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Periodontitis and atherosclerotic cardiovascular disease: consensus report of the Joint EFP/ AAP Workshop on Periodontitis and Systemic Diseases

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Abstract

Background: This consensus report is concerned with the association between periodontitis and atherosclerotic cardiovascular disease (ACVD). Periodontitis is a chronic multifactorial inflammatory disease caused by microorganisms and characterized by progressive destruction of the tooth supporting apparatus leading to tooth loss; as such, it is a major public health issue.
Aims: This report examined biological plausibility, epidemiology and early results from intervention trials.
Plausibility: Periodontitis leads to entry of bacteria in the blood stream. The bacteria activate the host inflammatory response by multiple mechanisms. The host immune response favors atheroma formation, maturation and exacerbation.
Epidemiology: In longitudinal studies assessing incident cardiovascular events, statistically significant excess risk for ACVD was reported in individuals with periodontitis. This was independent of established cardiovascular risk factors. The amount of the adjusted excess risk varies by type of cardiovascular outcome and across populations by age and gender. Given the high prevalence of periodontitis, even low to moderate excess risk is important from a public health perspective.
Intervention: There is moderate evidence that periodontal treatment: (i) reduces systemic inflammation as evidenced by reduction in C-reactive protein (CRP) and improvement of both clinical and surrogate measures of endothelial function; but (ii) there is no effect on lipid profiles – supporting specificity. Limited evidence shows improvements in coagulation, biomarkers of endothelial cell activation, arterial blood pressure and subclinical atherosclerosis after periodontal therapy. The available evidence is consistent and speaks for a contributory role of periodontitis to ACVD. There are no periodontal intervention studies on primary ACVD prevention and there is only one feasibility study on secondary ACVD prevention.
Conclusions: It was concluded that: (i) there is consistent and strong epidemiologic evidence that periodontitis imparts increased risk for future cardiovascular disease; and (ii) while in vitro, animal and clinical studies do support the interaction and biological mechanism, intervention trials to date are not adequate to draw further conclusions. Well-designed intervention trials on the impact of periodontal treatment on prevention of ACVD hard clinical outcomes are needed.

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This consensus statement addresses the association between periodontitis and ACVD. The deliberations of the Working Group are based on a formal review and analysis of the recently published world literature on the topic.

Periodontitis

Periodontitis is a chronic multifactorial inflammatory disease caused by microorganisms and characterized by progressive destruction of the tooth supporting apparatus leading to tooth loss. This is to be distinguished from gingivitis. Periodontitis is a major public health issue because (not in hierarchical order, Baehni & Tonetti 2010, Eke et al. 2012): it is common, it is a source of social inequality, it reduces quality of life, it reduces chewing function and impairs aesthetics, it causes tooth loss and disability, it is responsible for a substantial proportion of edentulism and masticatory dysfunction, it has an impact on escalating dental costs and it is a chronic disease with possible impact on general health. Periodontitis disproportionately affects certain groups: it is more prevalent and severe in (i) socially disadvantaged and specific ethnic groups; and (ii) smokers, people with diabetes and the obese.

"The global burden of oral diseases is among the most common (non-communicable diseases). Their impact on individuals and communities is considerable in terms of pain and suffering, impairment of function and reduced quality of life and cost of treatment" (FDI, World Dental Parliament, 2012). Article 19 of the recent United Nations General Assembly declaration of 2011 further states "… renal, oral and eye diseases pose a major health burden for many countries and (that) these diseases share common risk factors and can benefit from common responses to non-communicable diseases." Preservation of periodontal health is a key component of oral and overall health and as such is a fundamental human right (Consensus of the European Workshop on Periodontal Education, Baehni & Tonetti 2010).

As there are effective preventive and treatment approaches, periodontal health is an attainable goal both at the individual and at the population level. The subject of this workshop is to assess the available evidence whether prevention and treatment of periodontitis has an impact on cardiovascular health.

Cardiovascular Diseases

Atherosclerotic cardiovascular diseases (ACVD) are a group of diseases that include fatal and non-fatal coronary heart disease (angina, myocardial infarction), ischemic cerebrovascular disease (stroke/TIA) and peripheral arterial disease.

The charge of the discussions of this group was:

1 To assess biological plausibility of mechanisms underpinning the relationship between periodontitis and cardiovascular diseases
2 To review the available epidemiological evidence with an emphasis on longitudinal studies allowing measures of excess cardiovascular risk attributable to periodontitis
3 To review the results of initial intervention trials on the benefits of periodontal therapy on surrogate cardiovascular outcomes
4 To critically evaluate the available evidence spanning biological plausibility of mechanisms, epidemiological evidence and initial intervention trials

5 To identify key issues for the design of future trials

6 To provide reasonable action/recommendations for the public, the dental and medical profession at this stage of incomplete knowledge

Biological Plausibility

What are the biologically most plausible mechanisms linking periodontitis to atherothrombogenesis?

Based on the evidence outlined in the review articles (Reyes et al. 2013, Schenkein & Loos 2013) the group reached the following consensus of the most biologically plausible mechanisms illustrated in Fig. 1. The chronic oral infection periodontitis leads to entry of bacteria (or their products) into the blood stream. The bacteria activate the host inflammatory response by multiple mechanisms. The host immune response favors atheroma formation, maturation and exacerbation.

Is it possible to convincingly isolate bacterial exposure from inflammatory mediator exposure? If so, how?

It would be very challenging to discriminate the role of bacteria from the inflammatory response, but the use of specific pharmacotherapeutic (antimicrobial, anti-inflammatory) interventions may shed light on this matter. In animal studies, specific mediators of resolution of inflammation with potent anti-inflammatory actions block development of atheromas induced by periodontal bacteria and periodontitis (Jain et al. 2003).

Is bacteremia/endotoxinemia from daily activities and or/dental procedures more prevalent in periodontitis patients and associated with periodontal status?

The best available evidence suggests a role of periodontal status in the prevalence of bacteremia after chewing, brushing, flossing or scaling, with a higher prevalence/incidence and higher bio-diversity, including periodontal pathogens, in periodontitis patients, *versus* gingivitis or healthy patients. In addition a systematic review reported an association between the prevalence of bacteremia and plaque/gingival indices (Tomás et al. 2012).

Is there an association between periodontal microbiota, clinical periodontal parameters and recovery of periodontal pathogens in atheroma lesions?

Among the selected studies, evaluating the presence of bacterial antigens and molecular signatures in the atherothrombotic lesions, at least two reported a correlation between the periodontal status (either moderate *versus* severe periodontitis or healthy *versus* periodontitis) and the presence of periodontal pathogens. In addition, at least eight studies describe a correlation between the subgingival microbiota and the pathogens detected in the vascular lesions. There is some evidence for bacterial viability in the atheroma.

What is the role of adaptive immunity?

It is feasible that adaptive immune responses enhance the inflammatory response in the atheroma which may lead to exacerbation. Antibodies produced in response to plaque bacteria can be pro-inflammatory, cross-reacting with endothelial cells and with modified LDL to enhance incorporation of lipids into inflammatory cells within the vessel wall. Some of these antibodies as well as inflammatory cytokines can promote Th1 responses within the atheroma to increase activation of macrophages to enhance inflammation in the atheroma.

Does periodontal treatment cause a short-lived increase in systemic inflammation?

Periodontal treatment often elicits a transient increase of systemic inflammatory/pro-thrombotic mediators and an overall decrease of the endothelial function within 24–48 hours (D'Aiuto et al. 2013). These results are most likely related to the bacteremia and the trauma following the therapeutic event.

Epidemiological Evidence

What clinical characteristics of periodontitis have been associated with cardiovascular disease?

The outcome in all studies in the background paper (Dietrich et al. 2013) was incident ACVD indicating the occurrence of periodontitis was prior to an incident cardiovascular event ACVD. Therefore the discussions are reporting on a higher level of evidence of association that allows making statements of risk. Periodontitis measured using clinical attachment loss/periodontal probing depth and/or radiographic assessment of bone loss has been associated with increased risk for various measures of ACVD independent of established cardiovascular risk factors.

How strong are the measures of excess risk?

Statistically significant excess risk for ACVD in individuals with periodontitis was reported to be independent of established cardiovascular risk factors. However, the amount of the excess risk adjusted for other ACVD risk factors varies by type of cardio-
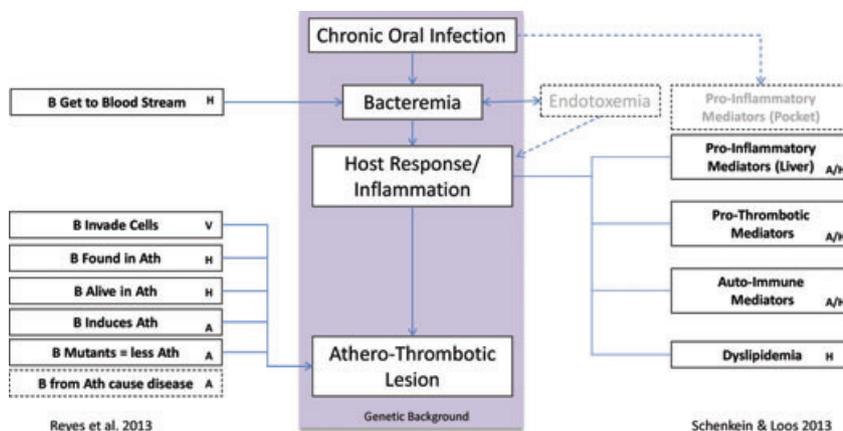

Figure 1. Biologically plausible mechanisms: Periodontitis and increased risk for atherothrombogenesis. Ath = Atheroma; B = bacteria; H = human studies; A = Animal studies; V = in vitro studies. Dotted boxes indicate limited/no evidence.

vascular outcome and across populations by age and gender. Specifically, the risk is greater for cerebrovascular disease than with coronary heart disease, and greater in males and in younger individuals. There is no excess risk reported between measures of periodontitis and incident coronary heart disease in subjects older than 65 years. This finding is consistent with findings reported in many studies that the strength of established individual ACVD risk factors are weaker in older adults.

There is insufficient evidence to indicate whether or not periodontitis is associated with the incidence of secondary (a second ACVD event after the original event) cardiovascular events. This finding has implications for future clinical trials and, under ideal circumstances, more epidemiologic evidence would be needed for the planning of such intervention trials. Even low to moderate excess risk reported in studies is enough to be important from a public health perspective because of the high prevalence of periodontitis.

Are there confounders that can account for the association?

There are many potentially important confounders of the association between periodontitis and ACVD risk, including co-morbidities such as diabetes and lifestyle factors such as smoking. However, established cardiovascular risk factors do not completely explain the excess cardiovascular risk in subjects with periodontitis. All studies included in the review controlled for smoking status and excess risk was demonstrated in never-smokers in a number of the studies. In studies that controlled for diabetes, excess risk associated with periodontitis was also demonstrated.

However, excess risk could be due to unknown confounders. Recent findings from the ENCODE project, a deep sequencing project to identify all functional elements of the genome, indicate that there are common genetically determined pathways underpinning various complex inflammatory diseases. Therefore, confounding by these genetic determinants could be due to unknown confounders.

Clinical and public health implications

Periodontal treatment requires individual professional intervention. Therefore, primary prevention becomes more important and novel strategies to prevent disease at the population level would be highly desirable. A diagnosis of periodontitis may contribute to cardiovascular risk stratification, if shown to improve cardiovascular risk prediction over and above currently established prediction models (e.g. Framingham score).

Intervention Studies

Atherosclerotic cardiovascular disease is a complex multifactorial disease and individuals may present with one or a combination of risk factors. Periodontitis has been shown to increase the risk of future ACVD events, independent of other well-known risk factors. The group reviewed (D'Aiuto et al. 2013) and graded (van Tulder et al. 1997) the available evidence from periodontal intervention trials on ACVD outcome.

The group concluded that with periodontal treatment there is moderate evidence for reduction of systemic inflammation as evidenced by reduction in CRP and improvement of both clinical and surrogate measures of endothelial function. Both CRP and endothelial function have been associated with increased future risk of cardiovascular disease. However, there is moderate evidence that periodontal treatment does not have an effect on lipid profiles. There is limited evidence that periodontal intervention reduces other ACVD biomarkers of inflammation, coagulation and biomarkers of endothelial cell activation. There is limited evidence that periodontal treatment reduces arterial blood pressure and subclinical ACVD.

There are no periodontal intervention studies on primary (first ischemic event) ACVD prevention and there is only one feasibility study on secondary (subsequent ischemic event) ACVD prevention. We recognize that well designed intervention trials on the impact of periodontal treatment on prevention of primary and secondary ACVD hard clinical outcomes are needed. Two experimental designs of intervention trials can be utilized: primary ACVD prevention trials and secondary ACVD prevention trials.

Unless surrogate ACVD outcome measures are used, proper controlled primary prevention trials are unjustified. Although the group recognizes the need for additional epidemiological evidence informing clinical intervention trial design, secondary ACVD prevention trials should be performed. The group recognizes a number of challenges for designing definitive intervention studies. The group used the PICO (population, intervention, comparison, outcome) framework to address some of these challenges.

How should periodontitis populations be selected?

A number of previous trials have included heterogeneity of case definitions. This may explain the diversity of findings from these studies. Thus, researchers should consistently adopt the same minimal levels of severity of periodontal disease. Study populations should present with substantial gingival inflammation (e.g. bleeding on probing or PISA scoring system, Nesse et al. 2008) and well-defined periodontal destruction (Tonetti & Claffey 2005). Target study populations can be recruited from medical offices rather than dental offices and we recognize that younger (<65 years) study populations are most appropriate.

What are the appropriate interventions for periodontitis?

The group recognizes that there are multiple effective treatment strategies to control periodontal inflammation. Some previous studies have employed treatment regimens that did not resolve periodontitis sufficiently. The intervention trials should be designed based on ACVD outcomes and include a pre-specified goal to eliminate dental biofilm and clinical gingival inflammation (Friedewald et al. 2009) using any therapeutic strategy deemed necessary. Thus, multiple strategies have to be employed to restore and maintain periodontal health in the treatment group of RCTs. Following a ACVD event, the AHA guidelines Adams et al 2007, Jneid et al 2012 should be followed. Based on limited evidence, minimizing the potential bacteremia by restoration of oral hygiene and staggering

periodontal treatment in multiple sessions, rather than one session of intensive treatment, is desirable.

What are the appropriate controls for intervention trials?

A previous feasibility study (PAVE) highlighted the challenges in the management of subjects in the control group of such studies. Control subjects in this particular study were told to continue receiving their standard care; however, 30% of these control patients obtained additional periodontal treatment, which confounded the outcomes. Thus, future trials should increase sample size to account for such factors also taking into consideration ethical concerns for long-term absence of additional periodontal treatment.

What are the outcome measures for ACVD that can be used in intervention trials?

The group acknowledges the challenges in selection of appropriate single or composite cardiovascular outcomes. Primary hard clinical outcomes (e.g. MI, stroke, death) are the most relevant measures for intervention trials. In addition, surrogate outcome measures (ACVD biomarkers such as CRP, endothelial function) can provide insight into mechanisms of the association between the ACVD and periodontitis as reviewed in D'Aiuto et al. 2013.

What is the evidence that ACVD treatment may impact the treatment outcomes for periodontitis?

Emerging evidence suggests that some pharmacological agents may be beneficial in reducing periodontal inflammation (e.g. aspirin, statins, fish oil, vitamin D).

Conclusions

1 There is consistent and strong epidemiologic evidence that periodontitis imparts increased risk for future ACVD
2 The impact of periodontitis on ACVD is biologically plausible: translocated circulating oral microbiota may directly or indirectly induce systemic inflammation that impacts the pathogenesis of atherothrombogenesis

3 While in vitro, animal and clinical studies do support the interaction and biological mechanism, intervention trials to date are not adequate to draw further conclusions

Recommendations for Oral Health Practitioners

1 Practitioners should be aware of the emerging and strengthening evidence that periodontitis is a risk factor for developing ACVD, advising patients of the risk.
2 The rationale for prevention, diagnosis and treatment of periodontitis remains the preservation of the dentition and avoidance of the crippling effects of periodontitis induced alveolar bone loss and tooth loss.
3 Based on the weight of the evidence, periodontitis patients with other risk factors for ACVD, such as hypertension, overweight/obesity, smoking, etc. who have not seen a physician within the last year, should be referred for a physical.
4 Modifiable lifestyle associated risk factors for periodontitis (and ACVD) should be addressed in the dental office 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.
5 Treatment of periodontitis in subjects with a history of cardiovascular events needs to follow AHA guidelines for elective procedures.

Recommendations for Research

The working group recognized that significant progress has been made in understanding the relationship between periodontitis and ACVD in spite of the relatively new field of investigation. Significant gaps in knowledge exist and these impact on the best way to manage patients and populations at risk.

More basic research is needed to:

1 Enhance understanding of bacteremia associated with periodontal diseases
2 Better define the role of oral microbiota within the atherothrombotic lesion
3 Clarify the role inflammatory mediators produced in the periodontium in contributing to systemic host response
4 Identify genetic and epigenetic factors that influence susceptibility to systemic inflammation
5 Investigate short term vs. chronic inflammation and endothelial dysfunction following periodontal treatment in high risk individuals

In terms of epidemiology, the following gaps in knowledge need to be addressed:

1 Further prospective epidemiologic studies are needed to clarify relationships between periodontitis and components of commonly used ACVD endpoints, in particular in the context of secondary prevention studies
2 The majority of studies has used measures of periodontitis ascertained at one point in time. Therefore, the impact of periodontal exposure over time is poorly understood. Studies that look at history of periodontitis over a period of time are lacking. This means that currently we do not know whether there were any changes in periodontal status and ACVD risk factors during any longitudinal study
3 More information is required on the temporal relationship of the exposure to periodontitis and ACVD outcome measures
4 Case-control studies (including biomarkers) in younger individuals (< 65 years) to improve precision of estimates are needed

With regards to intervention trials:

1 Further research is needed to define the parameters of future randomized controlled trials on the impact of treating periodontitis on ACVD
2 Once missing information is available, well-designed intervention trials are justified by: (i) the concordance of the biological plausi-

bility data, the epidemiologic data and the preliminary intervention trials on surrogate markers; (ii) the ability to effectively treat and prevent periodontitis; and (iii) the high prevalence of periodontitis in the population.

References

Adams, H. P., del Zoppo, G., Alberts, M. J., Bhatt, D. L., Brass, L., Furlan, A., Grubb, R. L., Higashida, R. T., Jauch, E. C., Kidwell, C., Lyden, P. D., Morgenstern, L. B., Qureshi, A. I., Rosenwasser, R. H., Scott, P. A. & Wijdicks, E. F. M. (2007) Guidelines for the early management of adults with ischemic stroke. *Stroke* **38**, 1655–1711.

Baehni, P. & Tonetti, M. S.; Group 1 of the European Workshop on Periodontology. (2010) Conclusions and consensus statements on periodontal health, policy and education in Europe: A call for action–consensus view 1. Consensus report of the 1st European Workshop on Periodontal Education. *European Journal of Dental Education* **14**, Suppl 1:2–3.

D'Aiuto, F., Orlandi, M. & Gunsolley, J. C. (2013) Evidence that periodontal treatment improves biomarkers and ACVD outcomes. *Journal of Clinical Periodontology* **40** (Suppl 14), 85–105.

Dietrich, T., Sharma, P., Walter, C., Weston, P. & Beck, J. (2013) The epidemiological evidence behind the association between periodontitis and incident atherosclerotic cardiovascular disease. *Journal of Clinical Periodontology* **40** (Suppl 14), 70–84.

Eke, P. I., Dye, B. A., Wei, L., Thornton-Evans, G. O. & Genco, R. J.; CDC Periodontal Disease Surveillance workgroup: James Beck (University of North Carolina, Chapel Hill, USA), Gordon Douglass (Past President, American Academy of Periodontology), Roy Page (University of Washington). (2012) Prevalence of periodontitis in adults in the United States: 2009 and 2010. *Journal of Dental Research* **91**,914–920.

Friedewald, V. E., Kornman, K. S., Beck, J. D., Genco, R. J., Goldfine, A., Libby, P., Offenbacher, S., Ridker, P. E., Van Dyke, T. E. & Roberts, W. C. (2009) The American Journal of Cardiology and Journal of Periodontology Editors' Consensus: Periodontitis and atherosclerotic cardiovascular disease. *Journal of Periodontology* **80**, 1021–1032.

Jain, A., Batista, E., Serhan, C., Stahl, G. & Van Dyke, T. E. (2003) A role of periodontitis in the progression of lipid deposition in an animal model. *Infection and Immunity* **71**, 6012–6018.

Jneid, H., Anderson, J. L., Wright, R. S., Adams, C. D., Bridges, C. R., Casey, D. E. Jr., Ettinger, S. M., Fesmire, F. M., Ganiats, T. G., Lincoff, A. M., Peterson, E. D., Philippides, G. J., Theroux, P., Wenger, N. K. & Zidar, J. P. (2012) ACCF/AHA focused update of the guideline for the management of patients with unstable angina/non–ST-elevation myocardial infarction (updating the 2007 guideline and replacing the 2011 focused update): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation* **126**, 875–910.

Nesse, W., Abbas, F., van der Ploeg, I., Spijkervet, F. K., Dijkstra, P. U. & Vissink, A. (2008) Periodontal inflamed surface area: Quantifying inflammatory burden. *Journal of Clinical Periodontology* **35**, 668–673.

Reyes, L., Kozarov, E., Herrera, D., Roldan, S. & Progulske-Fox, A. (2013). Periodontal bacterial invasion and infection: Contribution to cardiovascular disease. *Journal of Clinical Periodontology* **40** (Suppl 14), 30–50.

Schenkein, H. A. & Loos, B. G. (2013) Inflammatory mechanisms linking periodontal diseases to cardiovascular diseases. *Journal of Clinical Periodontology* **40** (Suppl 14), 51–69.

Tomás, I., Diz, P., Tobías, A., Scully, C. & Donos, N. (2012) Periodontal health status and bacteraemia from daily oral activities: Systematic review/meta-analysis. *Journal of Clinical Periodontology* **39**, 213–228.

Tonetti, M. S. & Claffey, N.; European Workshop in Periodontology group C. (2005) Advances in the progression of periodontitis and proposal of definitions of a periodontitis case and disease progression for use in risk factor research. Group C consensus report of the 5th European Workshop in Periodontology. *Journal of Clinical Periodontology* **32**, Suppl 6:210–213.

van Tulder, M. W., Koes, B. & Bouter, L. M. (1997) Conservative treatment of acute and chronic non-specific low back pain: A systematic review of randomized controlled trials of the most common interventions. *Spine* **22**, 2128–2156.

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