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THALASSEMIA AND NUTRITIONAL STATUS IN CHILDREN
(TALASEMIA DAN STATUS GIZI PADA ANAK)

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ABSTRACT

Thalassemia is an autosomal recessive single gene disorder due to an imbalance in the production of globin chains, namely α-globin and β-globin chains, which until now the case is increasing with manifestations of severe anemia and can have an impact on nutritional status. Malnutrition is one of the effects of thalassemia due to rapid erythrocyte turnover. The purpose of this paper is to discuss and provide information regarding the definition, epidemiology, classification, pathogenesis, diagnosis, complications, management, and nutritional status to minimize growth disorders in thalassemia patients. This research is a literature study, which is a type of research that collects, manages, uses, and reviews research data sourced from scientific research journals, previous research manuscripts, and textbooks. The results of the literature review are a factor of good nutritional status in thalassemia patients can be affected by various factors, one of which is increased energy expenditure which can offset good intake and consumption patterns. One of the assessments of nutritional status in thalassemia patients is the Upper Arm Circumference (UAC) because it can be used

in organomegaly patients. Many factors can affect the nutritional status of children, especially in children with thalassemia.

Keywords: children; nutritional status; thalassemia

ABSTRAK

Talasemia adalah kelainan gen tunggal resesif autosom akibat ketidakseimbangan produksi rantai globin, yaitu rantai globin-α dan globin-β yang hingga kini kasusnya semakin meningkat dengan manifestasi anemia berat dan dapat berdampak kepada status gizi. Perburukan gizi merupakan salah satu dampak talasemia akibat pergantian eritrosit yang cepat. Tujuan penulisan ini membahas dan memberikan informasi mengenai definisi, epidemiologi, klasifikasi, patogenesis, diagnosis, komplikasi, penatalaksanaan, dan status gizi sehingga dapat meminimalisasi gangguan pertumbuhan pada pasien talasemia. Penelitian ini merupakan penelitian studi kepustakaan atau literature review yaitu jenis penelitian yang mengumpulkan, mengelola, menggunakan dan mengkaji data penelitian bersumber dari jurnal penelitian ilmiah, naskah penelitian terdahulu dan textbook yang memiliki relevansi dengan tema. Hasil penelusuran literatur menunjukkan bahwa faktor status gizi baik pada pasien talasemia dapat dipengaruhi oleh berbagai faktor seperti salah satunya akibat energy expenditure yang meningkat dapat mengimbangi asupan dan pola konsumsi yang baik. Penilaian status gizi pada pasien talasemia salah satunya dengan lingkar lengan atas (LiLA) karena manfaatnya dapat digunakan pada pasien organomegali. Terdapat beberapa faktor yang dapat memengaruhi status gizi anak, terutama pada anak talasemia.

***Kata kunci**: anak; status gizi; talasemia*

INTRODUCTION

Thalassemia is a genetic hematological disease that is inherited due to impaired synthesis of hemoglobin (Hb), especially in the production of globin chains. Thalassemia generally consists of 2 types, namely α-thalassemia and β-thalassemia. Clinically, thalassemia consists of transfusion-dependent and non-transfusion-dependent thalassemia.[1] Physical examination manifestations of transfusion-dependent thalassemia children include icteric sclera, pallor, thalassemia facies, or Cooley's facies (squinted eyes, prominent forehead, wide eye distance, maxillary hypertrophy, and dental malocclusion), hepatosplenomegaly, short stature, malnutrition, skin hyperpigmentation, and late puberty.[2]

The world data shows that 7% of the population is carriers of thalassemia traits. Every year that 300,000 – 500,000 babies are born with hemoglobinopathies and 80% of 50,000 – 100,000 children in developing countries die because of β-thalassemia.[2] The data from the Hematology Coordination Unit of the Indonesian Children's Association (2019) reported that the prevalence of thalassemia major in Indonesia reached 10,555 people spread to various regions. West Java occupies the first province with the highest prevalence of thalassemia in Indonesia, which is 4,199 (2019). Data from the Indonesian Thalassemia Foundation/Indonesian Thalassemia Patient Parents Association 2021 reported that there were 1000 thalassemia patients in West Bandung and Cimahi.[3]

Malnutrition is one of the effects of thalassemia due to rapid erythrocyte turnover. The increase in the hemolysis process results in the body needing sufficient energy and nutrients to produce new erythrocytes. More nutrients than intake cause malnutrition.[4] The anthropometric standard of children according to the Minister of Health of the Republic of Indonesia Number 2 of 2020 is a reference for assessing the nutritional status of children.[5] Upper Arm Circumference (UAC) is an anthropometric parameter to describe muscle tissue and subcutaneous fat content with one of its benefits being used in patients with organomegaly.[6,7] In 2019, 50% of thalassemia respondents in Semarang were malnutrition based on the UAC measurement.[8] Research in West Java (2020) as many as 74% of patients with β-thalassemia major are good nutrition.[4] A linear regression study in India (2021) found that 328 thalassemia patients were malnutrition.[9] Research at Dustira Cimahi Hospital in 2022 showed that 39 thalassemia patients were good nutrition.

METHOD

The design of this research is a literature review research. Literature review research design is a research method used to collect data related to the formulation of the problem in research papers obtained from various literature sources such as scientific research journals, previous research manuscripts, and related textbooks and can answer the number of samples of scientific research journals used in research.

A literature search was performed combining “thalassemia” and “nutritional status”, after previously identifying the chosen descriptors in articles published on the topic and in the Medical Subject Headings (MeSH). The PubMed, MEDLINE, BBO, LILACS, and SciELO databases were accessed covering the period from January 2017 to November 2021.

Inclusion and exclusion criteria English-language publications with the title and abstract related to the topic were included. Incomplete articles, duplicated ones, studies on animals, and those that, when read, did not fit the proposed theme were excluded from the research.

RESULT

The search resulted in 46 published papers, with 23 potentially eligible identified after applying the inclusion and exclusion criteria. After reading these papers in full, 23 pieces of literature remained**.**

DISCUSSION

Classification of Thalassemia

Thalassemia generally consists of 2 types, namely α-thalassemia and β-thalassemia. The clinical classification of thalassemia consists of thalassemia major, intermedia, and trait or minor which can reflect the degree of anemia.[10] β-thalassemia syndrome consists of β-thalassemia major, thalassemia intermedia, β-thalassemia trait, δ-thalassemia, δβ-thalassemia, $\delta\beta^{0}$-thalassemia, γδβ-thalassemia, and γ-thalassemia. Thalassemia trait is a "silent carrier" who generally has no symptoms except for mild anemia and microcytosis.[1]

The α-thalassemia is usually due to a deletion mutation of the α-globin gene, but can also be caused by a non-deletion α-globin gene mutation, namely Constant Spring (αCSα) which causes more severe anemia than a deletion mutation.[1,10]

In addition, there are Transfusion Dependent Thalassemia (TDT) where patients have occasional or intermittent transfusions, and Non-Transfusion Dependent Thalassemia (NTDT), which are patients who need transfusions for life. Mild and moderate β-thalassemia/HbE, β-

thalassemia/HbC, and deletion HbH are included in NTDT, whereas β-thalassemia major, β-thalassemia/HbE severe, and non-deleted HbH are TDT.[1,3]

Pathogenesis of Thalassemia

Total globin production is the main pathology in thalassemia.[1,11] The globin chain is a protein that makes hemoglobin (Hb) in the blood.[4,8]

Hemoglobin consists of heme and globin. Heme is composed of 4 groups of iron atoms, each consisting of a group that can bind to oxygen. Globin is a protein made up of four polypeptide chains. Hemoglobin synthesis is affected by 3 processes, first, sufficient iron storage and supply, protoporphyrin synthesis (heme precursor), and globin synthesis. Hemoglobin synthesis occurs initially in the pronormoblast and then in the stage of erythrocyte formation in the reticulocyte stage. Succinyl-CoA formed in the Krebs cycle will bind to glycine to form four pyrrole molecules, which is the initiation step of hemoglobin synthesis. The four pyrroles form protoforphyrin IX which mixes with iron to form heme. Each heme contains a long polypeptide chain, namely globin.[12] The synthesis of hemoglobin can be seen in Figure 1.[12]

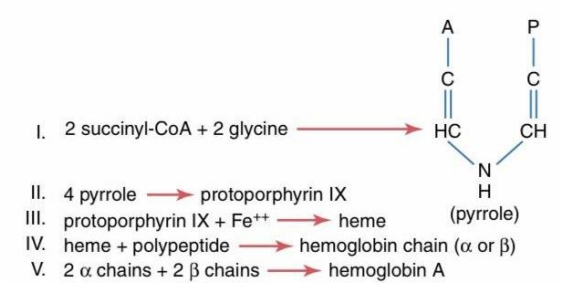

Figure 1. The synthesis of hemoglobin.12

α-thalassemia mutations occur on chromosome 16 and there is also an increase in and globin chains derived from the Hb Bart (γ4) tetramer in fetal life and unstable HbH (β4) after birth. This abnormal tetramer is non-functional hemoglobin with a very high oxygen affinity so that oxygen cannot be transported and results in extravascular hemolysis.[1,2]

β-thalassemia occurs as a result of mutations in the β-globin gene on chromosome 11 which causes the production of β-globin chains to be reduced or not formed at all due to an imbalance of globin chains. When the α-globin chain is formed, not all of it can bind to the β-globin chain so that HbF (due to an increase in the γ-globin chain) and

HbA2 (due to an increase in the δ-globin chain) increases to form alpha-globin tetramer (α4) that appears as erythrocyte inclusions. Free α-globin chains and inclusions are very unstable, deposited in erythrocyte precursors, damaging

erythrocytes which eventually triggers erythrocyte lysis in the microcirculation (spleen) causing ineffective erythropoiesis in the bone marrow.[1,2]

Table 1. Hemoglobin analysis based on thalassemia classification.[1]

THALASSEMIA	GLOBIN GENOTYPE	RED BLOOD CELL FEATURES	CLINICAL FEATURES	HEMOGLOBIN ANALYSIS
α-Thalassemia				
1 Gene deletion	−,α/α,α	Normal	Normal	Newborn: Bart: 1–2%
2 Gene deletion (α-thalassemia trait)	−,α/−,α −, −/ α,α	Microcytosis, mild hypochromasia	Normal, mild anemia	Newborn: Bart: 5–10%
3 Gene deletion hemoglobin H	−,−/−,α	Microcytosis, hypochromic	Mild anemia, transfusions not required	Newborn: Bart: 20–30%
2 Gene deletion + Constant Spring	−,−/ α,α$^{Constant\ Spring}$	Microcytosis, hypochromic	Moderate to severe anemia, transfusion, splenectomy.	2–3% Constant Spring, 10–15% HbH
4 Gene deletion	−,−/−,−	Anisocytosis, poikilocytosis	Hydrops fetalis	Newborn: 89–90% Bart with Gower-1, Gower-2, and Portland
Nondeletional	α,α/α,α^{variant}	Microcytosis, mild anemia	Normal	1–2% variant hemoglobin
β-Thalassemia				
β^0 or β^+ heterozygote: trait	β^0 /A,β^+ /A	Variable microcytosis, mild anemia	Normal	Elevated A_2 , variable elevation of F
β^0 or β^+ - Thalassemia severe	β^0 /β^0 , β^+ /β^0 , β^+ β^+ E/β^0	Microcytosis, nucleated RBC	Transfusion dependent	F 98% and A_2 2%, E 30–40% (E/β^0); variably low Hb A with β^+
β^0 or β^+ thalassemia intermedia		Hyopchromic, microcytosis	Mild to moderate anemia, intermittent transfusions	A_2 2–5%, F 10–30%, Hb A variably low levels
Dominant (rare)	B^0 /A	Microcytosis, abnormal RBCs	Moderately severe anemia, splenomegaly	Elevated F and A_2
δ-Thalassemia	A/A	Normal	Normal	A_2 absent
$(\delta\beta)^0$ - Thalassemia	$(\delta\beta)^0$ /A	Hypochromic	Mild anemia	F 5–20%
$(\delta\beta)^+$ - Thalassemia Lepore	β^{Lepore} /A	Microcytosis	Mild anemia	Lepore 8–20%
Homozygous Hb Lepore	β^{Lepore} / β^{Lepore}	Microcytic, hypochromic	Thalassemia intermedia	F 80%, Lepore 20%
γδβ-Thalassemia	$(\gamma A\ \delta\beta)^{0/}$ A	Microcytosis, microcytic, hypochromic	Moderate anemia, splenomegaly, homozygote: thalassemia intermedia	Decreased F and A_2 compared with δβ-thalassemia
γ-Thalassemia	$(\gamma A\ \gamma G\ )^0$ /A	Microcytosis	Insignificant unless homozygote	Decreased F

Complication of Thalassemia

Thalassemia is chronic anemia that results in increased iron absorption. Transfusion-induced iron overload is a major concern in thalassemia patients. There is no physiological mechanism for eliminating excess iron from the body.[1]

Iron is initially stored in the liver and deposition occurs in endocrine organs and the heart. This causes hypothyroidism, hypogonadotropi gonadism, growth hormone deficiency, hypoparathyroidism, diabetes mellitus, and splenomegaly. Complications of thalassemia such as heart failure and growth retardation at puberty due to hormonal disturbances generally appear in the early first decade. Iron deposition in the heart causes death in patients not receiving iron chelation. Finally, the majority of patients who do not receive adequate iron chelation therapy die because of heart failure or cardiac arrhythmias due to hemosiderosis.[1,2]

Excess iron in myocytes causes free radicals to suppress antioxidant mechanisms and eventually cardiac dysfunction occurs. Patients with thalassemia major can maintain normal cardiac function with severe iron overload, although only temporarily, this is due to their intracellular metabolism, especially to deal with oxidants. Currently, 90 genes that play a role in iron metabolism have been detected and each individual has a different type. Thalassemia patients who have the genetic factor apo-lipoprotein (apo) E4 are at greater risk for left ventricular dysfunction due to decreased ability to handle oxidative stress.[13]

Late puberty in thalassemic patients is more common in the male because of failure of the hypothalamic-pituitary axis with deficiency of gonadotropin secretion and primary gonadal failure. The disorder is due to the lipid peroxidation process due to the

accumulation of iron in the cells of the pituitary gland and damage to the pituitary causing decreased gonadotropin secretion. The delay in male development of the testicles is impaired, while in women there is a delay in the growth of breasts and pubic hair.[14]

Management of Thalassemia

Patients with thalassemia major should receive blood transfusions for life while thalassemia minor only occasionally. Transfusions are generally every month with pre-transfusion hemoglobin levels between 9.5 and 10.5 g/dL. Transfusion therapy improves health and avoids the consequences of ineffective erythropoiesis, but excessive iron stores from transfusion cause complications that can be prevented by using iron chelation therapy, namely deferoxamine, deferasirox, and or deferiprone. Iron chelation therapy should be started as soon as the patient is significantly iron overloaded, which generally occurs after 1 year of transfusion therapy and is associated with serum ferritin >1,000 ng/mL.[1,15]

Deferoxamine iron chelation is administered subcutaneously or intravenously due to poor oral bioavailability and continuous infusion for at least 5 – 7 days/week. Deferoxamine is initially started at 25 mg/kg and may be increased to 60 mg/kg in patients with iron overload. Side effects are that some patients cannot tolerate the drug because of local skin reactions, neurotoxicity, changes in visual acuity, color vision disturbances, sensory hearing deficits, and bone dysplasia. These abnormalities are dose-related, in patients receiving more than 50 mg/kg/day of deferoxamine, but can be prevented by reducing the dose.[1,10]

Deferasirox is an oral iron chelator now approved by the US Food and Drug Administration (FDA). Deferasirox was given a single oral dose of 20 – 30 mg/kg/day which prevented iron overload in all patients. Side effects include abdominal pain, nausea and vomiting, diarrhea, rash, and a slight increase in serum creatinine, and are rarely associated with changes in visual acuity or deafness.[10]

Deferiprone is a second-line oral iron chelator. Deferiprone has a half-life of about 3 hours and requires dosing 3 times a day. The initial dose is 75 mg/kg/day and may be increased to 99 mg/kg/day based on the level of iron overload. Combination therapy of deferoxamine and deferasirox or deferasirox and deferiprone is effective in patients with severe iron overload. Splenectomy may be indicated for thalassemia patients with hypersplenism and thalassemia intermedia, but splenectomy can have serious consequences

such as pulmonary hypertension, venous thrombosis, and foot ulcers than patients without splenectomy.[1]

Nutritional Status

A good environment, sufficient economic status, free from disease and disability, and good nutritional status are factors that affect a person's level of health. Nutritional status is one of the factors in achieving optimal health status. Each individual needs a different intake of nutrients, this depends on age, gender, weight, daily body activities, and others. A person will have a good nutritional status if the nutritional intake is following the needs of his body. Inadequate intake of nutrients in food can cause malnutrition, on the other hand, people who have excess nutritional intake will suffer from excess nutrition. In addition, nutritional problems are a reflection of the consumption of nutrients that are not sufficient for the body's needs. People with good nutritional status are not susceptible to diseases, either infectious or degenerative diseases.[16]

Nutritional Status in Children

Child development is based on the consideration of the Regulation of the Minister of Health of the Republic of Indonesia Number 2 of 2020 concerning Child Anthropometry Standards point (a) that optimal growth in children supports the creation of quality human resources and point (b) to achieve optimal child growth requires monitoring and status assessment nutrition for children's growth according to standards. The basis of the Regulation of the Minister of Health of the Republic of Indonesia Number 2 of 2020 concerning Child Anthropometric Standards paragraphs 1 and 2 that anthropometry is a technique for assessing the size, proportion, and composition of the human body as a reference for assessing the nutritional status of children. Indonesia decided this standard to be the official standard through the Decree of the Minister of Health Number 1995/Menkes/SK/XII/2010 concerning Anthropometric Standards for Assessment of Child Nutritional Status. This standard has many benefits, one of which is as a reference for health workers to identify children who are at risk of failure to thrive. Children who grow normally follow a trend that is generally parallel to the median line. Most children will grow along with one of the growth paths, either between the lines or parallel to the median, but the growth path may be below or above the median number.[5]

Assessment of children's nutritional status can compare the results of measurements of weight and length/height with anthropometric standards of children.

The classification of nutritional status assessment based on anthropometric indices is by the nutritional status category in the World Health Organization (WHO) Child Growth Standards for children aged 0 – 5 years and The WHO Reference 2007 for children 5 – 18 years. Anthropometric standards of children are assessed by parameters of weight and length/height which consist of four indices, including the weight index according to age, body length according to age or height according to age, body weight according to length/height, and body mass index according to age. Then, plotted on the Z-Score line, and also Upper Arm Circumference (UAC) was adjusted to the standard.[5]

Upper Arm Circumference (UAC) is an anthropometric parameter that can be used to describe muscle tissue and subcutaneous fat content. These parameters are correlated with body weight index for age or weight for height and, like weight, UAC is an unstable parameter that can change rapidly so it is good for assessing current nutritional status.[6]

The weakness of the UAC index is that it can only identify children with severe Protein Energy Deficiency (PEM), it is difficult to see the growth of children, especially at the age of 2-5 years whose changes are not very obvious, and it is difficult to determine thresholds such as weight or height. However, the excess of the UAC index is a good indicator to assess a person experiencing severe PEM, using a simple, fast, inexpensive, and very light measuring instrument, also the instrument or measuring tape can be color-coded to assess nutritional status so that it can be used by someone who is cannot read, write, and can also be easily done by anyone as long as it is done correctly so that the results will be appropriate.[6,16]

This method can be used in pediatric patients > 1 year, adults, and the elderly. The benefit of measuring UAC is if weight and height cannot be measured accurately, for example in patients with edema, hydrocephalus, and patients with organomegaly, such as thalassemia patients, the majority of whom have hepatosplenomegaly.[7] In addition, the use of UAC is more appropriate to identify children with severe nutritional/physical growth disorders.[17] The UAC indicator is also considered to be better for identifying the risk of death in malnourished children in the community.[18]

The body optimizing nutrients is affected by two factors, which are primary and secondary. Primary factors are related to food intake factors that cause insufficient or excessive nutrients due to poor quality or quantity of food consumed. Insufficient nutrition can be caused by a lack of food

availability in the family or the inability of the family to provide sufficient food for family members. Excessive nutrients, for example, having the wrong eating habits, having taboos or preferences for certain foods.[16]

Secondary factors are factors that affect the utilization of nutrients in the body. Nutrients that do not attend to the needs such as when a person has consumed sufficient amounts of food, but the nutrients are not utilized optimally. Another example is the disruption of the digestive process of food in the teeth, digestive organs, or enzymes as a result of which food is not digested properly so that nutrients are not absorbed properly and result in not fulfilling the body's needs. Children with worms will be malnourished because of the nutrients consumed by worms and disturbances in the metabolism of nutrients. In addition, due to liver disorders, diabetes mellitus, or the use of certain drugs that cause absorption disorders, and excretion disorders such as too much urine, and a lot of sweating interfere with the utilization of nutrients.[16]

The relationship between host, agent, and environmental factors can also affect nutritional status. These three factors must be balanced so that a person is in good nutritional status. Nutritional problems will arise due to an imbalance of these three factors. The host is a factor found in humans themselves. These factors include genetics, age, gender, ethnicity, body physiology, immunology, and habits that determine the nutritional needs of different individuals. The absence of aggregate agents can cause nutritional problems such as vitamins which if deficient can cause sprue, while the presence of aggregates can also cause nutritional problems, for example, the use of certain antibiotics can interfere with milk absorption. Psychological factors and mental conditions affect nutritional intake, such as individuals who have mental problems, will be compensated in the form of food. The biological condition of patients with infectious diseases as well as their nutritional needs will increase because nutrients are needed for wound healing due to infection. In addition, the environment can affect a person's nutritional status which is divided into three conditions, there is the physical environment (weather/climate, water, and soil), the biological environment (population density, limited food production), and the socio-economic environment (work, level of urbanization, economic development, and natural disasters).[16]

The quality of human resources can develop if nutrition and food are within sufficient limits and also as a condition for the successful development of a nation. Nutrition is very influential on intelligence

and work productivity. For efforts to improve good nutrition, all affecting aspects such as aspects of food patterns, socio-culture, and the effect of food consumption on nutritional status need to be studied.[19]

Thalassemia and Nutritional Status in Children

Thalassemia patients with good nutritional status may be due to many factors such as getting a good level of nutritional intake and consumption patterns, and thalassemia patient who transfusion was given food and confirmed to have eaten the food provided before going home. In addition, this is also related to the socio-economic level as reflected by the education of the patient's parents. The better the economy, the fulfillment of nutrients in a family will be higher.[20] Good nutritional intake and consumption patterns can offset the increase in energy expenditure in thalassemia patients so that their nutritional status will be good. However, if the food intake is balanced with energy, which is called energy expenditure, it can cause changes in body weight or nutritional status.[4] Total energy expenditure (TEE) is an individual's total energy expenditure derived from three components, that is basal metabolism, the effect of food consumption, and physical activity. Basal metabolism is the use of energy at rest that utilizes 10 - 20% of the body's energy expenditure. Total energy expenditure is affected by the thermic effect of food, which is heat energy from the digestive process of food. The largest component of energy expenditure is used for physical activity.[21] A good consumption pattern can also cause nutritional needs to be met so that nutritional status can be maintained properly.[4,20] In addition, it is possible that there should not be certain dietary restrictions and optimal utilization of sufficient nutrients in the body so that there is no poor nutrition or malnutrition.[16]

While malnutrition in thalassemia patients may be due to ineffective erythropoiesis and rapid red blood cell turnover increasing the body's need for energy. In addition, prolonged use of iron chelation, endocrinopathy (hypogonadism, delayed puberty, and hypothyroidism), hypoxia due to anemia, dysregulation of Growth Hormone-Insulin Like Growth Factor 1 (GH-IGF-1), and a high number of blood transfusions further complicate the growth process normal.[9,22] In addition, maternal education has a significant impact on nutritional status in the form of being underweight in thalassemia patients. However, research with a smaller sample shows that there is no relationship between parental education and nutritional status.[9,23]

CONCLUSION

Many factors can affect the nutritional status of children, especially in children with thalassemia. More information regarding the definition, epidemiology, classification, pathogenesis, diagnosis, complications, management, and nutritional status is to minimize growth disorders in thalassemia patients.

CONFLICT OF INTEREST

We hereby declare that there is no conflict of interest in the scientific articles that we write.

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