REVIEW ARTICLE

Relationship between Cardiovascular Diseases and Periodontal Disease – A Systematic Review

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SUMMARY

To review and explore the published literature to establish an association between cardiovascular diseases and periodontal ailments, identifying shared risk factors, examining potential mechanisms, and assessing the clinical impact of this association. The systematic review was conducted at Army Medical College, National University of Medical Sciences, Rawalpindi, Pakistan from April 2023 to September 2023. A literature search was carried out following PRISMA guidelines using suitable databases, such as ScienceDirect and PubMed, by entering keywords, e.g., 'Periodontal disease and CVDs', 'Periodontal disease and heart disease', 'Periodontitis and CVDs', and 'Periodontitis and heart disease', to find relevant articles published between 2014 and 2023, as per the set inclusion and exclusion criteria. Shortlisted articles were assessed by four reviewers, followed by closer scrutiny by an additional two reviewers to ensure their suitability for final inclusion. Finally, a Qualitative assessment of included studies was done to minimize the risk of bias. Of the 97 studies found, only 10 (10.31%) met the inclusion criteria. The common tests run to identify periodontal diseases were periodontal pocket depth, complete visual oral examination, including radiograph examinations, and plaque index monitoring. To assess patients' cardiovascular health, polymerase chain reactions (PCRs), blood picture, Platelet function tests, blood pressure measurement, and testing for biomarkers were conducted. Out of the 10 included articles, 3 showed low bias, 4 articles showed medium bias, and 3 showed high bias. This systematic review revealed a positive correlation between, cardiovascular diseases, and periodontal health. Collaboration between dental and cardiovascular experts, coupled with advanced research methods, is essential for a profound understanding of these connections, thus enabling tailored interventions, offering significant improvements in both cardiovascular and periodontal health.

Keywords: *Cardiovascular Disease, Heart Disease, Periodontal Disease, Periodontitis*.

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Introduction

Cardiovascular diseases (CVDs) are the leading cause of death globally. In 2019, about 17.9 million individuals passed away from CVDs, with an estimated 32% of deaths globally.[1] Although chronic inflammatory state is linked to CVD, with contributions from recognized risk factors, i.e., gender, age, diabetes, tobacco smoking, and high cholesterol levels. However, little attention has been focused at the involvement of inflammatory conditions such as periodontal diseases (PDs) that may further contribute to CVD.[2] There is compelling evidence that PDs may not be exclusively a local phenomenon and may contribute to systemic inflammation which may serve as evidence to establish a possible relation between CVDs and PD.[2,3] According to the literature, PD exhibits significant associations with elevated systemic levels of inflammatory mediators triggered by bacteria and their products at sites distant from the mouth. Periodontitis also led to elevated levels of haemostatic and thrombotic markers that encourage an inflammation and prothrombotic

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state.[3-5] While others show a relation with biomarkers of endothelial dysfunction and dyslipidaemia, which may facilitate the relationship between PD and CVD.[6] The decrease in prevalence and incidence of PD can not only decrease its associated systemic diseases but can also curtail their financial impact on the healthcare systems.[7]

Inflammation plays a key part in the occurrence of CVD, and PD is related with a systemic inflammatory state. Evidence suggests a strong relationship between the two diseases, with inflammation appearing to be one of the primary links.[3] New cases of periodontal disease, not only those that are pre-existing, expose women at significantly higher level of risks for approaching cardiovascular events.[8]

Although several studies have been conducted correlating the PDs with CVDs, so far they have failed to establish a causal relationship between the two. The challenge is whether PD can be considered as one of the traditional risk factors for CVD as the connection established from multiple studies is not confined to a recent CVD. The objective of this systematic review is to go through the literature for evidence for establishing a possible relationship between CVDs and PD and the degree to which the strength of this relationship has been established through various scientific studies in the past few years. On the whole, periodontal ailments appear to be related to no more than a modest increase in cardiovascular risk in the overall population.[9]

The purpose of this systematic review is to conduct a comprehensive examination of the literature for evidence of a possible relationship between Parkinson's disease (PD) and cardiovascular diseases (CVDs). The primary aim of this systematic review is to assess the relationship between CVD and PD based on existing literature. The secondary objectives include identifying shared risk factors, examining potential mechanisms linking the two conditions, and assessing the clinical implications of their association. The null hypothesis assumes no powerful association between CVD and PDs.

Methods

This systematic review was carried out at Army Medical College Rawalpindi, Pakistan from April 2023 to September 2023 after taking ethical approval from the Ethical Review Committee of the college vide letter no: ERC/ID/362, dated: 17th February 2023. Following Prisma guidelines, a comprehensive search of relevant literature was done using reputable databases, namely PubMed and ScienceDirect, which are recognized as reliable sources for biomedical research to ensure a thorough exploration of studies pertaining to the association between CVD and PD, with a limitation to their registered published papers in English. The keywords that were used to search for the articles included “PDs and CVDs”, “PDs and heart disease”, “Periodontitis and CVDs”, and “Periodontitis and heart disease”.

This systematic review included original full-text articles published between 2014 and 2023 in the English language, investigating all forms of PDs and patients with a generalized form of CVDs, such as endocarditis, atherosclerosis, valvular diseases, hypertension, and vascular deposits. The included clinical trial, case reports and clinical studies involved physiologically normal patients, both male and female subjects, encompassing all age groups, from children to adults and the elderly. The studies published before 2014, articles with missing free full-text, reviews, systematic reviews, magazines, newspapers, opinions, non-scientific sources, articles on oral diseases other than PD, such as oral cancers and malocclusions and studies focusing on different forms of systemic diseases, pregnant and postmenopausal females were excluded from this systematic review.

Identified studies underwent a systematic screening process by four reviewers based on title, abstract, and full-text review, followed by closer scrutiny by an additional two reviewers to ensure their suitability for final inclusion in this study as per the inclusion and exclusion criteria. Data extraction included collecting relevant information from each selected study, such as study characteristics, participant demographics, methodologies, and key findings. Any inaccessible article was searched using the Google Scholar search engine. The methodology outline is given via Prisma flow chart in figure.1.

Finally, the included studies' quality assessment was done using established tools, such as the Newcastle-Ottawa Scale for observational studies and the Cochrane Risk of Bias tool for clinical trials.

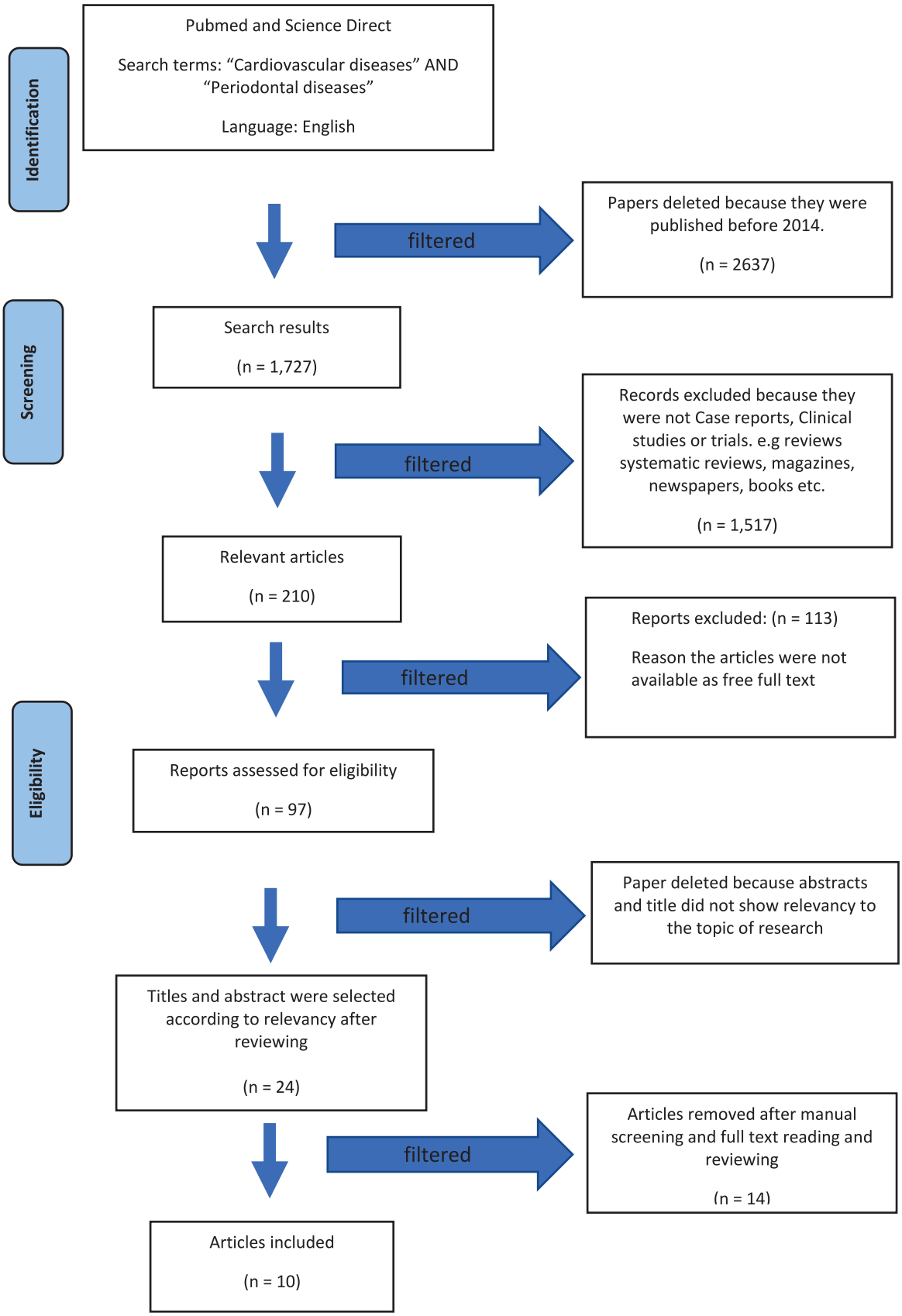

Fig.1: Methodology Outline via Prisma Flow Chart

Data synthesis involved a qualitative analysis of the extracted data to recognize common themes and patterns across the selected studies.

Results

After screening of 97 available articles at the title and abstract level, 24 were recognized as eligible for inclusion in this review. Of these, 14 articles were omitted as per our inclusion exclusion criteria and inclusion-exclusion criteria, as they were deemed irrelevant to the research after full article review. All articles included were published from 2014 to 2023. The characteristics of the study groups were extracted and calculated from table 1 according to types of exposure of periodontal variables. Of the 10 studies, 4 were cohort studies, 3 were randomized clinical trials, 2 were case-control studies, and 1 was a cross-sectional study.[10-19] The measures of periodontal disease used in the studies utilized periodontitis history taking and the common clinical examination tests, i.e., periodontal pocket depth (PPD) using probing, complete visual oral examination, including radiograph examinations for bone loss and plaque index. For establishing any solid relationship of the PDs with CVDs, several tests are employed for identifying patients' cardiovascular health, including blood picture, Platelet function tests, measuring blood pressure (BP), and polymerase chain reactions (PCRs) to test for the effect on Biomarkers.[13-14,19]

Out of the 10 studies, 3 showed low bias, 4 articles showed medium bias and 3 with high bias as shown on table 2. Overall, the studies demonstrated a positive association between CVDs and PDs, but there is a need of a more in depth and intensive research to be conducted to establish a firm relation between the two.[10-19]

Table-1: Summery of the studies included

Study design/ No of participants	CVS disease	Biomarkers tested	Tests	Results	Remarks	Ref
Retrospective cohort study / Taiwanese patients with PD: Treated = 27,146; Mild form = (13,573; Severe form = 13,573	Major adverse cardiovascular events (MACE): atherosclerosis , Coronary heart disease & stroke.	C-Reactive Protein (CRP), fibrinoge, Heat shock proteins such as GroEL & host HSP60-endotoxin, Inflammatory cytokines	-Complete oral examination -Diagnosis of MACE through International classification of diseases.	Severe treated PD showed association with amplified risk of MACE amongst old Taiwanese patients only.	Only patients with mild & severe PD were evaluated. Data lacked socioeconomic status & education.	10
Cohort study / Total = 2643 Malmö Offspring Study. Only 831 had a dental exam	Atherosclerosis , Carotid plaque		Non-invasive B-mode ultrasound of carotid arteries, Carotid intima media thickness / total plaque area (TPA) reported. PD assessment via probing.	Moderate-to-severe PD is linked with higher carotid plaque build-up risk. Individuals within the highest PPD are likely to have 9mm^2 larger TPA than those with no pockets.	Link between prevalence & extent of PD and carotid plaque incidence & severity was observed.	11

Prospective cohort study / 1676 838 men & 838 women	286 had PD, (2.5%) had diagnosed Stroke (1985-2012)	_	Plaque / Gingival inflammation / Calculus – index. Stroke data was collected from center of epidemiology	Substantial association was observed between gingivitis & cerebral infarction.	Periodontal disease like gingivitis may cause a serious stroke threat.	12
Prospective therapeutic trial (PTT) / 26 Patients	Generalized CVD	Platelet activation markers	Complete blood picture, Bleeding time, Platelet function tests, Flow cytometry, PD CAL, Gingival BOP	Platelet activation remains mostly intact in response to PD management	Subgingival debridement is a harmless practice & does not surge thrombotic events risk.	13
Randomized clinical trial / 101: 51 under intensive & 50 under control periodontal treatment	Hypertension (HTN)	IFN-c, IL-1b, IL-6, IL-10, IL-17A, IL-17E, IL-23, IL-33, MIP-3a/CCL20 & TNF-a	-Monitoring 24h Ambulatory blood pressure (BP) -Flow mediated dilation -Blood samples & plasma samples centrifuged - Periodontal pocket depth (PPD)	Substantial causal relationship between periodontitis (PD)-linked SNPs (single nucleotide polymorphism) & Systolic BP or pulse pressure	Causal relationship b/w PD & HTN observed.	14
Randomized controlled trial / 30 patients given non-surgical periodontal therapy (NSPT) + systemic antibiotic, 30 given NSPT only, 30 given no NSPT	Peripheral arterial disease – Vascular inflammation	Blood CRP; interleukin-6 IL-6); Hemoglobin A1c; Lipid Profile	Periodontal inflamed surface area (PISA); bleeding on probing (BOP); Periodontal pocket depth (PPD) & PD clinical attachment level	No evidence exists that PD treatment will result in a reduction of the risk of CVD.	PD appears to be an effective marker for atherosclero tic damage. Cardiovascul ar risk factors exist in both ailments.	15

Randomized control trial. Parallel group (1:1), 3month follow-up, open-label / 110 (Early PD) → Control = 56 standard periodontal care & Test = 54 Advanced self-care	Atherosclerotic CVD	Serum asymmetric dimethyl arginine; Atherosclerotic CVD-related vascular function markers	PPD & BOP score; Flow mediated brachial artery dilation (FMD) via high resolution ultrasonography system	No substantial improvement in FMD & serum asymmetric dimethylarginine level, BOP score decreased in test group.	Periodontal care showed no improved endothelial function but showed periodontal improvement in patients with early-stage PD.	16
Observational case control study / Total Patients = 44 (22 with & 22 without PD)	Generalized CVD	Subgingival red complex bacteria, MPO, sICAM-1, MMP-9, PAI-1, E-Selectin, Adiponectin and sVCAM-1 (ng/ml)	Polymerase chain reaction, Mirobial Culture (gram stain, colony morphology and catalase +ve test), CPR, FMD, CPITN, TVC.	Association between PD & systemic inflammation could surge CVD risk.	PD treatment lessen microbial load & systemic inflammation reducing CVD risk.	17
Observational case control study / 143 Caucasians (71 cases & 72 control) with Systemic lupus erythematosus (SLE) of average 13 years	Atherosclerosis	Levels of homocysteine, CRP, Insulin & triglycerides,	CVD risk via Framingham criteria; Subclinical SLE status: carotid–femoral pulse wave velocity, Homocysteine levels, CRP & erythrocyte sedimentation rate; Periodontal exam = BOP, PPD, CAL, Plaque index & tooth loss.	PD is more common among SLE patients, indicating greater fraction of subclinical atherosclerosis	PD worsens SLE leading to Endothelial dysfunction & atherosclerosis	18

Cross sectional study / 4021 patients	BP	CRP	Homocysteine & CRP levels, periodontal epithelial surface area (PESA), periodontal inflamed surface area (PISA), PPD, CAL, BOP. In blood complete picture WBC Count, segmented neutrophil, HbA1c, vitamin B12 & Folate.	PD cases presented >Homocysteine levels, PISA & PESA exhibited possible arbitrating effects linked between Homocysteine & BP.	Association between HCY & BP (Systolic & Diastolic) was mediated by PISA & PESA.	19

**Adenosine Diphosphate (ADP); Blood Pressure (BP); C- Reactive Protein (CRP); Clinical Attachment Loss 20; Control Periodontal Treatment (CPT); Flow Mediated Dilation (FMD); Function markers flow-mediated brachial artery dilatation (FMD); Hypertension (HTN); Intensive Periodontal Treatment (IPT); Periodontitis (PD); Periodontal Inflamed Surface Area (PISA); Major Adverse Cardiovascular Events (MACE); Non-Surgical Periodontal Therapy (NSPT); Periodontal Epithelial Surface Area (PESA); Probing Pocket Depth (PPD); Single Nucleotide Polymorphism (SNPs); Serum asymmetric dimethylarginine (ADMA); Total Plaque Area (TPA); Total Variable Count (TVC)*

Table-2: Bias Risk Assessment of the Included Studies

Generalization (Specific for hypertension)	Control Group	Sample Size (Large)	Peer Review	Study Design	Clinical Tests Performed	Score	Bias	Ref
Yes	No	Yes	Yes	Yes (FUS)	Yes	5/6	Low	10
No	Yes	No	Yes	Yes (OS)	Yes	4/6	Medium	11
No	No	Yes	Yes	No (DBS)	Yes	3/6	High	12
No	No	No	Yes	Yes (PTT)	Yes	3/6	High	13
No	Yes	Yes	yes	Yes (RCT)	Yes	5/6	Low	14
No	Yes	No	Yes	Yes (RCT)	Yes	4/6	Medium	15
No	Yes	No	Yes	Yes (RCT)	Yes	4/6	Medium	16
Yes	Yes	No	Yes	Yes (CCS)	Yes	5/6	Low	17
No	Yes	No	Yes	Yes (OCCS)	Yes	4/6	Medium	18
No	No	Yes	Yes	No (ES)	Yes	3/6	High	19

**Exploratory Study (ES); Case Control Study (CCS); Database Study (DBS); Follow up Study (FUS); Observational Study (OS); Observational Case Control Study (OCCS); Prospective therapeutic trial (PTT); Randomized Control Trial (RCT)*

Discussion

Cardiovascular disease and PD are two prevalent health conditions with a potential interrelationship. This systematic review investigates the existing evidence on the relationship between CVD and PD. By synthesizing data from reputable databases and employing specific inclusion criteria, the association between CVD and PD was comprehensively assessed. The review encompassed various study designs, including case reports, clinical trials, and clinical studies. The findings contributed to a greater understanding of the possible shared machines and implications for clinical practice, public health interventions, and future research. Ultimately, this review aimed to bridge the knowledge gap and provide insights for improved management strategies in cardiovascular and periodontal health.

In a study led by Czesnikiewicz-Guzik et al. the analysis of single nucleotide polymorphisms (SNPs) in specific loci linked with periodontitis revealed a significant connection with blood pressure (BP) phenotypes through Mendelian randomization. A randomized trial involving 101 hypertensive patients compared Intensive Periodontal Therapy (IPT) and Conventional Periodontal Therapy (CPT). Despite insufficiently controlled BP, the study found no statistically significant difference in 24-hour BP between intensive and standard treatment groups. The research implies a potential causal link between periodontitis and hypertension, emphasizing the need for further validation in a larger hypertensive cohort, urging ongoing research.[14]

In a case-control study by Chou SH. et al. periodontal probing depth (PPD) and bleeding on probing (BOP) were the primary periodontal tests conducted, alongside assessments of biomarkers such as high-sensitivity C-reactive protein (CRP) and tumor necrosis factor-alpha (TNF-α).[10] These biomarkers served as crucial indicators of systemic inflammation, elevated in participants with untreated periodontitis. This discovery highlights the critical role of early periodontal intervention and urges healthcare providers to integrate oral health into preventive cardiovascular care frameworks, considering periodontal health as integral to overall well-being.[10]

In the randomized controlled trial by Jönsson, D. et al. PPD and clinical attachment level were monitored as primary periodontal tests; however, endothelial function was assessed through flow-mediated dilation (FMD) and nitric oxide (NO) levels.[20] Early interventions in periodontal health improved oral well-being and positively influenced vascular health. Reduced levels of inflammatory biomarkers such as vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1) were noted, indicating decreased systemic inflammation following periodontal intervention. These findings advocate for proactive oral healthcare and patient education, empowering individuals to maintain their oral and cardiovascular health.[11]

In a comprehensive database study by Seinost G. et al., periodontal probing depth (PPD), BOP, and the presence of periodontal pockets were primary periodontal tests.[15] Stroke occurrence was validated through neuroimaging and clinical assessments. Specific biomarkers such as matrix metalloproteinases (MMPs) and myeloperoxidase (MPO) indicated a potential link between periodontal inflammation and vascular damage. This collaborative approach is crucial in developing targeted interventions for at-risk populations, potentially reducing the global burden of stroke-related morbidity and mortality.[15]

The population-based follow-up study by Söder B. et al., verified major adverse cardiovascular events through medical records and diagnostic tests, while PPD and CAL were primary periodontal tests.[12] Biomarkers like lipoprotein-associated phospholipase A2 (Lp-PLA2) and cardiac troponin I (cTnI) indicated the presence of cardiovascular risk factors. Thus, highlighting that integrating periodontal care into cardiovascular prevention is economically beneficial, urging a holistic public health approach.[12]

PPD, CAL, and the presence of carotid plaques were primary tests in the study conducted by Ramírez J. et al., thus correlating periodontal disease with carotid plaque area. Specific biomarkers such as soluble intercellular adhesion molecule-1 (sICAM-1) and plasminogen activator inhibitor-1 (PAI-1) suggested a potential link between periodontal inflammation and atherosclerotic processes; thus, oral health assessment not only aids in cardiovascular risk

identification but also urges comprehensive patient evaluations and targeted preventive strategies.[17]

In the study by Zamora-Pasadas M. et al., PPD, BOP, and subgingival plaque were primary periodontal tests investigating periodontitis and subclinical atherosclerosis in patients with systemic lupus erythematosus.[18] Specific biomarkers like oxidized low-density lipoprotein (ox-LDL) and anti-phospholipid antibodies hinted at accelerated atherosclerosis. Thus, suggesting that tailored periodontal interventions and personalized healthcare are crucial for systemic disease patients, emphasizing the need for interdisciplinary collaboration.[18]

PPD, CAL, and the presence of periodontal pockets were primary periodontal tests in the randomized controlled trial by Laky, M. et al., showcasing periodontal treatment's potential in reducing vascular inflammation in peripheral arterial disease. Levels CRP and erythrocyte sedimentation rate (ESR) indicated reduced inflammation upon provision of periodontal treatment, thus, highlighting that integrating oral health into inflammatory disease protocols promotes holistic healthcare and interdisciplinary collaboration.[13]

Okada A. et al., explored periodontal inflamed surface area via clinical assessment of PPD, BOP, and the presence of periodontal pockets; homocysteine levels, and blood pressure connections and reported that specific biomarkers such as endothelin-1 (ET-1) and nitric oxide (NO) offer avenues for personalized treatment.[16] Understanding periodontal-systemic connections aids tailored interventions, encouraging deeper research into molecular aspects of periodontal diseases.[16] In another study by Botelho J. et al., PPD, BOP, and platelet aggregation were examined in addition to investigating platelet activation following periodontal treatment.[19] Despite limited platelet activation, the study prompts detailed exploration of platelet physiology. Optimizing periodontal treatments ensures tailored approaches to local and systemic health concerns, emphasizing the need for further research in both the dental and cardiovascular fields.[19]

This systematic review is significant as it will comprehensively evaluate the association between CVD and PD. These findings will contribute to the existing scientific literature by consolidating current knowledge and identifying gaps for future research. The study's results may have implications for clinical practice, leading to improved preventive strategies and interdisciplinary collaboration between cardiology and dentistry.

This systematic review's limitations are that it includes only original free full-text articles published between 2014 and 2023 in English. The included studies' lack of standardization and interdisciplinary approach make them insufficient to clearly reflect on the association of CVDs and periodontal health.

Conclusion

The systematic analysis of the relevant articles of choice have revealed a substantial positive association between CVDs and periodontal health. These verdicts underscore the need for further research to establish a causal association between the two conditions. Exploring the long-term impacts of periodontal treatments on heart health and investigating specific genetic markers could pave the way for personalized prevention strategies. Understanding the influence of lifestyle and social factors is vital for creating effective, patient-centered interventions. Collaboration between dental and cardiovascular experts, coupled with advanced research methods, is essential for a profound understanding of these connections. This nuanced understanding enables tailored interventions, offering significant health. As we progress, continuous research efforts are crucial for refining treatments and enhancing overall patient well-being.

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Author Contributions

HG: Revising, editing, and supervising for intellectual content
AI: Conception and design of the work
SS: Manuscript writing for methodology design and investigation
AA: Data acquisition, curation, and statistical analysis
SR: Validation of data, interpretation, and write-up of results
AB: Data acquisition, curation, and statistical analysis