al. [20]	South Korea	Optovue	45 21	23.64±3.82 21.93±2.93	27.11±1.02 23.58±1.17	−8.62±1.67 −0.76±0.33	8
Milani et al. [21]	Germany	Optovue	42 40	51.8±10.87 56.24±16.64	NA	−10.26±3.83 −0.07±1.44	7
Sung et al. [22]	USA	Optovue	71 36	23.63±4.01 23.11±4.31	26.73±0.63 23.46±0.55	−7.44±1.70 −0.08±0.38	7
Al-Sheikh et al. [23]	USA	Optovue	50 34	57.00±17.93 56.05±19.27	NA	−8.29±2.94 −0.04±1.06	8
Mo et al. [24]	China	Optovue	41 45	38.0±11.7 38.3±13.1	29.55±1.73 23.19±0.58	−6.90±1.23 0.07±0.35	7
Wang et al. [25]	China	Optovue	18 20	16.3±0.5 16.6±0.9	26.58±0.87 23.85±0.62	−8.0±0.83 −0.11±0.39	8
Fan et al. [26]	China	Optovue	30 28	36.33±14.73 34.14±15.79	29.01±2.69 23.28±0.48	−11.63±5.36 −0.68±0.68	8
Yang et al. [27]	China	Optovue	70 81	26.1±1.7 26.1±2.0	26.15±0.93 24.23±0.94	−7.14±0.94 −1.75±0.72	7
Min et al. [28]	South Korea	Optovue	52 52	45.7±15.0 46.5±16.6	27.5±1.1 24.0±1.1	−8.5±4.9 −2.0±3.0	7

HM, high myopia; NOS, Newcastle-Ottawa Scale; NA, not available; AL, axial length; D, diopters.

base, and the Cochrane Library were searched up to June 2020 using the following key terms: “myopia,” “nearsightedness,” “OCTA,” “OCT angiography,” and “optical coherence tomography angiography.” All articles in English were considered eligible. Conflicts on the inclusion of data were resolved by consensus (between X.W. and L.Z.).

Inclusion criteria were as follows: (1) original research studies published in English; (2) cohort study or cross-sectional study; (3) HM defined as SE refractive error ≥ -6.0 D and/or AL ≥ 26.0 mm, and without pathological changes; control group was allowed as SE between $+3.0$ D and -3.0 D; (4) OCTA data were reported as mean $\pm$ standard deviation; (5) differences reported in OCTA data between HM and controls; (6) OCTA scan size of macular was a 3×3 mm² region; and (7) inclusion of at least 2 of the following outcomes – FAZ, whole superficial vessel density, whole deep vessel density, foveal superficial vessel density, parafoveal superficial vessel density, parapapillary superficial vessel density, parapapillary RNFL thickness, foveal RNFL thickness, parafoveal RNFL thickness, sub-foveal choroidal thickness (SFCT), and/or chorio-capillary density. Exclusion criteria were as follows: (1) case reports, conference abstracts, letters, reviews, and meta-analyses; (2)

studies with insufficient data; (3) eyes with common diseases other than myopia; and (4) animal experimental and optics studies.

Terminology

Each set of scans was acquired over a 3×3 mm² macular region and a 4.5×4.5 mm² region of the optic disc. The FAZ was defined as the round capillary-free zone. The fovea was defined as the area within a central 1 mm circle on the macular. The parafoveal area was defined as an annulus surrounding the fovea with an inner diameter of 0.6 mm and an outer diameter of 2.5 mm. The parapapillary area was defined as a 700 or 750 μ m elliptical annulus extending outward from the optic disk boundary. The OCTA software used and automated segmentation algorithm to identify the superficial retinal plexus extending from the inner limiting membrane to the inner plexiform layer and the deep retinal plexus extending from the inner nuclear layer to the outer plexiform layer. Choroidal thickness was defined as the distance between the hyper-scattering outer border of the retinal pigment epithelium and the inner border of the sclera. The chorio-capillaries were automatically segmented from 31 to 59 μ m inferiorly to the retinal pigment epithelium [16].

Fig. 2. Meta-analysis of whole superficial and deep vessel density between HM and control eyes. HM, high myopia.

Data Extraction and Quality Assessment

Two authors independently retrieved and obtained the following information from the included articles. The extraction data were customized to record the first author, year of publication, study area, number of eyes, age, AL, refractive error, OCTA device, and outcomes. Any discrepancies in the inclusion of data were addressed by consensus. The quality of each study was assessed by the Newcastle-Ottawa Scale (NOS) [17] and the total scores ranging from 0 to 9 points applied to the evaluation. Studies with NOS scores >7 were defined as high quality and considered in the final analysis.

Statistical Analysis

Statistical analysis was performed using Review Manager 5.3. For continuous variables, outcomes were reported as the mean $\pm$ standard deviation and the mean difference (MD) with a 95% confidence interval. To obtain reliable results, heterogeneity was evaluated using the I^2 test. If the homogeneity test showed $p \geq 0.1$ and $I^2 \leq 50\%$, which indicated a low homogeneity between the included studies, a fixed-effects model was used for the analysis. If the value of I^2 was $>50\%$ or p value <0.1 , which suggested a high heterogeneity, then a random-effects model was applied to the data.

Funnel plot was employed to assess publication bias. A p value <0.05 was regarded as statistically significant.

Results

A total of 440 potentially relevant reports were initially obtained in our literature search, of which 196 studies were removed due to duplication. After applying the inclusion and exclusion criteria, 11 eligible articles including 525 HM eyes and 491 normal control eyes with sufficient data were eventually selected for the meta-analysis [18–28] (Fig. 1). The demographic and clinical characteristics of the included articles are summarized in Table 1. Seven studies had high-quality scores of 7, and 4 studies had scores of 8. All studies met the quality requirement. In addition, sensitivity analysis was conducted on the included articles for each outcome which showed that no

Fig. 3. Meta-analysis of foveal, parafoveal, and parapapillary superficial vessel density between HM and control eyes. HM, high myopia.

articles had a high influence which indicated the results of this study were stable.

Seven studies reported whole superficial vessel density, and the meta-analysis of these data indicated that it was lower in HM than in control eyes (Fig. 2). For whole deep vessel density, 6 studies were included in the analysis between the HM eyes and control eyes, which showed that whole deep vessel density was also reduced in HM (Fig. 2). Assessment of foveal and parafoveal superficial vessel density showed no significant changes in HM compared to control eyes (Fig. 3). However, the MD in para-

papillary superficial vessel density was shown to be lower in HM eyes (Fig. 3).

Analysis of the FAZ in 5 studies showed it was not statistically different in HM compared to control eyes (Fig. 4). Meta-analysis of the foveal thickness indicated small increases in foveal thickness in HM compared to control eyes (Fig. 4). Assessment of parafoveal RNFL thickness showed that parafoveal RNFL thickness in HM was thinner than that of the control eyes by 5.36 μm and the difference was statistically significant (Fig. 5). In addition, the parapapillary RNFL thickness appeared to be

Fig. 4. Meta-analysis of FAZ and foveal thickness between HM and control eyes. HM, high myopia; FAZ, foveal avascular zone.

slightly lower in HM eyes than in control eyes (Fig. 5). Furthermore, SFCT in HM eyes was significantly lower than that of controls (Fig. 6). Choriocapillaris density between the 2 groups was shown that no significant changes were observed in HM (Fig. 6).

From the funnel plot analysis, there was no correlation between study size and effect size or any other evidence of publication bias (Fig. 7). Sensitivity analysis showed that none of the studies had an excessive impact on the results of the meta-analysis, indicating that the results of the remaining studies are stable and reliable.

Discussion

To the best of our knowledge, this is the first study to provide a comprehensive meta-analysis comparing alterations of the retinal and choroidal vascular and thickness measured by OCTA in HM and normal controls. In the current study, we analyzed the mean whole vessel density

of study participants along with several other parameters. Specifically, these included parapapillary superficial vessel density, chorio-capillary vessel densities, FAZ, foveal thicknesses, SFCT, and parafoveal and parapapillary RNFL thickness.

Based on the presented data, whole vessel density at both the superficial and deep macular layers was significantly lower in HM eyes which strongly supports the findings from Yang et al. [11], Fan et al. [26], and Yang et al. [29] studies. However, Yang et al. [27] reported contrary findings showing no significant differences across various levels of myopic severity. When the foveal and parafoveal superficial vessel densities were analyzed, no changes occurred in HM compared to control eyes. When we evaluated the FAZ measured by OCTA, our findings showed the FAZ remained unchanged in HM eyes compared to control eyes, which is in agreement with data from Li et al. [13] study. However, the outcome of other articles indicated the diameter of the FAZ was enlarged in HM eyes [30–32]. While discrepancies among these stud-

Fig. 5. Meta-analysis of parafoveal and parapapillary RNFL thickness between HM and control eyes. HM, high myopia; RNFL, retinal nerve fiber layer.

ies limit definitive conclusions, the reported changes may be related to numerous factors such as AL, age, sex, and segmentation method impacting FAZ measurements [16].

Furthermore, small increases in foveal thickness and SFCT were simultaneously observed in HM compared to control eyes. A thinning of SFCT in HM eyes is consistent with findings reported in Ohsugi et al. [33] and Gupta et al. [34] studies. In this meta-analysis, the data suggest that parafoveal RNFL thickness showed that no change in thickness occurred in HM compared to control eyes. Our results show that parapapillary superficial vessel density and chorio-capillary density were reduced in HM, suggesting that vessel density decreases with progression of HM [35].

The RNFL thickness in the peripapillary region was significantly thinner in HM than in control eyes, which was again in line with Leung et al. [36] and Hoh et al. [37] studies. Parapapillary RNFL thinning leads to a diminished requirement of retinal blood supply and decreased

metabolic demand ultimately reducing parapapillary vessel density. We hypothesize that the reduced thickness of the retina and choroid, and reduced capillary density reduction may be due to excessive axial elongation of the eyeball in HM eyes causing biomechanical stretching of the retina, choroid, and sclera [38, 39].

The current study is the first synthesis that detected alterations of retinal and choroidal microvasculature in HM through a comprehensive search strategy with strict criteria of inclusion. A previous study found that there was no difference between emmetropia and low-to-moderate myopia groups in retinal vessel density except for the deep parafoveal vessel density [31]. So according to Yang et al. [11], Su et al. [12], and Cheng et al. [31] studies, we selected SE between +3.0 D and -3.0 D as control group. However, some unavoidable factors could have potentially contributed to the heterogeneity of the data. First, potentially confounding factors such as a different refractive error, age, and baseline state may be related to the significant heterogeneity. Moreover, data were com-

Fig. 6. Meta-analysis of choroidal thickness and choriocapillaris density between HM and control eyes. HM, high myopia; SFCT, sub-foveal choroidal thickness.

Fig. 7. A funnel plot study assessing the publication bias. SE, spherical equivalent; MD, mean difference.

piled data from 3 different OCTA brands (7 Optovue, 1 Carl Zeiss, and 1 Nidek) which may have contributed to heterogeneity of the meta-analysis.

Our study has a number of limitations that should be considered when interpreting the data. Firstly, we did not search for original data, unpublished articles, or papers written in other languages, which inevitably leads to some bias. Secondly, while patients with HM were including, patients with myopic maculopathy were omitted from the study, and so it was not possible to assess changes in these patients with more advanced disease. Furthermore, we evaluated the macular area selecting a $3 \times 3 \text{ mm}^2$ scan pattern, whereas a $6 \times 6 \text{ mm}^2$ scan pattern may provide more accurate and more reproducible data [40, 41]. Further studies in HM eyes should be conducted on a larger area to elucidate the changes in the macular microvasculature.

Conclusions

In conclusion, the present meta-analysis demonstrated that OCTA is effective for the noninvasive and rapid evaluation of vascular changes in HM. We showed that macular and parapapillary retinal vessels were attenuated in HM eyes. Furthermore, we found that the FAZ, and

foveal and parafoveal superficial vessel density remained unchanged in HM. Finally, our findings suggested that thickness of parafoveal RNFL, parapapillary RNFL, and sub-foveal choroid in HM was decreased. Otherwise, the foveal thickness in HM has a small increase. These microvascular parameters of the retina and choroid may have significant value in the progression of myopia. Future studies will provide more comprehensive assessment of these changes in retina and choroid.

Statement of Ethics

All analyses were based on published studies; therefore, this study is exempt from ethical committee approval. Nonetheless, the study was conducted in accordance with the tenets of the Declaration of Helsinki.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

X.-Q.W. designed the study. X.-Q.W., L.-Z.Z., and L.-Q.L. performed and processed the experimental data. X.-Q.W. wrote the manuscript. L.-Z.Z., M.C., and L.-Q.L. revised the manuscript. All authors read and approved the final manuscript.

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