



Association between Periodontitis and Heart Disease: A Literature Review

Noha Algallai^{1*}

¹*School of Health Professions, Rutgers University, New Jersey, USA.*

Author's contribution

The sole author designed, analysed, interpreted and prepared the manuscript.

Article Information

Editor(s):

(1) Dr. Vinej Somaraj, Rajas Dental College & Hospital, India.

Reviewers:

(1) A. Selvam, Government Theni medical College and Hospital, India.

(2) Antonenko M. Yu, Bogomolets National Medical University, Ukraine.

(3) Drg. Yennata Saputra, Hasanuddin University, Indonesia.

Complete Peer review History: <http://www.sdiarticle4.com/review-history/63256>

Review Article

Received 14 September 2020

Accepted 19 November 2020

Published 09 December 2020

ABSTRACT

Background: Heart disease is a multi factorial disease that arises from both; genetic and environmental factors. Genetic factors include hypertension, diabetes, platelet aggregations, and cholesterol. Environmental factors include imbalanced diet, a sedentary lifestyle, stress life, smoking, infections, and the intake of non-steroid anti-inflammatory medications. Heart disease death rates are approximately 30% of total deaths. Periodontal disease, a progressive inflammation; leads to damage dental tissue that surrounds teeth due to bacterial infections that release toxins and cause inflammatory reaction. Poor oral hygiene is the main cause of periodontitis. Therefore, oral infections due to poor oral hygiene might increase systemic inflammation. Scientists have hypothesized that the connection between two diseases is due to the same bacteria. Bacteria which founded in infected periodontal tissue around teeth are causing inflammation, so during normal chewing or brushing, bacteria can enter the bloodstream and move to other parts of the circulatory system, contributing to the formation of heart disease. This literature review was conducted to examine the research evidence for an association between periodontal disease and risk of heart disease.

Method and Results: A literature review of Pub Med abstracts was undertaken. Identified studies were reported in the period (1993- 2017) determining the evidence for periodontitis and its association with increasing risk of heart disease and some pathologic pathways.

Conclusion: Many studies focused on the role of oral infections and periodontal infection in

*Corresponding author: Email: nea42@shp.rutgers.edu;

incidence of atherosclerotic. In addition, these studies determined that periodontal disease is a risk factor for heart disease. Though, it requires more considerable future studies to prove the cause-and-effect relationship between periodontal disease and heart disease.

Keywords: Heart disease; periodontitis; bacteria; inflammation.

1. INTRODUCTION

Heart disease arises from many factors; genetic and environmental. The factors which are genetic include diseases such as hypertension [1], diabetes [2], blood disorders such as platelet aggregations [3], cholesterol which developed due to obesity [4] or high lipid level [5]. The factors that are related to environment include eating imbalanced diet [6], no activity by sitting for long time, stressful life [7,8], smoking [9,10], infections [11,12], and intake of non-steroid anti-inflammatory medications [13]. Heart disease death rates are approximately 30% of entirely.

Many studies have shown that periodontal and gum diseases are associated with cardiovascular disease, but there are no studies indicated cause and effect of periodontal disease on heart disease.

Researchers are certain of that inflammation caused by periodontitis may be responsible for this association; especially if the patient have some unhealthy habits and / or conditions such as smoking, having diabetes, obesity or high blood pressure. Periodontitis can intensify existing cardiac disease, so dental patients at risk for infective endocarditis or other heart diseases may need antibiotics before some dental procedures.

According to scientists, inflammation or swelling can lead to stiffen the arteries. This solidity is called atherosclerosis. This condition will interrupt the flow of blood to the heart. It leads to an increased risk for heart attack and stroke [14,15].

Gingiva sometimes has signs of inflammation. There are two types of gingival disease; gingivitis, which causes red, painful, tender and bleeding of gum, and periodontitis, which leads to infected pockets and loss of surrounding tissues and accumulate bacteria inside infected area as pus. This type of gingival disease "Periodontitis" is considered a concern for cardiac problems.

Porphyromonas gingivalis is a gram-negative, non-motile, anaerobic bacterium occupied as a main pathogen in periodontitis. This bacterium has also been found in coronary artery plaques of cardiac attack patients. Some investigators in

the department of clinical medicine, school of health sciences, Örebro University, Sweden, monitored two species of animal models, they found out *Porphyromonas gingivalis* causes formation of coronary and aortic atherosclerosis.

They started with culturing human aortic smooth muscle cells [16], and infected them with *Porphyromonas gingivalis*. They noticed that *Porphyromonas gingivalis* produce a virulence factors named gingipains. These factors increase angiotensin 2, while reduce of the anti-inflammatory angiotensin 1 in the smooth muscle cells, which lead to increase the inflammation. This inflammation is strongly implicated in atherosclerosis [17].

Scientists also think that the connection between the two diseases is due to the same bacteria. Bacteria found in infected periodontal tissue around teeth causing inflammation. During normal chewing or brushing, bacteria can enter the bloodstream and move to other parts of the circulatory system which leads to plaque formation of the artery [18], contributing to the formation of heart disease (Fig. 1) [19,20].

In this article, there is a determination of evidence for periodontitis and its association with increasing risk of heart disease, and some pathologic pathways that clarify this association by reviewing some literatures which indicate this association.

2. EVIDENCE FROM LITERATURES

In a follow up epidemiological study, DeStefano et al. analyzed the mortality of coronary heart disease (CHD) according to the National Health and Nutrition Examination Survey I (NHANES I), that followed 9,760 participants for 14 years. They established that participants with periodontal disease had a 25% increased risk of CHD compared to those with insignificant periodontal disease by controlling for confounding factors such as age, gender, race, socioeconomic status, hypertension, cholesterol, diabetes, consumption of alcohol. This association was more among males younger than 50 years. This study provides evidence for an association between periodontal disease and CHD [21].

Gum Disease and Heart Disease: **The Bacteria Connection**

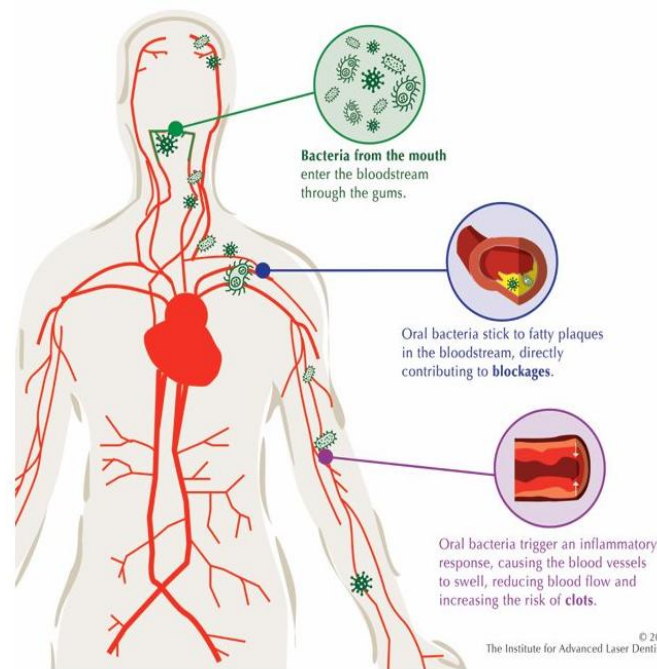


Fig. 1. The bacteria connection between gum disease and heart disease

A study was conducted by James Beck et al. to investigate the relation between periodontitis and heart disease. The researchers hypothesized that this relation may be as a result of an underlying inflammatory response trait that occurs in people at high risk for developing both periodontitis and atherosclerosis. They suggested that periodontitis, once initiated, provides a load of endotoxin such as lipopolysaccharide and inflammatory cytokines (especially TxA_2 , $\text{IL-1}\beta$, PGE_2 , and $\text{TNF-}\alpha$) that help to begin and aggravate both of atherogenesis and thromboembolic occasions. A cohort study was done by using data from the Normative Aging Study and the Dental Longitudinal Study sponsored by the United States Department of Veterans Affairs. Means of alveolar bone loss scores and poorest probing depth scores for every tooth were measured on 1,147 males in the period (1968 – 1971). 207 males developed coronary heart disease, 59 died of coronary heart disease (CHD), and 40 had strokes. Odds ratios after modifying confounder factors were 1.5, 1.9, and 2.8 for bone loss and CHD, fatal CHD, and stroke, respectively. Bone loss levels and incidence of CHD and fatal CHD indicated the association between severity of exposure and incidence of CHD [22].

According to Afrodite Loubakos, Yu Ping Yuan, et al, a study was done to determine the activation of protease-activated receptors by gingipains from *Porphyromonas gingivalis* leads to platelet aggregation. This study examined the effects of the interaction between gingipains, important virulence factors, and the clotting cascade on cellular elements of the coagulation system. The enzymes prompted a rise in intracellular calcium in human platelets at nanomolar concentrations and caused aggregation of platelets. Based on studies achieved with thrombin and peptide receptor agonists, and immunoinhibition experiments, gingipains-R appeared to be activating the protease-activated receptors, (PAR)-1 and -4, appeared on the surface of platelets. This was confirmed by the result that HRgpA and RgpB potentially activated PAR-1 and PAR-4 in transfected cells stably expressing these receptors. Overall results indicate the presence of a novel pathway of host cell activation by bacterial proteinases through PAR cleavage. This mechanism not only inspects a new trait in pathogenicity of the bacteria, but may also clarify the link between periodontitis and heart disease [23].

Armin J. Grau, et al. did a study to determine whether periodontal disease is as a risk factor for ischemic stroke. They executed a case-control

study with 303 cases inspected within 1 week after ischemic stroke, 300 controls from population and 168 controls from hospital were with nonvascular and no inflammatory neurological diseases. All participants were received a clinical and radiographic dental investigation. The clinical attachment loss measured at 4 sites per tooth functioned as the main indicator for periodontitis. Patients had higher attachment loss than controls of population ($P < 0.001$) and controls of hospital ($P = 0.010$). After adjusting confounder factors such as age, gender, teeth number, vascular diseases, socioeconomic status, and lifestyle factors, the risk of ischemia increased with more severe periodontitis. Participants with severe periodontitis (CAL > 6 mm) had a 4.3-times-higher risk of ischemia than participants with mild or without periodontitis ($< \text{or} = 3$ mm). Severe periodontitis was a risk factor in younger men who are < 60 years. This study indicates that severe periodontitis is risk factor for cerebral ischemia in men and younger subjects [24].

Fabio Angeli and others investigated the association between Periodontitis and Left Ventricle Mass (LVM) in Essential Hypertension. 104 participants, who were untreated with hypertension, went through clinical examinations, including ECG, lab tests, and evaluation of periodontal status according to the community periodontal index of treatment needs (CPITN). With aggregating severity of periodontitis, there was a progressive increase in left ventricle mass. Mean values were 39.0 in CPITN 0 (periodontal health), 40.2 in CPITN 1 (gingival bleeding), 42.7 in CPITN 2 (calculus), 51.4 in CPITN 3 (pockets 4 to 5 mm), and 76.7 in CPITN 4 (pockets > 6 mm) (overall $P < 0.0001$). Systolic ($P < 0.0001$) and diastolic ($P < 0.01$) blood pressure, and left ventricular mass ($P < 0.0001$) were determining factor of a composite of CPITN 3 and 4. Left ventricular mass was the only determinant factor in a multivariate logistic analysis, ($P < 0.0001$) of CPITN stages 3 and 4. The results presented a direct relation between severity of periodontitis and left ventricular mass in participants with hypertension [25].

Oelisoa Mireille, Andriankaja et al, did a case control study to observe the association between periodontitis and acute myocardial infarction. This study was conducted both of counties Erie and Niagara in New York State. About 574 cases were diagnostic with MI. 887 controls were randomly chosen from the New York State Department of Motor Vehicles rolls and Health Care Financing Administration files. Periodontitis

was evaluated using clinical attachment loss. Among 415 males' cases, the odds ratio (OR) of the relation between mean of clinical attachment loss (mm) and Myocardial Infarction, adjusting for age, body mass index, physical activity, blood pressure, diabetes, and smoking was 1.34. In 120 female cases, OR was 2.08. The estimate of this relation among non-smokers, by adjusting previous factors was 1.40, while it was 1.49 among those who are smokers. According to these findings the researchers concluded that there is an association between PD and incident MI in both genders. This association seems to be independent of the possible confounding effect of smoking [26].

Cesar de Oliveira also conducted a study to inspect whether tooth brushing, inflammation, are risk of cardiovascular disease. A self-reported tooth brushing behavior is connected with heart disease and indicator of inflammation and coagulation. The author did a national population based survey, Scottish Health Survey, which appealed a sample of the population that is living in Scotland. Participants were 11869 from males and females, mean age 50. Oral hygiene evaluated from self-reported tooth brushing. Surveys were connected to hospital records. Cox proportional hazards statistics models were done to determine the possibility of heart disease according to oral hygiene. The relation between oral hygiene and inflammatory and coagulation indicators was investigated in 4830 participants by using linear models with adjustments. Total of 555 heart disease occasions over an average of 8.1 years of follow-up, 170 occasions were fatal. 411 of heart disease occasions, the diagnosis was coronary heart disease. Participants who never/rarely brushed their teeth had an increased possibility of a heart disease occasion ($P < 0.001$). He concluded that Poor oral hygiene is related with risk of heart disease [27].

Zhang, Elmabsout et al determined whether the periodontal pathogen *Porphyromonas gingivalis* changes the gene expression in vascular smooth muscle cells involving the TGF beta/Notch signalling pathway and increased cell proliferation. Human Aortic Smooth Muscle Cells (AOSMCs) were subjected to *P. gingivalis* for 24 h. Fluorescence microscope was used to investigate *P. gingivalis* invasion of AOSMCs which was evaluated by neutral red assay. In addition, human genome microarray and western

blot and ELISA were used to examine how *P. gingivalis* alters AoSMCs's gene and protein expression. They established that *P. gingivalis* attacks AoSMCs and increases cell proliferation. Microarray findings displayed that, 982 genes were recognized that they differentially expressed ($p < 0.05$). Using bioinformatics data mining, the researchers established that up-regulated genes are enhanced in gene function of positive control of cell proliferation and down-regulated genes are enhanced in the function of negative control of cell proliferation. This study demonstrates that *P. gingivalis* is able to invade AoSMCs and stimulate their proliferation [28]. In addition, they conducted another study to examine the important role of *P. gingivalis* infection in the alteration of Angiopoietin1 and Angiopoietin2 (Angpt 1 and 2) in aortic smooth muscle cells of human (AoSMCs). They exposed AoSMCs to *P. gingivalis* strains such as wild-type, gingipain mutant (E8 and K1A), and fimbrial mutant (DPG-3 and KRX-178) in addition to different concentrations of tumor necrosis factor (TNF). This factor used as a positive study control. They founded that wild type, K1A, DPG3, and KRX178 also TNF up regulated the expression of Angpt2 and its transcription factor ETS1 in AoSMCs. However, Angpt1 was inhibited by both *P. gingivalis* and TNF. The findings further support the association between periodontitis and cardiovascular disease [29].

FeiCheng investigated whether tooth loss has association with risk of cardiovascular disease and stroke. A dose-response meta-analysis was achieved to illuminate and evaluate the correlation between tooth loss, heart disease and risk of stroke. Up to March 2017, 17 cohort studies were included in meta-analysis, involving about 879084 subjects with 43750 incident cases. The findings showed statistically significant increment association between tooth loss, heart disease and stroke risk. Subcategories analysis showed that tooth loss was associated with a significant risk of heart disease and stroke in Asia and Caucasian. In addition, tooth loss was also associated with heart disease and stroke in fatal and nonfatal cases. Moreover, a significant dose-response relationship was observed between tooth loss, heart disease and stroke. Increasing per 2 of tooth loss was associated with a 3% increment of coronary heart disease risk; increasing per 2 of tooth loss was associated with a 3% increment of stroke risk. Considering these findings, tooth loss might associate with harmful health issues [30].

3. DISCUSSION

Overall, the results of these studies showed that there is an association between periodontal disease and risk of heart disease. However, a critical question is whether this association is causal. In DeStefano et al's study, the association in entire participants especially with periodontal disease was not clear and weak; that can be due to small bias or not doing enough control of smoke confounder in baseline. The association was found in younger men. The reason for this stronger association in the younger men is not clear. James Beck et al. suggested that once periodontal disease started, it provides exaggerated amount of endotoxin such as lipopolysaccharide and inflammatory cytokines that lead to atherogenesis' and thromboembolic events. They conducted a cohort study. They found out that subgroups of men who have bone loss in their teeth developed coronary heart disease, and some have stroke, so that indicated the association between both periodontal and coronary heart diseases.

Afrodite et al's study focused whether *Porphyromonas gingivalis* proteases would have an indirect role in increasing chronic inflammation. According to sprightly accumulated data, however, it is appealing to consider that gingipains may have a direct role in heart complications.

Armin J. Grau et al. confirmed that their results support the hypothesis of that periodontitis is an independent stroke risk factor. However, this study has some limitation such as bias occurrence toward the control group, and the study was not blinded between the examiner and the participants. In addition, the study should be restricted to patients with transient ischemic attack and mild to moderately severe stroke. They indicated that periodontitis is a chronic inflammatory disease and can become worse, and periodontal disorders at the time of acute ischemia may be of major consideration [31]. Fabio Angeli et al. disclosed in their study an independent association between Left Ventricle Mass (LVM) and severe periodontal disease which is defined by community periodontal index of treatment needs (CPTIN), in untreated participants with hypertension. In a multivariate analysis, LVM was superior to systolic and diastolic BP for prediction of moderate-to-severe periodontitis. The mechanisms which lead to the association between LVM and periodontal disease remain theoretical. In patients with

hypertension, hypertrophic heart and periodontal tissue may share dysfunction in microcirculation and rarefaction of artery and capillary [32,33]. Therefore, the high blood pressure could develop left ventricular hypertrophy and narrowing of luminal diameter of micro vessels which may lead to ischemia at heart and periodontal level. Oelisoa Mireille Andriankaja et al. examined the association between periodontitis and coronary heart disease, but this study was done in weak to moderate relationship. However, this study has limitation in reporting data in women and also the role of smoking confounder was not clarified, this study provided an evidence of an association between periodontal disease and incidence of Myocardial infarction in both genders. This association seems to be independent of smoking confounder factor. Cesar de Oliveira detected whether a self-reported frequency of tooth brushing (as a substitution of periodontal disease) was associated with risk of heart disease in a group of adults from the Scottish Health Survey. Also, he investigated the association between frequency of tooth brushing and C reactive protein and fibrinogen's inflammatory markers in a subgroup of participants. The survey is nationally representative, with data related to a patient database of hospital admissions and deaths with follow-up. The Scottish population is relatively the same, with a high occurrence of heart disease and bad oral health, thus the findings is highly significant to this population. This was one of the limitations of this study. However, data regarding the status of periodontal disease and self-report might have supported the findings [34]. There is no follow-up data on the behavior of tooth brushing; however, evidence display constancy of oral health related to tooth brushing and dental flossing [35], thus small changes can have effect on the existing findings. Boxi Zhang et al. concentrated in their study on the interaction between *P. gingivalis* and vascular smooth muscle cells by using confocal microscopy 3D analysis. They found that *P. gingivalis* enters AoSMCs and causes AoSMCs proliferation which leads to atherosclerosis. When they used microarray analysis, they found that 982 genes were expressed in different ways in *P. gingivalis*-infected AoSMCs, compared to control samples which were uninfected. Ontology analysis was done to simplify whether genes causing the cell proliferation are involved during *P. gingivalis* infection. In addition, they found an abundant number of genes related to Notch and TGF-beta pathway. They detected that the TGF-beta

pathway was considerably activated in AoSMCs by *P. gingivalis*, and it can collaborate with Notch pathway in SMCs differentiation's regulation. Therefore, there is a suggestion that *P. gingivalis* motivates AoSMCs proliferation by activating of the TGF-beta and Notch pathways and subsequently cause the development of atherosclerosis, which further supports an association between periodontal disease and heart disease.

Also, Zhang et al. indicated that periodontal disease is a mild. However, it is a significant risk factor for developing heart disease. The pathogenic bacterium in periodontal tissue is *Porphyromonas gingivalis* which is considered to be directly or indirectly has a role in the development of atherosclerosis and heart disease. According to their study, they found that *Porphyromonas gingivalis* infection prompts comparable effects on Angpt1, Angpt2, and ETS1's expression of in AoSMCs, and gingipains are essential for this regulation. These findings put forward that Angpt2 has a role in the association between periodontal disease and atherosclerosis. Fei cheng et al. had done meta-analysis which was based on seventeen cohort study. This meta-analysis provides epidemiological evidence which support that tooth loss is harmful for heart disease and stroke. A dose-response analysis showed that every time tooth loss happen per 2 increments that was associated with a 3% increment of heart disease as well as stroke risk, so people with few or no teeth would increase risk of heart disease and stroke. In addition, the essential cause of tooth loss is dental decayed, and sugar intake is the main cause of dental caries. Sugar intake also associated with increasing risk of heart disease and stroke, therefore teeth loss has indirect effect on the risk of heart disease and stroke [36]. Furthermore, increasing tooth destruction will destroy normal periodontal tissue. That will allow accumulation of the bacteria which increase in growth, thus leading to heart disease and stroke [37]. Tooth loss also is the final stage of periodontitis and may associate with increasing in C-reactive protein (CRP), which associated in atherosclerosis and lead to stroke [38]. Some limitations were considered. First, they only choose literature that written by English, which leads to a language bias. Second, there might be insufficient statistical power when analysis of subgroup in different ethnic population.

4. CONCLUSION

Many studies focused on the role of the periodontal infection in incidence of atherosclerotic, and also on that periodontal disease is a risk factor for heart disease. Though, it requires more consider able future studies to prove the cause-and-effect relationship between periodontal disease and heart disease since there is feeble proof regarding that. In meanwhile, because some studies have clear evidence about the association between periodontitis and heart disease, dental health professionals should motivate and aware the patients to maintain their periodontal health in order to reduce the risk of developing the heart disease [39].

CONSENT AND ETHICAL APPROVAL

As per university standard guideline, participant consent and ethical approval have been collected and preserved by the authors.

ACKNOWLEDGEMENTS

I have done solo work on this research paper. However, I thank my husband, Mohamed Elsoussi, for his support and encouragements and appreciate his helping to be at this level of profession.

COMPETING INTERESTS

Author has declared that no competing interests exist.

REFERENCES

1. Rakugi H, Yu H, Kamitani A, et al. Links between hypertension and myocardial infarction. *Am Heart J.* 1996;132:213–221.
2. Stern MP, et al. Do non-insulin dependent diabetes mellitus and cardiovascular disease share common antecedents? *Ann Intern Med.* 1996;124:110–116.
3. Weiss EJ, Bray PF, Tayback M, et al. A polymorphism of a platelet glycoprotein receptor as an inherited risk factor for coronary thrombosis. *N Engl J Med.* 1996; 334:1090–1094.
4. Lonnqvist F, Arner P, Nordfors L, Schalling M. et al. Overexpression of the obese [ob] gene in adipose tissue of human objects. *Nat Med.* 1995;1:950–953.
5. Kesaniemi YA, Et al. Genetics and cholesterol metabolism. *Curr Opin Lipidol.* 1996;7:124–131.
6. Stampfer MJ, Sacks FM, Salvini S, Willett WC, Hennekens CH, et al. A prospective study of cholesterol, apolipoproteins and the risk of myocardial infarction. *N Engl J Med.* 1991;325:373–381.
7. Grignani G, Soffiantino F, Zucchella M, et al. Platelet activation by emotional stress in patients with coronary artery disease. *Circulation.* 1991;83(Suppl 4):128–136.
8. Yeung AC, Vekshtein VI, Krantz DS, et al. The effect of atherosclerosis on the vasomotor response of coronary arteries to mental stress. *N Engl J Med.* 1991;325: 1551–1556.
9. Hung J, Lam JY, Lacoste L, Letchacovski G, et al. Cigarette smoking acutely increase platelet thrombus formation in patients with coronary artery disease taking aspirin. *Circulation.* 1995;92:2432–2436.
10. Kuller LH, Tracy RP, Shaten J, Meilahn EN. et al. Relation of C-reactive protein and coronary heart disease in the MRFIT nested case-control study. *Am J Epidemiol.* 1996;144:537–547.
11. Nieminen MS, Mattila K, Valtonen V. et al. Infection and inflammation as risk factors for myocardial infarction. *Eur Heart J.* 1993;14:12–16.
12. Buja LM, et al. Does atherosclerosis have an infectious etiology? *Circulation.* 1996; 94:872–873.
13. Ridker PM, Cushman M, Stamper MJ, Tracy RP, Hennekens CH, et al. Inflammation, aspirin and the risk of cardiovascular disease in apparently healthy men. *N Engl J Med.* 1997;336: 973–979.
14. Karnoutsos K, Papastergiou P, Stefanidis S, Vakaloudi A, et al. Periodontitis as a risk factor for cardiovascular disease: The role of anti-phosphorylcholine and anti-cardiolipin antibodies. *Hippokratia Journal.* 2008;12(3):144-149
15. Ambrose JA, Weinrauch M, et al Thrombosis in ischemic heart disease. *Arch Intern Med.* 1996;156:1382–1394.
16. Zhang B, Elmabsout AA, Khalaf H, Basic VT, Jayaprakash K, Kruse R, Sirsjo A, et al The periodontal pathogen *Porphyromonas gingivalis* changes the gene expression in vascular smooth muscle cells involving the TGFbeta/Notch signalling pathway and

- increased cell proliferation. BMC Genomics. 2013;14:770.
DOI: 10.1186/1471-2164-14-770
17. Gomez D, Owens GK, et al. Smooth muscle cell phenotypic switching in atherosclerosis. Cardiovasc Res. 2012;95: 156–164.
DOI: 10.1093/cvr/cvs115
 18. Freire MO, Van Dyke TE, et al. The mechanisms behind oral-systemic interactions. In: Glick M, ed. The Oral-Systemic Health Connection: A Guide to Patient Care. Chicago, IL: Quintessence. 2014;5:103-119.
 19. Leishman SJ, Do HL, Ford PJ, et al. Cardiovascular disease and the role of oral bacteria. J Oral Microbiol. 2010;2.
DOI: 10.3402/jom.v2i0.5781
 20. Robert H. The surprising link between periodontal disease and heart health: What dental professionals need to know” Breakthrough Clinical; 2017.
Available: <https://www.dentistryiq.com/clinicall/article/16366436/the-surprising-link-between-periodontal-disease-and-heart-health-what-dental-professionals-need-to-know>
 21. De Stefano F, Robert F Anda, Henry S Kahn, David F Williamson, Carl M Russell, et al. Dental disease and risk of coronary heart disease and mortality. British Medical Journal. 1993;306:688-691.
 22. James Beck, Raul Garcia, Gerardo Heiss, Pantel S. Vokonas, Steven Offenbacher, et al. Periodontal disease and cardiovascular disease. Journal of Periodontology. 1996; 67:1123-1137
 23. Afrodite Lourbakos, YuPing Yuan, Alison L. Jenkins, James Travis, Patricia Andrade-Gordon, Rosemary Santulli, et al. Activation of protease-activated receptors by gingipains from *Porphyromonas gingivalis* leads to platelet aggregation: A new trait in microbial pathogenicity. American Society of Hematology. 2001; 97:3790-3797.
 24. Armin J. Grau, Heiko Becher, Christoph M. Ziegler, Christoph Lichy, Florian Buggle, Claudia Kaiser, et al. Periodontal Disease as a Risk Factor for Ischemic Stroke. Stroke Journal. 2004;35:496-501.
 25. Fabio Angeli, Paolo Verdecchia, Concetta Pellegrino, Rosaria Giulia Pellegrino, Giacinto Pellegrino, Lucio Prosciutti, et al. Association Between Periodontal Disease and Left Ventricle Mass in Essential Hypertension. Journal of the American Heart Association. 2003;41:488-492.
 26. Oelisoa Mireille Andriankaja, Robert J Genco, Joan Dorn, Jacek Dmochowski, Kathy Hovey, Karen L. Folkner, et al. “Periodontal disease and risk of myocardial infarction: the role of gender and smoking. European Journal of Epidemiology. 2007;22:699–705
 27. Cesar de Oliveira Toothbrushing, inflammation, and risk of cardiovascular disease: results from Scottish Health Survey” Cite this as: British Medical Journal 2010;340:1-6.
 28. Boxi Zhang, Ali Ateia Elmabsout, Hazem Khalaf, Vladimir T Basic, Kartheyaene Jayaprakash, Robert Kruse, Torbjörn Bengtsson, et al. The periodontal pathogen *Porphyromonas gingivalis* changes the gene expression in vascular smooth muscle cells involving the TGFbeta/Notch signalling pathway and increased cell proliferation BioMed Central Genomics 2013;14(770):1-12.
 29. Boxi Zhang, Hazem Khalaf, Allan Sirsjö, and Torbjörn Bengtsson. Gingipains from the periodontal pathogen *Porphyromonas gingivalis* play a significant role in regulation of Angiopoietin 1 and Angiopoietin 2 in human aortic smooth muscle cells. Infection and Immunity. American Society for Microbiology Journal. 2015;83:4256–4265
 30. Fei Cheng, Mi Zhang, Quan Wang, Haijun Xu, Xiao Dong, Zhen Gao, et al. Tooth loss and risk of cardiovascular disease and stroke: A dose-response meta-analysis of prospective cohort studies. Plos one Journal; 2018.
Available: <https://doi.org/10.1371/journal.pone.0194563> pp 1-14
 31. Grau AJ, Buggle F, Becher H, Zimmermann E, Spiel M, Fent T, et al. Recent bacterial and viral infection is a risk factor for cerebrovascular ischemia: Clinical and biochemical studies. Neurology. 1998;50:196–203.
 32. Sernè EH, Gans ROB, Maaten JC, Tangelder G, Donker JM, Stehouwer C. Impaired skin capillary recruitment in essential hypertension is caused by both functional and structural capillary rarefaction. Hypertension. 2001;38:238–24.
 33. Chapple CC, Kumar RK, Hunter N. Vascular remodelling in chronic

- inflammatory periodontal disease. J Oral Pathol Med. 2000;29:500–506
34. Miller K, Eke PI, Schoua-Glusberg A. Cognitive evaluation of selfreport questions for surveillance of periodontitis. J Periodontol. 2007;78:1455-62.
 35. Astrøm AN. Stability of oral health-related behaviour in a Norwegian cohort between the ages of 15 and 23 years. Community Dent Oral Epidemiol. 2004;32: 354-62.
 36. He J, Li Y, Cao Y, Xue J, Zhou X. The oral microbiome diversity and its relation to human diseases. Folia Microbiol (Praha). 2015;60(1):69–80.
 37. Dehghan M, Mente A, Zhang X, Swaminathan S, Li W, Mohan V, et al. Associations of fats and carbohydrate intake with cardiovascular disease and mortality in 18 countries from five continents (PURE): A prospective cohort study. Lancet. 2017;390(10107): 2050–62.
 38. You Z, Cushman M, Jenny N, Howard G. Tooth loss, systemic inflammation, and prevalent stroke among participants in the reasons for geographic and racial difference in stroke (Regards) study. Atherosclerosis. 2009;203(2):615–9.
 39. Henry H. Chang et al, Periodontics: Periodontal disease as a risk factor for cardiovascular disease. Oral Health Group; 2000. Available: <https://www.oralhealthgroup.com/features/periodontics-periodontal-disease-as-a-risk-factor-for-cardiovascular-disease/>

© 2020 Algallai; This is an Open Access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Peer-review history:

*The peer review history for this paper can be accessed here:
<http://www.sdiarticle4.com/review-history/63256>*