Periodontal Medicine – Periodontal Hubris?

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Outline

- The Perio-Systemic link
- When did politics hijack perio?
- Some facts about diabetes mellitus
- The “Engebretson scandal”
- Which lessons are to be learnt?

FLOSS OR DIE!*

*Robert J Genco, AAP Annual Meeting 1996, New Orleans

https://scholarlyperio.wordpress.com/2012/11/14/motivation-and-instruction-in-oral-hygiene/

~~FLOSS~~ OR DIE!

Sälzer et al., EFP Workshop 2014, Segovia, Spain

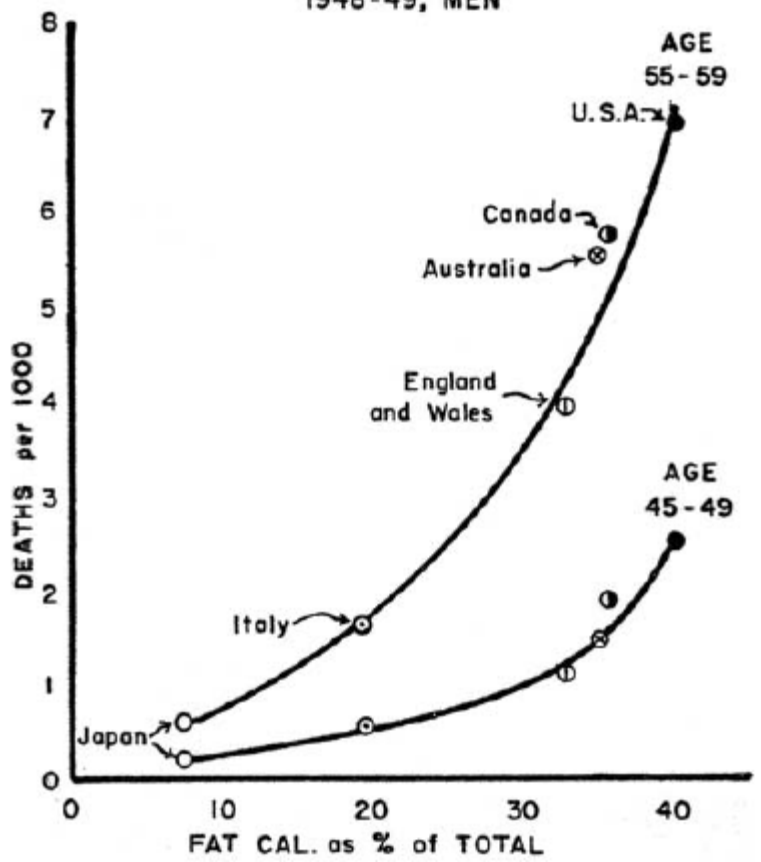
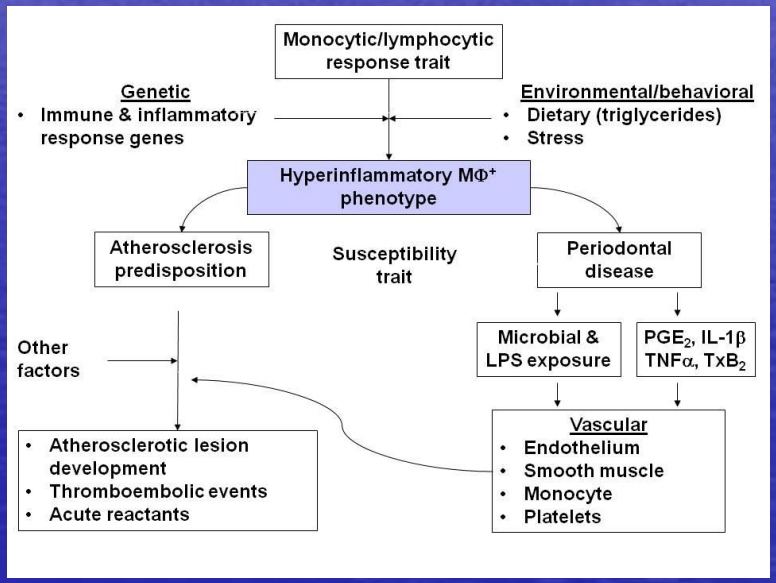


Figure 1. Mortality from degenerative heart disease according to dietary fat (fat calories as a percentage of total calories) among men aged 45–49 years (lower curve) and men aged 55–59 years (upper curve), 1948–1949. Results were calculated from national food balance data for 1949 supplied by the Nutrition Division of the Food and Agriculture Organization of the United Nations. (Reproduced with permission from the *Journal of Mount Sinai Hospital* (8).)

Keys A. Atherosclerosis: a problem in newer public health. *J Mt Sinai Hosp* 1953; **20**: 118-139

- Offenbacher and Beck (2014)

  "The model [Beck et al. 1996] is now more than 15 years old, and *we would modify it only* by adding specific details, such as the hyperinflammatory trait likely being attributable to genetic differences in the innate immune response."



A Sneaking Suspicion

- Dr. Hujoel's and coworkers' analysis (*JAMA* 2000; 284: 1406-1410, published on 20 September 2000) of NHANES I Follow-up data
  - Follow-ups 1971-1975, 1982-1984, 1987, and 1992
  - Population-based prospective cohort study
  - Risk assessment for coronary heart disease in patients with/without periodontitis or gingivitis

- Primary variable: first event of CHD
  - Death due to CHD
  - Hospitalization due to CHD
  - Coronary revascularization

- 8032 dentate adults, 25-74 years of age, no CHD
  - 1859 with periodontitis (Russell's PI* 4+, ie. pockets with attachment loss)
  - 2421 with gingivitis
  - 3752 with healthy periodontal conditions (RPI lower than 0.05)

**Russell's Periodontal Index* (PI):
1 or 2: localized or circumferential gingivitis, resp.
6: initial periodontitis without impairment of function
8: advanced periodontitis with functional impairment

Unadjusted

Event CHD, HR (95% CI)		Death due to CHD, HR (95% CI)	
Periodontitis	Gingivitis	Periodontitis	Gingivitis
2.66 (2.34-3.03)	1.20 (1.05-1.39)	3.09 (2.50-3.81)	1.20 (0.94-1.52)

Adjusted for

- Demographic factors and socioeconomic status

Event CHD, HR (95% CI)		Death due to CHD, HR (95% CI)	
Periodontitis	Gingivitis	Periodontitis	Gingivitis
1.24 (1.08-1.43)	1.02 (0.88-1.18)	1.28 (1.02-1.61)	0.99 (0.77-1.28)

Adjusted for

- Demographic factors and socioeconomic status
- Risk factors for CHD (I): Smoking, blood pressure, serum cholesterol, diabetes mellitus

Event CHD, HR (95% CI)		Death due to CHD, HR (95% CI)	
Periodontitis	Gingivitis	Periodontitis	Gingivitis
1.14 (0.98-1.33)	1.03 (0.88-1.21)	1.19 (0.91-1.55)	1.09 (0.82-1.45)

Adjusted for

- Demographic factors and socioeconomic status
- Risk factors for CHD (I): Smoking, blood pressure, serum cholesterol, diabetes mellitus
- Risk factors for CHD (II): Height, weight, alcohol consumption, physical activity, nervous breakdown

Event CHD, HR (95% CI)		Death due to CHD, HR (95% CI)	
Periodontitis	Gingivitis	Periodontitis	Gingivitis
1.14 (0.96-1.36)	1.05 (0.88-1.25)	1.21 (0.90-1.62)	1.17 (0.86-1.59)

- No dose-effect relationship
  - No relationship with the number of teeth at outset
  - No association with extent and severity of periodontitis/gingivitis

- Dr. Hujoel's conclusions
  - "The results of this study do not provide convincing evidence that periodontitis and gingivitis are associated with CHD. Gingivitis was not associated with CHD. Periodontitis was associated with a non-significant increased risk for CHD

- "While this study did provide convincing evidence regarding absence of a moderate-to large association between periodontitis and CHD, a small causal association could not be ruled out."

- On 2 January 2001, a *Letter to the Editor* by Genco, Trevisan, Wu & Beck was published in *JAMA*

Letters | January 3, 2001

Periodontal Disease and Risk of Coronary Heart Disease

Robert J. Genco, DDS, PhD; Maurizio Trevisan, MD; Tiejian Wu, MD, PhD; James D. Beck, PhD

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JAMA. 2001;285(1):40-41. doi:10.1001/jama.285.1.39.

To the Editor: Dr Hujoel and colleagues[1] analyzed the First National Health and Nutrition Examination Survey (NHANES) I to assess the relationship between periodontal disease (PD) and coronary heart disease (CHD) and concluded that their study provided "convincing evidence regarding the absence of a moderate-to-large association . . ." between these 2 diseases. We believe that their conclusion about the lack of an association between PD and CHD is premature and unsubstantiated.

Several limitations in the NHANES I data may limit the apparent association between PD and CHD. First, the measure of periodontal disease in NHANES I is subjective and less accurate than objective measures like those used in NHANES III. Hence, misclassification of PD is likely. A longitudinal study[2] that used an objective measure of PD showed a strong association between PD and CHD in men.

A further limitation is that PD was measured at baseline only, and changes in periodontal status during the 20-year follow-up were not taken into account. Some of those who had no PD at baseline would be expected to develop the disease later because the prevalence of PD increases markedly with age. Also, the extent of PD in those who already had PD may have been reduced by treatment. Because there are no available data that measure changes over time in periodontal status, the association between PD and CHD might be biased toward the null hypothesis. This issue becomes more problematic as the length of follow-up increases.

Finally, many of the pathophysiologic mechanisms that have been hypothesized as links between PD and CHD relate to the triggering of clinical coronary events.[3] These triggering factors are most significant when they occur close in time to the clinical outcomes; therefore, longitudinal studies may not represent the best study design to investigate these associations.

Stephen J. Lurie, MD, PhD **Senior Editor**

REFERENCES

[2] Beck et al. 1996

- Hujoel et al. had responded and provided the first meta-analysis of 3 at that time available large prospective studies (including their own)
  - More than 74,000 subjects, follow-up between 6 and 16.1 yr with more than 6800 CHD events
  - The relative risk for CHD events was 1.07 (95% CI 0.96; 1.19) in subjects with periodontitis

- In their critique of the paper by Hujoel et al., Genco et al. did not mention that their group had just published their own paper on periodontal disease and cerebrovascular accidents (CVA, cerebrovascular event) which exploited the same data set, *NHANES I* follow-up

- The paper by Wu et al. had appeared on 9 October 2000 in *Arch Int Med* (now merged with *JAMA*), 19 days after that by Hujoel et al. (2000)

ORIGINAL INVESTIGATION

Periodontal Disease and Risk of Cerebrovascular Disease

The First National Health and Nutrition Examination Survey and Its Follow-up Study

Tiejian Wu, MD, PhD; Maurizio Trevisan, MD, MS; Robert J. Genco, DDS, PhD; Joan P. Dorn, PhD; Karen L. Falkner, PhD; Christopher T. Sempos, PhD

Background: Periodontal disease has been found to be a potential risk factor for coronary heart disease. However, its association with cerebrovascular accidents (CVAs) is much less studied.

Methods: This study examines the association between periodontal disease and CVA. The study cohort comprises 9962 adults aged 25 to 74 years who participated in the First National Health and Nutrition Examination Survey and its follow-up study. Baseline periodontal status was categorized into (1) no periodontal disease, (2) gingivitis, (3) periodontitis, and (4) edentulousness. All CVAs (*International Classification of Diseases, Ninth Revision [ICD-9]*, codes 430-438) were ascertained by hospital records for nonfatal events and death certificates for fatal events. The first CVA, nonfatal or fatal, was used to define incidence. Relative risks were estimated by hazard ratios from the Cox proportional hazard model with adjustment for several demographic variables and well-established cardiovascular risk factors. Weights were used to generate risk estimates.

Results: Periodontitis is a significant risk factor for total CVA and, in particular, nonhemorrhagic stroke (*ICD-9*, 433-434 and 436-438). Compared with no periodontal disease, the relative risks (95% confidence intervals) for incident nonhemorrhagic stroke were 1.24 (0.74-2.08) for gingivitis, 2.11 (1.30-3.42) for periodontitis, and 1.41 (0.96-2.06) for edentulousness. For total CVA, the results were 1.02 (0.70-1.48) for gingivitis, 1.66 (1.15-2.39) for periodontitis, and 1.23 (0.91-1.66) for edentulousness. Increased relative risks for total CVA and nonhemorrhagic stroke associated with periodontitis were also seen in white men, white women, and African Americans. Similar results were found for fatal CVA.

Conclusion: Periodontal disease is an important risk factor for total CVA and, in particular, nonhemorrhagic stroke.

Arch Intern Med. 2000;160:2749-2755

From the Departments of Social and Preventive Medicine (Drs Wu, Trevisan, Dorn, and Falkner) and Oral Biology (Dr Genco), State University of New York at Buffalo; and the Office of Research on Minority Health, National Institutes of Health, Bethesda, Md (Dr Sempos).

THE ROLE of infection in the etiology of atherosclerosis and the development of cardiovascular disease has recently received considerable attention.[1] Periodontal disease, one of the most common human infections, has been found to be a risk factor for coronary heart disease in a number of studies.[2-9] However, the association between periodontal disease and the risk for cerebrovascular accident (CVA) is much less studied. The purpose of this study was to examine the association between baseline periodontal status and subsequent incidence and mortality of CVA in a representative sample of US adults.

RESULTS

Characteristics of the study cohort are given in **Table 1**. Among the unweighted study sample of 9962 participants, 62.0% were women; 16.8%, African Americans; and 36.7%, current smokers at baseline. The mean age for the whole sample was 48.31 years; mean BMI, 25.7 kg/m^2; and mean serum total cholesterol level, 5.68 mmol/L (219.77 mg/dL). The baseline weighted prevalence rates for periodontal disease were gingivitis, 25.3%; periodontitis, 16.8%; and edentulousness, 16.8%.

For the study cohort as a whole, total person-years of follow-up were 158 294.05 for incident and 161 065.13 for fatal CVAs (**Table 2**). During the follow-up period, there were 803 incident CVAs, including 596 nonhemorrhagic strokes, 91 hemorrhagic strokes, and 116 transient cerebral ischemic events (*ICD-9* 435). Fatal CVAs totaled 282, including 230 nonhemorrhagic and 52 hemorrhagic strokes. The incidence rates per

- While the material was the same (subjects, crude periodontal examination, long follow-up), case definitions differed somewhat

	Hujoel et al. (2000)	Wu et al. (2000)
Periodontitis	1859	1800
Gingivitis	2421	2346
Healthy	3752	3634
Edentulous		2082

- Wu et al. report that,

  "[c]ompared with no periodontal disease, the relative risks (95% confidence intervals) for incident nonhemorrhagic stroke were 1.24 (0.74-2.08) for gingivitis, 2.11 (1.30-3.42) for periodontitis, and 1.41 (0.96-2.06) for edentulousness. For total CVA, the results were 1.02 (0.70-1.48) for gingivitis, 1.66 (1.14-2.39) for periodontitis, and 1.23 (0.91-1.66) for edentulousness."

- They conclude that,

  "[t]his prospective study suggests that periodontitis is significantly associated with risk of developing CVA and, in particular, nonhemorrhagic stroke."

- The models had been adjusted for NHANES I design features and baseline information on sex, race, age, education, poverty index, diabetes status, hypertension, smoking status, average alcohol use, BMI, and serum cholesterol

- So, if and when a moderate association of periodontitis with cardio- or cerebrovascular disease can be found, it seems to be irrelevant whether the study has design or methodological problems (NHANES I and its epidemiologic follow-up certainly has)

- However, if the analysis yields no association, it must be due to problems with design and methods

A Common Pattern

- Similarly agitated disputes could later be noted when a large intervention study by Michalowicz et al. (2006) did not yield a significant effect on pregnancy outcomes (which had later to be confirmed by Offenbacher et al. (2009) in a twice as large intervention trial)

- In 2012, Lockhart et al., in an exhaustive systematic review published in *Circulation*, concluded that there is currently no evidence[1] that periodontal interventions prevent atherosclerotic vascular disease or modify its outcomes

[1] Based on PAVE, the only multicenter pilot study which has examined the influence of periodontal treatment on the secondary prevention of cardiac events

- On 18 April 2012, the day when the SR went online, Lockhart said in an interview with *HealthDay*,

  "So far, there is no conclusive evidence [of a cause-effect relationship between periodontitis and AVD]. If cause and effect is someday proven, it will probably be fairly minor."

http://podcasts.jwatch.org/index.php/tag/peter-b-lockhart/

- Then president of the AAP, Pamela McClain partly disagreed,

  "The academy [sic] agrees that science doesn't support a causal relationship between periodontal disease as a direct cause of cardiovascular disease.

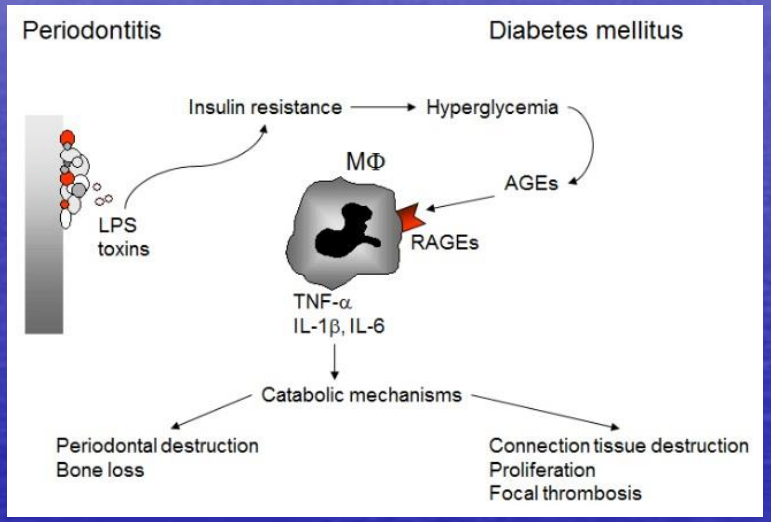
  "It's hard to predict [the size of the possible causal relationship]. We may find a stronger link."

- EFP and AAP decided to organize the joint workshop of 2012, apparently to fix independently conducted systematic reviews and unwelcome results of large intervention studies by creating new systematic reviews, in particular also of observational studies, which do not provide evidence for causality

- Apart from supersaturation (which ultimately leads to ignorance among the medical profession rather than respect for our specialty), the usually complicated messages were boiled down into an easy to digest "Manifesto" and youtube video which may mislead the obvious target, the busy practitioner

Diabetes mellitus and Periodontitis

- Observational studies have suggested a bi-directional relationship
  - Prevalence, extent and severity of periodontitis are all greater in diabetics (both types I & II)
  - Poor diabetic control is associated with poor periodontal health

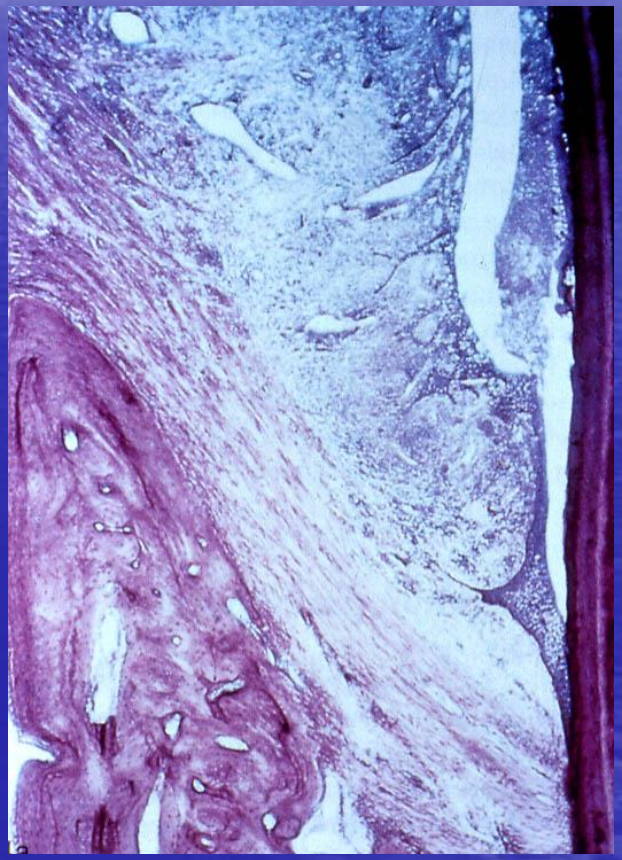


Poor oral hygiene as risk factor in relation to other risk factors for periodontitis

Risk factor	Preventable?	Relative risk	Prevalence (%)	Attributable risk (%)
Poor oral hygiene	yes	1.9[a]	25[a]	18
Smoking	yes	2.5-6[b]	18[d]	21-47
Diabetes mellitus	No? (controllable)	2.8-3.4[c]	8[e]	13-16

[a] Haffajee et al., 1991
[b] AAP, 1999
[c] AAP, 2000
[d] WHO, USA 2009
[e] CDC, 2011

- Inflamed periodontal tissue may act as an endocrine organ
  - Proinflammatory mediators (such as TNF-α, IL-1, IL-6), acute phase proteins and oxidative stress molecules are excessively released in inflamed periodontal tissue,
  - may interfere with lipid metabolism and act as insulin antagonists



- Periodontal infection adversely affects glycemic control in diabetes
- Diabetics with poorer periodontal health have more diabetes-related complications, i.e. microvascular (retino-, nephro-, neuropathy including foot ulcers) and macrovascular diseases
- Periodontitis patients may even be at higher risk for developing type 2 diabetes

- Does periodontal therapy has an effect on diabetic control (HbA1c) in patients with type 2 DM?
  - Between 2010 and 2013, 5 SRs were published by Simpson et al. (2010), Teeuw et al. (2010), Liew et al. (2013), Sgolastra et al. (2013) and Engebretson & Kocher (2013)
  - One RCT was considered in all five SRs, 1 in four, 3 in three, and 4 in two SRs.

- Three months after perio tx, HbA1c levels were significantly reduced
  - Simpson et al. 2010 -0.40% (95% CI -0.78; -0.01%)
  - Teeuw et al. 2010 -0.40% (-0.77; -0.04%)
  - Liew et al. 2013 -0.41% (-0.73; -0.09%)
  - Sgolastra et al. 2013 -0.65% (-0.88; -0.43%)
  - Engebretson & Kocher 2013 -0.36% (-0.73; -0.09%)

"A major limitation […] is that no single randomized clinical trial reported here [9 are reported] would be defined as a phase 3 (pivotal study), and hence, validation of these findings in a large clinical trial is needed. Results from one such study may be expected by early 2013 (ClinicalTrials.gov: NCT00997178)." Engebretson & Kocher 2013

The "Engebretson Scandal"

- On 18 December 2013, results of the announced "pivotal" multicenter Diabetes and Periodontal Therapy Trial (DPTT) by Engebretson et al. were published in *JAMA*
  - >500 patients with T2DM and periodontitis had been randomized
  - Periodontal intervention: at least 160 min subgingival scaling, 0.12 CHX rinses bid for 2 weeks; and additional motivation and 1 h scaling at 3 and 6 months
  - Control subjects received oral hygiene instructions at baseline, after 3 and 6 months. Periodontal tx was postponed for 6 months
  - Primary outcome: Difference in change of HbA1c after 6 months

Original Investigation

The Effect of Nonsurgical Periodontal Therapy on Hemoglobin A_{1c} Levels in Persons With Type 2 Diabetes and Chronic Periodontitis

A Randomized Clinical Trial

Steven P. Engebretson, DMD, MS, MS; Leslie G. Hyman, PhD; Bryan S. Michalowicz, DDS, MS; Elinor R. Schoenfeld, PhD; Marie C. Gelato, MD, PhD; Wei Hou, PhD; Elizabeth R. Seaquist, MD; Michael S. Reddy, DMD, DMSc; Cora E. Lewis, MD, MSPH; Thomas W. Oates, DMD, PhD; Devjit Tripathy, MD; James A. Katancik, DDS, PhD; Philip R. Orlander, MD; David W. Paquette, DMD, MPH, DMSc; Naomi Q. Hanson, MS; Michael Y. Tsai, PhD

Supplemental content at jama.com

IMPORTANCE Chronic periodontitis, a destructive inflammatory disorder of the supporting structures of the teeth, is prevalent in patients with diabetes. Limited evidence suggests that periodontal therapy may improve glycemic control

OBJECTIVE To determine if nonsurgical per hemoglobin (HbA_{1c}) in persons with type 2 periodontitis.

DESIGN, SETTING, AND PARTICIPANTS The D 6-month, single-masked, multicenter, rand diabetes, were taking stable doses of medi than 9%, and untreated chronic periodonti enrolled between November 2009 and Ma communities affiliated with 5 academic me

INTERVENTIONS The treatment group (n = chlorhexidine oral rinse at baseline and sup The control group (n = 257) received no tre

MAIN OUTCOMES AND MEASURES Differenc groups at 6 months. Secondary outcomes i attachment loss, bleeding on probing, ging Model Assessment (HOMA2) score.

RESULTS Enrollment was stopped early because of futility. At 6 months, mean HbA_{1c} levels in the periodontal therapy group increased 0.17% (SD, 1.0), compared with 0.11% (SD, 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%]; $P = .55$). 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 to 0.37) for probing depth, 0.25 mm (95% CI, 0.14 to 0.36) for clinical attachment loss, 13.1% (95% CI, 8.1% to 18.1%) for bleeding on probing, and 0.27 (95% CI, 0.17 to 0.37) for gingival index ($P < .001$ for all).

CONCLUSIONS AND RELEVANCE Nonsurgical periodontal therapy did not improve glycemic control in patients with type 2 diabetes and moderate to advanced chronic 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}.

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT00997178

JAMA. 2013;310(23):2523-2532. doi:10.1001/jama.2013.282431

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Sample size was estimated assuming 0.6% HbA1c difference after 6 months (SD 2.0%), α=0.05 and 1-β =0.90. Due to expected attrition, the planned sample size was 600 patients.

Table 1. Baseline Participant Characteristics

Characteristic	Treatment (n = 257)	Control (n = 257)
Age, mean (SD), y	56.7 (10.5)	57.9 (9.6)
Women, No. (%)	114 (44.4)	123 (47.9)
Race/ethnicity, No. (%)		
African American/black	76 (29.6)	70 (27.2)
White	140 (54.5)	140 (54.5)
Hispanic	81 (31.5)	85 (33.1)
Other (eg, Native American, Asian)	41 (16.0)	47 (18.3)
Smoking history, No. (%)		
Never	129 (50.2)	144 (56.0)
Former	89 (34.6)	86 (33.5)
Current	39 (15.2)	27 (10.5)
Diabetes factors, mean (SD)		
HbA_{1c}, No. (%)		
<7.0	12 (4.7)	10 (3.9)
≥7.0 to <8.0	143 (55.6)	154 (59.9)
≥8.0 to <9.0	93 (36.2)	86 (33.5)
≥9.0 to <10	9 (3.5)	7 (2.7)
Fasting glucose, median (IQR), mg/dL	150 (125-174)	147 (122-172)
Duration of diabetes, mean (SD), y	12.3 (8.2)	11.3 (8.4)
Fasting insulin, excluding insulin use, median (IQR), pmol/L[a]	95 (61-138)	88 (61-133)
HOMA2 insulin sensitivity, excluding insulin use, median (IQR), %S[a,b]	50.1 (34.1-77.0)	53.9 (38.0-79.0)
HOMA2 β-cell function, excluding insulin use, median (IQR), %β[a,b]	55.5 (34.1-76.2)	52.0 (36.7-76.0)
Hypoglycemic medications, No. (%)		
No diabetes medications	7 (3)	4 (2)
Oral agents only	117 (46)	127 (49)
Insulin only	40 (16)	40 (16)
Combination of medications	93 (37)	86 (33)
Anthropometrics, mean (SD)		
Weight, kg	99.5 (24.3)	97.5 (21.7)
BMI[c]	34.7 (7.5)	34.2 (6.7)
Blood pressure, mean (SD), mm Hg[d]		
Systolic	133.1 (20.7)	135.1 (20.4)

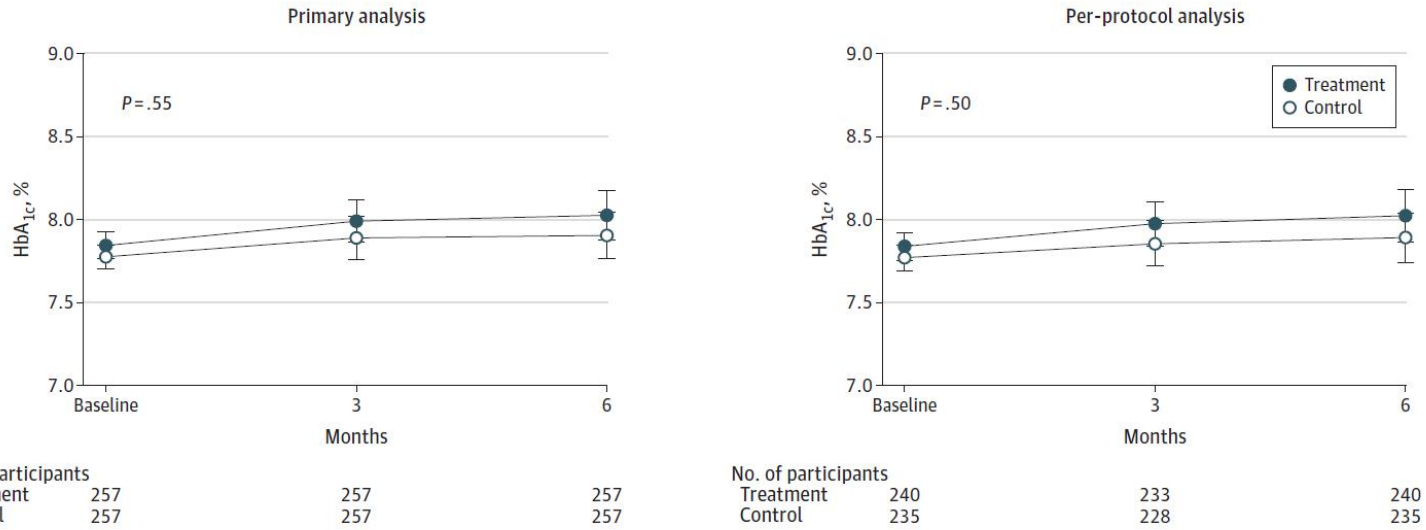
Anthropometrics, mean (SD)		
Weight, kg	99.5 (24.3)	97.5 (21.7)
BMI[c]	34.7 (7.5)	34.2 (6.7)
Blood pressure, mean (SD), mm Hg[d]		
Systolic	133.1 (20.7)	135.1 (20.4)
Diastolic	78.8 (12.3)	78.8 (10.9)
Cardiovascular disease factors		
Lipids, excluding statin use, median (IQR), mg/dL[e]		
Total cholesterol	189 (162-211)	185 (161-212)
LDL-C	113 (92-135)	108 (94-130)
HDL-C	46 (38-53)	41 (37-48)
Triglycerides[d]	117 (89-169)	126 (93-231)
Creatinine, median (IQR), mg/dL	0.81 (0.68-1.0)	0.81 (0.67-0.98)
Periodontal measurements, mean (SD)[f]		
No. of teeth, count/person	25.4 (3.7)	24.7 (3.6)
Probing depth, mm	3.3 (0.6)	3.3 (0.7)
Mean sites/person, by probing depth category		
≥4	51.3 (27.3)	49.2 (27.5)
≥5	28.9 (21.6)	28.0 (22.3)
≥7	3.5 (6.3)	3.5 (8.2)
% sites/person, by probing depth category		
≥4	33.8 (17.6)	33.6 (18.7)
≥5	19.0 (14.2)	19.3 (15.6)
≥7	2.3 (4.2)	2.5 (6.1)

(continued)

Table 1. Baseline Participant Characteristics (continued)

Characteristic	Treatment (n = 257)	Control (n = 257)
Clinical attachment loss, mm	3.5 (0.8)	3.5 (0.9)
Mean sites/person, by clinical attachment loss category		
≥4	60.1 (30.7)	57.5 (30.7)
≥5	35.9 (25.9)	33.6 (26.0)
≥7	6.6 (9.7)	6.9 (11.9)
% sites/person, by clinical attachment loss category		
≥4	40.3 (21.1)	39.5 (21.3)
≥5	24.3 (18.2)	23.4 (18.6)
≥7	4.7 (7.3)	5.0 (9.2)
Bleeding on probing, % sites/person	61.2 (24.1)	59.6 (26.0)
Gingival index, mean sites/person	1.4 (0.4)	1.4 (0.4)
Plaque score, % sites/person	86.7 (17.9)	84.5 (20.8)
Self-reported overall health, No. (%)		
Excellent-very good	50 (19.5)	59 (23.0)
Good	123 (47.9)	138 (53.7)
Fair-poor	84 (32.6)	60 (23.3)
Other medical history, No. (%)		
Angina	21 (8.2)	11 (4.3)
Myocardial infarction	22 (8.6)	21 (8.2)
Stroke	12 (4.7)	12 (4.7)
Hypertension	180 (70.0)	184 (71.6)
Kidney disease	14 (5.4)	12 (4.7)
Other medication use, No. (%)		
Blood pressure	202 (78.6)	210 (81.7)
Cholesterol	172 (66.9)	170 (66.1)

Figure 2. Glycated Hemoglobin (HbA_{1c}) Levels at Baseline and Follow-up



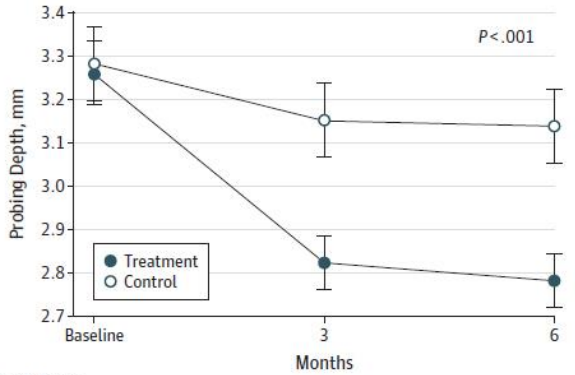
Error bars indicate ±2 SEs. *P* values comparing 6-month change in HbA_{1c} levels between the 2 treatment groups were based on *t* tests from linear regression models, with 6-month change in HbA_{1c} level as a dependent variable and treatment group and clinical site as covariates.

- Only one day later, on 19 December, then AAP President Stuart Froum responded in a press release

  "It is important to note that the nonsurgical therapy employed in this study did not eradicate periodontal disease, which may be why researchers did not see an effect on glycemic control

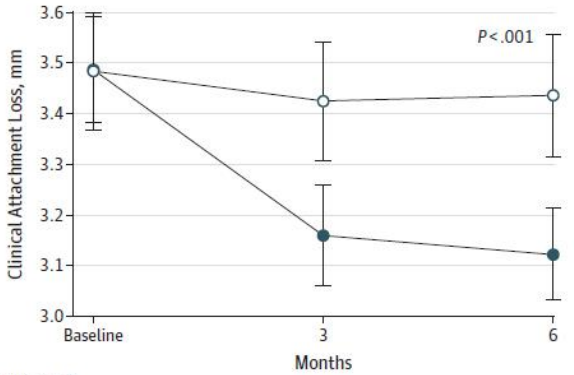
"A major indicator of periodontal disease – bleeding on probing – decreased only 19 percent [sic], suggesting that the nonsurgical therapy was not successful in controling moderate to advanced periodontal disease. The failure to eliminate periodontal disease may be why glycemic control was not impacted"

Figure 3. Periodontal Measurements at Baseline and Follow-up (Per-Protocol Analysis)



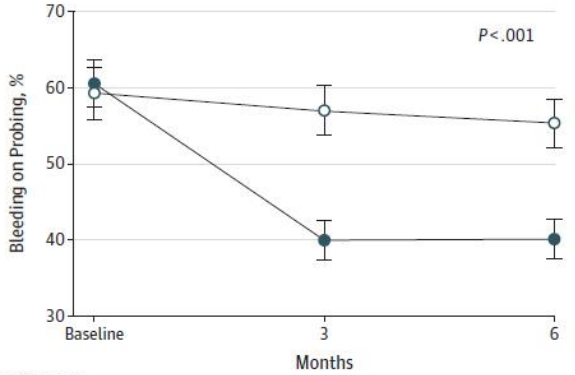
No. of participants

Treatment	240	233	240
Control	235	227	233



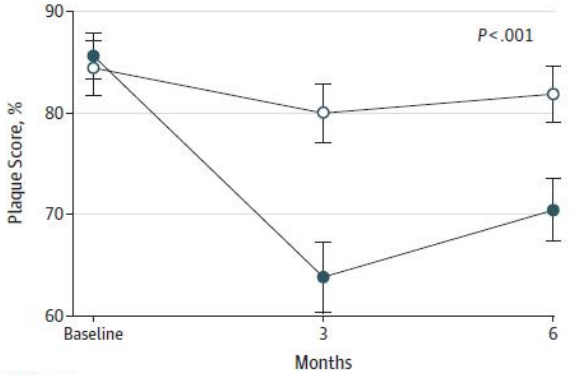
No. of participants

Treatment	240	233	240
Control	235	227	233



No. of participants

Treatment	240	232	240
Control	235	227	232



No. of participants

Treatment	240	233	240
Control	235	227	233

Error bars indicate ±2 SEs. *P* values comparing 6-month changes in periodontal outcomes between the 2 treatment groups were based on *t* tests from linear regression models, with 6-month periodontal change as a dependent variable and treatment group and clinical site as covariates.

- On 14 May 2014, three *Letters to the Editor* were published in *JAMA*. One letter by Chapple, Borgnakke and Genco identified problems as regards
  - Failure to deliver the expected standard of care
  - Almost normal HbA1c levels at the outset
- Anwar T. Merchant, a biostatistician at the University of South Carolina, pointed to the very high BMI of participants (mean 34) in the study by Engebretson et al.

- In their response to these *Letters*, Drs. Engebretson, Hyman and Michalowicz point to subgroup analyses, some of them provided in the Supplementary material of their article
  - There was no indication that change in HbA1c was associated with the magnitude of the periodontal treatment response
  - There was no difference in the treatment effect in groups stratified by baseline HbA1c values (p=0.83)
  - Likewise, subgroup analyses of different BMI cut points found no effect of periodontal therapy on glycemic control ($p \geq 0.1$)

eTable 1. 6-month Change in HbA_{1c} by Levels of Response to Periodontal Therapy in the Treatment Group and the Control Group (Per Protocol[a])

	Baseline HbA_{1c}		6-month change in HbA_{1c}[c] (Δ=Follow up- Baseline)		
Level of Periodontal Response to Treatment (Tertiles[b])	**Treatment mean (SD)**	**Control mean (SD)**	**Treatment Mean[a] *(95% C.I.)***	**Control Mean[a] *(95% C.I.)***	***P value*[d]**
Probing Depth (mm, mean sites/person[e])					
Most (n=80)	7.79 (0.65)		0.20		***0.43***
(Reduction > 0.64 mm)			*(-0.07, 0.47)*		
Moderate (n=80)	7.83 (0.63)	7.77 (0.60)	0.21	0.09	***0.39***
(Reduction 0.24 to 0.64 mm)			*(-0.04, 0.46)*	(-0.08, 0.26)	
Least (n=80)	7.89 (0.68)		0.05		***0.31***
(Reduction < 0.24 mm)			*(-0.20, 0.31)*		
Clinical Attachment Loss (mm, mean sites/person[e])					
Most (n=80)	7.79 (0.65)		0.19		***0.46***
(Reduction > 0.58 mm)			*(-0.07, 0.45)*		
Moderate (n=78)	7.88 (0.69)	7.77 (0.60)	0.24	0.09	***0.29***
(Reduction 0.15 to 0.58 mm)			*(-0.02, 0.50)*	(-0.08, 0.26)	
Least (n=82)	7.84 (0.62)		0.04		***0.74***
(Reduction < 0.15 mm)			*(-0.21, 0.30)*		
Bleeding on Probing (% sites/person[e])					
Most (n=79)	7.82 (0.65)		0.20		***0.42***
(Reduction > 28% sites)			*(-0.06, 0.47)*		
Moderate (n=79)	7.95 (0.72)	7.77 (0.60)	0.18	0.09	***0.51***
(Reduction 11% to 28% sites)			*(-0.08, 0.44)*	(-0.08, 0.26)	
Least (n=82)	7.76 (0.59)		0.08		***0.98***
(Reduction < 11% sites)			*(-0.17, 0.34)*		

[a] Per protocol: Analyses were based on all participants with HbA_{1c} data at the 6-month visit (n=240 in the Treatment group, n=235 in the Control Group).

[b] Based on the distributions of changes in periodontal measurements (Reduction= 6-month minus Baseline) in the Treatment Group.

[c] A positive change in HbA_1c indicates worsening over time.

- At the same time, a much more serious attempt to discredit the unwelcome results of Engebretson et al. was already underway
  - The first version of a polemic in *J Evid Based Dent Pract,* went online just 33 days after Engebretson's paper, but was withdrawn
  - Reasons were not given

Article in Press

WITHDRAWN: The randomized controlled trial (RCT) published by the *Journal of the American Medical Association (JAMA)* on the impact of periodontal therapy on glycated hemoglobin (HbA1c) has fundamental flaws

Wenche S. Borgnakke, Phoebus N. Madianos, Iain L.C. Chapple*[1], Shinya Murakami[6], Robert J. Genco, Panos N. Papapanou, Gary Armitage, Philip M. Preshaw, P. Mark Bartold[2], Amin ur Rahman, Francesco D'Aiuto, Mariano Sanz[7], Paul I. Eke†, Jorgen Slots[8], William V. Giannobile[3], Maurizio S. Tonetti[9], Ken S. Kornman[4], Thomas E. Van Dyke, Niklaus P. Lang[5]

* contributed equally

† The findings and conclusion in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and prevention.

[1] Associate Editor, Journal of Clinical Periodontology; Editorial Board Member, Periodontology 2000

[2] Editor in Chief, Australian Dental Journal; Associate Editor, Journal of Periodontal Research; Editorial Board Member, Periodontology 2000

[3] Editor in Chief, Journal of Dental Research

[4] Editor in Chief, Journal of Periodontology

[5] Editor in Chief, Journal of Clinical Oral Implants Research

[6] Editor in Chief, Journal of Periodontal Research

[7] Associate Editor, Journal of Clinical Periodontology

[8] Editor in Chief, Periodontology 2000

[9] Editor in Chief, Journal of Clinical Periodontology

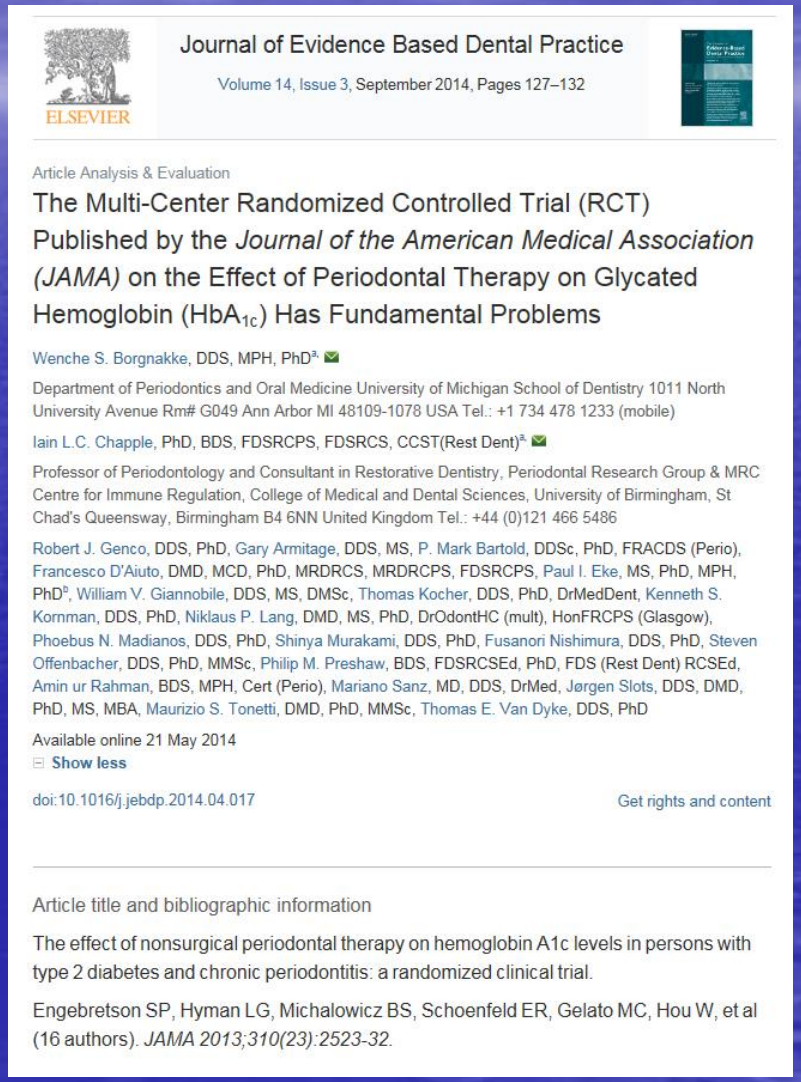
DOI: http://dx.doi.org/10.1016/j.jebdp.2014.01.011

Article Info

Publication History

Published Online: January 22, 2014

- Borgnakke's final version went online on 21 May 2014
  - A slightly moderated title speaks of "fundamental problems" rather than flaws
  - Among the 21 authors, Panos Papapanou was no longer listed
  - Thomas Kocher and Fusanori Nishimura (co-author of the Hiroshima study) had joined



Journal of Evidence Based Dental Practice
Volume 14, Issue 3, September 2014, Pages 127–132

Article Analysis & Evaluation

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

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Available online 21 May 2014

Show less

doi:10.1016/j.jebdp.2014.04.017

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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.*

- Concerns regarding the "problems"

  (1) Low baseline HbA1c levels with a lower limit of 7.0%* were included (mean 7.84 and 7.77% in test and control groups) that are close to good glycemic control and thus unlikely to further improve

*In fact, 4.7% of screened test subjects had at baseline less than 7% HbA1c

SR by Engebretson & Kocher 2013: 9 small, single center trials

	BL % HbA1c
Kiran 2005	T: 7.31; C: 7.00
Jones 2007	T: 9.9; C: 9.3
Yun 2007	T: 8.26; C: 8.22
Singh 2008	T: 7.9 & 8.3; C: 8.1
Katagiri 2009	T: 7.2; C: 7.0
Koromantzos 2011	T: 7.87; C: 7.59
Sun 2011	T: 7.1; C: 7.1
Chen 2012	T: 7.31 & 7.29; C: 7.25
Moeinthagavi 2012	T: 8.15; 8.72

WMD after 3 months: -0.36% (-0.54; -0.19)

(2) Poor outcomes reported for the administered periodontal therapy

- 0.37 mm mean CAL gain*
- 0.48 mm mean PD reduction
- 19% points BOP reduction
- 14.6% points plaque reduction

*after 6 months

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]

Note that Cobb (2002) does not provide any point estimate of meta-analyses as suggested above. In particular, the alleged GI reduction of 1.0 was not based on data

Note that the 1.18 mm PD reduction in van der Weijden & Timmerman (2002) refers to a weighted mean in ≥5 mm deep pockets as derived from 10 controlled studies. The figures 1.23 and 2.26 mm PD reduction for mild and severe periodontitis, respectively, cannot be found in the paper

ADA CE Program ARTICLE 2

Systematic review and meta-analysis on the nonsurgical treatment of chronic periodontitis by mea[illegible] planing with or witho[illegible]

Christopher J. Smiley, DDS; Sharon L. Tracy, PhD; Elliot Abt, DDS, MSc, MS; Bryan S. Michalowicz, DDS; Mike T. John, Dr med dent, PhD, MPH; John Gunsolley, DDS, MS; Charles M. Cobb, DDS, PhD; Jeffrey Rossmann, DDS, MS; Stephen K. Harrel, DDS; Jane L. Forrest, EdD; Philippe P. Hujoel, DDS, MSD, MS, PhD; Kirk W. Noraian, DDS, MS, MBA; Henry Greenwell, DMD, MSD; Julie Frantsve-Hawley, PhD; Cameron Estrich, MPH; Nicholas Hanson, MPH

ABSTRA

Backgroun gical treatme root planing
Methods. Council on S Embase for adjuncts with months in d assessed indi conducted m precision an Egger tests t The authors methods to a
Results. Th without the t (subantimicr (chlorhexidi spheres), an diode laser, a erbium laser
Conclusion certainty, the improvemen resulted in a over SRP alo beneficial wi doxycycline, namic therap benefits of th clinical reco
Key Words MEDLINE; JADA 2015:

methods to assess the overall level of certainty in the evidence.

Results. The panel included 72 articles on the effectiveness of SRP with or without the following: systemic antimicrobials, a systemic host modulator (subantimicrobial-dose doxycycline), locally delivered antimicrobials (chlorhexidine chips, doxycycline hyclate gel, and minocycline microspheres), and a variety of nonsurgical lasers (photodynamic therapy with a diode laser, a diode laser, neodymium:yttrium-aluminum-garnet lasers, and erbium lasers).

Conclusions and Practical Implications. With a moderate level of certainty, the panel found approximately a 0.5-millimeter average improvement in CAL with SRP. Combinations of SRP with assorted adjuncts resulted in a range of average CAL improvements between 0.2 and 0.6 mm over SRP alone. The panel judged the following 4 adjunctive therapies as beneficial with a moderate level of certainty: systemic subantimicrobial-dose doxycycline, systemic antimicrobials, chlorhexidine chips, and photodynamic therapy with a diode laser. There was a low level of certainty in the benefits of the other included adjunctive therapies. The panel provides clinical recommendations in the associated clinical practice guideline.

Key Words. Antibiotics; chlorhexidine; evidence-based dentistry; lasers; MEDLINE; minocycline; periodontitis; root planing.

JADA 2015:146(7):508-524

http://dx.doi.org/10.1016/j.adaj.2015.01.028

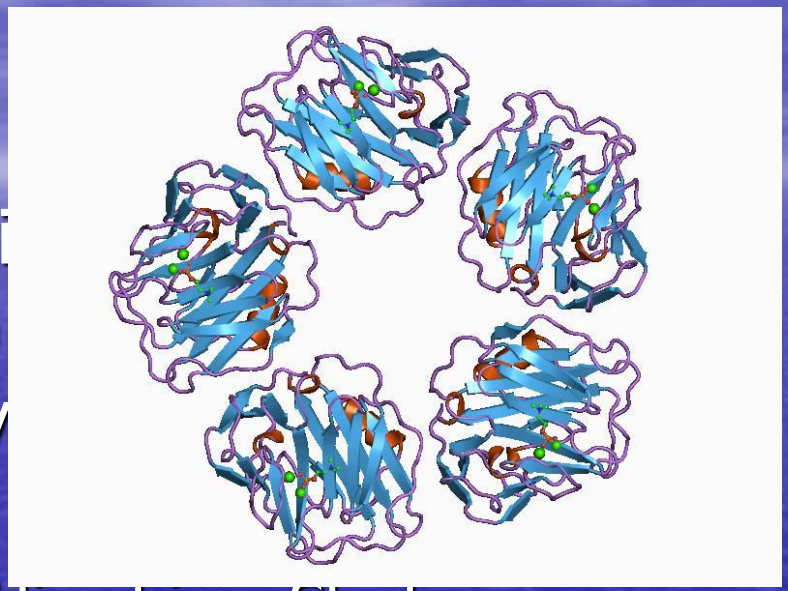
Chronic periodontitis is a prevalent condition, affecting 47.2% of the adult US population aged 30 years or older.[1] Chronic periodontitis results in the loss of tooth-supporting connective tissue and alveolar bone and, if untreated, is a major cause of tooth loss in adults.[2] According to the Centers for Disease Control and Prevention and American Academy of Periodontology case definitions,[3] the prevalences of moderate and severe periodontitis are estimated as 30.0% and 8.5%, respectively, among US adults.[4]

Supplemental material is available online.

This article has an accompanying online continuing education activity available at: http://jada.ada.org/ce/home.

The most recent SR on non-surgical periodontal therapy by Smiley et al. (2015)

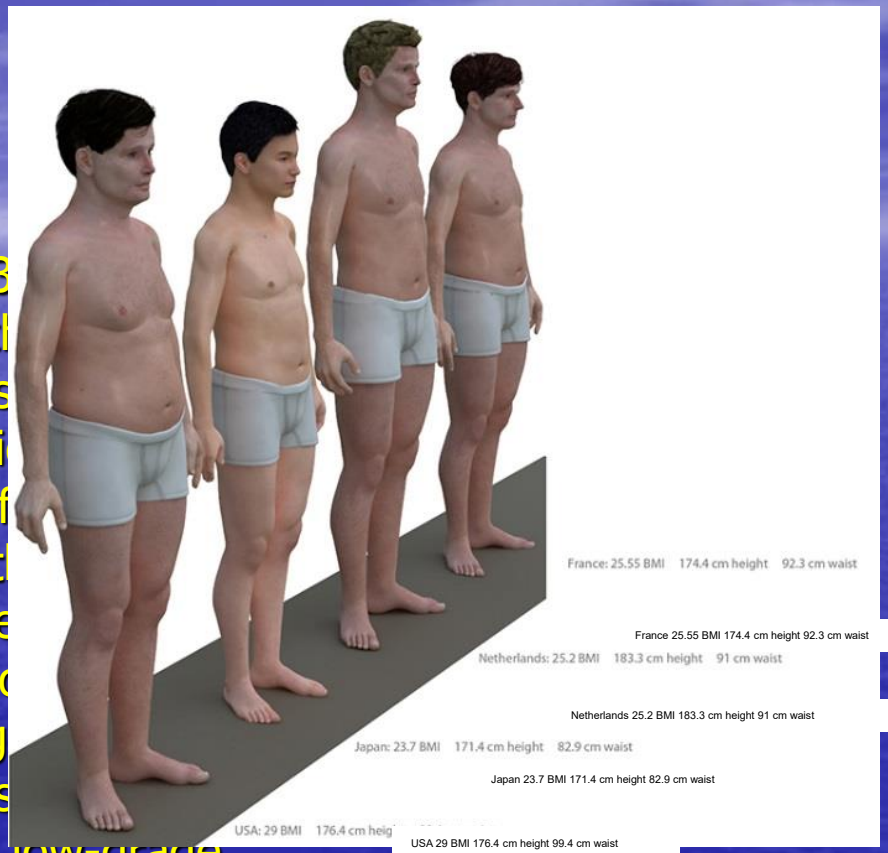
(3) Obesity (72% of parti
and mean BMI was >34)
decrease in inflammatory
successful periodontal tx



- Borgnakke et al., "The Hiroshima Study demonstrated that HbA1c 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]

From the Hiroshima Study (2013): “A multiple comparison by ANOVA revealed that only group A [subjects with high hsCRP >500ng/ml treated with topical tetracycline-HCl ointment once a week for 4 weeks combined with conventional mechanical debridement] showed a significant reduction in HbA1c over time ($P<0.001$).”

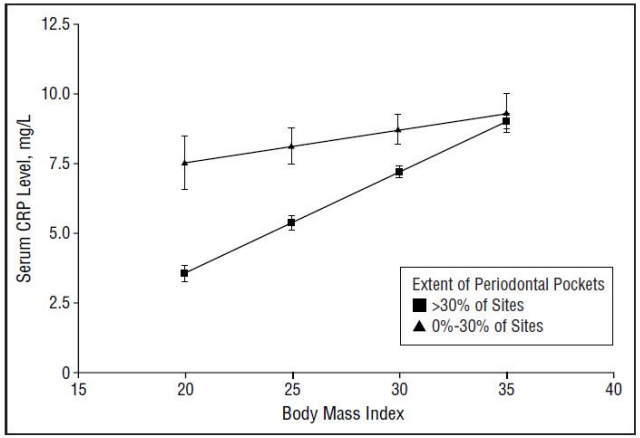
From the Hiroshima Study (2013
diabetic subjects are unique in th
divided into two categories, thos
resistance and those with insuffi
secretion [6,7]. In about 40% of
type 2 diabetic subjects, the pat
the disease is primarily associate
resistance, as most newly diagno
are not obese, having an averag
24.0 kg/m^2 [6,7]. Therefore, in s
severe periodontitis that evokes low-grade
inflammation periodontal inflammation may have
a greater influence in Japanese than Caucasian
subjects with diabetes, as periodontal
inflammation is not masked by obesity-induced
inflammation in less obese Japanese subjects."



- Borgnakke et al., "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]

*In ARIC, extent, not severity of periodontitis was considered

From the ARIC Study (2003): "The **Figure** depicts the interaction between BMI and periodontal disease. Based on the regression model, when BMI equaled 20, there was a predicted 2-fold difference in mean CRP levels between high and low [sic] periodontal pocket groups (7.5 vs 3.6 mg/L)*, but the difference decreased with increasing BMI and was negligible when BMI equaled 35 (9.0 vs 9.3 mg/L)."



Predicted mean serum C-reactive protein (CRP) values by body mass index (calculated as weight in kilograms divided by the square of height in meters) and periodontal status in the dental component of the Atherosclerosis Risk in Communities study, 1996-1998. The CRP values are least squares means from the analysis of covariance model (Table 4), which also controls for age, sex, diabetes mellitus, cigarette use, and nonsteroidal anti-inflammatory drug use. Extent of periodontal pockets is the percentage of periodontal sites with probing pocket depth of 4 mm or more. Error bars represent SE.

*Iapparently, i the graph symbols for isolated (0-30%) and frequent pockets (>30%) had erroneously been exchanged

- Borgnakke et al., “Furthermore, the Periodontitis and Vascular Events (PAVE) multi-centered trial demonstrated that systemic inflammation persisted among obese individuals following scaling and root planing.[17]”

From the PAVE Study (2009): "Usi
intent-to-treat analyses, there was
significant effect [of protocol provi
scaling and root planing] on serum
CRP levels at 6 months.

"Secondary analyses [sic] demonst
that consideration of any preventiv
periodontal care (i.e., any treatme
compared to no treatment [some t
provided also in the community ca
control group] showed a significan
reduction in the percentage of peo
with elevated hs-CRP (values >3 m
6 months. However, obesity nullifie
periodontal treatment effects on hs
reduction."

Table 4.

One-Year Follow-Up of Periodontal Assessments, GCF-IL-1β Levels, and Serum Measures of hs-CRP by Treatment Group

Variable*	Community Control (n = 12)	Protocol Treatment (n = 25)	*P* Value†
Extent PD ≥4 mm	19.5 (6.12)	14.3 (3.51)	0.76
Mean PD	2.77 (0.22)	2.49 (0.16)	0.55
N PD ≥5 mm	9.08 (4.72)	9.48 (3.30)	0.89
Extent AL ≥3 mm	46.8 (8.10)	33.9 (4.94)	0.11
Mean AL	2.95 (0.46)	2.25 (0.19)	0.20
Extent BOP	45.8 (9.06)	37.09 (5.00)	0.88
Extent subgingival calculus	63.8 (12.10)	29.2 (6.06)	0.009
GCF-IL-1β	202.6 (102.20)	163.8 (42.30)	0.74
Serum hs-CRP	2.79 (0.71)	3.41 (0.78)	0.74
High CRP (>3 mg/l) (n [%])	5 (33.3)	8 (34.8)	0.93

* Values reflect means (SE) unless otherwise indicated.
† *P* values reflect ANCOVA adjusting for baseline values.
IL-1β levels are pg/ml; serum hs-CRP levels are mg/l.
Complete results from 1-year follow-up were only available for 37 subjects.

The Verdict

- Borgnakke et al. conclude,

  "[W]e recommend that the existing body of evidence in which meta-analyses consistently conclude that successful [sic] 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 [Engebretson's] as a basis for future scientific texts, new research projects, guidelines, policies, and advice** regarding the incorporation of necessary periodontal treatment in diabetes management."


Thomas Kocher. My Presentation.

Some Remarks

- Very modest BOP and, in particular, plaque reductions in Engebretson's study are certainly fact
- However, Borgnakke's arguments are largely based on
  - **Ignorance**, as available small, single-center intervention studies suffer from problems very similar to those described for Engebretson's large, multi-center trial
  - **Irrelevant deep pockets comparisons** as regards expectations about results after periodontal treatment

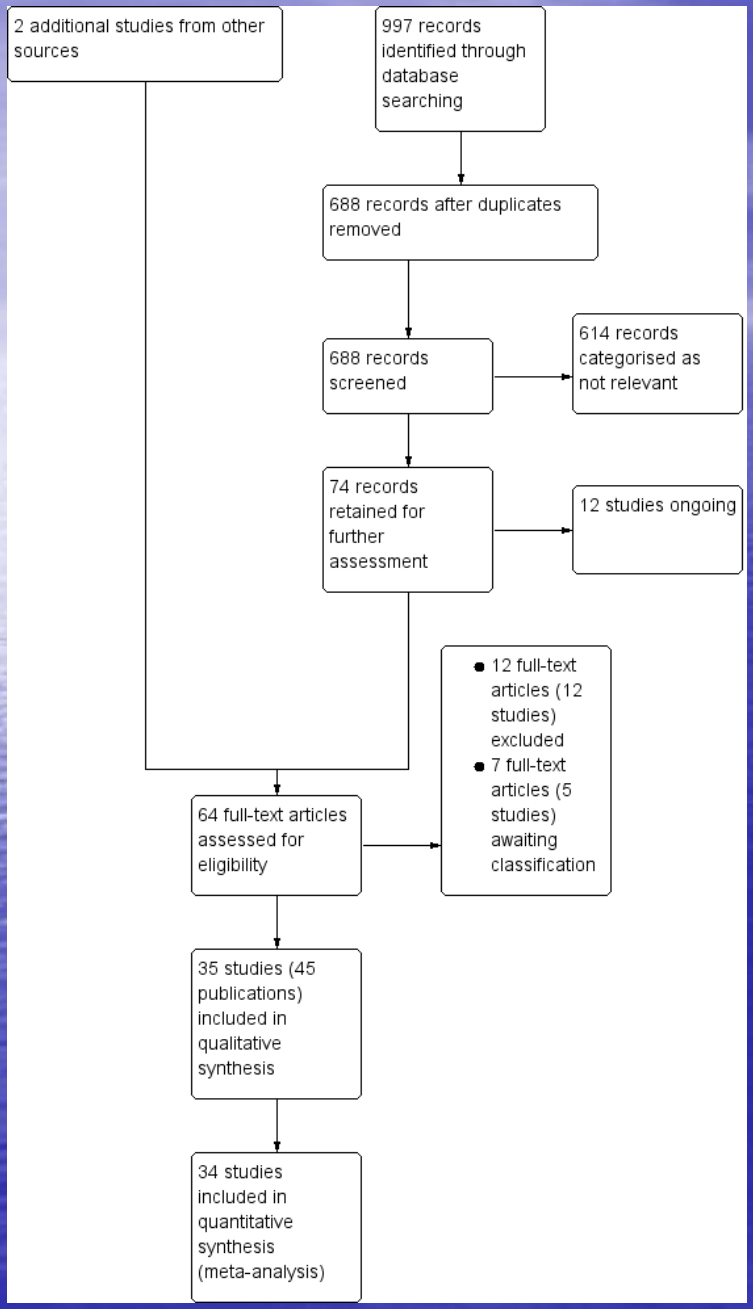
- **Circular reasoning** as regards possible effects of periodontal treatment on obese T2DM patients
- Careless and/or biased quotation of marginally related other papers

- One must assume that Borgnakke's paper has not **independently been peer-reviewed**

- Despite having produced unwelcome, for some, results, the DPTT is a high-quality RCT in fact representing the mostly obese US American population suffering from both T2DM and periodontitis
- The recommendation, expressed by 21 leading periodontists including all chief-editors of our professional journals, is certainly overbearing and has actually been regarded as brazen attempt of censorship

Simpson's Cochrane Review (2015)

- Types of studies
  - RCT with follow up ≥90 d
- Type of participants
  - T1DM or T2DM and ChP
- Types of intervention
  - NSPT, SPT, antimicrobial therapy, other drug therapy, novel interventions
- Types of outcome measures
  - Primary: % change HbA1c (DCCT OR IFCC)
  - Secondary: periodontal measures, adverse effects, HRQoL, costs, diabetic complications


2 additional studies from other sources
997 records identified through database searching
688 records after duplicates removed
688 records screened
614 records categorised as not relevant
74 records retained for further assessment
12 studies ongoing
12 full-text articles (12 studies) excluded
7 full-text articles (5 studies) awaiting classification
64 full-text articles assessed for eligibility
35 studies (45 publications) included in qualitative synthesis
34 studies included in quantitative synthesis (meta-analysis)


Random sequence generation (selection bias)
Allocation concealment (selection bias)
Blinding of participants
Blinding of clinical operator
Incomplete outcome data (attrition bias)
Selective reporting (reporting bias)
Other bias
Al-Zahrani 2009
Calbacho 2004
Chen 2012
Engebretson 2011
Engebretson 2013
Gay 2014
Gilowski 2012
Grossi 1997
Haerian Ardakani 2014
Jones 2007
Katagiri 2009
Kiran 2005
Koromantzos 2011
Kothiwale 2013
Li 2011
Llambés 2008
Macedo 2014
Madden 2008
Miranda 2014
Moeintaghavi 2012
NCT00801164
O'Connell 2008
Pradeep 2013
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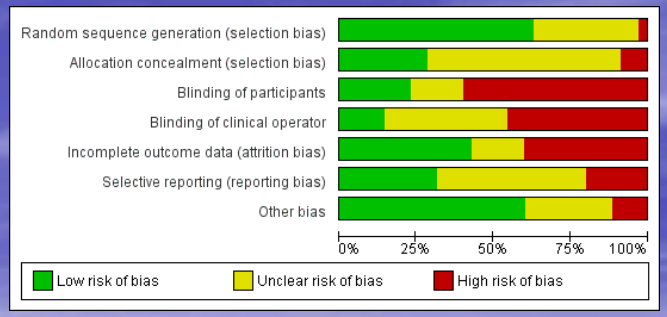
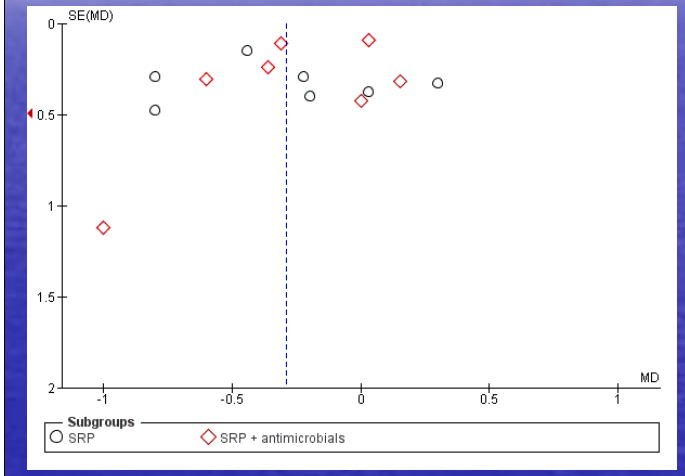
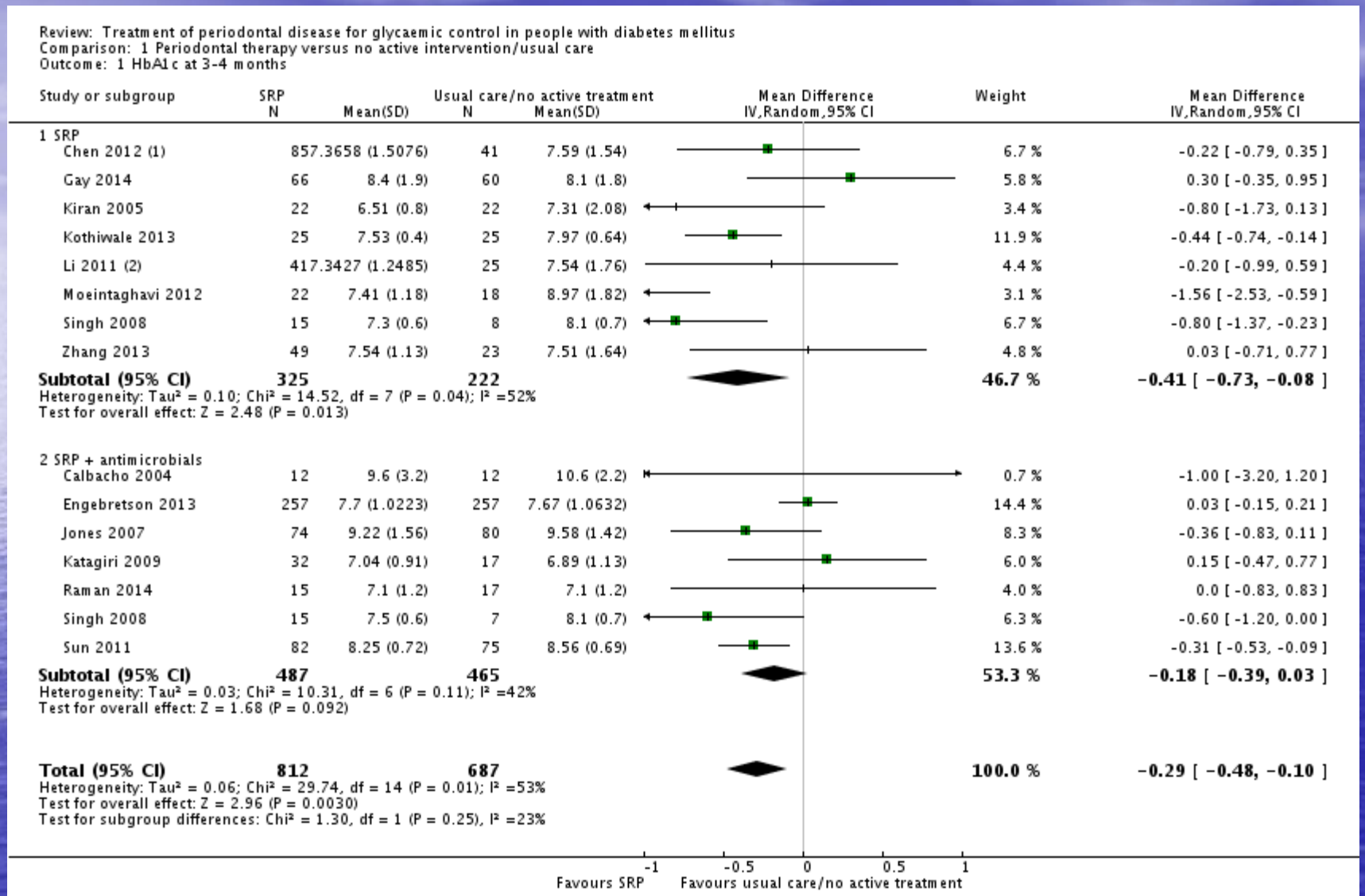
Sun 2011
Tsalikis 2014
Yun 2007
Zhang 2013


Random sequence generation (selection bias)
Allocation concealment (selection bias)
Blinding of participants
Blinding of clinical operator
Incomplete outcome data (attrition bias)
Selective reporting (reporting bias)
Other bias
0%
25%
50%
75%
100%
Low risk of bias
Unclear risk of bias
High risk of bias


SE(MD)
0
0.5
1
1.5
2
-1
-0.5
0
0.5
1
MD
Subgroups
SRP
SRP + antimicrobials

Review: Treatment of periodontal disease for glycaemic control in people with diabetes mellitus
Comparison: 1 Periodontal therapy versus no active intervention/usual care
Outcome: 1 HbA1c at 3-4 months



(1) SRP + additional mechanical therapy
(2) Periodontal therapy described as "mechanical therapy"

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Periodontal therapy versus no active intervention/usual care for glycaemic control in people with diabetes mellitus

Patient or population: Patients with diabetes mellitus
Settings: Hospital, primary care, community
Intervention: Periodontal therapy
Comparison: Usual care/no active treatment

Outcomes	Illustrative comparative risks* (95% CI)		Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk			
	Usual care/no active treatment	Periodontal therapy			
HbA1c Follow-up: 3-4 months	The weighted mean HbA1c at 3-4 months follow-up was 8.07%	Mean HbA1c in the periodontal therapy group was **0.29% lower** (0.48% to 0.10% lower)	1499 (14 studies)	⊕⊕○○ **low**[1,2]	The weighted mean HbA1c at 6 months follow-up in the usual care/no active treatment group was 7.58% The mean effect on HbA1c at 6 months follow-up (826 participants in 5 studies) was 0.02% lower (0.20% lower to 0.16% higher) in the periodontal therapy group
Adverse effects	Insufficient evidence to determine whether SRP for glycaemic control is associated with any harms				

*The basis for the **assumed risk** (eg the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI)
CI: confidence interval; **SRP:** scaling and root planing

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very low quality: We are very uncertain about the estimate

[1] High risk of bias, largely due to lack of blinding: quality of evidence downgraded once
[2] Moderate heterogeneity (I^2 = 53%): quality of evidence downgraded once

- Simpson et al. on Borgnakke's concerns
  - "[W]e believe that the inclusion of such patients [HbA1c close to therapeutic goals, high BMI] reflects the breadth of population likely to be seen in clinical practice, and the inclusion of the trial enhances estimation of the true effect of periodontal treatment for glycaemic control in diabetic patients.

- "[I]n meta-analysis to derive treatment effect estimates for periodontal indices, Engebretson 2013's outcomes were consistent at both time points [3 and 6 months] for all reported outcomes with the other included studies. Consequently, we are satisfied that Engebretson 2013's clinical conduct is not of sufficient concern to warrant post-hoc sensitivity analyses excluding its contribution, and have confidence in its findings being consistent with those of other included studies."

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Microbiome

RESEARCH Open Access

In silico analyses of metagenomes from human atherosclerotic plaque samples

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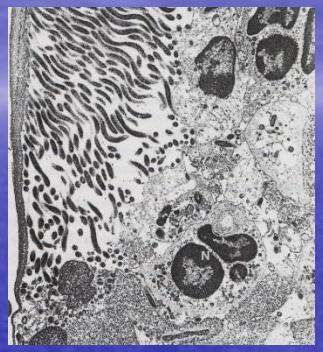
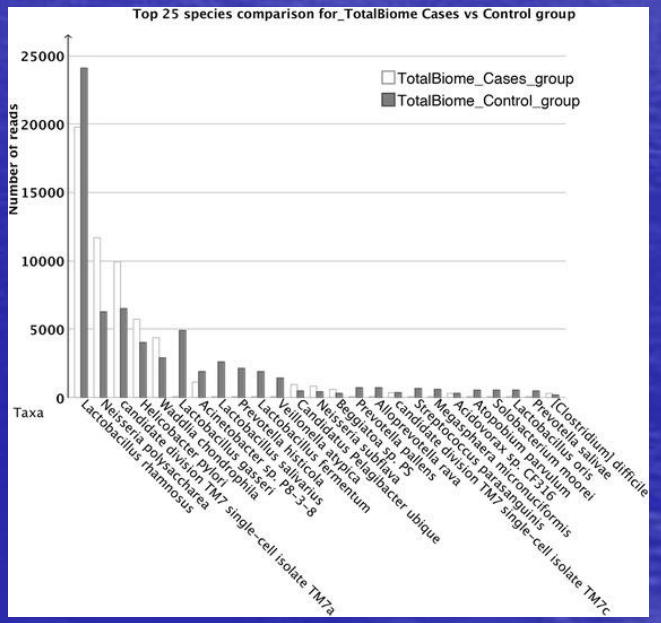
Abstract

Background: Through several observational and mechanistic studies, microbial infection is known to promote cardiovascular disease. Direct infection of the vessel wall, along with the cardiovascular risk factors, is hypothesized to play a key role in the atherogenesis by promoting an inflammatory response leading to endothelial dysfunction and generating a proatherogenic and prothrombotic environment ultimately leading to clinical manifestations of cardiovascular disease, e.g., acute myocardial infarction or stroke. There are many reports of microbial DNA isolation and even a few studies of viable microbes isolated from human atherosclerotic vessels. However, high-resolution investigation of microbial infectious agents from human vessels that may contribute to atherosclerosis is very limited. In spite of the progress in recent sequencing technologies, analyzing host-associated metagenomes remain a challenge.

Results: To investigate microbiome diversity within human atherosclerotic tissue samples, we employed high-throughput metagenomic analysis on: (1) atherosclerotic plaques obtained from a group of patients who underwent endarterectomy due to recent transient cerebral ischemia or stroke. (2) Presumed stabile atherosclerotic plaques obtained from autopsy from a control group of patients who all died from causes not related to cardiovascular disease. Our data provides evidence that suggest a wide range of microbial agents in atherosclerotic plaques, and an intriguing new observation that shows these microbiota displayed differences between symptomatic and asymptomatic plaques as judged from the taxonomic profiles in these two groups of patients. Additionally, functional annotations reveal significant differences in basic metabolic and disease pathway signatures between these groups.

Conclusions: We demonstrate the feasibility of novel high-resolution techniques aimed at identification and characterization of microbial genomes in human atherosclerotic tissue samples. Our analysis suggests that distinct groups of microbial agents might play different roles during the development of atherosclerotic plaques. These findings may serve as a reference point for future studies in this area of research.





"I think that the dentist's arena is pretty well described – it's intraoral and also maxillofacial in a sense but the dentist shouldn't be a pseudo-doctor for all types of disorders. A dentist may meet with patients more frequently than a physician, but the responsibility should not be with the dentist to diagnose diabetes or other inflammatory diseases."

Jan Lindhe, *Br Dent J* 2014; **217**: 396-397

Just Keep Flossing!