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BLUE CROSS

Medical Bulletin

BIDIRECTIONAL RELATIONSHIP BETWEEN PERIODONTITIS AND DIABETES

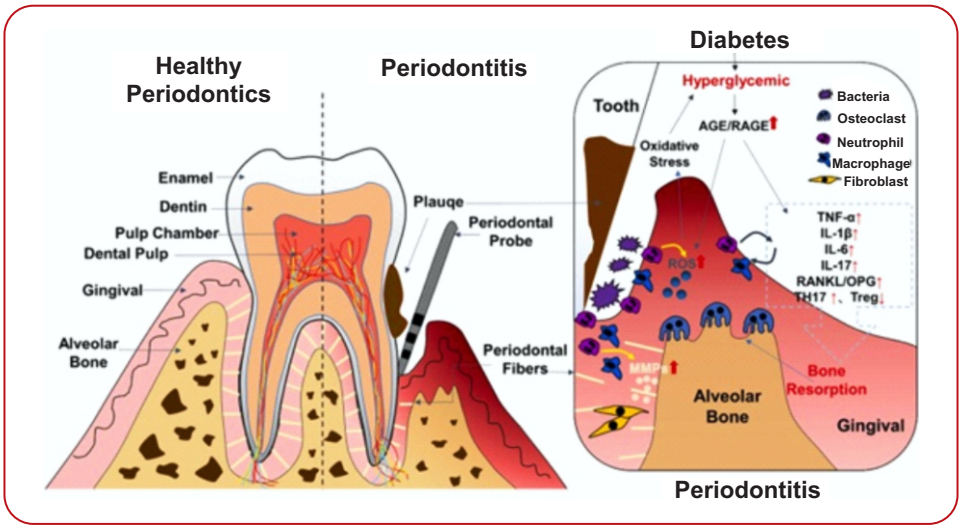
The oral cavity is the habitat for microbial colonization and changes in this biological ecosystem may be associated with several local and systemic disorders.

Periodontitis is a chronic inflammatory disease with a global prevalence of 62% in adults. Microorganisms in combination with individual host susceptibility and environmental factors are the main etiologic factors of periodontal diseases. *Periodontitis is linked to several systemic diseases, one of them being Diabetes.*

Periodontitis and diabetes share a bidirectional relationship i.e. diabetes promotes the occurrence and progression of periodontitis, and periodontitis affects glycemic control in diabetes and even promotes the development of diabetic complications. In fact, periodontal disease is now being considered as the 6th major complication of type 2 diabetes mellitus (T2DM). Studies have reported that patients with diabetes had a 24% increase in the incidence of periodontitis compared with non-diabetic patients, and patients with periodontitis had a 26% higher risk of developing diabetes.

✤ Bidirectional mechanism of periodontitis and diabetes

Numerous factors such as microbes, inflammatory cytokines, immune cell activity, glucose levels, and metabolic disorders, contribute to the bidirectional pathophysiology of periodontitis and diabetes.



1. Microbial factors

- Microbial action is the main source of the bidirectional link between periodontitis and diabetes.
- Periodontal microbial infections may promote the production of lipopolysaccharides (LPS),

which increase inflammatory factors and immune cell aggregation and promote diabetes.

- Whereas, diabetic patients provide a high-sugar environment that promotes the growth of certain pathogenic bacteria, resulting in dysbiosis.

2. Inflammatory cytokine factors

- Inflammatory cytokines are elevated in the gingival sulcus fluid of periodontitis patients with diabetes.
- They participate in the bidirectional mechanism of diabetic periodontitis by regulating bone resorption, insulin resistance, and periodontal tissue destruction.
- The release of bacterial LPS and other inflammation-associated immune cell pro-inflammatory mediators [such as tumor necrosis factor -α (TNF-α), Interleukin-1β (IL-1β), IL-6, IL-17, receptor activator of nuclear factor-κB ligand (RANKL)] leads to the injury of periodontal soft and bone tissues, promotes insulin resistance in a high-glucose environment and exacerbates periodontal inflammatory manifestations.
- Therefore, inflammation is the core mechanism of the bidirectional relationship between periodontitis and diabetes

3. Altered immune cell functions

- Alterations in immune cell function play a significant role in the bidirectional mechanism of periodontitis and diabetes, with neutrophils / polymorphonuclear leukocytes (PMNs) and macrophages, being the most important factors.
- PMNs are abundant in patients with diabetic periodontitis due to reduced chemotaxis, phagocytosis, and intracellular killing capacity of neutrophils resulting from decreased membrane fluidity in high-glucose environments.
- PMNs accumulates with continuous release of matrix metalloproteinase (MMP) and reactive oxygen species (ROS) causing severe periodontal tissue destruction. Oxidative stress causes neutrophil recruitment and increases the number and activity of osteoclasts leading to more severe periodontal soft and hard tissue destruction.

4. Glycation end-products (AGEs) and their receptors (RAGEs) in high glucose environments

- Periodontitis patients with diabetes experience irreversible glycation reactions.
- AGEs bind to RAGE and promote the apoptosis of periodontal-membrane cells through ROS and MMP released by mitochondria, exacerbating the destruction of periodontal bone tissue, inducing cell apoptosis, impairing islet function, and exacerbating the development of diabetes.

5. Metabolic factors

- Glucolipid metabolism balance has significance in the bidirectional promoter of periodontitis and diabetes.
- As the severity of periodontitis increases, serum total cholesterol (TC), triglyceride (TG), low-density lipoprotein (LDL), and free fatty acids (FFAs) levels increase in diabetic patients with poor glycemic control.
- Consequently, T2DM may promote the development of periodontitis and aggravate periodontal tissue destruction due to imbalance in the glucolipid metabolism.

Improvement in the control of diabetes and/or periodontal disease has the potential to improve significantly the quality of life in diabetic individuals

Source: *Kudiyirickal MG, et al. World J Diabetes. 2024; 15(3): 318-325, Shi Naixu, et al. Biomed Pharmacother. 2023; 165: 115219, Llambés F, et al. World J Diabetes. 2015; 6(7): 927–935.*

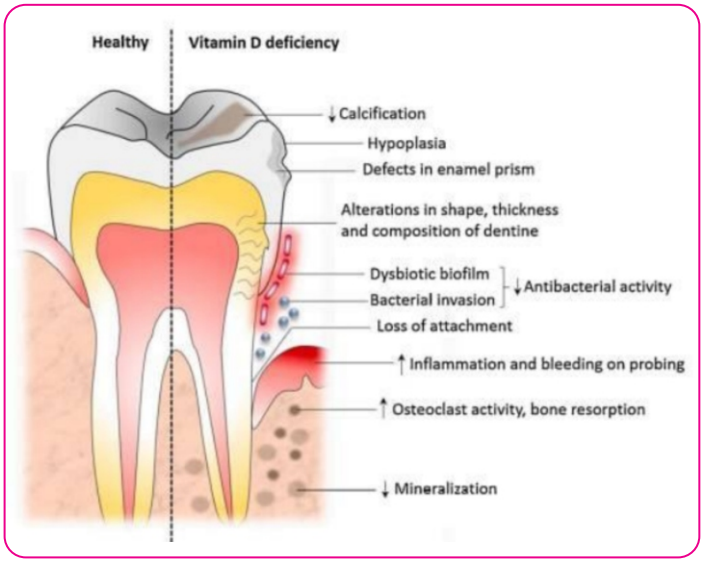
ASSOCIATION OF VITAMIN D DEFICIENCY AND DENTAL CARIES IN CHILDREN

Dental caries is a multifactorial disease and represents one of the most prevalent health problems in children and adolescents. Worldwide prevalence of dental caries in primary and permanent teeth is estimated at 46.2% and 53.8% respectively whereas prevalence in India is reported to be 57% in 3-18 years of age group.

Emerging evidence suggests that Vitamin D may influence the resistance of teeth to cariogenic bacteria and the demineralization process. The protective role of Vitamin D against dental caries may be due to its influence on the overall immune system and modulation of the adaptive immune response which could contribute to the prevention of infections in the oral cavity, including those that lead to caries development. Currently, it is known that most cells in the body, including odontoblasts (dentin-forming), ameloblasts (enamel-forming) and salivary glands, contain vitamin D receptors (VDR) and binding of vitamin D with its receptor modulates the expression of numerous coding genes related not only to mineral metabolism but also to cell life cycle, immune response, and energy metabolism.

Several clinical studies have assessed how vitamin D deficiency is highly linked with dental caries in children and have suggested that vitamin D exposure in early life may play a role in caries prevention;

- A recent systemic review (8 studies) from 2024 revealed that Vitamin D insufficiency and deficiency were prevalent in children ranging from 17.3% to 69.4%. Specifically, children and adolescents with Vitamin D insufficiency (<50 nmol/L) were found to have significantly higher odds of developing caries. Two of its studies even indicated a protective effect of higher Vitamin D levels against caries with serum levels ≥ 50 nmol/L, suggesting an inverse relationship between Vitamin D status and caries risk.



✤ Proposed mechanisms by which vitamin D deficiency interacts with dental caries process in children:

I. Intrauterine enamel defects:

Vitamin D deficiency during pregnancy may cause intrauterine enamel defects and through childhood is accompanied by insufficient activity of antibacterial peptides. Vitamin D has a significant role in odontogenesis. The vitamin D - VDR complex modulates the transcription of genes encoding various structural proteins synthesized by odontoblasts and ameloblasts that make up the unmineralized extracellular matrix. In addition, vitamin D induces the intrauterine mineralization of tooth dentin and enamel. Therefore, vitamin D has a significant role in forming oral hard tissue, comprising tooth enamel and dentin. There is evidence that vitamin D deficiency during pregnancy affects the formation and mineralization of primary teeth and results in developmental defects such as dentin hypomineralization and enamel hypoplasia and/or hypomineralization in the offspring.

- A clinical study has shown that high-dose vitamin D supplementation during pregnancy (2400 IU/d from pregnancy week 24 to 1-week post-partum) was linked to lower risk of enamel

defects in the offspring and suggests that prenatal supplementation constitutes a preventive intervention to reduce the prevalence of enamel defects and consequently the risk of childhood dental caries.

II. Antimicrobial proteins:

Vitamin D acts as an immune system modulator both in the innate and adaptive immune systems. The immunological role of vitamin D in innate immunity is stimulating the arrangement of some antimicrobial proteins (AMPs) synthesized by barrier and immune cells involved in innate immune system, including the mucosal lining of the gastrointestinal system. Vitamin D-VDR complex modulates the transcription of genes of certain AMPs and activates the synthesis of cathelicidin which has both antimicrobial and antiendotoxin activity. Some studies have found a relation between salivary antimicrobial protein levels and changes in streptococcal composition in dental plaque.

- Clinical studies on saliva in school children have found that the concentration of cathelicidin in saliva in patients with vitamin D deficiency was significantly lower.

III. Salivary dysfunction:

Saliva plays a protective role against caries since salivary flow on one hand facilitates the dilution and elimination of ingested fermentable sugars and on the other hand has a neutralizing capacity of the degree of acidity in the oral cavity. So, once the sugars are removed from the mouth by swallowing and salivary dilution, the biofilm acids can be neutralized by the buffering action of saliva. In addition, if the salivary flow was sufficiently saturated with calcium and phosphorus ions, demineralization would be stopped and remineralization would be favoured. Experimental studies have shown that fluid and electrolyte secretion from salivary glands is directly dependent on vitamin D. Vitamin D deficiency decreases salivary flow and alters its composition by reducing the amount of calcium ions consequently diminishing its protective role against caries.

D Guideline recommendations to prevent Vitamin D deficiency

- The US Endocrine Society recommendation in pregnant women is a daily oral cholecalciferol supplementation of 1500-2000 IU which should begin as early as possible.
- The American Academy of Paediatrics, the US Endocrine Society and the ESPGHAN (The European Society for Paediatric Gastro-enterology Hepatology and Nutrition) recommend that the adequate intake and recommended dietary allowances for children 0-1 and 1-18 year should be at least 400 and 600 UI/day, respectively.
- Children and adolescents who do not achieve the recommended dietary allowances of vitamin D, even with the intake of vitamin D-fortified foods, should be administered with oral cholecalciferol supplement of 600 IU daily.

Optimal levels of vitamin D throughout pregnancy and childhood with appropriate vitamin D supplementation should therefore be maintained as a preventive measure for dental caries in the primary and permanent dentition.

Source: *Trave TD, et al. Eur J Pediatr. 2024; 183(2): 523–528, Buzatu R, et al. Dent J (Basel). 2024; 12(4): 117, Induja D, et al. Indian J Public Health. 2022; 66(1): S3-S11.*

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