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Exploring the Relationship of Thalassemia Major and Gingival Health: A Narrative Review

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ABSTRACT

Background: *Periodontal disease is characterized by the inflammation of the tooth's supporting tissues, and its etiology is multifactorial. Defense against pathogens depends on the host's immune response, since both innate and adaptive immune cells contribute by releasing their substances and modes of action to preserve harmony in periodontal tissues. Bacterial persistence and immune system dysregulation, characterized by an exaggerated response, can exacerbate periodontal disease. Thalassemia major is an autosomal recessive genetic disorder caused by a mutation in the gene responsible for the β-globin component of the hemoglobin molecule, resulting in either absent or reduced synthesis of this protein in erythroid cells. Individuals with thalassemia major exhibit significant immunological impairments, increasing susceptibility to infectious and inflammatory conditions. The current review aims to explore the relationship between this systemic disease and its effect on the gingival health. The details about gingival health and disease, as well as thalassemia major-associated complications and therapy, have been discussed in this review.* **Conclusion:** *Patients with thalassemia major exhibit a greater likelihood of gingival inflammation compared to systemically healthy individuals.*

Keywords: Thalassemia Major, Iron Overload, Gingival Inflammation, Ineffective Erythropoiesis.

Article Information

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INTRODUCTION

Periodontal disease is characterized by the inflammation of the tooth's supporting tissues, and its etiology is multifactorial. Defense against pathogens depends on the host's immune response, since both innate and adaptive immune cells contribute by releasing their substances and modes of action to preserve harmony in periodontal tissues. Bacterial persistence and immune system dysregulation, characterized by an exaggerated response, can exacerbate periodontal disease. "Health is not just the absence of disease or infirmity; it is a state of complete physical, mental, and social well being." According to this World Health Organization (WHO) definition, gingival health is the absence of clinically detectable inflammation. It is a state devoid of inflammatory gingival inflammation that permits a person to live normally and evade consequences (physical or mental) from existing or previous disease (WHO, 1948). The gingival health and hemostasis align with a biological state of immune surveillance (Chapple et al., 2018).

Gingivitis is the initial indication of periodontal disease, a localized gingival inflammation caused by pathogens in the microbial biofilm that develops on the teeth and gingiva (Jeffcoat et al., 2003; Abdulmajeed & Mahmood, 2023; Nasr & Ali, 2017). Gingivitis is an inflammatory condition localized to specific sites, initiated by the development and accumulation of pathogenic biofilm. It is characterized by the gingival

irritation, redness, and oedema, in the absence of periodontal clinical attachment loss (Trombelli et al., 2004).

The condition is contained within the gingiva and does not involve the periodontal attachment, including the cementum, periodontal ligament, and alveolar bone. Gingivitis results from the interaction between dysbiotic microbial populations and abnormal responses in the periodontium (Sedghi, Bacino, & Kapila, 2021). Periodontal disease can increase the overall inflammatory burden in the body. Research has also shown that periodontal disease plays a significant role in exacerbating systemic diseases, including Alzheimer's disease, inflammatory bowel diseases, and oral cancer. This points out the critical role of oral health in overall systemic health (Jeffcoat et al., 2003).

Immune-inflammatory response in gingival inflammation

The oral cavity hosts around 700 bacterial species that collectively form the oral microbiome (Deo & Deshmukh, 2019). The oral microbiome consists of a distinct and varied ecosystem of microbial organisms that engage in metabolic and physical interactions. Interactions lead to the development of complicated biofilm communities, where physicochemical gradients establish unique microbial niches with varying metabolic requirements (Kim H, Kim S, & Jung, 2020). Microbial dysbiosis occurs when the highly complex ecosystem of the oral biofilm is disrupted.

The disruption of microbial community dynamics significantly contributes to the onset of gingivitis and the progression of periodontal disease. The ongoing accumulation of supra- and subgingival microbial biofilm communities triggers a sustained host immune response in the periodontium. Periodontal pathogens have developed mechanisms to manipulate the host inflammatory response, promoting inflammation while simultaneously evading these responses (Hajishengallis & Lamont, 2012).

The host applies multiple immune-response systems to regulate microbial colonization and preserve homeostasis in the oral cavity.

The systems consist of three interconnected entities: the salivary immune system, systemic (serum) immune system, and gingival tissue immune system. Each has been assessed for its role in resistance to periodontal infections (Ebersole et al., 2013). The host organism's immune response to microbial dental biofilm may be protective, destructive, or a combination of both, leading to the diverse changes in tissues seen in periodontal disease (Karimzadeh & Morrison, 1999). In gingivitis, pro-inflammatory cytokines have elevated levels observed in the affected cells, altering the equilibrium between pro-inflammatory and anti-inflammatory cytokines in favour of local inflammation (Neurath & Kesting, 2024). Gingival inflammation leads to the production of neutrophils and macrophages, which typically exert beneficial effects in preventing disease; however, their infiltration into tissues can ultimately result in tissue damage (Ebersole et al., 2013).

The mechanisms behind the microbial dysbiosis and inflammatory responses in the host are evolving, enhancing our awareness of these processes. Additionally, different mechanisms for periodontal tissue destruction are being found. Neutrophils that are recruited release reactive oxygen species (ROS) and pro-inflammatory cytokines to eradicate pathogens from diseased tissues. Host immunity inevitably exacerbates the severity of periodontal disease by further promoting microbial dysbiosis (Ebersole et al., 2013; Ali, Alpdogan, Hasturk, & Van Dyke, 2014). The rise in periodontal disease incidence and

severity has been associated with various pathologies located at distant sites from the oral cavity. Systemic diseases associated with periodontal disease that have gained significant recognition include diabetes, cardiovascular diseases, and rheumatoid arthritis. The oral manifestations of different systemic pathologies, including Crohn's disease, have been documented (Hajishengalis & Chavakis, 2021).

Beta Thalassemia

Thalassemia originates from the Greek words Thalassa, meaning sea, and haima, meaning blood. Thalassemia syndromes are inherited hemolytic disorders caused by an unbalanced production of globin chains in the hemoglobin molecule. Resulting in atypical red blood cells. The normal hemoglobin molecules of humans (Hb) comprise two pairs of globin chains, $\alpha_2\beta_2$, with synthesis typically meticulously coordinated to assure consistent production. Beta Thalassemia results from an autosomal mutation in the gene responsible for β-globin, leading to either a complete absence or reduced synthesis of this protein in erythroid cells (Weatherall, 2001). Mutations disturb β-globin chain synthesis, particularly in homozygous forms, increasing free α-globin chains that form extremely harmful aggregates (Khandros & Weiss, 2010).

Thalassemia Major

Cooley's anemia or thalassemia major represents the most serious and severe form of beta-thalassemia, occurring in individuals who are either compound heterozygous (B+/B+) or homozygous (B+/B0, B0/B0) for more severe mutations in the β chain. This type of β-thalassemia demands regular blood transfusions; hence, it is referred to as transfusion-dependent thalassemia (TDT). The clinical signs and symptoms of thalassemia major typically manifest between six and twenty-four months of age, characterized by failure of growth and progressive pallor in the affected infants. Feeding difficulties, diarrhea, recurrent fevers, irritability, and splenomegaly and hepatomegaly with progressive abdominal enlargement may manifest. The clinical presentation of untreated or inadequately treated thalassemia major is marked by jaundice, pallor, poor muscle development, growth retardation, hepatosplenomegaly, extramedullary haematopoiesis, leg ulcers, and skeletal abnormalities from bone marrow expansion.

Skeletal alterations consist of abnormalities in the legs' long bones and characteristic craniofacial modifications, including skull bossing, prominent malar eminence, depression of the nasal bridge, a tendency towards a mongoloid eye slant, and maxillary hypertrophy (Galanello& Origa, 2010).

Ineffective Erythropoiesis

Erythropoiesis is the physiological process responsible for the continuous production of red blood cells (RBCs), regulated by a complicated system of oxygen sensors and modulating cytokines, which maintains hemoglobin (Hb) concentration at a highly stable level during an individual's lifetime (Tusi et al.,2018). Erythroid precursors in thalassemia patients are elevated by 5 to 6 times compared to healthy individuals, indicating an early stage of precursors that reflects the inhibition of erythroid maturation in the bone marrow. Ineffective erythropoiesis is characterized by inadequate production of fully developed erythrocytes from immature erythroblast islands. Consequently, this is evident through the acceleration of erythroid differentiation, the inhibition of maturation at the polychromatophilic stage, and the mortality of erythroid progenitors.

Ineffective erythropoiesis serves as the primary mechanism underlying thalassemia,

significantly contributing to the clinical manifestations and complications associated with this condition. Elevated apoptosis is a significant characteristic of ineffective erythropoiesis in thalassemia major. Consequently, there is an increase in apoptosis of erythroid progenitors in the bone marrow (Arlet et al., 2014).

Iron Overload

Thalassemia Major is characterized by excessive iron metabolism; the primary source of iron overload in these individuals is the regular transfusion therapy necessary for managing severe anemia. The elevated iron absorption is driven by elevated erythroferrone production from erythroid precursors and the downregulation of hepatic hepcidin production, leading to enhanced iron absorption (Kautz et al., 2014).

Iron and erythropoiesis function together through bidirectional crosstalk, significantly influencing the characteristic features of iron overload in thalassemia. RBC progenitors that do not mature contribute to an increase in the body's total iron pool via both direct as well as indirect pathways. The elevated accumulation of iron promotes the enhancement of erythropoiesis. In beta-thalassemia, the erythron undergoes significant expansion, necessitating an increased iron requirement for its metabolic processes.

In transfusion-dependent thalassemia (TDT) patients, regular blood transfusions lead to inevitable iron overload due to the absence of a physiological mechanism for excess iron excretion. Iron accumulation is detrimental to various tissues, leading to heart failure, cirrhosis, liver cancer, growth retardation, and multiple endocrine disorders (Farmakis et al., 2022). Reports indicate that iron accumulation also affects periodontal tissues. Erythroid cells exhibit a significant dependence on iron for their survival. Iron absorption and recycling are influenced by factors such as inflammation, hypoxia, and erythropoiesis, potentially via different mechanisms (Calişkan et al., 2011).

Blood transfusion

Transfusion is the primary treatment for patients with thalassemia major, frequently started during their first two years of life (Galanello& Origa, 2010). Transfusion in thalassemia improves anemia, inhibits elevated intestinal iron absorption, and is generally an effective intervention. The TIF (Thalassemia International Federation), along with guidelines from the US, Canada, and the UK, offers recommendations for the management of Thalassemia Major, specifically regarding transfusion therapy. These guidelines exhibit a general consensus, though some offer more extensive guidance (Farmakis et al., 2022). A clinical evaluation to determine the need for regular transfusion therapy should be performed after genetic diagnosis of the beta thalassemia disease. These guidelines indicate that the initiation of regular blood transfusion should not rely solely on the presence of anemia. It is recommended that the patients be monitored over time, with careful observation of indicators reflecting the severity of ineffective erythropoiesis, quality of life, growth and development, and associated clinical complications. Anemia necessitating intervention in this context is characterized by a HB level below 7 g/dl, assessed throughout an episode of acute infection (Neufeld, 2006; Musallam, Angastiniotis, Eleftheriou, & Porter, 2013).

Prior to the beginning of transfusion, it is essential to provide a hepatitis B vaccination and conduct comprehensive RBC antigen typing, including Rh factor, as well as serum immunoglobulin assessment. The suggested intervention for TM consists of blood transfusions given at intervals of 2 to 4

weeks. This regimen facilitates normal growth and physical activities, reduces transfusional iron accumulation, and inhibits bone marrow expansion in the majority of patients (Cappellini et al., 2008).

Thalassemia Major and Gingival Inflammation Correlation

Periodontal diseases are prevalent globally and occur due to alterations in bacterial biofilm, resulting in inflammation and damage to periodontal structures, potentially leading to tooth loss and a subsequent decline in oral health-related quality of life. The life expectancy of individuals with thalassemia major has significantly improved due to the implementation of combined transfusion and chelation therapy (Gollo G. et al, 2013). Thus, the significance of preserving the oral health of these individuals has become increasingly critical. Although oral health issues in TM are not regarded as life-threatening, they are inadequately addressed in the existing literature. Understanding the complicated link between oral health maintenance and systemic health is crucial (Abdulkareem et al., 2020; Mohammed, Fadhil, Mahmood, & Al-Waeli, 2024).

Previous research findings indicate a significant correlation between periodontal diseases and various genetic and systemic disorders (Mealey, 1999). Thalassaemia is a genetic haematological disease characterized by autosomal recessive inheritance. Although periodontal disease may not play a role in the etiology of Thalassemia Major, individuals with thalassemia may exhibit increased vulnerability to oral health problems, including periodontal disease, as a result of systemic consequences such as iron overload, immune alterations, and skeletal changes. The pathophysiology of periodontal disease is influenced by immune and inflammatory responses, which may exacerbate the systemic complications associated with TM. This emphasizes the critical and often overlooked association between oral health and overall systemic health, where abnormalities of lymphocytes arising from systemic hematological disease in TM may potentially contribute to gingival inflammation (Tonetti, Jepsen, Jin, & Otomo-Corgel, 2017; Keshk, Hablas, Esheba, & Abd-Elsalam, 2019).

The immune-inflammatory responses of the host significantly influence disease susceptibility. These complex biological processes impact the ability of the body to resist infections and its vulnerability to various health challenges. Understanding this interplay is essential for improving oral and systemic health outcomes (Hamad & Mahmood, 2022; Akram et al., 2024). Activating innate and adaptive immune cells is pivotal in influencing the outcome of inflammation. An appropriate immune response can effectively resolve inflammation, facilitating healing and the restoration of tissue function. Conversely, dysregulation or overactivation of these immune cells may worsen inflammation and contribute to the progression of disease pathology. This imbalance can profoundly affect the severity of the condition and its associated complications, particularly in the context of TM. In typical circumstances, the subgingival environment contains elevated levels of inflammatory and immune mediators, presenting a challenge to the survival of pathogenic bacteria. Dysregulation of the host's immune response, either due to alterations in the microbial communities or immune-regulatory issues, it becomes challenging to limit bacterial growth, resulting in the manifestation of pathogenicity (Linhartova et al., 2020).

Blood transfusion and the resulting induction of chronic immune responses can stimulate T cells that subsequently suppress

the effector actions of T cells. The relationship between the expression marker of activated T lymphocytes and multiple transfusions indicates persistent immunologic stimulation (Kirkley S. A., 1999). Iron overload in individuals with thalassemia (TM) can disturb immune equilibrium, facilitating the onset of infections by pathogenic microorganisms. This encompasses diminished phagocytosis by monocytes and the macrophage system, modifications in T lymphocytes, and compromised secretion of immunoglobulins (Galanello & Origa, 2010).

Decreased erythrocyte survival, overstimulation of the bone marrow, and altered erythropoiesis may result in the expansion of cranial and facial bones, characterized by a mongoloid appearance. Oral health issues in TM are primarily characterized by facial deformities, which manifest in various forms, as well as incorrect relationships or variations of the dental arches (Abu Alhaija, Hattab, & Al-Omart, 2002; Hattab & Yassin, 2011; Hattab, 2012). Al-Wahadni et al (2002) found no significant association between periodontal diseases and TM in a group of people aged 6 to 18 years. Several studies reached comparable conclusions, indicating that TM patients did not exhibit significantly higher levels of gingivitis or plaque accumulation relative to the control group (Kaur & Hiremath, 2012; Veera,2006).

Most of the studies were conducted on a younger population (ages 2 to 18), indicating that hormonal changes may influence gingival health throughout puberty. Older subgroups of patients with beta-thalassemia major demonstrated higher scores for the Gingival Index (GI) and Probing Pocket Depth (PPD) compared to younger patients. This observation may be linked to the increasing prevalence of periodontitis in adults (Taani, 1995).

There is little evidence regarding the molecular mechanisms of clinical periodontal health and the potential correlation between anti-inflammatory and pro-inflammatory cytokine levels in biological fluids and gingival inflammation in patients with TM (Singh et al., 2013)—a study by Gumus. P. et al. (2016) indicated an exacerbation in the local inflammatory reaction in individuals with TM. It showed an elevated of MMP-8, MMP-9, and TIMP-1 level in the saliva and serum of TM patients compared to healthy subjects. This observation is consistent with prior research by the same authors, which reported elevated levels of serum interleukin-6 and interleukin-8; the serum levels of these biomarkers are significant for understanding the pathophysiological pathways underlying TM, which suggested that TM may influence an existing systemic hematologic condition and potentially impact gingival inflammation through lymphocyte dysregulation and increased cytokine activation (Akcali et al., 2015).

Local variables such as malocclusion, poor oral hygiene, and drying of gingival tissues due to lip incompetence may be the leading cause of the comparatively high frequency of periodontal disease seen in TM patients. This problem may also be exacerbated by systemic causes such as chronic anemia, dietary deficits, and decreased infection resistance. In addition to affecting the patients themselves, thalassemia has a major psychological effect on their family members.

Furthermore, the need for frequent blood transfusions leads to significant financial difficulties, which are made worse by the expenses of dental care programs that promote preventive and restorative care. The results of this research may provide valuable insights into the relationship between systemic health and oral conditions within this specific patient population. Poor oral

hygiene practices and malocclusion in patients, exacerbated by their illness, immune dysregulation, and frequent hospitalizations, may negatively impact periodontal health and elevate the risk of gingival inflammation (Siamopoulou-Mavridou et al., 1992; Al-Wahadni, Taani, & Al-Omari, 2002).

CONCLUSION

Patients with thalassemia major exhibit a greater likelihood of gingival inflammation compared to systemically healthy individuals. Consequently, it is crucial to enhance awareness regarding oral health maintenance through regular periodontal assessments in this patient group to improve their oral health-related quality of life.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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