Brush Up Your Teeth to Brush Up Your Heart: A Clinical Review on the Association of Oral Hygiene with Cardiovascular Diseases

Hayder Abdul-Amir Makki Al-Hindy
College of Pharmacy,
University of Babylon, Babylon, Iraq

Ghazi Mohamad Ramadan
Ahlulbayt University College,
Karbala, Iraq.

Mohammed Ihsan Chabuk
Ph.D., Department of dentistry,
Al-Safwa University College, Iraq.

Amal Talib Al Sa'ady
Prof. (Microbiology), College of Pharmacy,
University of Babylon, Babylon, Iraq.

Safa Jihad, Suhad Hafidh
College of Pharmacy,
University of Babylon, Babylon, Iraq.

Abstract:- Several pieces of the research described a cross-talk between oral hygiene and CVDs. Oral hygiene was linked with CVDs, and the relations between the two issues are signified by oral bacterial colonies and their by-products released into the bloodstream, initiating endothelial dysfunction in addition to presenting proatherogenic influences, inflammatory as well as immune responses. These mechanisms elucidate the described relations of PD with strok, coronary artery diseases, and peripheral vascular diseases. Dental caries and PD were also linked with diabetes mellitus (DM) and dyslipidemia. Several experimental trials did not affirm the relationship between oral hygiene and CVDs. Dental loss, the most significant equal of PD, has been also related to CVD. Carious teeth were also described as a risk factor for arteriosclerosis independently, where as dental restorations were associated with the arteriosclerotic burden inversely. Improving cognizance of perfect dental health can heighten cardiovascular health.

The existing article aims to have a review on the vital biological pathways associated with oral and CVDs, the important path physiologies which might be related, and potentials for interventional therapeutic measures.

Keywords:- Oral hygiene, oral health, cardiovascular diseases, ischemic heart diseases, atherosclerosis, arteriosclerosis, periodontitis, periodontal diseases, dental loss, dental caries, inflammation.

I. INTRODUCTION

Universally, the main causes of mortality are cardiovascular disorders (CVD) [1-4]. The conventional risk factors for CVD are well recognized, but they possibly account simply for 50- 70% of arteriosclerotic events. Although arteriosclerosis is the most common substrate for CVD, several risk factors include dyslipidemia, DM, genetic, obesity, hypertension, smoking, stress, inflammations, and others [5, 6]. CVD constitutes a spectrum of disorders affecting the heart and circulation. Arteriosclerosis is a commonly shared pathology from which several other vascular modalities originate, like ischemic cardiac disease, cerebro vascular disease as well as peripheral vascular diseases. Failure of early diagnosis and management can dispose of possibly lethal events [7].

Several lines of evidence give reason to believe that an oral pathology could be one of the putative candidate risk factors for CVD [8, 9]. Oral disorder, the most prevalent chronic illness, is an essential public medical issue regarding its prevalence, its influence on wellbeing and life quality, as well as therapy expenditures[10].In the last decades, shreds of evidence have accumulated that correlates oral health to CVD through inflammatory or immune mechanisms [11]. Periodontal medicine was invented to define the potential several systemic effects induced by periodontitis on other body systems away from the mouth [12]. The interrogation consequently a rose, do oral inflammations have impacts on other human systems? The preliminary acceptance of the idea brings about the extensive practice of annoying unjustified tooth extractions[13]. Up till now, different antibiotics are still suggested, in predisposed cardiac subjects, for prophylaxis of infective endocarditis. Such trend lends appreciation to the "focus of infection" concept of old.

Dental caries and periodont it is are the two most mutual forms of oral diseases distressing the majority of people, with an incidence rate that may reach 90% together[14-16]. There are plentiful studies that link dental pathologies to IHD [8, 17]. The hallmark of periodontitis involves inflammation of the dental supportive attachment, besides loss of alveolar bone, of periodontitis, which could have been associated with loss of gingival attachment[18]. Periodontitis is a long-lasting inflammation caused by odontopathogenic bacteria, superadded by susceptible host immune response that has an essential contribution in its pathogenicity [19]. Both hard and soft depositions on the tooth on supra gingival and sub gingival are as may subsidize the destructive process. dental mobility or migration may issue in advanced cases of periodontitis[14].

The present global incidence of periodontal disease (PD) is not well distinct but the severe type is ranged from 5-15% among the population of the developed world. Owing to the marked variable research designs, the incidence rates from various countries are hard to compare. Moreover, no standardized tools of PD extent were performed[18].

This review considers the contemporary evidence for the association of oral hygiene with CVD.

II. PERIODONTAL DISEASES

The mouth habitat hundreds of microbes that colonize dental exteriors, and dental plaque is covered by certain bio film, which acclimates to the environmental micro flora variations[20]. Gingival inflammation progresses when the plaque spreads to the nearby gingiva, initiating host immunity and inflammatory response. Gingivitis could evolve to PD once microbial inflammation migrates apically alongside the root exterior and invade the dental supportive structures, plus the alveolar bony tissue. As well, chronic PD can induce permanent loss of connective tissue fibers near the alveolar bone, tooth resorption, and eventual dental loss. Several predisposing risk factors had detected for periodontitis include tobacco smoke, genetic, defective oral health, DM, psychosocial stresses, bad teeth, immunological dysfunction, imperfect fillings, interventions causing dry mouth, unfit bridges, and female physiological changes (pregnancy and oral contraceptives)[21]. Dysbiosis is a discrepancy of the micro flora of the oral cavity that may generate bacteremia in addition to systemic spreading of oral micro biota [20]. Consequently, periodontitis by triggering bacteremia can result in intense local and systemic inflammation and immune reactions[9, 22].Notably, the risk factors for PD are the same as the CVD thereby confusing the association between PD and arteriosclerosis [9, 11, 23]. Several clinical, experimental cohorts confirmed a positive link between PD and CVD, perhaps due to endothelial dysfunction, and atherosclerotic vascular diseases [2, 24].

III. BIOLOGICAL LINKAGE ASSOCIATING ORAL HEALTH WITH CVD

A. Bacteria, oral health, and CVD

Systematic analyses have delivered indications for periodontal infections as a latent mediator of atherosclerosis, either by direct bacterial translocation or via inflammatory/immune-mediated process[25]. The severity of bacteremia is influenced by the intensity of PD [24]. The mouth and dental pocket mutually present reservoirs of anaerobes and bacteria of gram-negative species, that are capable to invade the vascular tissue [26]. Several systemic biomarkers of inflammation have been correlated with bacteremia, which has been reported by many researchers directly after tooth brushing or extraction[27]. Odontopathogenic bacterial DNA has also been identified in thrombotic plaques of the aorta[28] and emboli from patients with acute coronary syndrome[29], signifying direct systemic influences of oral flora. Along the same channel, oral bacteria like *A. actinomycetemcomitans* and *P. gingivalis*, have also been reported as a cause of vascular endothelial dysfunction by the lipopolysaccharide-mediated process [30].

B. Inflammation, oral health, and CVD

Similar inflammatory biomarkers are intricate in arteriosclerosis and PD [31].PD is a good site of immunological mediators, like TNF-α,IL-1, and IL-6 [32]. Immunoglobulin's against *P. gingivalis* interact biologically with "heat shock proteins", which are expressed by vascular endothelium, subsidizing injurious vascular consequences [33]. Meanwhile, oral microbes and their injurious products may release into the blood and cause insulin resistance and systemic inflammatory response, which are involved in all atherogenic stages, explaining the periodonto-systemic link [34].

Additionally, *P. gingivalis* can infiltrate the aortic endothelium by its own"fimbriae, and fimbrillin peptides" causing expression of "monocyte chemotactic protein"and IL-8 [35]. This bacterium can proliferate inside the endothelium and trigger TLR2, and the release of inflammatory cytokines [24]. Vascular endothelium invaded by *P. gingivalis* highly expressing adhesion molecules that has a proatherogenic activity [35]. Bacteria or their noxious products may directly trigger vascular endothelium and several inflammatory cells inducing an inflammatory response and expressing metalloproteinase's [33]. Periodontal microbes can induce plaque rupture resulting from endothelial apoptosis and degeneration of the extracellular matrix [24].

Adhesins, proteases, and lectins are toxic products of periodontial flora, can regulate the dental bio film; also deteriorate the host immunity, by affecting interleukins; and allows clerotic plaque synthesis by activating vascular smooth muscle cells proliferation and platelets aggregation [36].

Finally, probiotics can be beneficial, by inhibiting dental decay and decreasing incidences of streptococcal throat infections, pocket depth, as well as plaque index [33]. Several benefits of probiotics have been also defined for CVD, like decreasing systemic blood pressure and lipidemic profile [37].

C. Oral interventions and outcomes of CVD

Oral interventions decreased the risk of CVD, systemic inflammatory response, lipidemic state, arterial pressure, vascular endothelial dysfunction, which possibly will inhibit thromboembolic events and recurring attacks of arrhythmias [38, 39]. Dental scaling more than twice/year was related to a reduced risk of a trial arrhythmias, by its protecting influence on PD [40]. Oral interventions do not always improve cardiovascular outcomes even with the link between PD and CVD [41].

D. Biological linkage associating oral health with risk factors of CVD

Oral hygiene is linked with numerous CVD risk factors, specially arterial hypertension, tobacco smoke, DM, and lipidemic disorders [31]. Cigarette smoking is identified to influence the blood supply of periodontium, immune response, fibroblast functions, and body tissue healing, and also causing vascular endothelial dysfunction [32]. Several CVDs were related to PD, including stroke, coronary artery diseases, peripheral vascular diseases, cardiac arrhythmias, and aortic aneurysm [26].

E. Oral health and abdominal aortic aneurysm

Abdominal aorta aneurysm has been associated with oral health[26]. Periodontal micro flora and their byproducts may be intricate in local and systemic patho physiology related to the progress and development of aortic aneurysms,

signifying an infective model of aneurysmal pathogenesis [42]. As mentioned previously, a trans located oral micro biota from the gingival to the circulation and then to the wall of the aorta, which might subsidize to the weekend aortic wall or secondary colonization of aneurysm [43]. Suzuki et al. described more severe bleeding on probing and deeper gingival pocket in aortic aneurysm patients compared to non-aneurysmal patients [44].

F. Oral health and peripheral artery diseases

Atherosclerosis may disturb the gums also and impair local blood vessels flow and this might elucidate the link of CVD or peripheral vascular diseases with PD [41]. Poor oral health and elevated biomarkers of inflammation were reported in patients with peripheral arterial disease. A shared inflammatory mechanism in subjects with both PD and peripheral vascular diseases was reported earlier [45].

G. Oral health and myocardial diseases

Oral health was connected with cardiac hypertrophy too[46]. Remodeling of the ventricles and myocardial hypertrophy after myocardial ischemia were intensified by *A. actinomycetemcomitans*[47]. Oral microbes upsurge the level of matrix metalloproteinase's, which destroy the gingival extracellular matrix. Metalloproteinase's are also secreted and are causing myocardial inflammatory response, myocardial hypertrophy, perivascular and interstitial myocardial fibrotic changes, triggering systolic/diastolic dysfunction [46].

H. Periodontitis and cardiac arrhythmias

Cardiac arrhythmia revealed significant associations in some recent studies with PD. Study In a study comprising 227 patients with atrial fibrillation, PD was an independent predictor of arrhythmic events[38]. This link is partially described by the inflammation of atriomyocytes producing hypertrophy, oxidative stress, and injured myocardium prompted by antibodies synthesized as an immune response to *P. gingivalis* and *P. intermedia* bacteria [48]. It was reported that control of PD may amend inflammation and may inhibit arrhythmia recurrence [38]. Chen et al. failed to repeat the relationship between periodontitis and atrial arrhythmia (flutter or fibrillation) in hyper thyroid subjects, an illness closely related to arrhythmias [40]. Other cardiac arrhythmias, like atrial and ventricular tachycardia or premature beats, were also more prevalent in patients with PD [38]. Tachyarrhythmia progress may be influenced by PD. Specifically, *P.intermedia* plus *P. gingivalis* were identified from the salivaoftachyar rhythmic subjects as well as both bacteria may contribute to ventricular remodeling also [49].

I. Periodontitis and lipidemic profile

The association between PD and lipid metabolism has been evaluated by quite a few scholars. PD was significantly linked with high LDL and triglyceride and low HDL concentrations in a meta-analysis included19 studies, conducted among patients with chronic PD [50]. The relation between PD and lower HDL might enhance periodontal inflammation. Specific bacteria may as well, elevatelevels of VLDL and LDL and prompt apoprotein-B100 proteolysis, explaining the influential effects of lipoproteins in relating PD with arteriosclerosis [36].Lipoprotein lipase action may be inhibited by TNF-α, which may increase triglycerides [51].However, the relation between dyslipidemia and PD was not established by all studies[52, 53].

J. Periodontitis, inflammation, and dyslipidemia

A bi-directional link of PD with dyslipidemia was proposed also. Dyslipidemia rises the vulnerability for PD owing to the concomitant inflammatory response, and at the same time, Periodontal inflammatory response constrains lipids metabolism[36].**"Pro-protein convertase subtilisin/Kexin-9 (PCSK9)"**regulates plasma LDL cholesterol levels critically, and appears to be upregulated in patients with PD with *P. gingivalis* immunoglobulins [54]. According to a study Japanese including 108 males, the serum levels of PCSK9 correlated with oral parameters [55].

K. Oral hygiene and arterial hypertension

Periodontitis was linked with poorly controlled hypertension, mainly in elders; while a good oral health status can improve systolic blood pressure during an antihypertensive course [56]. An elevated systolic pressure. has also been related to the severity of PD. Based on research comprising 3352 cases with a history of arterial hypertension and myocardial infarction, the number of the remaining teeth and dental pockets were significantly linked to hypertension [57]. Reduced inflammatory biomarkers and systolic pressure and better lipidemic states and risk of CVD in cases of severe PD, in a prospective clinical trial[39].

L. Periodontal diseases and diabetes

The reciprocal association between DM and PD was detected by several biochemical and clinical studies. DM results in vascular changes of periodontium caused by macro- and micro-angiopathy and bone loss due to several postulated mechanisms including protein glycation, upturns collagenase action, impaired functions polymorph nuclear leukocytes, and immune response. Other potential explanations can be attributed to the following facts: PD is a good body source for immune mediators into the circulation and high insulin resistance. Shared pathological mechanisms and genetic components had been described for DM and periodontitis, [32].

M. Association of periodontitis with aging

Age is an unmodifiable risk factor for CVD, and the populace of oral flora increases with age [58]. Several researchers described a greater arterial stiffness in patients with POD. A higher arterial stiffness specifies reduced vascular wall elasticity, and hence arteriosclerosis, which is a predictor of coronary vascular events [59].

N. Association of dental loss and CVD

Dental caries among adults is the most significant reason for the dental loss, while in subjects more than 40years,PD is the more common cause. In subjects with PD, chronic inflammation is accountable for alveolar bone resorption, and dental loss[8, 16, 17]. The dental loss reflects poor oral hygiene, which intern affects dietary consumption and nutrient selections result in decreased ingestion of vegetables and nutritional fibers. A healthy food, enriched

with fruits, fibers, and vegetables, is a keystone of preventing CVD [60]. Dental loss is also linked with risk factors of CVD including aging, coronary artery disease, peripheral vascular disease, cardiac failure, stroke, and cardiovascular mortality [17, 41]. This linkage might be clarified by the presence of oral bacteria, specially *A. actinomycetemcomitans*, and *S. sanguis* which subsidize a systemic inflammatory response accompanied by increased concentrations of plasma C-reactive protein[3-5, 9], vascular endothelial dysfunction, arteriosclerosis evolution, and instability of thrombotic plaque [61].

O. Carious teeth and endodontic lesions

PD of the chronic dental apex and carious teeth are varied steps for a similar inflammation, and this local infective model has gained concern[31, 51].Bacteria like *S. mutans*, generally related to tooth caries and recognized in the sclerotic plaques, signifying a pro-atherogenicity of carious teeth that may result in bacterial endocarditis[31]. For the dental flora to reach the myocardium or the distal capillaries, it takes <1 minute after any periodontal intervention[31]. The inflammatory injury round the dental apex (Apical PD), caused by bacteria of gram-negative species, may arouse systemic inflammation induced by inflammatory cytokines (IL-1β, IL-2, 6, 8, & 17, and TNF-α), matrix metalloproteinase, and reactive oxygen species, like chronic PD[31, 51]. The levels ofIL-1that existed in injuries of endodontic originareintricate in the evolution, progress, and destabilization of the atheromatous plaques. The pro-inflammatory IL-6 was linked with the acute coronary syndrome (unstable angina), left ventricle dysfunction, arterial hypertension, obesity, and DM and its sequels. Interleukin-8 is related to permanent pulp inflammation and osteolytic abscesses of the dental apex and with plaque synthesis and angiogenesis. TNF-α was linked to alveolar bone resorption, synthesis of Il-6, and smooth muscle cell proliferation, besides lipid metabolism. Interleukin-17 regulates MMPs, vascular endothelial damage, and cell apoptosis [51].

P. Periodontitis and vascular endothelial effects

Subjects with a severe form of periodontit is have revealed tempered"flow-mediated dilatation" of the brachial artery in comparison to controls [62]. Thorough periodontal therapy improves endothelial function and hence, improved the flow of the brachial artery [63]. In addition, PD can subsidize the synthesis of reactive O2speciesinside vascular walls, and treatment of PD lessens markers of oxidative stress[64]. Periodontal diseases might increase the proteoglycan number of the vascular intimal-matrix and trap the residual lipoproteins inside the vascular intima [65]. Finally, the inflammatory response of PD has been related to disparities in the production of body vasodilators (NO, PGE2), with alterations in arterial wall dispensability[66].

Q. Biomarkers linking oral pathologies and CVD

More than a few circulatory markers linked chronic PD to sclerotic CVD, through peripheral inflammation, immune response, and oxidative stress [38, 55]. The gingival index was linked with fibrinogen and WBCs in PD [67]. C-reactive protein is a well-recognized biomarker of low-grade inflammations, linked with periodontal inflammation and

lesions of endodontic source and a risk factor of coronary vascular events [8, 9, 38]. Raised cytokine levels were linked with a trial fibrillation in PD patients [38]. Brain natriuretic peptides, secreted from ventricular myocytes stimulated by volume and pressure overload, were also elevated in patients with PD [36]. A biomarker of ischemic myocardium and end product of oxidative stress,"ischemia-modified albumin"was found to be high in long-lasting PD compared with controls and declined once a conservative periodontal treatment was initiated [68]."Matrix metalloproteinase's", a biomarker of vulnerable plaque, and subclinical arteriosclerosis were also related to PD [46].

R. Future suggested works

Researches that inspect genetic predisposition and molecular pathways are desirable to expand our appreciation of the association between oral hygiene and CVDs. It would be remarkable to perform a prospective study follow up subjects with periodontal diseases and screen them for the progress of clinical CVDs, and on the contrary, screen those with clinical CVDs for the progress of periodontal diseases. As well, there is a necessity for high-standard records from several random clinical studies to assess whether oral hygiene subsidizes the evolution of CVD when the confounders are being adjusted.

IV. CONCLUSIONS

Despite the absence of causation, oral hygiene and CVD are inflammations sharing several mutual etiopathology and a collection of risk factors like biological, pro-inflammatory, and molecular biomarkers. Hence, it is crucial to identify the significance of oral hygiene, chronic oral inflammation in particular, for better cardiovascular wellbeing and better life quality, since the oral diseases are easily and early detected compared with CVD.

Dentists, physicians, and other medical staff should extend their knowledge, given these interactions between oral hygiene and CVDs. As well, biomarkers used for oral hygiene support screening of diseases of the cardiovascular base.

REFERENCES

[1.] Amir Al-Mumin, H.A.-A.M.A.-H., Mazin JM., Combined Assessments of Multi-panel Biomarkers for Diagnostic Performance in Coronary Artery Disease: Case-Control Analysis. Sys Rev Pharm, 2020. **11**(6): p. 7.

[2.] Amir Al-Mumin, H.A.-A.M.A.-H., Hyperuricemia has a Deleterious Role in Patients with Acute Coronary Syndrome Presented with Poor Oral Hygiene. International Journal of Pharmaceutical Research, 2020. **Jan-Jun**(1): p. 7.

[3.] Asseel K. Shaker, R.A.-S., Raad Jasim, Hayder Abdul-Amir Makki Al-Hindy, Biochemical Significance of Cystatin-C and High Sensitive CRP in Patients with Acute Coronary Syndrome; any Clinical Correlation with Diagnosis and Ejection Fraction. Sys Rev Pharm, 2020. **11**(3): p. 8.

[4.] Hajir Karim Abdul-Husseein, F.S.D., Ameera Jasim Al-Aaraji, Hayder Abdul-Amir Makki Al-Hindy,

Mazin Jaafar Mousa, Biochemical causal-effect of circulatory uric acid, and HSCRP and their diagnostic correlation in admitted patients with ischemic heart diseases. Journal of Cardiovascular Disease Research 2020. **11**(2): p. 25-31.

[5.] Hayder Abdul-Amir Maki Al-hindi, M.J.M., Thekra Abid Jaber Al-kashwan, Ahmed Sudan, Saja Ahmed Abdul-Razzaq, On Admission Levels of High Sensitive C- Reactive Protein as A Biomarker in Acute Myocardial Infarction: A Case-Control Study. Indian Journal of Public Health Research & Development 2019. **10**(4): p. 5.

[6.] Hayder Abdul-Amir Maki Al-Hindi, M.J.M., Thekra Abid Jaber Al-Kashwan, Ahmed Sudan, Saja Ahmed Abdul-Razzaq, Correlation of on Admission Levels of Serum Uric Acid with Acute Myocardial Infarction: Case: Control Study. Journal of Global Pharma Technology, 2019. **11**(7): p. 6.

[7.] Lockhart PB, B.A., Panos N. et al Periodontal disease, and atherosclerotic vascular disease: does the evidence support an independent association?: A scientific statement from the Ameri-can Heart Association. Circulation, 2012. **125**: p. 2520-44.

[8.] Raghdan Z., A.K.S., Dleikh F., Al-Hindy H., Is There any Association Between Highly Sensitive C-Reactive Protein and Dental-Status in Ischemic Heart Diseases? A Comparative Stud. Biochemical and Cellular Archives, 2020. **20**(2): p. 6069-6075.

[9.] Samer MM., A.S., Hayder AA., Mazin JM., C-Reactive Protein is Associated with the Severity of Periodontal Disease — An Observational Study Among Acute Myocardial Infarction Patients. Sys Rev Pharm 2020. **11**(10): p. 252-257.

[10.] Sheiham, A., Oral health, general health and quality of life. Bulletin of the World Health Organization, 2005. **83**(9): p. 644-644.

[11.] Gianos, E., et al., Oral health, and atherosclerotic cardiovascular disease: A review. American Journal of Preventive Cardiology, 2021. **7**: p. 100179.

[12.] Williams, R.C. and S. Offenbacher, Periodontal medicine: the emergence of a new branch of periodontology. Periodontol 2000, 2000. **23**: p. 9-12.

[13.] Dentino, A., et al., Principles of periodontology. Periodontol 2000, 2013. **61**(1): p. 16-53.

[14.] Pihlstrom, B.L., B.S. Michalowicz, and N.W. Johnson, Periodontal diseases. Lancet, 2005. **366**(9499): p. 1809-20.

[15.] Hayder Abdul- Amir Maki Al-hindi, S.F.A.-S., Basim MH Zwain, Thekra Abid Al-Kashwan Jaber, Relationship of Salivary & Plasma Troponin Levels of Patients with AMI in Merjan medical city of Babylon Province: Cross-Sectional Clinical Study. Al-Kufa University Journal for Biology, 2016. **8**(3): p. 53-58.

[16.] Hayder Abdul- Amir Maki Al-Hindy, A.S.A.M., Basim MH Zwain, Decayed, Missed, Filled Teeth Scores in Iraqi Patients with Acute Myocardial Infarction. Al-Kufa University Journal for Biology, 2016. **8**(3): p. 7.

[17.] Yesar MH. Al-Shamma, A.A.A.A., Hayder Abdul-Amir Al-Hindy, Caries Burden is associated with serum uric acid and CRP in Patients Treated for Acute Coronary Syndrome. Journal of Chemical Health Risks, 2022. **12**(2): p. (Accepted).

[18.] Jeftha, A. and H. Holmes, Periodontitis and cardiovascular disease. Sadj, 2013. **68**(2): p. 60, 62-3.

[19.] Yucel-Lindberg, T. and T. Båge, Inflammatory mediators in the pathogenesis of periodontitis. Expert Reviews in Molecular Medicine, 2013. **15**: p. e7.

[20.] Kilian M, C.I., Hannig M, Marsh PD, Meuric V, Pedersen AM, et al, The oral microbiome - an update for oral healthcare professionals. Br Dent J 2016. **221**(10): p. 657–66.

[21.] Thornton-Evans G, E.P., Wei L, Palmer A, Moeti R, Hutchins S, et al, Periodontitis among adults aged ≥30 years-United States, 2009-2010. MMWR Suppi, 2013. **62**(3): p. 129–35.

[22.] Libby P, L.J., Ridker PM, Farkouh ME, Hsue PY, Fuster V, et al, Inflammation, immunity, and infection in atherothrombosis: JACC review topic of the week. J Am Coll Cardiol, 2018. **72**(17): p. 2071–81.

[23.] YA., A., Risk factors of periodontal disease: review of the literature. Int J Dent, 2014. **2014**: p. 182513-182513.

[24.] Kebschull, M., R.T. Demmer, and P.N. Papapanou, "Gum bug, leave my heart alone!"--epidemiologic and mechanistic evidence linking periodontal infections and atherosclerosis. J Dent Res, 2010. **89**(9): p. 879-902.

[25.] Chhibber-Goel, J., et al., Linkages between oral commensal bacteria and atherosclerotic plaques in coronary artery disease patients. NPJ Biofilms and Microbiomes, 2016. **2**(1): p. 7.

[26.] Kurihara, N., et al., Detection and localization of periodontopathic bacteria in abdominal aortic aneurysms. Eur J Vasc Endovasc Surg, 2004. **28**(5): p. 553-8.

[27.] Habbab, K.M., et al., Molecular markers relevant to myocardial injury following dental extraction in patients with or without coronary artery disease. BDJ Open, 2019. **5**: p. 9-9.

[28.] Piñon-Esteban, P., et al., Presence of bacterial DNA in thrombotic material of patients with myocardial infarction. Scientific Reports, 2020. **10**(1): p. 16299.

[29.] Holland, T.L., et al., Infective endocarditis. Nature Reviews Disease Primers, 2016. **2**(1): p. 16059.

[30.] Stoll, L.L., G.M. Denning, and N.L. Weintraub, Potential role of endotoxin as a proinflammatory mediator of atherosclerosis. Arterioscler Thromb Vasc Biol, 2004. **24**(12): p. 2227-36.

[31.] Bains, R. and V.K. Bains, Lesions of endodontic origin: An emerging risk factor for coronary heart diseases. Indian Heart J, 2018. **70 Suppl 3**(Suppl 3): p. S431-s434.

[32.] Publishing, M.I.S.L.A., Pathophysiology. In: Lecture Notes for Dental Medicine. 2015.

[33.] Ettinger, G., et al., The influence of the human microbiome and probiotics on cardiovascular health. Gut Microbes, 2014. **5**(6): p. 719-28.

[34.] Mozos, I., et al., Inflammatory Markers for Arterial Stiffness in Cardiovascular Diseases. Front Immunol, 2017. **8**: p. 1058.

[35.] Khlgatian, M., et al., Fimbria-dependent activation of cell adhesion molecule expression in Porphyromonas gingivalis-infected endothelial cells. Infect Immun, 2002. **70**(1): p. 257-67.

[36.] Mesa, F., et al., Periodontitis and mechanisms of cardiometabolic risk: Novel insights and future perspectives. Biochim Biophys Acta Mol Basis Dis, 2019. **1865**(2): p. 476-484.

[37.] Bronzato, S. and A. Durante, Dietary Supplements and Cardiovascular Diseases. Int J Prev Med, 2018. **9**: p. 80.

[38.] Im, S.I., et al., Impact of periodontitis as representative of chronic inflammation on long-term clinical outcomes in patients with atrial fibrillation. Open Heart, 2018. **5**(1): p. e000708.

[39.] D'Aiuto, F., et al., Periodontal infections cause changes in traditional and novel cardiovascular risk factors: results from a randomized controlled clinical trial. Am Heart J, 2006. **151**(5): p. 977-84.

[40.] Chen, D.Y., et al., Risk of Atrial Fibrillation or Flutter Associated with Periodontitis: A Nationwide, Population-Based, Cohort Study. PLoS One, 2016. **11**(10): p. e0165601.

[41.] Joshy, G., et al., Is poor oral health a risk marker for incident cardiovascular disease hospitalisation and all-cause mortality? Findings from 172 630 participants from the prospective 45 and Up Study. BMJ Open, 2016. **6**(8): p. e012386-e012386.

[42.] Salhi, L., et al., Can Periodontitis Influence the Progression of Abdominal Aortic Aneurysm? A Systematic Review. Angiology, 2019. **70**(6): p. 479-491.

[43.] Paraskevas, K.I., D.P. Mikhailidis, and A.D. Giannoukas, Periodontitis and abdominal aortic aneurysms: a random association or a pathogenetic link? Int Angiol, 2009. **28**(6): p. 431-3.

[44.] Suzuki, J., et al., High incidence of periodontitis in Japanese patients with abdominal aortic aneurysm. Int Heart J, 2014. **55**(3): p. 268-70.

[45.] Kure, K., et al., Accelerated inflammation in peripheral artery disease patients with periodontitis. J Periodontal Implant Sci, 2018. **48**(6): p. 337-346.

[46.] Sekinishi, A., et al., Periodontal pathogen Aggregatibacter actinomycetemcomitans deteriorates pressure overload-induced myocardial hypertrophy in mice. Int Heart J, 2012. **53**(5): p. 324-30.

[47.] Hanatani, T., et al., The periodontal pathogen Aggregatibacter actinomycetemcomitans deteriorates ventricular remodeling after myocardial infarction in mice. Int Heart J, 2012. **53**(4): p. 253-6.

[48.] Yu, G., et al., Effect of periodontitis on susceptibility to atrial fibrillation in an animal model. J Electrocardiol, 2010. **43**(4): p. 359-66.

[49.] Aoyama, N., et al., Detrimental effects of specific Periodontopathic bacterial infection on tachyarrhythmia compared to Bradyarrhythmia. BMC Cardiovasc Disord, 2017. **17**(1): p. 267.

[50.] Nepomuceno, R., et al., Serum lipid levels in patients with periodontal disease: A meta-analysis and meta-regression. J Clin Periodontol, 2017. **44**(12): p. 1192-1207.

[51.] Garg, P. and C. Chaman, Apical Periodontitis - Is It Accountable for Cardiovascular Diseases? J Clin Diagn Res, 2016. **10**(8): p. Ze08-12.

[52.] Sridhar, R., et al., A study to evaluate the relationship between periodontitis, cardiovascular disease, and serum lipid levels. Int J Dent Hyg, 2009. **7**(2): p. 144-50.

[53.] Saxlin, T., et al., Association between serum lipid levels and periodontal infection. J Clin Periodontol, 2008. **35**(12): p. 1040-7.

[54.] Miyazawa, H., et al., Increased serum PCSK9 concentrations are associated with periodontal infection but do not correlate with LDL cholesterol concentration. Clin Chim Acta, 2012. **413**(1-2): p. 154-9.

[55.] Tabeta, K., et al., Increased serum PCSK9, a potential biomarker to screen for periodontitis, and decreased total bilirubin associated with probing depth in a Japanese community survey. J Periodontal Res, 2018. **53**(3): p. 446-456.

[56.] Pietropaoli, D., et al., Poor Oral Health and Blood Pressure Control Among US Hypertensive Adults. Hypertension, 2018. **72**(6): p. 1365-1373.

[57.] Holmlund, A., G. Holm, and L. Lind, Severity of periodontal disease and number of remaining teeth are related to the prevalence of myocardial infarction and hypertension in a study based on 4,254 subjects. J Periodontol, 2006. **77**(7): p. 1173-8.

[58.] Vlachojannis, C., et al., Determinants of serum IgG responses to periodontal bacteria in a nationally representative sample of US adults. J Clin Periodontol, 2010. **37**(8): p. 685-96.

[59.] Hayashida, H., et al., Association of periodontitis with carotid artery intima-media thickness and arterial stiffness in community-dwelling people in Japan: the Nagasaki Islands study. Atherosclerosis, 2013. **229**(1): p. 186-91.

[60.] Piepoli, M.F., et al., 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts)Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). Eur Heart J, 2016. **37**(29): p. 2315-2381.

[61.] Peng, J., et al., The relationship between tooth loss and mortality from all causes, cardiovascular diseases, and coronary heart disease in the general population: systematic review and dose-response meta-analysis of prospective cohort studies. Biosci Rep, 2019. **39**(1).

[62.] Amar, S., et al., Periodontal disease is associated with brachial artery endothelial dysfunction and systemic inflammation. Arterioscler Thromb Vasc Biol, 2003. **23**(7): p. 1245-9.

[63.] Tonetti, M.S., et al., Treatment of periodontitis and endothelial function. N Engl J Med, 2007. **356**(9): p. 911-20.

[64.] da Silva, J.C., et al., The effect of periodontal therapy on oxidative stress biomarkers: A systematic review. J Clin Periodontol, 2018. **45**(10): p. 1222-1237.

[65.] Gianos, E., et al., Oral Health, and Atherosclerotic Cardiovascular Disease: A Review. American Journal of Preventive Cardiology, 2021. **7**: p. 100179.

[66.] Nicolosi, L.N., et al., Relation between periodontal disease and arterial stiffness. J Periodontal Res, 2017. **52**(1): p. 122-126.

[67.] Beck, J.D., et al., Periodontitis: a risk factor for coronary heart disease? Ann Periodontol, 1998. **3**(1): p. 127-41.

[68.] Tayman, M.A., et al., A Novel Systemic Indicator of Periodontal Tissue Damage: Ischemia Modified Albumin. Comb Chem High Throughput Screen, 2018. **21**(8): p. 544-549.