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REVIEW

Periodontal disease, systemic inflammation and the risk of cardiovascular disease

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Periodontal and cardiovascular disease are both major health issues. Poor oral health has long been associated with the development of systemic diseases, with the typical example being the risk of endocarditis posterior to dental procedures. Through the years, the association of periodontal disease with other non-infectious systemic diseases has been brought to attention. One of the most interesting associations is the one that exists with the development of cardiovascular disease. Many studies, including systematic reviews and meta-analyses, suggest an important association between periodontal disease and ischaemic heart disease, cerebrovascular disease, heart failure, atrial fibrillation and peripheral artery disease. Among the proposed mechanisms of this relationship, systemic inflammation appears to play a major role. Evidence suggests that periodontal inflammation triggers a systemic inflammatory state that, added to the damage mediated by antibodies that cross react between periodontal pathogens and components of the intimal wall, and the direct lesion of the intima by bacteria entering the circulation, promotes atheroma plaque development and progression. There are other studies that show a clear relationship between periodontal disease severity, elevations of inflammatory markers, and the presence of atherosclerosis. Here, we give a review of the available evidence supporting this association, and the possible mechanisms involved.

Keywords Periodontal disease • Systemic inflammation • Cardiovascular disease • Atherosclerosis

Introduction

The oral cavity serves as home for a large number of microorganisms whose species differ as they are found in the teeth, gum, cheek, gingival sulcus or palate, and interact with their human host, both in health and disease [1]. In total, an adult can have nearly one billion bacteria in the oral cavity. It is well known that, in patients with some degree of periodontal disease (PD), episodes of bacteraemia can occur after daily procedures such as teeth brushing or use of chewing gum, and that this can occur in multiple occasions throughout the day [2]. The mouth has been long recognised as a source of systemic infections, from where the passage of bacteria into the bloodstream is allowed from interruptions of tissue integrity secondary to inflammation in conditions such as periodontitis [3]. The clearest relationship exists between dental procedures and bacterial endocarditis, from whence the still valid recommendations of antimicrobial prophylaxis for patients with risk factors prior to undergoing a dental procedure arise [4,5]. From these observations, a lot of evidence has been generated about the relationship between PD and the occurrence of non-infectious systemic diseases like rheumatoid arthritis (RA) [6], and atherosclerotic cardiovascular diseases (ASCVD) such as ischaemic heart disease (IHD) [7], cerebrovascular disease (CBVD) [8], peripheral artery disease (PAD) [9,10], heart failure (HF) [11] and atrial fibrillation [12].

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Epidemiology of Cardiovascular and Periodontal Disease

Cardiovascular Disease

According to the World Health Organization (WHO), ASCVD remains the leading cause of death worldwide. In 2012 it accounted for about 17.5 million deaths, representing nearly 31% of the total of deaths globally [13]. Ischaemic heart disease is the most frequent form of ASCVD. In its 2017 report, the American Heart Association (AHA) estimates that every 40 seconds a person will suffer an acute myocardial infarction (AMI), also, that nearly 695,000 persons will suffer a new acute coronary event and about 325,000 will have a recurrent event, with 21% of these events being silent myocardial infractions [14]. In Mexico in 2011, IHD accounted for 71,072 deaths, nearly 11% of the total of deaths in the country [15,16]. Cerebrovascular disease is another frequent form of ASCVD, which represents one of the leading causes of death worldwide. According to the AHA, every year, 795,000 people suffer a new cerebrovascular event (CVE) with 610,000 being first events and 185,000 recurrent events [14]. In Mexico, the accumulated incidence is 232.2 cases per 100,000 persons, with a prevalence of 18.2 cases per 1000 persons in those aged 60 years or older [17]. Peripheral artery disease affects almost 8.5 million people aged 40 years or older. Prevalence rises with ageing, being 22.7% in people of 80 years or more and 1.6% in those of 40 to 49 years [14].

Periodontal Disease

Through the years, estimating the incidence and prevalence of PD has represented one of the main challenges of the study of this disease. The existence of diverse diagnostic criteria and evaluation methods and the lack of consensus with regard to definition and disease severity has generated imprecise estimates of the real global impact of this condition [18,19]. In 1982, the WHO developed the ''Community periodontal index of treatment needs'' (CPITN), which they later modified. This assessment tool aimed to standardise the evaluation of patients with suspected disease and with this, to obtain more reliable and reproducible data [20,21]. Recent data compilations for North and South America show that the average prevalence of severe forms of PD for adults in ages between 35 and 44 years is 20%, and 40% for less severe forms of the disease. In North America, the prevalence of severe disease seems to be low, suggesting that severe forms are more prevalent in South America [22]. Gingival bleeding and dental calculus are the most frequent forms of affection in every group of age. In Mexico, periodontal calculus are present in 31.9 to 35.7% of people between 35 and 44 years and 31.5 to 39% in those between 65 to 74 years [23]. An epidemiological survey showed that up to 56.8% of the population had some degree of PD. Twenty-one per cent had gingivitis, 3.9% shallow periodontal pockets and 0.8% deep periodontal pockets [23]. A consistent fact between epidemiological studies is that prevalence and severity of PD rise with ageing [19,23,24].

Periodontal Disease: Physiopathology and Risk Factors

In the oral cavity, teeth are supported by the periodontal ligament. The space between the higher point of the gingival margin and the point where the gingiva meets the dental surface is called the gingival sulcus, which is colonised with bacteria that form a biofilm or dental plaque. In PD, bacteria trigger an inflammatory process that deepens the gingival sulcus and eventually forms a periodontal pocket; moreover, there is apical displacement of the gingival union to the root surface and of the biofilm, loss of support tissue and alveolar bone, and gingival recession. Over 500 microbial species recovered from the dental plaque have been described [25]. The clean teeth are covered with a plaque of glycoproteins called ''pellicle'' that binds to the hydroxyapatite on the tooth surface. Microorganisms inhabit this pellicle above and below the gingival margin as supra and subgingival plaque. The composition of microbial plaque above and below the gingival margin differs [24]. Supragingival space is colonised by *Streptococcus sanguis, Streptococcus oralis, Streptococcus mutans, Actinomyces naeslundii* and *Actinomyces odontolyticus*. In the absence of PD, subgingival space is colonised by *A. naeslundii, S. sanguis, S. oralis, Vellionella parvula, A. odontolyticus*, and *F. nucleatum* [26]. Gingival inflammation represents an intermediate state between health and periodontitis, inflammation shifts the composition of bacteria to microaerophilic gram negative bacilli and anaerobes [27,28]. In periodontitis, subgingival microflora turns from being predominately gram positive, to gram negative and obligated anaerobes like, *Porphyromonas gingivalis, Tannerella forsythia, Treponema denticola, Selemonas noxia, Campylobacter rectus, Aggregatibacter actinomycetecomitans, Prevotella intermedia*, and spirochetes [25–28].

Risk factors for PD are divided between those that can be modified or at least controlled, like, smoking, diabetes mellitus (DM), obesity, alcoholism, osteoporosis and stress; and those that can't be modified, such as gender, ethnicity, age and genetic factors. Males seem to be more affected by PD. The ''National Health and Nutrition Examination Survey'' (NHANES), showed that risk of PD is 50% higher in males than in females [29]. Smokers have four to five times greater odds of having PD than non-smokers [30]; and there's a relationship between intensity of smoking and the severity of PD [31]. The relationship between PD and DM has long been known, and it seems to be bidirectional. Most studies come from Pima Indians, where DM prevalence is of 40 to 50%, and these show that PD prevalence and severity is higher in diabetics [32]. Other studies have suggested that glucose intolerance is also related to PD [33]. Some systematic reviews and meta-analyses have shown an association between obesity and frequency and severity of PD [34].

Relationship Between Periodontal Disease and Cardiovascular Disease

Although periodontal inflammation has been associated for more than 20 years with a greater incidence of cardiovascular events [35], some issues have been raised about the validity

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