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Correlation of Hepatocyte Growth Factor Levels with Myopia Degree and Axial Length in Outpatient Myopic Adolescents

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Abstract

Myopia is the most common ophthalmic condition worldwide, with an estimated 22.9% of the population or 1.406 billion people affected. Studies of candidate gene-associated refraction abnormalities have also identified several genes that cause vulnerability myopia, including the hepatocyte growth factor (HGF) and hepatocyte growth factor receptor (MET) genes. The purpose of the study was to analyze the correlation between hepatocyte growth factor (HGF) levels, degrees of myopia, and long axial in adolescents with myopia treated as outpatients in Universitas Sumatera Utara Hospital. This study applied the cross-sectional analytical approach. The inclusion criterion for the participants was patients diagnosed as suffering from myopia by the Ophthalmology Outpatient Clinic of the Universitas Sumatera Utara Hospital. Sampling was performed consecutively with a minimum sample size of 25 patients in control group and 25 patients in the case group. This study revealed that the mean axial length of the right eye in the case group was 23.82 mm, with a significant difference in the axial length between the case and control groups. The mean HGF level in the myopia group was 510.49 ng/mL, which was not significantly different from the mean HGF level in the control or emmetropic group. The HGF levels were highest in the group of subjects with moderate myopia, with an average of 551.87 ng/mL, and differences in HGF levels were identified in different degrees of myopia. Thus, no significant correlation is identified between the HGF levels, axial length, and myopia degree.

Keywords: Axial length, hepatocyte growth factor, myopia

Introduction

Myopia is the most common ophthalmic disease in the world, with an estimated 22.9% of the population affected, or 1.406 billion people.[1,2] Prevalence and incidence of myopia throughout the world have increased dramatically in the past 50 years, especially in East Asia and Southeast Asia. In 2050, the amount will reach 4.8 billion.[3] The prevalence of myopia in Indonesia is estimated at 26.1%.[4] Report from Indonesia Research Health Basis (RISKESDAS) 2013 shows prevalence abnormality refraction that has been corrected in Indonesia by 4.6% and in North Sumatra by 4.0%.[5] Estimated interference vision in preschool children will increase by 26% by 2060, with error refraction that doesn't correct as many as 69% of cases.[6]

The underlying mechanism of myopia is a molecular change on the sclera caused by the remodeling process. During this process, depletion and changes in the architecture of the sclera cause enhancement and elongation axial. Remodeling sclera is generated from changing the composition and content of collagen. Hepatocyte growth factor (HGF) and its receptor (MET), which are highly expressed in the retina, epithelium pigment, and choroid, presumably play a key role in matrix metalloproteinase and blocker network track metalloproteinases and may also play a role in remodeling the sclera, lengthening the axial, and developing myopia. Studies on candidate gene association abnormality refraction have also identified several genes that cause vulnerability to myopia, including These include the hepatocyte growth factor receptor (MET) gene and the HGF gene.[7,8]

Identification of molecular and genetic variables in myopia might provide insight into the diagnostic, prediction, treatment, and

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prevention of myopia, especially in adolescents, in whom sight would be vital to ensuring a productive quality of life. A study on HGF might be a pioneering study that could describe the pathophysiology, treatment, or diagnosis of myopia.

Methods

This study uses an analytic observational research method with a cross-sectional approach. The study was done in the Eye Polyclinic, Pediatric Ophtalmology Division, Universitas Sumatera Utara Hospital. This study lasted from March 2022 until June 2022, when the sample size was reached.Population case study This is because all patients in this study had a diagnosis of myopia, whereas the affordable population was patients with myopia Opthalmology Polyclinic of the Pediatric Opthalmology Division in Universitas Sumatera Utara Hospital.

The patient will undergo inspection refraction, examination biometry, and taking blood at Universitas Sumatera Utara Hospital. The sample size was determined by the correlation test method, i.e., all patients who visited the Ophtalmology Polyclinic at Universitas Sumatera Utara Hospital. A sample size formula for an analytical study is used to calculate the sample size. Through the formula, we observed that to gain statistical power, minimal samples of 25 patients per group were necessary. The sample size formula used for correlative analysis research will be used, and samples will be collected using the consecutive sampling method until all the samples have been fulfilled.

Criteria for inclusion in the study This is 12–25 years old, with myopia with >-1.00 spherical equivalent -6.00 D and ready to becomes sample research. Criteria for exclusion from the study are: systemic disease inflammation, moderate consumption of systemic drugs (e.g., steroids, anti-inflammatory nonsteroidals, vitamins), infection on the eye, history of trauma to the eye, and amblyopia.

Ethical clearance has been obtained from the USU Health Research Ethics Committee through letter number 321/KEPK/USU/2022.

Results

This study was followed by as many as 52 subjects. Subjects were divided into two groups, namely the case group and the control group. The case group included 26 myopic patients who visited the Ophthalmology Polyclinic, Pediatric Opthalmology Division, and Universitas Sumatera Utara Hospital. And the control group consisted of 26 subjects with normal eyes at the Universitas Sumatera Utara Hospital. All subjects have met the inclusion criteria. The average HGF level in the myopia group was 510.49 ng/mL (SD =90.76 ng/mL), with the lowest level of 337.81 ng/mL and the highest level of 676.08 ng/mL,

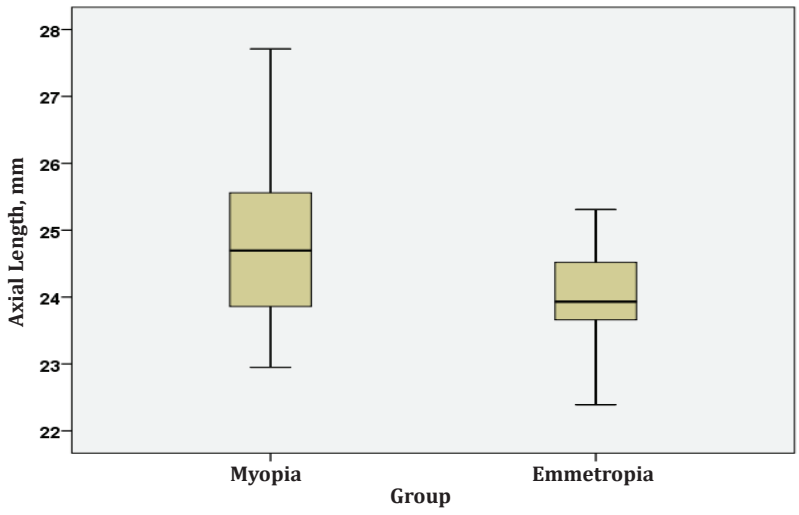

Figure 1 Axial Length Boxplot Graph Myopia Group and Emmetropia Group

Table 1 Characteristics Demographics Subject with myopia and Emmetropia

Characteristics Demographics	Myopia (n=26)	Emmetropia (n=26)	p
Type Gender, n (%)			
Male	10 (38.5)	11 (42,3)	0.777 [a]
Female	16 (61.5)	15 (57.7)	
Age, years			
Average (SD)	21 (2.90)	22.42 (0.5)	0.115 [b]
Median (Min–Max)	22 (12 – 23)	22 (22 – 23)	
Axial Length, mm			
Average (SD)	24.74 (1.18)	23.98 (0.65)	<0.001 [b]
Median (Min–Max)	24.70 (22.95–27.71)	23.93 (22.39–25.31)	
HGF, ng/mL			
Average	510.49	466.53	0.077*
SD	90.76	102.05	
Median (Min–Max)	501.42 (337.81–676.08)	492.94 (208–620.18)	
Degrees of Myopia			
Emmetropia		52 (50)	
Mild Myopia		30 (28.8)	
Moderate Myopia		14 (13.5)	
Severe Myopia;		8 (7.7)	

[a] *Chi Square;* [b] *T Independent;* * Mann Whitney U Test

while the control group showed a lower value. with a mean of 466.53 ng/mL (SD=102.05 ng/mL), with the lowest level of 208 ng/mL and the highest level of 620.18 ng/mL. Using the Mann-Whitney test, the mean HGF levels in the myopia and emmetropia groups did not significantly vary from one another (p=0.077).

The demographic characteristics of the subjects are shown in Table 1.

The average HGF level in male subjects in the myopia group was 525.13 ng/mL, much higher than the HGF level in the emmetropic group, with an average of 432.28 ng/mL. Male subjects with myopia and emmetropia had significantly different amounts of HGF, according to the analysis's findings using the independent T test (p=0.006). However, HGF levels in the two study groups of female participants did not significantly differ from one another (p=0.955). All of these results can be observed in Table 2.

Table 2 Differences in HGF Levels in Group Case and Control based on Type Sex

Type Sex	n	HGF, ng/mL Myopia	n	HGF, ng/mL Emmetropia	p*
Male	20		22		
Average (SD)		525.13 (86.21)		432.28 (115.28)	0.006 [a]
Median (Min–Max)		509.6 (350.82–652.21)		471.83 (208–620)	0.363 [b]
Female	32		30		
Average (SD)		501.35 (93.66)		491.65 (84.55)	0.955 [c]
Median (Min–Max)		492.72 (337.81–676.08)		506.36 (337.41–614.88)	0.049 [d]

[a] T Independent (Myopia vs Emmetropia Male), [b] T Independent ([Male Myopia vs Girls Myopia), [c] Mann Whitney (Myopia vs Emmetropia Female), [d] Mann Whitney (Male Emmetropia vs Girls emmetropia)

Table 3 HGF Levels Based on Degrees of Myopia

Degrees myopia	n	HGF level, ng/L		p *	Posthoc [a]		
		Average (SD)	Median (Min- Max)		Mild	Moderate	Severe
Emmetropia	52	466.53 (102.05)	492.94 (208-620.18)	0.026	0.190	0.008	0.486
Mild	30	508.21 (96.76)	493.83 (337.81-652.21)			0.207	0.115
Moderate	14	551.87 (66.97)	510.2 (492.02-676.08)				0.006
Severe	8	446.68 (69.24)	428.96 (384.71-544.06)				

* Kruskal Wallis, [a] Mann Whitney

Table 4 Correlation of HGF Levels with Axial Length and Degrees of Myopia

	Axial Length	Degrees of Myopia
HGF levels	p=0.127	p=0.720
	r=0.151	r=0.036
	n=104	n=104

The average HGF level in male subjects in the myopia group was 525.13 ng/mL, much higher than the HGF level in the emmetropic group, with an average of 432.28 ng/mL. The results of the analysis using the independent T test showed that the myopia and emmetropia groups in male subjects had significantly different levels of HGF (p=0.006). The levels of HGF in the two study groups of female participants, however, did not differ significantly from one another (p=0.955). In the myopia group, there was also no difference in HGF levels between male and female subjects (p=0.363). In the emmetropic group, differences in HGF levels were found between male and female subjects (p=0.049).

Table 3 shows the distribution of differences in HGF levels based on the degree of myopia, which is shown in the table below.

HGF levels appear to be the highest on group moderate myopia subjects with a mean of 551.87 ng/mL (SD=66.97), followed by group myopia light with a mean of 508.21 ng/mL (SD =96.76 ng/mL), and the lowest on the group with severe myopia with a mean of 446.68 ng/mL (SD=69.24 ng/mL). Using the Kruskal Wallis test, it was discovered that there was a difference in HGF levels based on degrees of myopia (p=0.026). After a post hoc analysis, different HGF levels were significant among subjects with

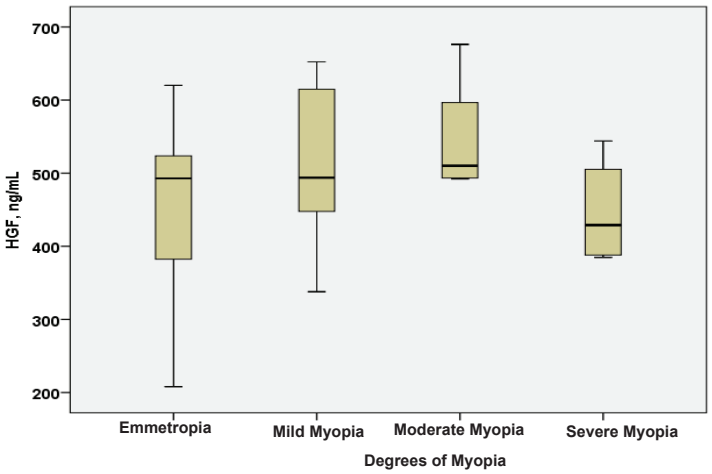

Figure 2 Boxplot Graph of HGF Levels Based on Degrees of Myopia

emmetropia with myopia medium (p=0.008) and among those with myopia currently and myopia weight (p=0.006). By using the Spearman correlation test, it was found that there was no significant correlation between HGF levels with axial length (p=0.127) and the degree of myopia (p=0.720). The result is shown in Table 4.

Discussion

The study had performed to examine HGF and MET levels in myopic adolescents. Subjects in the case and control groups were mostly female, amounting to 16 people (61.5%) in the case group and 15 people (57.7%) in the control group. In the case group, the mean age was 21 years, with the youngest being 12 years old and the oldest being 23 years old. Meanwhile, in the control group with a mean age of 22.42 years, the youngest was 22 years old and the oldest was 23 years old. However, it must be underlined that there are more women than men, and there are studies that have found a sex relationship, especially among women, to the incidence of myopia. There could be two possible gender differences. The first is that biological factors determine differences. The second possibility is that they are influenced by social and behavioral factors.

One study determined that Orthodox Jewish boys who received an intensive religious education were more likely to be shortsighted than their sisters and other age groups who received a more secular education. Perhaps the high incidence and rate of myopia seen in the group of Orthodox men is a result of their distinct study habits, which cause them to utilize their accommodating eyes a lot more than other people do. Recent, extensive research on the incidence of myopia has found that girls are more likely to have the condition. The causes of sex differences are related to puberty and are influenced by diet, genetics, and the amount of close work. Girls start puberty earlier than boys do, which causes them to grow to their final height one or two years earlier. As a result, myopia becomes more prevalent. 10 The result is that there is no relationship between gender and the incidence of myopia, with the ratio seen being 54% (13756 people) in women and 46% (11707 people) in men, where the significance is 0.718, proving no significant relationship.[10]

Eyes with mild myopia were 30 (28.8%). There were 14 eyes with moderate myopia (13.5%) and 8 people (7.7%) with severe myopia. These results are consistent with research conducted in Indonesia, namely Avliwani and Aryani's[10] research that in fact mild myopia remains the majority of myopia cases followed by moderate and severe cases. This is further strengthened by Avliwani and Aryani's [10] research design which compares urban and rural populations where the results are the same that mild degrees remain the highest. This research can be compared with research conducted by researchers because the research sample came from the Polyclinic of Universitas Sumatera Utara Hospital while Avliwani and Aryani's research took samples from SMA Negeri 2 Medan and SMA Istiqlal Private in Deli Serdang where this shows both that in community and home settings pain degree of myopia does not change the proportion.[11]

Myopia sufferers are more commonly found in high school students in urban areas compared to high school students in rural areas. Genetics, prolonged reading, watching TV and using computers as risk factors for myopia degree. Therefore, refractive examination should be performed on children from primary school to protect myopia.

The mean axial length of the right eye in the case group was 23.82 mm (SD=1.69 mm) with the shortest axial length 21.44 mm and the longest 27.17 mm. The mean axial length OD in the control group was 22.28 mm (SD=0.72 mm) with the shortest axial length 20.89 mm and the longest 23.82 mm. Using the Mann Whitney test, a significant difference in axial length was found between the case and control groups for the right eye. These results are consistent with a study conducted by Damara and Ismail [11] where when tested the significance of the axial length and myopia degree using the Kruskal Wallis test, it was found that there was a significant relationship with mild myopia having an average axial length of 19.75 followed by moderate myopia 23.02 and severe myopia. 25,72. The results of the Kruskal Wallis test are p=<0.001.[12]

Basically, myopia occurs due to an increase in the axial length of the eyeball without being followed by changes in other refractive components. Likewise, changes in the refractive power of the cornea, lens and aqueous humor will cause myopia if it is not compensated for by changes in the axial length of the eyeball. Because it is contrasted with these pathogenesis explanations, this study reinforces that axial length will be more influential in the pathogenesis of myopia. The cause of myopia is a mismatch between optical power and the

axial dimensions of the eye. An imagine is distorted as a result of the light rays intersecting in front of the photoreceptor retinal layer. The primary determinants of eye axial length growth include genetic, environmental, and aging factors. According to recent studies, myopia is characterized by a longer axial length, a flatter corneal curvature, and a thinner lens.[13]

Myopia is a refractive error of the eye characterized by blurring of distant vision due to parallel rays of light entering the eye and hitting a focal point in front of the retina. Refractive errors such as myopia are actually caused by disturbances in the development of vision, such as alterations to the scleral component that make the axial length of the myopic eye significantly longer than that of the emmetropic eye. Changes in scleral composition are related to hepatocyte growth factor (HGF) and its cMET receptor, which regulate the matrix metalloproteinase (MMP) pathway, and tissue inhibitor MMP (TIMP), which plays an active role mediated by interactions. regulates scleral remodeling, which can lead to myopia. Mutations and polymorphisms in genes play an important role in altering the major structural components of the scleral extracellular matrix. The SNPs rs 3735520 and rs 12536657 are part of a polymorphism in the HGF gene that predisposes to myopia. In addition, the cMET gene polymorphism (MET 110703) is also involved in the pathogenesis of myopia. Polymorphisms in the HGF gene and its receptor, cMET, lead to an increase in MMP enzyme levels and a decrease in TIMP enzyme levels. This situation causes remodeling of the extracellular matrix that forms the sclera, resulting in myopia. This is because the anteroposterior diameter of the eyeball is elongated so that the incident light hits the preretinal focal point.[14]

HGF can be a promising finding because of the possibility of this gene playing a role in the scleral remodeling process in myopic conditions. There were significant correlations between HGF levels and various myopia severity levels in this study. HGF has been investigated by various studies to be able to increase the expression of MMP-2, which can cause degradation of various cells and tissues. In myopia, the specific mechanism of action of MMP-2 is not yet known, but it has been shown that MMP-2 in the sclera can cause extracellular matrix degradation and axial elongation which eventually develops into myopia. Therefore, HGF indirectly plays a role in the development of myopia. In vitro studies on animal samples have proven this.[15]

The study limitation was the study's single-center design, a multi-center study could better be able to capture a phenomenon. A larger sample size might also be more representative to capture HGF effect toward myopia pathophysiology however it must be noted that our sample size was calculated according to statistical rule and should have scientific power to some degree.

Myopia is a refractive eye disorder that is still common throughout the world. The mechanism underlying myopia is a molecular change in the sclera through the scleral remodeling process. Axial elongation rises as a result of sclera architecture alterations and sclera thinning throughout this process. Changes in the collagen content's composition lead to scleral remodeling. Hepatocyte growth factor (HGF) is thought to play a role in scleral remodeling, axial elongation, and myopia development. The results of this study were based on the degree of myopia, eyes with mild myopia were 28.8%, moderate myopia was 13.5%, and severe was 7.7%. The mean axial length of the right eye in the case group was 23.82 mm and there was a significant difference in axial length between the case and control groups. The mean HGF level in the myopia group was 510.49 ng/mL and did not significantly differ between the myopia and emmetropia groups. HGF levels appeared to be the highest in the group of subjects with moderate myopia with an average of 551.87 ng/mL and differences in HGF levels were found based on the degree of myopia. This study concluded that there was no significant correlation between HGF levels and axial length and myopia degree.

Further study should be done with multi-center and larger sample size to further recognize the role of HGF in myopic patients. In vitro or in vivo study might also describe the phenomenon in a more coherent manner.

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