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Review Article

Association between Periodontal Disease and Atherosclerotic Cardiovascular Diseases - A Systematic Literature Review

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Abstract

The COVID 19 is associated with several worsening of chronic inflammatory, including periodontal and coronary artery disease. Following the COVID-19 pandemic, there are indicators that noncommunicable diseases are increasing in prevalence globally and associated with population aging, sedentary lifestyle and increase consumption of caloric diets. It is currently accepted the hypothesis that both groups of these diseases have several similar etiopathogenic factors, including inflammation route. The aim of this systematic review of randomized clinical trials was to investigate the association between periodontal disease and coronary artery disease. From 1786 studies, 30 studies were selected. There is an association between periodontal disease and coronary artery diseases, especially in individuals diagnosed with stage III and IV periodontitis, regardless of the degree, and ischemic stroke after COVID hospitalization.

***Keywords:** Periodontal Disease; Cardiovascular Disease; Stroke; Clinical trial; Systematic Review.*

Introduction

After the pandemic of COVID-19, an increase in the global prevalence of non- transmitted diseases was observed. Associated with this, one notes the increasingly ageing, sedentary and avid population consuming refined diets. Each year, 41 million deaths, or approximately 70% of all global deaths are computed[1].

Atherosclerotic cardiovascular diseases and periodontal diseases are the main health problems present in this population[2]. Atherosclerotic cardiovascular diseases are composed of cerebrovascular disease (stroke), coronary artery disease or peripheral arterial disease of atherosclerotic origin. Together they represent the leading cause of morbidity and mortality worldwide[3].

The incidence of coronary artery disease in 2019 worldwide was 126 million (1,655 per 100,000), which represents 1.72% of the human population. It is estimated that up to 2030 the incidence of coronary artery disease will increase to 1,845 per 100,000. Moreover, coronary artery disease is the number one cause of human death, disability and suffering worldwide[1]. The incidence of peripheral arterial disease and stroke in 2019 was 113 million and 101 million, respectively[1,4].

The high frequency of atherosclerotic cardiovascular diseases is associated with the spread of several risk factors for these diseases. The main risk factors for atherosclerotic cardiovascular diseases include poor diet; diabetes; hyperlipidemia; sedentary lifestyle; obesity; smoking; hypertension; chronic kidney disease; hyperuricemia; excessive stress; rheumatological diseases (systemic lupus erythematosus and rheumatoid arthritis); inflammatory bowel disease; human immunodeficiency virus infection; thyroid disease; menopause; and genetic predisposition[5-7].

The pathogenesis of atherosclerosis is complex. Inflammation plays an important role[8]. Concomitantly, immune activation plays a central role in atherosclerotic plaque instability, triggering a thromboembolic episode[9]. Thus, periodontal disease, by increasing the inflammatory response and inducing a microbial dysbiosis, may assume an important role in the pathogenesis of atherosclerotic cardiovascular diseases[10].

In 2019, a joint workshop was held between the European Federation of Periodontology and the World Heart Federation to review the literature linking periodontitis and systemic diseases, including atherosclerotic cardiovascular diseases[11]. The consensus report was based on four technical papers that systematically reviewed the evidence for epidemiological associations between periodontitis and atherosclerotic cardiovascular disease[12], mechanistic links[13], results of intervention studies[14], and the potential risk and complications of periodontal therapy in patients on antithrombotic (antiplatelet and anticoagulant) therapy. The workshop concluded that there was epidemiological evidence that periodontitis increases the risk of future atherosclerotic cardiovascular disease via translocated circulating oral microbiota, which may directly or indirectly induce systemic inflammation that impacts on the development of atherothrombogenesis[11]. In vitro, preclinical studies have supported the interaction and associated biological mechanisms. However, intervention trials were not yet adequate enough to draw further conclusions at that time.

The purpose of this study is to conduct a systematic review of randomised clinical trials of the association between periodontal disease and coronary artery disease.

Method

Design of the Study

A systematic review of randomised clinical trials and longitudinal cohort studies examining the risk of atherosclerotic cardiovascular disease in people with periodontal disease compared with populations without periodontal disease.

Bibliographic Strategy

The guiding search sentence considered alternative terms and a variety of atherosclerotic cardiovascular disease outcomes incorporating several relevant keywords/descriptors (DeSC) and Medical Subject Headings (MeSH) titles. The final Boolean search sentence was: (periodon* OR tooth loss OR missing teeth) AND (atrial fibrillation OR heart failure OR cerebrovascular accident OR stroke OR angina OR acute coronary syndrome OR myocardial infarction OR peripheral vascular disease OR hypertension OR cardiovascular disease) AND (incidence) AND (cohort OR longitudinal OR randomi*ed controlled trial OR RCT).

The guiding search sentence was applied from database design until 12 August 2022 in PubMed, EMBASE and Cochrane databases to ensure retrieval of a broad scope of literature. Additional methods of reference checking and "citation snowballing" of key articles were also performed to maximise search sensitivity.

Study Selection

As per PRISMA protocol [19], after database searches, studies were imported into a citation manager and screened for duplicates using an automated system. One author has selected, after critical reading of the title and abstract for eligibility, with validation by a second author. Entire articles were screened by a third, more experienced author for eligibility before performing data extraction and quality assessment. Consensus for included studies was reached between the authors and disagreements were resolved by in-depth discussion between the three authors. A data extraction form was developed prior to the database search to identify key study information. Population demographics, data source, exclusion criteria, follow-up period, outcome measure and study limitations were included. The results of the data extraction were monitored by a fourth author and queries were discussed in detail to ensure adherence to the protocol.

Criteria for Eligibility

The strict eligibility criteria guided the search to ensure the inclusion of relevant studies, reduce heterogeneity and increase the power of the results. The inclusion criteria were described as follows:

- Design of retrospective/prospective longitudinal cohort study or randomised clinical trials;
- Population with periodontal disease free of pre-defined systemic disease at baseline;
- Minimum follow-up period of 1 year;
- Clinically diagnosed or self-reported periodontal disease;
- Clearly defined classification of atherosclerotic cardiovascular diseases;
- Peer-reviewed articles published in English.

The minimum follow-up period was 1 year after diagnosis of periodontal disease. Populations with pre-diagnosed atherosclerotic cardiovascular disease conditions were not eligible to ensure accurate calculation of the incidence of atherosclerotic cardiovascular disease, rather than the prevalence of an undiagnosed condition that may have preceded periodontal disease. Clinical classifications of periodontal disease included clinical examination or identification of appropriate International Classification of Diseases (ICD-10/11) codes in electronic health records or insurance databases. Questionnaire or interview responses were classified as self-reported periodontal disease. Assessment of dental hygiene, presence of dental caries, cysts or lesions and other conditions such as gingivitis, peri-implantitis and odontogenic infection were not accepted as case definitions for periodontal disease as they are not directly attributed to periodontal disease.

Risk of bias was analysed and quality of evidence assessment was determined for meta-analysis of outcomes using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach [24].

Results

A total of 1,786 studies were retrieved from the initial search. After screening, 132 studies were screened for full content and 30 studies were included. Two studies were excluded from the meta-analysis because raw data on sample sizes could not be extracted [17, 18].

The selected studies were published between 2000 and 2022. Most studies were conducted in the United States (n = 16; 57.1%). The remaining studies used data from developed countries in Europe, Asia and Australia. The median follow-up period was 16.2 years (interquartile range: 11.1-21.5 years). Of the 28 studies included, 20 (71.4%) of them were prospective cohort studies and used cohorts with a clinical diagnosis of periodontal disease. Fifteen studies (53.5%) examined atherosclerotic cardiovascular disease risk in men, while 6 studies (21.4%) reported atherosclerotic cardiovascular disease risk in women. All studies reported age-adjusted risk of cardiovascular disease. However, only 5 studies (17.8%) did not adjust for smoking, this being an important common risk factor between periodontal diseases and atherosclerotic cardiovascular diseases. In this sense, we chose to exclude these studies in the overall analysis, thus reducing the bias of association between the primary conditions, totalling 23 studies to be discussed (see Table 1 for more details on the selected studies). Overall, the random effects meta-analysis shows that there is a significant increase in the risk of all incident atherosclerotic cardiovascular diseases in the population with periodontal disease compared with the population without periodontal disease (RR = 1.18; 95% CI: 1.05-1.32). The highest relative risk was seen in the stroke outcome subgroup (RR = 1.26). The risk of bias was intermediate.

Table 1: Methodological detail of the selected clinical trials:

Study	Design	Total sample	Country	Periodontal diagnosis	Outcome	Follow-up (years)	Risk of bias
Beukers et al. (2022)[23]	Prospective	1,200,000	Netherlands	Clinical	Cardiovascular Disease	8	Critical
Lin et al. (2019)[31]	Retrospective	161,923	Taiwan	Clinical	Stroke	10	Critical
Batty et al. (2018)[32]	Prospective	626,100	South Korea	Clinical	Cardiovascular Disease	21	Serious
Sen et al. (2018)[33]	Retrospective	6,736	US	Clinical	Stroke	15	Serious
Holmlund et al. (2017)[34]	Prospective	8,999	Sweden	Clinical	Cardiovascular Disease	7	Serious
LaMonte et al. (2017)[35]	Prospective	57,001	US	Auto declaração	Cardiovascular Disease + Stroke	12	Critical
Lee et al. (2017)[36]	Retrospective	354,850	South Korea	Clinical	Stroke + Acute Myocardial Infarction	12	Critical
Chen et al. (2016)[37]	Retrospective	787,490	Taiwan	Clinical	Atrial fibrillation	10	Critical

Hansen et al. (2016)[38]	Prospective	100,694	Denmark	Clinical	Stroke + Acute Myocardial Infarction	15	Critical
Chou et al. (2015)[39]	Retrospective	27,146	Taiwan	Clinical	Cardiovascular Disease	9	Critical
Lee et al. (2015)[40]	Retrospective	719,436	Taiwan	Clinical	Acute Myocardial Infarction	10	Critical
Yu et al. (2015)[41]	Prospective	39,863	US	Auto declaração	Stroke + Acute Myocardial Infarction	16	Critical
Noguchi et al. (2014)[42]	Prospective	3,081	Japan	Auto declaração	Acute Myocardial Infarction	5	Serious
Lee et al. (2013)[43]	Retrospective	720,343	Taiwan	Clinical	Stroke	10	Critical
Rivas et al. (2012)[44]	Prospective	31,543	US	Auto declaração	Hypertension	20	Critical
Choe et al. (2009)[45]	Prospective	679,170	South Korea	Clinical	Stroke	14	Critical
Jimenez et al. (2009)[46]	Prospective	1,231	US	Clinical	Stroke	34	Critical
Mucci et al. (2009)[47]	Prospective	15,273	Sweden	Auto declaração	Cardiovascular Disease + Stroke	37	Serious
Dietrich et al. (2008)[48]	Prospective	1,203	US	Clinical	Cardiovascular Disease	35	Critical
Heitmann, Gambourg (2008)[49]	Prospective	2,932	Denmark	Clinical	Cardiovascular Disease	7	Serious
Tu et al. (2007)[50]	Prospective	12,631	UK	Clinical	Cardiovascular Disease + Stroke	57	Serious
Abnet et al. (2005)[51]	Prospective	29,584	China	Clinical	Stroke	15	Critical
Hung et al. (2004)[52]	Retrospective	44,119	US	Auto declaração	Cardiovascular Disease	12	Critical
Hung et al. (2003)[53]	Retrospective	100,381	US	Auto declaração	Cardiovascular Disease	12	Critical
Joshipura et al. (2003)[54]	Prospective	41,380	US	Auto declaração	Stroke	12	Critical
Howell et al. (2001)[55]	Randomized clinical trial	22,037	US	Auto declaração	Stroke + Acute Myocardial Infarction	13	Critical
Hujoel et al. (2001)[56]	Prospective	8,032	US	Clinical	Cardiovascular Disease	20	Serious
Wu et al. (2000)[57]	Prospective	9,962	US	Clinical	Stroke	22	Serious

Discussion

The findings of the present study indicate an important association between the prevalence of atherosclerotic cardiovascular diseases and periodontal diseases, mainly stroke. In this regard, a recent study [20] that analysed the National Health and Nutrition Examination Survey (NHANES), the main epidemiological bulletin of the USA, data from 2013 to 2014, evaluated 2,830 adult participants, aged over 30 years. Subjects underwent a home interview, followed by a standardised clinical assessment at a mobile examination centre. A strong association between periodontal diseases and atherosclerotic cardiovascular diseases was found, corroborating our result. This association was observed mainly in individuals with stage III and IV periodontal disease, according to the latest classification of the American Academy of Periodontology [21]. In this sense, this is the first study that uses the new systematic classification of periodontal diseases as a process of comparison to systemic conditions, using the methodology of population-based epidemiological survey. The other studies selected in this review used the classification of periodontal diseases defined by Armitage (1999) [22]. Further studies using this new classification system for periodontal diseases may help to elucidate the possible causes of this stronger association.

In this review study, the causal association between periodontal diseases and atherosclerotic cardiovascular diseases was not quantified. However, in other recent reviews [2, 20, 25], the causal relationship and mechanism between periodontal diseases and atherosclerotic cardiovascular diseases have been explored, suggesting a connection through shared inflammatory pathways [26]. Increased platelet counts and C-reactive protein levels, which are indicators of systemic inflammation in the presence of periodontal disease and atherosclerotic cardiovascular disease [2] can also be observed.

Additionally, there is also strong evidence that neutrophils from periodontitis patients produce higher levels of total and extracellular reactive oxygen species (ROS) than healthy control patients. Under these conditions, there is disrupted cell signalling induced by inflammation that can induce cell death, instabilisation of atherosclerotic plaques and result in systemic symptoms, such as those seen in various triggers of atherosclerotic cardiovascular diseases [27].

A systematic review evidences that treatment of periodontal disease can stabilise the symptoms of atherosclerotic cardiovascular diseases. The control of inflammation is the association between the conditions, and may be bidirectional [28].

The other association is based on the evidence of distant bacteraemia. The study by Chukkapalli and colleagues (2015) [29], in which they used mice modified for ApoE expression, induced hyperlipidemic condition after infection with *Porphyromonas gingivalis* and also with experimental polymicrobial infection (*Porphyromonas gingivalis*, *Treponema denticola*, *Tannerella forsythia* and *Fusobacterium nucleatum*). The study evidenced that after a polymicrobial infection the aortic toll-like receptor (TLR) is significantly more expressed, generating the increase of oxidative stress metabolites within the aortic endothelial cells, instabilizing the arteriosclerotic plaques for atherosclerotic cardiovascular diseases. In the same perspective, the study by Yang and collaborators [30], demonstrated *in vivo* and *in vitro* the importance of fimbriae from *Porphyromonas gingivalis* in attaching and entering host endothelial cells, accelerating the process of lipid incorporation, the development and instabilization of atherothrombotic lesions.

It should be understood that there are some limitations in this review. Since most of the selected studies were observational by design, there is a high risk of bias, confounding effects and heterogeneity in pooled estimates. In this regard, the risk of bias was identified by performing random effects subgroup meta-analysis and meta-regression by adjusting for heterogeneity, in addition to exploration by sensitivity analysis. Some demographic data of the population, such as age, could not be measured because complete data were not available for all selected studies.

Thus, the data from this systematic review corroborate the findings of other previous reviews showing a significant association between periodontal diseases and atherosclerotic cardiovascular diseases. We note that the new classification of periodontal diseases will enable the recognition of the group at higher risk of developing one of the atherosclerotic cardiovascular diseases. We also consider that good oral hygiene practices and targeted interventions in populations with periodontal diseases are therefore essential to prevent atherosclerotic cardiovascular diseases, especially in individuals with stage III and IV periodontitis, regardless of the degree.

Conclusion

There is an association between periodontal disease and atherosclerotic cardiovascular diseases, especially in individuals diagnosed with stage III and IV periodontitis, regardless of degree.

Conflict of Interest

The authors declare no conflict of interest.

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