

Literature Review

Relationship between Vitamin D Deficiency and Lipopolysaccharides *Porphyromonas gingivalis* Bacteria in Stunting Children

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Abstract

Background: *Stunting* is a condition of growth and development disorders in children under 5 years of age who appear shorter than their age caused by nutritional deficiencies. The stunted growth and development of children can be influenced by deficiencies in the intake of macronutrients such as protein and micronutrients such as calcium, phosphorus, zinc, and vitamin D. One nutrient that is relevant to current dental health research is vitamin D.

Objective: This review article will further analyze the relationship between vitamin D deficiency and *Porphyromonas gingivalis* bacterial lipopolysaccharide in *stunting* children.

Literature review: Vitamin D deficiency can cause various problems related to the oral cavity such as a decrease in salivary flow rate, buffer capacity, and salivary content such as protein. A decrease in salivary flow rate causes secretory Immunoglobulin A (IgA) to decrease, thus disrupting the colonization of normal microflora in the oral cavity. Reduced vitamin D levels can potentially increase the number of *Porphyromonas gingivalis* bacteria and also lipopolysaccharides (LPS), thus inhibiting the proliferation and differentiation of alveolar bone cells.

Conclusion: Therefore, lack of micronutrient intake such as vitamin D deficiency can trigger the growth of *Porphyromonas gingivalis* bacteria and an increase in bacterial products such as lipopolysaccharides, especially in *stunted* children.

Introduction

Stunting is a growth and development disorder where children under 5 years of age are shorter than their age due to nutritional deficiencies. According to studies, the variables that cause stunting indirectly include family food security, health education, parenting and family diet, environmental health, and health services, but the direct factor is a lack of nutritional intake. Inhibition of nutrition intake may cause stunted child development [1].

Both direct and indirect factors contribute to stunting, such as the association between educational level and oral health status. The educational level can influence a child's oral health and nutritional state; thus, it is critical to offer adequate information to preserve dental health from an early age. This is because childhood, particularly throughout primary school, is a vital growth and developmental stage, including

the transition from primary to permanent teeth and the need for preventative and promotional measures to preserve oral health, which will affect dental health in adulthood [2,3].

According to UNICEF, WHO, and the World Bank Group, 22.2%, or 150.8 million, of children under the age of five worldwide were stunted in 2017. Asia has the world's second-highest frequency of stunting, after only Africa. Furthermore, Indonesia, like many other Asian nations, has 30.8% of infants under the age of five (toddlers) suffering from stunting. Shortages in macronutrients such as protein and micronutrients such as calcium, phosphorus, zinc, and vitamin D may impact children's stunted growth and development [1,4].

Vitamin D intake in newborns typically begins after birth. Breast milk serves as the primary natural source of nutrition for infants in the initial months of life [5]. Vitamin

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D compounds, whether of animal origin (cholecalciferol) or plant origin (ergocalciferol), enter the bloodstream and are transported to the liver bound to vitamin D binding protein (VDBP). The biological functions of vitamin D are facilitated by a nuclear transcription factor called the vitamin D receptor (VDR) [6].

The predominant cells and organs storing VDR and the activating enzyme (1-alpha-hydroxylase) responsible for the synthesis of 1,25(OH)₂D likely facilitate the execution of a local autocrine or paracrine function [6]. Vitamin D exhibits biological pathways that influence both genomic and non-genomic effects on cellular growth, skeletal muscle, the immune system, and Nerve Growth Factor (NGF). It plays a regulatory role in cell differentiation and the reactivation of proteins. This can facilitate the growth and development of children who are in the early stages, extending from early development to those approaching the end of this phase (under and above 5 years) [7].

Vitamin D deficiency may lead to many oral cavity issues, including reduced salivary flow rate, diminished buffer capacity, and altered salivary composition, such as protein levels. A reduction in salivary flow rate alters the oral cavity's immune system, resulting in a drop in secretory immunoglobulin A (IgA) and hence disturbing the colonization of normal microflora [8,9]. Consequently, diminished vitamin D levels in the body may elevate the presence of bacteria in saliva, including *Porphyromonas gingivalis*, as well as bacterial byproducts like lipopolysaccharide (LPS), which can impede bone cell proliferation and differentiation, thereby exacerbating the issue of stunting.

Based on the description above, this review article will further analyze the relationship between vitamin D deficiency and *Porphyromonas gingivalis* bacterial lipopolysaccharide in stunting children.

Stunting

Stunting is a disorder characterized by inadequate growth in children under five years old, resulting from chronic malnutrition and frequent illnesses, particularly during the first 1,000 days of life. Stunting is identified by comparing a child's height to the standard height of children of the same age and sex within all the inhabitants. A stunted toddler is defined as one whose body length (PB/U) or height (TB/U) for their age falls below the WHO-MGRS guideline, exhibiting a z-score between <-2 SD and -3 SD (standard deviations). Height-for-age (H/A) and Body Mass Index (BMI)-for-age curves were turned into percentiles and Z-scores to determine health or nutrition problems like linear growth retardation, wasting, or body fatness [4,10].

According to the World Health Organization (WHO) threshold for public health relevance regarding stunting, Indonesia exhibits a high incidence of stunting (30% - 39%).

The country ranks fifth among countries with the highest burden of stunting children. The reduction in stunting prevalence over the last decade has been gradual, decreasing from 42% to 36%. The 2013 Indonesian Basic Health Survey showed that around 37.2% of children under five in Indonesia had stunting, with rates varying from approximately 27% in Riau Islands Province to over 50% in East Nusa Tenggara Province [1,4].

Factors of stunting

Nutrition intake: The nutritional content of food is correlated with the quantity consumed. Nutrition is crucial for achieving optimal health and growth. Macronutrients constitute the primary components of nutrition, including energy, carbohydrates, proteins, and fats. Micronutrients, including vitamins, calcium, iron, zinc, and various minerals, are crucial components of a healthy diet. Nutrition is critical for a child's growth and development. Nutrition significantly influences both the preservation and recovery of health; thus, an individual's nutritional status is intrinsically linked to their overall health status, with each impacting the other. Insufficient access to nutritious food contributes to stunting [11].

Health care system and environmental sanitation

Environmental health and sanitation significantly influence children's growth and development. Food hygiene and safety may elevate the risk of infectious diseases. Inadequate sanitary environmental conditions facilitate the invasion of various bacteria into the body, leading to diseases such as diarrhea, parasites in the intestinal tract, fever, and malaria, among others. Infections of this nature can disrupt the digestion of nutrients, resulting in inadequate nourishment and impaired growth. To enhance child health and nutrition and to fulfill broader Sustainable Development Goals (SDGs), it is essential to provide safe sanitation and eliminate open defecation [12].

Economic factors

Family income is another factor linked to stunting. The economic crisis significantly impacts delays in child development and various nutritional issues, as evidenced by the characteristics of family revenue. Children experiencing stunting predominantly originate from economically disadvantaged backgrounds. Low economic status influences food insufficiency and quality as a result of limited purchasing power. These economic conditions hinder stunted children from obtaining sufficient nourishment [13].

Education factors

Education constitutes a process through which individuals enhance their potential, encompassing both knowledge acquisition and skill development. Education significantly influences the development of malnutrition, as it pertains to an individual's capacity to acquire and comprehend



information. The educational attainment of parents can influence the behavioral patterns and dietary habits of their families, particularly those of their children. Consequently, a lower level of parental education is associated with a greater likelihood of deteriorating quality of life, particularly in the growth and development of children [14].

Oral hygiene

Stunting is associated with poor oral hygiene, as indicated by the Oral Hygiene Index (OHIS). Previous research conducted on children in NTT Province indicates a high prevalence of stunting alongside a low Oral Health Impact Scale (OHIS). This is attributable to insufficient knowledge regarding proper tooth brushing, as only 3.7% of children engaged in this practice at the appropriate time. Poor oral hygiene is defined by the accumulation of dental plaque.

Dental plaque consists of a biofilm, which is a structured community of interconnected bacterial cells. These bacteria are capable of producing a polymer matrix that adheres to both inanimate and living surfaces, such as dental surfaces [15].

Oral microbiome

The oral microbiome comprises a consortium of bacteria residing in the oral cavity. Coexistence in homeostasis may avert sickness and sustain certain environmental conditions conducive to the survival of commensals. The homeostatic condition may be disrupted by the host's diet or their ability to engage with commensal microbes. This may disrupt the equilibrium in the oral cavity and alter the environment, resulting in a loss of homeostasis, referred to as oral dysbiosis [16,17].

Joshua Lederberg, a Nobel Prize recipient, invented the term "microbiome" to denote the ecological community of symbiotic, commensal, and pathogenic microorganisms. The organisms that constitute the microbiome include bacteria, fungi, viruses, archaea, and protozoa. The variety of species in the oral microbiome belongs to each person and region of the oral cavity. This results from the oral microbiome's continual contact and significant effects from the environment [18,19]. The environmental parameters include nutrients from the host's nutrition, temperature, pH level, moisture, anaerobic conditions, host immunological response, and bacterial interactions. The oral microbiota often manifests as biofilms [20].

The microbiome of the oral cavity during infancy is a dynamic community characterized by significant compositional changes before achieving a more stable environment in adolescents [19,21]. Prior research indicates that the saliva of young infants has more bacterial diversity compared to that of young adults. The age range of 10 to 11 years is during the late mixed dentition phase, during which

the canines, premolars, and second molars erupt. Throughout this age, a distinction exists between the variety and composition of microorganisms at the sites of primary teeth and permanent teeth [22].

Porphyromonas gingivalis

Porphyromonas gingivalis is a nonsaccharolytic bacterium classified as part of the gram-negative anaerobic category. It has a black pigment and exhibits a coccobacillus morphology, demonstrating considerable aerotolerance and the ability to proliferate in low-oxygen environments. *Porphyromonas gingivalis* has two specific fimbriae. Long fimbriae consist of the structural protein fimbrial protein fibrillin (FimA) and facilitate the adhesion of early colonies such as *S. gordonii* to salivary proline proteins and statherin. They consist of epithelial cells, endothelial cells, fibroblasts, and matrix proteins such as fibronectin and fibrinogen. The short fimbriae consist of Mfa proteins, facilitating bacterial adhesion to other bacteria [23,24].

Porphyromonas gingivalis produces two proteins belonging to the Internalin J class and the Leucine-Rich Repeat (LRR) class, which are implicated in adhesion and biofilm formation. *Porphyromonas gingivalis* also releases hemagglutinins that bind to host cells, as well as proteinases containing hemagglutinin domains, which may play a role in biofilm adhesion. The invasion of *Porphyromonas gingivalis* begins with the interaction between FimA fimbriae and integrin receptors on gingival epithelial cells. Integrin receptor interaction is accompanied by signaling induced by *Porphyromonas gingivalis*, such as serine phosphatase (SerB), which leads to the regeneration of host microfilaments and microtubule cytoskeleton via lipid components [23].

Porphyromonas gingivalis possesses bioactive cellular structures, including the plasma membrane, cytoplasm, peptidoglycan, outer membrane proteins, Lipopolysaccharides (LPS), capsule, and fimbriae on its surface. Phospholipids accumulate in the outer membrane of *Porphyromonas gingivalis* during the development of cells, leading to outward swelling of the membrane and subsequent pinching off to form outer membrane vesicles (OMVs). These structures can elicit and regulate heightened cytokine production in periodontal tissues.

Furthermore, *Porphyromonas gingivalis* LPS is recognized as a significant factor in the onset and advancement of periodontal disease, as it is a potent inflammatory stimulant that induces cytokine production and bone resorption [25].

Vitamin D

Vitamin D acts as a steroid hormone essential for bone metabolism and the regulation of calcium levels in the body. Vitamin D is sourced from dietary intake, including both plant and animal origins, as well as from supplements. Additionally,



it is produced endogenously through skin exposure to sunlight, resulting in vitamin D3 (cholecalciferol) or vitamin D2 (ergocalciferol). These forms undergo hydroxylation in the liver to produce 25(OH)D, which is further hydroxylated in the kidneys to create the active metabolism product, calcitriol (1,25[OH]2D) [26,27].

Vitamin D insufficiency may regulate bone density and contribute to circumstances of microorganism imbalances [28]. Furthermore, vitamin D may directly restrict the autophagy process, thereby suppressing osteoclast formation and promoting differentiation. Conversely, vitamin D stimulates autophagy via receptor activator of nuclear factor kappa-B ligand (RANKL), thereby facilitating osteoclastogenesis. Vitamin D supplementation demonstrated a reduction of cytotoxic T cells and pro-inflammatory cytokines, alongside an elevation of autophagy-related proteins in peripheral blood mononuclear cells, particularly among patients with periodontitis. Conversely, active vitamin D enhanced atrophic activity via the activation of the Forkhead Box O3 (FOXO3) factor and atrogens by inhibiting autophagy [29].

Autophagy is a homeostatic mechanism that eliminates damaged organelles and protein aggregates within cells, thereby safeguarding cellular integrity and facilitating energy production. The body's immune cells mediate the same molecular processes to combat and deteriorate pathogenic microorganisms. Research indicates that dysfunctional autophagy-related proteins can increase susceptibility to infections, chronic infections, and autoimmune illnesses [30]. Periodontal disease is a condition initiated by bacteria that colonize the subgingival environment early on and subsequently become more harmful to the host. The effectiveness of the host immune response in combating invasive microbes may serve as a critical factor in identifying disease progression [31].

Biological pathway of vitamin D

The active metabolite of vitamin D, 1,25(OH)D, demonstrates its effects. The impact on the receptors manifests as either a genomic effect or a non-genomic effect. The genomic effect manifests as gene transcription through nuclear VDR, occurring directly throughout a period. Vitamin D regulates over 200 genes. Most gene expression studies concerning vitamin D highlight that its active form guides approximately 0.8–5% of the entire genome, either directly or indirectly. Active vitamin D regulates the growth of cells, the repairing of DNA, differentiation, cell death, the transport of membranes, the metabolism of cells, and attachment. It is involved in various processes, including cellular oxidative stress. CYP2R1 serves as the primary 25-hydroxylase, while CYP27B1 functions as the principal 1hydroxylase. CYP24A1 catabolizes both 25OHD and 1,25(OH)₂D. The vitamin D receptor (VDR) functions as a transcription factor that interacts with 1,25(OH)₂D. The VDR binds to vitamin D response elements (VDRES) within DNA [7].

The non-genomic impact transpires through the vitamin D receptor (VDR) located on the cell membrane, occurring within a brief timeframe, typically in minutes. The non-genomic impact arises from modifications to the transient calcium-chloride transmembrane ion transitions or the activation of intracellular signaling channels, including cAMP, PKA, phospholipase C, PI-3 kinase, and MAP kinase. Alterations in the VDR gene may result in modifications to the protein sequence. These alterations can lead to significant problems affecting the immune system, cellular proliferation, and calcium homeostasis. Active vitamin D influences calcium channels, pancreatic beta cells, vascular smooth muscle, intestines, and monocytes by activating secondary messengers like MAP or cAMP by adhering to plasma membrane receptors, demonstrating a non-genomic effect [7,32].

Relationship of vitamin D deficiency to Increased *Porphyromonas gingivalis* and Lipopolysaccharide (LPS) Products

Oral health is integral to overall body health, indicating that the two cannot be considered independently. Oral health conditions, dietary habits, nutritional status, and general health status are interconnected factors. Malnourished patients, involving children with stunting, exhibit salivary gland hypofunction. Vitamin D deficiency can lead to stunting and is linked to several problems in the mouth, such as lower salivary flow rate, buffer capacity, and protein content. A reduction in salivary flow rate leads to a decrease in secretory IgA, thereby disrupting the colonization of normal microflora in the oral cavity. Compared to normal children, stunted children may have lower levels of salivary protein, which may increase the number of bacteria in their saliva, including *Porphyromonas gingivalis*. This could lead to some oral diseases, especially dental caries and periodontitis [33].

Porphyromonas gingivalis insists on heme for iron acquisition and protoporphyrin IX for survival within host cells, facilitating the onset of infection. Heme is present in the form of μ -oxo bisheme in the pigment located on the cell surface of *Porphyromonas gingivalis*. Two methods exist for the formation of μ -oxo bisheme from heme. Heme derived from hemoglobin can react with molecular oxygen and various other forms of oxygen, or it may be synthesized from hemein molecules. Heme sources include hemoproteins found in saliva, gingival fluid, and erythrocytes. *Porphyromonas gingivalis* acquires heme primarily via hemagglutinin, hemolysin, and gingipains. These proteins can utilize the systems of other bacteria to acquire heme. Heme influences both the binding capacity for additional heme and the structural integrity of lipopolysaccharides. *Porphyromonas gingivalis* requires heme for growth and dissemination; however, excessive heme can be harmful to the cell, particularly in conditions of heightened proteolysis. Kgp exhibits proteolytic activity that can release heme from hemoglobin. Alkaline conditions facilitate the formation and maintenance of μ -oxo bisheme.



Porphyromonas gingivalis exhibits optimal growth in slightly alkaline environments, such as those present in inflamed periodontal pockets [23].

Periodontitis is characterized by its polymicrobial nature and multifactorial origins, involving various host-associated factors. Periodontal disease frequently occurs in children and young adults, with 70% prevalence observed in those aged 7 years. The bacterial composition in the dental plaque of children with periodontal disease includes 68% *Porphyromonas gingivalis* and 20% *Tannerella forsythia*. *Porphyromonas gingivalis* is a bacterium.

Significantly linked to the onset of periodontal disease in healthy children aged 12 to 14 and is classified as a keystone pathogen due to its predominant role in the disease's progression.

Periodontal bacterial substances can enhance the expression of cytokines such as interleukin.

(IL)-1, IL-6, and tumor necrosis factor (TNF)- α , which are involved in osteoclastogenesis. Reduced vitamin D levels may further increase the prevalence of *Porphyromonas gingivalis* and lipopolysaccharide (LPS), which inhibit bone cell proliferation and differentiation, and activate nuclear factor kappa B (NF- κ B), leading to periodontal tissue destruction [34,35].

Vitamin D has the potential to mitigate alveolar bone damage and influence the Aryl Hydrocarbon Receptor (AhR)/nuclear factor (NF)-B/Nucleotide-binding oligomerization domain, Leucine-rich Repeat, and Pyrin domain-containing (NLRP)-3 inflammatory pathway in mice infected with *Porphyromonas gingivalis*. Vitamin D demonstrates significant antimicrobial activity against periodontal pathogens by directly suppressing bacterial proliferation and LPS-induced inflammation, as well as promoting the synthesis of antimicrobial peptides, including defensins and cathelicidin. Cathelicidin exhibits significant antimicrobial efficacy against gram-negative bacteria, including *Porphyromonas gingivalis*. A study conducted in vitro by Yang et al. demonstrated that cathelicidin enhanced autophagy in keratinocytes and decreased the quantity of *Porphyromonas gingivalis* bacteria. Cathelicidin influences multiple components of the innate host immune response, such as chemotaxis, expression of cytokines, bloodstream permeability, and the neutralization of bacterial endotoxins [36,37].

Recommendations

Stunted children have nutritional deficiencies, including vitamin D deficiency, which contribute to impaired growth and oral health problems. Therefore, vitamin D supplementation is required for linear growth among children under the age of five, such as encouraging a balanced diet rich in vitamin D and safe sunlight exposure to enhance natural vitamin

D synthesis. Finally, maintain good oral hygiene practices, including regular tooth brushing and routine dental check-ups, to control bacterial colonization and prevent dental caries. It's important to consult with healthcare professionals to tailor vitamin D supplementation to the individual needs of the child, especially in cases of stunted growth, to support both general and oral health effectively.

Study limitations

Many studies about the role of vitamin D in oral health and stunting have limitations, including a lack of consideration for confounding factors like concurrent nutritional deficiencies (e.g., protein, zinc, or calcium). While vitamin D is associated with reducing the risk of dental caries, its effects are not universally consistent. Other factors, such as oral hygiene practices and sugar intake, play a more direct role in oral health.

Future directions

Future directions for vitamin D research in the context of stunting and oral health should adopt a comprehensive and interdisciplinary approach. Combining clinical trials, community interventions, and advanced technologies will provide a robust framework for addressing the multifaceted challenges associated with stunting and oral health. This approach could ultimately lead to sustainable improvements in children's health and development.

Future clinical trials will be necessary to ensure the minimum effective dose for the prevention of vitamin D deficiency in the infant through maternal supplementation with high-dose vitamin D, as well as to establish the safety of such regimens for use in the general population. In addition, mobile apps and digital platforms to monitor supplementation adherence, track vitamin D status, and educate caregivers about oral and general health.

Conclusion

Based on a review of articles, it was found that a lack of micronutrient intake, such as vitamin D deficiency, can trigger the growth of *Porphyromonas gingivalis* bacteria and an increase in bacterial products such as lipopolysaccharides, especially in *stunting* children. A decrease in salivary flow rate causes secretory immunoglobulin A (IgA) to decrease, thus disrupting the colonization of normal microflora in the oral cavity, which means potentially increasing the number of *Porphyromonas gingivalis* bacteria and also lipopolysaccharides (LPS). Therefore, it can trigger various diseases in the oral cavity, especially periodontal disease. In a previous study, the average number of bacteria was higher in stunting with poor oral hygiene.

It has been previously explained that vitamin D can exert potent antimicrobial effects against periodontal pathogens by inhibiting bacterial growth and facilitating the production

of antimicrobial peptides such as defensins and cathelicidin. Cathelicidin has strong antimicrobial activity against gram-negative bacteria such as *Porphyromonas gingivalis*. An in vitro study by Yang et al. on keratinocytes showed that cathelicidin promoted autophagy in keratinocytes and reduced the number of *Porphyromonas gingivalis* bacteria. Cathelicidin affects various aspects of the innate host immune response, including chemotaxis, cytokine production, vascular permeability, and neutralization of bacterial endotoxins.

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