

## The Association between Periodontitis and Atherosclerotic Cardiovascular Disease: A Scoping Review

Agus Susanto<sup>1\*</sup>, Dyah Nindita Carolina<sup>1</sup>, Siti Sopiati<sup>1</sup>, Ina Hendiani<sup>1</sup>

1. Department of Periodontics, Faculty of Dentistry, Universitas Padjadjaran, Bandung, Indonesia.

### Abstract

Periodontitis is the disease of dental surrounding tissue with the 11th most prevalent condition in the world. Considering the important role of periodontitis in the development of atherosclerosis as the dominant cause of cardiovascular disease, this scoping review conducted with the aim of assessing and analysing current studies to see the association between periodontitis and atherosclerotic cardiovascular disease.

This scoping review was conducted using Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines. Electronic searches were carried out from 4 electronic databases include the National Library of Medicine, The Cochrane Library, EbscoHOST, and SAGE Journal.

13 articles in the past 5 years were obtained based on inclusion and exclusion criteria to be analyzed qualitatively. 12 articles showed a positive correlation between those two conditions directly and indirectly with clear findings on their studies. 1 article remained also found that there is a lack of awareness and an ignorant attitude about the relationship between atherosclerotic cardiovascular disease and periodontitis.

This present study concluded that periodontitis and atherosclerosis have an association both in direct and indirect pathway with the most reported link is indirect pathway through systemic inflammation marked by several measurable indicators.

**Review (J Int Dent Med Res 2022; 15(2): 909-915)**

**Keywords:** Atherosclerosis, inflammation, periodontitis, periodontal disease.

**Received date:** 15 February 2022

**Accept date:** 23 April 2022

### Introduction

Periodontal disease is a disease of the oral cavity that is often found in the world of community.<sup>1</sup> Periodontal disease is resulted from a complex interaction between the subgingival biofilm and the host immune-inflammatory events that develop in the dental surrounding tissues in response to the challenge presented by the periodontal pathogenes.<sup>1,2</sup> The most common periodontal diseases is periodontitis, an oral infection resulting in progressive destruction of the periodontal ligament and alveolar bone due to inflammation process.<sup>1,3</sup> According to the Global Burden of Disease Study in 2016, severe

periodontal disease was the 11<sup>th</sup> most prevalent condition in the world.<sup>4</sup>

Periodontitis as an oral infection has an impact to systemic diseases and conditions, one of those is cardiovascular disease.<sup>5,6</sup> Cardiovascular disease is a disease that attack the heart and blood vessels.<sup>7</sup> According to WHO (World Health Organization) in 2016, cardiovascular diseases also known as the number one cause of death globally, taking an estimated 17.9 million lives, representing 31% of all global deaths.

The mayor contributing factor in cardiovascular disease is atherosclerosis, leading to atherosclerotic cardiovascular diseases such as coronary heart disease, cerebrovascular disease, ischemic heart disease, peripheral artery disease, and aneurysm.<sup>8,9</sup> Atherosclerosis is a progressive chronic inflammatory process of the vessels, which may cause plaque accumulation and lead to increase in arterial wall thickness.<sup>10</sup> Common risk factors for atherosclerosis include tobacco smoking,

#### \*Corresponding author:

Dr. Agus Susanto  
Departement of Periodontics,  
Faculty of Dentistry, Universitas Padjadjaran,  
Jalan Sekeloa Selatan 1 Bandung, 40134, West Java, Indonesia.  
E-mail : [agus.susanto@fkg.unpad.ac.id](mailto:agus.susanto@fkg.unpad.ac.id)

abnormal circulating lipid levels, and diabetes mellitus.<sup>11</sup> Apart from them, some studies also mentioned that periodontal infection plays a role in the stages of atherosclerosis.<sup>12,13</sup>

A study has reported the presence of periodontal pathogens DNA in atherosclerotic plaques of patients with chronic periodontitis, suggesting these periodontal pathogen may migrate from the oral cavity to another site of the body by entering systemic blood stream.<sup>14,15</sup> However, the role of periodontal bacteria to the pathogenesis of atherosclerosis has remained unclear.<sup>2</sup> Another study reported that product released from the bacteria has an impact to promote the formation of atherosclerotic plaque by inducing platelet activation and aggregation and promoting inflammatory responses.<sup>16,17</sup> There are also some RCTs reported that the initial periodontal treatment has a significant positive effect for the prognosis in patient with atherosclerotic cardiovascular disease and periodontitis.<sup>18-21</sup> The association between these two diseases was proven by clinical trials and further confirmed by systematic review and meta-analyses.<sup>22,23</sup>

Considering the important role of periodontitis in the development of atherosclerosis as the dominant cause of cardiovascular disease, this scoping review will be conducted with the objective of assessing and analysing current studies to see the association between periodontitis and atherosclerotic cardiovascular disease in a broad view.

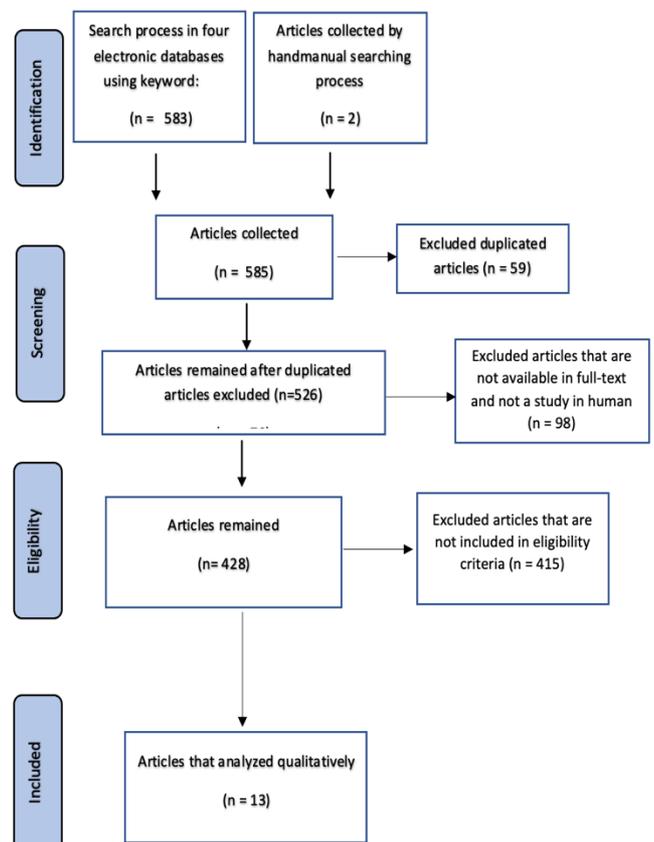
### Materials and methods

This scoping review was conducted in accordance with the guidelines of Preferred Reporting of Systematic Reviews and Meta-Analyses (PRISMA).<sup>24</sup> The review followed by the outline of PCC: Patients with periodontitis and atherosclerotic cardiovascular disease (P = Population) ; Association between periodontitis and atherosclerotic cardiovascular disease (C = Concept) ; Periodontal medicine (C = Context). Thus, this scoping review was focused on the following research question: How is the association between periodontitis and atherosclerotic cardiovascular disease?

#### Search Strategy

An electronic search for appropriate studies was carried out from four electronic literature databases. These included the National

Library of Medicine (MEDLINE/PubMED), The Cochrane Library, EbscoHOST, and SAGE Journal. The search used the terms combined with boolean operator as follows: (“periodontal disease” OR “periodontitis”) AND (“atherosclerosis” OR “coronary heart disease”) AND (“relationship” OR “association”). In order to focus our search and find more relevant citations, we used MeSH (Medical Subject Headings) thesaurus for the MEDLINE/PubMED database and freetext for other databases. Additional sources were collected by reviewing reference lists of relevant studies. The PRISMA flow diagram can be seen in Figure 1.



**Figure 1.** Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) flow diagram for the scoping review process<sup>24</sup>.

#### Eligibility Criteria

The selected articles are published in the last 5 years and written in English. After selection from title and abstract analysis, we carefully read all full-text articles and analysed them for the eligibility criteria. The inclusion and exclusion criteria were summarized in **Table 1**. Results and

findings from included study was analysed qualitatively.

Inclusion Criteria	Exclusion Criteria
1. Full-text available	1. Non human study
2. Human studies	2. Language other than English
3. Observational studies include cohort, case control, cross sectional study, randomized controlled trial study.	3. Systematic review and meta-analyses study design
4. Evaluate the presence of periodontitis in atherosclerotic cardiovascular disease patient or vice versa	

**Table 1** Inclusion and Exclusion Criteria.

## Results

After searching and selecting articles, 13 articles were included in the inclusion criteria. 6 articles were written in randomized controlled trial study design, 2 articles were written in case control study design, and 5 articles were written in cross sectional study design. Generally, participants who included in most of studies were adults and elderly that have been diagnosed with both periodontitis and atherosclerotic cardiovascular disease. Then, the results of data extraction from the 13 articles are summarized in Table 2.

## Discussion

The relationship between periodontal disease and cardiovascular disease (CVD) has been quite widely studied. In the last few decades, researchers have focused on the effect of periodontal disease on CVD.<sup>38</sup> Several evidences from literature over the last decades have demonstrated the role of periodontitis as a risk factor for CVD, especially in conditions caused by atherosclerosis.<sup>39-42</sup> Mechanisms that have been assumed to explain the association between periodontitis and atherosclerotic CVD include the inflammatory biomarkers common to both conditions, the presence of periodontal pathogens, and etiologic factors common to both disease processes.<sup>38,43</sup> However, this link is not clear enough to be explained and it could be complicated by the presence of other factors such as systemic diseases, genetic factors, and life style.<sup>38,39,44</sup>

13 studies were selected to evaluate the association of periodontal disease and atherosclerosis. 12 of them showed a positive correlation between those two conditions with

clear findings on their studies. 1 study remained also found something related to both conditions and that was conclude that there is a lack of awareness and an ignorant attitude about the relationship between atherosclerotic CVD and periodontitis.<sup>33</sup>

Periodontitis can affects atherosclerotic CVD in two mechanisms, directly and indirectly.<sup>38</sup> In direct mechanisms, periodontal pathogenes have a role in infiltrating to endothelial cells and causing damage with those products.<sup>17,45</sup> Two articles showed relationship between periodontal pathogens and atherosclerotic plaque formation through their possible role.<sup>29,45</sup> Moghadam et al (2018) conducted cross sectional study that carried out an examination on atheroma plaques. The study found that the DNA of Gram negative periodontal pathogenes is positive in atheroma plaques.<sup>45</sup> This can be proposed to existence of direct invasion of microorganisms to arterial wall or atherosclerotic plaques as said in previous studies.<sup>46,47</sup>

*Porphyromonas gingivalis* are known to be the main pathogens in chronic periodontitis, which are known to contribute to the pathogenesis of atherosclerosis with endotoxin in the form of lipopolysaccharides (LPS) and the ability of bacteria to translocate into systemic blood vessels from the oral cavity.<sup>22,35</sup> The presence of Gram negative bacteria plays a role in triggering low density lipoprotein (LDL) oxidation in the formation of foam cells as one of the stages of atherosclerotic plaque formation.<sup>48,49</sup> RCT by Bozoglan et al (2019) revealed that amount of periodontal pathogenes found out to change the level of serological risk factors such as high density lipoprotein (HDL), LDL, high sensitive-C Reactive Protein (hs-CRP), white blood cells (WBC) levels, platelet levels, creatinine and fibrinogen levels in patients who have been diagnosed with atherosclerosis-chronic periodontitis and systemic healthy-chronic periodontitis, following nonsurgical periodontal treatment (NSPT) in the form of scaling root planing (SRP) and oral hygiene instruction (OHI).<sup>29</sup> This finding shows the positive effect of NSPT in reducing the risk of atherosclerosis in periodontitis patients.

The relationship between periodontitis and atherosclerosis in indirect pathway showed in several studies.<sup>25-28,36</sup> RCT by Montenegro et al. (2019) showed that SRP and OHI given to test group had a positive effect on reducing

inflammation biomarker levels such as CRP, interleukin-6, and interleukin-8.<sup>26</sup> Participants who took part in the study were stable coronary artery disease (CAD) patients with periodontitis.<sup>26</sup> It also found that HDL and CRP levels were uncontrolled in some patients in both the test and control groups. This indicates that even though the patient has received cardiovascular treatment so that their conditions are stable, there was still on going systemic inflammation marked by abnormal levels of sensitive biomarkers such as CRP. CRP is also known as the gold standard biomarker that measures systemic inflammation and its change has been used as the primary outcome after intervention.<sup>21,50</sup> Another studies also reported positive effect of periodontal treatment on cytokines and lipid profile in patients with both periodontitis and atherosclerotic CVD.<sup>18,21,28,29</sup>

Noteworthy, several inflammation biomarker such as fibrinogen and white blood cells are also being in charge.<sup>31</sup> Significantly increased levels of fibrinogen and leukocytes also commonly found in patients with atherosclerotic lesions.<sup>12,31,50</sup> Another study also showed effect of NSPT to improve endothelial function of artery in MI patient through the FMD and circulating EMP assessment.<sup>25,27,28</sup> Endothelial dysfunction is one of the factor that plays an important role in atherosclerosis, since its beginning of advanced stages of the disease.<sup>7,23,51</sup>

2 RCTs showed the positive effect of NSPT in the form of SRP and OHI to reduce FMD values, BP, and circulating EMP levels in patients with periodontitis and myocardial infarction.<sup>25,52</sup> This result proved that NSPT can improve the endothelial function in atherosclerotic CVD with periodontitis. Contrary, RCT by Saffi et al (2018) demonstrated that the NSPT did not provide better vasodilation in patients with CAD in a short-term follow-up period.<sup>27</sup> After NSPT, there were no significant improvements in FMD observed in both control and test group in 3 months.<sup>27</sup> This can be affected by the sample selected in that study that already received cardiovascular treatment and being under pharmacological interventions at the time of the study, which may explain the improvement in FMD observed not only in test group but also in the control group as well. However, it also showed that blood markers were maintained stable in the test and not in the

control group.<sup>27</sup> This still can be a prove that periodontal therapy has an effect on cardiovascular conditions.

Beside inflammation biomarker, risk level of atherosclerosis can be measured by CIMT level and detection of CCAA that defined relationship between periodontitis and atherosclerosis<sup>32,53,54</sup> The image of CCAA in periodontitis patients might be assumed that MI found higher in subject with periodontitis. Strong association between periodontal health parameter such as recession level, PD, and CAL were also assessed with degree of CAO measured by angiography in cross sectional study by Ketabi et al (2016).<sup>37</sup> This evidence supported another study that suggested periodontitis as a risk factor for atherosclerotic CVD.

Several studies explained about oral hygiene care programme as one of ways to treat periodontitis and maintain oral health especially for those with systemic disease related to oral conditions.<sup>5,55,56</sup> Cross sectional study by Nitya et al (2020) concluded that periodontal disease and poor OH were more severe among the subjects with CIMT > 1 mm. In order to impede the progression of increasing CIMT, preventive oral health programmes need to be given to help patients lower their risks. Dai et al (2020) also proved that AOHCP including toothbrushing, daily rinsing, OHI, and oral hygiene training in systematic way was more effective than the COHCP in reducing levels of plaque and gingival bleeding.<sup>30</sup> So that this simple and low cost intervention should be advocated for atherosclerotic CVD rehabilitation.

## Conclusions

This scoping review concluded that periodontitis and atherosclerosis have an association both in direct and indirect pathway with the most reported link is indirect pathway through systemic inflammation marked by several measurable indicators such as serological biomarker level, flow-mediated dilations level, carotid artery intima media thickness, detection of calcified carotid artery atheromas in panoramic radiograph, and degree of coronary artery obstruction. Further study of larger trials with huge samples and longer follow-up period about the clearer and detail mechanisms happened in both conditions need

to be conducted to get more reliable result.

### Acknowledgments

The study was supported by Grant of Universitas Padjadjaran Nomor: 1959 / UN 6.3.1 / PT.00 / 2021.

### Declaration of Interest

The authors report no conflict of interest.

No.	Author (Year)	Study Design	Participants	Research Result	Conclusion
1.	Lobo M, et al. <sup>25</sup> (2020)	RCT	1. A total of 48 ST-segment elevation MI patients: 2. Test group: 24, given SRP and OHI 3. Control group: 24, given OHI in the end of session	After 6 months: 4. Statistically significant reductions in all indices (PD, CAL, BOP, and visible plaque number) after periodontal treatment 5. FMD significantly improved in test group, but not significantly in the control group	There was a positive correlation between NSPT with endothelial function. Treatment of periodontal disease improves the endothelial function of patients with a recent MI without adverse clinical events. Larger trials are needed to assess the benefit of periodontal treatment on clinical outcomes.
2.	Montenegro et al. <sup>26</sup> (2019)	RCT	6. A total of 82 patients with stable CAD and chronic periodontitis: 7. Test Group: 39, given SRP and OHI 8. Control Group: 43, given dental prophylaxis	After 3 months: 1. Significant decrease in biomarker concentrations in the test group, include CRP, IL-10, IL-8, IL-6, TNF- $\alpha$ 2. No significant difference in the levels of glycated Hb. 3. More than 80% of patients in the test and control groups had LD, HDL, and total cholesterol under control.	There was a positive correlation between NSPT with biomarker inflammation of CAD. NSPT has been shown to reduce levels of CRP, IL-6, and IL-8 as indicators of systemic inflammation in CVD patients as well as to reduce local periodontal tissue inflammation.
3.	Saffi M, et al. <sup>27</sup> (2018)	RCT	9. A total of 69 patients with stable coronary disease and severe periodontitis: 10. Test group: 31, given SRP and OHI 11. Control group: 38, given delayed treatment	After 3 months: 1. Significant changes statistically in periodontal parameters (plaque, PD, CAL, and BOP) in test group. 2. No significant improvements were observed in the control (1.37%) and test (1.39%) groups in FMD levels with no significant between-groups difference.	Periodontal treatment did not provide better vasodilation in patients with coronary disease in a short-term follow-up period, although it maintained blood concentrations of markers of vascular inflammation.
4.	Zhou Q, et al. <sup>28</sup> (2017)	RCT	12. A total of 95 prehypertensive adults with moderate to severe periodontitis: 13. Test group: 47, given SRP, OHI, and minocycline hydrochloride ointment 14. Control group: 48, given supragingival scaling	After 6 months: 1. The periodontal conditions were significantly improved (P <0.05) after intensive NSPT 2. The primary outcomes including systolic BP, diastolic BP and EMPs were markedly reduced in the test group 3. Reduction in BP levels and EMPs was related to the improvement in PD	There was a positive correlation between NSPT with prehypertensive conditions. Intensive NSPT reduces BP levels and EMPs in prehypertensive patients with periodontitis.
5.	Bozoglan et al. <sup>29</sup> (2017)	RCT	15. A Total of 40 patients: 16. Test group: 20 patients with periodontitis and atherosclerosis, given NSPT 17. Control Group: 20 periodontitis with a healthy systemic condition, given NSPT	After 6 months: 1. Significant decrease in levels of CRP, LDL, PLT, fibrinogen, and WBC which was also in line with the decrease in the number of periodontal pathogens.	There was a positive correlation between periodontal pathogens with inflammation biomarkers. An association between decreased microorganisms and inflammatory biomarkers after NSPT may indicate that NSPT has the potential to reduce the risk of atherosclerosis.
6.	Dai, R et al. <sup>30</sup> (2017)	RCT	18. A total of 94 stroke patients: 19. Test group: 47, given AOHCP 20. Control group: 47, given COHCP	After 6 months: 1. Participants of both programmes had a significant reduction in the percentages of sites with moderate to abundant dental plaque (p<0.001) and with gingival bleeding (p<0.05). 2. Those with AOHCP had significantly less plaque and gingival bleeding than those with COHCP controlling for other factors at the end of the clinical trial period	Although both oral hygiene care programmes were effective in terms of plaque and gingival bleeding control, the AOHCP was more effective than the COHCP in reducing levels of plaque and gingival bleeding. This relative simple and low cost intervention should be advocated for inclusion in stroke rehabilitation.

7.	Wojtkowska A, et al. <sup>31</sup> (2021)	Case control study	21. A total of 71 patients < 65 years old with acute MI. 22. Study Group: 67 23. Control Group: 40	The BOP value significantly correlated with fibrinogen All indices regarding the PD correlated significantly with the number of leukocytes PD and NoPD ≥ 4 mm were also associated significantly with the level of hsCRP.	There was a positive correlation between periodontitis and acute MI. Patients with acute MI have worse periodontal status compared to people without CHD. Periodontitis is a risk factor for MI and also affects the degree of post-infarction left ventricular damage
8.	Gustafson N, et al. <sup>32</sup> (2020)	Case control study	24. A total of 82 patients with periodontitis and CCAA 25. Case Group: 738 26. Control Group: 744	In a multivariable model, MI was associated with CCAA combined with periodontitis, as assessed by degree of bone loss Participants with combined periodontitis and CCAA had a higher risk of having MI	There was a positive correlation between periodontitis and CCAAs. Periodontitis patients displayed CCAA in panoramic radiographs significantly more frequently than those without periodontitis, independent of whether the person had a recent MI
9.	Bawankar P, et al. <sup>33</sup> (2021)	Cross sectional study	27. 500 patients with a known history of CVD and suffered from moderate to severe periodontal disease	The fact that gum disease can affect the general body health was known to just 46 (19.74%) males and 37 (13.85%) females Only 11 females and 8 males were of the view that patients with periodontal disease have an increased prevalence and incidence of CVDs 469 patients disagreed that treatment of periodontitis helps to improve your biochemical profile in cases of CVDs	Within the limitations of the study, it can be concluded that there is a lack of awareness and an ignorant attitude about the bidirectional relationship between CVD and periodontitis among the CVD patients. Special efforts should be taken by dental as well as medical professionals to increase the awareness in this regard and thereby deliver quality health-care services at earlier stages.
10.	Nitya K, et al. <sup>34</sup> (2020)	Cross sectional study	28. 30 subjects undergoing ultrasonography to measure CIMT test	Significantly higher mean scores were observed for all oral parameters among subjects with CIMT > 1 mm aged > 45 years and among males (p ≤ 0.05*). Subjects with periodontal disease and poor OH were having CIMT level > 1 mm	The results of the study concluded that periodontal disease and poor OH were more severe among the subjects with CIMT > 1 mm. To halt the progression of increasing CIMT, preventive oral health programmes need to be integrated in the cardiac setting with established dental referral which can bring out positive health behaviours.
11.	Atarbashi-Moghadam et al. <sup>35</sup> (2018)	Cross sectional study	29. 23 patients scheduled for CABG due to CAD and have periodontal inflammation sign at least 2 teeth with periodontal pocket > 5mm	The DNA of Pg, Aa, and Cr were found to be positive in subgingival plaques and atherosclerotic plaques The bacterial species found in atherosclerotic plaques were also found in the subgingival plaques of the same patient	There was a positive correlation between periodontal pathogens and atherosclerosis. These periopathogens may contribute to the pathogenesis of atherosclerosis directly or indirectly. Further studies are required to ascertain the underlying mechanism of these periopathogens in the atherosclerotic process.
12.	Kudo, et al. <sup>36</sup> (2018)	Cross sectional study	30. 104 patients from dental and medical clinic	LDL levels and percentage (%) of mobile teeth were positively related to plasma IgG antibody titer against P.g with multivariate analysis. Corresponding to improvements in periodontal clinical parameters after treatment, right and left max IMT levels were decreased significantly after treatment	There was a positive correlation between periodontal treatment with the improvement in max carotid IMT. Periodontal treatment is considered to be important for preventing the onset of cerebral and MI caused by atherosclerosis.
13.	Ketabi M et al. <sup>37</sup> (2016)	Cross sectional study	31. 82 patients that were referred for angiography	There were significant positive correlation between variables R, PD, CAL, DMF, BOP, and degree of CAO. The mean of variables PD, CAL, and DMF in patients with obstructed arteries were significantly higher than subjects without CAO.	This study showed an association between periodontal disease and dental parameters with the severity of CAO measured by angiography. However, this association must not interpret as a cause and effect relationship.

**Table 2. Data Extraction.**

SRP: Scaling Root Planing, OHI: Oral Hygiene Instruction, PD: Pocket Depth, CAL: Clinical Attachment Loss, BOP: Bleeding On Probing, CAD: Coronary Artery Disease, NSPT: Nonsurgical Periodontal Treatment, CRP: C-Reactive Protein, IL-10: Interleukin 10, IL-8: Interleukin 8, IL-6: Interleukin 6, TNF-α: Tumor Necrosis Factor-alpha, sVCAM-1: soluble-Vascular Cell Adhesion Molecule-1, EMP: Endothelial Microparticles, BP: Blood Pressure, PLT: Platelet, LDL: Low Density Lipoprotein, WBC: White Blood Cell, PI: Plaque Index, GI: Gingival Index, AOHCP: Advance Oral Hygiene Care Programme, COHCP: Conventional Oral Hygiene Care Programme, API: Apical Plaque

Index, BNP: Brain Natriuretic Peptides, CCAAs: Calcified Carotid Artery Atheromas, CVD: Cardiovascular Disease, CIMT: Carotid Intima Media Thickness, OHI-s: Oral Hygiene Index-simplified, LoA: Loss of Attachment, WHO: World Health Organization, CABG: Coronary Artery Bypass Graft, Pg: Porphyromonas gingivalis, Cr: Camphylobacter rectus, Aa: Aggregatibacter actinomycetemcomytans, DNA: Deoxyribonucleic Acid, PCR: Polymerase Chain Reaction, IMT: Intima-Media Thickness, CAO: Coronary Artery Obstruction, R: Recession, DMF: Decay Missing Filling.

## References

1. Newman MG, Takei HH, Klokkevold PR, Carranza FA. Newman and Carranza's Clinical Periodontology. 13th ed. Philadelphia: Elsevier; 2019.
2. Bui FQ, Almeida-da-Silva CLC, Huynh B, Trinh A, Liu J, Woodward J, et al. Association between periodontal pathogens and systemic disease. Biomedical Journal. 2019; 42: 27–35.
3. Komara, I, Sopiati S, Hendiani I, Rusminah N, Susanto A. Effect of Carbonate Apatite Membrane as Adjunctive Therapy of Scaling and Root Planing on Gingival Crevicular Fluid Matrix Metalloproteinase-8 in Chronic Periodontitis Patient. Journal of International Dental and Medical Research. 2021;14(4): 1517-22.
4. Vos T, Abajobir AA, Abbafati C, Abbas KM, Abate KH, Abd-Allah F, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990-2016: A systematic analysis for the Global Burden of Disease Study 2016. The Lancet. 2017;390(10100): 1211-59.
5. Sabharwal A, Gomes-Filho IS, Stellrecht E, Scannapieco FA. Role of periodontal therapy in management of common complex systemic diseases and conditions: An update. Periodontology 2000.2018;78:212–26.
6. Liljestrand JM, Paju S, Pietiäinen M, Buhlin K, Persson GR, Nieminen MS, et al. Immunologic burden links periodontitis to acute coronary syndrome. Atherosclerosis. 2018; 268:177–84.
7. Lilly L. Pathophysiology of Heart Disease. 6th ed. Lily L, editor. Philadelphia: Wolters Kluwer; 2016.
8. Loscalzo J. 2nd Edition Harrison's Cardiovascular Medicine. 2nd ed. Longo D, Kasper D, Jameson JL, Fauci A, Hauser S, Loscalzo J, editors. New York: McGraw-Hill Education; 2013.
9. Shrivastava AK, Singh HV, Raizada A, Singh SK. C-reactive protein, inflammation and coronary heart disease. Egyptian Heart Journal. Egyptian Society of Cardiology; 2015;67: 89–97.
10. Fatimatu Zahra N, Christedy R, Susilawati I D A, Fajrin W. Pulpitis Induced Carotid Atherosclerosis. Journal of International Dental and Medical Research. 2020;13(2):513-8.
11. Katsiari CG, Bogdanos DP, Sakkas LI. Inflammation and cardiovascular disease. World J Transl Med. 2019;31:1-8.
12. Roca-Millan E, González-Navarro B, Del Mar Sabater-Recolons M, Mari-Roig A, Jané-Salas E, López-López J. Periodontal treatment on patients with cardiovascular disease: Systematic review and meta-analysis. Med Oral Patol Oral y Cir Bucal. 2018 ;23(6):e681–90.
13. Pietiäinen M, Liljestrand JM, Kopra E, Pussinen PJ. Mediators between oral dysbiosis and cardiovascular diseases. Eur J Oral Sci. 2018 ;126:26–36.
14. Reinhardt B, Klocke A, Neering SH, Selbach S, Peters U, Flemmig TF, et al. Microbiological dynamics of red complex bacteria following full-mouth air polishing in periodontally healthy subjects—a randomized clinical pilot study. Clin Oral Investig. 2019 ;23(10):3905–14.
15. Suzuki JI, Aoyama N, Ogawa M, Hirata Y, Izumi Y, Nagai R, et al. Periodontitis and cardiovascular diseases. Expert Opinion on Therapeutic Targets. 2010;14: 1023–7.
16. Loftus I. Mechanisms of plaque rupture. In: Mechanisms of Vascular Disease: A Reference Book for Vascular Specialists. University of Adelaide Press; 2011.
17. Teles R, Wang CY. Mechanisms involved in the association between periodontal diseases and cardiovascular disease. Oral Diseases. 2011;17: 450–61.
18. Caúla AL, Lira-Junior R, Tinoco EMB, Fischer RG. The effect of periodontal therapy on cardiovascular risk markers: A 6-month randomized clinical trial. J Clin Periodontol. 2014;41(9):875–82.
19. Koppolu P, Durvasula S, Palaparthi R, Rao M, Sagar V, Reddy SK, et al. Estimate of CRP and TNF-alpha level before and after periodontal therapy in cardiovascular disease patients. Pan Afr Med J. 2013;15(1): 1-10.
20. Hada DS, Garg S, Ramteke GB, Ratre MS. Effect of Non-Surgical Periodontal Treatment on Clinical and Biochemical Risk Markers of Cardiovascular Disease: A Randomized Trial. J Periodontol. 2015 ;86(11):1201–11.
21. Bokhari SAH, Khan AA, Butt AK, Azhar M, Hanif M, Izhar M, et al. Non-surgical periodontal therapy reduces coronary heart disease risk markers: A randomized controlled trial. J Clin Periodontol. 2012 ;39(11):1065–74.
22. Almeida APCPSC, Fagundes NCF, Maia LC, Lima RR. Is there an Association Between Periodontitis and Atherosclerosis in Adults? A Systematic Review. Curr Vasc Pharmacol. 2019;10:1-9.
23. Teeuw WJ, Slot DE, Susanto H, Gerdes VEA, Abbas F, D'Aiuto F, et al. Treatment of periodontitis improves the atherosclerotic profile: A systematic review and meta-analysis. Vol. 41, Journal of Clinical Periodontology. 2014 ;41(1):70–9.
24. Moher D, Liberati A, Tetzlaff J, Altman D. G. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. International journal of surgery (London, England). 2010; 8(5):336-41.
25. Lobo MG, Schmidt MM, Lopes RD, Dipp T, Feijó IP, Schmidt KES, et al. Treating periodontal disease in patients with myocardial infarction: A randomized clinical trial. Eur J Intern Med. 2020 ;71:76–80.
26. Montenegro MM, Ribeiro IWJ, Kampits C, Saffi MAL, Furtado M V., Polanczyk CA, et al. Randomized controlled trial of the effect of periodontal treatment on cardiovascular risk biomarkers in patients with stable coronary artery disease: Preliminary findings of 3 months. J Clin Periodontol. 2019;46(3):321–31.
27. Saffi MAL, Rabelo-Silva ER, Polanczyk CA, Furtado M V., Montenegro MM, Ribeiro IWJ, et al. Periodontal therapy and endothelial function in coronary artery disease: A randomized controlled trial. Oral Dis. 2018 ;24(7):1349–57.
28. Zhou Q-B, Xia W-H, Ren J, Yu B-B, Tong X-Z, Chen Y-B, et al. Effect of Intensive Periodontal Therapy on Blood Pressure and Endothelial Microparticles in Patients With Prehypertension and Periodontitis: A Randomized Controlled Trial. J Periodontol. 2017;88(8):711–22.
29. Bozoglan A, Ertugrul AS, Taspınar M, Yuzbasioglu B. Determining the relationship between atherosclerosis and periodontopathogenic microorganisms in chronic periodontitis patients. Acta Odontol Scand. 2017;75(4):233–42.
30. Dai R, Lam OLT, Lo ECM, Li LSW, McGrath C. A randomized clinical trial of oral hygiene care programmes during stroke rehabilitation. J Dent. 2017 ;61:48–54.
31. Wojtkowska A, Zapolski T, Wysokińska-Miszczuk J, Wysokiński AP. The inflammation link between periodontal disease and coronary atherosclerosis in patients with acute coronary syndromes: case-control study. BMC Oral Health. 2021;21(1):1-17.
32. Gustafsson N, Ahlqvist J, Näslund U, Buhlin K, Gustafsson A, Kjellström B, et al. Associations among Periodontitis, Calcified Carotid Artery Atheromas, and Risk of Myocardial Infarction. J Dent Res. 2020;99(1):60–8.
33. Bawankar P, Kolte A, Kolte R. Assessment of knowledge, awareness, and attitude among patients with cardiovascular disease about its association with chronic periodontitis. J Indian Soc Periodontol. 2021;25(2):156–61.
34. Nitya KN, Doshi D, Kulkarni S, Reddy MP, Srilatha A, Satyanarayana D. Assessment of periodontal status based on carotid artery intima media thickness. Oral Health Prev Dent. 2020;18(1):511–9.
35. Atarbashi-Moghadam F, Havaei SR, Havaei SA, Hosseini NS,

- Behdadmehr G, Atarbashi-Moghadam S. Periopathogens in atherosclerotic plaques of patients with both cardiovascular disease and chronic Periodontitis. *ARYA Atheroscler*. 2018;14(2):53–7.
36. Kudo C, Shin WS, Sasaki N, Harai K, Kato K, Seino H, et al. Effects of periodontal treatment on carotid intima-media thickness in patients with lifestyle-related diseases: Japanese prospective multicentre observational study. *Odontology*. 2018;106(3):316–27.
37. Ketabi M, Meybodi F, Asgari M. The association between periodontal disease parameters and severity of atherosclerosis. *Dent Res J (Isfahan)*. 2016;13(3):250–5.
38. Zardawi F, Gul S, Abdulkareem A, Sha A, Yates J. Association Between Periodontal Disease and Atherosclerotic Cardiovascular Diseases : Revisited. 2021;7:1-17.
39. Berlin-Broner Y, Febbraio M, Levin L. Association between apical periodontitis and cardiovascular diseases: a systematic review of the literature. *International Endodontic Journal*. 2017;50: 847–59.
40. Li C, Lv Z, Shi Z, Zhu Y, Wu Y, Li L, et al. Periodontal therapy for the management of cardiovascular disease in patients with chronic periodontitis. *Cochrane Database Syst Rev*. 2017;8.
41. Leira Y, Seoane J, Blanco M, Rodríguez-Yáñez M, Takkouche B, Blanco J, et al. Association between periodontitis and ischemic stroke: a systematic review and meta-analysis. *Eur J Epidemiol*. 2017;32(1):43–53.
42. Muñoz Aguilera E, Suvan J, Buti J, Czesnikiewicz-Guzik M, Barbosa Ribeiro A, Orlandi M, et al. Periodontitis is associated with hypertension: A systematic review and meta-analysis. *Cardiovascular Research*. 2020;116:28–39.
43. Frostegård J. Immunity, atherosclerosis and cardiovascular disease. *BMC Med*. 2013;11(1):1-13.
44. Wu F, Chen Y, Demmer RT, Parvez F, Paul RR, Shaheen I, et al. Periodontal diseases and carotid intima-media thickness in Bangladesh. *J Clin Periodontol*. 2016 ;43(11):909–17.
45. Atarbashi-moghadam F, Havaei SR, Havaei SA. Periopathogens in atherosclerotic plaques of patients with both cardiovascular disease and chronic periodontitis Abstract Original Article. 2018;14(2):53–7.
46. Wijayanti PM, Setyopranoto I. Hubungan Antara Periodontitis , Aterosklerosis, Stroke Iskemik Akut. *Mutiara Medika*. 2016;8: 120–8.
47. Cho HJ, Shin MS, Song Y, Park SK, Park SM, Kim HD. Severe Periodontal Disease Increases Acute Myocardial Infarction and Stroke: A 10-Year Retrospective Follow-up Study. *J Dent Res*. 2021;100(7):706-13
48. Tonetti MS, Van Dyke TE. Periodontitis and atherosclerotic cardiovascular disease: Consensus report of the Joint EFP/AAP Workshop on Periodontitis and Systemic Diseases. *Journal of Clinical Periodontology*. 2013;40:24–9.
49. Ramirez JH, Arce RM, Contreras A. Periodontal treatment effects on endothelial function and cardiovascular disease biomarkers in subjects with chronic periodontitis: Protocol for a randomized clinical trial. *Trials*. 2011;12(1):1-10.
50. López NJ, Quintero A, Casanova PA, Ibieta CI, Baelum V, López R. Effects of Periodontal Therapy on Systemic Markers of Inflammation in Patients With Metabolic Syndrome: A Controlled Clinical Trial. *J Periodontol*. 2012;83(3):267–78.
51. Bacchiega BC, Bacchiega AB, Usnayo MJG, Bedirian R, Singh G, Pinheiro G da RC. Interleukin 6 inhibition and coronary artery disease in a high-risk population: A prospective community-based clinical study. *J Am Heart Assoc*. 2017;6(3): e005038.
52. Zhou Q-B, Xia W-H, Ren J, Yu B-B, Tong X-Z, Chen Y-B, et al. Effect of Intensive Periodontal Therapy on Blood Pressure and Endothelial Microparticles in Patients With Prehypertension and Periodontitis: A Randomized Controlled Trial. *J Periodontol*. 2017 ;88(8):711–22.
53. Skilton MR, Maple-Brown LJ, Kapellas K, Celermajer DS, Bartold M, Brown A, et al. The effect of a periodontal intervention on cardiovascular risk markers in Indigenous Australians with periodontal disease: The PerioCardio study. *BMC Public Health*. 2011;11(1):1-8.
54. Orlandi M, Suvan J, Petrie A, Donos N, Masi S, Hingorani A, et al. Association between periodontal disease and its treatment, flow-mediated dilatation and carotid intima-media thickness: A systematic review and meta-analysis. *Atherosclerosis*. 2014;236(1):39-46.
55. Mizuno H, Ekuni D, Maruyama T, Kataoka K, Yoneda T, Fukuhara D, et al. The effects of non-surgical periodontal treatment on glycemic control, oxidative stress balance and quality of life in patients with type 2 diabetes: A randomized clinical trial. *PLoS One*. 2017 ;12(11): e0188171.
56. Rastogi P, Singhal R, Sethi A, Agarwal A, Singh VK, Sethi R. Assessment of the effect of periodontal treatment in patients with coronary artery disease: A pilot survey. *Journal of Cardiovascular Disease Research*. 2012;3(2):124–7.