Periodontal Treatment May Reduce Levels of Systemic Inflammation Markers Associated With Atherosclerotic Profile

SUMMARY

Selection Criteria
Two reviewers independently screened titles and abstracts from three literature databases (Medline-PubMed, the Cochrane Central Register of Controlled Trials [CENTRAL], and EMBASE) for randomized clinical trials and controlled trials that evaluated the effect of periodontal therapy on the atherosclerotic profile that were conducted in the period up to June 2013.

Key Study Factor
The criteria for selecting the trials were as follows: (1) Human subjects with periodontitis; (2) intervention group receiving periodontal treatment (PT) and a non-intervention group receiving no periodontal treatment (NPT); and (3) outcome variables must be clinical CVD parameters and/or markers of atherosclerosis and CVD risk, including markers of systemic inflammation and thrombosis, lipid and glucose metabolism, and vascular function.

Main Outcome Measure
Because none of the trials used a cardiovascular event as the outcome, the reported outcomes of all trials were divided into three groups: (1) markers of systemic inflammation and thrombosis (serum high sensitive C-reactive protein [hsCRP], interleukin-6 [IL-6], tumor necrosis factor alpha [TNF-alpha], and fibrinogen); (2) parameters of lipid and glucose metabolism (triglycerides, total cholesterol, high-density lipoprotein [HDL]- cholesterol, low-density lipoprotein [LDL]- cholesterol, glycated hemoglobin [HbA1c]); and (3) vascular function (systolic and diastolic blood pressure).

The difference in mean values of a given parameter between baseline and end of the observation period was calculated for both the PT and NPT groups. Weighted medium difference (WMD) and 95% confidence interval (CI) values between PT and NPT groups at both baseline and end of study were calculated. The effect of PT on markers of inflammation was analyzed in a series of meta-analyses using a random or fixed effect model. Sub-analyses were performed on hsCRP levels by differentiating trials with otherwise healthy subjects and subjects with co-morbidities, on smoking habits, on average body mass index (BMI), and on trials lasting less than 6 months and those with 6 months’ follow-up or longer.

Main Results
From 3928 screened studies, 20 publications representing 25 trials met the eligibility criteria and 4 were excluded. The included studies enrolled 1748 patients. Seven trials included periodontitis patients in good systemic health and 18 trials included periodontitis patients with co-morbidities, such as coronary heart disease, coronary artery disease, diabetes mellitus, idiopathic edema, metabolic syndrome, impaired glucose tolerance,
hypercholesterolemia, hypertension, chronic kidney disease, and rheumatoid arthritis. When all the trials were included in the analyses, a significant WMD favoring PT was found for hsCRP (−0.50 mg/l, CI −0.78; −0.22, \( p = 0.0005 \)), IL-6 (−0.48 ng/l, CI −0.90; −0.06, \( p = 0.03 \)), TNF-alpha (−0.75 pg/ml, CI −1.34; −0.17, \( p = 0.01 \)), fibrinogen (−0.47 g/l, CI −0.76; −0.17, \( p = 0.002 \)), total cholesterol (−0.11 mmol/l, CI −0.21; −0.01, \( p = 0.02 \)), and HDL-cholesterol (0.04 mmol/l, CI 0.03; 0.06, \( p < 0.00001 \)). Periodontitis patients with co-morbidity benefitted more from PT than otherwise healthy patients with periodontitis. The effect of PT on reducing hsCRP levels was more marked in non-smokers and in trials that included subjects with an average normal weight (BMI < 25).

A significant heterogeneity (\( I^2 > 50\% \)) was found in the meta-analysis that included all the trials and when sub-analyses were performed, except when the analysis included only trials with follow-up of 6 months or greater.

The funnel plot analysis (a graph designed to check the existence of publication bias in systematic reviews and meta-analyses) revealed that scattered PT effects of the majority of biomarkers suggested a publication or other bias in the meta-analysis.

Conclusions

According to the authors of the meta-analysis, PT improves endothelial function and reduces biomarkers of atherosclerotic disease, especially in those already suffering from CVD and/or diabetes.

COMMENTARY AND ANALYSIS

The systematic review and meta-analysis appear to be well conducted. However, the conclusions of the meta-analysis should be considered cautiously. The authors declared that systematic review and meta-analysis were conducted in accordance with the guidelines of the Transparent Reporting of Systematic Reviews and Meta-analysis (PRISMA) statement. The authors did not provide information indicating whether a review protocol and registration number exist, as the PRISMA statement recommended.

Assessment of the methodological quality of the individual studies included in the systematic review is an essential component of meta-analysis. The overall risk of bias for a systematic review is dictated by the risk of bias and the methodological quality of the individual studies. Some concern may arise about the assessment of the risk of bias for the trials included in the meta-analysis. The authors used a criterion proposed by Van der Weijden et al and not the Cochrane risk of bias tool as recommended by the PRISMA statement. The Cochrane risk of bias tool is based on domains for which there is good empirical evidence and strong clinical grounds.

The principal finding of the meta-analysis is that PT improves endothelial function and reduces hsCRP levels in periodontitis patients, especially in those with CVD and/or diabetes. However, hsCRP elevation can be caused by many conditions other than inflammation. Thus, studies designed to determine the effect of PT on hsCRP levels must control all the other known factors associated with hsCRP elevation to prevent a possible confounder effect. It may be possible that among there were trials included in the meta-analysis were some where confounders were not well controlled. For example, the results of one of the studies included in the meta-analysis showed that PT significantly reduced hsCRP. However, BMI, a risk factor for both systemic inflammation and high level of hsCRP, showed a significant decrease in the treatment group and a significant increase in the group that received no treatment between baseline and re-evaluation. Thus, BMI may have acted as a confounder of the PT effect in that study.

It is expected that some variation in the results of the combination of different studies in meta-analysis may occur due to chance alone. However, variability in excess or heterogeneity that may not totally be ascribed to chance may reflect true differences in the results of the trials or in the risk of bias of the trials.

The current meta-analysis combined clinical trials of different sample sizes, included patients with different levels of periodontitis severity and a large variety of co-morbidities, used different types of periodontal treatment, and had markedly different reported outcome measures among the trials. Some trials used only standard periodontal therapy, whereas others combined standard therapy with a systemic antibiotic such as doxycycline, or intensive treatment with adjunctive locally delivered minocycline. It has been shown that these antibiotics have anti-inflammatory effects. Thus, the possible anti-inflammatory effect on the reduction of markers of systemic inflammation of the antibiotic used in some trials cannot be excluded. Overall, it appears that the conclusions of the meta-analysis should be considered cautiously based on several factors.

REFERENCES


**REVIEWER**

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