

Oral Health, Periodontal Pathogens and Carcinogenesis: New Evidence to Support the Oral-Systemic Link?

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Editorial

Periodontitis and Cancer: is there a link?

For years, dental professionals and their medical colleagues have paid attention to their own respective fields of discipline. However, the gap between allopathic medicine and dentistry has begun to close at an alarmingly fast rate [1], as we begin to appreciate how oral health is indicative of systemic health, and this also holds true the other way around as well. The events and activities in the tissues within the oral cavity can induce inflammatory processes in other areas of the body, and this is principally thought to be a result of the actions of periodontal pathogens residing in the tissues and on top of the tooth surfaces as well [1].

The purpose of this paper is to introduce a new and potentially plausible disease connection between oral cavity and the rest of the human body, and its presence could see clinical implications for the way in which routine and actively employed dental care is carried out.

Whilst some argument can be made that gingivitis is highly prevalent and almost universally present to some extent, periodontitis is a destructive, irreversible disease, which affects around 10% of the global population [2]. The dysbiotic, chronic inflammatory condition destroys and compromises the integrity of gingival and periodontal ligament connective tissues, as well as leading to the loss of alveolar bone, and thus the apical migration of the functional epithelium [3]. The disease is thought to be caused by gram-negative anaerobic or microaerophilic bacterial species that colonise the sub-gingival space, and examples include *Porphyromonas gingivalis*, *Aggregatibacter actinomycetemcomitans* and *Tannerella forsythia* [4]. However, recent study findings demonstrate that an increased diversity of the microbiota is more likely to lead to disease, than specific strains of bacteria [5]. However, it may be true that the presence of certain strains is more likely to influence disease progression and severity. Further research is required to confirm and validate this thought. What is known is that the presence of bacteria represents the primary aetiological agent of the disease process, and the initiation, progression and severity of the disease depends on other factors such as medicinal drugs, smoking, immunosuppression, genetics and hormonal/immune factors. Diet may also have a role [6].

Periodontitis has been linked with several disease forms, including type 2 diabetes mellitus [7], cardiovascular disease [8], adverse pregnancy outcomes [9], respiratory disease [10], and both osteoporosis and rheumatoid arthritis [11]. The thought processes behind most of this is that the periodontal pathogens are able to secrete inflammatory mediators and proteins, which reduce the strength of the immune system and create an opportunity for opportunistic pathogens to create burden on the rest of the body.

The concept and understanding of the events taking place within the oral tissues, influencing the activity elsewhere within the body, is not a new concept. It has, however, undergone lots of changes in the level of understanding over the years [12-14]. During the earlier years, there was widespread debate and dispute regarding the existence of this so-called 'oral-systemic link', however nowadays it is widely accepted.

Pathogenesis of human periodontitis

Page and Schroeder first placed the understanding of human periodontics on an understandable and logical platform in 1976, and the concepts they proposed at the time are still very much acknowledged and accepted even to this very day, despite our understanding continuing to remain as an incomplete picture due to the complex nature of the disease process [15].

Global leaders in the field of periodontics agree that the disease is initiated by bacterial plaque, principally by the presence of gram-negative anaerobic or microaerophilic bacterial species that form residence within the sub-gingival pocket. Primary species believed to have an influential role in the disease process include *Porphyromonas gingivalis*, *Aggregatibacter*

actinomyces comitans and Tannerella forsythia; as this was concluded at the 1996 World Workshop on Clinical Periodontitis [16]. We have now collected enough evidence to confidently establish that periodontitis is a collection of closely linked/related disease which will vary in their onset, severity and treatment affectivity. It is no longer considered to be a single disease process. The presence of bacterial plaque causes the capillary endothelial cells to separate, enabling fluid penetration into the extravascular tissue compartments. This is an important process as it allows immune cells to come into close contact with the bacterial cells, and also creates an opportunity to remove waste products from and transport nutrients to the immune cells. Many inflammatory mediators are present in the host tissues, including complement activation products, kinins and matrix metalloproteinases [17].

Epidemiological studies

Attention will now be paid to two cohort studies, which examine a possible periodontitis-cancer relationship at the population level. Whilst many studies may well have demonstrated a relationship between these two variables, Ren et al. [17] demonstrates that no relationship has been seen. The study looked at a total of around 1,063 patients with colorectal cancer, as well as 5,556 controls matched for age, sex, exercise, diet, alcohol and smoking levels. All participants were interviewed and categorized by the number of teeth that they had lost – none; 1-5 missing teeth; 5-10 missing teeth; and more than 10 missing teeth. Smoking levels, red meat consumption, BMI and exercise levels were adjusted for using linear regression curves.

Two important considerations are that *Fusobacterium nucleatum*, a pathogen associated with chronic periodontitis, has been demonstrated to increase colorectal cell growth in mice. In addition, the human micro biome project has concluded that the microbial populations in the mouth and intestines are similar.

Some problems with this study are that oral health levels are self reported, and therefore may well be prone to recall errors, and we have a limited understanding of the oral micro biome composition and of the process of chronic inflammation. How can we even think of investigating the mechanisms at play when we lack the understanding about key molecules and substances that may be important in the process? In addition, this study looks at periodontitis in the form of missing teeth, whereas missing teeth are a surrogate measure for periodontitis and trauma and caries can also lead to missing teeth. It would be advantageous to use the 1999 Page and Eke AAP CDC case classification definition system, which takes into account levels of clinical attachment loss.

Laprise et al. [18] conducted a cohort study, which looked into the potential relationship between periodontitis and cancer, between the years 2008 and 2012 in Kerala, India. A life course questionnaire was used for information gathering and periodontal disease levels were measured by gingival inflammation and recession. Generalised gingival recession (a measure of past disease) was strongly associated with an increased risk in the development of oral cancer.

A major challenge right from the beginning of this study was to appreciate that oral cancer and periodontitis share many mutual risk factors, such as smoking.

350 patients participated in the study with 371 controls. The patients with histologically confirmed squamous cell carcinoma (by brush biopsy) were analysed via professional dentists under halogen light. Inflammation was noted (mild, moderate, severe), as were recession levels and distribution. Generalised recession means more than one quadrant was involved. Generalised gingival recession was demonstrated to almost double the risk of oral cancer development.

Potential disadvantages of this study are that recession is an indication of past disease, whereas the use of clinical attachment loss would represent presenting disease levels. In addition, oral health variables were not accounted for, particularly important as periodontal disease is a plaque-induced condition (in most cases).

Biological plausibility

Abnet et al. believe that the periodontal pathogens may be directly triggering the carcinogenesis process, and historical cases have seen bacterial species linked with malignancy, such as *Helicobacter pylori* linked with gastric cancers, *Salmonella typhi* with hepatic cancers and *Streptococcus bovis* with several tumour forms [19].

Porphyromonas gingivalis has demonstrated an ability to speed up the action of nitrate reducing microorganisms in the oral cavity, leading to an explosion in the level of carcinogenic nitrosamines. It has also demonstrated an ability to enter into epithelial cells and produce apoptosis silencing proteins and molecules.

Aggregatibacter actinomycetemcomitans has demonstrated an ability to release toxic compounds, which can increase the level of interleukin 1 and prostaglandin E2, as well as disrupt DNA and generate point mutations/gene deletions. By increasing the level of prostaglandin E2, there is a knock on effect of accelerated osteoclast activity, furthering alveolar bone loss, and ultimately amplifying the signs and symptoms of periodontitis. It is clear from the points mentioned that this two-way relationship does have the backbone of biological plausibility [20,21].

Conclusion

There has been limited research conducted within this potential relationship, but the early epidemiological data has demonstrated a potential relationship may be present. It would be of vital importance to take this proposition into lab based studies, particularly analysing the actions of *Porphyromonas gingivalis* and *Aggregatibacter actinomycetemcomitans* on cellular samples. The epidemiological studies can only provide us with potential trends, and the lab-based studies will allow us to analyse the exact impacts of particular bacteria strains on cellular function. The epidemiological research to date does generate clinical implications. It emphasizes a need for thorough assessment, regular recall and maintenance as well as expanding the primary prevention initiatives employed at the population

level. Root surface debridement will be important in those suffering from periodontitis, as it will reduce the bacterial loads in the pockets, reducing systemic inflammation and perhaps even the potential for carcinogenesis. In addition, we can only examine clinical presentation, which does not always correlate

with levels of infection and inflammation. To measure those we must detect vascular changes, oedema and tissue fragility via the use of genetic testing and biochemical marker analysis and profiling techniques. It may be some time within dentistry before we can employ these research methods.

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