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The importance of the oral microbiome in patients with thalassemia

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Abstract

Thalassemia is a hereditary blood disorder that negatively impacts a patient's health and overall well-being by causing abnormal hemoglobin production. The group of microorganisms residing in a particular environment is called the microbiome. While the oral microbiome has gained considerable attention, recent studies underscore the importance of exploring oral microbiome diversity in thalassemia patients and integrating oral health care as a fundamental component of comprehensive treatment. Dysbiosis, or the disruption of the normal microbiome balance, can increase vulnerability to infections and systemic health issues. Probiotics play a critical role in restoring oral microbiome balance, thereby contributing to improved oral health and rehab preventing problems such as dental caries and gingivitis. This review discusses current knowledge on oral microbiome diversity and its discovery through metagenomics, emphasizing the need for further research to investigate the role of probiotics as an effective treatment.

Keywords: Thalassemia, oral microbiom, dysbiosis, probiotics, metagenomics.

1. Introduction

Thalassemia is a hypochromic microcytic anemia that results from either decreased or absent globin chain production. A quantitative flaw in the production of hemoglobin is called thalassemia (Need et al., 2023). The word "thalassemia" comes from the Greek word "Thalassa," which means sea. This congenital autosomal recessive hemoglobin (Hb) disorder was common in the Mediterranean, Middle East, Southeast Asia, and the Indian subcontinent. Due to migration, it has now spread to North America, South America, Australia, and North Central Europe (Yousuf et al., 2022). Hemoglobin is formed from iron (heme) and protein (globin). Hemoglobin is responsible for transporting oxygen from the lungs to the body's tissues. Hemoglobin A consists of one pair of alpha and one pair of beta hemoglobin chains. It makes up 95% to 98% of adult hemoglobin. The percentages vary based on age, genetics, drugs, and underlying illnesses (Harewood & Azevedo, 2024). Globally, an estimated 300,000–400,000 infants are born each

year with serious hereditary hemoglobin disorders, and about 80 million are β-thalassemia carriers (Yousuf et al., 2022). Depending on the severity of the anemia, blood transfusions are the main form of treatment if needed. Iron overload and marrow enlargement with extramedullary hematopoiesis that deforms bones are among the complications associated with thalassemia major (Needs et al., 2023). Compared to non-thalassemia patients, transfusion-dependent patients were found to have a lower health-related quality of life due to underlying problems such as splenectomy, small build, malnourishment, and extended hospital stays. Hopelessness, low self-esteem, low Intelligence Quotient (IQ), subpar academic performance, and social constraints were observed to be expressed by them. Patients experience severe physical, psychological, and social trauma, as do members of their families, particularly mothers (Yousuf et al., 2022). Each person has a unique oral cavity microbiome, and maintaining good health depends on this microbiome being in a state of delicate equilibrium (Tagg et al., 2023). It is rare to find microorganisms in the natural world existing alone; instead, they always form microbial communities, each of which fills a specific niche. A vast variety of biotic and abiotic settings can be found in their habitats as well. The microbiome is the population of microorganisms that have lived together with the human body for a very long time (Aggarwal et al., 2023). Unfortunately, treatment, nutrition, or host physiological changes can occasionally cause our mouth microbiota to become unstable, and this dysbiosis can endanger both oral and systemic host tissues (Tagg et al., 2023). Naturally, a disturbance in one leads to a disruption in the other because of the complex interaction that exists between microbial populations and their biological hosts. That is, a variety of the host's illness states, from metabolic to immunological and behavioral diseases, can be linked to a dysbiotic microbiome. Recent years have seen a sharp rise in the study of the human microbiome and its relationships to various illnesses (Aggarwal et al., 2023). The fundamental characteristics of the core oral microbiome are likely to be as unique to each individual as our fingerprints since they arise as a direct result of the host's lifestyle and genetic variables (Tagg et al., 2023). Microbes have provided us with an exponential amount of genome sequencing data since technological advancements made it possible to sequence entire organisms' genomes (Aggarwal et al., 2023). Despite being the most studied microorganisms in the oral cavity, only 57% of the bacterial species there have official names. In healthy individuals, facultative anaerobic Gram-positive bacteria make up the majority of the oral microbiota. Since the lungs and the digestive system are directly accessible through the mouth cavity, the microbiomes of these organs are linked throughout the human body. This explains why several systemic disorders are linked to the oral microbiome. Probiotics have been shown to have positive effects on oral health, reducing periodontal disease and dental caries, and Candida (Kozak & Pawlik, 2023).

Thus, the purpose of this study is to provide light on the oral microbiota of thalassemia patients. Examining the oral microbiota is an exciting and rapidly evolving field of research, and Next-Generation Sequencing (NGS) technologies and techniques enable reasonably quick and easy exploration of microbiomes within certain environments.

2. Thalassemia Disease

A broad group of hereditary illnesses are known as thalassemias (Yousuf et al., 2022). It is the most prevalent monogenic illness in the world, with the β-thalassemia allele being carried by about 1.5% of people and the α-thalassemia allele by about 5% (Lin et al., 2023). Thalassemia is caused by a reduction in the production of hemoglobin's alpha or beta chains (Hb). Hemoglobin in red blood cells is responsible for delivering oxygen throughout the body. It consists of two proteins: an alpha and a beta chain. Anemia, which starts in early childhood and lasts throughout life, occurs when the body does not produce enough of one of these two proteins, preventing red blood cells from forming properly and carrying sufficient oxygen. Since thalassemia

is an inherited condition, it requires at least one parent to be a carrier. It results from a genetic mutation or the deletion of specific important gene segments (Bajwa & Basit, 2023). Patients with thalassemia are currently divided into two main categories based on their need for red blood cell transfusions: those with transfusion-dependent thalassemia (TDT) and non-transfusion-dependent thalassemia (NTDT). The term "transfusion-dependent thalassemia" describes individuals with severe forms of the disease, such as homozygous β0-thalassemia or hemoglobin E/β-thalassemia, who need regular blood transfusions to survive. Patients with non-transfusion-dependent thalassemia are individuals who occasionally need a red blood cell transfusion under specific conditions, such as pregnancy, surgery, or infection. Among the patients with NTDT are those with hemoglobin H disease, certain cases of hemoglobin E/β-thalassemia, and individuals with mild forms of thalassemia (Chuncharunee et al., 2019).

2.1 Types of thalassema

There are two commonly found kinds of thalassemia: α and β. This is predicated on the globin chain involvement. The Hb β gene (HBB), which is found on chromosome 11, encodes the β chain, while the two types of the Hb α gene (HBA1 and HBA2) are found on chromosome 16. A complex form of thalassemia involves either non-functioning or malfunctioning formation of 2 to 4 non-identical globin sequences. Clinically, homozygotes for β-thalassemia often present as thalassemia major or intermedia (Yousuf et al., 2022).

2.1.1 Alpha thalassemia

Alpha thalassemia is generally found in nations in East and Southeast Asia, the Middle East, the Mediterranean area, and Sub-Saharan Africa. For example, in certain parts of Africa, the prevalence of α-thalassemia ranges from 10% to 20%, whereas in other Middle Eastern nations, it reaches 40%. The prevalence of α-thalassemia varies throughout Southeast Asian nations, with Thailand having a 20% prevalence and Vietnam having a 51% prevalence. Interestingly, more than 80% of the native population in Papua New Guinea's north coastline area has the α-thalassemia deletion (-α4.2) (Vadolas et al., 2024).

Alpha-globin gene deletion, which leads to decreased or nonexistent alpha-globin chain formation, is the cause of alpha-thalassemia (Bajwa & Basit, 2023). These are linked to about fifteen distinct genetic mutations. The type of mutation determines the clinical condition's severity. Depending on which of the two alpha-globin loci is mutated, the mutation's severity changes (Harewood & Azevedo, 2024). The most severe type is a four-allele deletion, in which the excess gamma chains (existing during the embryonic stage) form tetramers, and no alpha globins are formed. It causes hydrops fetalis and is incompatible with life (Bajwa & Basit, 2023). On the other hand, extra γ-globin chains generate γ-globin tetramers (also called Hb Bart), which have an extremely high oxygen affinity and hence essentially no oxygen delivery when α-globin production is removed during early intrauterine development. As a result, the growing baby has significant developmental defects and perinatal death, which is referred to as Hb Bart's hydrops fetalis, because of the significant intrauterine hypoxia (Vadolas et al., 2024).

For the most part, one allele deletion is clinically silent and represents the mildest type (Bajwa & Basit, 2023). Homologous recombination between mismatched chromosomes including a single or two globin genes (HBA1 and HBA2) results in deletions that cause the most prevalent types of α-thalassemia (-α3.7 or -α4.2). There are more than 70 different mutations that have been found in non-deletion α-thalassemia patients. Since the HBA2 gene contains a large number of non-deletion mutations, their impact on the expression of the α-globin gene is more significant (Vadolas et al., 2024).

2.1.2 Beta-thalassemia

Beta-thalassemia refers to a hereditary mutation of the beta-globin gene that results in a decreased

beta-globin chain of hemoglobin. The β chain is encoded by the HBB gene, which is found on Chromosome 11. Multiple genotypic and phenotypic differences in the disease are caused by a different set of beta-globin gene mutations that have been found. The clinical and analytical results of the three beta-thalassemia classifications define them (Needs et al., 2023). The two clinically relevant types of beta-thalassemia, known as β-thalassemia major and β-thalassemia intermedia, are characterized by either diminished or missing production of the hemoglobin subunit beta, also known as the beta globin chain (Langer, 2024).

The disease presents with anemia in addition to significant pathology associated with extramedullary hematopoiesis and bone marrow hypertrophy (Needs et al., 2023). Almost all known stages of gene expression have been affected by the more than 300 disease-causing mutations that have been found, the great majority of which are point mutations. Examples of frequent β-mutations found in Southeast Asia include CD41/42(-TCTT), CD17, and IVS2-654. In the Mediterranean area, the most common splicing mutations are found in CD39, IVS1-1, and IVS1-110. Soon after birth, the fetal γ-globin gene gradually becomes silent and is replaced by incorrect β-globin gene production, resulting in the first sign of β-thalassemia. The disease's pathogenesis can vary greatly, from almost asymptomatic to very anemic to potentially fatal (Vadolas et al., 2024).

Between the ages of six and twenty-four months, individuals with β-thalassemia major appear with pallor as a result of severe anemia, poor weight gain, stunted development, moderate jaundice, and hepatosplenomegaly. There may be frequent episodes of fever, diarrhea, agitation, and feeding issues. Regular red blood cell transfusions and iron chelation treatment enhance prognosis and permit normal growth and development. Growth retardation, endocrinopathies, dilated cardiomyopathy, and liver disease are among the long-term effects of iron excess (Langer, 2024).

B-thalassemia intermedia patients show at a wider range of ages because of a milder type of anemia that does not require frequent transfusions of red blood cells starting in early childhood. Leg ulcers, pulmonary hypertension, extramedullary masses of hyperplastic erythroid marrow, cholelithiasis, hepatosplenomegaly, skeletal changes (long bone deformities, characteristic craniofacial features, and osteoporosis), and an increased risk of thrombotic complications are possible additional clinical features. B-thalassemia intormedia patients are susceptible to iron overload due to increased intestinal absorption of iron resulting from dysregulated iron metabolism from inadequate erythropoiesis (Langer, 2024).

3. Oral microbiota

Joshua Lederberg coined the term "microbiome," which describes the community of commensal, pathogenic, and symbiotic microorganisms. Oral health is significantly influenced by the interactions and the structure of any microbiome, which also contributes to general health. The oral microbiome is essential for maintaining overall health, since it may aggravate noncommunicable and chronic illnesses (Aggarwal et al., 2023). Since the mouth is the main entrance point to the human body, bacteria living there have the ability to move to other parts of the body and cause illness. Thus, the oral microbiome's makeup is essential for maintaining immunity and maintaining human health. For example, nitrate is converted to nitrite by the microbiome's metabolism of nitrate. After that, nitrite is transformed into nitric oxide, which is essential for vascular health and has an antibacterial impact. Many oral microorganisms, such the strain K12 of *Streptococcus salivarius*, aid in host defense by preventing the colonization of harmful bacteria by fostering an unfavorable environment. It generates a bacteriocin that inhibits Gram-negative bacteria linked to periodontal disease from growing (Kozak & Pawlik, 2023).The foundations of the oral microbiome are established in the perinatal period and comprise an impressive repertoire of microbes that are indigenous to this habitat. At birth, the baby may

harbor some microbes obtained from the mother during passage through the birth canal, but soon will also acquire from its various close contacts a rich menagerie of attached, planktonic and intracellular microbes. The foundations of the oral microbiome are established in the perinatal period and comprise an impressive repertoire of microbes that are indigenous to this habitat. Since *Streptococci* are the most prevalent type of bacteria in the oral cavity, they unavoidably play a major role in our oral health (Tagg et al., 2023). The oral microbiota often coexists peacefully with the host and offers significant advantages that support general health. Instead of existing as individual cells, the bacteria in oral biofilms coexist closely with one another. Both antagonistic and synergistic microbial interactions are possible. Furthermore, the makeup of the microbiome is influenced by the oral environment. Variations in the surrounding environment can impact the way bacteria interact in the mouth and raise the risk of periodontitis (Kozak &Pawlik, 2023). There are two regions in the oral cavity colonized by microorganisms—dentures, or the hard surfaces of the teeth, and the soft tissue of the oral mucosa. (Aggarwal et al., 2023). Since the mouth mucosa acts as the body's main defense mechanism, many oral health issues and serious systemic diseases have similar risk factors (Kale et al., 2023).

Lipid and carbohydrate metabolism have been demonstrated to be impacted by the microbiome. Products of the microbiome can also cause disturbances in the circulation of bile acid. It has been demonstrated that Short-Chain Fatty Acids can alter insulin synthesis and pancreatic β-cell activity, which can aid in the onset of diabetes. A disturbed microbiome, or dysbiosis, can be observed in a variety of the host's disease states, from metabolic to immune and mood disorders. Because microbial communities and the living host have such a complex relationship, it is not surprising that a disruption in one frequently results in the disruption of the other (Aggarwal et al., 2023).Diabetes and insulin resistance may result from microbiome dysbiosis, which can further exacerbate oxidative stress and chronic systemic inflammation (Kozak & Pawlik, 2023).

Recent years have seen a sharp rise in the study of the human microbiome and its relationships to various illnesses. Many environmental variables influence the variety and quantity of microbes at different places throughout the body, including temperature, pH, oxygen concentration, pressure, osmolarity, and nutrition availability. The microbiome of humans adjusts to its natural surroundings in response to several stimuli, including nutrition, lifestyle, treatment, and route of delivery. Because older persons have weakened immune systems and are hence more vulnerable to infections, alterations in their total microbiome can also be attributed to this. Because *Bifidobacterium* species activate the immune system and metabolic processes, a decline in *Bifidobacteria* in older people may lead to malnourishment and a low level of systemic inflammation. The ideal development circumstances for the human microbiome are contingent upon the body's natural environment. When the body's natural environment changes, the variety and composition of microbes change to adapt to new conditions, which may lead to illness (Aggarwal et al., 2023).

4. Are Probiotics Considered a Treatment?

Probiotic supplementation has gained increasing attention as a medicinal complement or alternative for supporting oral health (Gheisary et al., 2022). Research suggests that consuming probiotics, prebiotics, and synbiotics can help maintain a healthy microbiota or alter the microbiome to establish a beneficial microbial environment (Aggarwal et al., 2023). In the context of health, novel species such as *Streptococcus salivarius* and *Streptococcus dentisani*, which may have probiotic properties, are associated with the management of various oral diseases, including periodontal diseases (Kozak & Pawlik, 2023). Probiotics are living organisms, often bacteria, administered to patients to improve their health and help prevent or treat specific conditions (Gheisary et al., 2022).

In periodontal treatment, the genus *Lactobacillus* is well known for its beneficial effects on health. Species like *Bifidobacterium*, *Streptococcus*, and *Weissella* are also known for their positive impact on dental health. Other species, such as *Saccharomyces cerevisiae* and *Bacillus subtilis*, also positively affect the oral cavity. Moreover, certain bacterial strains isolated from the oral cavity—such as *Lactobacillus reuteri*, *Lactobacillus brevis*, and *Streptococcus salivarius*—have been commercially manufactured as probiotics. *Limosilactobacillus fermentum*ALAL020 has been proposed by Kawai et al. as a potential probiotic in the future. The cyclic dipeptide produced by this bacterium exhibits antibacterial properties against *Prevotella intermedia* and *Porphyromonas gingivalis* (Kozak & Pawlik, 2023).

Probiotics can work in various ways, such as by producing antibacterial metabolites, enhancing the mucosal barrier, modulating the immune system, and shifting the microbial flora by competing with pathogenic strains for cell adherence (Gheisary et al., 2022). Scientific research is currently very interested in the health benefits of synbiotics. A synbiotic is described as "a combination consisting of living microorganisms and substrate(s) that are preferentially used by host microorganisms and contribute to the host's health." It has been found that giving probiotics together with a synbiotic can help reduce several metabolic diseases. However, there is limited data supporting this. Synbiotics may decrease the amount of *Streptococcus mutans* in children's saliva, although they may not be more effective than probiotics alone, as reported by Duraisamy et al. (Kozak & Pawlik, 2023).

5. Metagenomics

The development of microscopes in the latter part of the 18th century brought microorganisms into our visual field and helped us recognize them. The molecular biology and genomics revolutions of the latter half of the 20th century brought together our understanding of the underlying genetic basis of the physiological processes that were first gained from the development of laboratory cultivation techniques in the middle of the 1800s, which revealed to us how a small number of microbes survive on their own cells. Metagenomics, a relatively new field of study, will allow researchers to study microorganisms in the complex communities in which they often reside. It will cause changes in biology, medicine, ecology, and biotechnology that might be just as significant as those brought about by the development of the microscope. The use of 16S ribosomal RNA (rRNA) sequences has led to a significant shift in the taxonomic status of the microbiome. It has been suggested that the 16S rRNA-based phylogenetic marker is an essential tool for taxonomic investigations of microorganisms, and 16S rRNA is still a useful tool in microbial study today. The word "metagenome," which describes a group of genomes found in samples used to research functional analysis and cloning. The growth of microbial investigations based on whole genomes and 16S rRNA has accelerated with the introduction of sequencing technology. Studies looking at the genetic information of microorganisms have been referred to as "metagenomics," which is further classified into two categories: amplicon or targeted gene date and shotgun or untargeted gene data. Shotgun metagenomics research mostly focuses on analyzing functional genes and metabolisms, whereas amplicon metagenomics studies usually investigate microbial diversity. The variety of microorganisms discovered in various settings has spurred research into the uses of microbes in the food, pharmaceutical, and agricultural sectors in addition to human health (Nam et al., 2023).

6. Conclusion

The community of microorganisms that inhabit a certain environment, such as the human body, is referred to as the microbiome. These microorganisms include bacteria, fungi, and viruses. A large and varied community of microbes is essential to preserving human health and well-being. The generation of vitamins, digestion, pathogen protection, and immune

system regulation are all influenced by the microbiome. The microbial population found in the mouth is referred to as the oral microbiome.

In thalassemia, a hereditary blood disorder marked by abnormal hemoglobin production, disturbances in the oral microbiome are commonly observed. These disturbances can be linked to several factors associated with thalassemia, such as chronic blood transfusions, iron overload, and underlying health conditions. As a result, changes in the composition and diversity of the oral microbiome may occur, potentially affecting overall health. The oral and gut microbiomes are interconnected through dynamic interactions between molecular signaling pathways and bacteria. Variations in the oral microbiome's composition can influence the diversity and function of intestinal bacteria, thereby impacting general health outcomes. This relationship underscores the importance of understanding and managing both the oral and gut microbiomes in thalassemia patients to achieve optimal health outcomes.

Probiotics are recognized as a promising therapeutic approach to enhance individual health. These beneficial bacteria can positively influence microbial balance. Probiotics have the potential to support the immune system and overall health by restoring microbial balance in both the gut and oral microbiomes. They achieve this by inhibiting the growth of pathogenic bacteria and promoting the proliferation of beneficial bacteria.

Metagenomics is an effective method in microbiome research that makes it possible to analyze the genetic and molecular composition of microbial communities in great detail. Researchers may learn more about the range, makeup, and activity of microbiomes in illness and good health by analyzing the genetic information of whole microbial ecosystems. New studies into metagenomics have the potential to enhance the knowledge of the complicated relationships within microbial ecosystems while helping the development of specific treatments that adapt to patient requirements.

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