

## What are the links between periodontitis and systemic disease?

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**Title: What are the links between periodontitis and systemic disease?**

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Title: What are the links between periodontitis and systemic disease?

**Abstract:** That the mouth and the body are not disconnected should come as no surprise. In this article, we will review the links between periodontal and systemic health by investigating these in both directions. We will start with the more familiar effects of systemic conditions on periodontal health and progress to the emerging effects of periodontal health on systemic health. Where suitable, we will provide tips for practitioners caring for patients with periodontitis and systemic diseases.

**Clinical relevance statement:** In recognition of the important role that the oral cavity plays in the body and the important role that oral healthcare providers play in the management of the general well-being of patients, this manuscript highlights the link between periodontitis and systemic health. This allows practitioners to care more holistically for their patients.

**Objective statement:** The reader should appreciate the important impact of systemic conditions on periodontal health and the role that the management of periodontitis and maintenance of periodontal health may play in the general well-being of patients.

In this paper, we will examine the links between systemic health and periodontal health, in both directions. We will start with the effects of systemic health/factors on periodontal health and then effects in the opposite direction. Here, we will limit the scope of this review to periodontal diseases, not gingival diseases, even though there are systemic factors, like hormonal changes in pregnancy and puberty and genetic conditions, like hereditary gingival fibromatosis, that influence gingival health (Holmstrup, 1999; Mariotti, 1999). Again, to limit the scope of this review, “systemic factors” exclude factors like smoking, ageing, gender and attitudes to healthcare which have a clear effect on periodontal health but where an effect in the other direction is conceptually unlikely, for example periodontitis is unlikely have a causal influence on smoking. Similarly, to limit the scope of the review, discussions on the oral microbiome are also excluded from this review.

### **Effect of systemic health on periodontal health**

The following systemic factors will be briefly discussed to establish the association between them and various forms of periodontitis. The aim is not to provide a comprehensive review of these associations, most of which have been the focus of multiple reviews and workshops of their own but to provide a conceptual framework highlighting the plausible associations and causal relationships between systemic conditions and periodontal health.

#### *Diabetes*

The effect of *diabetes*, or poor diabetic control, on the periodontal health is well recognised in the dental community and needs little introduction. The evidence for the impact of diabetes on the periodontal health of individuals is derived from a host of observational studies, summarized in a meta-analysis which shows a significantly higher

probing depth and attachment loss in patients with type 2 diabetes compared with patients without (Chavarry, Vettore, Sansone, & Sheiham, 2009). There is a recognition that diabetes or poor diabetic control is causally linked with the development and progression of periodontitis. This is perhaps conceptually easy to believe as the effects of poor diabetes on other organ systems or disease processes, such as macro and micro-vascular diseases, poor wound healing, etc. are well established so it is not a big leap of faith to say that periodontitis is *likely* to be a complication of diabetes, in the absence of robust clinical trials pointing to this fact. There are several pathways including shared risk factors that might explain why patient with poorly controlled type II diabetes have a threefold increased risk of periodontitis (Mealey & Ocampo, 2007). The World Health Organization (WHO) defines risk factor as “any attribute, characteristic or exposure of an individual that increases the likelihood of developing a disease or injury” (WHO). Diabetes is thought to alter the host response to the presence of periodontal pathogens, as well as altering the microbiota to a more pathogenic variety, by reducing neutrophil function (Preshaw et al., 2012). Among the shared risk factors for diabetes and periodontitis, obesity, smoking and ageing are the most prominent ones and the presence of these might lead to the development of both diabetes and periodontitis independent of each other. A further shared risk factor for both periodontitis and diabetes is that of poor nutrition.

#### *Poor nutrition*

Poor nutrition can also affect the periodontium in other ways, the most apparent example being a lack of ascorbic acid (vitamin C) leading to the clinical presentation of scurvy. This is mediated via the critical role of vitamin C in the production of collagen with a deficiency in vitamin C leading to compromise in the connective tissues of the periodontium, making them more vulnerable to breakdown (Kaye, 2012). When assessing the diet of patients suffering from periodontitis, is it important to ascertain the level of fresh fruit and

vegetables, high in anti-oxidants, that the patient is consuming. The availability of micro-nutrients, which have an anti-oxidant effect may provide a protective advantage to the development and progression of periodontitis. In a similar vein, diets high in saturated fats, refined sugars and carbohydrates are known to increase the oxidative stress burden in patients. At present, the evidence is lacking to support the need for dietary supplementation (tablets etc) to improve periodontal health but a balanced diet, rich in micro-nutrients, can be advised due to the benefits this might have on the patient's general and therefore oral health.

#### *Rheumatoid arthritis or xerostomia*

Patients with rheumatoid arthritis or xerostomia may experience an increased prevalence and severity of periodontitis brought on by an increased burden of oral microbiota. Patients with such chronic conditions might also have an increased experience of stress. *Stress*, as a systemic factor, has a dampening effect on the immune system which may, in turn, tip the host-microbial balance in periodontitis towards greater periodontal destruction (Warren et al., 2014). Finally, we can cite the example of systemic conditions that are known to directly influence periodontal breakdown via either i) affecting the quality of periodontal tissues, as the case in Ehlers-Danlos syndrome with deficiencies in collagen or ii) alter the host response to bacteria as in the case of Chediak-Higashi syndrome or Papillon-Lefevre syndrome with deficiencies in leucocyte function (Kinane, 1999).

#### **Effect of periodontal health on systemic health**

That there is a link between the systemic health of a patient and their periodontal health is apparent from the examples above which highlight the effect of the former on the latter. The reverse, the effect of periodontal health on systemic health, has been the focus

of a great deal of research in recent years and the links here remain elusive. There are established associations between periodontitis and diabetes and cardiovascular disease and associations are emerging with other, chronic, non-communicable diseases such as rheumatoid arthritis, chronic obstructive pulmonary disease, obesity, cognitive decline, chronic kidney disease and adverse pregnancy outcomes. Some of these associations were the focus of a joint workshop between the European Federation of Periodontology and American Academy of Periodontology in 2013, and the papers are freely available [<http://onlinelibrary.wiley.com/doi/10.1111/jcpe.2013.40.issue-s14/issuetoc>]. The mechanisms underpinning these associations are debatable, however, it is possible that there are shared mechanisms that explain most of these associations and that these are not, for the most part, disease specific. The mechanisms are likely to be initiated by the micro-ulceration of the gingival epithelium, in response to local bacterial insult, breaching in the natural barrier function of the epithelium. This may lead to:

1) *metastatic infection* where whole bacteria enter the blood stream, during processes like eating or brushing, and setup a locus of infection at a site distant to the oral cavity. This distant infection then has systemic health consequences.

2) *metastatic inflammation* where local inflammatory mediators, produced in the gingival epithelium, spill over into the systemic circulation and cause collateral damage to distant organs/tissues, leading to systemic diseases.

3) *metastatic injury* where either whole bacteria or pro-inflammatory bacterial products enter the circulation, triggering an immune response in the host, which then causes organ/tissue damage leading to systemic diseases. (Thoden van Velzen, Abraham-Inpijn, & Moorer, 1984; Van Dyke & van Winkelhoff, 2013)

At this point, the authors would like to make an important distinction, and one that particularly plagues the field of periodontal-systemic disease research, and that is the

distinction between an “association” and a “causal relationship”. When two things are commonly seen together, they are said to have an association. For example, smoking and lung cancer are commonly seen together in individuals and hence are known to have an association. It is now fairly widely accepted that smoking *causes* lung cancer therefore smoking and lung cancer also have a “causal relationship”. Associations are relatively easy to establish and can hint towards a possible causal relationship but the jump from association to causation is often made, even subconsciously, prematurely. For example, the latest headline saying your favourite food or beverage is either killing you or making you immortal is probably based on a study showing an *association* between said food/drink and the effect it is claimed to be *causing*. That being said, establishing a causal relationship is exceedingly complicated and a whole range of studies, both observational and interventional, may be needed, if the causal effect can be demonstrated at all.

In this section, we will explore the associations between periodontitis and various systemic diseases. As mentioned earlier, these associations are more established for some diseases, such as diabetes and cardiovascular disease and less established for others, such as adverse pregnancy outcomes, rheumatoid arthritis and chronic kidney disease.

### *Diabetes*

The following section on the links between periodontitis and diabetes (primarily type II diabetes) follow from publications following a joint workshop between the European Federation of Periodontology (EFP) and the International Diabetes Federation (IDF) in 2017 and which were summarised in the workshop’s consensus report (Sanz et al., 2018). This consensus report has useful guidelines for patients, dental and other healthcare professionals which are also available as infographics which are free to download via the British Society of Periodontology (BSP)



[\[https://www.bsperio.org.uk/professional/infographics/index.html\]](https://www.bsperio.org.uk/professional/infographics/index.html)

Diabetes is the pathological consequence of a number of physiological changes and the resulting metabolic deregulation, hyperglycaemia and chronic inflammation potentially impact on tissue integrity and repair. Patients who do not have diabetes but have with periodontitis are known to have poorer glycaemic status as represented by serum levels of glycated haemoglobin (HbA1C), a longer-term marker of glycaemic control, fasting blood glucose levels and oral glucose tolerance tests than patients without diabetes who do not have periodontitis. Patients with periodontitis are also more likely to develop diabetes than patients who are periodontally healthy. Patients with both diabetes and periodontitis also have worse glycaemic control than patients with diabetes who are periodontally healthy. Following treatment of periodontitis, patients with diabetes may experience, at least a short-term improvement on their glycaemic control of a similar magnitude to the addition of a second medication to their pharmacological regime, commonly metformin.

Recommendations for oral healthcare providers include:

- Advise patients with diabetes of the increased risks of gingivitis and periodontitis
- Collect details of the patient's diabetes history either from the patient or from their GP. The BSP have a template for a letter to the GP here  
[\[https://www.bsperio.org.uk/professional/periodontal-disease-and-diabetes/index.html\]](https://www.bsperio.org.uk/professional/periodontal-disease-and-diabetes/index.html)
- Periodontal health of patients, with or without diabetes, should be improved and maintained. This includes the importance of home care with twice daily brushing and interdental cleaning.

*Atherosclerotic cardio vascular diseases (ACVD)*

Atherosclerotic vascular diseases (ACVD) is a group of disorders of the heart and blood vessels including:

- Coronary heart disease (angina/heart attack).
- Cerebrovascular disease (stroke or transient ischaemic attack/ mini-stroke)
- Peripheral arterial disease

The following section discusses the associations between periodontitis and ACVD and is primarily based on the consensus report of the 9<sup>th</sup> European Workshop in Periodontology, jointly with the EFP and American Academy of Periodontology (AAP) in 2012 (Tonetti & Van Dyke, 2013). This found a consistent association between periodontitis and new cases of ACVD (incident ACVD), independent of some other risk factors for ACVD. This effect was greater in younger individuals (aged <65 years) and in males. When it comes to the treatment of periodontitis, this may lead to a reduction in systemic markers of inflammation, such as C-reactive protein (CRP) and an improvement in vascular function. These markers are important as they indicate an increased risk of adverse ACVD events. More studies are needed to detect a reduction in either first or recurrent ACVD events, following periodontal therapy. The logistics of running such trials, the length of follow-up, the numbers of patients required and the ethical dilemma of not treating periodontitis in the control group make such trials very challenging. The recommendations to practitioners include:

- Being aware of the links between periodontitis and ACVD
- Addressing shared risk factors that contribute to both periodontal and cardiovascular health including smoking cessation, diet and exercise and maintaining a healthy weight.
- Periodontal treatment in patients who have suffered an ACVD event should be staggered over a number of visits to limit the dissemination of bacteria/pro-

inflammatory cytokines which may increase systemic CRP and add to the risk of an ACVD event.

- Current rationale for treatment of periodontitis is limited to the retention of teeth and cardiovascular benefit can be thought of as secondary to this.
- Patients with periodontitis who also have other risk factors for ACVD, such as smoking, over weight/obesity and hypertension, who have not visited their GP in over a year should be advised to do so.

### *Other emerging links*

Periodontitis is associated with a range of other, chronic, non-communicable diseases although the evidence for these associations is not as robust as that for diabetes and ACVD. That being said, the mechanisms by which periodontal health may influence diabetes and ACVD is likely to be shared with other chronic, non-communicable diseases such as rheumatoid arthritis, chronic kidney disease, cognitive decline, chronic obstructive pulmonary disease and adverse pregnancy outcomes, to name a few. Hence, at the very least, the management of risk factors of periodontitis may reduce the risk factor burden for these diseases. As with ACVD however, the primary reason for management of periodontitis and maintenance of periodontal health in such patients is for the retention of teeth and any systemic benefit is secondary to that.

### **Conclusion**

The influence of systemic factors on periodontal health, which may be evident to practitioners, as well as the influence of oral health on systemic disease processes should highlight the vital role that the oral cavity plays. As oral healthcare practitioners, we are in a unique position to influence not only the oral but also the general health of our patients.

This can be done via the physical or psychological benefits of oral care as well as the management of shared risk factors between periodontitis and other systemic diseases.

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