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OTHER FORMS OF DIABETES AND ITS COMPLICATIONS (JJ NOLAN AND H THABIT, SECTION EDITORS)

Updates from the Evidence Base Examining Association between Periodontal Disease and Type 2 Diabetes Mellitus: Current Status and Clinical Relevance

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Abstract

Purpose of the Review Epidemiological surveillance documents an escalating epidemic prevalence of both type 2 diabetes (T2DM) and periodontal disease (PD). The principal goals of this review are to: 1) re-examine the clinical significance of associations between PD and T2DM, based on strength of collective evidence as determined by systematic review and meta-analysis, and 2) review findings of the systematic reviews and meta-analyses in light of the current understanding of PD-associated pathophysiology and intersection with T2DM pathophysiology.

Recent Findings Tooth loss predicts risk for chronic disease and mortality. PD is significantly associated with complications of diabetes, including retinopathy. Based on systematic reviews and meta-analyses, the adjunctive use of certain antibiotics enhances non-surgical periodontal treatment (NSPT) in patients with T2DM. Systematic reviews and meta-analyses support NSPT efficacy in achieving metabolic control.

Summary Systematic reviews and meta-analyses support the association between PD and T2DM, albeit the effect size may be modest. PD-T2DM interactions have important clinical implications.

Keywords Periodontal disease · Diabetes mellitus, type 2 · Systematic reviews as topic · Meta-analysis as topic · Tooth loss · Delivery of healthcare, Integrated

Introduction

The potential association between periodontal disease (PD) and type 2 diabetes mellitus (T2DM) was first proposed approximately 50 years ago [1]. Examination of potential associations and physiological processes underlying disease progression and emergence of complications of T2DM remain in progress. PD was declared an early complication of T2DM in the early 1990s [2]. T2DM was proposed as a risk factor for PD. Moreover, observational evidence projected a two to three-fold increase in risk for PD in individuals with T2DM [3]. Comorbid bi-directionality between T2DM and PD was proposed based on overlapping pathophysiological processes [3].

The historical evidence base surrounding association of PD and T2DM has been subjected to critical appraisal by systematic review and meta-analysis. Strictly defined methodological approaches have established these types of reviews as the highest level of critical appraisal of the collective quality of previously published studies including methodological approaches, assessment for bias, and focus on defining gaps or flaws in research designs that require adjustment to limit bias. Examination of relevant recent systematic reviews and meta-analyses was selected as the focus of this review because these studies are relevant to clinicians seeking to manage glycemic status and periodontal health in patients with diabetes, while reducing risk for complications.

The principal goals of this review are to: 1) re-examine clinical significance of associations between PD and T2DM based on strength of collective evidence as determined by systematic reviews and meta-analyses, and 2) review findings of the systematic reviews and meta-analyses in light of current

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understanding of PD-associated pathophysiology and intersection with T2DM pathophysiology.

Epidemiological Overview of Type 2 Diabetes Mellitus (T2DM) and Periodontal Disease (PD): Cause for Concern

Epidemiological surveillance documents a trend for steady increase in global prevalence of both T2DM and PD. The World Health Organization (WHO) has documented increased prevalence of diabetes from 108 million affected individuals in 1980, to 451 million in 2017 supported by estimates of the International Diabetes Federation (IDF) [4]. Global prevalence is estimated to reach 693 million by 2045 [4]. Growing numbers of countries are reporting epidemic status [5]. These trends are attributable to behavioral and lifestyle changes, and parallel documented rises in rates of obesity, sedentary lifestyle and unhealthy changes in dietary intake.

In 2014, the United States ranked third in the world for prevalence of diabetes, contributing 7.5% of the global disease burden, outranked only by China and India, which contributed 19% and 11%, respectively [4]. The prevalence in the US is projected to increase from 26 million (8.5%) in 2015 to 42 million (13%) in 2030 [6]. The Center for Disease Control's (CDC) 2017 National Diabetes Statistics Report [6] reported that 9.4% of the US population (30.3 million individuals) carried a diagnosis of diabetes. Rates of undiagnosed diabetes are expected to increase from 9.5 million in 2015, to 13 million in 2030. Rates of prediabetes, estimated at 90.6 million in 2015, are projected to reach 107.7 million US adults in 2030, effectively, one third of the U.S. population. An estimated 25% and 90% of individuals are unaware of their diabetic and pre-diabetic status, respectively.

Although highly preventable, PD has achieved global epidemic status and represents the most prevalent human oral disease [7]. Epidemiological estimates of global prevalence are projected by WHO, which maintains a global oral health databank that monitors PD rates by applying the community periodontal index (CPI) scale, which measures periodontal health at a population level. Current estimates project PD to affect 20–50% of the global population based on large epidemiological studies [7]. Eke et al. (2018) [8•] recently reviewed National Health and Nutrition Examination Survey (NHANES) data collected between 2009 and 2014 on 10,683 participants and updated USA PD prevalence estimates. Calibrated dental examiners collected measures for periodontal probing depth and gingival recession at each tooth (excluding third molars) and conducted PD prevalence assessment applying CDC/American Academy of Periodontology (AAP) surveillance definitions based on periodontal probing performed at four interproximal sites. The authors reported PD prevalence among dentate US adults >/= 30 years at 42%, with approximately one fifth meeting criteria for severe PD. [8•] Prevalence of severe PD approaching 11% was noted among individuals reporting a diabetes diagnosis compared to 7.5% for individuals without diabetes [8•].

Tooth Loss Consequential to PD and its Potential Significance as a Predictive Biomarker for DM, Cardiovascular Disease (CVD) and Other Complications of Diabetes

Clinically, tooth loss is the inevitable outcome of untreated or refractory PD. Recent studies have evaluated potential clinical significance of tooth loss. Lijestrand et al. (2015) [9] included number of missing teeth as a variable during multivariable Cox regression modeling in a cohort of 8446 individuals with 13 years of follow-up data to project hazard ratios for prediction of onset of DM or all-cause mortality. These investigators also reported the threshold for increased risk for diabetes to be >/=5 missing teeth. Further, adding number of missing teeth to their model moderately improved prediction of all-cause mortality. Kebede et al. (2017) [10] also evaluated potential interaction between PD and DM, CVD or all-cause mortality in a cohort of 3327 individuals with 11 years of available follow-up data applying multivariable Cox proportional hazard modeling. Variables modeled included: 1) two measures of PD or 2) missing teeth or 3) diabetes as the exposure, and mortality as the outcome of interest. Analyses found independent interaction of oral variables with DM, cardiovascular disease and all-cause mortality, but no additive interaction between DM and PD relative to mortality outcomes.

CVD is a highly prevalent chronic condition and a major cause of mortality worldwide, contributing 32% of mortality globally [11]. Notably, systematic review of 57 articles published between 2007 and 2017 estimated global prevalence of approximately 32% for CVD among nearly 4,550,000 individuals with T2DM [12]. CVD was the cause of mortality in nearly 10% of the subjects with T2DM and represented ~50% of all-cause mortality [12]. Collectively, these data support that PD, T2DM and CVD may independently contribute attributable risk to each of the other respective conditions.

Key findings of the consensus report and guidelines emanating from expert review by the 2018 Joint Workshop on PD and diabetes published by the International Diabetes Federation and European Federation of Periodontology are highlighted in Table 1 [13•]. Based on analysis of data from 14 studies with nearly 32,000 participants, the report posited association of PD with complications of T2DM including retinopathy, nephropathy, neuropathic foot ulceration, CVD outcomes and mortality. Data synthesis from four studies reported odds ratios (OR) between 1.2 to 2.8 for retinopathy, with significant parallels in severity across the two conditions [15]. Two studies applying multivariate regression analysis to

Table 1 Recent key findings surrounding T2DM and PD association summarized by the IDF/EFP Consensus Report and updated current clinical practice guidelines informed by expert review of the evidence base [13•].

Impact of PD on T2DM: Epidemiological evidence reported by systematic review and meta-analysis of observational evidence [14•]
• Baseline HbA1c measures are higher when PD is present compared to individuals with no or mild PD.
• Evidence from 3/5 cohort studies observed a significant association between PD and reduction in glycemic control;
• Potential for greater insulin resistance was reported by some studies in subjects with PD.
• Evidence base supports associations between PD and onset/severity of diabetic complications.
• Data from 32,000 individuals support association of PD with nephropathy, foot ulceration, CVD and mortality and significant association between PD and retinopathy.
• Whether PD intervention reduces risk for complication onset/exacerbation is lacking.
• Mortality risk was substantially elevated in subjects with T2DM and PD (HR 3.5-4.5)
Risk for T2DM in individuals with PD
• Synthesis of data from >77,700 individuals supported that individuals with PD were at increased risk for dysglycemia (T2DM or prediabetes) (HR 1.2-1.3)
Pathophysiological factors linking PD and T2DM
• Definition of a causal microbiota profile in association with PD in the absence of presence of PD is currently lacking.
• Proinflammatory cytokine activity detected in GCF in the presence of diabetes may promote PD exacerbation;
• Increased levels of pro-inflammatory meditators that increase oxidative stress were observed in individuals with comorbid T2DM and PD.
• Improvement in glycemic control for persons with T2DM is associated with decrease in levels of systemic inflammatory mediators.
• Studies defining whether metabolic shifts impact PD status are lacking.
• Clinical trials support that PD treatment reduces levels of inflammatory mediators and systemic inflammation.
Evidence supporting an impact of PD intervention on glycemic control
• Significant reductions in glycemic measures 3 months post PD intervention were observed in randomized clinical trials.
• Reductions in HbA1c reported following PD treatment ranged from 0.27 to 0.48%.
• No threshold for magnitude of PD reduction to leverage improved clinical significant glycemic control is currently established.
• Patients with T2DM treated with non-surgical PD treatment plus adjunctive antibiotics compared to patients with PD treatment and no antibiotics showed a modest reduction in HbA1c ranging from 0 to 0.24%

survey data collected in large Japanese ($n > 27{,}000$) [16] and Korean ($n = 45{,}811$) [15] cohorts validated the associations. Horikawa et al., (2019) reported 15% and 7.8% prevalence of retinopathy among participants with and without PD, respectively ($P < 0.001$) [16]. Song et al. (2017) reported a significant 8-fold increase in risk of severe retinopathy among Korean participants with <20 teeth compared to those with >/=28 teeth ($p < 0.001$) [15].

Overview of PD and Current Understanding of Pathophysiology Linking DM and PD

PD is generally reversible when treated early by a dentist via scaling and root planing (SRP), a mechanical process applied to remove the dental plaque and reduce infectious processes. Most PD is entirely preventable by maintaining good oral hygiene and having teeth professionally cleaned by dental professionals at prescribed intervals annually. However, in the presence of T2DM, particularly uncontrolled diabetes, resolution of PD may become more challenging.

While only a brief, high-level overview of the prevailing insights surrounding pathophysiological mechanisms that impact on PD in the presence of comorbid T2DM can be summarized here, a recent review by Polak and Shapira (2018) provides more detailed definitions [17]. Briefly, T2DM contributes to heightened systemic oxidative stress and inflammation via multifactorial processes including deposition of advanced glycation endproducts (AGEs) resulting in glycosylation of host tissues and lipotoxicity induced by insulin resistance and contributes to exacerbation of macro- and microvascular disease. These pathophysiological mechanisms in turn, drive dysregulation of inflammatory and anti-inflammatory homeostasis mediated by cytokine and/or chemokine activity and heighten injury-inducing immune responses.

A systematic review and meta-analysis of literature assessing the relative contribution of cytokines to

chronic PD in patients with T2DM, was published by Atieh et al. (2014) [18]. Authors reported significantly increased levels of interleukin I beta (IL1β) in gingival crevicular fluid of subjects with chronic PD and T2DM compared to individuals with PD and no T2DM. However, no significant differences in levels of additional proinflammatory cytokines in gingival crevicular fluid were measurable among patients with PD irrespective of diabetes status [18].

Systemic perturbations caused by T2DM impact on health of periodontal tissue, which exhibits heightened inflammation due to physiological consequences of dysglycemia. In the presence of PD, early periodontal damage occurs due to metabolic activity of pathogens (Fig. 1). Bacterial endproducts consequential to periodontal infection stimulate chemotactic signaling which attracts neutrophils and monocytes for help in removing the pathogenic presence and cellular debris associated with tissue damage. In the presence of DM and PD, cytokine/chemokine signaling is further amplified, causing heightened immune response including hyper-activation of neutrophils whose increased enzymatic activity further escalates periodontal destruction, thereby amplifying PD.

Reduction in bone mineral density and increased risk for bone fracture are additional hallmarks of T2DM. When PD and T2DM occur as comorbid conditions, systemic hyperglycemia is posited to promote disruption of alveolar bone homeostasis and accelerated bone loss in the presence of PD (reviewed by Wu et al., 2015) [19]. Prevailing theory posits occurrence of dysregulated alveolar bone homeostasis and decreased bone turnover driven by perturbations within cytokine- chemokine regulatory pathways and pathophysiology associated with T2DM [19] Collectively, dysregulation of these physiological processes appears to lead to 'uncoupling' of programmed osteoclast and osteoblast activity involved in bone turnover despite upregulation of osteoclast activity.

Approaches to Examining Strength of the Evidence Base Supporting Associations between PD and T2DM

A substantial evidence base has explored:

1) potential associations exist between PD and T2DM;
2) bidirectional interaction between T2DM and PD; and
3) outcomes of clinical management of PD in the presence of uncontrolled T2DM are adversely affected, while conversely, presence of PD interferes with glycemic control.

This has prompted evaluation of this literature base by systematic reviews, meta-analyses, and meta-regression analyses. In order to achieve Level 1 evidence assignation, which holds the highest level of relevance relative to clinical care, systematic review and meta regression analysis of a minimum of three comparable randomized controlled trials (RCTs) meeting defined criteria is required. Notably, an early systematic review exploring PD and T2DM association, (Janket et al., (2005)) proposed a minimum sample size requirement of 246 patients to observe a 10% reduction (0.7% reduction in HbA1c measure) with 90% power [20]. However, many RCTs meeting eligibility for inclusion are underpowered due to

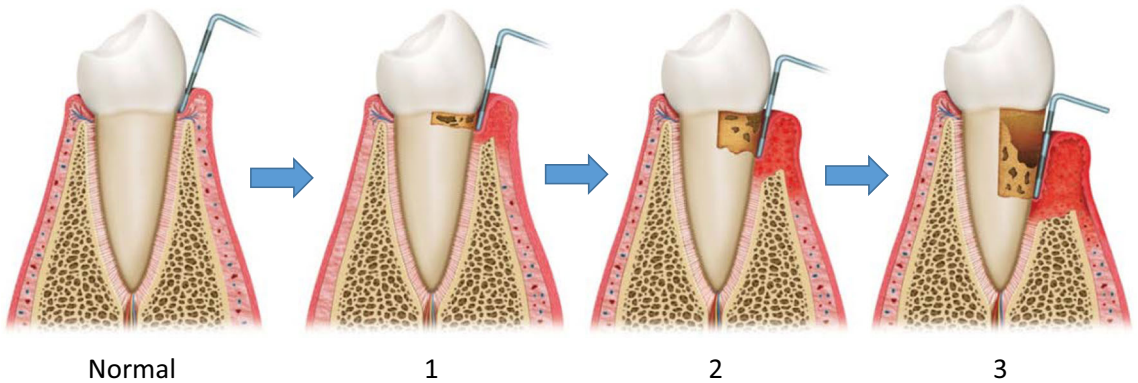

Fig. 1 Overview of periodontal disease pathophysiology. Frame 1: Periodontal pathogens create a biofilm on the tooth surface at the gingival margin to establish a favorable anaerobic environment that simultaneously protects them from host immune response. Frame 2: With chronic establishment of the infection, the biofilm expands deeper into the periodontium causing loss of structural support for the tooth. Localized pro-inflammatory signaling by gingival tissue in response to bacterial activity attracts hyper-reactive neutrophils and other cells mediating immune response. Immune mediators released by these cells escalate local inflammation and cause collateral injury to gingival tissue providing structural support to teeth. Inflammation increases with advancing PD severity. Frame 3: In the presence of uncontrolled T2DM, accelerated deepening of periodontal pockets promotes clinical attachment loss from the periodontal ligament, (the connective tissue covering the tooth root that joins it to the underlying alveolar bone that structurally supports the tooth), thus contributing to tooth mobility. PD and immune response to PD also contribute directly to alveolar bone loss. Ultimately, structural support is compromised and tooth loss occurs

small sample size. Meta-analysis supports synthesis of data from smaller studies meeting systematic review patient/intervention (exposure)/comparison/outcome (PICO) requirements, allowing for re-analysis of collectively pooled data from all eligible RCTs, its statistical significance and its relative effect size to inform potential clinical significance.

With respect to the relative impact of PD treatment on improving glycemic control, systematic reviews and meta-analyses have been applied across a range of endpoints. Endpoints reviewed herein include:

a) *impact of PD intervention on glycemic control at defined follow up intervals post treatment at three months, six months; and duration studies (3 and >/= 6 months)*;
b) *outcomes of non-surgical PD treatment in the absence or presence of adjunctive treatment (mouthwash or treatment with local of systemic antibiotics);*
c) *risk of PD onset or progression in the context of diabetes;*
d) *resolution of PD in the presence of HbA1C </= 8.5%*

Results of systematic review and meta-analysis surrounding the following endpoints PD/T2DM endpoints

a) *Impact of PD intervention on glycemic control across time*

An umbrella review (Botero et al., 2016) [21] and two systematic reviews and meta-analyses (Faggion et al., 2016 [22], Hasuike A et al., (2017) [23]) undertook meta-analysis of previously published systematic reviews and meta-analyses whose focus was assessment of the impact of PD intervention on glycemic control. These three *meta* reviews included independent reanalysis of subsets of studies drawn from among the same 13 systematic reviews and meta-analyses (Botero $n = 12$; Faggion ($n = 11$); Hasuike ($n = 9$)) that assessed RCTs or controlled clinical trials (CCTs) published no later than 2015. All three studies applied the following PICO definitions:

> P: *patients:* with a T2DM and PD diagnosis (derived using any PD classification definitions);
> I: *intervention/exposure*: periodontal treatment (non-surgical) with or without adjunctive antibiotics;
> C: *comparison*: control group included that received no, or delayed, treatment;
> O: *outcome*: Percent HbA1c level improvement evaluated at some specified timeframe >/= 3 months post PD intervention.

A MeaSurement Tool to Assess systematic Reviews' (AMSTAR) quality assessment tool was used across all three *meta* reviews. While over 60% of the studies received high AMSTAR quality scores, a significant level of outcome heterogeneity was also detected among 58% of studies based on Cochran's Q testing. Heterogeneity was assessed in these *meta* meta-analyses applying the I^2 statistic. Determination of I^2 >/=50% indicated lower generalizability of results. Notably, four meta-analyses reviewed by the *meta* meta-analyses were associated with $I^2 < 30\%$. Interestingly, each of the three *meta* reviews came to different conclusions. Botero et al. [21] reexamined data from 55 studies including 39 RCTs via meta-analysis and reported HbA1c level reduction of 0.23–1.03% and a mean statistically significant reduction in 10/12 studies. The authors concluded that PD intervention was modestly associated with reduction in glycemic measures. By contrast, meta-regression analysis conducted on 11 meta-analyses by Faggion et al. [22] reported an average reduction in HbA1C of 0.46% post PD treatment which was not deemed clinically significant. Hasuike et al. [23] conducted meta-analysis on 13 meta-analyses including re-analysis of data from four meta-analyses to improve alignment with their study criteria. The authors reported HbA1C reduction ranging from −0.93 to 0.13 which they deemed a significant, albeit modest effect of periodontal intervention on glycemic measures. Overall, examination of the forest plots of these studies uniformly depicted declines in HbA1c levels favoring the intervention group and with no change noted among controls receiving no, or delayed, intervention.

Subsequently, a systematic review and meta-analysis by Teshome and Yitayeh (2018) [24] examined data from 940 individuals of various nationalities included in seven RCTs conducted between 2005 and 2015. These investigators examined reductions of either HbA1C or fasting plasma glucose (FPG) three months post PD intervention. Sub-analysis demonstrated a similar effect sizes of 0.51 ($p = 0.04$) and 0.53 ($p = 0.002$), in subjects treated with SRP alone and those receiving SRP plus adjunctive antibiotic therapy or mouthwash, respectively. These investigators concluded that the observed reduction was therefore likely attributable to SRP. Pooled analysis of reduction in HbA1c (range: 0.02 to 0.88), achieved a modest random effect size of 0.48 ($p = 0.002$) for the SRP + antibiotics group at 3 months post-treatment comparable to those reported by meta-systematic review and meta-analyses studies. Notably they also reported a mean effect of 0.53 at 6 months ($p = 0.0003$) (overall effect: $Z = 3.63$). Only few studies have examined sustained reduction in glycemic levels >/= 6 months compared to controls. Such studies reported on small sample sizes, identified no treatment benefit beyond 3 months or reported non-significant reduction at six months.

b) *Outcomes of non-surgical PD treatment in the absence or presence of adjunctive antibiotic treatment*

Several systematic reviews and meta-analyses (Grellman AP et al., 2016 [25]; Lira Junior, R et al., 2017 [26]; Souto, MLS et al., 2018 [27]) have explored adjunctive use of systemic

antibiotics with mechanical SRP and effect on glycemic outcomes in patients with T2DM, arriving at variable conclusions. Grellman et al. (2016) [25] conducted a meta-analysis across 13 CCTs and RCTs conducted across international populations that met PICO criteria. Authors applied random- or fixed-effect modeling and weighted mean differences for measures including: periodontal probing depth ($n = 12$ RCTs), clinical attachment loss ($n = 10$ RCTs), plaque index and reduction in bleeding on probing as a measure of inflammation. These authors concluded that adjunctive antibiotics may improve efficacy over SRP alone based on a significant reduction in periodontal probing depth in the treatment arm. ($p < 0.001$).

While the meta-analysis by Lira-Junior et al., (2017) [26] reviewed the same studies as Grellman et al. and four additional studies [25] they concluded that systemic antibiotics offered no benefit beyond SRP. Applying the Cochrane Collaboration Tool Lira-Junior et al. [26], also reported high risk for bias or no capacity to evaluate bias across most studies. Incidence of adverse drug events associated with antibiotic exposures was also noted.

In 2018, Souto et al. [27], comprehensively reexamined RCTs investigating efficacy of non-surgical periodontal treatment (NSPD)/with antibiotics vs. NSPD alone in leveraging clinically significant improvement in PD measures. These authors synthesized data from 11 articles representing outcomes of 496 patients with available follow-up measures and identified sources of inter-study variability regarding smokers: $n = 6$ excluded, $n = 2$ included and $n = 3$ did not report smoking status. Moreover, bias assessment applying the Cochrane Collaboration Tool found high bias across approximately 75% of studies. Meta-analysis found a significant overall reduction in PD among patients with T2DM in studies with both low and high-risk bias (WDM = 0.27 $p < 0.005$ and WDM = 0.12 $p < 0.002$, respectively) for two regimens: systemic doxycycline or combination therapy with amoxicillin and metronidazole.

c) *Risk for PD development/exacerbation based on level of T2DM control or advancing dysglycemia (pre-diabetes)*

Systematic review and meta-analysis by Nascimento et al. (2018) [28] examined longitudinal prospective cohort studies assessing PD risk based on extent of T2DM control. These investigators examined data from 3200 patients with T2DM across 13 studies and performed meta-analysis on six studies with available data. To standardize PD risk assessment, odds ratios were converted to relative risk (RR) estimates in order to adjust for heterogeneity across studies. Meta-regression analysis and sensitivity analyses determined that variables contributing to RR included: socioeconomic status, geographic location, sample less or greater than 500; follow-up less or greater than five years, glycemic measure applied for T2DM diagnosis, PD assessment, criteria used to establish PD diagnosis and parameters defining progression. Meta regression analysis determined increased risk for PD onset/progression in association with inadequately controlled diabetes across 86% of studies (overall weight-adjusted RR across all studies =1.86 (95% CI: 1.3–2.8).

d) *Resolution of PD in the presence of HbA1C </= 8.5%*

Hsu et al. (2018) [29] conducted a systematic review of 12 prospective cohort studies including 491 participants examining PD resolution following non-surgical periodontal therapy (SRP) (GRADE Level 2b or 3b evidence). Meta-regression analysis was conducted including the following clinical factors: length of follow-up; age; HbA1c level; and mean differences in periodontal probing depth and clinical attachment loss at baseline in subjects with PD and T2DM vs. those with only PD. Data surrounding reduction in periodontal probing depth, exhibited high heterogeneity ($I^2 = 71\%$; chi-squared $p < 0.001$) whereas improvement in clinical attachment loss exhibited low heterogeneity ($I^2 = 13\%$; chi-squared $p = 0.31$). Meta-analysis detected no significant differences in either periodontal measure across either study arm. Meta-regression analysis identified that with increasing mean age and reduced periodontal probing depth was more favorable in PD only group (no T2DM), and that greater levels of PD reduction were observed in the T2DM + PD group vs. the PD-only group when the T2DM + PD group had higher mean baseline levels of PD. GRADE analysis ranked overall quality of included studies as low. Notably, most study participants had average HbA1c </=8.0, consistent with metabolic control. Further, smoking status, a risk factor for PD, was not assessed.

Discussion and Conclusions

Collectively, systematic review and meta-analysis outcomes provide evidence for a bidirectional interaction between T2DM and PD. However, broadness of PICO terms applied by three *meta* meta-analyses exploring impact of PD intervention on glycemic control contributed to disparate interpretation following review of largely the same studies. For example, classification of PD derived "using any PD classification definitions" resulted in inclusion of studies that measured PD using definitions for population surveillance as well as clinical classification. Moreover, PD classification has undergone considerable re-definition over time. Earlier definitions under-estimated PD prevalence compared to current definitions. This introduces challenges in classification of patient status across time [30]. Similarly, changes in cut-offs defining diabetes status can be documented over time [31]. Thus, systematic review may require sub-setting of studies applying narrower definitions and comparing magnitude of the observed effect to pooled outcomes distilled by *meta* meta-analyses. Similarly, interventions by SRS alone or with adjunctive antibiotics were not examined independently. While meta-analyses published to date validate efficacy of SRP, impact of

adjunctive antibiotic treatment on glycemic measures remains equivocal, with *meta*-analyses arriving at disparate conclusions despite analysis of virtually the same studies. Despite the rigor of meta reviews, premises and conclusions require careful consideration.

Current evidence supports missing teeth as a candidate predictor for clinically significant pathology. Tooth loss documents historical evidence for destructive PD and clinicians should monitor rates across patients' lifespans. Number of missing teeth parallels increases in severity, morbidity and mortality in a dose-dependent manner. Emerging evidence of association between PD and complications of diabetes should promote heightened monitoring of oral health in clinical settings. Finally, clinicians are encouraged to consult the 2018 expert consensus report [•] available online to access the latest evidence-based clinical practice guidelines regarding current best practices for integrated care delivery surrounding prevention and management of patients with T2DM and PD.

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Compliance with Ethical Standards

Conflict of Interest Ingrid Glurich and Amit Acharya declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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