Beyond The Gums: The Systemic Impact of Periodontal Therapy – A Comprehensive Literature Review

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***Abstract*—Periodontitis is a chronic inflammatory disease initiated by dysbiotic biofilm accumulation and characterised by progressive destruction of the supporting structures of teeth. Increasing scientific evidence demonstrates that periodontitis contributes to systemic inflammatory burden and is associated with several systemic diseases, including diabetes mellitus, cardiovascular diseases, adverse pregnancy outcomes, rheumatoid arthritis, respiratory diseases, and neurodegenerative disorders. Periodontal therapy, particularly non-surgical mechanical debridement, has been proposed as a modifiable intervention capable of improving systemic health outcomes. This review critically examines the biological mechanisms underlying the periodontal-systemic link and evaluates current evidence regarding the impact of periodontal therapy on systemic disease markers and clinical outcomes. Strong evidence supports improved glycemic control following periodontal therapy in type 2 diabetes mellitus. Moderate evidence indicates beneficial effects on systemic inflammatory markers and endothelial function in cardiovascular disease. Evidence for pregnancy outcomes, rheumatoid arthritis, respiratory diseases, and neurodegenerative disorders remains emerging and heterogeneous. While definitive evidence for a reduction in hard systemic endpoints is limited, periodontal therapy represents an important component of comprehensive systemic disease management. Further large-scale randomised controlled trials are required to establish long-term systemic benefits.**

***Index Terms*—Periodontitis; Periodontal therapy; Systemic inflammation; Diabetes mellitus; cardiovascular disease; Periodontal medicine.**

I. INTRODUCTION

Periodontitis is a multifactorial inflammatory disease with a chronic nature, caused by microbial dysbiosis and host-mediated tissue destruction of the periodontium. [1, 2] This disease remains one of the most prevalent inflammatory disorders in the world, with an estimated prevalence of 62% in adults, and nearly 23% of those with a severe form of the disease. [3, 4] While this disease was once considered to have a localised impact limited to the oral cavity, it is currently recognised to have systemic implications and to represent a systemic inflammatory disorder. [5-7]

The concept of periodontal medicine was born in the 1990s with the results of epidemiological studies demonstrating associations between periodontitis and cardiovascular disease. [8, 9] This association was expanded to diabetes mellitus, adverse pregnancy outcomes, rheumatoid arthritis, respiratory diseases, metabolic syndrome, and neurodegenerative disorders with subsequent studies. [10-15]

Systemic implications of periodontitis have been attributed to the effects of chronic low-grade inflammation and bacteraemia. Gram-negative anaerobic micro-organisms in periodontal pockets, such as Porphyromonas gingivalis, Tannerella forsythia, and Treponema denticola, have been shown to induce the production of inflammatory mediators, including IL-1b, IL-6, TNF-alpha, and CRP, which enter the bloodstream and have been associated with endothelial dysfunction, insulin resistance, and immune system alterations.

Periodontal therapy is a potential solution to control systemic inflammation and influence disease

progression, considering the burden of systemic infection. This review aims to provide an in-depth examination of the biological mechanisms and available evidence on the effects of periodontal therapy on systemic conditions. [16-18]

II. BIOLOGICAL BASIS OF THE PERIODONTAL-SYSTEMIC RELATIONSHIP

1. Bacteraemia and the Microbial Translocation Phenomena

Mastication and tooth brushing may cause bacteraemia among patients with periodontitis. [19]

Periodontal bacteria were found in atherosclerotic plaques and placental tissue, indicating the possibility of the spread of periodontal bacteria into the body. The presence of bacteria in areas other than the oral cavity supports the idea that periodontitis may cause systemic diseases. [20, 21]

2. Systemic Inflammatory Spill Over

Periodontal tissue inflammation is a source of inflammatory mediators. Periodontitis patients were found to have elevated levels of systemic inflammatory biomarkers such as CRP, IL-6, and TNF-alpha. [22, 23]

Inflammatory mediators may cause:

- Endothelial dysfunction
- Insulin resistance
- Instability of atherosclerotic plaques
- Hypercoagulability.

Reducing the level of periodontal inflammation may help in the reduction of systemic inflammatory levels.

3. Molecular Mimicry and Autoimmunity

P. Gingivalis was found to produce peptidyl arginine deiminase (PAD), which is associated with the autoimmune disease rheumatoid arthritis (24).

III. PERIODONTAL THERAPY AND DIABETES MELLITUS

Diabetes mellitus is defined as a metabolic disorder characterized by high levels of blood glucose resulting from problems in insulin production, utilization, or both. Diabetes mellitus is considered one of the most common systemic diseases that affect the oral cavity. There have been studies proving the two-way relationship between diabetes mellitus and periodontal disease, whereby diabetes mellitus exacerbates the severity of periodontal disease, and periodontal disease also exacerbates the severity of diabetes mellitus.

Periodontitis is also called the sixth complication of diabetes mellitus because of the close relationship between diabetes mellitus and periodontitis, and the significant influence of periodontitis on diabetes mellitus and the whole body. [25]

How diabetes mellitus and periodontal disease are linked at the biological level

There are many ways in which diabetes mellitus and periodontal disease are linked at the biological level, and the main ones include the following:

1) Advanced Glycation End Products (AGEs)

Diabetes mellitus causes high levels of glucose in the blood, leading to the production of AGEs, which then attach to the RAGE receptors of the immune system and the endothelium, leading to increased oxidative stress and the inflammatory response in the gum tissues. [26]

2) Compromised Immune Response

Diabetes mellitus causes a compromised immune response, whereby the neutrophils of the immune system of the patient with diabetes mellitus fail to kill the causative pathogens of the periodontal disease, leading to the exacerbation of the disease.

3) Elevated Inflammatory Mediators

The gum disease causes the production of the main inflammatory cytokines, IL-1β, TNF-α, and IL-6, which then lead to the exacerbation of the disease.

4) Microvascular Changes

Diabetes also causes microvascular changes, leading to a reduction in the blood flow to the periodontal tissues, hence slowing the rate of healing and causing tissue damage. [27]

Non-Surgical Periodontal Therapy (NSPT)

The main treatment for diabetes is Non-Surgical Periodontal Therapy (NSPT), which includes the following procedures:

- Scaling and root planning
- Instruction in the practice of oral hygiene

- The need for antimicrobial treatment

These procedures reduce the bacterial load and the level of gum inflammation, with the potential to also control the metabolic syndrome associated with diabetes.

Impact on glycaemic control

Several studies through systematic review and randomized trials have confirmed that the treatment of periodontal disease results in the improvement of blood glucose levels in type 2 diabetes mellitus patients. This is through a reduction in HbA1c levels. (28)

A randomized clinical trial reported that intensive periodontal therapy improved glycemic control and reduced systemic inflammatory markers in diabetic patients. (29)

Evidence from Systematic Reviews

Systematic reviews and meta-analyses support the role of periodontal therapy in improving glycemic control in patients with diabetes. Improvements have been observed in:

- HbA1c levels
- C-reactive protein (CRP)
- Pro-inflammatory cytokines

However, the magnitude of improvement depends on factors such as severity of periodontal disease, baseline glycemic control, and type of periodontal therapy used. (30)

Clinical Evidence

After 3–6 months of non-surgical periodontal therapy, HbA1c levels range from 0.3% to 0.6%, as shown by statistically significant randomised controlled trials. (31-34) The evidence for improved glycaemic control after periodontal treatment has been validated by meta-analyses, with only moderate quality. (35)

The clinically significant reduction of HbA1c is comparable to the addition of a second-line pharmacologic agent in some patients. In addition, periodontal treatment can lower CRP and IL-6 levels, leading to an improvement in systemic inflammation. (36)

IV. PERIODONTAL THERAPY AND CARDIOVASCULAR DISEASE

Cardiovascular diseases continue to be the leading cause of illness and death in the world. In the last few years, however, scientists are recognizing the connection that is developing between periodontal diseases, or the chronic infection of the tissue that holds the teeth in place, and heart problems such as atherosclerosis, coronary disease, high blood pressure, and stroke. This is based on the fact that the inflammatory processes that are connected with the infection of the gums, as well as the bacteria that are connected with this infection, can travel throughout the body and affect other areas. (37)

Periodontitis is an infection that affects a huge number of adults in the world. This infection is known to induce a systemic inflammatory response that is a risk factor for cardiovascular diseases. (38)

Biological Mechanisms in which Periodontitis and Cardiovascular Disease Are Linked

There are several ways in which the infection in the teeth could affect the health of the heart:

1) Systemic Inflammation

The infection in the teeth is known to induce the inflammatory response in the body, or the body's way of fighting infection. This could then cause the lining of the blood vessels to become damaged, leading to the development of atherosclerosis. (39)

2) Bacterial Spread

The bacteria that are present in the gingivitis infection, such as P. gingivalis and F. nucleatum, could travel into the bloodstream as a result of the act of chewing or a dental procedure, leading to damage to the blood vessels.

3) Endothelial Dysfunction

The ongoing inflammation in the gums has the potential to damage the endothelium, resulting in increased vascular permeability and clotting.

4)Immune Response and Atherosclerosis

In addition, the immune system's response to the pathogens in the periodontal infection may also result in the deposition of lipids and inflammatory cells in

the arterial wall, leading to the development of plaque. (40)

Impact of Periodontal Therapy on cardiovascular system

Non-Surgical Periodontal Therapy (NSPT)

NSPT is the most extensively studied method, which includes:

- Scaling and root planning
- Oral hygiene instructions
- Use of antimicrobial agents when indicated

NSPT reduces the level of inflammation in the gums and the number of pathogens present in the infection. This, in turn, may lower the inflammatory markers that are linked to the risk of heart disease.

The systematic review and meta-analysis of randomized trials showed that NSPT significantly reduces inflammatory markers such as CRP and IL-6, as well as systolic blood pressure. (41)

Effects on Cardio-Marking Biomarkers

Review of the research findings on the impact of periodontal treatment on cardio risk factors reveals that the following changes are consistently observed:

- Cardio-marking biomarkers such as hs-CRP are reduced
- Pro-inflammatory cytokines are reduced,
- Endothelial function is improved,
- Glycaemic control is improved in diabetes patients.

Another meta-analysis reported that periodontal treatment significantly reduced inflammatory mediators including CRP, IL-6, TNF-α, and IL-8, particularly in patients with coronary artery disease. (42)

Evidence from Interventional Studies

Periodontal treatment can improve endothelial dysfunction, as shown by flow-mediated dilation (43) There is also strong evidence that CRP and fibrinogen levels decrease significantly (44) However, long-term studies showing a decrease in heart attacks or strokes are not available.

The current evidence only shows improvements in markers that indicate heart disease, not a direct reduction in the occurrence of cardiovascular diseases.

V. PERIODONTAL THERAPY AND ADVERSE PREGNANCY OUTCOMES

Periodontal disease is a chronic inflammatory condition affecting the supporting tissues of the teeth and is primarily caused by bacterial biofilm and host inflammatory response. Increasing evidence suggests that periodontal disease may influence systemic conditions, including adverse pregnancy outcomes such as preterm birth, low birth weight, pre-eclampsia, and fetal growth restriction. The association is thought to occur due to systemic dissemination of periodontal pathogens and inflammatory mediators affecting the fetoplacental unit. (45)

Pregnancy itself predisposes women to periodontal inflammation due to hormonal changes that increase vascular permeability and modify host immune responses, thereby exacerbating gingival inflammation. (46)

Mechanism Linking Periodontal Disease and Pregnancy Outcomes

Several biological mechanisms have been proposed:

- Bacterial dissemination

Periodontal pathogens such as Fusobacterium nucleatum and Porphyromonas gingivalis may enter the bloodstream and reach the placenta, contributing to infection-mediated complications.

- Inflammatory mediator release

Periodontal infections stimulate production of inflammatory cytokines such as IL-1β, IL-6, TNF-α, and prostaglandin E2, which may trigger uterine contractions and premature rupture of membranes.

- Immune response alteration

Maternal immune response to periodontal pathogens may induce systemic inflammation affecting the fetoplacental unit. (47)

These mechanisms may contribute to outcomes such as preterm birth (PTB), low birth weight (LBW), and pre-eclampsia.

Effect of Periodontal Therapy on Pregnancy Outcomes

Non-Surgical Periodontal Therapy

The most commonly studied treatment during pregnancy is scaling and root planning (SRP) with oral hygiene instruction.

Some studies suggest that periodontal therapy may reduce bacterial load and inflammatory mediators; however, the effect on pregnancy outcomes remains controversial. [48]

A systematic review evaluating randomized controlled trials found no consistent evidence that periodontal therapy significantly reduces preterm birth, although some reduction in low birth weight has been reported. [49]

Similarly, large clinical trials have demonstrated that standard periodontal therapy during pregnancy does not significantly alter rates of adverse pregnancy outcomes, despite improving periodontal health. [50]

Meta-analysis and Systematic Review Findings

Recent umbrella reviews and meta-analyses have reported mixed results:

Several studies reported an association between periodontal therapy and reduced low birth weight and preterm birth, but the evidence remains inconsistent. Most high-quality studies show limited or no significant reduction in adverse pregnancy outcomes following periodontal therapy. Importantly, periodontal treatment during pregnancy is considered safe and beneficial for maternal oral health. [51]

A recent meta-analysis also suggested that adjunctive antimicrobial therapy, such as chlorhexidine mouthwash combined with periodontal treatment, may reduce the risk of adverse birth outcomes in certain populations. [52]

Preterm birth, low birth weight, and pre-eclampsia have been correlated with negative outcomes in periodontal therapy. [53] Higher levels of inflammatory mediators may enter the placenta and cause contraction in the uterus.

'Clinical Evidence' Interventional studies yield conflicting results.

Some randomised trials demonstrate a decrease in the risk of preterm birth after periodontal therapy, while others do not show any statistical significance. [54] Disparities may arise from the timing of treatment and underlying disease severity.

Despite the apparent safety of periodontal therapy in pregnant women, its actual function and potential to prevent unfavourable outcomes are still uncertain.

VI. PERIODONTAL THERAPY AND RHEUMATOID ARTHRITIS

TNF- and the antigen IL-6 also play an important role in inflammation associated with Rheumatoid arthritis (RA). Research indicates that periodontitis is a more common and distressing condition among individuals with RA. The use of periodontal treatment has been linked to a decrease in both DAS28 and inflammatory markers, with only modest reductions.

Rheumatoid arthritis is a chronic inflammatory condition that mainly affects the joints of the body. This is an autoimmune disease that causes inflammation of the joints, characterized by pain, swelling, and stiffness of the affected joints. Rheumatoid arthritis can cause destruction of joints, deformity, disability, and even death. [55] Apart from the joints, rheumatoid arthritis can also cause inflammation of other body organs, such as the skin, eyes, lungs, blood vessels, and heart, which makes rheumatoid arthritis another cause of cardiovascular disease.

Besides, rheumatoid arthritis can cause other diseases such as interstitial lung disease, osteoporosis, and metabolic syndrome. Epidemiological research indicates that rheumatoid arthritis synovial tissue cells and circulating immune cells produce pro-inflammatory cytokines such as TNF-α and IL-6, which are the direct cause of systemic inflammation, pro-inflammatory state, and cardiovascular disease. [56-58]

Chronic inflammatory arthritis, which includes rheumatoid arthritis, ankylosing spondylitis, and psoriatic arthritis, refers to diseases that are at increased risk of morbidity and mortality, for which prognostic evaluation is mandatory for their proper management. Interestingly, inflammation-induced disease activity of rheumatoid arthritis patients is associated with metabolic syndrome, central obesity, dyslipidaemia, and hypertension.

Notably, in the group of patients with rheumatoid arthritis, ankylosing spondylitis, and psoriatic arthritis, metabolic syndrome is more common and is closely and directly related to their chronic systemic inflammation and disease activity. [59]

In conclusion, the systemic effects of rheumatoid arthritis elicit a pro-inflammatory state. Rheumatoid arthritis is considered a risk factor for metabolic syndrome and cardiovascular diseases. Similarly,

periodontitis is also a state and a risk factor for other diseases, as was presented in the previous review. Therefore, in light of the above facts regarding rheumatoid arthritis, periodontitis can also be seen as a systemic disease from that point of view.

VII. PERIODONTAL THERAPY AND RESPIRATORY DISEASES

Aspiration of periodontal pathogens may contribute to chronic obstructive pulmonary disease (COPD) exacerbations and pneumonia. (60) Institutionalized elderly populations benefit from improved oral hygiene programs, with reduced pneumonia incidence. (61)

The Global Initiative for Chronic Obstructive Lung Disease describes chronic obstructive pulmonary disease as "a heterogeneous lung disease characterized by chronic respiratory symptoms dyspnoea, cough, sputum production, and exacerbations) due to airway (bronchitis, bronchiolitis) and alveolar (emphysema) abnormalities causing persistent and often progressive airflow obstruction." (62) The pathogenesis of chronic obstructive pulmonary disease involves multiple factors, including genetic predisposition and environmental factors, although cigarette smoke is the most widely accepted cause of chronic obstructive pulmonary disease. The chemical components of cigarette smoke cause inflammation of the lung tissue, which leads to the production of chemokines, thereby allowing neutrophils and other inflammatory cells to accumulate in the lung tissue. (63)

A systematic review revealed that patients with chronic obstructive pulmonary disease are at increased risk of atherosclerotic CVD than the general population. Furthermore, chronic obstructive pulmonary disease is independently associated with stroke, especially during acute exacerbations of chronic obstructive pulmonary disease. (64)

The proposed mechanism of the association between chronic obstructive pulmonary disease and stroke is the systemic release of pro-inflammatory cytokines and other systemic inflammatory mediators, such as IL-6 and TNF-α, which cause systemic inflammation that may trigger the activation of inflammatory cells in the atherosclerotic plaque, which may worsen the lesion.(65) The proposed mechanism of the association between chronic obstructive pulmonary disease and stroke is similar to the proposed systemic pro-inflammatory mechanism of the association between periodontal disease and atherosclerotic CVD, which again confirms that periodontitis as a systemic disease does not differ from other systemic diseases, including COPD.

While periodontal therapy may reduce bacterial load, large-scale evidence linking treatment to reduced respiratory morbidity is still emerging.

VIII. PERIODONTAL THERAPY AND NEURODEGENERATIVE DISORDERS

In recent decades, the prevalence of neurodegenerative diseases such as Alzheimer's disease (AD) and Parkinson's disease (PD) has been rapidly increasing, with PD being the world's fastest growing neurological disorder. (66,67) This is of major health and public concern, especially due to the lack of cure up to this moment. Therefore, identifying possible risk factors that might help to prevent or to slow down the development and/or progression of neurodegenerative diseases is of utmost importance. Of particular interest are risk factors that can be affected, i.e., are modifiable. Neuroinflammation triggered by systemic inflammation is suspected to play a role in the pathogenesis of non-hereditary neurodegenerative diseases. Periodontitis is a very common local inflammatory disease that can induce systemic inflammation. In view of that, it appears relevant to explore and discuss whether periodontitis has the potential to qualify as a risk factor for neurodegenerative diseases. (68)

Periodontitis is a multifactorial, microbiome-driven inflammatory disease of the tooth-attachment apparatus. It affects between 45 and 50% of the population worldwide, and its incidence increases with age. (69)

periodontal pathogens (i.e., communities of mainly Gram-negative anaerobes) induce gingival inflammation, which in turns creates local conditions (i.e., periodontal pockets) that are suitable for the survival and expansion of these pathogens, which on their turn reinforce and enhance the gingival inflammation. Hence, a vicious circle of low-grade chronic inflammation develops. This low-grade local inflammation is known to trigger systemic inflammation via direct mechanisms (i.e., bacteria, their toxic products and local cytokines, such as IL-6, IL-1β and TNF-α enter the bloodstream) or indirect

mechanisms (via immune host response; innate and acquired immunity). The consequences could be detrimental and may occur at distant sites, as suggested by the multiple comorbidities of periodontitis. [70]

In periodontitis, oral microbial dysbiosis triggers exaggerated chronic inflammation in susceptible individuals. As mentioned previously, in the current model of pathogenesis of periodontitis microbial dysbiosis and local inflammation co-develop in a reciprocally reinforced manner. [71] Microbial communities of key stone pathogens and pathobionts with synergetic virulence withstand the host response and propagate by inducing tissue-destructive inflammation medicated by the host immune system. In this way, a self-sustaining vicious circle of escalating dysbiosis and uncontrolled inflammation arises, which if not broken can lead to tooth loss and systemic complications.

Currently, potential direct and indirect mechanisms through which periodontitis may contribute to the development and progression of neurodegeneration diseases have been described in the literature. In summary, humoral, neuronal and cellular pathways have been hypothesized with clear role of the periodontal pathogens that can exert their effects via different routes

1) Proinflammatory cytokines locally released in periodontitis or induced by the low-grade systemic inflammation can enter the brain via the bloodstream.
2) Periodontal pathogens can reach the guts via the bloodstream or by swallowing. These have the potential to disrupt the gut microbiota. The inflamed gut epithelial cells release proinflammatory mediators that travel through the bloodstream and enter the brain, i.e., “oral–gut–brain axis”. Another way to enter the brain is via the vagus nerve.
3) Periodontal pathogens can reach the brain through the trigeminal nerve.
4) Periodontal pathogens might trigger trained myelopoiesis (trained immunity) that might induce with hyperinflammatory response that could affect the brain.

Recent studies suggest a potential link between periodontitis and Alzheimer’s disease. [72]

For example, gingipains of P. gingivalis have been found to be present in the tissues of Alzheimer’s patients. [73] Experimental models have demonstrated a reduction of neuroinflammation post-antimicrobial therapy.

However, clinical studies showing improvement in cognitive function post-periodontal therapy are lacking.

IX. DISCUSSION

The systemic effects of periodontal therapy, however, have been strongly supported in type 2 diabetes mellitus patients. The results in glycaemic control and inflammatory markers have been consistent in all studies.

The absence of long-term results does not allow the cardiovascular benefits to be supported, but surrogate inflammatory and endothelial markers do improve, supporting the cardiovascular benefits of periodontal therapy.

The biological plausibility of the association with pregnancy outcomes, rheumatoid arthritis, and other respiratory diseases, as well as neurodegenerative diseases, remains uncertain but requires further investigation.

The major gaps in current literature regarding periodontal therapy include:

- Short duration of follow-up.
- Small number of patients.
- Lack of homogeneous diagnostic criteria.

Insufficient exploration of difficult systemic factors.

Periodontists and medical practitioners must collaborate to include periodontal therapy in their treatment plan.

X. CONCLUSION

Periodontal therapy has shown promise for the reduction of the systemic inflammatory burden and the improvement of metabolic control in diabetes mellitus. Although there are moderate levels of evidence for the effects on cardiovascular surrogate markers, the effects on other systemic conditions remain to be explored.

It is important to consider the role of periodontal health as a modifiable risk factor when managing systemic conditions. Long-term follow-up needs to be conducted to assess the ultimate effectiveness of the

intervention through future large-scale randomised Controlled trials.

REFERENCES

[1] Pihlstrom BL, Michalowicz BS, Johnson NW. Periodontal diseases. Lancet. 2005 Nov 19;366(9499):1809-20. doi: 10.1016/S0140-6736(05)67728-8. PMID: 16298220.

[2] Kinane, D., Stathopoulou, P. & Papapanou, P. Periodontal diseases. Nat Rev Dis Primers 3, 17038 (2017). https://doi.org/10.1038/nrdp.2017.38

[3] Kassebaum NJ, Bernabé E, Dahiya M, Bhandari B, Murray CJ, Marcenes W. Global burden of severe periodontitis in 1990-2010: a systematic review and meta-regression. J Dent Res. 2014 Nov;93(11):1045-53. doi: 10.1177/0022034514552491. Epub 2014 Sep 26. PMID: 25261053; PMCID: PMC4293771

[4] Tonetti MS, Greenwell H, Kornman KS. Staging and grading of periodontitis: Framework and proposal of a new classification and case definition. J Periodontol. 2018 Jun;89 Suppl 1: S159-S172. doi: 10.1002/JPER.18-0006. Erratum in: J Periodontol. 2018 Dec;89(12):1475. doi: 10.1002/jper.10239. PMID: 29926952.

[5] Loos BG. Systemic markers of inflammation in periodontitis. J Periodontol. 2005 Nov;76(11 Suppl):2106-15. doi: 10.1902/jop.2005.76.11-S.2106. PMID: 16277583.

[6] D'Aiuto F, Nibali L, Parkar M, Patel K, Suvan J, Donos N. Oxidative stress, systemic inflammation, and severe periodontitis. J Dent Res. 2010 Nov;89(11):1241-6. doi: 10.1177/0022034510375830. Epub 2010 Aug 25. PMID: 20739696; PMCID: PMC3318025

[7] Villoria GEM, Fischer RG, Tinoco EMB, Meyle J, Loos BG. Periodontal disease: A systemic condition. Periodontol 2000. 2024 Oct;96(1):7-19. doi: 10.1111/prd.12616. Epub 2024 Nov 4. PMID: 39494478; PMCID: PMC11579822.

[8] Sanz M, Marco Del Castillo A, Jepsen S, Gonzalez-Juanatey JR, D'Aiuto F, Bouchard P, Chapple I, Dietrich T, Gotsman I, Graziani F, Herrera D, Loos B, Madianos P, Michel JB, Perel P, Pieske B, Shapira L, Shechter M, Tonetti M, Vlachopoulos C, Wimmer G. Periodontitis and cardiovascular diseases: Consensus report. J Clin Periodontol. 2020 Mar;47(3):268-288. doi: 10.1111/jcpe.13189. Epub 2020 Feb 3. PMID: 32011025; PMCID: PMC7027895.

[9] De Tapia B, Bonnin M, Valles C, Mozas C, Herrera D, Sanz M, Nart J. Clinical outcomes and associated factors in the treatment of peri-implant mucositis, combining mechanical debridement and prosthesis modification: A 30-month follow-up prospective case series. J Clin Periodontol. 2022 Dec;49(12):1357-1365. doi: 10.1111/jcpe.13711. Epub 2022 Aug 26. PMID: 36054620; PMCID: PMC9805102.

[10] Isola G, Polizzi A, Serra S, Boato M, Sculean A. Relationship between periodontitis and systemic diseases: A bibliometric and visual study. Periodontol 2000. 2025 Jun;98(1):228-240. doi: 10.1111/prd.12621. Epub 2025 Jan 8. PMID: 39775963; PMCID: PMC12842847

[11] Chapple IL, Genco R; working group 2 of the joint EFP/AAP workshop. Diabetes and periodontal diseases: consensus report of the Joint EFP/AAP Workshop on Periodontitis and Systemic Diseases. J Periodontol. 2013 Apr;84(4 Suppl): S106-12. doi: 10.1902/jop.2013.1340011. PMID: 23631572.

[12] Dietrich T, Sharma P, Walter C, Weston P, Beck J. The epidemiological evidence behind the association between periodontitis and incident atherosclerotic cardiovascular disease. J Clin Periodontol. 2013 Apr;40 Suppl 14: S70-84. doi: 10.1111/jcpe.12062. Erratum in: J Clin Periodontol. 2013 Apr;40 Suppl 14: S210-5. PMID: 23627335.

[13] Humphrey LL, Fu R, Buckley DI, Freeman M, Helfand M. Periodontal disease and coronary heart disease incidence: a systematic review and meta-analysis. J Gen Intern Med. 2008 Dec;23(12):2079-86. doi: 10.1007/s11606-008-0787-6. Epub 2008 Sep 20. PMID: 18807098; PMCID: PMC2596495

[14] P. B. Lockhart, A. F. Bolger, P. N. Papapanou, O. Osinbowale, M. Trevisan, M. E. Levison, K. A. Taubert, J. W. Newburger, H. L. Gornik, M. H. Gewitz, W. R. Wilson, S. C. Smith Jr., and L. M. Baddour, “Periodontal disease and atherosclerotic vascular disease: Does the evidence support an independent association? A scientific statement from the American Heart Association,”

Circulation, vol. 125, no. 20, pp. 2520–2544, May 2012, doi: 10.1161/CIR.0b013e31825719f3.

[15] Linden GJ, Lyons A, Scannapieco FA. Periodontal systemic associations: review of the evidence. J Clin Periodontol. 2013 Apr;40 Suppl 14: S8-19. doi: 10.1111/jcpe.12064. PMID: 23627336.

[16] Paraskevas S, Huizinga JD, Loos BG. A systematic review and meta-analyses on C-reactive protein in relation to periodontitis. J Clin Periodontol. 2008 Apr;35(4):277-90. doi: 10.1111/j.1600-051X.2007.01173. x. Epub 2008 Feb 20. PMID: 18294231.

[17] Ebersole JL, Graves CL, Gonzalez OA, Dawson D 3rd, Morford LA, Huja PE, Hartsfield JK Jr, Huja SS, Pandruvada S, Wallet SM. Aging, inflammation, immunity and periodontal disease. Periodontol 2000. 2016 Oct;72(1):54-75. doi: 10.1111/prd.12135. PMID: 27501491.

[18] Tonetti MS, D'Aiuto F, Nibali L, Donald A, Storry C, Parkar M, Suvan J, Hingorani AD, Vallance P, Deanfield J. Treatment of periodontitis and endothelial function. N Engl J Med. 2007 Mar 1;356(9):911-20. doi: 10.1056/NEJMoa063186. Erratum in: N Engl J Med. 2018 Jun 13;378(25):2450. doi: 10.1056/NEJMx180022. PMID: 17329698

[19] D'Aiuto F, Parkar M, Andreou G, Brett PM, Ready D, Tonetti MS. Periodontitis and atherogenesis: causal association or simple coincidence? J Clin Periodontol. 2004 May;31(5):402-11. doi: 10.1111/j.1600-051X.2004.00580. x. PMID: 15086624.

[20] Ide M, McPartlin D, Coward PY, Crook M, Lumb P, Wilson RF. Effect of treatment of chronic periodontitis on levels of serum markers of acute-phase inflammatory and vascular responses. J Clin Periodontol. 2003 Apr;30(4):334-40. doi: 10.1034/j.1600-051x.2003.00282. x. PMID: 12694432.

[21] Teeuw WJ, Gerdes VE, Loos BG. Effect of periodontal treatment on glycemic control of diabetic patients: a systematic review and meta-analysis. Diabetes Care. 2010 Feb;33(2):421-7. doi: 10.2337/dc09-1378. PMID: 20103557; PMCID: PMC2809296.

[22] Engebretson SP, Hyman LG, Michalowicz BS, Schoenfeld ER, Gelato MC, Hou W, Seaquist ER, Reddy MS, Lewis CE, Oates TW, Tripathy D, Katancik JA, Orlander PR, Paquette DW, Hanson NQ, Tsai MY. The effect of nonsurgical periodontal therapy on hemoglobin A1c levels in persons with type 2 diabetes and chronic periodontitis: a randomized clinical trial. JAMA. 2013 Dec 18;310(23):2523-32. doi: 10.1001/jama.2013.282431. PMID: 24346989; PMCID: PMC4089989.

[23] Lalla E, Papapanou PN. Diabetes mellitus and periodontitis: a tale of two common interrelated diseases. Nat Rev Endocrinol. 2011 Jun 28;7(12):738-48. doi: 10.1038/nrendo.2011.106. PMID: 21709707.

[24] Chapple IL, Genco R; working group 2 of the joint EFP/AAP workshop. Diabetes and periodontal diseases: consensus report of the Joint EFP/AAP Workshop on Periodontitis and Systemic Diseases. J Periodontol. 2013 Apr;84(4 Suppl): S106-12. doi: 10.1902/jop.2013.1340011. PMID: 23631572.

[25] Marco G, Pelta R, Carnés J, Iraola V, Zambrano G, Baeza ML. Occupational allergic asthma induced by Liposcelis decolor. Allergol Int. 2016 Apr;65(2):210-211. doi: 10.1016/j.alit.2015.10.007. Epub 2015 Dec 9. PMID: 26666472.

[26] Marco G, Pelta R, Carnés J, Iraola V, Zambrano G, Baeza ML. Occupational allergic asthma induced by Liposcelis decolor. Allergol Int. 2016 Apr;65(2):210-211. doi: 10.1016/j.alit.2015.10.007. Epub 2015 Dec 9. PMID: 26666472.

[27] Taylor JJ, Preshaw PM, Lalla E. A review of the evidence for pathogenic mechanisms that may link periodontitis and diabetes. J Periodontol. 2013 Apr;84(4 Suppl): S113-34. doi: 10.1902/jop.2013.134005. PMID: 23631573.

[28] Walsh JP, Bremner AP, Feddema P, Leedman PJ, Brown SJ, O'Leary P. Thyrotropin and thyroid antibodies as predictors of hypothyroidism: a 13-year, longitudinal study of a community-based cohort using current immunoassay techniques. J Clin Endocrinol Metab. 2010 Mar;95(3):1095-104. doi: 10.1210/jc.2009-1977. Epub 2010 Jan 22. PMID: 20097710.

[29] D'Aiuto F, Gkranias N, Bhowruth D, Khan T, Orlandi M, Suvan J, Masi S, Tsakos G, Hurel S, Hingorani AD, Donos N, Deanfield JE; TASTE Group. Systemic effects of periodontitis treatment

in patients with type 2 diabetes: a 12 month, single-centre, investigator-masked, randomised trial. Lancet Diabetes Endocrinol. 2018 Dec;6(12):954-965. doi: 10.1016/S2213-8587(18)30038-X. Epub 2018 Oct 24. Erratum in: Lancet Diabetes Endocrinol. 2019 Mar;7(3): e3. doi: 10.1016/S2213-8587(19)30036-1. PMID: 30472992.

[30] Engebretson S, Kocher T. Evidence that periodontal treatment improves diabetes outcomes: a systematic review and meta-analysis. J Periodontol. 2013 Apr;84(4 Suppl): S153-69. doi: 10.1902/jop.2013.1340017. PMID: 23631575; PMCID: PMC4100543.

[31] Simpson TC, Clarkson JE, Worthington HV, MacDonald L, Weldon JC, Needleman I, Iheozor-Ejiofor Z, Wild SH, Qureshi A, Walker A, Patel VA, Boyers D, Twigg J. Treatment of periodontitis for glycaemic control in people with diabetes mellitus. Cochrane Database Syst Rev. 2022 Apr 14;4(4):CD004714. doi: 10.1002/14651858.CD004714.pub4. PMID: 35420698; PMCID: PMC9009294.

[32] D'Aiuto F, Gkranias N, Bhowruth D, Khan T, Orlandi M, Suvan J, Masi S, Tsakos G, Hurel S, Hingorani AD, Donos N, Deanfield JE; TASTE Group. Systemic effects of periodontitis treatment in patients with type 2 diabetes: a 12 month, single-centre, investigator-masked, randomised trial. Lancet Diabetes Endocrinol. 2018 Dec;6(12):954-965. doi: 10.1016/S2213-8587(18)30038-X. Epub 2018 Oct 24. Erratum in: Lancet Diabetes Endocrinol. 2019 Mar;7(3): e3. doi: 10.1016/S2213-8587(19)30036-1. PMID: 30472992.

[33] Baeza M, Morales A, Cisterna C, Cavalla F, Jara G, Isamitt Y, Pino P, Gamonal J. Effect of periodontal treatment in patients with periodontitis and diabetes: systematic review and meta-analysis. J Appl Oral Sci. 2020 Jan 10;28: e20190248. doi: 10.1590/1678-7757-2019-0248. PMID: 31939522; PMCID: PMC6919200.

[34] Herrera D, Sanz M, Kebschull M, Jepsen S, Sculean A, Berglundh T, Papapanou PN, Chapple I, Tonetti MS; EFP Workshop Participants and Methodological Consultant. Treatment of stage IV periodontitis: The EFP S3 level clinical practice guideline. J Clin Periodontol. 2022 Jun;49 Suppl 24:4-71. doi: 10.1111/jcpe.13639. PMID: 35688447.

[35] Steven Offenbacher, Vern Katz, Gregory Fertik, John Collins, Doryck Boyd, Gayle Maynor, Rosemary McKaig, James Beck First published: 01 October 1996 https://doi.org/10.1902/jop.1996.67.10s.1103

[36] Michalowicz BS, Hodges JS, DiAngelis AJ, Lupo VR, Novak MJ, Ferguson JE, Buchanan W, Bofill J, Papapanou PN, Mitchell DA, Matseoane S, Tschida PA; OPT Study. Treatment of periodontal disease and the risk of preterm birth. N Engl J Med. 2006 Nov 2;355(18):1885-94. doi: 10.1056/NEJMoa062249. PMID: 17079762.

[37] Hopkins S, Gajagowni S, Qadeer Y, Wang Z, Virani SS, Meurman JH, Krittanawong C. Oral Health and Cardiovascular Disease. Am J Med. 2024 Apr;137(4):304-307. doi: 10.1016/j.amjmed.2023.11.022. Epub 2023 Dec 22. PMID: 38141902.Isola G et al. Periodontol 2000. 2025; 98:228–40.

[38] Xin-nian, L., Xin-yi, L. Association of periodontal disease with risk atrial fibrillation: systematic review. *BMC Oral Health* 25, 1756 (2025). https://doi.org/10.1186/s12903-025-07135-3

[39] Bechina C, Pockpa AD, Amador Del Valle G, Soueidan A, Lamirault G, Struillou X. Effects of Periodontal Therapy on Cardiovascular Risk Biomarkers: A Systematic Review. Oral Health Prev Dent. 2025 Aug 22; 23:457-467. doi: 10.3290/j.ohpd.c_2173. PMID: 40842443; PMCID: PMC12371565.

[40] INTERNATIONAL JOURNAL OF CARDIOVASCULAR RESEARCH & INNOVATION Oct-Dec 2024, VOL. 2, ISSUE 4, pp. 13-17 https://doi.org/10.61577/ijcri.2024.1000021

[41] Meng R, Xu J, Fan C, Liao H, Wu Z, Zeng Q. Effect of non-surgical periodontal therapy on risk markers of cardiovascular disease: a systematic review and meta-analysis. BMC Oral Health. 2024 Jun 14;24(1):692. doi: 10.1186/s12903-024-04433-0. Erratum in: BMC Oral Health. 2024 Jul 18;24(1):819. doi: 10.1186/s12903-024-04559-1. PMID: 38877442; PMCID: PMC11177403.

[42] Su Y, Cao Y, Bing X, Chen C, Yan H, Zhao H, Wang Y, Liu S, Xie Y, Li C, Wang Y, Yuan J. Effect of nonsurgical periodontal therapy on

coronary artery disease or metabolic syndrome: a systematic review and meta-analysis. J Evid Based Dent Pract. 2025 Sep;25(3):102136. doi: 10.1016/j.jebdp.2025.102136. Epub 2025 Mar 11. PMID: 40716835.

[43] James Beck, Raul Garcia, Gerardo Heiss, Pantel S. Vokonas, Steven Offenbacher First published: 01 October 1996 https://doi.org/10.1902/jop.1996.67.10s.1123

[44] Reis e Sousa C. Immunology. Eating in to avoid infection. Science. 2007 Mar 9;315(5817):1376-7. doi: 10.1126/science.1140002. PMID: 17347432.

[45] AlSharief M, Alabdurubalnabi E. Periodontal Pathogens and Adverse Pregnancy Outcomes: A Narrative Review. Life (Basel). 2023 Jul 13;13(7):1559. doi: 10.3390/life13071559. PMID: 37511934; PMCID: PMC10381683.

[46] AlSharief, M.; Alabdurubalnabi, E. Periodontal Pathogens and Adverse Pregnancy Outcomes: A Narrative Review. *Life* 2023, *13*, 1559. https://doi.org/10.3390/life13071559

[47] Jiang, H., Xiong, X., Su, Y. *et al*. A randomized controlled trial of pre-conception treatment for periodontal disease to improve periodontal status during pregnancy and birth outcomes. *BMC Pregnancy Childbirth* 13, 228 (2013). https://doi.org/10.1186/1471-2393-13-228

[48] Monali Shah, Arti Muley, Prasad Muley. Effect of nonsurgical periodontal therapy during gestation period on adverse pregnancy outcome: a systematic review [Internet]. Informa UK Limited; 2013. Doi: 10.3109/14767058.2013.799662

[49] AlSharief, M.; Alabdurubalnabi, E. Periodontal Pathogens and Adverse Pregnancy Outcomes: A Narrative Review. *Life* 2023, *13*, 1559. https://doi.org/10.3390/life13071559

[50] Michalowicz BS, Gustafsson A, Thumbigere-Math V, Buhlin K. The effects of periodontal treatment on pregnancy outcomes. J Clin Periodontol. 2013 Apr;40 Suppl 14: S195-208. doi: 10.1111/jcpe.12081. PMID: 23627329.

[51] Sajjad Khan, N., Craven, R., Rafiq, A., & Rafiq, A. (2023). Treatment of periodontal disease in pregnancy for the prevention of adverse pregnancy outcomes: a systematic review of systematic reviews. *Journal of the Pakistan Medical Association*, *73*(3), 611–620. https://doi.org/10.47391/JPMA.6432

[52] Merchant AT, Gupta RD, Akonde M, et al. Association of Chlorhexidine Use and Scaling and Root Planing with Birth Outcomes in Pregnant Individuals with Periodontitis: A Systematic Review and Meta-analysis. *JAMA Netw Open*. 2022;5(12): e2247632. doi:10.1001/jamanetworkopen.2022.47632

[53] Figuero E, Roldán S, Serrano J, Escribano M, Martín C, Preshaw PM. Efficacy of adjunctive therapies in patients with gingival inflammation: A systematic review and meta-analysis. J Clin Periodontol. 2020 Jul;47 Suppl 22:125-143. doi: 10.1111/jcpe.13244. PMID: 31869441.

[54] Pinto TM, de Freitas GC, Dutra DA, Kantorski KZ, Moreira CH. Frequency of mechanical removal of plaque as it relates to gingival inflammation: a randomized clinical trial. J Clin Periodontol. 2013 Oct;40(10):948-54. doi: 10.1111/jcpe.12135. Epub 2013 Aug 2. PMID: 23909568.

[55] Lin YJ, Anzaghe M, Schülke S. Update on the Pathomechanism, Diagnosis, and Treatment Options for Rheumatoid Arthritis. Cells. 2020 Apr 3;9(4):880. doi: 10.3390/cells9040880. PMID: 32260219; PMCID: PMC7226834.

[56] Taylor PC, Atzeni F, Balsa A, Gossec L, Müller-Ladner U, Pope J. The Key Comorbidities in Patients with Rheumatoid Arthritis: A Narrative Review. J Clin Med. 2021 Feb 1;10(3):509. doi: 10.3390/jcm10030509. PMID: 33535498; PMCID: PMC7867048.

[57] Chen J, Norling LV, Cooper D. Cardiac Dysfunction in Rheumatoid Arthritis: The Role of Inflammation. Cells. 2021 Apr 13;10(4):881. doi: 10.3390/cells10040881. PMID: 33924323; PMCID: PMC8070480.

[58] Błyszczuk P, Szekanecz Z. Pathogenesis of ischaemic and non-ischaemic heart diseases in rheumatoid arthritis. RMD Open. 2020 Jan;6(1): e001032. doi: 10.1136/rmdopen-2019-001032. PMID: 31958278; PMCID: PMC7046979.

[59] Cioffi G, Viapiana O, Tarantini L, Orsolini G, Idolazzi L, Sonographer FO, Dalbeni A, Gatti D, Fassio A, Rossini M, Giollo A. Clinical profile and outcome of patients with chronic inflammatory arthritis and metabolic syndrome. Intern Emerg Med. 2021 Jun;16(4):863-874. doi:

10.1007/s11739-020-02520-y. Epub 2020 Oct 20. PMID: 33083946; PMCID: PMC8195765.

[60] Mercado FB, Marshall RI, Bartold PM. Inter-relationships between rheumatoid arthritis and periodontal disease. A review. J Clin Periodontal. 2003 Sep;30(9):761-72. doi: 10.1034/j.1600-051x.2003.00371. x. PMID: 12956651.

[61] Jovanovic SA. Peri-implant tissue response to pathological insults. Adv Dent Res. 1999 Jun; 13:82-6. doi: 10.1177/08959374990130012001. PMID: 11276752

[62] Agustí A, Celli BR, Criner GJ, Halpin D, Anzueto A, Barnes P, Bourbeau J, Han MK, Martinez FJ, Montes de Oca M, Mortimer K, Papi A, Pavord I, Roche N, Salvi S, Sin DD, Singh D, Stockley R, López Varela MV, Wedzicha JA, Vogelmeier CF. Global Initiative for Chronic Obstructive Lung Disease 2023 Report: GOLD Executive Summary. Eur Respir J. 2023 Apr 1;61(4):2300239. doi: 10.1183/13993003.00239-2023. PMID: 36858443; PMCID: PMC10066569.

[63] Hoenderdos K, Condliffe A. The neutrophil in chronic obstructive pulmonary disease. Am J Respir Cell Mol Biol. 2013 May;48(5):531-9. doi: 10.1165/rcmb.2012-0492TR. PMID: 23328639.

[64] Ding C, Wang R, Gong X, Yuan Y. Stroke risk of COPD patients and death risk of COPD patients following a stroke: A systematic review and meta-analysis. Medicine (Baltimore). 2023 Nov 24;102(47): e35502. doi: 10.1097/MD.0000000000035502. PMID: 38013361; PMCID: PMC10681394

[65] Musher DM, Abers MS, Corrales-Medina VF. Acute Infection and Myocardial Infarction. N Engl J Med. 2019 Jan 10;380(2):171-176. doi: 10.1056/NEJMra1808137. PMID: 30625066.

[66] Dorsey E.R., Sherer T., Okun M.S., Bloem B.R. The Emerging Evidence of the Parkinson Pandemic. J. Park. Dis. 2018;8: S3–S8. doi: 10.3233/JPD-181474.

[67] Bloem BR, Okun MS, Klein C. Parkinson's disease. Lancet. 2021 Jun 12;397(10291):2284-2303. doi: 10.1016/S0140-6736(21)00218-X. Epub 2021 Apr 10. PMID: 33848468.

[68] Li X, Kiprowska M, Kansara T, Kansara P, Li P. Neuroinflammation: A Distal Consequence of Periodontitis. J Dent Res. 2022 Nov;101(12):1441-1449. doi: 10.1177/00220345221102084. Epub 2022 Jun 16. PMID: 35708472; PMCID: PMC9608094.

[69] Sanz M., del Castillo A.M., Jepsen S., Gonzalez-Juanatey J.R., D'aiuto F., Bouchard P., Chapple I., Dietrich T., Gotsman I., Graziani F., et al. Periodontitis and cardiovascular diseases: Consensus report. J. Clin. Periodontol. 2020; 47:268–288. doi: 10.1111/jcpe.13189

[70] Hajishengallis G., Chavakis T. Local and systemic mechanisms linking periodontal disease and inflammatory comorbidities. Nat. Rev. Immunol. 2021; 21:426–440. doi: 10.1038/s41577-020-00488-6

[71] Dziedzic A. Is Periodontitis Associated with Age-Related Cognitive Impairment? The Systematic Review, Confounders Assessment and Meta-Analysis of Clinical Studies. Int. J. Mol. Sci. 2022; 23:15320. doi: 10.3390/ijms232315320

[72] Harding A., Kanagasingam S., Welbury R., Singhrao S.K. Periodontitis as a Risk Factor for Alzheimer's Disease: The Experimental Journey So Far, with Hope of Therapy. Adv. Exp. Med. Biol. 2022; 1373:241–260. doi: 10.1007/978-3-030-96881-6_13

[73] De Pablo P, Dietrich T, McAlindon TE. Association of periodontal disease and tooth loss with rheumatoid arthritis in the US population. J Rheumatol. 2008 Jan;35(1):70-6. Epub 2007 Nov 15. PMID: 18050377.