MedNEXT
Journal of Medical an Health Sciences

REVIEW ARTICLE

DOI: 10.54448/mdnt24S104

Evidence of the relationship between periodontal diseases/caries and cardiovascular diseases: a systematic review

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DOI: https://doi.org/10.54448/mdnt24S104
Received: 12-13-2023; Revised: 02-13-2024; Accepted: 02-17-2024; Published: 02-21-2024; MedNEXT-id: e 24S104

Abstract

Introduction: Dental caries is highly prevalent worldwide and is responsible for significant morbidity. Metabolic diseases such as diabetes and obesity share several common environmental determinants with tooth decay. Cardiovascular disease is a common and complex disease, with high morbidity and mortality rates, representing a serious threat to human health. **Objective:** It was to develop a systematic review to present, through clinical studies and systematic reviews/meta-analyses, evidence of the relationship between periodontal diseases/cavities and cardiovascular diseases. **Methods:** The PRISMA Platform systematic review rules were followed. The search was carried out from November 2023 to January 2024 in the Scopus, PubMed, Science Direct, Scielo, and Google Scholar databases. The quality of the studies was based on the GRADE instrument and the risk of bias was analyzed according to the Cochrane instrument. **Results and Conclusion:** A total of 108 articles were found, 36 articles were evaluated in full and 17 were included and developed in the present systematic review study. Considering the Cochrane tool for risk of bias, the overall assessment resulted in 24 studies with a high risk of bias and 22 studies that did not meet GRADE and AMSTAR2. Most studies did not show homogeneity in their results, with X^2=64.7%<50%. It was concluded that dental diseases such as periodontitis and tooth decay increase the risk of cardiovascular diseases. The number of missing teeth is significantly associated with selfreported history of stroke. The bacterium *Streptococcus mutans*, harboring the Cnm gene encoding the Cnm collagen-binding protein, is associated with the development of hypertensive intracerebral hemorrhage.

Keywords: Caries. Periodontal disease. Infection. Cardiovascular diseases.

Introduction

Dental caries is highly prevalent worldwide and is responsible for significant morbidity [1,2]. Although there is a direct effect of untreated dental caries on oral health and associated quality of life, the identification of indirect associations between dental caries and systemic health is urgent. Associations have been most studied between periodontitis and systemic diseases, and the contribution of oral inflammation and microbiota to diseases such as atherosclerosis, diabetes mellitus, pneumonia, chronic obstructive pulmonary disease, rheumatoid arthritis, and Alzheimer's disease [3-6].

In this sense, dental caries is a biofilm-mediated disease with multiple factors that contribute to localized demineralization of teeth [7,8]. The systemic consequences of untreated dental caries and the mechanistic role of the associated oral microbial inflammatory process in these associations require further investigation. Involvement of the root canal space or marginal periodontium is the most likely pathway for direct systemic extension of the oral microbiota [9,10]. Host factors and pathogenic features in the oral microbiota can promote dental caries and increase the likelihood of oral systemic dissemination. Such factors would include diseases and medications that result in reduced saliva production, adhesin expression in *Streptococcus mutans* for collagen binding, dysbiosis of the oral microbiota, genetic factors that predispose to dental caries and share common mechanistic bases with systemic diseases [11].

In this context, metabolic diseases such as diabetes and obesity share several common environmental

determinants with dental caries, including a hyperglycemic state and a high-carbohydrate/high-sugar diet [12]. Our current understanding of the associations between metabolic disease and dental caries and the use of animal models may serve to expand our understanding of the associations between dental caries and other systemic diseases [13].

In this regard, cardiovascular disease (CVD) is a common and complex disease, with high morbidity and mortality rates, representing a serious threat to human health [1,2]. Every year, the number of people who die from CVD reaches 17 million, ranking first among all causes of death. Ischemic heart disease, stroke, heart failure (HF), cardiomyopathy, and atrial fibrillation (AF) are responsible for more than 95% of cardiovascular disease-related deaths. Currently, genetic studies have found a variety of CVD susceptibility genes. As knowledge about cardiovascular disease continues to increase, several chronic infectious, inflammatory, and immune diseases, such as periodontitis, have been discovered to be related to a significantly increased risk of adverse cardiovascular events [3].

Periodontitis is one of the most common inflammatory diseases worldwide, with an incidence rate of 20-50% [2]. Periodontitis is common in adults and is the 6th most prevalent disease in the world, characterized by the gradual disintegration of the dental support system. The World Health Organization reports that periodontitis is the leading cause of tooth loss in adults. Dental caries and periodontitis are prevalent in adults, especially older individuals, leading to significant financial and health burdens. Epidemiological studies have indicated that severe loss of supporting structure and tooth loss caused by advanced periodontitis affects approximately 15% of the world's population [2,3].

In this scenario, there is evidence supporting the association between severe periodontitis and CVD. Periodontal disease can lead to a general burden of inflammation in the body and may play a role in the pathogenesis of CVD [4]. Studies have revealed that dental diseases such as periodontitis, tooth decay, and tooth loss increase the risk of diabetes mellitus, atherosclerosis, stroke, coronary artery disease, heart failure, and atrial fibrillation. Research has shown that patients with moderate to severe periodontitis have a higher risk of an early cerebrovascular event than patients without periodontitis or with mild periodontitis [2-4].

Furthermore, people suffering from periodontitis have more than twice the risk of stroke than periodontally healthy people. Several studies have also reported a positive relationship between periodontitis and heart failure. Large cohort studies have indicated that both new-onset and prevalent periodontitis are related to an increased risk of coronary artery disease [2-5].

Therefore, the present study developed a systematic review to present, through clinical studies and systematic reviews/meta-analyses, evidence of the relationship between periodontal diseases/cavities and cardiovascular diseases.

METHODS

Study Design

The present study followed the international systematic review model, following the rules of PRISMA (preferred reporting items for systematic reviews and meta-analysis). Available at: http://www.prisma-statement.org/?AspxAutoDetectCookieSupport=1. Accessed on: 10/12/2023. The methodological quality standards of AMSTAR-2 (Assessing the methodological quality of systematic reviews) were also followed. Available at: https://amstar.ca/. Accessed on: 10/12/2023.

Data Sources and Research Strategy

The literary search process was carried out from November 2023 to January 2024 and was developed based on Scopus, PubMed, Lilacs, Ebsco, Scielo, and Google Scholar, covering scientific articles from various eras to the present. The descriptors (MeSH Terms) were used: *"Caries. Periodontal disease. Infection. Cardiovascular diseases"*, and using the Boolean "and" between the MeSH terms and "or" between historical discoveries.

Study Quality and Risk of Bias

Quality was classified as high, moderate, low, or very low in terms of risk of bias, clarity of comparisons, precision, and consistency of analyses. The most evident emphasis was on systematic review articles or meta-analyses of randomized clinical trials, followed by randomized clinical trials. The low quality of evidence was attributed to case reports, editorials, and brief communications, according to the GRADE instrument. The risk of bias was analyzed according to the Cochrane instrument by analyzing the Funnel Plot graph (Sample size versus Effect size), using the Cohen test (d).

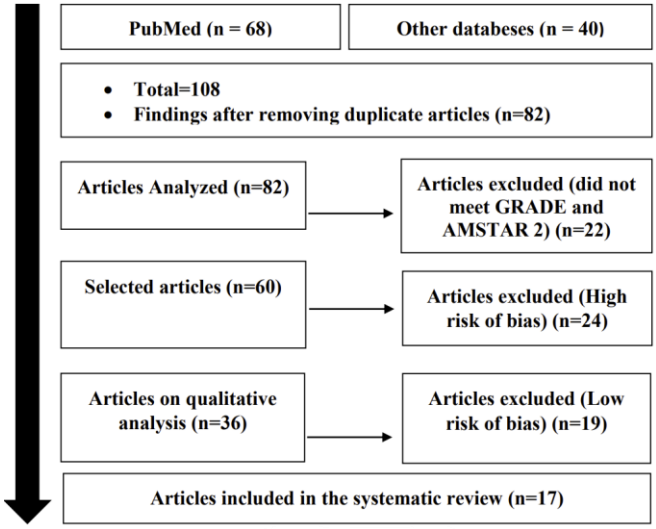
Results and Discussion

Summary of Findings

A total of 108 articles were found that were subjected to eligibility analysis, with 17 final studies being selected to compose the results of this systematic review. The studies listed were of medium to high quality (Figure 1), considering the level of scientific evidence of studies such as meta-analysis, consensus, randomized clinical, prospective, and observational. The biases did not compromise the scientific basis of the studies. According to the GRADE instrument, most

studies showed homogeneity in their results, with X^2=64.7%<50%. Considering the Cochrane tool for risk of bias, the overall assessment resulted in 21 studies with a high risk of bias and 21 studies that did not meet GRADE and AMSTAR-2.

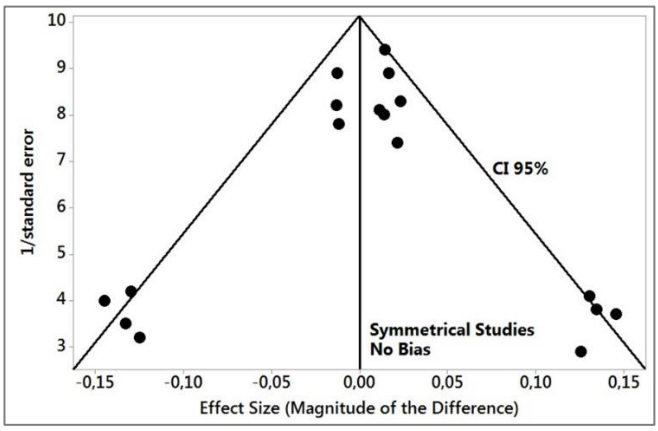
Figure 1. Article selection - exclusion process.



Source: Own authorship.

Figure 2 presents the results of the risk of bias of the studies using the Funnel Plot, showing the calculation of the Effect Size (Magnitude of the difference) using the Cohen Test (d). Precision (sample size) was determined indirectly by the inverse of the standard error (1/Standard Error). This graph had a symmetrical behavior, not suggesting a significant risk of bias, both between studies with a small sample size (lower precision) that are shown at the bottom of the graph and in studies with a large sample size that are presented at the top.

Figure 2. The symmetric funnel plot suggests no risk of bias among the small sample size studies that are shown at the bottom of the graph. High confidence and high recommendation studies are shown above the graph (n=17 studies).



Source: Own authorship.

Major Findings

One study looked at the potential association between dental disease and selfreported history of stroke in the United States based on data from the Third National Health and Nutrition Examination Survey (NHANES III). The number of missing teeth was found to be significantly associated with a self-reported history of stroke. The associations between self-reported history of stroke and caries, gingival bleeding, or periodontal pockets were not statistically significant. The number of missing teeth was an independent determinant of self-reported history of stroke [14].

The relationship between oral and systemic health appears to be more complex than suggested by the classical theory of focal infections. The contribution of the oral microbiota to some systemic diseases is gaining scientific evidence, since there are strong associations between periodontal disease and atherosclerotic vascular disease, diabetes, and hospital-associated pneumonia, among others. Thus, a study developed scoring algorithms for odontogenic inflammatory diseases and systemic risks, and standardized procedures for general use were developed. The designed oral-systemic axis algorithm will be useful to all healthcare professionals in guiding patient management protocol [15].

In this sense, observational studies have revealed that dental diseases such as periodontitis and tooth decay increase the risk of cardiovascular diseases (CVD). However, the causality between periodontal disease (PD) and CVD is not yet clear. A two-sample Mendelian Randomization (MR) study was performed to evaluate the association between genetic liability for periodontal diseases (dental caries and periodontitis) and major CVD, including coronary artery disease (CAD), heart failure (HF), atrial fibrillation (AF) and cerebral stroke, including ischemic stroke, as well as its three main subtypes based on large-scale genome-wide association studies (GWASs). Magnetic resonance (MR) analyses of two samples provided evidence of tooth decay and periodontitis as causes of cardiovascular disease; sensitivity analyses, including MR-Egger analysis and weighted median analysis, also supported this result [16].

Finally, the role of commensal microbiota in systemic diseases, including brain diseases, is of significant importance through clinical studies. Oral infectious diseases, such as tooth decay and periodontitis, are also involved in cerebrovascular diseases and cognitive impairment. The bacterium *Streptococcus mutans* (*S. mutans*), harboring the Cnm gene encoding the collagen-binding protein Cnm, is associated with the development of hypertensive intracerebral hemorrhage. There is a mechanism by

which circulating Cnm-expressing *S. mutans* causes intracerebral hemorrhage, binds to denuded basement membranes composed primarily of collagen IV through damaged tight junctions, or directly invades endothelial cells, resulting in injury to the blood-brain barrier. However, it is necessary to establish the role of Cnm-positive *S. mutans* in stroke and intracerebral hemorrhage [17].

Conclusion

It was concluded that dental diseases such as periodontitis and tooth decay increase the risk of cardiovascular diseases. The number of missing teeth is significantly associated with self-reported history of stroke. The bacterium *Streptococcus mutans*, harboring the Cnm gene encoding the Cnm collagen-binding protein, is associated with the development of hypertensive intracerebral hemorrhage.

Acknowledgement

Not applicable.

Ethical Approval

Not applicable.

Informed consent

Not applicable.

Funding

Not applicable.

Data sharing statement

No additional data are available.

Conflict of interest

The authors declare no conflict of interest.

Similarity check

It was applied by Ithenticate[@].

Peer Review Process

It was performed.

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