

# Periodontitis and systemic disease

Lewis Winning<sup>1</sup>, Gerard J. Linden<sup>2</sup>

In recent years there has been considerable interest in possible links between periodontal disease and systemic diseases. The general public are increasingly aware that such links may exist and in some cases are concerned about the implications for them as individuals. Nearly half of all adults in the United Kingdom have some form of periodontal disease,<sup>1</sup> and as such present to dental practices every day. It is essential that all members of the dental team are aware of the periodontitis-systemic disease link, and can provide clear evidence-based advice and information to patients. The aim of this article is to summarise the current state of knowledge so that members of the dental team can convey appropriate advice and guidance to patients.

## Basis for a possible relationship – Historical and Current

The notion that a relationship between oral disease and systemic disease might exist goes back over a century. Around 1900 William Hunter, a British Doctor, identified links between

oral sepsis and disease of other organs in the body and this was termed the theory of 'focal infection'.<sup>2</sup> The proponents relied heavily on clinical experience highlighting cases where the removal of infected teeth produced improvements in general health. These observations lacked the rigor of modern scientific studies and the theory of focal infection was later discarded.

Skipping forward to more recent times, evidence from well-designed studies began to emerge in the late 1980's of possible linkages between chronic periodontal disease and other systemic diseases.<sup>3,4</sup> Since then there has been an exponential rise in the number of studies that have investigated links between periodontal disease and various diseases with the main areas of interest being: atherosclerotic cardiovascular disease,<sup>5</sup> diabetes,<sup>6</sup> and adverse pregnancy outcome.<sup>7</sup> Associations between periodontitis and many

other diseases and conditions have also been reported including respiratory disease; chronic kidney disease; rheumatoid arthritis; cognitive impairment; obesity; metabolic syndrome; and cancer.<sup>8</sup> (Fig. 1)

## Possible mechanisms

Two main pathogenic mechanisms have been described to explain how periodontal disease could contribute to systemic disease.

**1. Direct mechanism:** As chronic periodontitis progresses, the epithelium lining periodontal pockets becomes ulcerated providing a direct entry point for periodontal bacteria into the systemic circulation. The circulating bacteria could then have direct effects on certain organs, for example periodontal bacteria have been detected in thrombi from patients with acute myocardial infarction suggesting a possible role in the pathological changes

<sup>1</sup> Research Fellow, Centre for Public Health, School of Medicine Dentistry and Biomedical Sciences, Queen's University Belfast

<sup>2</sup> Professor of Periodontology, Centre for Public Health, School of Medicine Dentistry and Biomedical Sciences, Queen's University Belfast

that occur in atheromatous plaques.<sup>9</sup>

2. **Indirect mechanism:** Alternatively, the inflammatory response to periodontal bacteria or their by-products may have indirect systemic effects. It is now well recognised that inflammation itself is involved in the pathogenesis of many chronic illnesses such as cardiovascular disease, type 2 diabetes, and rheumatoid arthritis. Chronic periodontitis therefore represents a source of chronic inflammation that may be a significant contributing factor in the pathogenesis of other inflammatory based diseases, (Fig. 2). The level of C-reactive protein (CRP) in the blood is an accepted method of measuring systemic inflammation in individuals. There is strong evidence that CRP levels are elevated in periodontitis subjects.<sup>10,11</sup>

### Difficulties - Confounding and Causality

One of the main difficulties in studying links between periodontitis and systemic disease is that risk factors for many systemic diseases overlap with those associated with periodontitis such as age, gender, smoking, obesity, socio-economic status, etc. This is called **confounding** and when we describe links between periodontitis and systemic disease to patients we should bear possible confounding factors in mind so we do not imply that periodontal disease is the only reason they might have a particular condition. A further difficulty is that most research cannot identify cause and effect relationships. Although plausible, based on the mechanisms outlined, the critical appraisal of studies completed to date cannot distinguish whether periodontitis and systemic disease develop due to similar shared disease pathways rather than because one actually causes the other. Evidence for causality may come in the future when we have more studies that definitively show a temporal sequence where the presence of periodontitis results in a subsequent increase in the frequency of a systemic disease. Alternatively demonstrating that successfully treating periodontal disease has a positive effect in reducing the signs and symptoms of a particular systemic disease would also support a causative link. Until then when we discuss links between periodontitis and systemic disease with patients it is better to describe 'association' rather than 'causation'.

### Periodontitis and Atherosclerotic Cardiovascular Disease (ACVD)

Atherosclerosis is a condition in which the artery wall thickens as a result of the accumulation of calcium and fatty materials



Fig. 1 Systemic diseases chronic periodontitis has been linked to.



Fig. 2 A patient with generalised severe chronic periodontitis. Ulcerated epithelium may allow an entry point for pathogenic bacteria and/or the by products of inflammation to enter the circulatory system.

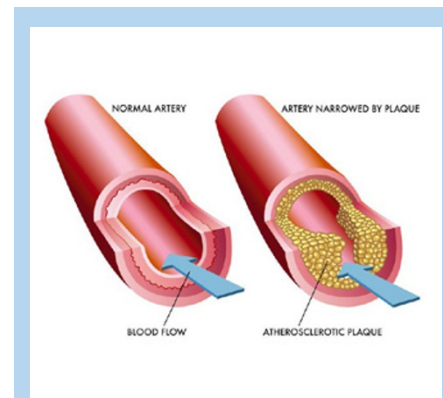


Fig. 3 Atherosclerotic cardiovascular disease (ACVD)

that form plaques and cause the arteries to harden and stiffen, (Fig. 3). Depending on location, complications of atherosclerosis include angina, myocardial infarction, stroke, or aneurysm. Together, cardiovascular diseases are the number one cause of death globally.<sup>12</sup> An estimated 17.5 million people died from CVDs in 2013, representing 31% of all global deaths.<sup>13</sup> Bacteria, central to the initiation and progression of periodontitis, may provide a direct or indirect mechanistic link to the development of atherosclerotic disease, (Fig. 4). The association between periodontal disease and atherosclerotic cardiovascular disease is independent of other known confounding risk factors.<sup>5</sup> The recent joint workshop of the American Academy of Periodontology (AAP) and the European Federation of Periodontology (EFP) which examined systemic disease links,<sup>5</sup> made the following key recommendations:

- Practitioners should be aware of the emerging and strengthening evidence that periodontitis is a **risk factor** for developing ACVD, advising patients of the risk.
- Periodontitis patients with other risk factors for ACVD, such as hypertension, overweight/obesity, smoking, etc. who have not seen a doctor within the last year, should be referred to their medical practitioner.
- Modifiable lifestyle associated risk factors for periodontitis (and ACVD) should be addressed in the dental practice setting, and in the context of comprehensive periodontal therapy, i.e. smoking cessation programs and advice on lifestyle modifications (diet and exercise). This may be better achieved in collaboration with appropriate specialists and may bring health gains beyond the oral cavity.



**Periodontitis and Diabetes**

Diabetes is a condition that results in the abnormal elevation of the blood glucose level (hyperglycaemia). Around 10% of cases are type 1 diabetes,<sup>14</sup> where the immune system attacks and destroys the cells that produce insulin. The remaining 90% of cases are type 2 diabetes where either the body does not produce enough insulin, or the cells have a lowered response to insulin (insulin resistance). The bidirectional relationship between periodontitis and diabetes has been known for some time.<sup>15</sup> Over the last 20 years, consistent evidence has emerged that severe periodontitis adversely affects glycaemic control in both diabetic and non-diabetic subjects. In patients with diabetes there is a direct and dose-dependent relationship between periodontitis severity and diabetes complications.<sup>6</sup> The biological rationale connecting periodontitis and diabetes relates back to the common theme of chronic inflammation. Based on the AAP/ EFP workshop,<sup>6</sup> key recommendations included:

- Patients with diabetes should be told that they are at increased risk for periodontitis. They should also be told that if they suffer from periodontal disease, their glycaemic control may be more difficult, and they are at higher risk for other complications such as cardiovascular and kidney disease.
- Patients presenting with diabetes should receive a thorough oral examination, which includes a comprehensive periodontal evaluation and management as appropriate.
- Patients with diabetes should also be evaluated for other potential oral complications, including dry mouth, burning mouth and candida infections.
- Patients who present without a diabetes diagnosis, but with obvious risk factors for type 2 diabetes and signs of periodontitis should be informed about their risk for having diabetes, assessed using a chair-side HbA1C test (if available), and referred to their doctor for appropriate diagnostic testing and follow-up care.

**Periodontitis and Adverse Pregnancy Outcome**

The link between periodontitis and pregnancy outcome has emerged mainly due to medical studies showing that inflammation plays an important role in pregnancy especially towards the end of gestation.<sup>16</sup> Maternal periodontitis represents a **potential** source of microorganisms that may enter the circulation, and similarly to mechanisms discussed previously, directly and/or indirectly have potential to influence the

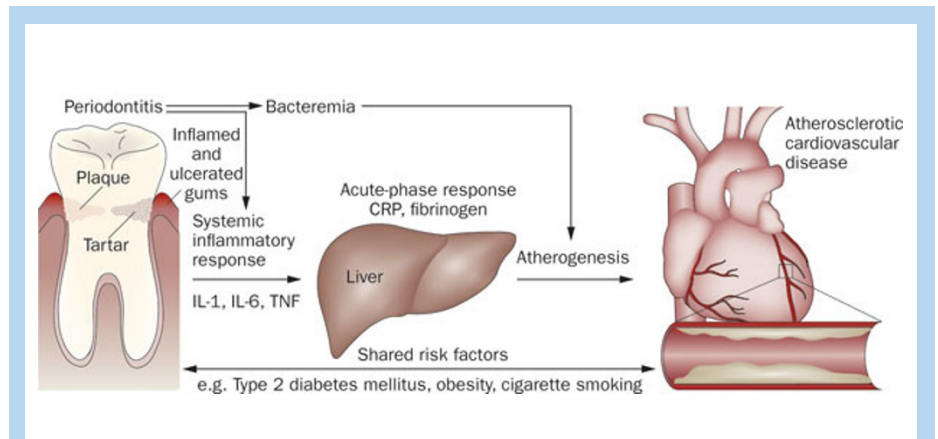


Fig. 4 Overview of postulated mechanisms linking periodontitis and ACVD. Reproduced from: Genco RJ & Van Dyke TE. Prevention: Reducing the risk of CVD in patients with periodontitis, (21).

health of the foetal-maternal unit. The main adverse pregnancy outcomes that have been associated with periodontal disease include low birth weight, pre-term birth and pre-eclampsia. Although the association of periodontitis with these adverse outcomes are biologically plausible, a recent review described the evidence for an association as ‘moderate’.<sup>7</sup> What’s more, although periodontal treatment during pregnancy results in improved oral health, the majority of studies have failed to show a consistent beneficial effect for adverse pregnancy outcome.<sup>17</sup> Key points based on the recent AAP/EFP review,<sup>7</sup> on this subject include:

- In the absence of clear evidence for the association between periodontitis and adverse pregnancy outcome, the emphasis of the message to patients should be better periodontal health means better oral health and wellbeing.
- The well-established risk of pregnancy gingivitis (Fig. 5) related to hormonal changes during pregnancy should be addressed by oral hygiene instruction, professional instrumentation and frequent monitoring as necessary.
- Providing non-surgical periodontal treatment to patients during pregnancy is safe and effective.

**Links between Periodontitis and other systemic diseases**

Periodontitis has been associated with a number of other systemic diseases including respiratory disease, chronic kidney disease, rheumatoid arthritis, cognitive impairment, obesity, metabolic syndrome and cancer. Key summaries for each of these purported links from the recent AAP/EFP review<sup>8</sup> include:

- **Respiratory disease.** Periodontitis has been linked with both Chronic Obstructive Pulmonary Disease (COPD) and Pneumonia. COPD is characterised

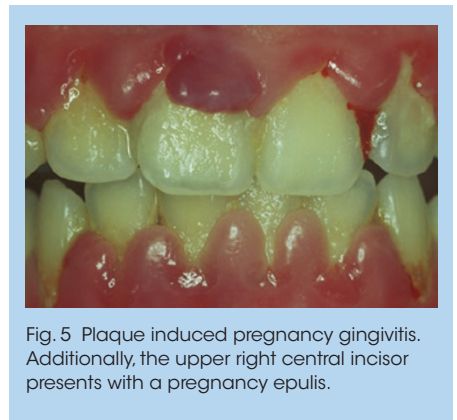


Fig. 5 Plaque induced pregnancy gingivitis. Additionally, the upper right central incisor presents with a pregnancy epulis.

by progressive airflow obstruction and inflammation in the airways with the main cause attributed to cigarette smoking. Studies investigating a link between COPD and periodontitis remain preliminary and as such there is no clear evidence. Pneumonia, involving infection within the airways, may associate with periodontitis especially as many potential opportunistic pathogenic bacteria are found within the oral cavity. Improved oral hygiene has been shown in randomised controlled trials to have an important role in the prevention of pneumonia in a variety of at risk-populations. However, there are few studies investigating the effects of established chronic periodontitis in relation to acquired lung infections.

- **Chronic Kidney Disease (CKD).** CKD is defined as kidney damage with decreased function (glomerular filtration rate <60 mL/min per 1.73 m<sup>2</sup>) for 3 months or more. Although periodontitis has been associated with CKD in several studies, the complex pathogenesis of CKD and its close linkage with diabetes and other co-morbid conditions means a direct link to periodontitis is as yet not completely clear.

- **Rheumatoid arthritis (RA).** RA is characterised by persistent synovial inflammation and associated damage to articular cartilage and underlying bone. Despite early studies reporting an association, there is currently little published evidence the periodontitis represents a risk factor for developing RA
- **Cognitive impairment.** Cognitive impairment includes early changes, which can precede progression to dementia of the Alzheimer's disease type. Evidence from current studies for an association between periodontitis and cognitive impairment is limited and further studies are required.
- **Obesity.** Obesity is defined as abnormal or excessive fat accumulation that presents a risk to health. A modest association between obesity and periodontitis is supported by multiple studies. However, obesity may in fact be a marker of an unhealthy lifestyle resulting in the associated increased risk of periodontitis and the habits of this unhealthy lifestyle may be confounding this link.
- **Metabolic syndrome.** Metabolic syndrome (MetS) is a clustering of multiple atherosclerotic risk factors, including abdominal obesity, dyslipidaemia, hyperglycaemia and hypertension, which identifies a 5-fold increase in risk for developing type 2 diabetes.<sup>18</sup> Currently, evidence of an association of MetS with periodontitis, is limited.<sup>19</sup> The strongly increased risk of type 2 diabetes in those with MetS may confound any association with periodontitis, and as such further studies are needed to clarify this link.
- **Cancer.** The higher incidence of cancer development in those with chronic inflammatory conditions<sup>20</sup> has underpinned research into possible links to periodontitis. Difficulties with studies linking periodontitis to cancer include confounding effects such as smoking and socioeconomic status. Despite this, periodontitis has been identified as a possible risk factor for oro-digestive and pancreatic cancer. Further studies, with long-term follow up are still needed in this area.

## Conclusions

The link between periodontitis and systemic disease remains the subject of intense research and debate within dentistry. Patients, whether through topical media or

sensationalised news reports, are increasingly aware of possible links between periodontal disease and other diseases. As members of the dental team it is important that we are aware of current research in this important area so that we can dispel myth and provide sound information to patients.

Whilst there is now good evidence for periodontitis **associating** with various systemic diseases (particularly atherosclerotic cardiovascular disease and diabetes), evidence for a **causative** role is still lacking. Many of the reviews in this area report that 'further studies are needed', but that should not prevent us taking a pragmatic approach in promoting a patient's good oral health benefiting their general health. Treating periodontal disease, where we also address shared modifiable risk factors such as smoking, diabetes control, and diet can only have a positive effect on related systemic disease and as dental professionals we are ideally situated as front line health staff to do this. It is acknowledged that the gaps in our knowledge remain large.<sup>8</sup>

## References

1. White D A, Tsakos G, Pitts N B, Fuller E, Douglas G V, Murray J J, et al. Adult Dental Health Survey 2009: common oral health conditions and their impact on the population. *Br Dent J* 2012; **213**: 567-572.
2. Newman H N. Focal infection. *J Dent Res* 1996; **75**: 1912-1919.
3. Mattila K J, Nieminen M S, Valtonen V V, Rasi V P, Kesaniemi Y A, Syrjala S L, et al. Association between dental health and acute myocardial infarction. *BMJ* 1989; **298**: 779-781.
4. Beck J, Garcia R, Heiss G, Vokonas P S, Offenbacher S. Periodontal disease and cardiovascular disease. *J Periodontol* 1996; **67**: 1123-1137.
5. Tonetti M S, Van Dyke T E, Working group 1 of the joint EFP/AAP workshop. Periodontitis and atherosclerotic cardiovascular disease: consensus report of the Joint EFP/AAP Workshop on Periodontitis and Systemic Diseases. *J Clin Periodontol* 2013; **40**: S24-29.
6. Chapple I L, Genco R, Working group 2 of joint EFP/AAP workshop. Diabetes and periodontal diseases: consensus report of the Joint EFP/AAP Workshop on Periodontitis and Systemic Diseases. *J Clin Periodontol* 2013; **40**: S106-112.
7. Sans M, Kornman K, Working group 3 of joint EFP/AAP workshop. Periodontitis and adverse pregnancy outcomes: consensus report of the Joint EFP/AAP Workshop on Periodontitis and Systemic Diseases. *J Clin Periodontol* 2013; **40**: S164-169.
8. Linden G J, Hersberg M C, working group 4 of the joint EFP/AAP workshop. Periodontitis and systemic diseases: a record of discussions of working group 4 of the Joint EFP/AAP Workshop on Periodontitis and Systemic Diseases. *J Periodontol* 2013; **84**: S20-23.
9. Ohki T, Itabashi Y, Kohno T, Yoshisawa A, Nishikubo S, Watanabe S, et al. Detection of periodontal bacteria in thrombi of patients with acute myocardial infarction by polymerase chain reaction. *Am Heart J* 2012; **163**: 164-167.
10. Linden G J, McClean K, Young I, Evans A, Kee F. Persistently raised C-reactive protein levels are associated with advanced periodontal disease. *J Clin Periodontol* 2008; **35**: 741-747.
11. Paraskevas S, Huisinga J D, Loos B G. A systematic review and meta-analyses on C-reactive protein in relation to periodontitis. *J Clin Periodontol* 2008; **35**: 277-290.
12. World Health Organisation., World Heart Federation., World Stroke Organisation. Global atlas on cardiovascular disease prevention and control. Mendis S, Puska P, Norrving B, editors. Geneva: World Health Organisation in collaboration with the World Heart Federation and the World Stroke Organisation; 2011.
13. GBD 2013 Mortality and Causes of Death Collaborators. Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet* 2015; **385**: 117-171.
14. Whiting D R, Guariguata L, Weil C, Shaw J. IDF diabetes atlas: global estimates of the prevalence of diabetes for 2011 and 2030. *Diabetes Res Clin Pract* 2011; **94**: 311-321.
15. Taylor G W. Bidirectional interrelationships between diabetes and periodontal diseases: an epidemiologic perspective. *Ann Periodontol* 2001; **6**: 99-112.
16. Fuchs A R, Fuchs F. Endocrinology of human parturition: a review. *Br J Obstet Gynaecol* 1984; **91**: 948-967.
17. Michalowicz B S, Gustafsson A, Thumbigere-Math V, Buhlin K. The effects of periodontal treatment on pregnancy outcomes. *J Periodontol* 2013; **84**: S195-208.
18. Grundy S M. Metabolic syndrome scientific statement by the American Heart Association and the National Heart, Lung, and Blood Institute. *Arterioscler Thromb Vasc Biol* 2005; **25**: 2243-2244.
19. D'Aiuto E, Sabbah W, Netuveli G, Donos N, Hingorani A D, Deanfield J, et al. Association of the metabolic syndrome with severe periodontitis in a large U.S. population-based survey. *J Clin Endocrinol Metab* 2008; **93**: 3989-3994.
20. Coussens L M, Werb S. Inflammation and cancer. *Nature* 2002; **420**: 860-867.
21. Genco R J, Van Dyke T E. Prevention: Reducing the risk of CVD in patients with periodontitis. *Nat Rev Cardiol* 2010; **7**: 479-80.

bdjteam2015163