Letters to the Editor

Authors' response:

We thank Ms. Pickett for her interest in "*The American Journal of Cardiology* and *Journal of Periodontology* Editors' Consensus: Periodontitis and Atherosclerotic Cardiovascular Disease" and her thoughtful comments, and we appreciate the opportunity to clarify some of the confusion regarding the aim of the document and the evidence. The consensus report attempted to translate what is currently known about the relationship between these two diseases into practical application, while recognizing that recommendations are based on judgments of potential risks and benefits given the current state of knowledge.

Ms. Pickett concludes that there is no evidence that atherosclerotic events can be prevented with periodontal therapy, and therefore suggests that the recommendations cannot be supported. We concur with Ms. Pickett that there is no current direct evidence that atherosclerotic cardiovascular disease (CVD) events can be prevented by treating periodontal disease, and we repeatedly indicated the same in the document. To emphasize this point, we placed the following statement immediately before the recommendations: "Although the treatment of periodontitis reduces systemic markers of inflammation and endothelial dysfunction, no prospective periodontitis intervention studies have evaluated CVD outcomes." Thus, we tried to make clear in the recommendations that clinicians should not be treating periodontal disease solely for the purpose of preventing CVD events. However, there is growing evidence that periodontal therapy can reduce traditional risk factors for cardiovascular events, for example, elevated C-reactive protein and impaired endothelial function. Clinicians are very interested in what these studies mean and how they should apply the information.

Ms. Pickett also suggests that an added risk of 24% to 35% reported in one systematic review and relative risk ratios between 1.1 and 2.2 are very weak to moderate associations. While this is true, periodontal disease and heart disease are very prevalent in the population, and an effect size that is weak to moderate can affect a large number of lives. For example, in 2005, there were 864,000 deaths from cardiovascular diseases in the United States, according to the American Heart Association.[1] These events occurred in an at-risk adult population, over age 18, of 296 million individuals (2005 U.S. census data[2]). A 25% increase in risk (i.e., a 1.25 odds ratio) would translate into roughly 216,000 new lethal events for that year. In our opinion, this is not a trivial health issue for practicing periodontists, since CVD is the most prevalent medical condition among our patients. We should also note that the meta-analysis effect size of the independent influence of periodontitis on atherosclerotic CVD events is in the same range as meta-analysis effect sizes of other accepted factors in the management of atherosclerotic CVD. For example, in a recent review of meta-analyses[3] on the benefits of statins in reducing cardiovascular outcomes, effect sizes of a 12% decrease in all-cause mortality and a 19% decrease in coronary heart disease mortality are reported.

As part of the support for a claim of inadequate evidence, Ms. Pickett discusses a review of a recent intervention study (Beck et al.[4]) "... that has addressed the outcome of periodontal intervention in subjects with heart disease suggesting that periodontal intervention may not induce more serious adverse events than what might be expected in the community over a 25 month period."[5] She additionally quotes: "Furthermore the study demonstrated that non-surgical routine periodontal therapy did not reduce the risk of serious cardiovascular events."[5] For readers not familiar with the Beck et al. study,[4] it was a report on adverse events that occurred subsequent to periodontal treatment consisting of scaling, root planing, and oral hygiene instruction. It was a pilot study, which means that it was not adequately sized to result in a reliable estimate of the effect of periodontal treatment on cardiovascular endpoints. Thus, all the results reported in this study focused on adverse events or serious adverse events (SAEs) to determine whether providing periodontal therapy was safe or whether it might be deleterious to patients with established heart disease. There were only 15 SAEs in the study, but 13 of the 15 involved some type of cardiovascular event. The article clearly states: "Thus, cardiovascular SAEs do not meet all of the standards for determining endpoints, and the trends shown for SAEs should not be equated with what an analysis of the effect of periodontal treatment on cardiovascular endpoints might show."[4] The stated conclusion of the study was: "For those individuals who remained in the study, it appears that provision of periodontal scaling and root planing treatment to individuals with heart disease resulted in a similar pattern of adverse events as seen in the community care group, which also received some treatment."[4] Perhaps by further reconsidering these key points and conclusions from this study, Ms. Pickett's expressed concerns may be resolved.

Ms. Pickett further cites our reference to meta-analyses which conclude that the associations require further study and our qualification that "... periodontitis *may* independently increase the risk for CVD." She concludes that she is confused as this appears to be in contrast with our stated aim, which is selectively presented in her letter. There are two considerations that can clarify our position. First, we state that the aim is contingent "on the basis of current information"; thus, our recommendations are qualified and not intended to be definitive. Secondly, Ms. Pickett states that "... the evidence-based science ... do[es] not appear to support that inference." To this point, we would emphasize that it is important to appreciate that interventions may be demonstrated to influence the impact of known risk factors on the primary outcome before being demonstrated to affect the primary outcomes, such as events in cardiovascular disease. For example, as noted in package inserts, many lipid-lowering agents currently approved by the U.S. Food and Drug Administration have not been shown to reduce events. Thus, the state of the science that we have outlined relates to these risk modifications, and we have qualified all statements to not imply a known effect on outcomes.

Ms. Pickett also expressed concern that "... there was not an adequate inclusion of negative studies ...." Although the report was not intended to be a systematic review of primary sources, conclusions from published systematic reviews and meta-analyses were included to represent the evidence supporting the key statements that form the basis for recommendations. We then tried to explicitly describe the limitations of current evidence. For example, in referring to the evidence for the association between periodontitis and atherosclerotic CVD, we stated: "The findings of these studies, however, have varied greatly, ranging from determinations of no causative relationship between periodontitis and CVD to strong causative connections between the two conditions." We attempted to provide a balanced perspective on the current state of knowledge in the field, but some readers may feel that we were overly conservative in our statements and others may feel that we did not go far enough.

As noted in the original editorial[6] accompanying the publication of this consensus report, practitioners are unsure how to apply the current evidence to clinical practice. One of our goals for the report was to clarify that current evidence does not support treatment of periodontal disease to reduce CVD events. However, this does not mean that periodontal therapy does not have a beneficial effect on the cardiovascular system. We think this is a step in the right direction, based on the current evidence. Of course, the entire premise underlying clinical guidelines and recommendations is that expert judgments of risk and benefit considerations may be used to guide clinical applications of current knowledge prior to the availability of definitive clinical evidence. That is the basis for clinical judgments that must be made daily in clinical practice, while we are waiting for more definitive evidence.

The process involved in developing clinical guidelines and clinical recommendations may have confused Ms. Pickett and other readers, since recommendations are often made in the absence of the highest level of evidence. For example, in the past 10 years, there have been 33 clinical practice guidelines issued jointly by the American College of Cardiology and the American Heart Association. Of the 2,711 recommendations included in the 16 guidelines that are current and report the level of evidence, 314 (11.5%) are based on a level of evidence of A (multiple randomized trials or meta-analyses), while 1,246 (46%) have a level of evidence of C (expert opinions, case studies, standards of care).[7]

One of the advantages of defining such clinical recommendations, based on current assessments of potential benefits and risks, is that it begins to focus and define critical research and funding agendas. Ms. Pickett urges investigation of the cost-effectiveness of the recommendations, and that is certainly a worthwhile goal. Some data are starting to emerge to support cost-effectiveness modeling relative to the relationships among various diseases. For example, a recent pilot study[8] suggests that elevated HbA1c levels may be found in >25% of patients with periodontitis and at a frequency twice that of dental patients without periodontitis.

Ms. Pickett expresses concern about insufficient evidence presented in the editors' consensus report to support the following statement made in the report: "Treatment of periodontal disease, especially in patients with elevated glycosylated hemoglobin, improves glycemic control." Ms. Pickett observes that the meta-analysis published by Darré et al.,[9] cited as one of the two references to support the statement in the consensus report, offers a more reserved conclusion regarding the evidence synthesized from their review in stating "... periodontal treatment could improve glycaemic control" than is stated in the consensus report. Ms. Pickett also observes that the improvement in glycemic control in the second reference cited in the consensus report[10] occurred only in participants receiving periodontal treatment and doxycycline. Finally, Ms. Pickett shares her belief that "... only positive studies were referenced ..." in the consensus report. Based on these observations, Ms. Pickett suggests that more appropriate wording for the statement in

the consensus report should have been: "Treatment of periodontal disease using various therapies plus doxycycline ... improves glycemic control for at least 3 months."

Drs. George W. Taylor and Wenche S. Borgnakke have recently reviewed the literature relative to the effects of periodontal treatment on glycemic control, including all of the articles reported in Darré et al.[9] (report in press; Delta Dental Plans). The 11 randomized clinical trials (RCTs) on this topic used control groups that were either non-treated controls, positive controls (i.e., the control group received a relatively less intense form of periodontal treatment), or controls advised to continue their usual dental care. Of the 11 RCTs reviewed by Taylor and Borgnakke, seven reported a beneficial effect of periodontal therapy on glycemic control. An important source of variation in the RCTs' characteristics was the use of adjunctive antibiotics with the non-surgical periodontal therapy. Among the seven RCTs that included adjunctive antibiotics, five used the antibiotics systemically[10-14] and two used local delivery.[15,16] The antibiotics used in these studies included systemic doxycycline, systemic amoxicillin and amoxicillin clavulanate, and locally delivered minocycline. Six of these seven RCTs using adjunctive antibiotics showed beneficial effects on glycemic control.[10,12-16] However, it is important to note the greatest improvement for one study was in the positive control group that did not receive the systemic antibiotic.[13] Also, one of the seven RCTs reporting a beneficial effect did not use any antibiotics.[17] Hence, to date, there is no clear-cut evidence to support a requirement for the use of antibiotics in combination with non-surgical periodontal treatment in order to observe an improvement in glycemic control associated with non-surgical periodontal therapy. The use of adjunctive (local or systemic) antibiotics remains controversial. Additional well-conducted studies would help to evaluate adjunctive antibiotic effectiveness in terms of type, route of administration, dose, and indication based on level of glycemic control. Therefore, based on systematic reviews and interpretation of the literature, the authors of the "Editors' Consensus: Periodontitis and Atherosclerotic Cardiovascular Disease" and colleagues consulted on this topic believe the evidence is encouraging in support of a beneficial effect of periodontal treatment on glycemic control; however, the evidence is not yet sufficiently firm to declare unequivocally that treatment of periodontal disease improves glycemic control. Our conclusion is consistent with the Darré et al.[9] conclusion. Ms. Pickett's suggestion for alternative wording in the consensus statement, "Treatment of periodontal disease using various therapies plus doxycycline ... improves glycemic control for at least 3 months" would not adequately reflect the evidence. The effectiveness of adjunctive antibiotics in contributing to glycemic control has not been established. Finally, Ms. Pickett's belief that "... only positive studies were referenced ..." is not entirely correct. The Darré et al.[9] meta-analysis included several studies showing a non-significant beneficial effect as well as one study that showed a non-significant worsening of glycemic control following periodontal therapy. We believe the collection of articles in the Darré et al. reference adequately represented the body of literature on this topic at the time it was published. As the focus of the consensus report was on CVD, using the Darré et al. reference was an efficient way to reasonably present the body of evidence to the reader.

Finally, Ms. Pickett implies that there is an inherent problem with educational grants from industry and with the authors' disclosed financial relationships. The *Journal of Periodontology* practices a policy of full disclosure of funding sources and financial relationships of authors, in order that readers may make informed decisions on the potential for conflicting interests. As is common practice today, we seek to manage and balance potential conflicts, rather than eliminate all participants who may have a potential conflict. The disclosed educational grant to the American Academy of Periodontology (AAP) was handled as is typical of such grants – i.e., the sponsor had absolutely no role in the planning, selection of participants, conduct of the conference, or drafting or review of the report. All expenses and faculty stipends were provided by the AAP.

CONCLUSIONS

Some clinical research findings, if validated, may have substantial health implications. In recent years, clinical practice recommendations have been developed in many areas based on the potential to derive health benefits by translating the research into clinical practice immediately. Such recommendations rarely have the benefit of perfect knowledge and overwhelming benefits but usually represent judgments on the relative benefits and risks based on confidence in the current evidence. Although not perfect, such judgments can lead to clinically useful information and have the potential to produce health benefits while we wait for more definitive evidence.

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