

The Relationship Between Periodontitis and Systemic Diseases – Hype or Hope?

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ABSTRACT

Investigations have definitely acknowledged a clinically relevant two-way relationship between periodontitis and certain systemic diseases and conditions, which are significant for the dentist in the daily practice and for a physician as well. This review article

yields the most up-to-date information on the role of periodontal diseases in systemic diseases, that include cardiovascular diseases and atherosclerosis, diabetes mellitus, respiratory diseases and unfavourable pregnancy outcomes. It debates the role of diabetes and smoking in the periodontal tissues.

Key Words: Periodontitis, Systemic diseases, Systemic conditions

INTRODUCTION

The race is on. The stakes are high. There are at least 2 scenarios: If periodontal disease is cleared of all the reasonable risks, the patients can breathe a sigh of relief about the deeper implications of their chronic periodontal disease. Or, when the researchers fight for a shrinking slice of grant funding, the dental organizations win, because their value increases with the life-or-death research findings which justify the medical necessity of the dental practitioners who treat a common human health scourge: periodontal disease. Whoever wins in this battle, it will have a deep impact on the current treatment modalities of periodontal and systemic diseases.

Dentists Confused Over the Periodontal-Systemic Research Findings

The National Institute of Dental and Craniofacial Research, National Institutes of Health, has long maintained that: "Oral health is not an independent entity which is cut off from the rest of the body. Rather, it is woven deeply into the fabric of the overall health [1]." What researchers are trying to determine is, whether the oral health is woven into that fabric with paper or steel threads.

Specifically, what is the relationship between periodontal disease and systemic diseases?

There are three possibilities:

- **No relationship:** Periodontal disease and systemic disease are random, concomitant occurrences/happenstances or coincidences.
- **An association:** Periodontitis is a marker for systemic disease — along with many others — which show that the patient is at an increased risk, but with no causation.
- **A causal relationship which requires intervention:** Periodontitis is a contributing cause that initiates or aggravates systemic diseases.

How Did It All Start?

This link came to the forefront in the late 1980s, when the preliminary research in dental journals identified systemic diseases

which were also seen in those with periodontal diseases [2]. Nery E.B. et al., observed that the periodontitis-plagued could also have cardiovascular diseases, and that the pregnant and the periodontitis-plagued could also have premature labours and deliveries [2]. By the 1990s, the term "periodontal medicine" was seen in the literature [3]. In the early 2000s, dentists were being instructed to warn their patients that these systemic diseases could worsen when they had periodontal diseases.

The proposed mechanisms behind the increased risk and the causation theories have tended to be in two camps: infection vs. inflammation, with some commonality between them. The century-old, "focal infection theory" [4] which is also called "oral sepsis", once held that bacteria migrated throughout the body, causing arthritis, mental disease, and a host of other ills. By the middle of the 20th century, medicine and dentistry concluded that medical surgery and tooth extraction had no effect on ending the ills. The more recent trials also negate the focal infection theory. A 2003 study which was conducted by O'Connor, Dunne et al., on 7,774 adults with a history of myocardial infarction and a known *Chlamydia pneumoniae* exposure, to check whether or not an antibiotic intervention would prevent heart attacks as a byproduct of preventing infections, came up empty [5]. Other large, double-blind, randomized studies (Grayston et al and Wells et al.) indicated that coronary heart disease outcomes were not reduced by eliminating infections by using antibiotics [6].

Meanwhile, antibiotics are not recommended routinely during pregnancy, and if they were, there is scant evidence that their prevention of infection would reduce preterm births [7]. In addition, the speculation that infectious bacteria of necrotic pulps leak out apices and seed elsewhere in the body to cause systemic diseases, has been dismissed by the American Association of Endodontists after decades of debate [8].

The winds of the microbial causation theory have changed the direction in recent years. The other camp has theorized that inflammatory enzymes from periodontitis lesions which were found to circulate in the bloodstream [9] may be the culprit [10]. Could the C-reactive protein and the cytokine markers — which were

increased in periodontitis patients — predict strokes and heart attacks? Another hypothesis is that periodontitis is linked to the presence of fibrinogen and ultimately, thrombogenesis [11]. Yet, some researchers (Danesh J, Wheeler et al.) say that it has not been established that the C-reactive protein is a strong predictor of coronary heart disease [12]. Inflammation is a sign of healing as well as infection and so it may not be as ominous as it has been charged. Others point out that the inflammation from other sources — for example, sinusitis, allergies, rheumatoid arthritis, and haemorrhoids — all should be guilty of causing systemic disease if this were the case. The truth emerges in science eventually, and the periodontitis-systemic disease question is no exception.

The Pregnant Worry for Their Foetuses

Surveys have not been done to assess what dentists are telling pregnant patients, or how dentists perceive about the risks of periodontal disease in the unborn. Therefore, the analysis must turn towards the kinds of messages which dentists are receiving. In published studies, the authors often provide clinical implications in the abstract, discussion, or conclusion sections of their articles; the dental and lay public media distribute these far and wide, but often without discussing the limitations of the study to place it into the right perspective. The hope is to educate the dental community to equip the patients with the research findings that can influence their oral care behaviours. The outcome, theoretically, would be to prevent morbidity, such as mental retardation, and mortality, such that occurs in greater numbers in low-birth-weight (5.5 pounds and less), preterm babies. Indeed, some dental researchers echo these sentiments [13]. A 2003 systematic review which was written by Scannapieco FA and Bush RB et al., suggested that scaling and root planing may significantly reduce a women's chances of having a preterm birth [14].

Studies may find an association, which they sometimes call an "increased risk." Some studies have failed to assess whether such women lacked a personal attention to their oral hygiene, suffered drug/alcohol use, had a history of bacterial vaginosis or antibiotic treatment during pregnancy, and so forth. This results in there being insufficient evidence as of 2011, to say that periodontal disease is a contributing cause of preterm labour and delivery. According to few authors, the studies so far, show associations of varying strengths between periodontal disease and systemic diseases. "But the evidence for a causal association is not available as yet. "One of the strongest ways to prove the causation is to demonstrate that reducing a 'risk factor' like periodontal disease will reduce the systemic disease. That is, if you treat periodontal disease, will it really reduce the systemic disease?"

The Atherosclerotic Keeping Teeth Clean

Media messages which swirl around the public say that the gum disease infection releases bacteria into the bloodstream that causes clots and may cause a heart attack or stroke. The patients assume that if the risk wasn't certain, their dentist wouldn't have told them about it, and the leading newspapers wouldn't have had a headline such as "Floss or Die?" Other news outlets have attention-grabbers such as "Are My Bad Teeth Killing Me?" and lead sentences such as "Severe gum disease may hasten death in people with diabetes." In a systematic review which was written by Scannapieco FA and Bush RB et al., the reviewers concluded that periodontitis was "modestly associated" with arterial disease and

that patients and health care providers should be informed that a periodontal intervention may prevent the onset or progression of atherosclerosis-induced diseases [15].

A 2004 meta-analysis which was done by Khader YS and Albashaireh ZS, et al., found a relative risk of cardiovascular disease in those with periodontitis [16]. It is possible that periodontitis has a causative role in coronary heart disease, but additional studies, especially interventional studies, are needed before this can be assumed [17]. Some believe that atherosclerotic cardiovascular disease is the most complicated multifactorial disease which is presently known. In the statistics section of many studies, only a sentence is provided, that states: "After controlling for risk factors, it was determined ..." but no factors are listed specifically. According to Philippe Hujoel, researcher and periodontist, confounding factors (especially behaviours such as smoking and factors such as the socioeconomic status, cholesterol medication, lipid profile, Diabetes Mellitus (DM), gender, a family history of coronary heart disease, stress, obesity, age and blood pressure) explain the small associations which are found in most of the studies, as of 2011 [18]. "Considering these commonalities in the causal risk factors, it would be surprising if such associations between periodontitis and cardiovascular disease were not shown."

As of 2011, there is insufficient evidence to say that arterial disease events can be prevented by reducing the periodontal disease. Many of the existing studies have either had small study sample sizes, mild-to-moderate odds ratios (1.2-1.5), or relative risks instead of absolute risk rates. The AHA Advisory on Oral Health and Cardiovascular Disease states that as yet, "No substantial evidence has been presented that oral microorganisms are aetiologic for cardiovascular disease, nor that they cause or exacerbate acute cardiovascular events ... [and] at this time, the promotion of the dental treatment expressly, for the purpose of the prevention of atherosclerotic cardiovascular disease and/or acute cardiovascular events, is not recommended" [19].

Periodontitis and respiratory diseases

As early as 1968, Potter et al., described the presence of dental diseases in subjects with pulmonary diseases [20]. Oral bacteria can enter the lower respiratory tract by aspiration and cause pneumonia. Severe infections of the lungs can develop after the aspiration of the salivary secretion, especially in patients with periodontitis [20]. 30-40% of aspiration pneumonia and predominantly necrotizing pneumonia or lung abscesses have anaerobes in their aetiology, the most frequent organisms being *Proteus gingivalis* (PG), *Bacteroides oralis*, *Eikenella corrodens*, *Fusobacterium nucleatum*, *Aggregatibacter actinomycetemcomitans* (AA), *Peptostreptococcus* and *Clostridium*. It is possible that even *Streptococcus viridans* plays a role in the development and/or progression of pneumonia [20].

Bacteria may have an influence in the exacerbations of Chronic Obstructive Pulmonary Disease (COPD) [20], where the dental plaque may serve as a reservoir of respiratory pathogens. There are a number of possible mechanisms by which bacteria can influence the pathogenesis of respiratory diseases:

- Aspiration of oral pathogens (PG or AA, for example).
- Alteration of the mucous surface by salivary enzymes in periodontitis, leading to an increase in the adhesion and colonization of respiratory pathogens [20].

- The periodontal disease-associated enzymes may destroy the salivary pellicles on the pathogenic bacteria [20].
- Alteration of the respiratory epithelium by cytokines from periodontal disease, which facilitate the infection of the epithelium with respiratory pathogens [20].

Smoking and Periodontitis

The effect of smoking on periodontal disease has been studied in detail in a number of reports. Smoking has immunosuppressive effects that impair the host defences by decreasing the motility, chemotaxis and the phagocytosis of the polymorphonuclear leukocytes (PMN-L) in peripheral blood. Therefore, the first line of defence against the subgingivally colonized bacteria is endangered. Smokers have a decrease in the antibody production, especially IgG2, which is the most responsible for the colonization of periodontal bacteria, additionally to the smaller percentage of immunoregulatory T-lymphocytes [20].

Periodontal pathogens evade the specific and non-specific immune defence and they colonize subgingivally. Smoking increases the adhesion of the microorganisms on epithelial cells. It has been proven that smokers are more easily infected by *B. forsythus* and *Porphyromonas gingivalis* than non-smokers. Nicotine has been found on the tooth root surfaces of smokers. Cotinine, the main metabolic product of nicotine, can be found in the serum, saliva and the sulcus fluid of smokers. The exposition of fibroblasts to nicotine, leads to a weakening of their proliferation, migration and adhesion to the root surface. They bind and phagocytose nicotine non-specifically, which can lead to the metabolism collagen synthesis and protein secretion alterations. Smoking causes a chain of unfavourable reactions that include a weakened immune response, a subgingival colonization of bacteria and toxicity of the connective tissue cells. Altogether, it leads to an increase of the periodontal disease expression and a weakened response of the periodontal tissue during the therapy [20].

The Influence of Periodontitis on the Glycaemic Control in Diabetes

Taylor et al. reported that initially, severe periodontitis presents a six times greater risk of a poor glycaemic control during a recall. In a case-controlled study which was done on adult DM patients with gingivitis and mild periodontitis, and on patients with DM and severe periodontitis, it was reported that the subjects with severe periodontitis had a significantly greater prevalence of cardiovascular and renal complications in 1 to 11 years, inspite of the fact that the haemoglobin A1c (HbA1c) values were similar - i.e. the same glycaemic control. It seems that the classic complications of DM stand in close relationship with those of periodontitis, and it is reasonable to speak of periodontitis as "the sixth complication of DM". The most difficult question that is yet to be answered in the future, is whether the treatment of periodontal disease, which points to the elimination of pathogenic microorganisms, will have a positive effect on the glycaemic control. It is one of the greatest tasks in the coming years [20].

An Evidence-based Approach to the Oral-Systemic Relationships

A significant recent advance in health care has been the movement towards a model of evidence-based practice, which is also gaining attention in dentistry. An important component of the evidence based approach is risk assessment, which involves

the classification of an individual's probability of acquiring a disease, based on scientifically determined risk factors. Such an assessment of the risk could provide important information for guiding the clinical decisions regarding the prevention and the treatment of diseases in individual patients. The concept of a universal susceptibility to periodontal disease has been discarded, as it has become clear that the susceptibility differs widely among people and that the disease is not evenly distributed throughout populations.

Increasing attention is now aimed at identifying the specific attributes and the exposures which are associated with an increased risk of developing periodontal disease and, in turn, with the systemic consequences of periodontitis. The multi-factorial causation of periodontal disease, coupled with the large number of risk factors and risk indicators that may impact the severity and the extent of the disease, makes the determination of the pathogenesis difficult. A risk factor is commonly defined as a particular characteristic, a behavioural aspect or an environmental exposure that is associated with a disease occurrence. In the case of periodontal disease, the risk factors may involve the host response and the pathogenic flora and they may include characteristics such as age, gender, education, and the frequency of the dental visits. To complicate further the quest, to elucidate a comprehensive causal model for periodontal disease, certain important indicators of the disease may not be causally related. For example, an increasing age does not in itself cause disease, but the older individuals may have more attachment loss due to the multiple periods of disease throughout their lives.

Currently, the most commonly used methods of assessing periodontal disease in populations, typically involve measures of clinical attachment loss or radiographic alveolar bone loss. However, due to the chronic and the episodic nature of periodontal disease, such assessments necessarily measure the cumulative effects of the disease process over time, rather than the current disease activity. Since there is currently no generally accepted assessment tool for reliably measuring the active periodontal disease, the value of longitudinal studies become apparent, as they permit the assessments of change over time. Such longitudinal studies are of particular value in evaluating the potential causal relationships, in a large part, as they allow the examination of the temporal sequence of the appearance of the risk factors and the subsequent occurrence of the disease and its progression. However, the strongest evidence for evaluating the role of the potential risk factors most often comes from experimental studies, such as a randomized controlled trial, in which the modification of the risk factor is randomly assigned to a test group as compared to a control group, that receives a placebo intervention, for example [21].

Implications for the Clinical Practice

What does all of this mean to the practising clinician? We know that although plaque is still the primary aetiology of the gingival and the periodontal diseases, the host response is probably the most important link in the causal chain. Unfortunately, there is no way to reliably (and cost-effectively) predict whether the patient with gingivitis, who is sitting in our chair, will develop attachment loss slowly, quickly or not at all. However, knowing some of the risk factors can assist with these predictions. Although we are not able to change our age, our gender or, our genetic composition, to date at least, there is a genetic test that will identify the people with the

IL-1 phenotype. By identifying the people who are at a greater risk of developing severe adult periodontitis, we may be able to carry out an earlier or a more aggressive intervention for these patients.

Due to the strong association of smoking with periodontal disease, it would be prudent to advise our patients that as compared to non-smokers and former smokers, they are at a greater risk of developing periodontal disease; less likely to respond well to the periodontal therapy; and more likely to suffer from postsurgical complications. The patients who require dental surgery may be referred for a smoking cessation counselling or they may be treated by a more conservative means. In people with an unexpected attachment loss, we should be suspicious of systemic problems, particularly diabetes mellitus. For people with diagnosed diabetes, who have a difficulty in maintaining their blood sugar at a constant level, we should monitor their periodontal situation closely.

Currently, the rationale for treating periodontal diseases is to preserve the structure, function and the aesthetics of the dentition. In fact, such a treatment may just be as important, in terms of preventing untoward effects on a patient's overall health.

The Limitation and the Further Avenues of the Study

The analysis of limited data from interventional studies suggests that a periodontal treatment generally results in favourable effects on the subclinical markers of systemic diseases like atherosclerosis, although such an analysis also indicates considerable heterogeneity in the responses. Experimental, mechanistic, *in vitro* and *in vivo* studies have established the plausibility of a link between periodontal infections and systemic diseases, and they have identified biological pathways by which these effects may be mediated. However, the utilized models are mostly the mono-infections of the host cells by a limited number of 'model' periodontal pathogens, and therefore, they may not adequately portray the human periodontitis as a polymicrobial, biofilm-mediated disease. The future research must identify the *in vivo* pathways in humans that may (i) lead to periodontitis-induced systemic diseases, or (ii) result in a treatment-induced reduction of the systemic risk. The data from these studies will be essential for determining whether periodontal interventions have a role in the primary or secondary prevention of systemic diseases.

CONCLUSION

Periodontitis can't be considered as a cause of atherosclerotic heart disease, stroke, diabetes or pre-term low birth weight, but it can be considered as an additional risk factor, with consistent findings of increased odds ratios and significant probability values.

The future of the dental practice will be dramatically altered if the subsequent research confirms that periodontal disease is a true risk factor for systemic diseases and that the initiation or progression of these medical conditions can be reduced by periodontal treatment. More dental research is needed to make sure that periodontal disease is not a non-causative bystander, or that the dentists who were told to promote the links will think that they were misled into 'crying wolf'.

Dentistry needs to be certain of these morbidity and mortality links before telling the world about them. If they aren't borne out, the patients who became convinced of the importance of dental care through these alleged risks may just think that dentistry isn't very important after all.

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