BG Loos

Systemic effects of periodontitis

Authors' affiliations:
Bruno G. Loos, Department of Periodontology, Academic Centre for Dentistry, Amsterdam, The Netherlands

Correspondence to:
Bruno G. Loos
Department of Periodontology
Academic Centre for Dentistry
Louwesweg 1
1066 EA Amsterdam
The Netherlands
Tel.: +31 20 5188558
Fax: +31 20 5188512
E-mail: b.g.loos@acta.nl

To cite this article:
Int J Dent Hygiene **4** (Suppl. 1), 2006; 34–38
Loos BG.
Systemic effects of periodontitis

Introduction

There are epidemiological studies which have shown that periodontitis could be an independent risk factor for mortality, for diabetes, for osteoporosis, for pulmonary infections, for premature low birth weight and for cardiovascular diseases (CVD). An important meta analysis (1) summarized several studies evaluating the relationship between periodontitis and coronary heart disease. The authors found that there is a relative risk of 1.2, meaning that there's a 20% increased risk of getting coronary heart disease when periodontitis is present. For cerebral vascular ischaemia – although the number of studies is not as large – Janket *et al*. found a 40% increased relative risk of having a cerebral ischaemic event, i.e. stroke, when periodontitis is present.

Background on CVD and possible mechanistic link with periodontitis

The underlying cause for CVD is atherosclerosis and the ensuing atherothrombosis. In atherosclerosis there is the formation of fibrous plaques inside the artery wall concomitant with an inflammatory reaction taking place inside the vessel wall. Whenever there is a rupture of such fibrous plaque, the formation of a thrombus will occur. Current thoughts are that bacteria originating from any source, but most likely from the oral cavity, may play a role. Bacteria that get into the circulation during a transient bacteraemia may get nested inside these atheromatous plaques and in this way exacerbate inflammatory reactions in the vessel wall.

Bacteraemia in periodontitis

There is ample evidence for transient bacteraemia in periodontitis to occur. For example, in a study in 2000 (2) it was shown

that periodontal pathogens were present in atheromatous plaque. It has been shown that there is bacteraemia after oral examination or probing (3, 4). Also it has been shown that there is bacteraemia after chewing, after tooth brushing and after periodontal therapy (4, 5). It doesn't mean that bacteraemia occurs every minute of the day, it doesn't mean it occurs maybe every day, but there are moments that patients with periodontitis, with inflamed gingivae in conjunction with dental plaque, may have bacteraemic events. Most likely these are short lived.

How could bacteraemia lead to an increased systemic inflammation? Without any periodontal lesion, in a situation without periodontal attachment loss, the total periodontal surface area amounts to 70–76 cm^2 (6). Then, if one imagines a patient with severe periodontitis, with generalized deep pockets, a lesion of about 15–20 cm^2 may be present. Here we have ulcerated pocket epithelium where bacteria can easily get dislodged into the underlying inflammatory tissues. It is generally accepted that such a lesion will have systemic effects. Unfortunately in the periodontal field such lesions are not very visible for the patient and for the dentist, they are inside the pocket epithelium, they don't hurt most of the time, and they may not alarm patient and professional.

Therefore, in a severe periodontitis case, when you have extensive plaque build up, you can be sure that there is bacteraemia occurring daily or at least frequently, that there is leakage of LPS, a major component of the periodontopathogens, and that there are cytokines from those lesions which are dumped into the circulation, and they can exacerbate other inflammatory lesions in the body.

Systemic markers of inflammation in periodontitis – blood cell results

We have been involved in several studies where we have been investigating systemic markers of cardiovascular and cerebral vascular diseases in periodontitis (6). We have taken peripheral blood from patients in our clinic and from controls in the dental school, on several occasions for the purpose of several studies. We collected plasma and serum and we analysed white cells, red blood cells and thrombocytes. Important marker molecules like acute phase proteins, proinflammatory cytokines and markers of a procoagulant state were also analysed. The number of white blood cells was by the end of the 1980s/early 1990s, already an established marker of CVD. It has been suggested that an increased number of white blood cells may increase viscosity of blood and the blood rheology is increased. Moreover, white blood cells also have a tendency to stick to the inside of blood vessels, and particularly where there is inflammation, there is a tendency to adhere. This may add to a reduced blood flow and thus increasing chance for microthombus formation. So wherever there is a subclinical atherosclerotic lesion, white blood cells, in particularly neutrophils and macrophages, may stick and contribute to the inflammatory process in the vessel walls.

We have found in Amsterdam a dose dependency: the highest numbers of white blood cells were found in patients with severe periodontitis and the lowest number of white blood cells in control subjects, while subjects with moderate periodontitis were in between (7). This was the first indication that in periodontitis it is possible that, if you simply take a tube of blood, you can see an effect of the disease. The main type of white blood cells is the neutrophil; neutrophils form the first line of the innate immune defence and are considered an important cell type in periodontitis. Again the controls have the lowest total number of neutrophils, while the severe periodontitis patients have the highest value of neutrophils in the circulation (7).

There are several intervention studies that have studied the effects of periodontal treatment on the levels of white blood cells. For example, 27 patients with aggressive periodontitis have been treated by non-surgical therapy and without antibiotic treatment (8). These latter investigators studied the numbers of leucocytes and neutrophils 3 months post-initial therapy. Both the number of leucocytes was reduced significantly and the number of neutrophils was reduced significantly (8). This is another line of evidence you could say that indeed the subtle elevation of white blood cells before therapy was due to periodontitis and not some other process. So a treatment study in this respect is very important to give some more grip on the suggestion that the elevation of cells is indeed due to the periodontal process.

With respect to thrombocytes, there are two studies which show that the number of platelets are slightly increased in patients with periodontitis (8, 9), which coincides with the general medical view that whenever there is an inflammatory or infectious disease, the number of platelets are increased.

Interestingly, the number of red blood cells shows a decrease from normal levels whenever there is an active chronic inflammation or infection present, without deficiency in nutrition, in iron and vitamins. This condition is called anaemia of chronic disease (ACD). We have also found in our patients that red blood cells are indeed lower in patients than in controls, and that the level of haemoglobin is lower in the patients than controls. These observations fit with the concept of ACD, i.e. periodontitis may tend to be associated with ACD (10).

Systemic markers of inflammation in periodontitis – the molecule IL-6 in blood plasma

Proinflammatory cytokines are considered important markers of CVD. In particular interleukin-6 (IL-6), because IL-6 is a prototypical proinflammatory cytokine, and it is produced by monocytes and B cells and it stimulates the hepatocytes, the liver cells, to produce acute phase reactants. IL-6 is produced in periodontitis in the periodontal lesion, but it is also produced whenever bacteria get into the circulation; the monocytes, neutrophils and endothelial cells respond to produce IL-6. A German study investigated patients with aggressive periodontitis and control subjects (11). This study reported a significant increase in the IL-6 levels in the patients with periodontitis compared to controls. It is important to realize that the measurement of the cytokines in plasma is very difficult, because the cytokines are at relative low levels, often at the borderline of the assays. If these cytokines, in particular IL-6 or IL-1, were at much higher levels which we could better quantify, then at the same time we would deal with patients who have a fever, which is normally not the case in periodontitis.

In our own study we also found IL-6 in a dose-dependent manner; in general, severe patients had much higher levels and were much more often positive for IL-6 then the controls, because in many controls we could not measure IL-6 at all (7). Sometimes in the patients with moderate periodontitis we could measure and found intermediate levels, but most of the severe patients had measurable IL-6 at higher levels. In a study from the Eastman Dental Centre (12), it was shown that when you treat patients with aggressive periodontitis, you get a decrease in the levels of IL-6. So this treatment study shows again that the elevation of IL-6, which we observe in periodontitis, is indeed related to the periodontitis disease process rather than to another condition. The conclusion on IL-6 is that this proinflammatory cytokine is elevated in periodontitis, there is dose dependence and treatment can reduce IL-6 levels. Encouraging for all of us who treat patients, we can have an effect on their IL-6 levels and on numbers of white blood cells as I showed before.

Systemic markers of inflammation in periodontitis – C-reactive protein in blood plasma

There are several acute phase proteins produced in the liver; the most studied is C-reactive protein (CRP). This acute phase protein is produced in the liver in reaction to an infection or inflammatory process. It is mainly induced due to elevated IL-6. When there is an infection and/or inflammation, IL-6 is elevated and IL-6 will be disseminated to the liver. CRP acts as an opsonin and it activates compliment and it has proinflammatory activity (6). Importantly, CRP is associated with CVD; the relative risk for CVD is increased with 90% (RR is 1.9), when CRP levels are ≥ 2 mg l^{-1} in plasma (13, 14).

As observed previously for other markers, CRP is elevated in periodontitis in a dose dependent manner. On average, patients with severe periodontitis had the highest levels of CRP and controls had the lowest levels, while moderate periodontitis patients had intermediate values (7). Several papers have now appeared in the literature, which have investigated levels of CRP in relation to periodontitis, and every study shows that in periodontitis the levels of CRP are higher than in controls (6). However, not all studies may be comparable to each other; not all have reported the mean values, some have reported medians, some studies included a measurement by ELISA, while others included measurements with a high-sensitivity technique. We set out to undertake a meta-analysis of all available studies in the literature (Huizinga JD and Loos BG, unpublished data); this project was supported by Philips Oral Health Care. Preliminary results will be presented below.

In a systematic review we investigated whether CRP was significantly elevated in periodontitis patients. The literature was screened in several databases using standard Cochrane strategies, full text searching, including several mesh terms and the important keywords 'C-reactive protein' and 'periodontitis'. We selected for case–control studies and (randomized) controlled clinical trials in humans. The studies needed to employ high-sensitivity CRP measurements and needed to report mean values and standard deviations. The study subjects could not have any systemic disorders including a history of CVD and atherosclerosis. Initially we identified 80 studies in the literature. They fulfilled the search criteria, but when we applied all the selection criteria only 13 studies were suitable. In those 13 studies we had 592 patients and 761 controls. For the case–control studies we present a weighted mean difference (WMD) between the patients and controls. We also calculated the weighted mean (WM) separately for the patients and for the controls.

We have a group of nine case–control studies, with periodontitis patients and control patients. The WMD for CRP levels between cases and controls among these nine studies was 1.54 mg l^{-1}, and this was highly significant. This means there are always higher levels of CRP in patients versus controls. If you look at the WM for the patients, it was 3.39 mg l^{-1}, while the controls had a WM of 1.61 mg l^{-1}. However, in this first

analysis we also found considerable heterogeneity, which means that all included studies may not have been completely comparable. Two studies contributed to the heterogeneity of this analysis, because of extreme differences in social economic status and gender inclusion, in comparison to the other selected studies. So in our next analysis we excluded those two studies and basically we got the same results, but now without any heterogeneity. The difference for CRP levels between periodontitis and the controls was 1.3 mg l^{-1}; the CRP WM of patients is 2.78 mg l^{-1}, and the CRP WM for controls was 1.44 mg l^{-1} (Huizinga JD and Loos BG, unpublished data). So again, it shows very consistently, applying strict inclusion criteria, that CRP is elevated in periodontitis and is elevated above a critical level of 2 mg l^{-1}, which, according to the literature, increases the chance for CVD with almost factor 2.

There were four treatment studies available in the literature for inclusion in our meat-analysis. Those treatment studies showed the following: before periodontal therapy CRP levels were 2.2 mg l^{-1}, while after treatment they were 1.37 mg l^{-1}. These four studies show that periodontal treatment is indeed able to lower the levels of CRP and that CRP can be brought below the critical level of 2 mg l^{-1}. This finding was highly significant, while there was no heterogeneity among these four studies (Huizinga JD and Loos BG, unpublished data). So I think on the basis of this latter meta-analysis, we clearly can conclude that with our periodontal treatment we are able to do something good for our patients, if it indeed is true that a level of 2 mg l^{-1} or higher for CRP is a risk for CVD.

Conclusions on C-reactive protein and future studies

In conclusion, CRP is significantly elevated in periodontitis and periodontal treatment can reduce plasma levels of CRP. Therefore, it seems clear that periodontitis may elicit a sufficient systemic challenge to trigger a mild acute phase response with an increase in CRP. However, the exact mechanism how CRP acts in relation to CVD is unknown. We want to further unravel the relation between elevated CRP in periodontitis and CVD. In a next study we are going to explore further the individual variations in CRP levels. Is it related to levels of *Porphyromonas gingivalis*, *Actinobacillus actinomycetemcomitans*, *Tannerella forsythensis*, *Fusobacterium nucleatum* or is it related to genetic polymorphisms in CRP or the combination of both? Another goal for the future which I'm very interested in is the question whether we can we use plasma CRP or maybe another marker to indicate oral health. Can we use CRP as a marker for the end point of periodontal treatment, have we done enough or do we have to continue supportive periodontal care?

General conclusions on systemic effects of periodontitis

Periodontitis has systemic effects and periodontitis is associated with markers of CVD. Periodontal treatment studies show a decrease in these markers, and I think at least some of the epidemiological findings on the association of CVD and periodontitis can now be better understood.

Acknowledgements

The author thanks Philips Oral Healthcare EMEA for their support of investigations into oral and systemic health.

References

1 Janket SJ, Baird AE, Chuang SK, Jones JA. Meta-analysis of periodontal disease and risk of coronary heart disease and stroke. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2003; **95:** 559–569.
2 Haraszthy VI, Zambon JJ, Trevisan M, Zeid M, Genco RJ. Identification of periodontal pathogens in atheromatous plaques. *J Periodontol* 2000; **71:** 1554–1560.
3 Daly CG, Mitchell DH, Highfield JE, Grossberg DE, Stewart D. Bacteremia due to periodontal probing: a clinical and microbiological investigation. *J Periodontol* 2001; **72:** 210–214.
4 Kinane DF, Riggio MP, Walker KF, MacKenzie D, Shearer B. Bacteraemia following periodontal procedures. *J Clin Periodontol* 2005; **32:** 708–713.
5 Geerts SO, Nys M, De MP et al. Systemic release of endotoxins induced by gentle mastication: association with periodontitis severity. *J Periodontol* 2002; **73:** 73–78.
6 Loos BG. Systemic markers of inflammation in periodontitis. *J Periodontol* 2005; **76:** 2106–2115.
7 Loos BG, Craandijk J, Hoek FJ, Wertheim-van Dillen PME, van der Velden U. Elevation of systemic markers related to cardiovascular diseases in the peripheral blood of periodontitis patients. *J Periodontol* 2000; **71:** 1528–1534.
8 Christan C, Dietrich T, Hagewald S, Kage A, Bernimoulin JP. White blood cell count in generalized aggressive periodontitis after non-surgical therapy. *J Clin Periodontol* 2002; **29:** 201–206.
9 Wakai K, Kawamura T, Umemura O et al. Associations of medical status and physical fitness with periodontal disease. *J Clin Periodontol* 1999; **26:** 664–672.
10 Hutter JW, van der Velden U, Varoufaki A, Huffels RA, Hoek FJ, Loos BG. Lower numbers of erythrocytes and lower levels of hemoglobin in periodontitis patients compared to control subjects. *J Clin Periodontol* 2001; **28:** 930–936.
11 Mengel R, Bacher M, Flores-De-Jacoby L. Interactions between stress, interleukin-1beta, interleukin-6 and cortisol in periodontally diseased patients. *J Clin Periodontol* 2002; **29:** 1012–1022.

12 D'Aiuto F, Parkar M, Andreou G, Brett PM, Ready D, Tonetti MS. Periodontitis and atherogenesis: causal association or simple coincidence? *J Clin Periodontol* 2004; **31:** 402–411.
13 Danesh J, Collins R, Appleby P, Peto R. Association of fibrinogen, C-reactive protein, albumin, or leukocyte count with coronary heart disease. Meta-analyses of prospective studies. *J Am Med Assoc* 1998; **279:** 1477–1482.
14 Rosenson RS, Koenig W. Utility of inflammatory markers in the management of coronary artery disease. *Am J Cardiol* 2003; **92:** 10i–18i.