Correlation between Endothelin-1 (Et-1) and Myopia in Adolescents at Ta'dib Al-Syakirin Modern Islamic Boarding School Medan Johor District

Ade Marlina[1]*, Fithria Aldy[2], Masitha Dewi Sari[2]
[1]Ophthalmology Resident of Opthalmology Department, Faculty of Medicine University of Sumatera Utara, University of Sumatera Utara General Hospital, Indonesia
[2]Ophthalmologist, Faculty of Medicine University of Sumatera Utara, University of Sumatera Utara General Hospital, Indonesia

Abstract. *Background:* Myopia is a refractive disorder caused by excessive axial lengthening. One of the factors affecting myopia is a cellular factor known as endothelin-1 (ET-1). Several studies have found that ET-1 is associated with various eye diseases such as glaucoma and diabetic retinopathy. However, studies relating to ET-1 to myopia are still limited.

Aim: To determine the relationship between Endothelin-1 and myopia in adolescents.

Methods: This study was an observational analytic study with a case-control design, conducted in October 2020. The population of this study was students aged 10-19 in Ta'dib Al-Syakirin Modern Islamic Boarding School Medan Johor Districts. Students were divided into two study groups, which were myopia and emmetropia groups.

Results: Out of 48 subject, the case group (myopia) with 25 people and the control group (emmetropia) with 23 people. In the case group, the mean endothelin level is 93.21 ± 61.29 ng/L, while in the control group the mean endothelin level was lower 70.94 ± 15.70 ng/L. The results of the Mann-Whitney test showed a difference in the mean endothelin-1 levels between the case group and the control group ($p = 0.012$). From the Spearman correlation test, there was a significant correlation between endothelin-1 levels and myopia degree in the case group ($p = 0.006$).

Conclusion: There was a correlation between endothelin-1 (ET-1) and myopia in adolescents at the Ta'dib Al-Syakirin Modern Islamic Boarding School Medan Johor Districts. High myopia patient was recommended to make a visit to ophthalmologist.

Keywords: Endothelin-1, myopia, emmetropia, adolescents

Introduction

Myopia is a refractive disorder considered as a disorder that can usually be treated using glasses, contact lenses, and refractive surgery (Flaxman et al., 2017). This ocular disorder has negative effects on social, education, economic status, and a person's quality of life. Myopia is one of the major health problems throughout the world and in Indonesia. The prevalence rate of refractive errors worldwide is astigmatism (40.4%) followed by hypermetropia (30.9%) and myopia (26.5%) but there are variations in the prevalence of refractive errors in each country (Hashemi et al., 2017). The report by Basic Health Research by Indonesia Government in 2013 showed the prevalence of corrected refractive errors in Indonesia was 4.6%, while in North Sumatra was 4.0% (Kementerian Kesehatan Republik Indonesia, 2013). The prevalence and incidence of myopia worldwide have increased drastically in the past 50 years, especially in East and Southeast Asia. It is estimated that 1.4 billion people suffer from myopia in 2000 and it is estimated that by 2050 the number will reach 4.8 billion (Grzybowski et al., 2020). The prevalence of myopia in Indonesia is described in different studies. The study of Kalangi, Rares, and Sumual (2016) revealed that the prevalence of myopia in RSUP DR. R.D. Kandou Manado was as much as 26.1%. Higher education levels were correlated with an increased

* Corresponding Author

prevalence of myopia. The study by Nugroho et al. (2020) concluded that the prevalence of myopia from medical students in UGM was 69.4% and the progression of myopia is -0.401 D per year. In addition, Hayatillah (2011) in the study revealed the prevalence of myopia among medical students in Faculty Medicine of UIN Syarif Hidayatullah was 62.50%.

Research on the pathophysiology of myopia had both genetic and cellular effects. Genetic factors have linked several growth factors to varying degrees of myopia. One of them is vascular endothelial growth factor (VEGF), and cellular factor, known as endothelin-1 (ET-1). Previous several studies found that ET-1 was associated with various eye diseases such as glaucoma and diabetic retinopathy (Tan & Sadda, 2017). ET-1 is an endogenous vasoconstrictor peptide secreted by vascular smooth muscle cells that resides in human tissues (Powierza et al., 2020). Stimuli such as hypoxia and stretching of the vascular walls will activate conversion enzymes to form active peptides. ET-1 will then bind to the endothelin A (ETA) and endothelin (ETB) receptors, which is a protein on the surface of the cell and a group of receptors that bind to a G protein. These two receptors will induce various effects and have different affinities. ETA receptors have the potential to induce vasoconstriction, proliferation, and pro-inflammatory effects. The ETB receptor has two subtypes, ETB1 on endothelial cells which may induce vasodilation, and ETB2 which may cause vasoconstriction. Powierza et al. (2020) showed that ET-1 levels in patients with severe myopia were significantly lower than in the control group (1.47 vs 1.94).

Several studies have shown there was the role of ET-1 levels in mediating vasoconstriction of blood vessels, but studies relating ET-1 to myopia are still very limited. This study aims to determine the relationship between ET-1 levels and myopia in the adolescent age group.

Materials and Methods

This study was an observational analytic study with a case-control design. This study was done in Ta'dib Al-Syakirin Islamic boarding school, Medan Johor District, Indonesia, carried out from November 2020 to January 2021 after approved by the Department of Ophthalmology, Faculty of Medicine, University of North Sumatra, and Research Ethics Committee in Faculty of Medicine, University of North Sumatra. The sample in this study was collected with consecutive sampling method and was calculated using the formula for unpaired numerical categorical analytic research with a minimum number of samples for each group of 23 people.

All subjects had gone through screening for inclusion and exclusion criteria. All patients were explained about the purpose of the study and the procedure for the examination to be carried out followed by signing the informed consent. Samples with uncorrected visual acuity up to 6/6, had the systemic inflammatory disease (autoimmune, diabetes, glomerulonephritis, thyroid dysfunction), had a history of previous drug use (steroids, non-steroidal anti-inflammatory drugs, antibiotics), had severe eye infections such as endophthalmitis and cellulitis, had refractive media errors, and a history of trauma to the eye was excluded from this study. The concentration of ET-1 in serum was measured using an enzyme-linked immunosorbent (ELISA) assay using the Human Endothelin 1 ELISA Kit with the sensitivity of 1.01ng/L.

The data obtained were analyzed by univariate and bivariate analysis. Categorical data are presented in the form of frequency distribution and percentages. Numeric data are displayed in the form of mean and standard deviation. Bivariate analysis was used to determine whether there was a relationship using the Mann-Whitney test, Kruskal Wallis test, and Spearman test. Variables with a p-value <0.05 were considered statistically significant. All data were processed and analyzed using SPSS.

Results

This study was followed by 48 subjects who were aged 12-19 years at the Ta'dib Al-Syakirin Islamic boarding school, Medan Johor District, which was divided into two groups, 25 people with myopia (case group) and 23 people with emmetropia (control group). All the demographic data findings of the subjects in this study are presented in Table 1.

Table 1. Baseline characteristics

Demographic Characteristics	Myopia (n = 25)	Emmetropia (n = 23)	P
Gender, n (%)			
Man	9 (36)	12 (52.2)	0.259[a]
Women	16 (64)	11 (47.8)	
Age, n (%)			
12-13 years	10 (40)	15 (65.2)	0.081[a]
14-19 years	15 (60)	8 (34.8)	
Family History of Myopia, n (%)			
Yes	18 (72)	8 (34.8)	0.01[a]
No	7 (28)	15 (65.2)	

Note: [a]*Chi Square*

The distribution of subjects based on the degree of myopia is presented in Table 2.

Table 2. Degree of myopia

Degree of Myopia	n= 25
Mild myopia	15 (60)
Moderate Myopia	5 (20)
Severe Myopia	5 (20)

This study showed that there was not much difference in the axial length of the left eye and the right eye, both in case groups and control groups. Table 3 shows the difference in axial length measures between myopia and emmetropia groups.

Table 3. Axial length in case and control group

Axial Length	Myopia (n = 25)	Emmetropia (n = 23)	P
OD Axial Length			
Mean ± SD, mm	23.82 ± 1.69	22.28 ± 0.72	<0.001[a]
Median (Min – Max), mm	23.22 (21.44–27.17)	22.29 (20.89–23.82)	
Short, n (%)	2 (8)	8 (34.8)	0.002[b]
Normal, n (%)	14 (56)	15 (65.2)	
Long, n (%)	9 (36)	0	
OS Axial Length			
Mean ± SD	23.76 ± 1.64	22.23 ± 0.69	<0.001[a]
Median (Min-Max)	23.26 (21.78-27.71)	22.24 (20.72-23.25)	
Short, n (%)	2 (8)	8 (34.8)	0.002[b]
Normal, n (%)	14 (56)	15 (65.2)	
Long, n (%)	9 (36)	0	

Note: [a]*Mann Whitney*, [b]*Kruskal Wallis*

Mann-Whitney test showed that there were differences in the mean levels of endothelin-1 between the case and control groups (p = 0.012). It is showed in Table 4.

Table 4. Differences in endothelin-1 levels in the case and control groups

Endothelin levels, ng / L	Myopia (n = 25)	Emmetropia (n = 23)	P
Mean± SD	93.21 ± 61.29	70.94 ± 15.70	0.012 *
Median (Min - Max)	73.5 (63.2-312)	68.8 (52.7-133)	

Note: * *Mann Whitney*

Kruskal Wallis test showed that there was a difference in endothelin-1 levels based on the degree of myopia (p = 0.041). It is showed in Table 5.

Table 5. Differences in endothelin-1 levels in case and control groups based on gender

Gender	n	Endothelin, ng/L Myopia	n	Endothelin, ng/L Emmetropia	p *
Man	9		12		
Mean ± SD		75.16 ± 7.98		74.48 ± 20.15	0.247[a]
Median (Min - Max)		73.5 (66.7-89.9)		70.95 (54.9-133)	0.296[b]
Women	16		11		
Mean ± SD		103.36 ± 75.3		67.06 ± 8.02	0.022[c]
Median (Min - Max)		73.85 (63.2-312)		67.8 (52.7-82.4)	0.295[d]

Note: * *Mann Whitney, Male Myopia vs Emmetropia, Male Myopia vs Female Myopia, Myopia vs Emmetropia Women, Emmetropic Men vs Emmetropic Women*

The Spearman Correlation test found that there was a significant correlation between levels of endothelin-1 and the degree of myopia (p = 0.006) with a value of r (correlation) of 0.392. This correlation value indicates that the level of endothelin-1 is positively correlated with the degree of myopia which means the increased level of endothelin-1 will be followed by an increase in the degree of myopia. It is described in Table 6.

Table 6. Correlation of endothelin-1 levels with degree of myopia

	Degree of Myopia
Endothelin-1 levels	p = 0.006
	r = 0.392
	n = 48

Discussion

This study found that there was a significant relationship and difference in endothelin levels between the emmetropia group and the myopia group (p <0.001 and p = 0.002). This is similar with the study by Powierza et al. (2020), who found that there was a correlation between the ET-1 concentration and the axial length of both eyes in patients with high myopia (p = 0.0558). In this study, we also found that there was a significant difference between the endothelin levels in the emmetropia group and the myopia group (p = 0.012). This is in line with the results of previous studies, in which, Powierza et al. (2020) also showed that the ET-1 concentration in high myopia patients was statistically different compared to the control group (p = 0.005). Previous studies have shown endothelin signaling pathways play a crucial part in the pathogenesis of various eye diseases and ET-1 levels are helpful markers in

evaluating the intraocular hemodynamic (Powierza et al., 2020). Amount of blood required throughout organs and tissues varies and perfusion pressure combined with local resistance, which is depending on the diameter of the blood pressure, are adjusted to fulfil (Flammer, Konieczka, & Flammer, 2013). On the eyeball, endothelin is found in various tissues such as the corneal epithelium, trabecular tissue cells, ciliary bodies, optic nerve astrocytes, and in vascular endothelial cells in the choroid and retina (Salvatore & Vingolo, 2010). ET-1 regulates pericyte contractility in adjusting retinal blood flow and was involved in aquoeus humor dynamics and intraocular pressure (Powierza et al., 2020). ET-1 expression factors include insulin, cortisol, cyclosporin, epinephrin, angiotensin II, thrombin, inflammatory mediators, hypoxia, and shear stress to the vessel wall. Endothelin expression is inhibited by nitric oxide (NO), dilator proteinoids, and natriuretic peptides. Several factors such as synthesis, receptor, and elimination from the body (lungs, liver, kidneys) were contributing factors of ET-1 concentration in plasma (Powierza et al., 2020).

Several previous studies have shown decreased arteriolar saturation in the retina concurrently with the narrowing of retinal vessel diameter in eyes with high myopia (Fujiwara et al., 2012; Chen et al., 2012; Zheng et al., 2015). Lower blood flow parameters in myopic eyes have also been consistenly reported, regardless of the diagnostic method used (Grudzinska & Modrzejewska, 2018). Growth of the axial eyeball in high myopia patient has impaired laminar blood flow and retinal vascular tone, and therefore affects the vascular shear stress required to form the active peptide ET-1 and leading to vasoconstriction (Jain, 2013).

This study has some limitations as there is relatively small sample size, and this study also lacks in analyzing the other factors that can affect the expression of endothelin-1. Therefore it needs further research with a larger sample size and should be considering the other cofounding factors to have better results.

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Conflict of Interest

The authors declare that there is no conflict of interest.

References

Chen, F.K., Yeoh, J., Rahman, W., Patel, P.J., Tufail, A., & Da Cruz, L. (2012). Topographic Variation and Interocular Symmetry of Macular Choroidal Thickness Using Enhanced Depth Imaging Optical Coherence Tomography. *Investigative Ophthalmololgy & Visual Science, 53*, 975-985. doi: 10.1167/iovs.11-8771

Flammer, J., Konieczka, K., & Flammer, A.J. (2013). The Primary Vascular Dysregulation Syndrome: Implications for Eye Diseases. *EPMA J, 14*(4). doi:10.1186/1878-5085-4-14

Flaxman, S.R., Bourne, R.R.A, Resnikoff, S., et al. (2017). Global causes of blindness and distance vision impairment 1990-2020: A Systematic Review and Meta-analysis. *Lancet Glob Health, 5*(12), 1221-1234. doi:10.1016/S2214-109X(17)30393-5

Fujiwara, A., Shiragami, C., Shirakata, Y., Manabe, S., Izumibata, S., & Shiraga, F. (2012). Enhanced Depth Imaging Spectral-domain Optical Coherence Tomography of Subfoveal Choroidal Thickness in Normal Japanese Eyes. *Jpn. J. Ophthalmol, 56*(3), 230-235. doi:

10.1007/s10384-012-0128-5

Grudzinska, E., & Modrzejewska, M. (2018). Modern Diagnostic Techniques for The Assessment of Ocular Blood Flow in Myopia: Current State of Knowledge. *Journal of Ophthalmoly, 2018*, Article ID 4694789. doi: 10.1155/2018/4694789

Grzybowski, A., Kanclerz, P., Tsubota, K., Lanca, C., & Saw, S. (2020). A Review on The Epidemiology of Myopia in School Children Worldwide. *BMC Ophthalmology*, *20*(1).

Hashemi, H., Fotouhi, A., Yekta, A., Pakzad, R., Ostadimoghaddam, H., & Khabazkhoob, M. (2017). Global and Regional Estimates of Prevalence of Refractive Errors: Systematic Review and Meta-analysis. *J Curr Ophthalmol*, *30*(1), 3-22. doi:10.1016/j.joco.2017.08.009

Hayatillah, A. (2011). Prevalensi Miopia dan Faktor-Faktor yang Mempengaruhinya pada Mahasiswa Program Studi Pendidikan Dokter UIN Syarif Hadayatullah Jakarta Tahun 2011.

Jain, A. (2013). Endothelin-1-induced Endoplasmic Reticulum Stress in Disease. *J. Pharmacol. Exp. Ther*, *346*(2), 163-172. doi: 10.1124/jpet.113.205567

Kalangi, W., Rares, L., & Sumual, V. (2016). Kelainan Refraksi di Poliklinik Mata RSUP Prof Dr R D Kandou Manado Periode Juli 2014-Juli 2016. *Jurnal KEDOKTERAN KLINIK (JKK)*, *1*(1).

Kementerian Kesehatan Republik Indonesia. (2013). *Riset Kesehatan Dasar; RISKESDAS*. Jakarta: Balitbang.

Nugroho, A., Prayogo, M., Widyandana, W., Indrawati, S., & Suhardjo, S. (2020). Progression of Myopia Among Medical Students: A one-year cohort study. *Journal of Community Empowerment for Health*, *3*(1), 28-33.

Powierza, K., Żelazowska-Rutkowska, B., Sawicka-Powierza, J., Mikołuć, B., Urban, B., Zaremba, W., et al. (2020). Endothelin-1 Serum Concentration is Lower in Children and Adolescents with High Myopia, a Preliminary Study. *J Clin Med*, *9*, 1327. doi:10.3390/jcm9051327

Salvatore, S., & Vingolo, E.M. (2010). Endothelin-1 Role in Human Eye: A review. *J. Ophthalmol, 2010*, Article ID 354645. doi:10.1155/2010/354645

Tan, C.S., Sadda, S.R. (2017). Anti-vascular Endothelial Growth Factor Therapy for the Treatment of Myopic Choroidal Neovascularization. *Clinical Ophthalmology, 11*, 1741–1746. doi:10.2147/OPTH.S124518

Zheng, Q., Zong, Y., Li, L., Huang, X., Lin, L., Yang, W., et al. (2015). Retinal Vessel Oxygen Saturation and Vessel Diameter in High Myopia. *Ophthalmic Physiol. Opt*, *35*(5), 562–569. doi: 10.1111/opo.12223