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Correlation between Leptin and Free Testosterone Levels in Transfusion-Dependent Thalassemia Male Patients

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ABSTRACT

Background: Male hypogonadism is a clinical disorder of low testosterone and spermatozoa due to impaired production that can occur at one or more levels in the hypothalamic-pituitary-gonadal (HPG) axis. Apart from iron accumulation, hypogonadism can also occur due to other mechanisms in thalassemia patients, such as the influence of adipose tissue and leptin. The study aimed to assess the relationship between leptin with free testosterone levels and BMI in transfusion-dependent thalassemia.

Method: The research design chosen was analytic cross-sectional. The study was conducted at the adult thalassemia polyclinic of Cipto Mangunkusumo General Hospital and Fatmawati General Hospital, during the period July - December 2022. The samples used were male transfusion-dependent thalassemia patients aged over 18 years who were under control at the Thalassemia Polyclinic during the study period. The diagnosis of Thalassemia had been previously established by high-performance liquid chromatography (HPLC) or microcapillary examination.

Result: Most patients were major ß thalassemia (87.8%), while HbE ß thalassemia was only 12.1%. Age distribution was with a median of 23 years (minimum-maximum 18-42 years). The clinical symptoms of hypogonadism were erectile dysfunction and decreased libido (12.1% and 9%, respectively). From body mass index examination were underweight 18 (54,5%), normal weight 13 (39,5%), overweight 1 (3%), and obese 1 (3%). Of the 33

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transfusion-dependent thalassemia patients, 95% did not reach puberty according to their age (Tanner stage V).

Conclusion: There is an association significantly between leptin levels with free testosterone and body mass index in transfusion-dependent thalassemia men.

Keywords: Leptin, Free Testosterone, Transfusion-Dependent Thalassemia

ABSTRAK

Latar Belakang: *Hipogonadisme pada pria adalah gangguan klinis testosteron dan spermatozoa yang rendah akibat gangguan produksi, dapat terjadi pada satu atau lebih pada sumbu hipotalamus-hipofisis-gonad (HPG). Selain akumulasi zat besi, hipogonadisme juga dapat terjadi karena mekanisme lain pada pasien thalassemia, seperti pengaruh jaringan adiposa dan leptin. Penelitian ini bertujuan untuk menilai hubungan antara leptin dengan kadar testosteron bebas dan IMT pada thalassemia yang bergantung pada transfusi.*

Metode: *Desain penelitian yang dipilih adalah analisa potong lintang. Penelitian dilakukan di poliklinik thalassemia dewasa RSUD Cipto Mangunkusumo dan RSU Fatmawati, selama periode Juli – Desember 2022. Sampel yang digunakan adalah pasien thalassemia laki-laki berusia di atas 18 tahun yang ditransfusi dan berada di Poliklinik Thalassemia. selama masa penelitian. Diagnosis Thalassemia sebelumnya telah ditetapkan dengan kromatografi cair kinerja tinggi (HPLC) atau pemeriksaan mikrokapiler.*

Hasil: *Sebagian besar pasien adalah thalassemia mayor (87,8%), sedangkan thalassemia HbE ß hanya 12,1%. Distribusi usia dengan median 23 tahun (minimum-maksimum 18-42 tahun). Gejala klinis hipogonadisme adalah disfungsi ereksi dan penurunan libido (masing-masing 12,1% dan 9%). Dari pemeriksaan indeks massa tubuh: underweight 18 (54,5%), normo weight 13 (39,5%), overweight 1 (3%), dan obesitas 1 (3%). Dari 33 pasien thalassemia yang bergantung transfusi, 95% tidak mencapai pubertas sesuai dengan usia mereka (Tanner stadium V).*

Kesimpulan*: Ada hubungan yang signifikan antara kadar leptin dengan testosteron bebas dan indeks massa tubuh pada pria thalassemia yang bergantung pada transfusi.*

Kata kunci: *Leptin, Testosterone bebas, Thalassemia tergantung transfusi*

1 Introduction

Male hypogonadism is a clinical disorder of low testosterone and spermatozoa due to impaired production that can occur at one or more levels in the hypothalamic-pituitary-gonadal (HPG) axis.[1,2] The incidence of hypogonadism varies widely, with population-based, community, treatment, or screening studies ranging from 2.1 to 12.8%.[1] In contrast to the general population, the incidence rate in the transfusion-dependent thalassemia population is quite high, reaching 70%.[3,4] This is thought to be due to iron accumulation in the endocrine organs, such as the

pituitary and testes.[5] Among the types of hypogonadism that occur in patients with transfusion-dependent thalassemia, the most common is hypogonadotropic hypogonadism (secondary) in 92.8% of patients.[6]

Apart from iron accumulation, hypogonadism can also occur due to other mechanisms in thalassemia patients, such as the influence of adipose tissue and leptin. Leptin has effects on carbohydrate, fat, and appetite metabolism, but it also has another effect, namely its role on the HPG axis, which can indirectly stimulate Kiss1 neurons in the arcuate nucleus.[7] Leptin is a 146 amino acid polypeptide produced by adipocytes. This hormone has receptors in various parts of the body. Besides regulating lipid and energy homeostasis, it also affects neuroendocrine function and immune function.[8] Leptin through its hypothalamic and pituitary stimulatory action is known to control gonadotropin secretion. This action may be explained by leptin's suppressive effect on neuropeptide Y (NPY) as NPY is known to be involved in gonadotropin suppression. Thus, due to the combined action of leptin on the gonads and brain, leptin is thought to have effects on the reproductive system. However, the mechanism is still unclear.[10] In a study conducted by Ozata et al, it was found that leptin levels were negatively and significantly correlated with testosterone levels in patients with idiopathic hypogonadotropic hypogonadism both before and after therapy.

Several studies have been conducted on leptin levels in different age groups of thalassemia patients, and in all these studies low leptin levels were found. Therefore, low circulating leptin may be one of the factors causing delayed puberty in thalassemia patients.[7] The pathomechanism of hypogonadotropic hypogonadism in transfusion-dependent thalassemia patients is still unclear. Data on leptin in the thalassemia population in Indonesia has also never been reported. Therefore, the researchers wanted to assess the relationship between leptin and free testosterone levels in transfusion-dependent thalassemia patients in Indonesia.

Data Analysis

The data analysis was used in univariate analysis. The relationship between leptin with free testosterone levels and BMI in transfusion-dependent thalassemia uses the Spearman correlation test when the data is unnormally distributed, and used Pearson tests when distributed data is normal. The results of the analysis are significant if the value of p-value < 0.05

2 Method

The research design chosen was analytic cross-sectional. The study was conducted at the adult thalassemia polyclinic of Cipto Mangunkusumo General Hospital and Fatmawati General Hospital, during the period July - December 2022. The samples used were male transfusion-dependent thalassemia patients aged over 18 years who were under control at the Thalassemia

Polyclinic at Cipto Mangunkusumo Hospital and Fatmawati General Hospital during the study period. Sample selection using convenient sampling. The exclusion criteria included the following: 1) Subjects with pituitary tumor; 2) Subjects with a history of surgery, irradiation, or testicular trauma; 3) Subjects with a history of pituitary tumor.

Following approval from the Ethics Committee of the Faculty of Medicine in our university, informed consent was obtained from each subject. Based on the correlation test, the minimum number of subjects was 8 patients. Data analysis was processed using the SPSS 21.0 program.

The patients recruited were old patients who came for control. The diagnosis of Thalassemia had been previously established by high-performance liquid chromatography (HPLC) or microcapillary examination.

3 Results

Table 1 shows the subjects' characteristics. Most patients were major ß thalassemia (87.8%), while HbE ß thalassemia was only 12.1%. Age distribution was found to be abnormal, with a median of 23 years (minimum-maximum 18-42 years).

Of the clinical symptoms associated with hypogonadism, erectile dysfunction, and decreased libido were found in 12.1% and 9%, respectively. There was no family history of hypogonadism or delayed sexual development. In the body mass index examination, 54% of subjects were underweight, 13% of subjects were normal weight, 3% of subjects were overweight, and 3% of subjects were obese. Of the 33 transfusion-dependent thalassemia patients, 95% did not reach puberty according to their age (Tanner stage V).

Table 1 Subjects characteristics

Characteristic	Total n=33
Age (year), median (minimum-maximum)	22 (18-42)
Thalassemia type, n (%)	
Major ß thalassemia	29 (87,8)
HbE ß thalassemia	4 (12,1)
Clinical, n(%)	
Family history of delayed sexual development	
No	
Yes	33 (100)
Erectile dysfunction	0 (0)
No	
Yes	4 (12.1)
Decreased libido	29 (87.8)
No	
Yes	3 (9.0)
	30 (90.9)
Physical examination, n (%)	
Body mass index (kg/m^2), median (minimum-maximum)	18.02 (14.7-25.0)
Underweight, n (%)	18 (54.5)
Normoweight	13 (39.3)
Overweight	1 (3)
Obesity	1 (3)
High-pitched voice	
No	21 (63.6)
Yes	12 (36.3)
Acne	
No	11 (33.3)
Yes	22 (66.6)
Facial hair	
No	10 (30.3)
Yes	23 (69.6)
Axillary hair	
No	9 (27.2)
Yes	24 (72.7)
Penile length (cm), median (minimum-maximum)	5 (3-6)
Testicle size, ml, mean (SD)	11.8 (6.795)
Pubic hair (Tanner stage), n (%)	
I	4 (12.1)
II	3 (9.0)
III	4 (12.1)
IV	17 (51.5)
V	5 (15.1)
Laboratory examination	
Hb (g/dL), median (minimum-maximum)	9.1 (6-14)
Ferritin serum (ng/mL), median (minimum-maximum)	6.923 (2.24-37.21)
FSH (mIU/mL), median (minimum-maximum)	8.06 (0.2-46.16)
LH (mIU/mL), median (minimum-maximum)	15.67 (0.76-50.70)
Free testosterone, pg/mL, mean (SD)	16.5 (10.3)
Leptin (pg/mL), median (minimum-maximum)	2.085 (411-15.21)

Correlation of leptin levels with free testosterone and body mass index

There was a significant negative correlation between free testosterone and leptin. Likewise, the correlation between serum leptin and body mass index was found to be significant. There was a positive correlation between leptin levels and body mass index. (Table 2)

Table 2 Correlation of leptin with free testosterone and BMI

Variables	Leptin	
	r value	p
Free testosterone	-0.522	0.002
Body mass index	0.505	0.003

4 Discussion

This study was a cross-sectional study of male thalassemia ß-major patients over 18 years old. In this study, the age above 18 years was chosen because the development of puberty first appears at the age of 11-12 years characterized by the development of testicular volume. The testicular volume will reach more than 4 ml by the age of 14, and 4 ml per year. Complete sexual development will be achieved less than 2 years later, and in some people, it can be achieved more than 4 years.[4] So it is expected that at the age of 18 years, all patients have reached complete sexual development.

In this study, the median body mass index (BMI) was 18.02 kg/m2. The majority of patients had an underweight BMI which reached 54.5%. This is in line with Yousefian et al's study which examined 740 patients with major-beta thalassemia, where the BMI rate was reported to be lower when compared to controls.[10] Patients with thalassemia are at risk for nutritional deficiencies due to increased nutritional requirements to maintain normal erythropoiesis and/or lack of intake and absorption of nutrients.[11,12]

In patients with delayed sexual development or hypogonadism, there may be a development that is not age-appropriate. In this study, secondary sexual development was assessed by facial hair growth (mustache and beard) in 69% and acne only occurred in 66% of patients. Armpit hair was found in 72%. On examination of the usual length of the penis, the median was 5 cm (minimum-maximum 3-6 cm). From a literature review, it was reported that the mean penis length differs in some countries. In Korea, the mean penis length was 7.7 cm, in China 6.5 cm, in Turkey 9.3 cm, and in America 10 cm. Penis length can vary depending on race, genetics, age, and comorbidities such as diabetes mellitus. Testosterone levels also influence the length of a person's penis.[13]

Measurement of testicular volume in this study using a Prader orchidometer, with a mean of 11.8 ml (SB 6.79 ml). In this study, 5 patients experienced late puberty (testicular volume smaller than 4 ml), and sexual development reaching Tanner stage V occurred in 15.1% of patients. Testicular volume is strongly influenced by age, body mass index, disease, FSH and LH levels, and race. Normal values of adult testicular volume vary widely. Studies in African Americans report testicular volume values >20 ml. In Asia, sizes are slightly smaller, with the average testicular volume of Japanese reported to be 18 ml. A study in a young adult thalassemia major and intermedia population found a minimum-maximum testicular size of 1.2-29 ml with a mean of 11 ml.[14-17]

The pubertal failure that occurred in this study is thought to be due to low nutritional status, as well as low levels of reproductive hormones. Tomova et al previously studied 4030 men and reported that at the age of 11-16 years, when the onset of pubertal development occurs, body weight can trigger sexual maturity as assessed by measures of penis length, pubic hair, and testicular volume. Meanwhile, at the age of 17-19 years (late puberty), body weight and body mass index still influence testicular volume and pubic hair, but not penis size. This is thought to be because the amount of fat mass gained during childhood can stimulate the secretory function of the hypothalamus. Adipose tissue also plays an important role in suprarenal androgen secretion, which can also affect testicular volume.[18}

In this study, there was a negative correlation between leptin levels and free testosterone ($r=-0.522$; $p=0.002$). This is in line with the research of Behre et al, who found a negative correlation between leptin levels and testosterone ($r=-0.84$; $p<0.001$). It is suspected that hypogonadism, which is assessed by low testosterone levels, can increase a person's serum leptin levels. This is reinforced by a study conducted by Behre et al, wherein patients were given intramuscular testosterone therapy, and leptin levels decreased to normal. Testosterone administration is reported to increase the size of muscle mass and free fat mass. In addition, repeated biopsies of adipose tissue in hypogonadal men showed that testosterone therapy has an important regulatory impact on adipose tissue metabolism and muscle mass. Leptin was reported to affect Leydig cell steroidogenesis in a rat model. While in other studies it is also known that low testosterone levels, can also affect serum leptin levels.[19-20]

Many studies have assessed the relationship between leptin and body mass index. In this study, there was also a positive correlation between leptin levels and body mass index. This is in line with Lima et al's study which showed a positive correlation between leptin and waist circumference. This is thought to be because leptin is produced from fat tissue so that it can correlate with body mass index and waist circumference, although in some cases, body mass index cannot describe a person's fat levels.[20]

5 Conclusion

In this study was found that leptin levels were significantly correlated with testosterone levels in patients with idiopathic hypogonadotropic hypogonadism both before and after therapy, and in all these studies low leptin levels were found. Therefore, low circulating leptin may be one of the factors causing delayed puberty in thalassemia patients

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