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The Multi-Center Randomized Controlled Trial (RCT) Published by the Journal of the American Medical Association (JAMA) on the Effect of Periodontal Therapy on Glycated Hemoglobin (HbA1c) Has Fundamental Problems

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ARTICLE TITLE AND BIBLIOGRAPHIC INFORMATION

The effect of nonsurgical periodontal therapy on hemoglobin A1c levels in persons with type 2 diabetes and chronic periodontitis: a randomized clinical trial.
Engebretson SP, Hyman LG, Michalowicz BS, Schoenfeld ER, Gelato MC, Hou W, et al (16 authors). *JAMA 2013;310(23):2523-32.*

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PURPOSE/QUESTION

Does non-surgical periodontal treatment reduce levels of HbA_{1c} in persons with type 2 diabetes and moderate to advanced chronic periodontitis?

SOURCE OF FUNDING

US Government – National Institute of Dental and Craniofacial Research, National Institutes of Health: Cooperative agreements ($15.4M): 1) UO1 DE018902 (Dr. Engebretson: $11.1M) and 2) U01 DE018886 (Dr. Hyman: $4.3M)

TYPE OF STUDY/DESIGN

Multi-center RCT. Trial Registration: clinicaltrials.gov identifier: NCT00997178.

LEVEL OF EVIDENCE

Level 2: Limited-quality, patient-oriented evidence

STRENGTH OF RECOMMENDATION GRADE

Not applicable

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The Multi-Center Randomized Controlled Trial (RCT) Published by the *Journal of the American Medical Association (JAMA)* on the Effect of Periodontal Therapy on Glycated Hemoglobin (HbA_{1c}) Has Fundamental Problems

SUMMARY

Subject

Participants had type 2 diabetes, were on stable medication regimens, had HbA_{1c} levels between 7% and <9%, retained at least 16 natural teeth, and had untreated chronic periodontitis. A total of 514 participants were enrolled between November 2009 and March 2012 from diabetes and dental clinics and communities affiliated with five participating academic medical centers. They were randomized with half ($n = 257$) allocated to a treatment group and the other half ($n = 257$) to a control group.

Key Exposure/Study Factor

The exposure was non-surgical periodontal treatment comprising scaling and root planing, oral hygiene instruction, and oral rinsing with chlorhexidine provided to the treatment group at baseline. Supportive periodontal therapy was also provided at 3 and 6 months. The control group received no treatment for the 6-month duration of the study.

Main Outcome Measure

The primary outcome measure was "the difference in change in HbA_{1c} level from baseline between the two groups at 6 months." Secondary outcomes included changes in periodontal probing depth (PPD), clinical attachment loss, bleeding on probing (BOP), gingival index, fasting glucose level, and Homeostasis Model Assessment (HOMA2) score.

Main Results

The authors report that enrollment into their Diabetes and Periodontal Therapy Trial (DPTT) was terminated early due to futility. At 6 months, mean HbA_{1c} levels in the periodontal therapy group increased 0.17 (±1.0)%, compared with 0.11 (±1.0)% in the control group, with no significant difference between groups based on a linear regression model adjusting for clinical site (mean difference, −0.05% [95% CI: −0.23% to 0.12%]; $p = 0.55$). Periodontal measures improved in the treatment group compared with the control group at 6 months, with adjusted between-group differences of 0.28 mm (95% CI: 0.18–0.37) for PPD; 0.25 mm (95% CI: 0.14–0.36) for clinical attachment loss; 13.1% (95% CI: 8.1%–18.1%) for BOP; and 0.27 (95% CI: 0.17–0.37) for gingival index ($p < 0.001$ for all).

Conclusions

The authors conclude: *"Nonsurgical periodontal therapy did not improve glycemic control in patients with type 2 diabetes and moderate to advanced chronic*

TABLE 1. Effect of non-surgical periodontal treatment on glycemic control in people with type 2 diabetes: meta-analyses published as of July 19, 2014.

Meta-analysis	# studies	# RCTs	Pooled # subjects	HbA_{1c} change	95% CI	*p*-value
Janket et al (2005)[2]	5	1	268	−0.66%[a]	−2.2; 0.9	ns
Darre et al (2008)[3]	9	9	485	−0.46%[c]	−0.82; −0.11	0.01
Teeuw et al (2010)[4]	5	3[b]	180	−0.40%[c]	−0.77; −0.04	0.03
Simpson et al (2010)[5] Cochrane Review	3	3	244	−0.40%	−0.78; −0.01	0.04
Sgolastra et al (2013)[6]	5	5	315	−0.65%	−0.88; −0.43	<0.05
Engebretson and Kocher (2013)[7]	9	9	775	−0.36%	−0.54; −0.19	<0.0001
Liew et al (2013)[8]	6	6	422	−0.41%	−0.73; −0.09	0.013

CI: confidence interval; HbA_{1c}: glycated hemoglobin; ns: non-significant; RCT: randomized controlled trial.
[a]Weighted.
[b]Remaining two non-RCT studies are clinical controlled trials.
[c]Standardized mean difference.

periodontitis. These findings do not support the use of nonsurgical periodontal treatment in patients with diabetes for the purpose of lowering levels of HbA_{1c}."

COMMENTARY AND ANALYSIS

When developing clinical recommendations and guidelines, it is important to consider the highest levels of evidence, which are typically derived from high-quality systematic reviews of high-quality RCTs that are sufficiently powered and well conducted to provide definitive evidence. However, individual large multi-center trials are often perceived by the busy reader to independently deliver definitive answers to the research question posed. Hence, the potential impact of the RCT discussed in this review[1] is significant because it will be considered to provide a higher level of evidence than previous systematic reviews of prior smaller studies. The majority of available studies have reported improvements in glycemic control (measured as HbA_{1c}) in people with type 2 diabetes after non-surgical periodontal therapy. HbA_{1c} measures long-term blood sugar levels over the lifespan of the red blood cell, weighted to the last 2 to 3 months. All seven systematic reviews and meta-analyses published conclude that such therapy does lead to improvements in glycemic control. They calculated similar magnitudes of HbA_{1c} improvement, ranging from 0.36 to 0.65 percentage points (Table 1). This reported impact is similar to that expected from adding a second oral antidiabetes medication to metformin and is therefore of clinical significance in the management of diabetes.

The US multi-center RCT under review[1,9] was anticipated to be a "definitive" study, unlike its smaller predecessors. Given the increasing global epidemic of type 2 diabetes and the need for novel approaches to manage and/or prevent diabetes and its complications, this multi-center study conducted in partnership with the funding agency, the US National Institute of Dental and Craniofacial Research (NIDCR), is very important because its findings are likely to influence the current scientific knowledge base, as well as evidence-based policy-making and clinical practice in many countries.

The basic goal underlying these intervention studies in persons with type 2 diabetes is to reduce the local microbial burden to a level sufficient to lead to clinically meaningful improvements in periodontal health. If successful, the systemic exposure and subsequent inflammatory burden would be reduced, which would in turn decrease long-term blood glucose levels, measured as HbA_{1c}. However, clinically meaningful improvement in periodontal health that is consistent with the standard of care reported in the world literature is an essential pre-requisite for a valid outcome. Otherwise, no effect on HbA_{1c} could reasonably be expected.

Concern 1: No Significant Effect of Periodontal Treatment Would Be Expected Because Baseline HbA_{1c} Levels Were Already Close to the Goal for Good Glycemic Control

Hyperglycemia defines diabetes, and its control is fundamental to diabetes care.[10] The goal for type 2 diabetes management is to attain and maintain an HbA_{1c} level of less than 7.0%, but lower (less than 6.5%) or higher (less than 8%) levels are acceptable for specific patient groups.[10] The HbA_{1c} value of 7.0% was selected as the lower limit for enrollment in the study, corresponding to average plasma glucose levels of 154 mg/dL (8.6 mmol/L). The upper limit was set at less than 9.0% (~212 mg/dL or 11.8 mmol/L). Nevertheless, 3.5% (9) of the test participants had HbA_{1c} levels of 9% or greater and 4.7% (12 subjects) had HbA_{1c} less than 7%, both in violation of the protocol's eligibility criteria. The baseline mean HbA_{1c} level was 7.84% in the treatment group (calculated

TABLE 2. Improvement in periodontal measures following non-surgical periodontal treatment: the reviewed RCT (n = 240; eTable 2[a])[1] *versus* literature-based expectations.

			Reported decrease	Expected decrease (non-diabetes)	
Periodontal parameter	**Baseline**[1]	**After treatment**[1]	**Engebretson (2013)**[1]	**Cobb (1996)**[12] **& (2002)**[13]	**Van der Weijden and Timmerman (2002)**[14]
Periodontal probing depth (PPD) [mean (mm)]	3.3 mm	2.9 mm	0.4 mm	• 1.29 mm (PPD 4–6 mm)[12] • 1.50 mm (PPD = 6 mm)[13] • 2.16 mm (PPD ≥ 7 mm)[12]	• 1.18 mm • 1.23 mm (mild periodontitis) • 2.26 mm (severe periodontitis)
Bleeding on probing (BOP) [proportion (%)]	60.6%	41.6%	19.0%	~45% (PPD 4.0–6.5 mm)[13]	n/a
Gingival index (GI)	1.4	1.0	0.4	1.0[13]	n/a

n/a: not available.
[a]Baseline figures differ slightly from Table 1 in the body of the report, which uses n = 257.[1]

from eTable 1) and 7.77% among controls (eTable 1). At baseline, 60.3% of the test group and 63.8% of the control group already had HbA_{1c} levels below 8.0%, leaving less than 40% with HbA_{1c} levels at 8.0% or greater. The potential for any intervention to improve glycemic control depends upon the baseline HbA_{1c} level: the higher the level, the greater the potential for improvement, and the lower the HbA_{1c} level, the more unlikely a further decrease becomes. Therefore the HbA_{1c} interval selected for inclusion in this study renders additional benefit from any adjunctive therapy less likely. With a mean baseline value of 7.8% and an upper limit for eligibility of less than 9%, the study subjects were already close to their target for glycemic control at enrollment.

Concern 2: No Conclusion Can Be Drawn Regarding Any Effect on Glycemic Control Because Periodontal Treatment Failed to Reach the Accepted Standard of Care

The reviewed study suffers from a second significant deficiency, namely the poor outcomes reported for the administered periodontal therapy. The clinical improvements in periodontal health are far below the expected standard of care and effectively negate the appropriateness of any conclusions based on this intervention. Fundamental to the appropriate interpretation of results from any periodontal intervention study is that the reductions in PPD, percent of sites with BOP (%BOP), plaque scores, and gains in clinical attachment are consistent with the world literature. When outcomes are below the expected standard of care, then the likelihood of incorrect conclusions being drawn is high.[11]

It is widely recognized that quoting statistically significant improvements in clinical outcomes that are based on the means or medians of hundreds of measures per patient is inappropriate unless the changes reported are of clinical significance and, most importantly, consistent with the literature. In Table 2, we have summarized the outcomes attained after non-surgical periodontal treatment in this study and compared them to the expected results in subjects without diabetes from systematic reviews. Table 3 displays the periodontal health status at baseline and at the end of the study. The periodontal treatment in this RCT resulted in poor levels of clinical improvement and left considerable inflammation (BOP) and very high dental plaque (infection) levels, which are highly likely to have precluded any reduction of HbA_{1c} in the test group and most likely explain the reported (but not statistically significant) increase in % HbA_{1c}.

It is unfortunate that these essential results are displayed exclusively in the online supplementary overview (eTable 2) and that the authors did not benchmark their results against the accepted literature.[12–14] A key question that should have been discussed is, "Why did the periodontal status of the individuals in the treatment arm not improve sufficiently and in a manner consistent with the periodontal outcomes in prior studies?" Because of the poor clinical improvement in periodontal conditions, the biological question of whether reducing periodontal infection/inflammation in a clinically signi-

TABLE 3. Periodontal health status in the treatment group ($n = 240$) at the beginning and at the end of the study (eTable 2[a]).[1]

Periodontal parameter	Baseline	End of study
Periodontal probing depth (PPD)		
PPD ≥4 mm [mean # sites/person]	50.9	30.6
PPD ≥5 mm [mean # sites/person]	28.8	15.7
PPD ≥4 mm [proportion sites (%)]	33.7%	20.1%
PPD ≥5 mm [proportion sites (%)]	19.0%	10.2%
Clinical attachment loss (CAL)		
CAL ≥4 mm [mean # sites/person]	59.7	44.0
CAL ≥5 mm [mean # sites/person]	35.7	23.6
CAL ≥4 mm [proportion sites (%)]	40.1%	29.8%
CAL ≥5 mm [proportion sites (%)]	6.6%	4.3%
Bleeding on probing (BOP)		
[proportion sites (%)]	60.6%	41.6%
Plaque score		
[% sites/person]	86.7%	72.1%

Study eligibility criterion: Moderate to advanced chronic periodontitis, defined as clinical attachment loss and probing depth of at least 5 mm in 2 or more quadrants.
[a]Baseline figures differ slightly from Table 1 in the body of the report[1] which uses n = 257.

ficant manner results in improved glycemic control cannot be answered by the results of this study.

The manner in which the authors portray the effect of the periodontal treatment implies that the treatment was successful, when in fact, it was not. The authors claimed: "*Using linear regression models, all periodontal clinical parameters improved significantly at 3 months and were sustained at 6 months in the treatment group but not in the control group.*" This statement directly leads the reader to believe that the periodontal treatment was successful. However, statistically significant improvements in periodontal outcome parameters are meaningless unless they have clinical relevance and are consistent with the standard of care and attainable results reported in the literature. These results are neither. At the end of the study, each person still had on average 30.6 sites (20.1%) with PPD 4 mm or greater, and half of those (15.7 sites or 10.2%) were 5 mm or deeper; 41.6% of all sites bled on probing; and 72.1% had plaque (Table 3).

Based on their periodontal status, it seems that a considerable proportion of the participants still had a level of periodontitis at the completion of the study that would render them eligible for enrollment into the study for periodontal therapy, based on their current level of periodontitis and the study's own inclusion criteria. The authors noted: "*improvements in plaque and bleeding scores were only modest and indicate that changing oral hygiene habits remains a challenge.*" However, previous intervention studies did manage to overcome this challenge and greatly improve periodontal health. Why could this large multi-center study not achieve sufficient plaque control consistent with the literature? The notion suggested by the authors that "*it is possible that periodontal inflammation and infection do not influence glycemic control. Indeed, the results of this trial indicate that glycemic control worsened, although not significantly, 6 months after study therapy*" assumes that periodontal treatment has been clinically effective. Because it was not, this statement is not supported by the study results.

Concern 3: Pronounced Obesity Would Mask Any Decrease in Inflammatory Response Caused by Successful Periodontal Treatment

A third significant problem is that the chronic, low-grade inflammatory state elicited by the prominent obesity in the treatment group (mean BMI 34.7(±7.5) kg/m^2) would have masked any anti-inflammatory effect of successful periodontal treatment. It is the decrease in inflammation due to periodontal infection that leads to the decrease in blood glucose levels, and thus we would not expect to be able to measure any significant decrease in glycated hemoglobin levels, even after successful periodontal treatment in such obese subjects. The Hiroshima Study demonstrated that HbA_{1c} levels improve by resolution of the periodontal infection-related systemic inflammation, but only in subjects with initially elevated levels of the acute-phase inflammatory marker C-reactive protein, measured with high sensitivity (hsCRP).[15] In fact, the initial hsCRP level is a significantly important independent variable influencing HbA_{1c} reduction rates, and the greatest reduction in HbA_{1c} level is experienced by the group with the highest hsCRP reduction following periodontal treatment.[15] Importantly, the subjects in the Hiroshima study were non-obese but had type 2 diabetes. An earlier US study called Atherosclerosis Risk in Communities (ARIC) already reported that, when the BMI of the subjects was in the 20s range, there was a predicted 2-fold difference in hsCRP between severe and no/mild periodontitis groups, but the difference decreased with increasing BMI and became negligible when BMIs reached 35 kg/m^2.[16] Furthermore, the Periodontitis and Vascular Events (PAVE) multi-centered trial demonstrated that systemic inflammation persisted among obese individuals following scaling and root planing.[17] In the current study, although the effect of periodontal therapy on the reduction in the systemic inflammatory burden was not reported, it is possible that most of the subjects were resistant to the

elimination of periodontal disease-related systemic inflammation due to the overwhelming influence of their obesity-related systemic inflammatory load.

Conclusion

Overall, this study actually raises more questions than it answers, which is an important outcome. Regrettably, it is not the definitive study for determining the effects of successful periodontal therapy on glycemic control in people with diabetes that it was anticipated to be.

There is no logical basis for expecting periodontal treatment that is not successful in controlling the periodontal infection and reducing inflammation to clinically acceptable levels to have any positive impact on glycated hemoglobin levels, in particular where obesity levels are high and glycemic control is close to target at enrollment. Consequently, the results of this large RCT are inconclusive and the results of this investigation do not permit meaningful statements to be made regarding whether or not *successful* non-surgical periodontal treatment contributes to glycemic control by decreasing HbA_{1c} levels in people with type 2 diabetes. Unfortunately, this study failed to achieve periodontal treatment outcomes comparable to those obtained by several existing studies among people with diabetes in several countries, as well as by studies enrolling persons without known diabetes.

We call on the periodontal community to urgently analyze why large multi-center RCTs appear incapable of effectively treating periodontitis to accepted standards of care. We also wonder why such costly studies do not specify in their protocols that periodontal treatment should be performed to defined clinical endpoints, as suggested in 2008 by Armitage[18] and in 2010 by Offenbacher and Beck.[19] Such adaptive treatment protocols would eliminate incomplete or inadequate therapeutic outcomes and their potential to mislead readers into believing that any treatment provided as "per protocol" would automatically lead to clinically significant improvements in periodontal health, which subsequently would affect the outcome studied.

Consequences

We are very concerned that, despite these inconclusive results, the outcomes of this RCT are quoted as "definitive." Despite the lack of clinically significant improvements in periodontal health, and because the authors claim there were significant improvements – without using the qualifier "statistically significant only" – the study is quoted by the press as demonstrating ("proving") that there is no effect of periodontal treatment on glycated hemoglobin. Additionally, this study did not address the degree of obesity of test subjects at all, and the title of the study may mislead the public into believing that the results are applicable to all cases of type 2 diabetes. This is an unsafe and incorrect conclusion and dangerously misleading to the profession, the public, and other stakeholders, such as policy makers, health plan managers, and insurance companies.

Given the inconclusive nature of these data, we recommend that the existing body of evidence in which meta-analyses consistently conclude that successful periodontal therapy appears to improve glycemic control, should instruct us until results from future studies are reported. We urge all interested parties to refrain from using these study results as a basis for future scientific texts, new research projects, guidelines, policies, and advice regarding the incorporation of necessary periodontal treatment in diabetes management.

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