

Periodontitis and systemic diseases: a record of discussions of working group 4 of the Joint EFP/AAP Workshop on Periodontitis and Systemic Diseases

Gerry J. Linden¹, Mark C. Herzberg²
and on behalf of working group 4 of
the joint EFP/AAP workshop*

¹Centre for Public Health, School of Medicine, Dentistry and Biomedical Sciences, Queen's University Belfast, Belfast, Northern Ireland, UK; ²Department of Diagnostic and Biological Science, School of Dentistry, University of Minnesota, Minneapolis, MN, USA

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Abstract

Background: There has been an explosion in research into possible associations between periodontitis and various systemic diseases and conditions.

Aim: To review the evidence for associations between periodontitis and various systemic diseases and conditions, including chronic obstructive pulmonary disease (COPD), pneumonia, chronic kidney disease, rheumatoid arthritis, cognitive impairment, obesity, metabolic syndrome and cancer, and to document headline discussions of the state of each field. Periodontal associations with diabetes, cardiovascular disease and adverse pregnancy outcomes were not discussed by working group 4.

Results: Working group 4 recognized that the studies performed to date were largely cross-sectional or case-control with few prospective cohort studies and no randomized clinical trials. The best current evidence suggests that periodontitis is characterized by both infection and pro-inflammatory events, which variously manifest within the systemic diseases and disorders discussed. Diseases with at least minimal evidence of an association with periodontitis include COPD, pneumonia, chronic kidney disease, rheumatoid arthritis, cognitive impairment, obesity, metabolic syndrome and cancer. The working group agreed that there is insufficient evidence to date to infer causal relationships with the exception that organisms originating in the oral microbiome can cause lung infections.

Conclusions: The group was unanimous in their opinion that the reported associations do not imply causality, and establishment of causality will require new studies that fulfil the Bradford Hill or equivalent criteria. Precise and community-agreed case definitions of periodontal disease states must be implemented systematically to enable consistent and clearer interpretations of studies of the relationship to systemic diseases. The members of the working group were unanimous in their opinion that to develop data that best inform clinicians, investigators and the public, studies should focus on robust disease outcomes and avoid surrogate endpoints. It was concluded that because of the relative immaturity of the body of evidence for each of the purported relationships, the field is wide open and the gaps in knowledge are large.

Key words: cancer; chronic kidney disease; cognitive impairment; epidemiology; metabolic syndrome; obesity; periodontal diseases; periodontitis; pneumonia; respiratory disease; rheumatoid arthritis

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***Working group participants:**

Mark Bartold, Australia; Michael Glick, USA; Mark Herzberg, USA; Francis Hughes, UK; Palle Holmstrup, Denmark; Gerry Linden, UK; Angelo Mariotti, USA; Marc Quirynen, Belgium; Frank Scannapieco, USA; Arie Jan van Winkelhoff, The Netherlands.

**Introduction**

This report outlines the discussions of working group 4 who were tasked with reviewing possible associations between periodontitis and less common systemic diseases and conditions. At the outset, there was unanimity within the group that the body of evidence for many of the purported relationships was relatively immature, and therefore, this report does not represent a traditional consensus view, more a record of discussions and recommendations to strengthen the evidence base in the future.

Association Versus Causation

It was accepted that scientific studies that show an association between a given factor and a health effect cannot be extrapolated to imply that the factor causes the specific disease. For example, a large number of early epidemiological studies suggested

that women taking hormone replacement therapy (HRT) had a reduced incidence of coronary heart disease (CHD). From these data, one might conclude that HRT is protective against CHD. Data from subsequent randomized controlled trials, however, support the conclusion that HRT causes a significant increase in the risk of CHD (Rossouw et al. 2002). Therefore, a cautious evaluation of any association must be undertaken and conclusions should be balanced in favour of the more robust study designs. The group also discussed the value of using the nine Bradford Hill criteria (Hill 1965) to establish the strength of evidence for complex conditions of infective aetiology, but where classical Koch's postulates cannot be satisfied. Hence, the body of available evidence should be evaluated for the following:

- (a) Statistical strength of association
- (b) Consistency
- (c) Specificity

- (d) Temporal relationship (e.g. cause precedes consequence)
- (e) Biological gradient or dose-response relationship (e.g. more periodontitis leads to more atherosclerosis)
- (f) Biological plausibility
- (g) Coherence
- (h) Experimental reversibility
- (i) Analogy – other precedents

Definitions of Disease

Epidemiological studies often analyse and encourage conclusions based on surrogate markers for example measures of atherosclerosis rather than cardiovascular events such as myocardial infarction. The working group agreed that data using surrogate markers often do not explain actual disease events and studies intended to impact upon human health and provider behaviours should strive to investigate health outcomes rather than intermediate or surrogate markers of disease process.

The group unanimously agreed that precise and community-agreed case definitions of periodontal disease status must be implemented systematically to enable reasonable interpretations of studies of their relationship to systemic diseases. The working group recognized that purported associations are often unclear because periodontal disease is a heterogeneous mix of conditions. This problem may be further confounded by imprecisely defined systemic outcomes (e.g. cardiovascular disease, which might include atherosclerosis, vasospasm, myocarditis, heart ischaemia and myocardial infarction) in the target disease. Meaningful relationships between the disease outcomes and measured endpoints will likely depend on a strict and narrow definition of the diseases under study. It was accepted that narrower case definitions will increase the likelihood of identifying a meaningful association should one exist.

Study Design

The working group recognized that studies of the relevant systemic disease associations with periodontitis and oral health are in their infancy. For chronic obstructive pulmonary disease (COPD), pneumonia, chronic kidney disease, rheumatoid arthritis, cognitive impairment, obesity, metabolic syndrome and cancer, the studies that have been performed are largely cross-sectional, case-control studies with few prospective cohort studies. The working group also recognized an absence of periodontal intervention studies or randomized clinical trials.

What Lesser Studied Diseases and Conditions are Reported to be Associated with Periodontitis and Other Oral Diseases?

The working group discussed only those diseases and conditions that were reviewed and evaluated by Linden et al. (2013). Better-known relationships with periodontitis such as diabetes (Borgnakke et al. 2013), cardiovascular disease (Dietrich et al. 2013) and adverse pregnancy outcomes (Ide & Papanou 2013) were the subject of other reviews and were not discussed. As described in Linden et al. (2013), diseases and conditions that show at least mini-

mal evidence of an association with periodontitis include COPD, pneumonia, chronic kidney disease, rheumatoid arthritis, cognitive impairment, obesity, metabolic syndrome and cancer. It was accepted that associations can be unidirectional or bidirectional, however, the working group generally focused on unidirectional associations whereby periodontitis and other oral conditions could influence systemic diseases. Interestingly, some conditions such as obesity may affect periodontal outcomes. The group also recognized that other associations with systemic conditions not considered here may exist.

Does the Diversity of Systemic Medical Conditions Associated with Periodontitis and Other Oral Conditions Reflect a Common Underlying Mechanism(s)?

The working group agreed that the best evidence to date suggested that infection and subsequent pro-inflammatory events occur in periodontitis and may variously contribute towards select systemic diseases and disorders. No causal relationships can be inferred to date, with the exception that organisms found in the oral microbiome cause lung infections.

The working group discussed how the systemic impact of a specific periodontal condition may be confounded by the subject's infectious disease history. As is the case for periodontal conditions, other infections can disseminate infectious and pro-inflammatory stimuli, which may have a chronic systemic impact. The specific contributions of periodontal infections to systemic disorders, therefore, may be confounded by total pathogen burden over time (Kinane & Bouchard 2008).

Review of the Purported Periodontal Disease Associations with Specific Systemic Diseases and Conditions

The working group agreed the following:

Chronic obstructive pulmonary disease

An association with periodontitis is suggested based on analyses of the NHANES data sets. There appears to be a dose effect, whereby greater periodontal disease is associated with

increasing loss of lung function. The primary aetiological factor is smoking as modified by underlying inflammation. It is plausible that the inflammatory status may be modified either by aspiration of dental plaque and/or hematogenous dissemination of inflammatory mediators and plaque organisms from periodontal pockets. Studies of the association between periodontal disease and exacerbations of COPD would be valuable.

Pneumonia

The association between dental plaque and pneumonia appears to be stronger than for plaque and COPD. That improved oral hygiene reduces the risk of health care-associated pneumonia is suggested by several meta-analyses. The relationship with periodontitis however is not known.

Chronic kidney disease

The association between chronic kidney disease (CKD) and periodontitis in several studies is statistically significant and consistent. Although hypertension and diabetes are the primary aetiological factors, periodontitis is hypothesized to modify both these aetiological factors and consequently the presentation of CKD. Studies of the effects of periodontal interventions on the emergence of CKD in patients with type 2 diabetes would be useful, particularly to adjust for confounding of diabetes with this condition. Similar studies examining the effect of periodontal interventions on CKD progression are warranted.

Rheumatoid arthritis

Reports of an epidemiological association with periodontal disease, including the NHANES data set and case-control studies, are inconsistent. Animal studies provide biological plausibility. For example, *Porphyromonas gingivalis* can induce and exacerbate a rheumatoid arthritis-like condition in susceptible rodents (Kinloch et al. 2011). In human rheumatoid arthritis, antibodies against citrullinated proteins and peptides are often detected in the blood reflecting the enzymic conversion of arginine residues to citrulline

in certain proteins. Biological plausibility for an association with periodontitis is also reflected in the detection of citrullinated proteins in inflamed gingiva, which may be associated with elevated auto-antibodies to self-antigens (Nesse et al. 2012).

Cognitive impairment

The results of epidemiological studies are difficult to interpret. Data from existing studies reflect imprecise case definitions for periodontitis and the heterogeneity of cases of cognitive impairment. There are few studies that point to underlying biological plausibility.

Obesity

Many clinical studies of obesity and periodontal disease have been reported including a number of systematic reviews. There are a few prospective studies indicating an association with periodontitis. More specifically, the literature suggests that obesity might adversely affect periodontitis, but there is little evidence from clinical data or for biological plausibility that periodontitis may affect obesity.

Metabolic syndrome

Metabolic syndrome is defined as a complex of five clinical signs (as defined by the International Diabetes Federation), which include central obesity, raised triglycerides, reduced HDL cholesterol, raised blood pressure and raised fasting blood glucose. Syndromic presentation of obesity and at least two other signs of metabolic syndrome indicate that the patient meets the diagnostic criteria. Evidence in support of a relationship with periodontitis needs to be more robustly developed. Relationships

with one or two of these clinical signs have been reported but whether these findings point to an association with metabolic syndrome is questionable. The limitations of the existing data are discussed further in the review by Linden et al. (2013).

Cancer

Prospective and case-control studies suggest an association between periodontitis and oral and oro-pharyngeal cancer. Whereas some oral microbes can alter cells and tissues consistent with features of malignant changes, additional biological plausibility, clinical and robust epidemiological data are needed to strengthen such associations.

Conclusions

Working group 4 agreed that the associations reviewed do not imply causality which will require new studies and fulfilment of the Bradford Hill or equivalent criteria. Since the systemic diseases under consideration are complex and often heterogeneous, it was accepted that there is generally justification to classify and analyse subgroups. The working group concluded that to have greatest public health utility, studies should focus on disease outcomes and avoid the use of biomarkers and surrogate measures. It was agreed that to assist the community in evaluating the quality of evidence, all clinical trials must be registered with internationally compliant registries as appropriate to the locale. Working group 4 accepted that the relative immaturity of the body of evidence for each of the purported relationships meant the field is wide open and the gaps in knowledge remain large.

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Address:

Gerry Linden
Periodontal Department
School of Dentistry
Queen's University,
Grosvenor Road
Belfast BT12 6BP
UK

E-mail: g.linden@qub.ac.uk

Clinical Relevance

Many studies have identified associations between periodontal disease and systemic diseases and

conditions. Patients with periodontitis are increasingly aware of research into possible links with systemic diseases. Dentists should be aware that

while outcomes to date support weak associations there is no evidence that periodontal disease has a causative role.