Review Article

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Dentistry Section

Contemporary Consortium of Periodontal Diseases and Atherosclerotic Cardiovascular Diseases- A Narrative Review

ROSHAN R RUGHWANI[1], PRIYANKA K CHOLAN[2], DHAYANAND JOHN VICTOR[3]

ABSTRACT

Periodontal medicine unravels the relationship between periodontal health and disease with systemic health and disease. Periodontal disease serves as a niche for abundant quantity of microorganisms and their byproducts that disseminate into the blood stream. This systemic spread of endotoxins is directly related to the amount of periodontal destruction occurring at any given point of time and is responsible for bridging the link between inflammatory periodontal disease and various other systemic diseases. It is a well-known fact that periodontal diseases have been linked to various systemic diseases including osteoporosis, kidney diseases, adverse pregnancy outcomes, diabetes and even atherosclerotic cardiovascular diseases. Both periodontal diseases and atherosclerotic cardiovascular diseases share the same risk factors. Although both the diseases are multifactorial, the complex pathogenic mechanism orchestrating periodontal and atherosclerotic cardiovascular diseases share a considerate portion of the proinflammatory trait and several biochemical mediators play a role in the pathogenesis and inflammatory response in periodontitis caused by bacterial infections, linking chronic periodontitis to atherosclerotic cardiovascular disease. This review focuses on enlightening the plausible mechanisms that link periodontal and cardiovascular diseases and highlights the various other aspects of periodontal medicine that establishes a two-way relationship between periodontal diseases and atherosclerotic cardiovascular diseases. Understanding the nature of this association would ultimately aid clinicians to carefully plan treatment for patients and emphasise the importance of maintaining optimal oral hygiene in atherosclerotic patients in a more comprehensive and acceptable manner.

Keywords: Association, Bacteraemia, Bidirectional link, Inflammation, Immune modulation, Periodontitis, Hyperlipidaemia, Periodontal medicine

INTRODUCTION

Periodontal disease is a chronic inflammatory disease that is initiated by a dysbiotic microbiome in the gingival sulcus which activates the immune response through an array of host cell-based receptors that initiate intra and intercellular signalling, thereby further activating the host immune-inflammatory response [1]. It is the sixth most common disease affecting the general population and is characterised by surface proteins and endotoxins such as the Lipopolysaccharides (LPS), that instigate the production of various proinflammatory cytokines which get involved in tissue destruction through the release of other mediators such as Matrix-Metalloproteinases (MMPs), prostaglandins, leukotrienes, nitrogen and oxygen derived free radicals through a cascading series of events initiated by the dysbiotic microflora [2]. These events link periodontal disease to various systemic diseases including cardiovascular diseases, osteoporosis, kidney diseases, adverse pregnancy outcomes, and diabetes. Since, both periodontal diseases and atherosclerotic cardiovascular diseases share the same risk factors and are multifactorial in nature, the existence of common complex pathogenic mechanism orchestrating periodontal and cardiovascular diseases contribute to a considerate portion of the inflammatory component [3]. This narrative review focuses on indoctrinating the plausible mechanisms that link periodontal and atherosclerotic cardiovascular diseases and highlights the various other aspects of periodontal medicine that establishes a two-way relationship between periodontal diseases and atherosclerosis.

IMMUNO-INFLAMMATORY PATHWAYS IN PERIODONTITIS

The usual symbiotic interaction between the host and the pathogen is dysregulated in periodontitis due to the abundance of pathogens in the biofilm and their virulence factors, which causes an exaggeration in the host immune response. This dysbiotic microflora's creation of a dangerous microenvironment causes an immunological reaction that is particularly prominent where the biofilm is located, which causes exponential damage to the periodontal tissues and is the primary trigger for the transformation of gingivitis into periodontitis [4]. A wide range of chemical mediators, including interleukins and prostaglandins, are produced when phagocytes like neutrophils and macrophages transmigrate to the site of bacterial insult. These mediators not only help to maintain local inflammation but also help to signal inflammatory cells to move closer to the site of periodontal destruction. These phagocytic cells have Toll-like Receptors (TLRs) on their surface that are capable of recognising Pathogen-associated Molecular Patterns (PAMPs). This triggers a series of events through the MyD88-dependent pathway that causes the production of Nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), which regulates the release of proinflammatory cytokines like Interleukin 1 (IL-1), Tumour Necrosis Factor (TNF) and Interleukin 6 (IL-6) [5].

First, phagocytes like neutrophils and macrophages transmigrate to the site of the bacterial insult, where they release a variety of chemical mediators like interleukins and prostaglandins that not only help to maintain the localised inflammatory response but also help signal inflammatory cells to move closer to the site of periodontal damage. These phagocytic cells have TLRs on their surfaces that are trained to detect PAMPs, or pathogen-associated molecular patterns. This triggers a series of events through the MyD88-dependent pathway that renders the production of NF-κB, which regulates the release of proinflammatory cytokines.

IMMUNE-INFLAMMATORY MECHANISMS EXACERBATING THE HYPERLIPIDAEMIC STATE IN ATHEROSCLEROTIC CARDIOVASCULAR DISEASE

Atherosclerotic cardiovascular disease is a lipid storage disorder that is characterised by the deposition of lipid-rich substances in the subendothelial connective tissue of vasculature that supplies

the heart, brain and other peripheral organs. It is the underlying cause of almost 50% of the mortality in the western world, and is characterised by focal thickening of the vasculature in response to an immune reaction that internalises the circulating lipids by a complex mechanism that activates the vascular endothelium and the vascular smooth muscle cells [6,7]. Although the aetio-pathogenesis of atherosclerosis is not clear, studies show that the major risk factors for atherosclerosis are obesity, diabetes, smoking and hyperlipidaemia.

Hyperlipidaemia, is the most important and validated risk factor for atherosclerosis, that is characterised by lipid accumulation in the vascular sub-endothelial spaces, which triggers an inflammatory response. Low Density Lipoprotein (LDL) also get trapped in the sub-endothelial layers of the artery by the binding of proteoglycans in the subendothelial connective tissue and the apoB present in the LDL [8]. These accumulated LDL molecules spontaneously undergo oxidation when it comes in contact with the ROS, generated by the macrophages and the endothelial cells which act as a ligand for the TLR2 surface receptor of the macrophages thereby directly triggering the proinflammatory signalling pathways [9]. This further enhances the activity of the inflammatory cells which is directly related to the coronary plaque accumulation consisting of a central lipid core surrounded by a layer of lipid laden macrophages (foam cells) and a collagenous cap encasing it. There is moderate strength of association between periodontitis and Atherosclerotic Cardiovascular Diseases (ACVD) as reported by many studies that have used to evaluate different surrogate measures such as endothelial function and C-Reactive Protein (CRP) levels [10]. The elevated levels of inflammatory cytokines are present during both periodontitis and cardiovascular disease, and several biologically plausible mechanisms have been demonstrated in previous studies which are in coherence with numerous animal and human studies thereby proving that an association exists between periodontal disease and cardiovascular disease [11].

PERIODONTITIS AND ATHEROSCLEROSIS- THE CONNECTING LINK

It is fascinating to know that several possible direct and indirect mechanisms may operate independently or synchronously to explain the association between periodontal diseases and atherosclerotic cardiovascular diseases [12].

Direct Mechanism

Direct bacterial Invasion: This mechanism involves the direct invasion of the periodontal microorganism into the endothelial cells. Pathogens present in the periodontal pockets are frequently present in the systemic circulation which may get localised to atherosclerotic lesions [13]. Marcelino SL et al., showed the presence of common periodontal pathogens like *Prevotella intermedia, Porphyromonas gingivalis, Aggregatibacter actinomycetemcomitans* and *Tannerella forsythus* by real time Polymerase Chain Reaction (PCR) method in atherosclerotic plaque samples of patients having periodontal disease [14]. Another study also suggests that atherosclerotic lesions harbour periodontal pathogens which enter the blood stream directly to reach the atheromatous tissues [15].

Streptococcus sanguis, a commensal of the oral cavity, is the most frequently isolated organism in dental plaque including sub gingival sites. While not considered to be a periodontal pathogen, this organism enters the circulation by contact with chronically inflamed and ulcerated periodontal tissues. In severe periodontitis the complex bacterial plaque can be exposed to wounded gingiva with a surface area of up to 50 cm^2. Surface fibrils expressed by certain strains of S.sanguis cause human platelets in plasma to agglutinate in-vitro. These fibril proteins have been directly implicated in the development of thrombi and the growth of experimental endocarditis in-vivo [16].

Porphyromonas gingivalis demonstrates the aggregate (Agg+) phenotype and a PAAP cross-reactive antigen, in addition to *S. sanguis*. Herzberg MC and Weyer MW, reported that *Porphyromonas gingivalis* possess properties similar to that of *Streptococcus sanguis*. If the Agg+ phenotype is thrombogenic, one could speculate that *P. gingivalis* as a putative periodontal pathogen may contribute to both the chronic lipopolysaccaride mediated and Agg+ mediated pathways to atherosclerosis and thrombosis [17]. Also *Fusobacterium nucleatum* and *T. forsythia* may work together to help *P. gingivalis* invade endothelial cells [18,19]. It was further reported that Matrix Metalloproteinase-2 (MMP-2) expression in the interstitial tissues increased significantly due to *Aggregatibacter actinomycetemcomitans* infection [20]. Thus periodontal pathogens are present in atherosclerotic plaques and may play a role in the development and progression of atherosclerosis leading to coronary artery disease and other clinical sequalae [21].

Indirect bacterial spread: In addition to this direct spread, pathogens may also invade the phagocytic cells and the ability of them to survive within the phagocytes (Trojan Horse approach) may allow them to reach anatomically distant sites. Another mechanism by which a dormant *Porphyromonas gingivalis* of the periodontium may reach distant sites, is by modulating the cellular machinery wherein they multiply within the epithelial cells and later gain access to the vasculo-endothelial system [21]. Once internalised, the periodontal pathogens causes the endothelium to dysfunction which could be seen as a potential association between reduced salivary nitric oxide level and endothelial dysfunction in periodontitis patients [22].

Monocyte-response to bacterial challenge - the ultimate regulator of periodontal disease expression: The important proinflammatory mediators - Prostaglandin E2 (PGE2), IL-1β, and TNFα -are secreted by the monocyte within the periodontium in response to the bacterial LPS from periodontal infections. By causing vasodilatation, increasing vasopermeability, inflammatory cell recruitment, connective tissue degradation, and alveolar bone disintegration, these mediators in turn have detrimental effects on the periodontium. Normal M2 anti-inflammatory phenotype people often exude less of these mediators in response to LPS in culture against M1 proinflammatory phenotype individuals [23].

Both atheroma development and periodontal disease are significantly aided by cells of the monocytic lineage and the accompanying cytokines. A systemic hyper inflammatory monocyte phenotype, which secretes abnormally high quantities of inflammatory cytokines, is seen in many individuals with severe types of periodontal disease and insulin dependent diabetes mellitus. This suggests that the underlying M1 phenotype may put a patient at risk for developing atherosclerosis and emboli [24].

These mechanisms depict that periodontal disease increases the systemic inflammatory burden and that the oral pathobionts, which are commonly found in circulation and in atherosclerotic tissues, are efficient enough to promote inflammation.

Indirect Mechanism

Role of LPS and bacterial byproducts: Recent research has demonstrated that bacteraemia not only causes the engagement of periodontal pathogens or their byproducts (lipopolysaccharide) in the liver, which activates systemic inflammatory mediators, but also direct seeding of periodontal pathogens in atheromas, providing a second mechanism by which periodontal diseases may promote atherosclerotic cardiovascular diseases. Lipopolysaccharides are released as extracellular blebs from microorganisms within the periodontal pocket and may enter the diseased periodontium. Intravascular infusion of LPS induces platelet adhesion and aggregation by the release IL-1β, TNF-α, and Thromboxane B2 (TxB2) which increases the expression of endothelial adhesion molecules, and encourages the growth of cholesterol-rich foam cells and intimal cholesterol deposition [25].

Kuramitsu HK et al., showed that the outer membrane vesicles of *P. gingivalis* was able to induce foam cell formation in a model system using human umbilical vein endothelial cells and the murine macrophage cell line J774 A1 [26]. This property appeared to be mediated by the Lipopolysaccharide (LPS) fraction of the cells. The ability of *P. gingivalis* to interact with endothelial cells which triggers the synthesis of Monocyte Chemo-attractant Protein-1 has been suggested [27]. This enhanced the recruitment of circulating monocytes to these sites.

Since, the rupture of the fibrous cap of plaque appears to be a key role in acute coronary syndrome, *P. gingivalis* 381 was found to disintegrate fibrous caps isolated from autopsy samples. Furthermore, strain 381 substantially enhanced MMP-9 protease activity, which has been linked to plaque rupture. These literature findings elicit that *P. gingivalis* exhibits several properties, which may play a role in foam cell formation and rupture of atherosclerotic plaque. Thus LPS as a systemic trigger can activate an impressive cascade of inflammatory cytokines, which are capable of eliciting most of the vascular, and coagulation complications associated with atherosclerosis.

Role of fibrinogen and white blood cell: In the literature it has been consistently reported that the presence of periodontal disease leads to an increased fibrinogen level and White Blood Cell (WBC) count thereby having direct impact on the blood rheology by increasing its viscosity [28].

Increased likelihood of thrombus formation may be seen as a consequence of increased blood viscosity that may encourage atherogenesis and thrombogenesis. The most significant contributor to the promotion of hypercoagulable condition is likely fibrinogen. Increased amounts cause blood viscosity since it is the precursor of fibrin, a crucial factor in platelet aggregation [29].

Elevated white blood cell count is also a predictor of heart disease and stroke and circulating leucocytes may promote occlusion of blood vessels and several authors have enlisted increased WBC as a risk factor for development of ACVD [30].

Role of C-reactive protein: C-reactive protein levels that are moderately high have been linked to an increased risk of myocardial infarction, stroke, and symptoms of peripheral artery disease in the future. It is shown to enhance LDL aggregation and production of Vascular Cell Adhesion Molecule-1 (VCAM-1) in endothelial cells [31]. Macrophages readily take up LDL bound to immobilised CRP aggregates and this uptake induces the expression of adipophillin, a specific marker of cholesterol-laden macrophages [32].

For CRP to be involved in the formation of foam cells it is necessary that this protein aggregates and binds to LDL molecules. Such aggregation occurs by a calcium dependent process. Despite the fact that CRP is a general indicator of inflammation, studies show that it is high in periodontal disease, which accelerates the development of atherosclerosis by binding to LDL and forming unstable plaque [33].

Role of other systemic inflammatory mediators: Periodontitis is known to emanate systemic biomarkers such as the CRP, LDL, TNFα, IL6 and IL1β that cause endothelial dysfunction and dyslipidaemia [34].

It has been well-recognised that inflammation induces marked changes in lipid metabolism which can be conveniently associated to the raised levels of an array of systemic inflammatory markers, predominantly CRP, IL1β, TNFα, and IL6. [Table/Fig-1] [27,35-43].

Role of heat-shock proteins: Recently is has been suggested that antibodies expressed by patients with periodontitis could also promote atheroma formation through the mechanism of 'molecular mimicry'. In patients with atherosclerosis compared to healthy controls, antibody levels to *Porphyromonas gingivalis* HSP60s were found to be higher, which suggested that Heat Shock Protein 60 was one such molecule that may be involved in the pathogenesis of both atherosclerosis and chronic periodontitis [44]. HSPs may have a significant pathogenic role in subgingival plaque as Chung SW et al., demonstrated elevated humoral immune response to HSP-60 family in periodontitis patients [45]. Antibodies against *P. gingivalis, Fusobacterium nucleatum* and human HSP were found in the sera and inflamed gingival tissues of periodontitis patients [46]. Further, HSP-60 in *Actinobacillus actinomycetemcomitans* is a potent bone-resorbing mediator. High levels of HSP-60 are stimulated by persistent oral infections in those at cardiovascular risk. There is a chance of an autoimmune reaction on the surface of the vessel if antibodies made against bacterial HSP interact with HSPs generated in the host tissue, particularly if they are located in the lining of blood vessels. In the presence of a risk factor, this might start a chain of host reactions that could lead to the development of atheromatous lesions [47].

Inflammatory and periodontitis biomarker	Association with ACVD	Relevant studies
IL6	Elevated in Chronic periodontitis and ACVD, causes greater thrombogenecity, role in expression of CRP and VEGF. Causes platelet activation, thrombus formation and vascular remodelling.	Al-Taweel FBH et al., [35]
IL18,IL4	Decreased in chronic periodontitis, anti-inflammatory in nature and causes progression of ACVD if levels are decreased.	Buhlin K et al., [36]
Matrix Metalloproteinase 9	High level in periodontitis and associated with increased carotid intimamedia thickness.	Söder PO et al., [37]
Serum amyloid A, Alpha 1 anti-chymotrypsin	Increased in patients with periodontitis and ACVD	Glurich I et al., [38]
VW Factor	Shows statistically significant association with clinical periodontal parameters in patients having both ACVD and chronic periodontitis.	Montebugnoli L et al., [39]
Plasminogen activator inhibitor-1	Increased in chronic periodontitis	Bizzarro S et al., [40]
Proprotein Convertase Subtilisin/Kexin Type 9	Elevated in periodontitis and ACVD patients. Released locally by inflammatory cells and has a direct role in elevating serum LDL levels.	Tabeta K et al., [41]
Malondialdehyde	Elevated in periodontitis and ACVD parients, Malondialdehyde has an inhibitory effect on NO levels.	Isola G et al., [42]
IL-1β	Elevated in periodontitis and hyperlipidemic patients, levels decrease after performing SRP.	Cutler CW et al., [43]
Monocyte Chemo-attractant Protein	Elevated in periodontitis patients, stimulated by *P. gingivalis* and causes initiation of atherosclerosis.	Kang IC and Kuramitsu HK, [27]

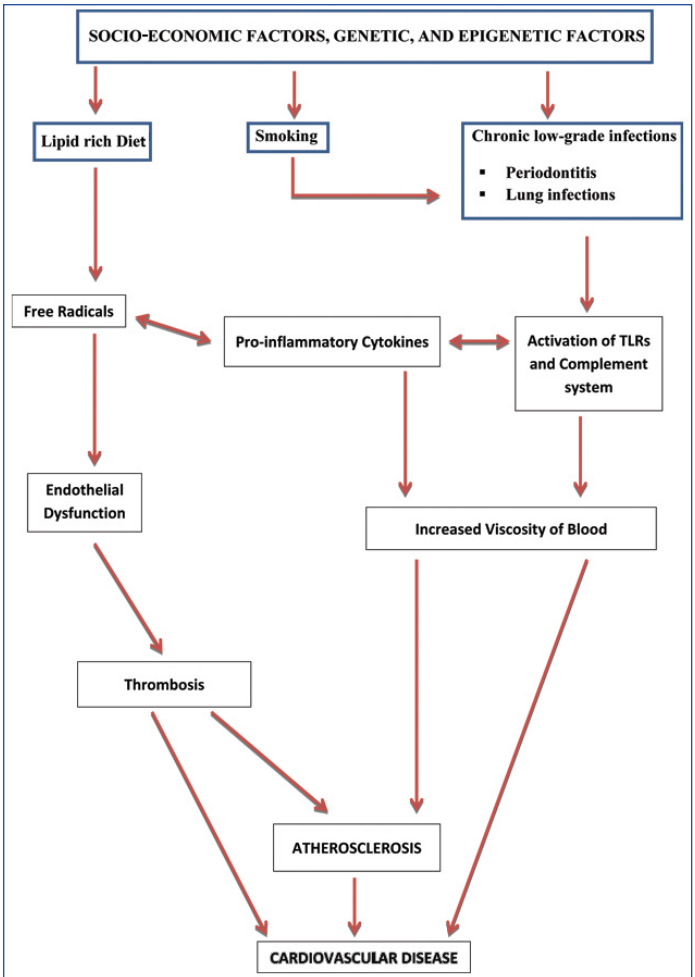
[Table/Fig-1]: Clinical studies showing increased systemic inflammatory mediators of inflammation that act as linking biomarkers for periodontitis and ACVD [27,35-43].

Hence, it can be suggested that inspite of the presence of various confounding variables, periodontal disease is an independent risk factor which increases the likelihood for the initiation and progression of ACVD [3].

ASSOCIATION BETWEEN ACVD AND PERIODONTITIS-CASUAL OR CAUSAL?

Elevated levels of inflammatory cytokines are present during both periodontitis and ACVD, and the aforementioned plausible mechanisms that have also been reported in previous studies are in coherence with previous animal and human data which explain the association of both the multifactorial diseases [Table/Fig-2] [4,5,8,11].

As evidence persisted indicating periodontitis was a significant risk factor for cardiovascular pathology in susceptible individuals, the term Periodontitis-Atherosclerosis Syndrome (PAS) was introduced as a diagnostic terminology to represent persons with both periodontal disease and ACVD [48].



[Table/Fig-2]: Flowchart showing the role of periodontal Inflammation in orchestrating atherosclerotic cardiovascular disease [4,5,8,11].

Various controlled trials and reviews have established periodontal disease to be an independent risk factor for development of ACVD. The literature has been surrounded with many studies examining the strength of the link between periodontitis and cardiovascular diseases and its biological plausibility ever since Mattile KJ, initially reported on the association between Cardiovascular Disease (CVD) and oral infections in 1989 [49]. Since then, ACVD and periodontal disease have been linked in several epidemiological studies. Sanz M et al., reported that the higher prevalence of subclinical atherosclerosis was associated with increased periodontal probing depth and clinical attachment loss [50]. Nordendahl E et al., reported an increased risk for MI in female periodontitis subjects aged below 65 years by reporting an odds ratio of 3.72 while correlating the probing depth, bleeding on probing and alveolar bone loss to the first MI [51]. Górski B et al., also reported an odds ratio of 2.4 while correlating the similar periodontal parameters to the incidence of MI [52]. Dietrich T et al., reported a hazard ratio of 2.12 while correlating the probing depth and alveolar bone loss to the risk of developing fatal cardiovascular events [53]. A recent meta-analysis has reported that decreased number of teeth confers to a greater risk of development of ACVD and mortality, while, other meta-analyses have consistently concluded that the available evidence indicates that periodontal diseases confer a moderate risk for atherosclerosis and its consequences [54,55].

These evidences show that there is a bidirectional association between two common inflammatory conditions- periodontitis and ACVD, where in the common denominator between the diseases is bacteraemia and the inflammatory trait and that periodontitis poses a moderate risk of development of ACVD.

Does Periodontal Treatment Reduce the Risk of Initiation and Progression of ACVD?

Periodontal therapy consists of mechanical debridement of root surfaces and elimination of biofilm. Patients treated by non surgical periodontal therapy displayed a significant increase in plasma TNFα, CRP, and IL-6 levels immediately after intervention measured by Enzyme Linked Immunosorbent Assay (ELISA), which suggests a systemic acute phase response, possibly caused by massive bacterial inoculation in conjunction with the instrumentation of periodontal tissue [56].

A systemic review of six treatment studies investigating the effects of non surgical periodontal therapy or serum CRP levels concluded that there is modest evidence of a treatment-induced reduction in CRP [57]. A recent systematic review by Teeuw WJ et al., also suggested that non-surgical periodontal therapy reduced the risk of ACVD by decreasing the levels of proinflammatory and thrombotic markers showing a significant Weighted Mean Difference (WMD) for CRP, IL-6, TNF-α, fibrinogen, total cholesterol and High-Density Lipoprotein (HDL) Cholesterol favouring periodontal treatment [58].

Several studies and randomised clinical trials have reported improvement of endothelial function and associated markers of inflammation among subjects with periodontitis who have undergone non surgical periodontal therapy with or without systemic antibiotic [59,60]. A landmark study by Bokhari SAH et al., suggested that non surgical periodontal therapy was successful in reducing the levels of CRP, fibrinogen and WBCs in cardiac patients [33].

The effect of surgical periodontal therapy on the improvement of cardiovascular risk markers were reported by Gupta B et al., where in, a decrease in the CRP level three months after completion of surgical periodontal therapy [61]. While, Moeintaghavi A et al., reported a decrease in all lipid profile parameters excepting HDL after three months of completion of surgical periodontal therapy [62].

Evidences related to the adjunctive use of antibiotics in addition to non surgical periodontal therapy also claim them to be beneficial as Jockel-Schneider Y et al., [63] who reported a greater decrease in the pulse-wave velocity at the end of 12 months in a group of subjects who were given amoxicillin (500 mg) and metronidazole (400 mg) as an adjunct to non surgical periodontal therapy. Montero E et al., reported a greater decrease in CRP and fibrinogen level after completion of non surgical periodontal therapy and adjunctive antibiotic treatment [60].

With these data it can be suggested that periodontal therapy not only reduces the levels of inflammatory markers for a short duration of time, but it also has long-term effects on the levels of these systemic inflammatory markers.

CONCLUSION(S)

Although periodontitis is an independent risk factor of ACVD, it still remains a complicated task to diagnose and treat an ACVD patient periodontally and to map its routes to poor periodontal health. Thereby, emphasising the significance of comprehending the reciprocal relationship between periodontitis and ACVD. Further, concept of minimising deleterious effects of periodontal disease on the progression of ACVD also represents an unprecedented challenge to the dental fraternity. Time is not far away when periodontists will work in unison with cardiovascular physicians and surgeons in crucial decision making and deliver optimal dental and medical treatment to patients ailing with cardiac diseases in a comprehensive and a sophisticated manner.

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PARTICULARS OF CONTRIBUTORS:
1. Postgraduate, Department of Periodontics, SRM Dental College, Ramapuram, Chennai, Tamil Nadu, India.
2. Associate Professor, Department of Periodontics, SRM Dental College, Ramapuram, Chennai, Tamil Nadu, India.
3. Professor and Head, Department of Periodontics, SRM Dental College, Ramapuram, Chennai, Tamil Nadu, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Roshan R Rughwani,
2F, Poonam Apartments, No-66 Old No.- 80, MG Road, Nungambakkam,
Chennai, Tamil Nadu, India.
E-mail: roshanrughwani@gmail.com

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