Published in final edited form as:

J Periodontol. 2016 October ; 87(10): 1113–1116. doi:10.1902/jop.2016.160433.

Periodontal Treatment and Inflammation in Diabetes – Association or Causation?

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Abstract

The causal effect of periodontal treatment on systemic outcomes is unclear because even randomized controlled trials (RCTs) have conflicting results. Two models are proposed to explain the apparently conflicting findings from RCTs evaluating the effect of periodontal treatment on inflammation and systemic outcomes among individuals with type 2 diabetes.

Geisinger and colleagues reported that early non-surgical scaling and root planing versus delayed treatment did not affect inflammatory markers among individuals with type 2 diabetes and HbA1c between 7% and 9% in the Diabetes and Periodontal Therapy Trial (DPTT) (N=475).¹ As inflammation related to periodontal disease is a key mechanism related to periodontal-systemic health connections,² the findings of the DPTT study have particular relevance in that context. It is therefore illustrative to examine these findings in the broader framework of inflammation, periodontal disease, and systemic health.

Periodontal disease has been positively associated with cardiovascular disease (CVD) and its risk markers in a number of observational studies, in which inflammation is hypothesized to play a key mediating role.^{3–5} Obesity also induces an inflammatory state,⁶ and is positively associated with periodontal disease⁷ and CVD.⁸ Taking these facts together, at least two models can explain these associations. These relations are summarized using Directed Acyclic Graphs (DAGs) in Figures 1 and 2. Each arrow in the DAGs represents a causal effect; U represents unmeasured variables with a causal effect. 1) Associational Model: Under this model periodontal disease and CVD share a common cause, such as an inflammatory state, possibly caused by some unknown combination of genetic polymorphisms (shown as U in the DAGs). This model can be tested in a randomized controlled trial (RCT) by randomizing individuals with periodontal disease to receive periodontal treatment or no treatment (discussed later). Under this model the expectation would be that periodontal treatment would affect periodontal disease but not CVD or inflammatory markers. Because obesity impacts inflammation, it is plausible that it modifies that relation (Figure 1). 2) Causal Model: Under this model periodontal disease causes inflammation, which then causes CVD. In an RCT testing the effect of periodontal treatment the expectation would be that periodontal treatment would affect periodontal disease,

inflammatory markers, and CVD (Figure 2). It is plausible that obesity, by impacting inflammation, could modify the relation between periodontal treatment and CVD.

No randomized controlled trial has been conducted to evaluate the effect of periodontal treatment on CVD incidence, but the effect of periodontal treatment on CVD risk markers has been studied in a few small sized RCTs.^{9, 10} D'Aiuto and colleagues summarized these results in a meta-analysis and reported that periodontal treatment reduced systemic inflammation and improved endothelial function,¹⁰ which are well-established risk factors of CVD. However, there was considerable variation in the studies with respect to participant characteristics, co-morbid conditions, severity of periodontal disease, and type of periodontal treatment.

Intensive periodontal treatment improved periodontal status and endothelial function, reduced systemic inflammation, and CVD risk factors at six months,¹¹ and serum lipids at two months¹² among healthy individuals with severe periodontal disease in a well-conducted RCT. The participants of this trial did not have any chronic conditions or current infections; they had a mean age of 48 years, and mean BMI of 27.3 kg/m². The findings of these studies,^{11, 12} and of the meta-analyses of RCTs,^{9, 10} are consistent with the Causal Model described above. The evidence suggests that periodontal treatment has a beneficial effect on inflammation and its downstream consequences such as CVD risk factors in at least some people.

However, these findings do not refute the Associational Model. It is possible that a group of people have a combination of polymorphisms predisposing them to have increased inflammation (U in the DAGs), raising their risk of periodontal disease and CVD. The Associational and Causal Models in combination could explain disease processes in such individuals. In this situation the effect of periodontal treatment on CVD would likely be attenuated because inflammation would be caused by both the unknown factor and periodontal disease.

Obesity can potentially impact the effect of periodontal treatment on CVD risk because it induces systemic inflammation.¹³ The normal inflammatory response differs for obese and non-obese populations; the inflammatory trigger in the obese population is metabolic, caused by an excess of nutrients.¹³ Dietary excess and obesity are associated with the accumulation of lipid into adipocytes and the expansion of the adipose tissue, where hypertrophic adipocytes may produce pro-inflammatory cytokines such as tumor necrosis factor- α (TNF- α), interleukin (IL-6), resistin, MCP-1, and PAI-1.¹⁴ Both TNF- α and IL-6 have been shown to impair intracellular insulin signaling, which may lead to insulin resistance.^{15, 16} Obesity likely raises the risk of diabetes through this mechanism. Obesity is also positively associated with periodontal disease in cross-sectional and prospective studies.¹⁷

Type 2 diabetes and decreased insulin sensitivity are associated with increased inflammation^{18, 19} and periodontal disease. Hyperglycemia resulting from type 2 diabetes and decreased insulin sensitivity result in the production of advanced glycation end-products (AGE) in various tissues including the periodontium, which trigger inflammatory cytokine

production, thus predisposing for inflammatory conditions such as periodontitis.²⁰ It is therefore plausible that type 2 diabetes and decreased insulin sensitivity impact the effect of periodontal treatment but this is understudied.

The effect of obesity on periodontal treatment outcomes has not been studied extensively.^{21, 22} Meta-analyses evaluating this question reported that periodontal treatment effects on oral health outcomes did not differ among obese and non-obese groups.^{21, 22} However, periodontal treatment had a greater beneficial effect on inflammatory markers, and glycemic profile in people with diabetes, among obese compared with non-obese individuals, even when there was no effect on oral health outcomes.²² These findings suggest that obesity may modify the effect of periodontal treatment on systemic inflammation.

In the DCTT study markers of systemic inflammation or HbA1c levels were not affected by periodontal treatment,²³ but inflammatory markers were positively correlated with fasting glucose and fasting insulin.¹ This is in contrast to the findings of Sun and colleagues who found that periodontal treatment reduced HbA1c, inflammatory markers, and CVD risk markers in an RCT conducted among individuals with type 2 diabetes and HbA1c between 7.5% and 9.5%.²⁴ There were important key differences in the DCTT study and the study by Sun and colleagues that could potentially explain the differing results. The participants of the study by Sun and colleagues had a BMI of approximately 24 kg/m² versus 34 kg/m² in the DCTT population.^{23, 24} Additionally the intervention in the DCTT study was restricted to non-surgical scaling and root planing,²³ while in the study by Sun and colleagues antibiotic and surgical therapy were used when indicated.²⁴ The DCTT study participants had more extensive periodontal disease than those in the study conducted by Sun and colleagues. These key factors need to be considered in generalizing the findings from the RCTs.

The findings of the DCTT study are consistent with the Associational Model (U in Figures 1 and 2 could represent diabetes in addition to pro-inflammatory polymorphisms).²⁵ However, the totality of evidence does not refute the Causal Model. The findings of the RCTs conducted by Sun and colleagues,²⁴ and D'Aiuto and colleagues,¹² support the Causal Model among people with²⁴ and without diabetes¹² respectively. The populations of these two RCTs had higher level of periodontal disease at baseline, received more intensive treatment, and had lower levels of obesity than the DCTT population. A strength of the DCTT study is that it was a well conducted, multicenter RCT. The findings from the DCTT study, therefore, are important. However, care must be taken to generalize the findings to obese individuals with HbA1c between 7% and 9%, with moderate prevalence of periodontal disease at baseline, who receive non-surgical scaling and root planing.

Acknowledgments

Funding:

Anwar T. Merchant R03 DE022785

Ronald J. Prinz T32 GM081740

Neither of the authors reported a conflict of interest.

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Figure 1.
Inflammatory state common cause of periodontal disease and CVD

Figure 2.
Periodontal disease affects inflammation which causes CVD