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ROLE OF MALONDIALDEHYDE LEVELS IN THE OCCURRENCE OF HYPOGONADISM IN TRANSFUSION-DEPENDENT THALASSEMIA MALE PATIENTS

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ABSTRACT

Background: Male hypogonadism is a clinical syndrome resulting from the failure of the testes to produce adequate testosterone. Thalassemia major is an autosomal recessive disorder characterized by the absence or severe deficiency of the synthesis of the ß-globulin chain of hemoglobin that causes severe anemia requiring lifelong transfusions. Chronic blood transfusion in patients with ß-thalassemia leads to the accumulation of transfusion-associated iron in the tissues. We aim to see the role of malondialdehyde levels in the occurrence of hypogonadism in male patients with transfusion-dependent thalassemia.
Methods. This study used a cross-sectional design conducted at the Thalassemia polyclinic of RSCM and Fatmawati from January to March 2023. The study samples were transfusion-dependent thalassemia patients who met the acceptance criteria of the study subjects. Each patient underwent venous blood collection and was examined for serum ferritin levels, transferrin saturation, FSH levels, LH levels, free testosterone levels, and MDA. The data obtained will be recorded and processed using the SPSS 20 program.
Results. Forty-one male subjects with transfusion-dependent thalassemia had a median free testosterone of 14.53 pg/mL (minimum-maximum 0.1-35.78). Twelve subjects (29%) of them had low testosterone levels. The median MDA level was 2.22 uM (0.18-2.61). There was no significant correlation between free testosterone and MDA (r=-0.18, p=0.261)..
Conclusion. There were high MDA levels in men with transfusion-dependent thalassemia. High MDA levels had no role in hypogonadism in men with transfusion-dependent thalassemia.

Keyword: Hypogonadism, Malondialdehyde, Transfusion-dependent Thalassemia

ABSTRAK

Latar belakang *Hipogonadisme pria adalah sindrom klinis yang diakibatkan oleh kegagalan testis untuk menghasilkan testosteron yang memadai. Thalassemia mayor adalah gangguan resesif autosomal yang ditandai dengan tidak adanya atau kekurangan parah sintesis rantai β-globulin hemoglobin yang menyebabkan anemia parah yang membutuhkan transfusi seumur hidup. Transfusi darah kronis pada pasien dengan ß-thalassemia menyebabkan akumulasi zat besi terkait transfusi dalam jaringan. Kami bertujuan untuk melihat korelasi antara kadar*

malondialdehida dan testosteron bebas pada pasien pria dengan talasemia yang bergantung pada transfusi.
***Metode**. Penelitian ini menggunakan desain cross-sectional yang dilakukan di poliklinik Thalassemia RSCM dan Fatmawati dari Januari hingga Maret 2023. Sampel penelitian adalah pasien thalassemia yang bergantung pada transfusi yang memenuhi kriteria penerimaan subjek penelitian. Setiap pasien menjalani pengambilan darah vena dan diperiksa kadar feritin serum, saturasi transferrin, kadar FSH, kadar LH, kadar testosteron bebas, dan MDA. Data yang diperoleh akan dicatat dan diolah menggunakan program SPSS 20.*
***Hasil**. Empat puluh satu subjek laki-laki dengan thalassemia yang bergantung pada transfusi memiliki testosteron bebas rata-rata 14,53 pg/mL (minimum-maksimum 0,1-35,78). Dua belas subjek (29%) di antaranya memiliki kadar testosteron yang rendah. Tingkat MDA rata-rata adalah 2,22 uM (0,18-2,61). Tidak ada korelasi yang signifikan antara testosteron bebas dan MDA (r = -0,18, p = 0,261).*
***Kesimpulan.** Terdapat kadar MDA yang tinggi pada pria dengan thalassemia yang bergantung pada transfusi. Kadar MDA yang tinggi tidak memiliki korelasi dengan testosteron bebas pada pria dengan talasemia yang bergantung pada transfusi.*

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***Keyword:** Hipogonadisme, Malondialdehida, Thalassemia yang bergantung pada transfusi*

1. Introduction

When the hypothalamic-pituitary-gonadal (HPG) axis is disrupted at one or more levels, the testes are unable to produce enough testosterone and spermatozoa, resulting in male hypogonadism, a clinical condition. In population-based, community-based, therapy, or screening investigations, the incidence of hypogonadism ranges greatly, from 2.1 to 12.8%. Nonetheless, transfusion-dependent thalassemia populations have an incidence rate as high as 70%. The accumulation of iron in endocrine organs including the pituitary and testes is hypothesized to cause impaired generation of reproductive hormones. The most prevalent form of hypogonadism in patients with transfusion-dependent thalassemia is hypogonadotropic hypogonadism (secondary), which affects 92.8% of the patients [1].

Patients with beta-thalassemia may experience excessive tissue iron levels as a result of repeated transfusions. The Fenton reaction may lead to the generation of free radicals and reactive oxygen species (ROS), which may have detrimental effects such as osteoporosis, endocrine problems, heart failure, liver failure, and multi-organ failure that could result in early death. A straightforward test called serum ferritin detection is routinely used to assess iron overload and track the effectiveness of iron chelation therapy in individuals with thalassemia [2,3].

Reactive free radicals and ROS cause tissue damage brought on by oxidative stress through the processes of lipid peroxidation, protein oxidation, and DNA hydroxylation in the affected organs. Furthermore, in thalassemia, the synthesis of faulty β globin chains causes an increased build-up of denatured α globin chains in red blood cells. The process of auto-oxidation, which is exacerbated by excess iron and results in cytoskeletal alterations and membrane lipid peroxidation that causes hemolysis, is another way that these extra α globin chains produce ROS. Owing to elevated ROS generation, several investigations have shown that thalassemia patients have an imbalance in the oxidant and antioxidant ratio. MDA, the active aldehyde, is typically produced when polyunsaturated lipid peroxidation damages cell membranes and organelles in iron-containing organs such as the liver, heart, pancreas, and endocrine organs. MDA is an eosinophilic enol molecule that combines with both structural and functional proteins in cells to create toxic epoxidation end products that are intended to cause harm to cells in the organs that are impacted. It is most frequently found using colorimetric techniques and is employed as a sensitive biomarker for oxidative stress. It is also known as thiobarbituric acid reagent material (TBARS) because it combines with thiobarbituric acid (TBA) to produce a colorful product (TBA-MDA) that can be quantified using a spectrophotometer [4,5].

The oxidative balance may be upset by high ROS concentrations, which could impact the HPG axis and reduce the release of reproductive hormones. Oxidative stress is primarily caused by either increased ROS production

or decreased antioxidant availability. ROS plays an important role as a second messenger in many intracellular signaling cascades that maintain cellular balance with the outside world. Random damage to biomolecules brought on by oxidative stress can lead to cell death or loss of function. [6,7].

The researcher wants to determine the role of MDA in hypogonadism in transfusion-dependent thalassemia patients since it hasn't been studied before.

2. Methods

This study is a cross-sectional design that analyzes the relationship between MDA and free testosterone levels in transfusion-dependent thalassemia male patients. The study will be conducted on outpatients with a diagnosis of transfusion-dependent thalassemia at the thalassemia polyclinic of Internal Medicine of Cipto Mangunkusumo Hospital and Fatmawati Hospital from January to March 2023. This study was approved by the Faculty of Medicine Universitas Indonesia's ethical board on 9th May 2022, with the registration number KET-435/UN2.F1/ETIK/PPM.00.02/2022.

Based on the test conducted, the correlation test, from the sample calculation, a sample size of 29 patients was obtained. The number of subjects in this study was at least 29 patients.

The target population was adult male transfusion-dependent thalassemia patients who attended the adult thalassemia clinic at Cipto Mangunkusumo Hospital and Fatmawati General Hospital. The target population was male transfusion-dependent thalassemia patients above 18 years old who attended the thalassemia clinic during the study period. The study sample was transfusion-dependent thalassemia patients who met the acceptance criteria of the study subjects. The acceptance criteria were TDT patients whose diagnosis was determined by a pediatrician and or an internist, male gender, age ≥ 18 years, and willing to participate in the study. The rejection criteria were patients with mental disorders, currently taking drugs that cause hyperprolactinemia, history of pituitary gland surgery, history of testicular trauma, irradiation, or testicular surgery, patients with pituitary tumors, diabetes mellitus, and patients who received testosterone therapy in the last 2 weeks. The sampling technique was performed using the convenient sampling method.

Statistical analysis

Data analysis was processed using the SPSS 21.0 program. Results were correlated and statistical analysis was conducted using Pearson's correlation (r) for normally distributed data, and Spearman's correlation (rho) test was used for data that was not normally distributed.

3. Results

The basic characteristics of the male transfusion-dependent thalassemia in this study are shown in **Table 1**. The data of this study showed the patients' age, body mass index, and laboratory results. The study's patients ranged in age from 18 to 42 years old, with a median age of 22. Pre-transfusion hemoglobin levels were 8.9 g/dL (normal 14–18 g/dL), 7.968 ng/mL (normal <1,000 ng/mL) for serum ferritin, and 14.5 pg/mL for free testosterone. The mean BMI was 18.5 kg/m2, among them, 23 patients (56%) were underweight, 15 patients (36%) were norm weight, and 3 patients (7%) were overweight. median MDA 2.22 uM (normal 1.07 uM) and median LH 15.6 mIU/mL. Among these patients, 32% had low free testosterone levels (< 5 pg/mL).

Table 1 Basic characteristics of subjects

Variables	Total (n=41)
Age (year, median, min-max)	22 (18-42)
BMI, kg/m^2, mean (SD)	18.5 $\pm$ 2.63
Pre-transfusion Hb (g/dL, median, min-max)	8.9 (5.1-14.2)
Serum Ferritin (ng/mL, median, min-max)	7968 (2243-37211)
Free testosterone (pg/mL, median, min-max)	14.5 (0.1-35.7)
Luteinizing hormone (mIU/L, median, min-max)	15.6 (0.76-50.7)
MDA (uM, median, min-max)	2.22 (0.18-2.61)

Table 2 shows a significant correlation between BMI and LH level (r = -0.632, p = <0.001), and pre-transfusion Hb (r = -0.380, p = 0.014). Meanwhile, the correlation between serum ferritin and MDA with LH level was not statistically significant.

Table 2 Correlation between BMI, pre-transfusion Hb, serum ferritin, and MDA with LH level

Variables	LH level	
	r	p
BMI	**-0.632**	**<0.001**
Hb pre-transfusion	**-0.380**	**0.014**
Serum Ferritin	-0.063	0.694
MDA	-0.009	0.956

Table 3 shows a statistically significant correlation only between LH levels and free testosterone (r = 0.403, p = 0.009). Neither BMI, pre-transfusion Hb, serum ferritin nor MDA had a significant correlation with free testosterone levels in men with transfusion-dependent thalassemia.

Table 3 Correlation between BMI, pre-transfusion Hb, serum ferritin, MDA, and LH level with free testosterone level

Variables	Testosterone level	
	r	p
BMI	-0.293	0.063
Pre-transfusion Hb	-0.153	0.341
Serum Ferritin	-0.027	0.866
Luteinizing hormone	**0.403**	**0.009**
MDA	-0.189	0.261

4. Discussions

Blood transfusions, the main treatment for thalassemia, can exacerbate iron overload, which can lead to oxidative stress. Patients with thalassemia may have cellular damage and reduced viability as a result of chronic oxidative stress caused by iron overload. Secondary issues that might result from oxidative stress include infections, hypercoagulable disorders, and organ damage. One of the main causes of transfusion-dependent thalassemia's pathogenesis is oxidative stress. When oxidants and antioxidants are out of balance, oxidative stress arises, which can harm cells and molecules. [3,8-11].

In this study, the mean BMI in patients was 18.5 kg/m2. The majority (56%) of patients' BMI was underweight. In boys during puberty, sexual development has a positive correlation with BMI. Patients with thalassemia, especially those who depend on transfusions, are susceptible to underweight because of several causes. Patients with thalassemia have greater metabolic rates, which means they need more calories to maintain their weight, and this is one of the main causes. However, patients may not be able to ingest enough calories to meet their energy needs due to persistent anemia and other problems associated with thalassemia, which can result in weight loss and underweight. Furthermore, oxidative stress and cellular damage brought on by iron overload—a typical condition in transfusion-dependent thalassemia—can result in decreased viability and weight loss [8,12-14].

The median MDA in this study was 2.22 uM. MDA levels have been investigated in transfusion-dependent thalassemia (TDT) patients; the findings show that MDA levels in TDT patients are considerably higher than in healthy controls. Iron excess has been demonstrated to promote oxidative stress, which raises MDA levels. Iron overload is a serious problem in TDT [2,3,14-16].

In this study, there was no relationship between MDA with LH and free testosterone. Numerous studies have examined the relationship between levels of MDA and hormones including testosterone, LH, and spermatozoa. Oxidative stress, linked to testosterone shortage, reduces the body's testosterone levels through lipid peroxidation. The relationship between MDA and testosterone levels is complex and influenced by various factors, such as age, health status, and lifestyle. Some studies have reported a negative correlation between MDA and testosterone levels, while others have found no significant correlation. The underlying mechanisms linking MDA and testosterone may be multifactorial and involve other biomarkers of oxidative stress and

inflammation. For example, a study on women during different reproductive phases of life found that MDA showed a positive correlation with LH and a negative correlation with estradiol and progesterone. This suggests that the relationship between MDA and testosterone is part of a broader network of interactions involving hormonal and molecular pathways [6,18-20].

Our study was the first study to evaluate the relationship between MDA and gonadal function in male TM patients. However, our study was limited by the cross-sectional design, and we did not perform an anti-oxidant biomarker.

5. Conclusions

Men with transfusion-dependent thalassemia had high MDA levels. However, there was no role of high MDA levels with hypogonadism in men with transfusion-dependent thalassemia.

Competing interests

The authors declare that there is no conflict of interest.

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References

[1] Al-Sharefi A, Quinton R. Current national and international guidelines for the management of male hypogonadism: Helping clinicians to navigate variation in diagnostic criteria and treatment recommendations. Endocrinology and Metabolism. 2020 Sep 30;35(3):526–40.
[2] Basu D, Adhya DG, Sinha R, Chakravorty N. Role of malonaldehyde as a surrogate biomarker for iron overload in the β-thalassemia patient: A systematic meta-analysis. Advances in Redox Research. 2021 Dec;3:100017.
[3] Atmakusuma TD, Nasution IR, Sutandyo N. Oxidative stress (Malondialdehyde) in adults beta-thalassemia major and intermedia: Comparison between before and after blood transfusion and its correlation with iron overload. Int J Gen Med. 2021;14:6455–62.
[4] D′souza D, Babu G, Shetty S, Balan P. Estimation of serum malondialdehyde in potentially malignant disorders and post-antioxidant treated patients: A biochemical study. Contemp Clin Dent. 2012 Oct 1;3(4):448–51.
[5] Bhutia Y, Ghosh A, Sherpa ML, Pal R, Mohanta PK. Serum malondialdehyde level: Surrogate stress marker in the Sikkimese diabetics. J Nat Sci Biol Med. 2011 Jan;2(1):107–12.
[6] Roychoudhury S, Chakraborty S, Choudhury AP, Das A, Jha NK, Slama P, et al. Environmental factors-induced oxidative stress: Hormonal and molecular pathway disruptions in hypogonadism and erectile dysfunction. Antioxidants. 2021;10(6).
[7] Sharifi-Rad M, Anil Kumar N V., Zucca P, Varoni EM, Dini L, Panzarini E, et al. Lifestyle, Oxidative Stress, and Antioxidants: Back and Forth in the Pathophysiology of Chronic Diseases. Vol. 11, Frontiers in Physiology. Frontiers Media S.A.; 2020.
[8] Patpan N, Banjerdpongchai R, Tantiworawit A, Poofery J, Komonrit P, Fanhchaksai Rattanathammethee KT, et al. The effect of transfusion-dependent thalassemia patient's serum on peripheral blood mononuclear cell viability. J Cell Death. 2019;12:1–8.
[9] Pizzino G, Irrera N, Cucinotta M, Pallio G, Mannino F, Arcoraci V, Squadrito F, et al. Oxidative stress: Harms and benefits for human health. Oxi Med Cel Long. 2017: 1-7.
[10] Al Neaimy K, Alkhyatt M, Jarjess I. New insights into oxidative stress and thalassemia may lead to antioxidant therapy. Pharmacogn J. 2024;16:202-4.
[11] Narahari JM, Guruswamy P, Jagadeesha NM, Shivashakar K, Kumar D, Narayana P, et al. Exploring the impact of iron overload on mitochondrial DNA in b-thalassemia: A comprehensive review. Gen Expr. 2024;23:197-210.
[12] Lidoriki I, Stavrou G, Schizas D, Frountzas M, Fotis L, Kapelouzou A, et al. Nutritional status in a sample of patients with β-thalassemia major. Cureus. 2022: 1-8.
[13] Yousefian S, Aliabad GM, Saleh R, Khedmati M. Association of body mass index and serum ferritin level in pediatrics with beta-thalassemia major disease. Iran J Ped Hematol Oncol. 2022;12: 34-40.
[14] Tomova A, Robeva R, Kumanov P. Influence of the body weight on the onset and progression of puberty in boys. J Pediatr Endocr Met. 2015: 1-7.

[15] Gensluckner S, Wernly B, Datz C, Aigner E. Iron, oxidative stress, and metabolic dysfunction-associated steatotic liver disease. Antioxidants. 2024;13: 1-12.
[16] Puntarulo S. Iron, oxidative stress and human. Mol Aspects Med. 2005;26: 299-312.
[17] Galaris D, Barbouti A, Pantopoulos K. Iron homeostasis and oxidative stress: An intimate relationship. Mol Cel Res. 2019: 1-15.
[18] Ogunro PS, Bolarinde AA, Owa OO, Salawu AA, Oshodi AA. Antioxidant status and reproductive hormones in women during reproductive, perimenopausal, and postmenopausal phases of life. Afr J Med Med Sci. 2014 Mar;43(1):49–57.
[19] Choobineh H, Gilani MA, Pasalar P, Jahanzad I, Ghorbani R, Hassanzadeh G. The effects of testosterone on oxidative stress markers in mice with spinal cord injuries. Int J Fer Ster. 2019;10: 87-93.
[20] Cordiano, R.; Di Gioacchino, M.; Mangifesta, R.; Panzera, C.; Gangemi, S.; Minciullo, P.L. Malondialdehyde as a Potential Oxidative Stress Marker for Allergy-Oriented Diseases: An Update. Molecules 2023, 28, 5979.