FIGURES

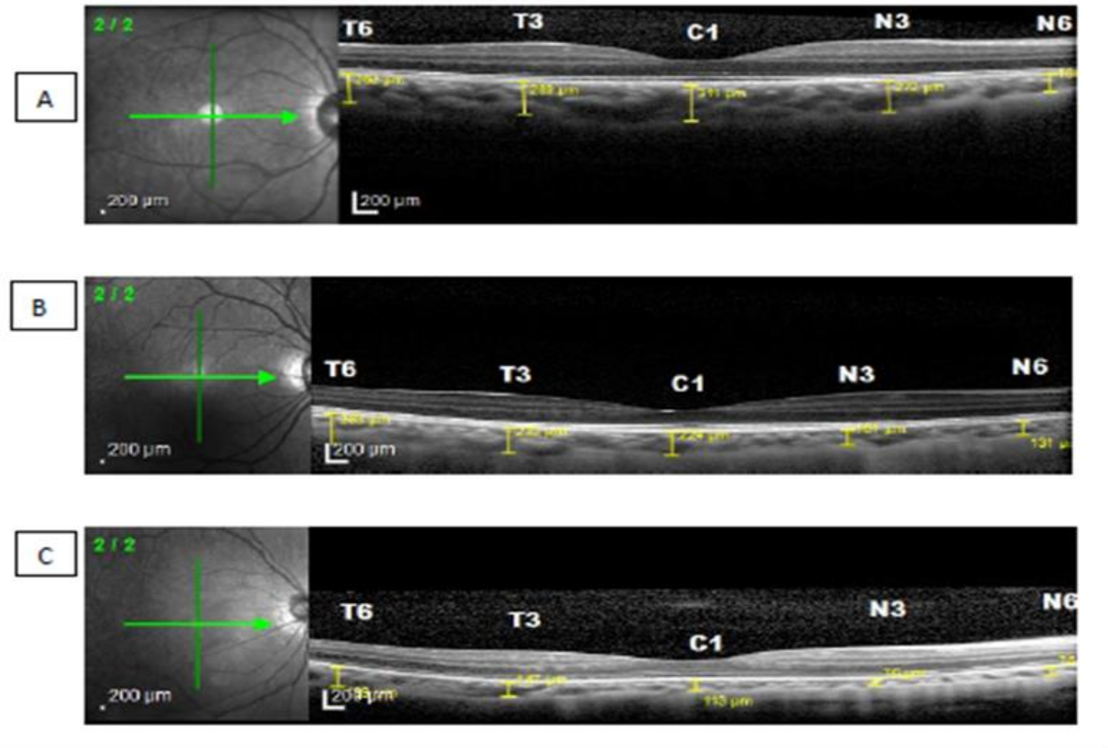

Figure 1. Choroidal thickness based on degrees of myopia horizontally.
(A) Low myopia 1.75D, (B) Moderate myopia 3.75D, (C) High myopia 10.25D

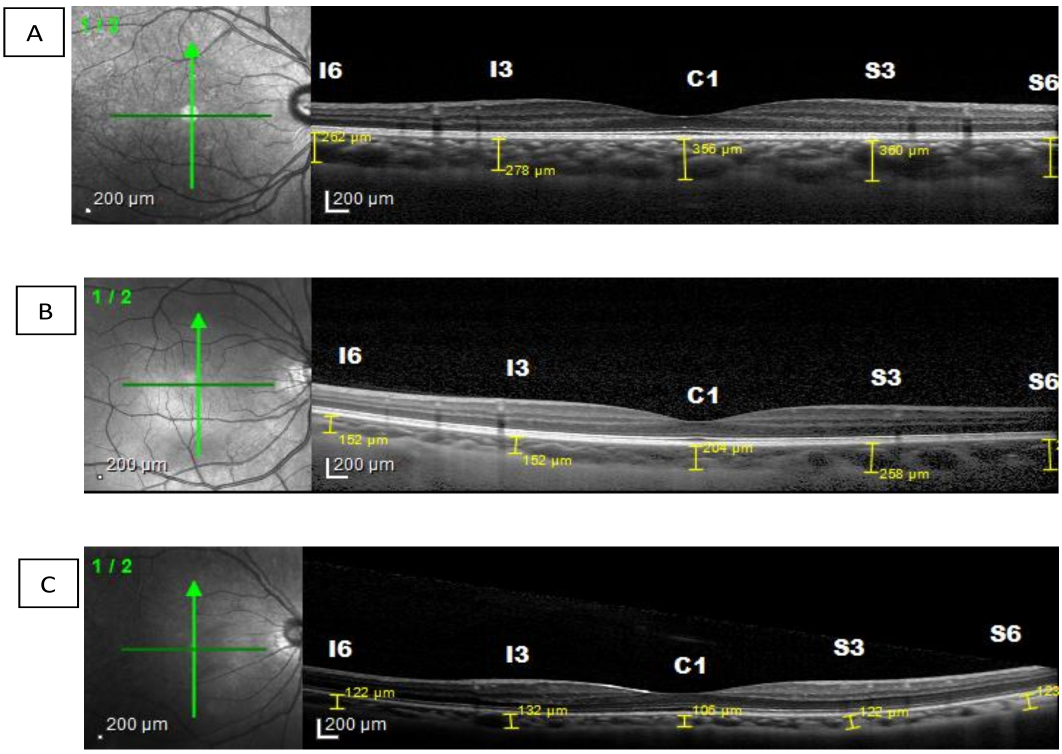

Figure 2. Choroidal thickness based on degrees of myopia vertically.
(A) Low myopia 1.75D, (B) Moderate myopia 3.75D, (C) High myopia 10.25D

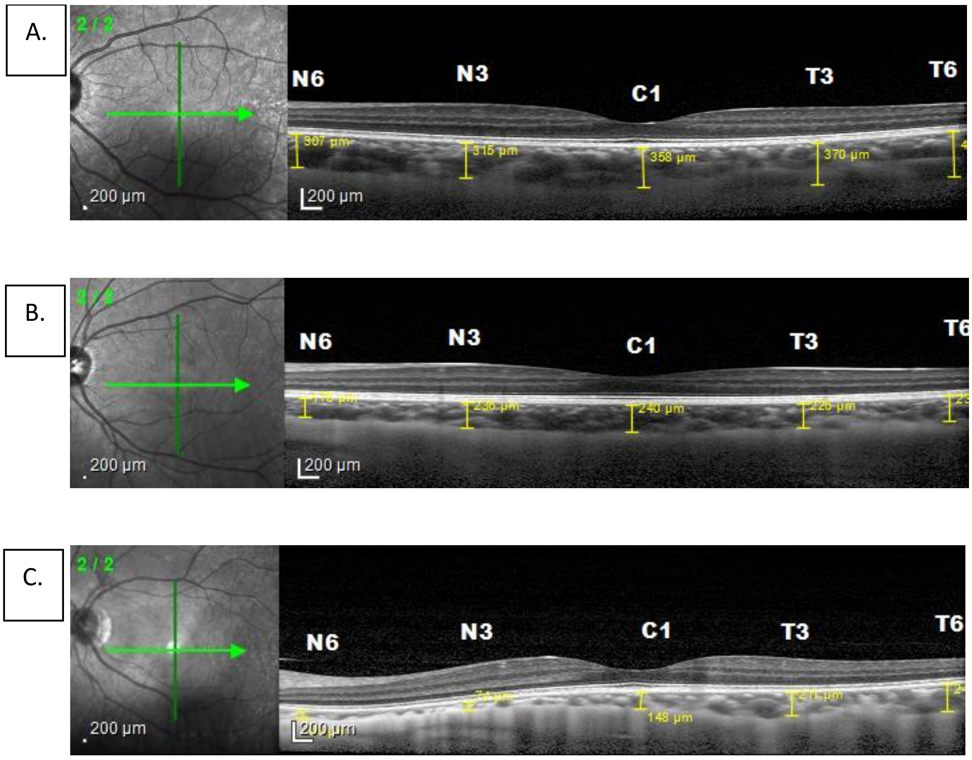

Figure 3. Choroidal thicknes based on axial length horizontally.
(A) Short axis (22,47 mm) (B) Medium axis (23,75 mm), (C) Long axis (27,60 mm)

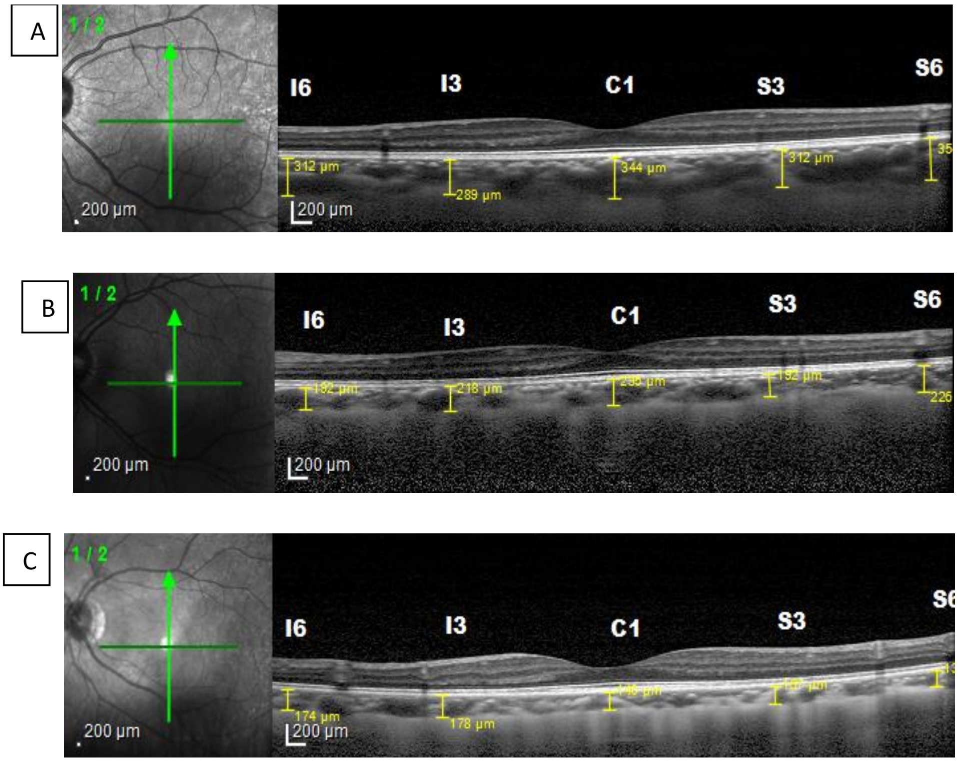

Figure 4. Figure 3. Choroidal thicknes based on axial length vertically.
(A) Short axis (22,47 mm) (B) Medium axis (23,75 mm), (C) Long axis (27,60 mm

COVER LETTER

Date: 12th January 2022

To
The Editor,
VISION JOURNAL

I am enclosing herewith a manuscript entitled:

CHOROIDAL THICKNESS IN CORRELATION WITH AXIAL LENGTH AND MYOPIA DEGREE

The aim of this paper is to determine the relationship between the degree of myopia, the axial length, and the choroidal thickness (CT). We hope that these results also meet the research scope that required in this journal and it could be published and disseminated for the benefit of science. We are looking for possible evaluation and also publication in Vision journal.

Submitted manuscript is an original article. The corresponding author of this manuscript is Andi Muhammad Ichsan (am_ichsan@unhas.ac.id) and contribution of the authors as mentioned below:

1. Habibah Setyawati Muhiddin
2. Andi Ratna Mayasari
3. Batari Todja Umar
4. Junaedi Sirajuddin
5. Itzar Chaidir Islam
6. Andi Muhammad Ichsan*

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Ophthalmology Department, Medical Faculty, Hasanuddin University, Makassar, South Sulawesi, Indonesia

With the submission of this paper, I would like to undertake that:

1. All authors of this paper have directly participated in the planning, execution, or analysis of this study;
2. All authors of this paper have read and approved the final version submitted;
3. All authors have approved the manuscript and agree with its submission to Vision journal;
4. The contents of this manuscript have not been copyrighted or published previously;
5. The contents of this manuscript are not now under consideration for publication elsewhere;
6. The contents of this manuscript will not be copyrighted, submitted, or published elsewhere;
7. We further certify that proper citation to the previously reported work has been given and no data / tables / figures have been quoted from other publications without giving proper acknowledgement;
8. The authors state there is no conflict of interest in writing this article;
9. The consent of all the concerned authority is also taken.

Thank you very much your kind attention.

Sincerely,

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Article

CHOROIDAL THICKNESS IN CORRELATION WITH AXIAL LENGTH AND MYOPIA DEGREE

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Abstract: Background: A major cause of visual disability is myopia. It occurs when there is an excessive and continuous expansion of the axial length (AL), resulting in a change in the secondary fundus leading to visual impairment, choroidal neovascularization, retinal detachment, zonal areas of chorioretinal atrophy, myopic macular schisis and hole. Purpose: This study aims to determine the relationship between the degree of myopia, the axial length, and the choroidal thickness (CT). Methods: This is an observational analytical study that made use of a cross-sectional design. A total of 49 participants with refractive errors, underwent treatment at Hasanuddin University Hospital and 69 eyes were measured and analyzed. The choroidal thickness was measured using the Enhance Depth Imaging OCT (EDI-OCT) tool which is divided into nine observational areas. Furthermore, all data obtained were compared using statistical analysis such as the one-way ANOVA and Pearson correlation test ($p<0.05$). Results: There was a significant relationship between the choroidal thickness with axial length (p,0.05), and myopia degrees ($p<0.05$). Conclusions: The thickness of the choroid decreases with an increase in the axial length and degree of myopia which further indicates that the higher the myopia degree the thinner the choroidal vasculature.

Keywords: Choroidal thickness; Myopia; Axial length

Citation: Muhiddin HS et al. CHOROIDAL THICKNESS IN CORRELATION WITH AXIAL LENGTH AND MYOPIA DEGREE. *Vision* **2022**, *6*, x. https://doi.org/10.3390/xxxxx

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1. Introduction

Myopia, also known as shortsightedness, is a major cause of visual disability around the world. In 1972 and 2004, the prevalence of myopia increased from 25 to 44% in the United States while in Asia, the prevalence is approx. >80%.[1] In 2010, it was noted that the uncorrected refractive error was the major cause of vision impairment and the second most frequent cause of blindness affecting 108 million persons globally. Furthermore, the cases of myopia are expected to increase by more than 5000 million by 2050.[2]

Myopia is more likely to occur within the ages of 8 and 15 and it is prevalent in persons who work extensively with the eyes such as microscopists.[3] According to the World Health Organization, the major cause of vision impairment and blindness around the world are macular degeneration, vitamin A deficiency, infectious disease, uncorrected refractive error with cataracts, and myopia.[4]

Furthermore, myopia has been classified according to anatomical and pathological features, the age of onset, the rate of progression, the degree and theory of development. Physiological myopia occurs when the refractive components of the eye fail to correlate, unlike pathologic myopia (alternatively, malignant or degenerative myopia) which occurs when the optical system of the eye lies outside the limit of normal biological variations. According to degree, myopia can be grouped into low (<3.00 D), medium (3.00 D-5.00 D), and high (>5.00 D).[5]

Myopia and refractive-error disorder may develop when there are irregular contributions of the ocular components to the eye structures. Four structures that contribute to the refractive status of a given human eye are aqueous and vitreous humor, cornea, and lens. When the lens and cornea fail to neutralize the axial length (AL) shortening or elongation, hyperopia or myopia may occur. Therefore, some parameters such as the anterior chamber depth (ACD), corneal curvature, vitreous chamber depth, axial length and, lens thickness are widely analyzed when studying eye diseases. However, among these components, more attention is paid to the axial length which is the major parameter for both hyper myopia and myopia.[6] Furthermore, studies have shown that the alteration of environmental factors and the identification of genetic correlations may play a significant role in axial elongation, myopia progression, and future ocular complications.[7,8]

Myopia is known to be the cause of multiple eye fatalities around the globe and investigation conducted on a particular population in various hospital have shown that when the axial length or refractive error is ~26.5 mm or –8.00 D, the parapapillary atrophy and optic disc becomes enlarged gradually. However, when these values are higher, the prevalence of glaucomatous optic neuropathy and myopic retinopathy is increased. Myopia is identified as the excessive and continuous expansion of the axial length, resulting in a change in the secondary fundus which leads to visual impairment, as well as choroidal neovascularization, retinal detachment, zonal areas of chorioretinal atrophy, myopic macular schisis, and hole.[9]

In high myopic eyes, recent changes start in the choroid therefore, studies have shown that the choroid is a very valuable structure that is required in the pathophysiology of high myopia.[10] The choroidal vasculature helps nourish the outer retina (including the photoreceptors), however, when there is a loss of the vascular tissue and an extreme thinning of the choroid, it leads to visual impairment and damage to the photoreceptors. The thickness of the choroidal is an essential parameter used for studying the pathogenesis of high myopia.[11] Furthermore, measurement of CT in vivo is suitable for determining the onset of diseases and their progression which causes thinning of the choroidal.[12] The presence of lacquer cracks and choroidal neovascularization (CNV) is seen mostly in eyes with thinner macular choroids.[13] Therefore, this study aims to determine the relationship between the degree of myopia, the axial length, and the choroidal thickness.

2. Materials and Methods

2.1 Study design

This is an observational analytical study that made use of a cross-sectional design. A total of 49 participants with refractive errors, underwent treatment at Hasanuddin University Hospital and 69 eyes were measured and analyzed. Each patient who meets the criteria was asked to fill out and sign an informed consent form after then examined according to applicable standards.

2.2 Ophthalmology examination

The examination was carried out by measuring the patient's visual acuity and correction using a Snellen chart projector, trial lens, and retinoscopy. The results obtained from retinoscopy were in the form of a spherical equivalent (SE). The anterior segment of the eye was then examined with a slit lamp biomicroscope, then the patient was made to undergo an indirect funduscopic examination with a 90D ocular lens to view the posterior segment of the eye. Subsequently, the length of the patient's eyeball axis was obtained using A-Scan Ultrasound which measures from the top of the cornea to the posterior segment, and the results were represented in millimeters (mm). The choroidal thickness was measured using the Enhance Depth Imaging OCT (EDI SD-OCT) tool which is divided into nine observation areas. It was performed semi-automatically by drawing a perpendicular line between the outermost part of the hyper-reflective line that represents the RPE with the hypo-reflective line that represents the choroid-scleral surface using a calipers software tool.

2.3 Data analysis and interpretation

All results obtained were recorded and compared using the One-way ANOVA and Spearman correlation test (sig. p<0.05) which was represented in tables and figures.

3. Results

The degree of myopia is divided into 3 categories; low (≤ -3.00 D), moderate (-3.25 to -6.00 D), and high (> -6.00 D) myopias. This was compared with the choroidal thickness found in various areas of the macula. The result obtained showed a significant difference except for the 1.5 mm temporal region (T3) (Table 1). This result indicates a significant relationship between the choroidal thickness and the degree of myopia. A high degree myopia showed a thinner choroidal vasculature.

From the horizontal image (Fig.1), the choroid found in the low myopia is thickest in the subfoveal unlike in medium and high myopia where it is thickest in the temporal. The thinnest area in all groups was the nasal area. Vertically (Fig.2), in low and moderate myopia, the choroid is thickest in the superior area while in high myopia it is thickest in the subfoveal area. The thinnest area in each group was the inferior region. Comparison of the choroidal thickness based on the axial length showed a significant difference (p<0.05), except for the superior region (S6).

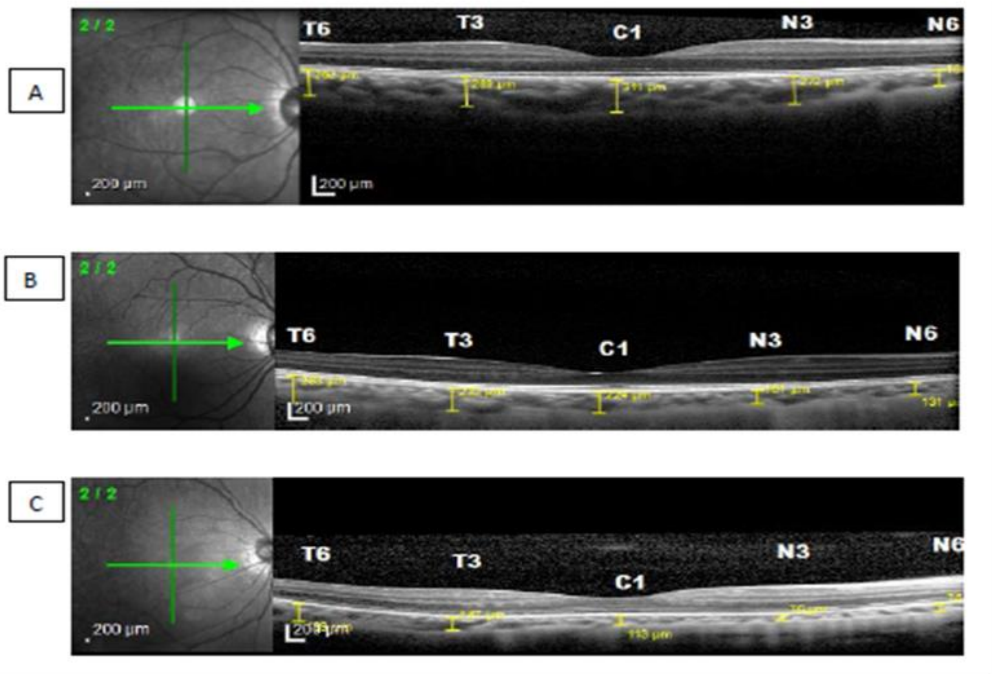

Figure 1. Choroidal thickness based on degrees of myopia horizontally.
(A) Low myopia 1.75D, (B) Moderate myopia 3.75D, (C) High myopia 10.25D

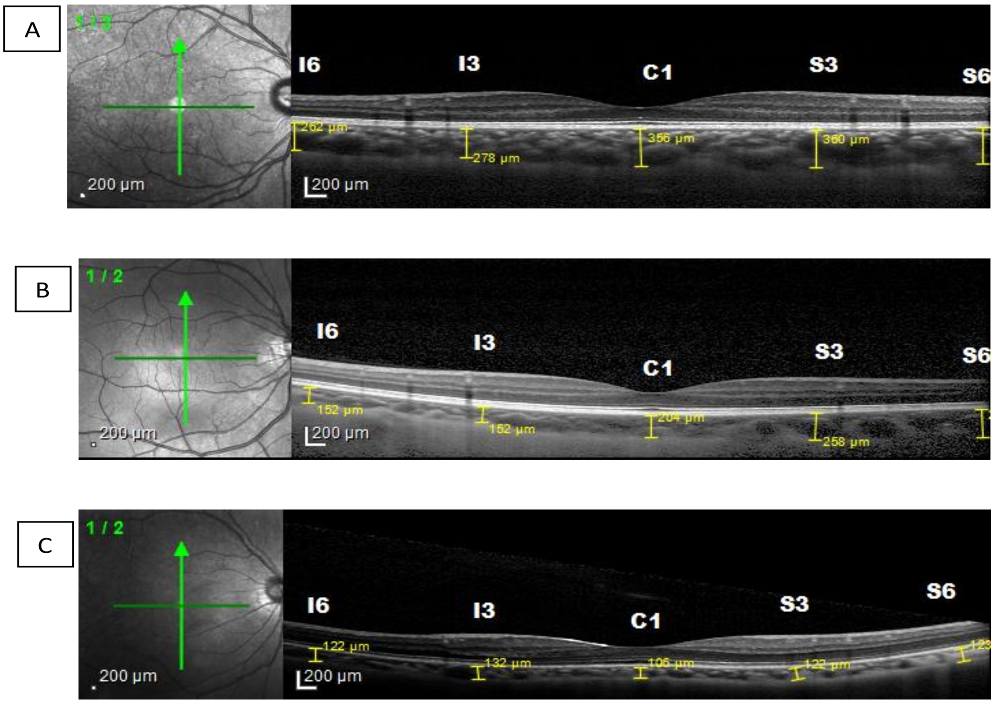

Figure 2. Choroidal thickness based on degrees of myopia vertically.
(A) Low myopia 1.75D, (B) Moderate myopia 3.75D, (C) High myopia 10.25D

Table 1. Comparison of choroidal thickness and the degrees of myopia

Choroidal Thickness based on area (Mean ± SD) µm	Myopia degree (D)			p
	Low myopia (n=50)	Moderate myopia (n=31)	High myopia (n=15)	
C=Sub Fovea	307.52±79.30	253.39±64.84	267.33±104.01	0.010
T6=Temporal 3	280.22±76.18	255.06±47.20	231.07±59.52	0.028
T3=Temporal1.5	298.12±78.30	262.58±54.02	267.80±83.84	0.076
N3=Nasal 1.5	252.50±64.89	208.23±48.70	196.07±89.16	0.002
N6=Nasal 3	173.00±50.72	151.06±47.20	132.33±77.61	0.027
S6=Superior 3	306.02±72.50	269.13±56.69	258.67±89.28	0.022
S3=Superior 1,5	314.18±80.06	261.52±52.95	257.73±93.38	0.003
I3=Inferior 1.5	307.12±71.74	249.97±62.72	244.73±76.31	<0.001
I6=Inferior 3	282.04±62.99	237.84±47.31	226±65.93^{bb}	0.001

***One-way Anova test**

The mean choroid thickness of the short (<22.5 mm), medium (22.5 to 25.0 mm) and long (>25.5 mm) axis in the horizontal section (Fig.3) were thickest in the fovea, while the thinnest in each group was found in the nasal area. Furthermore, vertical measurement (Fig.4) on the short axis, showed that the thickest area is on subfoveal area while on the medium and long axis it is thickest in the superior area. The thinnest area in the short and medium axis groups was the inferior region, while for the long axis it was the sub fovea area.

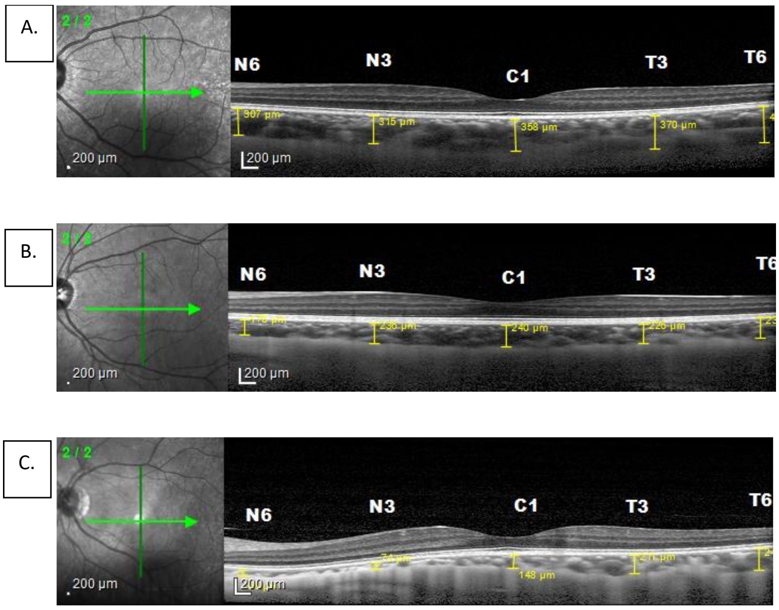

Figure 3. Choroidal thicknes based on axial length horizontally.
(A) Short axis (22,47 mm) (B) Medium axis (23,75 mm), (C) Long axis (27,60 mm)

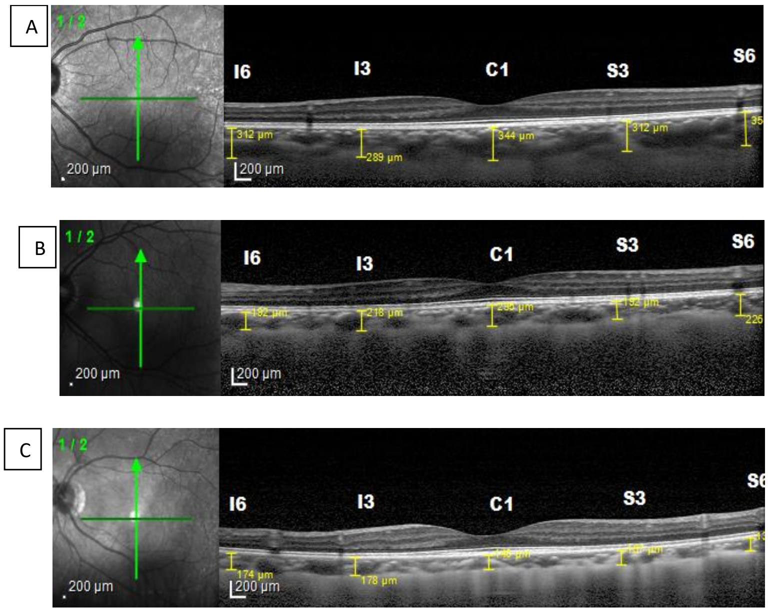

Figure 4. Figure 3. Choroidal thicknes based on axial length vertically.
(A) Short axis (22,47 mm) (B) Medium axis (23,75 mm), (C) Long axis (27,60 mm)

Table 2 showed that there is a significant correlation between choroidal thickness and axial length (p<0,05), except on S6 area. This indicates that the thickness of the choroid decreases with increasing axial length.

Table 2. Comparison of choroidal thickness and axial length

Coroidal thickness based on area (Mean±SD) µm	Axial lenght (mm)			p*
	Short (n=4)	Moderate (n=74)	Long (n=18)	
C=Sub Fovea	345,00±16,31	294,04±79,83	227,89±77,30	0.002
T6=Temporal 3	347,25±73,3	270,20±65,20	222,22±51,0	0.001
T3=Temporal 1,5	328,75±35,76	289,12±75,56	241,83±55,25	0.020
N3=Nasal 1,5	307±39,43	233,09±65,93	196,89±68,55	0.008
N6=Nasal 3	247,25±49,14	160,69±52,17	135,44±55,50	0.001
S6=Superior 3	332,75±49,25	291,73±71,58	255,83±74,45	0.074
S3=Superior 1,5	336±31,76	298,03±76,48	238±76,04	0.006
I3=Inferior 1,5	330,5±41,06	287,24±73,33	233,22±70,31	0.008
I6=Inferior 3	311,25±14,7	264,58±63,82	224,5±52,34	0.012

***One-way ANOVA test**

Table 3 shows the correlation coefficient between the axial length of the eyeball and the thickness of the choroid (r= 0.270 – 453) which is higher than the degree of myopia (r= 0.230 – 407).

Table 3. Correlation between axial length, degree of myopia and choroidal thickness in various regions

Choroidal Thickness based on area (Mean±SD) µm	Axial length (mm)		Myopia degree (D)	
	Coefficient correlation (r)	p*	Coefficient correlation (r)	p*
C=Sub Fovea	-0,400	<0,001	-0,274	0.003
T6=Temporal 3	-0,385	<0,001	-0,317	0.001
T3=Temporal1,5	-0,307	<0,001	-0,230	0.012
N3=Nasal 1,5	-0,427	0,001	-0,361	<0.001
N6=Nasal 3	-0,343	<0,001	-0,332	<0.001

S6=Superior 3	-0,270	<0,001	-0,300	0.002
S3=Superior 1,5	-0,389	0,004	-0,308	0.001
I3=Inferior 1,5	-0,453	<0,001	-0,388	<0.001
I6=Inferior 3	-0,431	<0,001	-0,407	<0.001

***Pearson correlation test**

The choroidal thickness showed a significant relationship ($p<0.05$) with the axial length and degree of myopia found in various areas of the macula and this has a negative correlation coefficient; Therefore, means, the longer the axis of the eyeball the higher the degree of myopia which will lead to choroidal thinning.

4. Discussion

Historically, some opticians have thought that myopia is a hereditary abnormality, whereas others have imagined it to be environmentally induced. However, several studies conducted on animals and humans over the last four decades have suggested that the occurrence of myopia is controlled by both genetic and environmental factors.[2]

The comparison between the degrees of myopia and choroidal thickness showed a significant correlation ($p<0.05$) that indicates that a higher degree of myopia will lead to thinning of the choroidal layer. Moreover, the mean choroidal thickness obtained by OCT examination was based on the degree of myopia found in the horizontal area. The low degree myopia was found to be thickest in the subfoveal area, while the moderate and high degree myopia was thickest in the temporal region. The thinnest choroid was found in the nasal area of all degrees of myopia.

Based on studies conducted, it is known that the thinning of the choroid reduces ischemia and perfusion of the choroid which leads to the upregulation of the angiogenic factors in the eyes and this may also lead to the formation of myopic choroidal neovascularization and other features of macular degeneration.[14]

In a cross-sectional study by El-Shazly *et al.* (2017) Macular CT was measured in different degrees of myopia and in normal control eyes, and a similar result was obtained which is significantly lower in myopes than in emmetropes. Moreover, it varies by location, where the thickest CT in low myopic eyes, is found in the subfoveal area, while the thinnest is located in the nasal region. However, for eyes with moderate myopia, the thickest is found in the temporal region while the thinnest region remained in the nasal direction.[15]

Another study by Deng *et al.* (2018) showed that the mean CT in the perifoveal, parafoveal, and central foveal regions where 215 ± 50 μm, 227 ± 60 μm, and 229 ± 65 μm respectively while the mean spherical equivalent (SE) of the patient was -1.71 ± 2.22 diopter (D) (range from -7.63 to 4.25 D). Furthermore, the mean global peripapillary choroidal thickness (PPCT) was 136 ± 33 μm.[16]

Based on the result obtained from different studies carried out on animals, an alteration in the thickness of the choroid may occur when maintaining a clear vision. Earlier studies on macaques, marmosets, and chicks have led to the hypothesis which states that the thickening of the choroid may occur when myopic defocus is induced due to changes in the position of the retina when maintaining a clear vision. This is possible because, in myopic defocus, the retina is at the back of the image plane so when thickening of the choroid occurs it moves the retina forward.[10]

Furthermore, this study also indicates that an increase in axial length leads to a decrease in the thickness of the choroid. (Table 2). Moreover, the choroidal thickness showed a significant relationship ($p<0.05$) between the axial length and the degree of myopia found in various areas of the macula that has a negative correlation coefficient. Therefore, this indicates that the longer the axis of the eyeball and the higher the degree of myopia the more choroidal thinning will occur.

In general, the Axial length increases rapidly at the early stage of life but slowly in adulthood and decreases in old age.(6) According to Lee *et.al* (2020) the best-corrected visual acuity (BCVA), baseline axial length, anterior chamber depth, and age were significantly associated with changes in axial length ($p=0.005$, $p<0.001$, $p=0.006$, and $p=0.045$ respectively).[17]

Furthermore, the choroid may stimulate axial growth by regulating the remodeling of the scleral extracellular matrix, which is important for emmetropization during eye formation. In experimental animals induced with hyperopia and myopia, a change in the thickness of the choroid exceeds that of axial length and scleral remodeling.[11]

According to histologic, clinical, and population-based investigations, it was shown that an increase in axial elongation led to a significant thinning of the choroid. Furthermore, in emmetropic subjects, the mean CT was 250 μm while in highly axially myopic patients it decreases to <30 μm. Therefore, this indicates that an increase in the axial elongation led to a decrease in the distance between the Bruch membrane and sclera.[15]

An increase in the axial length led to an increase in the retina thickness which aid in blood supply. This, however, caused an increase in length of the ocular axis resulting in a compensatory thickening of the choroidal capillary layer in the fovea centralis and an increase in the number of capillaries and volume. Moreover, an increase in the myopia degree will cause the axial length of the eye to increase as well. However, the retina may fail to compensate causing the capillary layer and choroid to become thinner.[18]

5. Conclusions

There was a significant correlation between the degree of myopia and choroidal thickness. Therefore, a higher degree of myopia will cause a decrease in the thickness of the choroid. Furthermore, it is necessary to screen for choroidal thickness in myopic patients using SD-OCT, especially in moderate and high degrees to prevent complications, because a significant increase in myopia degree will lead to a decrease in the choroidal thickness. Also, it is necessary to measure the length of the eyeball axis in myopic patients because a decrease in choroidal thickness is significant to the elongation of the eyeball.

Supplementary Materials: None

Author Contributions: HSM, ARM: Conception and design of the work, performing the medical examination, analysis and interpretation of data, drafting the work. BTU, JS, IP, AMI: performing the medical examination, giving supervision and quality control of the medical examination as a team, review and editing of the manuscript draft. ICI: project administration, drafting the work and revising it for publication.

Funding: This research received no external funding

Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Ethics Committee for Medical Research of Hasanuddin University (Approval No.: 751/UN 4.6.4.5.31 /PP36/2021).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Conflicts of Interest: The authors declare no conflict of interest.

Appendix A

None

Appendix B

None

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TITLE PAGE

TYPE OF MANUSCRIPT:

ORIGINAL ARTICLE

TITLE:
PLASMA ENDOTHELIN-1 ROLE ON INITIAL ATHEROSCLEROTIC LESION FORMATION IN YOUNG OBESE WISTAR RATS: AN EXPERIMENTAL STUDY

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DECLARATIONS

Ethical approval and consent to participate
This study protocol was reviewed and approved by The Ethics Committee of Medical Research, Faculty of Medicine, Hasanuddin University (Approval No: 234/H4.8.4.5.31/PP36-KOMITE/2018).

Consent for Publication.
Not applicable.

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The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Authors Contribution.
MIS: conception or design of the work, performing the medical treatment, experimental animal care, analysis and interpretation of data and drafting the work. II, AA: experimental animal care (follow up after induction), analysis and interpretation of data and drafting the work. MHC, ICI: analysis and interpretation of data, drafting the work and revising it critically for important intellectual content.

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TABLES

Table 1. Comparison of choroidal thickness and the degrees of myopia

Choroidal Thickness based on area (Mean ± SD) µm	Myopia degree (D)			p
	Low myopia (n=50)	Moderate myopia (n=31)	High myopia (n=15)	
C=Sub Fovea	307.52±79.30	253.39±64.84	267.33±104.01	0.010
T6=Temporal 3	280.22±76.18	255.06±47.20	231.07±59.52	0.028
T3=Temporal1.5	298.12±78.30	262.58±54.02	267.80±83.84	0.076
N3=Nasal 1.5	252.50±64.89	208.23±48.70	196.07±89.16	0.002
N6=Nasal 3	173.00±50.72	151.06±47.20	132.33±77.61	0.027
S6=Superior 3	306.02±72.50	269.13±56.69	258.67±89.28	0.022
S3=Superior 1,5	314.18±80.06	261.52±52.95	257.73±93.38	0.003
I3=Inferior 1.5	307.12±71.74	249.97±62.72	244.73±76.31	<0.001
I6=Inferior 3	282.04±62.99	237.84±47.31	226±65.93[bb]	0.001

***One-way Anova test**

Table 2. Comparison of choroidal thickness and axial length

Coroidal thickness based on area (Mean±SD) µm	Axial lenght (mm)			p*
	Short (n=4)	Moderate (n=74)	Long (n=18)	
C=Sub Fovea	345,00±16,31	294,04±79,83	227,89±77,30	0.002
T6=Temporal 3	347,25±73,3	270,20±65,20	222,22±51,0	0.001
T3=Temporal 1,5	328,75±35,76	289,12±75,56	241,83±55,25	0.020
N3=Nasal 1,5	307±39,43	233,09±65,93	196,89±68,55	0.008
N6=Nasal 3	247,25±49,14	160,69±52,17	135,44±55,50	0.001
S6=Superior 3	332,75±49,25	291,73±71,58	255,83±74,45	0.074
S3=Superior 1,5	336±31,76	298,03±76,48	238±76,04	0.006
I3=Inferior 1,5	330,5±41,06	287,24±73,33	233,22±70,31	0.008
I6=Inferior 3	311,25±14,7	264,58±63,82	224,5±52,34	0.012

***One-way ANOVA test**

Table 3. Correlation between axial length, degree of myopia and choroidal thickness in various regions

Choroidal Thickness based on area (Mean±SD) μm	Axial length (mm)		Myopia degree (D)	
	Coefficient correlation (r)	p*	Coefficient correlation (r)	p*
C=Sub Fovea	-0,400	<0,001	-0,274	0.003
T6=Temporal 3	-0,385	<0,001	-0,317	0.001
T3=Temporal1,5	-0,307	<0,001	-0,230	0.012
N3=Nasal 1,5	-0,427	0,001	-0,361	<0.001
N6=Nasal 3	-0,343	<0,001	-0,332	<0.001
S6=Superior 3	-0,270	<0,001	-0,300	0.002
S3=Superior 1,5	-0,389	0,004	-0,308	0.001
I3=Inferior 1,5	-0,453	<0,001	-0,388	<0.001
I6=Inferior 3	-0,431	<0,001	-0,407	<0.001

***Pearson correlation test**