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COMMENT & RESPONSE

Hemoglobin A_{1c} Levels Among Patients With Diabetes Receiving Nonsurgical Periodontal Treatment

To the Editor Dr Engebretson and colleagues¹ reported that nonsurgical periodontal treatment did not reduce levels of glycated hemoglobin (HbA_{1c}) among individuals with type 2 diabetes in a randomized clinical trial (RCT). This contrasts with the results of an RCT by Sun et al,² in which periodontal treatment was found to improve glycemic control, lipid profile, and insulin resistance and reduce systemic inflammation among individuals with type 2 diabetes. The intervention tested by Sun et al consisted of nonsurgical periodontal treatment plus administration of systemic antibiotics and, where indicated, surgical periodontal treatment and tooth extraction.

Another important distinction between these studies was the difference in the level of adiposity in the 2 study populations. The mean body mass index (BMI) of the participants in the study by Engebretson et al was approximately 34; in contrast, the study by Sun et al restricted inclusion to individuals with BMIs ranging from 19 to 26 for women and from 20 to 27 for men. The mean BMI of participants in an RCT by Jones et al³ was 32. This study also found that periodontal treatment (scaling and root planing) did not affect glycemic control among individuals with type 2 diabetes, even when systemic antibiotics were administered. An RCT by Tonetti et al⁴ among individuals with an average BMI of 27 without serious chronic diseases found that periodontal treatment reduced markers of systemic inflammation and improved endothelial dysfunction at 2 and 6 months.

In RCTs conducted among mostly nonobese individuals, periodontal treatment has been shown to reduce systemic inflammation^{2,4} and improve glycemic control among those with type 2 diabetes.² However, periodontal treatment has not been shown to affect glycemic control in RCTs conducted among predominantly obese individuals with type 2 diabetes.^{1,3} Obesity is positively correlated with inflammatory markers in the blood and strongly related to insulin resistance and metabolic dysregulation mediated by chronic systemic inflammation.⁵ These findings, taken together with results from RCTs evaluating the effects of periodontal treatment, suggest that the lack of effect of periodontal treatment on glycemic control observed in the study by Engebretson et al may be attributable to the high level of obesity in the study population. Therefore, the findings may be generalizable only to predominantly obese populations with type 2 diabetes.

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To the Editor The report by Dr Engebretson and colleagues¹ explored the effect of nonsurgical periodontal therapy (scaling and root planing) on glycemic control in persons with

type 2 diabetes and chronic periodontitis. Given the high global prevalence of both diseases, the adverse effect of periodontal infection on blood glucose levels and diabetes complications,² and the improvements in levels of HbA_{1c} following clinically effective periodontal therapy reported in meta-analyses,³ the results of this multicenter RCT require careful review to ensure that the conclusions drawn are supported by the data. We identified important problems with the study design, execution, data interpretation, and reporting that we think render the conclusions inappropriate.

First, the periodontal therapy provided failed to clinically manage the periodontal infection and associated inflammatory burden. Residual plaque levels of 72% and bleeding scores of 42% are far below the consensus for expected outcomes.⁴ Therefore, no conclusions can be drawn about the effect of clinically effective periodontal therapy on HbA_{1c} in patients with type 2 diabetes.

Second, control of diabetes at baseline was predominantly good (mean HbA_{1c} level, 7.8%), with less than 60% of patients having HbA_{1c} levels greater than 8.0% (HbA_{1c} level <9.0% was an inclusion criterion). With the mean HbA_{1c} value close to the therapeutic target, we would not expect an intervention to improve HbA_{1c} substantially.

We are concerned about the reliance on statistical significance to justify a conclusion of no effect when the clinical therapy failed to deliver the expected standard of care. The conclusions of the study are at odds with the conclusions of a recent workshop that comprehensively reviewed the evidence.⁵

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Conflict of Interest Disclosures: The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Drs Chapple and Genco reported being co-chairmen of the European Federation of Periodontology/American Academy of Periodontology Consensus Workshop held in November 2012 and coauthors of the consensus report. In addition, Drs Chapple reported being an executive committee member of the European Federation of Periodontology. Dr Borgnakke reported being first author and Dr Genco a coauthor of the systematic review² of observational evidence for the effect of periodontitis on hyperglycemia. In addition, Dr Borgnakke reported being a member of Group 2 of the European Federation of Periodontology/American Academy of Periodontology Consensus Workshop and coauthor of the consensus report and receiving financial support to her institution from the International Team for Implantology Foundation. In addition, Dr Genco reported receiving a grant from Sunstar America.

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To the Editor The study by Engebretson and colleagues¹ adds knowledge about the effect of periodontal treatment on glycemic control in patients with type 2 diabetes and moderate to advanced chronic periodontitis. The authors of this multicenter randomized study (the Diabetes and Periodontal Therapy Trial [DPTT]) concluded that nonsurgical periodontal therapy did not improve HbA_{1c} values. Despite its high internal validity, this trial raises some important interpretation issues, particularly regarding the interventions that were compared.

The choice of the researchers not to include antimicrobial therapy in the periodontal treatment is questionable. They have elsewhere cited “concerns about overall efficacy and gastrointestinal side effects, and growing concerns about antibiotic resistance.”² It is true that antibiotic treatment cannot be considered a routine procedure in patients with chronic periodontitis. However, recommendations for the general population might be suboptimal for the population of patients with poorly controlled diabetes for 2 reasons.

The first is that patients with uncontrolled diabetes are likely to be immunocompromised and thus at higher risk of local infection after periodontal treatment. It could be argued that less than 2% of the DPTT participants required generalized periodontal rescue therapy during the study. However, because “the choice, and even use, of antibiotics was left up to the discretion of the consulting periodontist,”² it is unclear under what conditions antibiotics were and were not prescribed.

The second reason is that, contrary to what is suggested in the Discussion section, administration of systemic antibiotics in addition to scaling and root planing has been shown to reduce levels of HbA_{1c} in several recent studies.^{3,4} This corroborates the idea that infections adversely affect glycemic control.² Although results are controversial, use of antibiotics could be a promising strategy for patients with diabetes undergoing periodontal treatment.

The periodontal treatment tested in the DPTT consisted of multistage scaling and root planing, polishing, and provision of chlorhexidine gluconate mouthwash, a toothbrush, toothpaste, and dental floss. Other strategies could be added more specifically targeting patients with diabetes, including oral hygiene instructions, education sessions to improve awareness of oral hygiene, antimicrobial therapy either locally applied or systemically administered,³ daily low-dose doxycycline,⁵ other drug therapies,³ and procedures such as photodynamic therapy.⁵

In conclusion, it is possible that suboptimal periodontal treatment explains the negative results observed in this trial.

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Conflict of Interest Disclosures: The author has completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and reported being involved as a researcher and trial designer in the DIAPERIO randomized controlled trial.

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In Reply Dr Merchant suggests that the relationship between periodontal therapy and glycemic control in persons with type 2 diabetes may vary by BMI. In the DPTT, participants were predominantly obese (72% had a BMI ≥ 30). Subgroup analyses of different BMI cut points found no effect of periodontal therapy on glycemic control ($P \geq .10$) in any subgroup examined. Differences in baseline periodontitis levels, use of antibiotics, and race/ethnicity may also explain the inconsistent findings among studies.

We disagree with Dr Chapple and colleagues that the trial was flawed based on failure to adequately treat periodontitis and enrollment of participants with predominantly good glycemic control. Nonsurgical periodontal therapy is considered the cornerstone of periodontal therapy and is known to improve clinical and microbiological measures of disease, regardless of initial severity. We found no indication that change in HbA_{1c} was associated with the magnitude of the periodontal treatment response (eTable 1 in the article).

The treatment response, defined by mean probing depth change, was similar to that reported in multicenter trials involving similar treatments.^{1,2} We acknowledged the modest improvements in dental plaque and bleeding scores (19% reduction) associated with treatment. For comparison, the review by van der Weijden and Timmerman cited by Chapple and colleagues included 4 studies (none limited to patients with diabetes) with bleeding assessments comparable with ours. Bleeding reductions in these studies ranged from 29% to 39%. However, another study reported that scaling and root plan-

ing lowered C-reactive protein level in serum as a result of "[controlling] the local infection"³; mean reduction in bleeding was 18%. In addition, a recent RCT⁴ reported similar 6-month reductions in bleeding (17.9% following scaling and root planing and 26.9% adding azithromycin).

The mean baseline level of HbA_{1c} in DPTT participants was 7.8%, which is higher than reported for US adults with diabetes (7.18%).⁵ At the time this trial was initiated, target HbA_{1c} levels of less than 7% were recommended, meaning that few participants would be considered as having well-controlled diabetes at baseline.⁶ The DPTT limited enrollment to those with screening HbA_{1c} levels of less than 9%, in part to minimize the number of participants with medication changes during the trial. Although not reported in our article, we also found no difference in the treatment effect in groups stratified by baseline HbA_{1c} values ($P = .83$ for interaction between treatment effect and baseline HbA_{1c}).

Dr Vergnes states that the DPTT did not use systemically administered antibiotics, which may be indicated in immunocompromised patients. We are not aware of any study demonstrating that patients with diabetes are at greater risk for infections after periodontal treatment than healthy individuals. Only 4 of 241 participants (1.7%) experienced generalized periodontitis progression following treatment. The fraction of participants reporting tooth soreness or gum swelling did not differ between groups, suggesting that treatment was not associated with an increased risk for postoperative infections. Systemic antibiotics were considered only for patients who experienced generalized disease progression following mechanical therapy.

Vergnes indicates that the use of antibiotics and host-modulating agents appears to enhance the effect of periodontal therapy on glycemic control. However, supporting trials have been relatively small, and any systemic effects of these agents confound the effect of improved periodontal conditions on glycemic control. Nonetheless, future large trials may be warranted to determine if more comprehensive periodontal treatments can improve glycemic control.

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Potential and Pitfalls of e-Cigarettes

To the Editor Dr Abrams¹ painted an optimistic picture about the promise of e-cigarettes due to their harm-reduction potential and the ability of US Food and Drug Administration (FDA) regulations to minimize their unintended consequences. However, the manufacture and marketing of a highly addictive product has 1 primary intention at its core: to hook as many people as possible. So what public health considers an unintended consequence is industry's intended effect.

The harm-reduction model, based on the potential of e-cigarettes to replace combustible cigarettes or help smokers quit, is incompatible with a sustainable business model for e-cigarettes, which requires a continuous influx of new users. The National Youth Tobacco Survey in the United States shows already that 20.3% of middle school students and 7.2% of high school students who have tried e-cigarettes have never used conventional cigarettes beforehand.² Therefore, a successful replacement and quitting aid will lead to its own commercial demise when all current smokers quit or die. Certainly this is not the business plan of e-cigarette manufacturers.

Abrams' solution to avoid recruiting new youth smokers is strict regulation of e-cigarettes. Yet he calls for more lenient regulations for adults to promote use of e-cigarettes by smokers. Such discrepancies in regulations are unlikely to be effective in a society in which adults and youth live together and influence each other's behavior and in which much of the marketing for e-cigarettes is happening in unregulated, youth-oriented cyberspace.

A final concern is whether the failure rate of regulations to limit e-cigarette use among youth will be the same as for other tobacco products (20.5% of high school students in the United States in 2012 were current users of tobacco products other than e-cigarettes³). It is possible that youth e-cigarette use could be higher, given the renormalization and glamorization of smoking through e-cigarettes and their associated safety claims.⁴ The psychosocial, health, and economic toll of nicotine addiction among youth that could result from the use of e-cigarettes may be a high price to pay to potentially reduce harm among current smokers.

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In Reply Dr Maziak's concerns are understandable, and I share his commitment to protecting youth. However, they are not currently protected: 5.6 million children alive today are expected to die as a result of cigarette use, along with 480 000 adults annually.¹ Moving cigarette users to safer e-cigarettes benefits adults and youth.

There is little evidence that e-cigarettes are a gateway to cigarettes. A recent study suggested this possibility, but confused correlation with causation.² Youth e-cigarette experimentation (2.1% in 2012) is not associated with increased cigarette use.³ On the contrary, youth smoking declined 10% annually between 2010 and 2013 to record lows (9.6%).³ Longitudinal surveillance is required to prove a direct causal gateway connection.

In addition, concern that e-cigarettes will addict another generation is not supported by evidence. Combustion delivers freebase nicotine in its most highly addictive form. Non-combusted nicotine delivery has reduced potential for addiction; nicotine is sold over the counter in nicotine replacement products with minimal addiction. The pharmacokinetic profile of e-cigarettes is much closer to nicotine replacement products in terms of addiction risk and harm.⁴ Both nicotine replacement products and e-cigarettes are now suggested for lifetime use instead of cigarettes,⁵ and a recent randomized trial found e-cigarettes were as effective as nicotine replacement therapy at stopping smoking.⁶

Because cigarettes make up 92% of a \$100 billion market, there is plenty of room for e-cigarettes in the market. e-Cigarette manufacturers do not need to addict youth. However, it is important to distinguish between Big Tobacco, which aims to promote cigarette and e-cigarette use, and independent manufacturers, which aim to eliminate cigarettes in favor of e-cigarettes. e-Cigarettes can create competition for entrenched tobacco products and speed the demise of cigarettes. Making it harder for independent e-cigarette manufacturers to compete with cigarettes will delay the obsolescence of cigarettes and perpetuate the status quo.

I agree with Maziak that e-cigarettes should not be marketed to youth. However, I disagree that strict regulation of e-cigarettes to youth is unlikely to be effective if more lenient regulations apply to adults. Regulation could be successful if it includes a 2-pronged approach: (1) restrictions on e-cigarettes ensuring that they are not targeted, advertised, or sold to youth, and (2) making cigarettes less appealing, accessible, and affordable (eg, doubling cigarette taxes and