



Congenital Heart Diseases and Periodontal Diseases—Is There a Link?

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An understanding in the field of periodontal medicine explains the fact that the oral cavity serves as a niche for numerous pathogenic microorganisms. When these microorganisms or their by-products disseminate to the various parts of the body, they are capable of triggering diseases characterized by an altered host immune-inflammatory response in the anatomically distinct organ. This mechanism is reported in the propagation of cardiovascular diseases with respect to periodontal medicine. Abundant amount of literature suggests an association between atherosclerotic cardiovascular disease and periodontal diseases. However, there is very less data available to highlight the association between periodontal disease and non-atherosclerotic cardiovascular disease, such as congenital anomalies of the heart. This review outlines the relationship between periodontal diseases and congenital heart diseases and also helps us understand whether the presence of periodontal disease can worsen the preexisting congenital cardiac disease.

Keywords: periodontitis, congenital cardiac diseases, periodontal medicine, infective endocarditis, bacteremia, linking mechanism

INTRODUCTION

The oral cavity gives asylum to commensal microflora, which is most commonly affected by prevalent human infectious diseases, such as dental caries and periodontitis (1). The theory of focal infection, which was proclaimed for more than a decade around nineteenth and twentieth centuries, states that focal sepsis, which are caused by oral microorganisms, is culpable of initiation and progression of many inflammatory diseases. This focal theory states that there is a casual link between most common oral diseases with systemic diseases, such as cardiovascular disease, diabetes, male and female reproductive disorders, osteoporosis, rheumatoid arthritis, neurodegenerative disorders, pulmonary diseases, and even cancers, namely, colorectal cancer and lung cancer. There is remarkable evidence that there is a presence of periodontal pathogens in atherosclerotic plaque of coronary heart disease thus stating that periodontitis may be a risk factor for development of cardiovascular diseases (2, 3). However, the nature of this association needs to be further studied and a reasonable understanding needs to be derived to indoctrinate whether this

association correlates periodontal disease with congenital cardiac diseases, which are caused due to genetic reasons.

THE ROLE OF PERIODONTITIS IN AUGMENTING IMMUNE-INFLAMMATORY PATHWAYS

In periodontitis, the pathogens in the biofilm, as well as their virulence factors dysregulate the normal symbiotic relationship between the host and the pathogen, leading to an exaggeration in the host immune response (4). The hazardous microenvironment created by this dysbiotic microflora triggers an immune response that is pronounced at the locus of the biofilm, leading to exponential damage of the periodontal tissues, which is the key triggering factor responsible for progression of gingivitis to periodontitis (5). Initially, phagocytes, such as the neutrophils and the macrophages, transmigrate to the site of bacterial insult, which produces a wide array of chemical mediators, such as the interleukins and prostaglandins, that not only sustain the process of inflammation locally but also aid in signaling of inflammatory cells to migrate to the site of periodontal destruction (6). These phagocytic cells express Toll-like receptors (TLRs) on their surface that are specialized to sense pathogen-associated molecular patterns (PAMPs) leading to a cascade of events through the MyD88-dependent pathway inducing the production of NF κ B, that controls release of proinflammatory cytokines, such as interleukin (IL)-1 β , tumor necrosis factor (TNF)- α , and IL-6 (7). This initial response to the biofilm initiates phagocytosis of the microorganisms and enables the elimination of the microbes that infringe on periodontal health.

The complement system gets activated synchronously, which enhances the susceptibility of these pathogens to the phagocytic action of neutrophils and macrophages. However, with the continuing maturation of the biofilm by pathobionts, there is a switch in the host to an adaptive immune response, wherein the bacterial antigen is sensed and processed by antigen presenting cells to the lymphocytes. This, in turn, leads to the differentiation and maturation of T-cells, B-cells, and the monocytes, which induce bone resorption and the dissolution of the periodontal ligament fibers through the coupling action of osteoclasts, and the matrix metalloproteinase (MMP)-mediated release of chemical mediators, such as RANKL, IL-1 β , TNF- α , and IL-6, that promote osteoclastogenesis through various inflammatory signaling pathways (8). The persistent and virulent nature of the periodontal pathogens and their continually exaggerated elaboration of proinflammatory cytokines that disseminate into the systemic circulation serve as the bedrock for the initiation and progression of destructive inflammatory diseases in anatomically distinct organs that are away from the initiator of the disease—periodontal microbiome. This is basis to the science of periodontal medicine, which highlights the probable link between periodontal disease and systemic wellbeing, as well as the development of diseases, such as cardiovascular diseases, respiratory diseases, diabetes, rheumatoid arthritis, and

reproductive disorders. This risk is further highlighted when the effects of periodontal diseases worsen the sufferings faced by patients with cardiovascular diseases.

CLINICO-IMMUNOLOGICAL PROFILE IN CONGENITAL HEART DISEASES

Cardiovascular diseases encompass a wide range of disorders that arise out of atherosclerotic and non-atherosclerotic origins. Atherosclerosis is a leading cause of vascular disease worldwide, and its major clinical manifestations include ischemic heart diseases, stroke, and peripheral artery disease. In high-income countries, there have been dramatic declines in the incidence and mortality from ischemic heart disease and ischemic stroke since the middle of the twentieth century, which suggests that adequate awareness, research, and treatment protocols are available to address these issues (9). However, non-atherosclerotic cardiovascular diseases, such as congenital heart disease (CHD), encompass abnormalities in heart structures that occurs before birth, mainly due to genetic or chromosomal abnormalities (10).

Mitchell et al. defined CHDs as “a gross structural abnormality of the heart or intrathoracic great vessels that is actually or potentially of functional significance” (11). It occurs due to excessive alcohol consumption, judicious use of medication, and maternal viral infection during 1st trimester of pregnancy (12). With the advent of better medical facilities, the epidemiological figures denoting the mortality rate associated with CHDs seem to have improved, but the morbidity rate is still alarming. It is suggested that CHD affects 1 of every 100 live births (13). Although the occurrence of CHD may attribute to many causes, 15% of the known cases of CHD can be mapped to a known etiology, thereby making it imperative for us to understand the etiological role of periodontal disease in the augmentation of CHDs (14).

There are two common forms of CHDs, namely, cyanotic and acyanotic, which are based on the amount of deoxygenated hemoglobin present in blood (15, 16). However the most commonly occurring CHDs are ventricular septal defects, atrial septal defects, patent ductus arteriosus, pulmonary stenosis, coarction, and tetralogy of fallot (TOF), which account for almost 80% of all the congenital diseases that occur in humans (17).

Tetralogy of fallot, the most common congenital cardiac disease, comprises ventricular septal defects, aortic overriding, infundibular stenosis, and hypertrophy right ventricle. There are no precise symptoms for CHDs. However, shortness of breath, limited ability to do exercise, fatigue, and abnormal sounds of heart as heart murmurs are noticed (12).

These congenital anomalies may occur alone or together or as a manifestation of syndromes. The most common syndromes associated with congenital cardiac diseases are Down, Edwards, Digeorge, Hurler, Noonan, Treacher Collin, and Turner's syndrome. These syndromes are associated with a multitude of effects that not only increase the morbidity but also play a

role in augmenting the immune-inflammatory profile in these syndromes thereby having a direct effect on the pathogenesis of congenital cardiac diseases. It is reported that Down's syndrome is associated with an increased TLR2 activity; however, there is a decrease in the activity of B- and T-lymphocytes and IgG production (18, 19). It has been suggested that elevated levels of IL-6 and TNF- α are seen in patients with Turner's syndrome (20). Overall, patients suffering with stand-alone congenital cardiac diseases or as a manifestation of a syndrome are known to have weak immune responses characterized by decreased T-cell maturation and an increase in the suppressors of T-cell function, which eventually decreases the quality and quantity of B- and T-lymphocytes (21–23). An alteration in the immune response in CHDs can pose an array of effects on the systemic wellbeing of the individuals, as well as the periodontal health.

POSSIBLE ASSOCIATION BETWEEN PERIODONTAL DISEASE AND CONGENITAL HEART DISEASE

A preliminary report was published by Kaner et al. to evaluate oral findings in CHDs. In the TOF, the most noticeable abnormalities were seen in the tongue papillae, mucosal membranes, and gingivae. Similar but less pronounced structural alterations were observed in Eisenmenger's tetralogy and in the transposition of the major vessels. The pulp canals in the maxillary incisors were observed to be significantly enlarged and funnel-shaped in patients with aortic coarctation. Dextrocardia, patent ductus arteriosus, and septal abnormalities all had no visible oral symptoms (24).

Due to the systemic effect of congenital cardiac diseases, the developing dentition also gets affected (25). Spivack discussed the dental implications of TOF after which Gedik et al. also showed an increase in dental caries, hypoplasia, and periodontal disease in the patients with TOF compared with controls (26, 27). When compared with gender- and age-matched healthy controls, nearly twice as many teeth in a sample of 60 children with severe congenital heart abnormalities showed symptoms of bacteria-induced gingivitis (28). This was supported in two recent studies, which indicated that children with CHDs have a higher gingival index (29, 30). Furthermore, more than two-thirds of the youngsters in one of these trials showed evidence of gingival and/or periodontal inflammation (30).

Various medications that are used to manage children with congenital cardiac disease found to have impact on oral health by altering saliva, plaque, mucosa, and gingiva. Also, the association between dental caries and digoxin has also been proved (31, 32). Similarly, beta-blockers and diuretics are known to induce a significant xerostomia and lichenoid reaction (33, 34). angiotensin-converting enzyme (ACE) inhibitors, such as captopril and enalapril, and calcium channel blockers, such as nifedipine, are known to cause gingival hyperplasia, while the use of oral anticoagulants may lead to bleeding gums (35, 36). The fact that children with congenital cardiac disease usually suffer with poor periodontal health compared with healthy

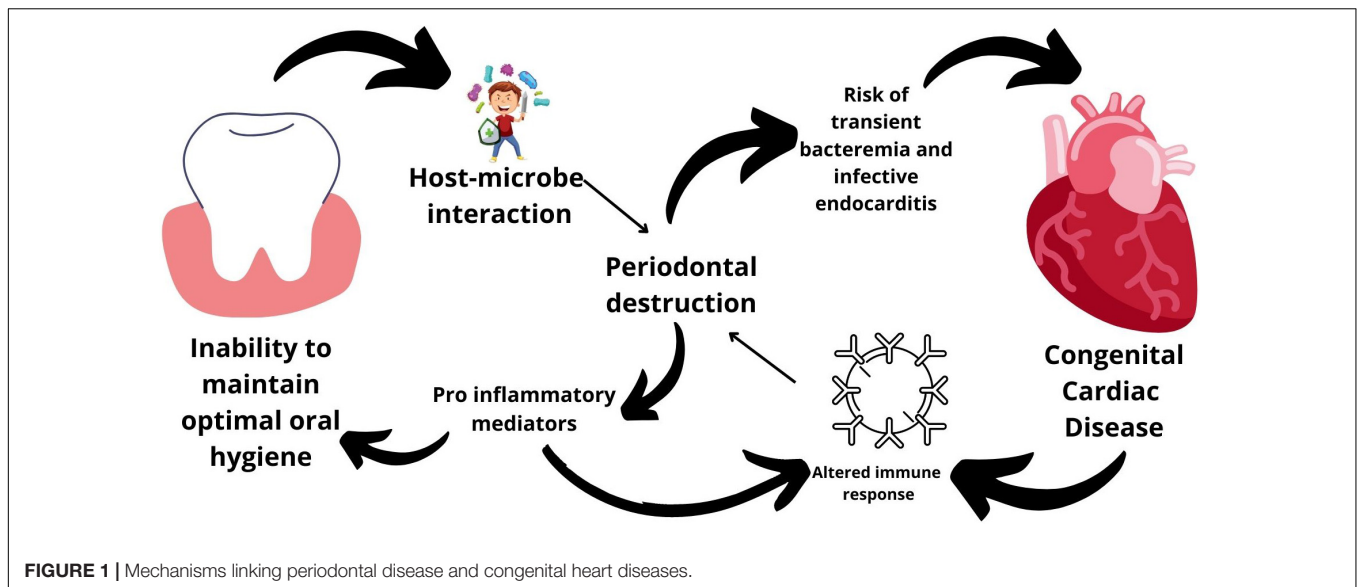
children may be due to inadequate professional and personal dental care or due to an alteration in the immune response experienced in CHD; however, none of the studies explain the actual pathophysiological mechanism that links periodontal health and CHDs.

MECHANISMS LINKING PERIODONTAL DISEASES AND CONGENITAL HEART DISEASES

Pathogens present in the periodontal pockets are frequently present in the systemic circulation, which may get localized to anatomically defective sites of the cardiovascular system. A study analyzed the thrombus tissues isolated from defective aortic valves, mitral valve, and aortic aneurysmal wall specimens and reported that *Streptococcus mutans* was the most abundant bacteria followed by *Actinobacillus actinomycetemcomitans* (37). Oliveira et al. reported the presence of oral bacteria in heart valves by PCR analysis, which showed the most abundant oral microorganism to be *Streptococcus mutans* followed by periodontal pathogens, such as *Prevotella intermedia* and *Porphyromonas gingivalis* (38). The isolation of these microorganisms from diseased or defective cardiac tissues not only proves their presence in congenital heart defects but also serves as bedrock for the initiation of infective endocarditis in subjects with preexisting CHDs.

Recently, it is shown that bacteremia not only leads to the seeding of periodontal pathogens in the diseased or defective cardiovascular tissues but also causes the engagement of these bacteria or their byproducts in the liver that triggers the activation of inflammatory mediators, which forms the basis of an indirect mechanism associating periodontal diseases to congenital cardiovascular diseases (39). Periodontal disease is also known to elevate the level of several systemic biomarkers that cause endothelial dysfunction and dyslipidemia, such as the C-reactive protein (CRP), low-density lipoprotein (LDL), TNF- α , IL-6, and IL-1 β (40). These findings were also recently supported by results from a study that elicited an elevation in the level of vascular inflammatory mediators after injecting rats with *P. gingivalis* LPS (41). Although CRP is a non-specific marker of inflammation, studies suggest that CRP is elevated in periodontal diseases, which further complicates the health status of the patient with CHD (42).

Conversely, in both saliva and gingival crevicular fluid samples, the levels of IL-1 β and PGE2 were considerably higher in patients with CHD compared with controls (43). Furthermore, greater levels of red complex bacterial counts were correlated with higher amounts of IL-1 β in gingival crevicular fluid (43). PGE2 and IL-1 β remained elevated in patients with CHD after correcting for gingivitis and plaque scores, indicating a systemic inflammatory component in both gingival crevicular fluid and saliva responsible for the maintenance of an inflammatory state in the periodontium of subjects with CHD (43). Hence, it can be understood that individuals with CHD have a greater systemic inflammation, which can be reflected in their oral fluids thereby linking periodontal and systemic inflammation (**Figure 1**).



SYSTEMIC EFFECT OF PERIODONTAL DISEASES AND BACTERIAL ENDOCARDITIS IN CONGENITAL CARDIAC DISEASE AND PERIODONTITIS PATIENTS

A typical tooth with periodontitis can nurture 10^7 – 10^8 bacteria in the subgingival pocket. Periodontal pockets are lined with ulcerated epithelium, which paves way for direct bacterial contact with both the subadjacent connective tissue and inflammatory infiltrate (44). Thus, high number of bacterial load, which are found to be associated with dental plaque and gingivitis, leads patients with cardiac disease into the risk of developing bacterial endocarditis (45). It is reasonable to infer that adult patients with CHD and poor oral hygiene are more likely to acquire periodontitis than healthy people. As a result, people with CHD who have periodontitis may be at an increased risk of infective endocarditis (46).

Periodontal pathogens cause bacteremia not only by directly invading the periodontal tissue, but also by paving a way for direct bacterial translocation when the epithelial integrity is lost within the periodontal pocket. This transient bacteremia is increased in patients with periodontal issues even while brushing the teeth or chewing the food, thereby explaining the cause for isolation of periodontal pathogens from samples obtained from the diseased cardiovascular tissues (47–50).

Several investigators have found periodontal pathogens, such as *P. gingivalis* and *A. actinomycetocomitans*, in the specimens of cardiovascular patients. *P. gingivalis* is found to play a role in aggregation of platelets, thereby playing a major role in homeostasis and thrombosis. Also, *P. gingivalis* is found to invade the aortic valve and endothelial cells *via* their fimbriae (51–53).

Patients with congenital cardiac disease are more susceptible to bacterial endocarditis due to poor oral hygiene, which is caused mainly by bacterial invasion and its consequences that alter the blood rheology. Since gingival and periodontal diseases

are the prime sources of bacterial invasion, understanding the association of poor oral health and preexisting CHD becomes indisputable. It is suggested that *streptococci* and *staphylococci* collectively account for 80% of the infective endocarditis cases (54). In some cases, even the diagnostic probing and subgingival scaling of periodontal pocket may cause soft-tissue damage accounting for 15–25% of transient bacteremia, which was evidenced by the findings of Hunter KM, which increases 1,000 times more after dental procedures (55). According to the American Association for Periodontology, 1 out of 4 infective endocarditis is caused by periodontal germs, such as *Eikenella corrodens*, a bacteria, which is highly relevant in juvenile periodontitis (56).

Most of the congenital anomalies pose an additional burden of the overall metabolism of the body, and the challenges that are faced by the patient often include fatigue, dyspnea on exertion, and arrhythmias in addition to the fatal risk of developing cyanosis and infective endocarditis. Children with congenital anomalies of the heart are mostly chronically sick, and expecting them to maintain good oral hygiene is not as easy as it can be expected from apparently healthy children. Such children visit hospitals on multiple occasions for checkups and treatments where in the emphasis on dental care is minimal, owing to the conduction of extensive cardiovascular therapies, thereby neglecting oral hygiene of such subjects. Hence, oral hygiene maintenance and enforcement become important in comprehensively managing such patients. Most children might also have undergone cardiac surgery prior to meeting a dentist in their life. Such children might be apprehensive or even anxious, and anxiety control becomes an important pillar based on which further dental treatment can be carried out in such children. However, the following steps must be taken to deliver optimal oral care to patients with CHDs:

1. Documenting a comprehensive medical and social history.
2. Specific inquest about the original defect, current medications, and previous treatment should be noted.

3. History regarding their oral care and dietary practices should be elicited.
4. After complete history and examination, an explicit diagnosis can be made and treatment plan can be formulated.
5. Collaboration with cardiologist or family medical practitioner is advised before providing active treatment. This can be procured in the form of letter.
6. It is important to provide preventive dentistry treatment, such as dietary advice, fluoride therapy, and oral hygiene maintenance, to all the patients with congenital cardiac disease.
7. Children should be advised to avoid vigorous brushing.
8. Appointments should be given in the morning with shorter duration, also with intervals of 2–4 weeks (25).
9. Before commencing dental procedure, children should be advised to rinse with 0.2% *Chlorhexidine* mouthwash.
10. Antibiotic prophylaxis should be given before dental procedures, such as extractions, dental prophylaxis, and surgeries, to place or remove orthodontic bands, local anesthesia injection, periodontal procedures, tooth replantation, and any bleeding procedure (57).
11. Pulp therapy should be carried out before extraction especially in primary dentition.
12. Stainless steel crown is often indicated to direct intracoronal restoration, especially for deciduous teeth. The reason to prefer stainless steel crown is it offers minimal technique sensitivity and often full coronal coverage (58, 59).
13. Chronic periodontitis without any signs or symptoms of infection should be monitored, and scaling and oral hygiene have to be provided.
14. Teeth with advanced periodontal disease need removal prior to surgery.
15. Extraction, periodontal, and other surgical treatment should be planned carefully due to the presence of preexisting coagulopathies.
16. Patients those who are warfarinized should undergo extraction with international normalized ratio (INR) up to 4. An INR should be obtained within 24 h of proposed surgery (25).

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17. Postoperative bleeding can be controlled by placing hemostatic gauze, sponges, and sutures (15, 60).

Patients with congenital cardiac disease need special care in dentistry as they are more susceptible to infective endocarditis due to periodontitis. It is mandatory that adults, who are having congenital cardiac diseases, need to be periodontally treated regularly, considering the abovementioned points to avoid unnecessary systemic risks of bacterial invasion.

CONCLUSION

These studies suggest that the presence of poor oral hygiene and increased chances of gingival inflammation in patients with congenital anomalies of the heart is merely casual or due to general weakness that prevents the patient from maintaining optimal oral hygiene, thereby emphasizing the importance of administering prophylactic antibiotics before dental procedures in order to prevent bacterial endocarditis. There exists an ambiguity in the preexisting data that explain the effect of altered immune responses in CHDs as studies have reported a decrease in the function of the B- and T-cell subsets, which may affect the periodontium. The altered immune-inflammatory mechanisms may bridge the lacunae in establishing the association between periodontal diseases and congenital cardiac diseases. However, long-term interventional studies are needed to understand the nature of association between both the diseases.

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RR generated the manuscript and the graphical image. PC assisted RR to correct the manuscript. DV assisted in proofreading the manuscript and correcting it along with collection of relevant data and articles. All authors contributed to the article and approved the submitted version.

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