Guest Editorial

Scrutinising the Link between Periodontal Disease and Systemic Conditions: Does Recent Evidence Continue to Support the European Federation of Periodontology's 2012 Manifesto?

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Abstract

During the 9th European Workshop in Periodontology, the evidence base for the link between periodontal disease and systemic conditions was scrutinised. In response, the European Federation of Periodontology (EFP) issued a manifesto that summarised these findings. This article has critically evaluated the research published after the 9th European Workshop in Periodontology in November 2012 to ascertain whether recent research has affected the merit of the manifesto.

It was found that recent research supports the manifesto regarding diabetes mellitus, cardiovascular disease and adverse pregnancy outcomes, although further high-quality randomised controlled trials are required to support the manifesto statement that "certain populations of pregnant women may benefit from periodontal therapy."

Furthermore, there is now good evidence from systematic reviews for an association between periodontal disease and chronic obstructive pulmonary disease, rheumatoid arthritis, chronic kidney disease and metabolic syndrome. This may be sufficient to warrant an update to the manifesto. Causal relationships remain debatable. There is also recent emerging evidence for an association with obstructive sleep apnoea. The recent evidence investigating obesity and periodontal disease is mixed, and no new systematic studies or randomised controlled trials were found relating to cognitive impairment.

Keywords: periodontal disease, systemic, EFP, diabetes, cardiovascular disease, rheumatoid arthritis

Introduction

During the 9th European Workshop in Periodontology, the evidence base for the link between periodontal disease and systemic conditions was scrutinised. In response, the European Federation of Periodontology (EFP) issued a manifesto that summarised these findings, calling upon all dental and health professionals to "act in the prevention, early diagnosis and effective treatment of periodontal disease in order to combat the devastating oral and general health effects for the individual and society" (European Federation of Periodontology, 2012).

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This article will critically evaluate the research published after the 9th European Workshop in Periodontology, between November 2012 and February 2016, to ascertain whether recent research has affected the merit of the manifesto. In line with the guidance for recommending evidence-based dentistry, the highest evidence grade – systematic review with meta-analysis of randomised controlled trials (RCTs) – is preferentially appraised before studies of lower-grade evidence (Richards, 2009; Oxford Centre for Evidence-Based Medicine, 2009).

Periodontal disease and diabetes mellitus (DM)

The manifesto states:

"Randomised clinical trials consistently demonstrate that mechanical periodontal therapy associates with approximately a 0.4% reduction in HbA1C at 3 months, a clinical impact equivalent to adding a second drug to a pharmacological regime for diabetes."

Since November 2012, several systematic studies of RCTs with meta-analyses have concluded that non-surgical periodontal surgery significantly improves glycaemic control in patients with chronic periodontitis and type 2 diabetes mellitus (T2DM), as summarised in *Table 1*. Only one systematic review (Wang *et al.*, 2014a) found that non-surgical periodontal treatment did not significantly improve glycaemic control in type 2 diabetics, however it included just three studies (n = 143) in its meta-analysis. The outcome measures used for glycaemic control have predominantly been glycated haemoglobin A1c (HbA1c) and fasting plasma glucose (FPG), which are used as diagnostic criteria for diabetes mellitus (Diabetes UK, 2016).

The improvement in glycaemic control is consistently reported after three months. After six months, the results from systematic reviews are inconclusive, with some reporting a maintained significant reduction (Sun *et al.*, 2014) whilst others found no significant reduction (Wang *et al.*, 2014b). On the whole, the merits of the EFP manifesto relating to diabetes mellitus remain well supported by the recent systematic reviews.

The aforementioned studies focus on patients with T2DM. A systematic review that assessed periodontal treatment in patients with T1DM found that "Fourteen of the studies reported a significant decrease in serum HbA1c levels ($p < 0.05$) after periodontal treatment. The remaining seven studies failed to find a significant decrease in serum HbA1c" (Mauri-Obradors *et al.*, 2014). They concluded that "…the published literature is insufficient and inconclusive to clearly support periodontal treatment as a means to improve serum HbA1c levels in patients with T1DM." The authors did not perform a meta-analysis, possibly due to the highlighted heterogeneity of the studies. Homogeneously designed RCTs with larger samples and longer follow-up periods are therefore required to assess the association between periodontal disease and T1DM.

Periodontal disease and cardiovascular disease (CVD)

The manifesto states:

"There is moderate evidence that periodontal treatment reduces systemic inflammation as evidenced by reductions in C-reactive protein (CRP) and oxidative stress, and leads to improvements of clinical and biochemical measures of vascular endothelial function."

Table 2 summarises the systematic studies examining the association of periodontal disease (PD), and the effect of non-surgical periodontal treatment (NSPT), on the biomarkers of cardiovascular disease. A systematic review of fifteen observation studies (n = 17,330) provided evidence for an association concluding that the "presence of periodontal disease was [significantly] associated with carotid atherosclerosis" (Zeng *et al.*, 2016). Since 2012, several systematic reviews have also reported a favourable effect of periodontal treatment on endothelial function (Orlandi *et al.*, 2014; D'Aiuto *et al.*, 2013; Teeuw *et al.*, 2014) and biomarkers of atherosclerotic disease (Teeuw *et al.*, 2014; Deng *et al.*, 2013). This improvement was particularly beneficial for patients already suffering from CVD and/or diabetes.

Table 1. Summary of the systematic studies of randomised controlled trials (RCTs) published since the 9th European Workshop in Periodontology reporting that non-surgical periodontal surgery (NSPT) significantly improves glycaemic control in diabetic patients with chronic periodontitis.

Study	RCTs included	Sample size	Measures of glycaemic control	Reported results
(Corbella *et al.*, 2013)	15	*n* = 913	HbA1c, FPG	NSPT significantly reduced HbA1c (-0.38%) and FPG (-9.01 mg/dL) after 3 months.
(Sgolastra *et al.*, 2013)	5	Unknown	HbA1c, FPG, TC, TG, HDL, LDL	NSPT significantly reduced HbA1c and FPG. No significant differences were found in the reduction of TC, TG, HDL, or LDL.
(Sun *et al.*, 2014)	8	*n* = 515	HbA1c, FPG	NSPT significantly reduced HbA1c after 3 months (-1.03%) and 6 months (-1.18%), and produced a non-significant decrease in FPG.
(Li *et al.*, 2015)	9	*n* = 1066	HbA1c	NSPT significantly reduced HbA1c after 3 months (-0.27%).
(Wang *et al.*, 2014b)	10	*n* = 1135	HbA1c	NSPT significantly reduced HbA1c after 3 months (-0.36%). No significant reduction observed after 6 months.
(Liew *et al.*, 2013)	6	*n* = 422	HbA1c	NSPT significantly reduced HbA1c after 3 months (-0.41%).

HbA1c, glycated haemoglobin A1c; FPG, fasting plasma glucose; TC, total cholesterol; TG, triglycerides; HDL, high-density lipoproteins; LDL, low-density lipoproteins.

Table 2. Summary of the systematic studies examining the association of periodontal disease (PD), or effect of non-surgical periodontal treatment (NSPT), on the biomarkers of cardiovascular disease.

Study	Studies included	Sample size	CVD biomarker/ endpoint investigated	Reported results
(Zeng *et al.*, 2016)	15	*n* = 17330	Carotid atherosclerosis	NSPT was associated with carotid atherosclerosis but statistical heterogeneity was substantial. Subgroup analysis of adjusted smoking and diabetes mellitus still showed borderline significance.
(Orlandi *et al.*, 2014)	22	*n* = 5713	c-IMT FMD	PD was associated with a mean increase in c-IMT of 0.08 mm and a mean difference in FMD of 5.1%. Periodontal treatment improved FMD by a mean of 6.64%.
(D'Aiuto *et al.*, 2013)	14	Unknown	CD40, amyloid A, vWF, MCP-1, CRP, leucocyte counts, fibrinogen, IL-6, TNF-α, sE-selectin, d-dimers, oxidative stress, endothelial function, metalloproteinases	NSPT triggers a short-term inflammatory response followed by (a) a progressive and consistent reduction of systemic inflammation and (b) an improvement in endothelial function.
(Teeuw *et al.*, 2014)	25	*n* =1748	hsCRP, IL-6, TNF-α, fibrinogen, total cholesterol, HDL-C	Meta-analyses demonstrated significant weighted mean difference for hsCRP, IL-6, TNF-α, fibrinogen, total cholesterol and HDL-C favouring periodontal intervention. PD patients with comorbidity benefitted most from NSPT.
(Deng *et al.*, 2013)	6	*n* = 682	CRP, total cholesterol, LDL-C, triglycerides, HDL-C	NSPT had no significant effect on CRP, total cholesterol, LDL-C and triglycerides, but did significantly affect HDL-C.
(Schmitt *et al.*, 2015)	10	*n* = 2569	Arterial stiffness	Patients with PD have increased arterial stiffness compared to controls ($p < 0.00001$). The two interventional studies showed contradictory results on the effects of NSPT on arterial stiffness.

c-IMT, carotid intima-media thickness; FMD, flow-mediated dilation; MCP-1, monocyte chemoattractant protein-1; TNF-α, tissue necrosis factor-α; vWF, von Willebrand factors; IL-6, interleukin-6; CRP, C-reactive protein; hsCRP, high-sensitivity C-reactive protein; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

However, it should be noted that Teeuw and colleagues stated that none of the 25 controlled intervention trials included in their meta-analysis used hard clinical endpoints of CVD. Thus, these results do not confirm an improvement in CVD events. This is supported by D'Aiuto and colleagues (2013) who concluded that there is "no evidence on the effects of periodontal therapy on subclinical atherosclerosis" but there is "moderate evidence [that it] reduces interleukin-6, lipids levels, […] C-reactive protein levels and improves endothelial function."

In addition to the beneficial effects of periodontal therapy, some systematic reviews since 2012 have found inconclusive evidence. A meta-analysis of six RCTs concluded that periodontal treatment had "no significant effect on C-reactive protein, total cholesterol, low-density lipoprotein cholesterol, and triglycerides" (Deng *et al.*, 2013), whilst another review of ten clinical trials stated that "the effect of periodontal treatment on arterial stiffness remains unclear" (Schmitt *et al.*, 2015). Arterial stiffness is considered a biomarker of arteriosclerosis.

As the meta-analyses are based on clinical trials that mostly use biomarkers as endpoints, it appears there is currently insufficient evidence to support or refute whether periodontal therapy can prevent CVD events in patients with chronic periodontitis (Li *et al.*, 2014). The recent research therefore supports the EFP manifesto regarding cardiovascular disease.

Periodontal disease and adverse pregnancy outcomes (APO)

The manifesto states:

"Low birth weight, pre-term birth and pre-eclampsia have all been associated with the presence of periodontitis in the mother […] with the strength of this association varying. Results from clinical trials have shown that scaling and root planing does not significantly improve adverse pregnancy outcomes, however certain populations of pregnant women may benefit from periodontal therapy."

Several recent systematic reviews have investigated the effect of periodontal surgery on APOs. In 2015, a large review of six meta-analyses concluded that "the lack of effect of periodontal treatment on pre-term birth rate concluded by four meta-analyses, and the positive effect of treatment for reducing pre-term birth risk concluded by the remaining two meta-analyses are not based on consistent scientific evidence" (López *et al.*, 2015). Well-conducted, randomised controlled trials using rigorous methodology are therefore required. This is supported by a further meta-analysis of thirteen RCTs in 2015 which reported that "periodontal treatment did not significantly affect perinatal mortality, but a [non-significant] trend was observed for populations with high occurrence (≥ 20%) of pre-term birth and low birth weight" where periodontal treatment seemed to reduce the risk of these APOs (Schwendicke *et al.*, 2015). Despite this, the study found that nine of the thirteen RCTs were at high risk of bias, echoing the need for high-quality RCTs. Other systematic reviews similarly concluded that NSPT does not improve APOs (Corbella *et al.*, 2012; Michalowicz *et al.*, 2013).

Therefore, these recent systematic reviews support the manifesto in that NSPT does not improve adverse pregnancy outcomes; however, they do not support the statement that "*certain populations of pregnant women may benefit from periodontal therapy*". Well-conducted, randomised controlled trials using rigorous methodology are required to investigate this.

Periodontal disease and "other diseases"

The manifesto states:

"There is emerging evidence for associations between periodontal diseases and chronic obstructive airways disease, chronic kidney disease, rheumatoid arthritis, cognitive impairment, obesity, metabolic syndrome."

Chronic obstructive pulmonary disease (COPD)

A systematic study of 14 observational studies (n = 3988) found that periodontal disease "is a significant and independent risk factor of COPD" (Zeng *et al.*, 2012). It is unclear if a causal relationship exists. Subsequent 1- and 2-year pilot RCTs have been conducted with 40 and 60 patients respectively to explore whether periodontal interventions are beneficial in regulating COPD pathogenesis and progression (Kucukcoskun *et al.*, 2013; Zhou *et al.*, 2014). Both studies reported decreased frequency of COPD exacerbations, and the latter also reported improved lung function. As these currently appear to be the only two RCTs assessing whether interceptive periodontal treatment can help COPD patients with their lung function, further larger RCTs are now required to confirm these results.

Rheumatoid arthritis (RA)

A systematic review (Kaur *et al.*, 2013) of 19 studies concluded there is good evidence supporting an association between PD and RA, moderate evidence for C-reactive protein and interleukin-1β, and some evidence for a positive outcome of periodontal treatment on the clinical features of rheumatoid arthritis.

A further systematic review (Tristiu *et al.*, 2015) of 41 studies found that 35 supported this association. They also found that five studies reported significantly increased periodontal attachment loss in periodontal patients with RA as compared to non-RA periodontal patients, ten studies showed an improvement in RA clinical parameters after periodontal treatment, and seven studies obtained the improvement of periodontal clinical parameters during the appropriate RA therapy.

Although this latter systematic review did not perform a meta-analysis, it suggests a bidirectional relationship between periodontal disease and RA. Meta-analyses of high-quality RCTs are required to confirm these findings, but there appears to be good evidence to conclude the presence of an association.

Chronic kidney disease (CKD)

One systematic review (Chambrone *et al.*, 2013) exploring periodontal disease and CKD was identified in the literature since November 2012. It included four cross-sectional, one retrospective, and three interventional studies. The meta-analysis provided good evidence to support the association between periodontitis and CKD, as well as the positive effect of periodontal therapy on eGFR. Estimated glomerular filtration rate (eGFR) is a measure of kidney function. Additional RCTs assessing the effects of non-surgical periodontal therapy in maintenance haemodialysis patients (Yazdi *et al.*, 2013) and end-stage renal disease patients (Fang *et al.*, 2015) have found significantly lowered C-reactive protein levels at 2, 3 and 6 months after periodontal treatment. These indicate a reduction in systemic inflammation, although not necessarily an improvement in the clinical outcome of CKD.

Although promising, further RCTs are needed that 1) include a larger sample size, 2) use clinical endpoints that are directly related to CKD, and 3) use a long timeframe to confirm whether periodontal treatment significantly improves CKD in patients with periodontal disease.

Obstructive sleep apnoea (OSA)

Although not included in the manifesto, a systematic study (Al-Jewair *et al.*, 2015) of six studies (and meta-analysis of four) revealed a statistically significant association between periodontal disease and OSA. Further research is required to confirm this association, and investigate whether there is causal relationship or if interceptive periodontal therapy can help patients with OSA.

Obesity

A systematic review of eight longitudinal and five intervention studies explored obesity and periodontal disease (Keller *et al.*, 2015). Although no meta-analysis was performed, it found that obesity "may be a risk factor for the development of periodontitis or worsening of periodontal measures," but that interventional studies on the influence of obesity on periodontal treatment effects were mixed: two studies found that the response to non-surgical periodontal treatment was better among lean than obese patients, whilst the remaining three found no difference. A further systematic review of 15 studies also found no difference in clinical periodontal parameters between overweight/obese and normal-weight patients (Papageorgiou *et al.*, 2015). Therefore, the evidence from these more recent studies is mixed and does not strongly support an association between periodontal disease and obesity, nor the beneficial effects of NSPT on obesity.

Metabolic syndrome (MetS)

A meta-analysis of 20 case-control, cross-sectional, cohort studies and population survey studies (n = 36,337) found "clear evidence for an association between MetS and periodontitis" (Nibali *et al.*, 2013). This was supported by a further qualitative systematic review of 26 studies (Watanabe and Cho, 2014). Based on these large systematic studies supporting an association, it is recommended that the direction of the association and factors influencing it should be investigated by longitudinal and treatment studies.

Cognitive impairment

No new systematic studies or randomised controlled studies assessing the relationship between periodontal disease and cognitive impairment were identified in the literature since November 2012.

Conclusion

This article has reviewed the research published since the 9th European Workshop in Periodontology in November 2012 to ascertain whether the EFP manifesto remains meritorious in light of recent research. It was found that recent research supports the manifesto regarding diabetes mellitus, cardiovascular disease and adverse pregnancy outcomes, although further high-quality randomised controlled trials are required to support the statement that "*certain populations of pregnant women may benefit from periodontal therapy*".

Furthermore, recent research has now provided good evidence from mostly systematic reviews for an association between periodontal disease and chronic obstructive pulmonary disease, rheumatoid arthritis, chronic kidney disease and metabolic syndrome. This may be sufficient to warrant an update to the manifesto. Causal relationships remain debatable. There is also recent emerging evidence for an association with obstructive sleep apnoea. The recent evidence investigating obesity and periodontal disease is mixed, and no new systematic studies or RCTs were found relating to cognitive impairment.

In addition to an association, several recent studies have investigated the effects of NSPT on the above systemic conditions. Pilot RCTs have found a beneficial effect of NSPT in chronic obstructive pulmonary disease. There is some evidence supporting a beneficial effect of NSPT on the clinical features of rheumatoid arthritis, and several RCTs have reported that NSPT can reduce biomarkers of chronic kidney disease. Additional well-designed RCTs with larger sample sizes are now required to confirm whether interceptive periodontal therapy can improve the clinical features of the above systemic conditions.

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