REVIEW ARTICLE

Effects of Iron Accumulation on Dental Caries, Gingivitis, and *Candida albicans* Infection in Children with Beta Thalassemia Major: A Narrative Review

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ABSTRACT

Background. Thalassemia is a common inherited hemolytic disorder characterized by the absence or reduction of one of the globin chains. Beta thalassemia major generally has oral cavity manifestations. Patients with beta thalassemia major often require routine blood transfusion. However, this treatment has the side effect of accumulating iron in the salivary glands, which increase the risk of dental caries, gingivitis, and secondary infection from *Candida albicans*.

Objective. The aim of this review is to explain the relationship of salivary iron levels and the effects of iron accumulation on dental caries, gingivitis, and *Candida albicans* infection.

Methods. A comprehensive search was performed on PubMed, Scopus, and Google Scholar databases using the keywords beta thalassemia major, iron, dental caries, gingivitis, *Candida albicans*.

Results. Iron is an essential micronutrient needed by *Candida albicans* for its growth and virulence. Blood transfusion in patients with beta thalassemia major can lead to a buildup of iron in the salivary glands and trigger the formation of non-transferrin bound iron (NTBI). NTBI can circulate in plasma and form a reactive oxygen species (ROS) that stimulate the formation of biofilms and increase dental caries. ROS may affect several genes associated with the inflammatory process and increase the incidence of gingivitis. It can also reduce salivary secretion in patients with thalassemia-β major that cause dysbiosis, which triggers an overgrowth of *Candida albicans*.

Conclusion. The excess iron in patients with beta thalassemia major increase the risk of dental caries, gingivitis, and *Candida albicans* infection.

Keywords: beta thalassemia major, iron, dental caries, gingivitis, Candida albicans

INTRODUCTION

Thalassemia is an inherited blood disorder characterized by impaired production of alpha (α) or beta (β) hemoglobin chains.[1,2] It is a genetic disease associated with an autosomal recessive gene, resulting in a homozygous form called thalassemia major and a heterozygous form called thalassemia minor.[3,4]

The World Health Organization estimated that 7% of the world's population are carriers; with 80% coming from developing countries.[5] In Indonesia, 3–10 out of 100 people are thalassemia carriers. With a thalassemia carrier rate of around 5%, a birth rate of 20%, and a population of 200 million people, it is estimated that 2,500 babies will be born with thalassemia congenital disease per year.[6]

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The clinical features of the oral cavity in thalassemia patients include a pointed and short root shape, taurodontism, and a chipmunk facies. Patients with thalassemia also generally have a higher caries index, hypertrophy of the gingiva, which is a sign of inflammation of the gingiva, and are susceptible to infections either caused by bacteria or fungi, including the fungus *Candida albicans.*[7-10]

Currently, the standard treatment for beta thalassemia major is lifelong blood transfusions to maintain hemoglobin levels above 10 g/dl. This can cause complications, one of which is iron overload.[11-13] This paper reviews and discusses the role of iron overload in the dental problems of patients with beta thalassemia. The objective of this review is to explain the relationship of salivary iron levels and the impact of iron accumulation on dental caries, gingivitis, and *Candida albicans* infections.

MATERIALS AND METHODS

A comprehensive search was performed on PubMed, Scopus, and Google Scholar databases using keywords beta thalassemia major, iron, dental caries, gingivitis, *Candida albicans*. We included textbook and scientific journal articles in English and Indonesian, published in the past 10 years (2010–2020). Older articles were included as our references when they were the only article related to our topic. The keywords used in the search engines included: "beta thalassemia major", "iron", "dental caries", "gingivitis", "*Candida albicans*". We included references that had a complete citation component. We excluded articles that did not focus on thalassemia beta major or the subjects of the article were not children.

LITERATURE REVIEW

Iron Overload

Repeated blood transfusions in patients with beta thalassemia major may cause iron overload. Continuous iron accumulation may tax the body and its very limited ability to excrete iron. Furthermore, iron overload in patients with thalassemia is also caused by the increased absorption of iron in the gastrointestinal tract due to ineffective erythropoiesis. The excess iron that accumulates is toxic to body tissues and may cause heart failure, cirrhosis, growth disorders, and endocrine disorders.[5]

Iron overload in thalassemia is the most crucial complication of thalassemia and the main focus of therapeutic management. Blood transfusion is a comprehensive source of iron loading. However, iron overload can also occur in patients who have not received transfusions such as patients with thalassemia intermedia.[14] Due to iron accumulation, the iron-binding protein, transferrin, exceeds its capacity to bind with circulating free iron releasing the non-transferrin bound iron into the blood circulation. As a result, free iron begins to accumulate in the tissues and blood. Free iron can catalyze the formation of reactive oxygen species (ROS), which are very dangerous and harmful compounds, such as hydroxyl radicals (OH) through the Fenton reaction. Hydroxyl radicals are highly reactive, and may damage lipids, proteins, and DNA. The mechanisms of iron uptake in cell host shown in Figure 1. The initial reaction is the formation of peroxides (lipid peroxides) that can cross link with other molecules in lipid membranes and cell membranes. Unlike most other cells, the red blood cells of patients with thalassemia lose the elasticity needed to pass through the microcirculation. The damaged red blood cells are released by reticulooendothelial cells, especially in the spleen.[15]

It is not only red blood cells that bear the ROS burden. Damage to other organs began to accumulate within a year from blood transfusion therapy. Hepatocytes are the body's main iron storage organ. Due to excess iron in the liver and binding to ROS, cells die and are replaced by fibroblast cells. Collagen produced by fibroblasts results in liver fibrosis and eventually cirrhosis.[16,17] If the production of ROS exceeds the existing antioxidant capacity as an intrinsic defense, oxidative stress will occur.[18,19] Oxidative stress can cause shortened erythrocyte lifespan, primary or secondary amenorrhea, hypogonadism, heart failure, liver damage, endocrine disorders, and mortality in patients with thalassemia.[20]

In the oral cavity, the effect of iron overload can be seen in the saliva of patients with thalassemia major who have significantly increased oxidative stress levels compared to normal people.[22] The increased oxidative stress is due to unstable hemoglobin levels and iron overload, which may stimulate biofilm formation in the oral cavity.[11,23] The increase in ROS and oxidative stress levels is cytotoxic, causing the oxidation of cellular components resulting in cell death and organ damage.[24] In vitro, oxidative stress due to iron overload also reduces the mineralization process and inhibits the formation of hydroxyapatite crystals.[25]

Oral Manifestations in Patients with Beta Thalassemia Major

A disturbance of facial bones and the skull (Cooley facies) is often found in patients with beta thalassemia major. The Cooley facies is the hallmark of beta thalassemia major and includes a mongoloid facial characteristic with wide eye spacing, wide forehead, protruding nose bridge, prominent cheekbones, and enlarged maxilla. This condition as an impact of increasing erythropoiesis that causes hyperplasia of erythroid cells in the bone marrow.[26-28] The hyperplasia of erythroid cells causes the expansion or enlargement of the bones that leads to changes in bone shape. This is due to the overworked bone marrow to overcome the lack of hemoglobin.[29]

In the orofacial area, the maxilla grows exponentially due to the expansion of bone marrow, causing a class II malocclusion with protrusion of maxilla and atrophy of mandible. The protrusion of the maxilla, an increased overjet, an open anterior bite, and a saddle nose are characteristics of patients with beta thalassemia major (chipmunk facies).[9,29]

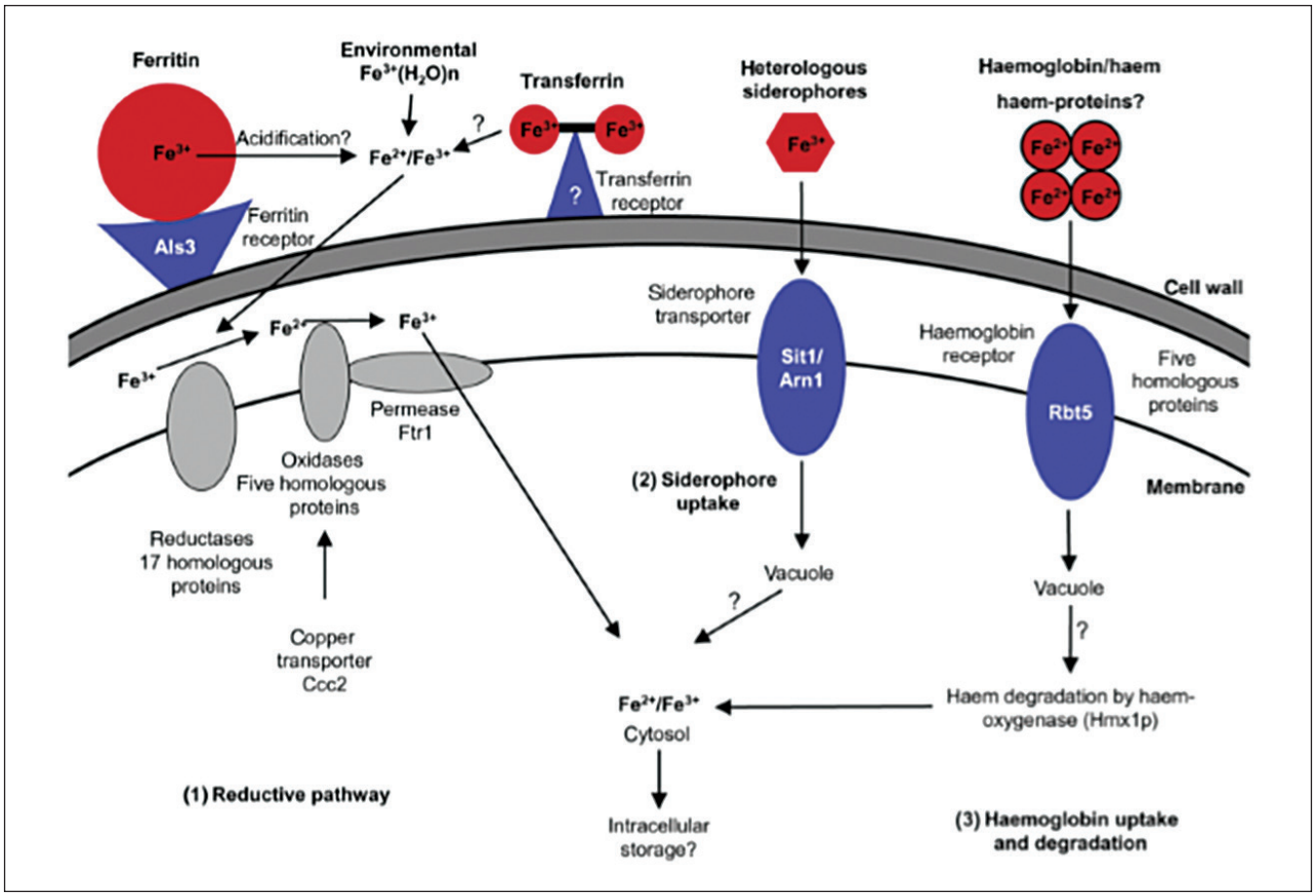

Figure 1. The mechanisms of iron uptake in cell host.[21]

Dental caries and periodontal disease in patients with thalassemia are still being studied. Based on several studies, the DMFT index, which assesses the presence of dental caries in children with thalassemia is higher than in normal children.[30,31] Other studies found a higher prevalence of gingivitis in children with thalassemia related to local factors related to the maxillofacial characteristics (open anterior bite increased overjet, crossbite, and mouth breathing). A disturbance in hemoglobin also affects the nutrition supply and gas exchange in the gingiva, making it appear pale due to low hemoglobin. However, sometimes, the color of the gingiva becomes darker due to a high level of iron (ferritin) in the blood.[8,32]

The poor general condition of patients with beta thalassemia major makes them susceptible to infection caused by bacteria or fungi, including *Candida albicans*. The higher risk can be caused by side effects of treatment in patients with beta thalassemia major.[9,10] There is no study that specifically discussed the three variables (dental caries, gingivitis, and *Candida albicans* infection) related to iron overload. This study aims to determine the effect of these variables and their role in the comprehensive oral care of patients with beta thalassemia major in the future.

Dental Caries in Patients with Beta Thalassemia Major

Blood transfusion in patients with beta thalassemia major can cause iron overload in vital organs such as the heart, pancreas, and endocrine gland. This condition causes tissue damage and lead to organ dysfunction or organ failure.[33,34] Iron is an essential element for bacterial growth, an excess iron can increase the virulence of bacteria and compromise many of the body's defense mechanisms. Children with beta thalassemia major are susceptible to immune system disorders that can reduce resistance to infection.[35-37]

Dental caries is a multifactorial disease; the main cause being the presence of cariogenic bacteria (agent), carbohydrates (substrate), and susceptible teeth (host).[38] These factors interact over time and cause an imbalance of demineralization and remineralization. The saliva is a very important component for the existence of the host. In patients with beta thalassemia major, the saliva contains iron deposits that cause swelling and impaired function of the salivary glands.[39,40] This condition can decrease the saliva flow rate, buffering capacity, and some components of the innate salivary defense such as salivary immunoglobulin A (sIgA) and salivary lysozyme.[41-43] The saliva is the main host

defense against caries; if a condition causes a decrease in salivary flow and its defense components, the teeth become susceptible to caries.[41,42,44,45]

Iron is also an important nutrient required for the growth of microorganisms and associated with the formation of biofilms in several types of bacteria. These are stimulated by oxidative stress from iron deposition due to repeated blood transfusions.[23,35,46] As a result, there is a risk of an increasing number of *Streptococcus mutans*. In addition, increased oxidative stress also has an impact on tooth structure during growth and development in the oral cavity.[47,48] Some of the above conditions increase the risk of dental caries in children with beta thalassemia major.

Gingivitis in Patients with Beta Thalassemia Major

Free radicals (ROS) can cause damage to the salivary glands resulting in a reduced amount of saliva; this may change the antimicrobial components in saliva including lysozyme and sIgA. The lysozyme component in patients with thalassemia major is lower than in normal people. The role of salivary lysozyme is to lyse bacterial cells by interacting with chaotropic ions (thiocyanate, perchlorate, iodide, bromide, nitrate, chloride, and fluoride) and bicarbonate.[39,49-51]

Due to changes in the components of saliva, it will automatically have an impact on the function of saliva itself in maintaining the balance of the oral flora, including the gingivitis-causing bacteria. Increased virulence of *Porphyromonas gingivalis,*[8,45,52,53] one of the main bacteria in the subgingival area, plays an important role in the course of periodontal disease.[54,55] To survive in the periodontal tissues, *P. gingivalis* need iron as one of the nutrients.[56,57] The iron utilized by this pathogen has a major role in the growth and virulence of *P. gingivalis.*[56,58,59]

In *P. gingivalis*, iron utilized in the heme form regulates the expression of several virulence factors, particularly gingipains; at the same time, the bacteria use gingipains to obtain the iron/heme. Gingipains are a group of endopeptides expressed by *P. gingivalis*. Gingipains are also directly associated with periodontal disease pathogenesis because of their ability to degrade host structure and maintain bacterial proteins, as well as their ability to bind heme and iron. In addition, gingipains themselves are also involved in the destruction of periodontal tissue matrix and alveolar bone, adhesion and invasion of host cells, and dysregulation of the host immune response. This increases the risk of gingivitis.[55,56,58,60]

ROS can also occur in gingival tissue and may cause direct damage to cells and the extracellular matrix. Nuclear factor-κB and activator protein play an important role in the pathogenesis of periodontal disease. Nuclear factor-κB is believed to affect several genes associated with the inflammatory processes such as interleukins (IL 1, IL 6, IL 8). Therefore, through the nuclear factor-κB system, it can cause inflammation in the periodontal tissue, which increases the incidence of gingivitis.[61,62]

Candida albicans Infection in Patients with Beta Thalassemia Major

The weakened immune system in patients with beta thalassemia major causes immune system abnormalities such as a disturbance in neutrophil and macrophage chemotaxis, phagocytosis and B-lymphocyte cell differentiation, leading to *Candida albicans* penetration into the tissue.[63]

Repeated blood transfusions cause the accumulation of iron in salivary glands and triggers the formation of non-transferrin bound iron (NTBI), which can circulate in plasma and trigger the formation of reactive oxygen species (ROS). ROS are highly active molecules that can cause cell apoptosis and epithelial tissue damage. Iron sedimentation in the acini cells of salivary glands causes inflammation in the salivary glands and triggers a decrease in salivary secretion and its components. The salivary components act as a front line of immune system against *Candida albicans* infections by limiting its invasion and protecting the mucosal epithelial barrier. Decreased salivary secretion in patients with beta thalassemia major can cause dysbiosis, which triggers the overgrowth of *Candida albicans* by increasing its adhesion to oral epithelium.[64,65]

Iron is a micronutrient needed by microorganisms for their growth and a very important factor for their virulence. Iron in host cells can be taken up by *Candida albicans* through three different mechanisms: the reductive pathway, siderophores uptake, and heme acquisition. Iron may serve as an important signal during the transition from commensal to invasive pathogens. The changes in morphology of *Candida albicans* enable it to adhere to the epithelial cells and penetrate into the tissue.[21,66]

A deficiency in folic acid and vitamin B12, and a high carbohydrate intake can increase the ability of *Candida sp.* organisms to adhere to epithelial cells. A lack of awareness in oral hygiene leads to a conducive environment for *Candida albicans* growth. Due to low oxygen and pH, the attachment of *Candida albicans* to oral epithelium increases.[42,67]

CONCLUSION

Iron overload in patients with beta thalassemia major may cause damage to the salivary glands and trigger the formation of ROS leading to higher risk of dental caries, gingivitis, and *Candida albicans* infection. The limitation of this study is that this study does not involve direct examination of such patients. Further research is needed to confirm the findings of this literature review.

Statement of Authorship

All authors contributed in the conceptualization of work, acquisition and analysis of data, drafting and revising and approved the final version submitted.

Author Disclosure

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