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Relationship between the caries-cardiovascular disease axis and immunological aspects: a systematic review

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Abstract

Introduction: According to the World Dental Federation, the hypothesis is that more than 90.0% of the world's population will have any oral disease in their lifetime. In addition, only 60.0% of the population has access to oral hygiene. In childhood and adolescence, caries and periodontal diseases are the most common diseases in the world, and in Brazil, caries is the main oral health problem. Many recent studies have focused on the association between dental caries and systemic diseases such as cardiovascular disease. **Objective:** It was to systematically analyze the world literature to list the main considerations regarding the relationship between the axis of caries and cardiovascular diseases, highlighting the immunological aspects. **Methods:** The PRISMA Platform systematic review rules were followed. The search was conducted from April to July 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:** 148 articles were found, 40 studies were evaluated, and 25 were included in this systematic review. Considering the Cochrane tool for risk of bias, the global assessment resulted in 22 studies with a high risk of bias and 28 studies that did not meet GRADE. Most studies showed homogeneity in their results, with X^2 =92.7% >50%. It was concluded that there is an important network and cascade of defense events between immunological processes and caries disease. Thus, it is necessary to have a healthy immune response to reduce the incidence of cavities. Dental caries was independently associated with the risk of ischemic stroke and death, with the effect being greatest in African-American participants. Regular dental care was associated with a lower chance of cavities, highlighting its relevance in preventing these events. Higher scores of decayed, missing, and filled teeth correlated positively with increased prevalence of cardiovascular disease. Among patients with type 2 diabetes, dental disease, and oral hygiene care are important determinants of the development of heart failure.

Keywords: Caries. Cardiovascular diseases. Immunological aspects. Dental Health.

Introduction

According to the World Dental Federation, the hypothesis is that more than 90.0% of the world's population will have any oral disease in their lifetime. In addition, only 60.0% of the population has access to oral hygiene. In childhood and adolescence, caries and periodontal diseases are the most common diseases in the world, and in Brazil, caries is the main oral health problem [1,2].

Even with all the scientific evolution and positive results achieved with oral health research, dental caries

is still a serious public health problem that deserves all the attention to be faced, affecting a large part of the Brazilian population and present worldwide, especially in underdeveloped countries. It is known that the occurrence of dental caries can have consequences for different vital functions of the individual, which causes a great impact on the quality of life, especially in children, causing pain and suffering [3,4].

The discovery of a mucosal immunoenzymatic defense system, combined with advances in immunology, demonstrates the need to know their concepts and their possible interrelations with the installation and progression of the cariogenic process [4-7]. Dental caries is a chronic progressive disease, multifactorial and mediated by bacteria that results in the phasic demineralization and remineralization of dental hard tissues. Many recent studies have focused on the association between dental caries and systemic diseases [8].

The correct evaluation of patients with cardiovascular impairment is based on a detailed anamnesis and prior knowledge of the main coronary disorders and their sequelae [8]. Complications such as myocardial infarction and bacterial endocarditis may be described in clinical dental procedures. The management of this information is important in determining the patients' cardiac risk to classify it as high, moderate, or minimal. Thus, the acquired ones are the most frequent in the routine of a dental practice, so the dentist should be able to attend to those patients who need special care, regarding the correct use of medications due to the risk of drug interactions, the type of local anesthetic to be used and the management of patients who use anticoagulant therapy [9].

The recommendations of the American Heart Association emphasize that some surgical procedures, dental procedures, and instrumentations involving mucosal surfaces or contaminated tissues may cause transient bacteremia. While recognizing that the efficacy of antibiotic protection is uncertain in some cases, it recommends the administration of antibiotics to patients with a potential risk of developing endocarditis [10]. Continued administration of antibiotics should be considered in patients with established infection before the procedure. However, it is not possible to predict which patients will develop this infection or which particular procedure will be responsible [10,11].

Given the above, the present study analyzed the world literature systematically to list the main considerations regarding the relationship between the axis of caries and cardiovascular diseases, highlighting the immunological aspects.

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: 06/19/2024. The methodological quality standards of AMSTAR-2 (Assessing the methodological quality of systematic reviews) were also followed. Available at: https://amstar.ca/. Accessed on: 06/19/2024.

Research Strategy and Search Sources

The literary search process was carried out from April to Julho 2024 and was developed based on Scopus, PubMed, Science Direct, Scielo, and Google Scholar, covering scientific articles from various eras to the present. The Health Science Descriptors (DeCS/MeSH Terms) were used: *"Caries. Cardiovascular diseases. Immunological aspects. Dental Health"*, and using the Boolean "and" between the terms MeSH 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).

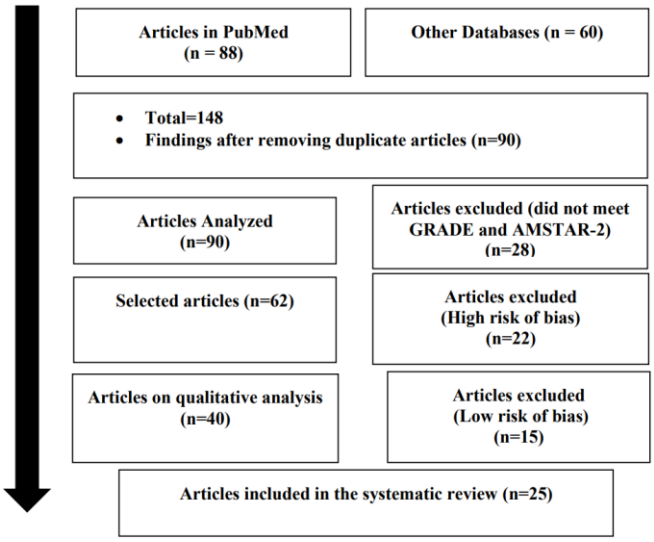
Results and Discussion

Summary of Findings

As a corollary of the literary search system, a total of 148 articles were found that were subjected to eligibility analysis and, subsequently, 25 final studies were selected to compose the results of this systematic review. The studies listed were of medium to high quality (Figure 1), considering in the first instance 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=92.7%>50%. Considering the Cochrane tool for risk of bias, the overall assessment resulted in 22

studies with a high risk of bias and 28 studies that did not meet GRADE and AMSTAR-2.

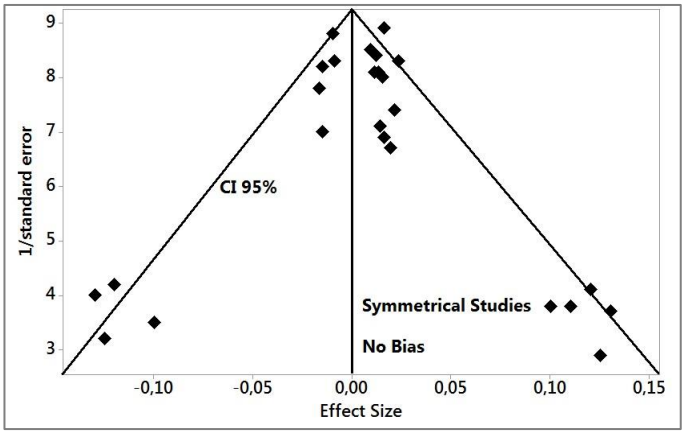
Figure 1. Flowchart showing the article selection process.



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 plot. High confidence and high recommendation studies are shown above the graph (n=25 studies).



Source: Own Authorship.

Major Results

One of the justifications for assessing the origin of severe caries in the present case report can be attributed to the high percentage of microorganisms that cause caries in maternal saliva. This favors transmission during the eruption of deciduous teeth in children and the development of caries depends on the moment when an infection, due to earlier colonization, is associated with a higher prevalence of dental caries [1-3].

The oral microbiota is the most complex of our whole body and there are bacteria with more than 30 different genera, covering more than 500 different species, the authors showed that, in the mouth, there are about 350 bacterial species were developed and 200 were distinguished by genetic studies [5-9]. Since dental caries is a multifactorial disease, the presence of microorganisms is essential for its development. The main etiological agents are the *Streptococcus mutans* and *Streptococcus sobrinus* species, observing that Lactobacilli play a great potential role in the progression of this disease, but not in the etiology of this disease [8].

The mechanisms of the immune response against extracellular bacteria can be distinguished into innate or natural immunity and acquired or adaptive immunity. The mechanisms of innate immunity are represented by macrophages and macrophages or polymorphonuclear neutrophils and by the complement system as a representative factor of humoral immunity [8,9].

In acquired immunity, we highlight the humoral factors, all classes of immunoglobulins produced by the plasma cells, which result from the activation of B lymphocytes, modulated by regulatory T lymphocytes, as well as T and B lymphocytes [6-9]. In this sense, the T and B lymphocytes of the sulcular fluid and the gingival conjunctival stroma are stimulated by the antigens present in the bacterial plaque, causing them to produce innumerable cytokines. These molecules act synergistically, blocking the migration of macrophages and fixing them in the infectious focus, mainly by the action of Interleukin 1 (IL 1) [9].

In this context, among the immunoglobulins present in saliva, we highlight that secretory IgA (IgA-s), in a higher concentration, is actively secreted by the glandular stromal plasmocytes, and the IgG and IgM immunoglobulins. Unlike serum IgA, which is a monomeric molecule, IgA-s is an IgA molecule dimer associated with a secretory component and a protein. This secretory component increases the resistance of this immunoglobulin to the proteolytic enzymes of the oral cavity and is added during its passage through the secretory cells of the epithelium of the salivary gland [8].

In addition, IgA-s acts mainly on the supragingival plaque, covering the bacterial surfaces, preventing its

adhesion to the acquired enamel film, since, besides blocking the receptors present on the surface of the bacteria, IgA-s promotes also bacterial agglutination, thus facilitating its removal from the oral cavity through the salivary flow [6,9]. IgA-s is also an extremely efficient agglutinin since each molecule of this immunoglobulin has four antigenbinding sites [9]. Despite this ideal ability of IgA-s and the numerous studies in this field, the researchers are still not decisive in affirming this possibility of action against *Streptococcus mutans* in humans, emphasizing that the immunity by IgA-s would be dependent on dental colonization, since when they already adhere to its surface, the protection exerted by this antibody is minimal [5-9].

In turn, IgG and IgM play a similar action to IgA, however, they act mainly at the subgingival plaque level. In addition, IgM antibodies are associated with IgA deficiency, in which the first group of antibodies is synthesized locally on the mucosal surfaces to compensate for the low or absent amount of IgA [6]. Furthermore, there is the ability of the cellular immune response in defense against caries. Most cariogenic microorganisms, especially *Streptococcus mutans,* can stimulate lymphocyte proliferation, especially TCD4 and cytokine production, leading to a negative correlation between the caries index and lymphocyte stimulation [1,6]. In this respect, the cariogenic bacteria infect, colonize, and accumulate on the surface of the teeth and can cause caries. Dental eruption is necessary for the initial colonization of several bacterial types such as *Streptococcus mitis* and *salivarius*, occurring around the first or second year of life, and in the case of *Streptococcus mutans* its colonization happens around the third and fourth year of life [6].

In this context, at birth, IgA is absent in saliva, increasing rapidly as the child is exposed to bacterial, viral, and alimentary antigens. After the first few weeks of life, it is possible to detect IgA levels against some types of streptococci, such as *Streptococcus mitis, salivarius, and mutans*, wherein the following years the increase in the level of these antibodies is detected, on average at 28 months of age in the case of IgA against *Streptococcus mutans*. This increase in IgA is important in the colonization of the oral cavity of infants, which is facilitated by the increase in the number of retentive surfaces [9].

The development of antibodies against *Streptococcus mutans* shortly after birth is related to exposure to this microorganism and not to the response to other antigens such as bacterial, viral, and food [10-12]. Given the presence of an immune response to *Streptococcus mutans* in the apparent absence of infection in some studies, it may represent an immune response to the maternal bacterial clone, suggesting the influence of the mucosal immune response and breast milk in this event [13-16]. Thus, health education represents one of the main elements for the promotion of health and a way of caring that leads to the development of a critical and reflexive awareness [17-19] and for the emancipation of the subjects by enabling the production of a knowledge that helps people to take better care of themselves and their families [20-22].

A recent clinical study examined the relationship between dental caries and incident ischemic stroke, coronary heart disease (CHD) events, and death. Participants with ≥1 dental caries had an increased risk of stroke (adjusted hazard ratio [HR], 1.40 [95% CI, 1.10-1.79]) and death (adjusted HR, 1.13 [95% CI, 1.01-1.26]) but not for CHD events (adjusted HR, 1.13 [95% CI, 0.93-1.37]). The association of dental caries and incident ischemic stroke was significantly greater in the African American population compared with the white subgroup (interaction term P = .0001). Increased decayed, missing, and filled surfaces were significantly associated with stroke (adjusted HR, 1.006 [95% CI, 1.001-1.011]) and death (adjusted HR, 1.003 [95% CI, 1.001-1.005]) but not with CHD (adjusted HR, 1.002 [95% CI, 1.000-1.005]). Regular use of dental care reduced (adjusted odds ratio, 0.19 [95% CI, 0.16-0.22]; p < .001) the odds of caries [23].

Furthermore, a cross-sectional study analyzed the prevalence of dental caries using the decayed (DT), missing (MT), and filled (FT) teeth index (DMFT) and investigated its relationship with cardiovascular disease. A total of 3,996 individuals aged 35-70 years were included. The mean DMFT score was 18.18 ± 19, indicating a high burden of oral diseases. Specifically, 60.04% had TD, 37.82% had more than 16 MT, and 38.83% had FT. Only 13.21% reported flossing regularly, and 43.17% brushed less than daily, showing suboptimal oral hygiene. The overall prevalence of CVD was 9.21%. Among men, DMFT remained a significant predictor for CVD after age adjustment, with an odds ratio of 2.37 (95% CI: 1.22– 4.60). Therefore, higher DMFT and MT scores positively correlated with increased prevalence of CVD [24].

Finally, a study evaluated the association of dental diseases and oral hygiene care with the incidence of heart failure (HF) among patients with type 2 diabetes. This study included 173,927 patients with type 2 diabetes aged ≥40 years who underwent health examinations. During a median follow-up of 9.3 years, 1.94% of participants developed HF. A higher number of missing teeth was associated with a higher risk of HF. HF risks increased among individuals with ≥15 missing teeth compared with those with no missing teeth. Reduced risk of HF was observed in individuals with ≥1

time/year of professional dental cleaning and in those with ≥2 times/day of tooth brushing compared with those without these practices. While the combined presence of missing teeth and periodontal disease or dental caries increased the risk of HF. Combined oral hygiene care was associated with a greater reduction in the risk of HF [25].

Conclusion

It was concluded that there is an important network and cascade of defense events between immunological processes and caries disease. Thus, it is necessary to have a healthy immune response to reduce the incidence of caries. Dental caries was independently associated with the risk of ischemic stroke and death, with the effect being greatest in African-American participants. Regular dental care was associated with a lower chance of caries, emphasizing its relevance in preventing these events. Higher scores of decayed, missing, and filled teeth correlated positively with increased prevalence of cardiovascular disease. Among patients with type 2 diabetes, dental disease, and oral hygiene care are important determinants of the development of heart failure.

CRediT

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Conflict of Interest

The authors declare no conflict of interest.

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