Published in final edited form as:

J Clin Periodontol. 2014 July ; 41(7): 643–652. doi:10.1111/jcpe.12258.

Periodontal Infection, Impaired Fasting Glucose and Impaired Glucose Tolerance: Results from The Continuous National Health and Nutrition Examination Survey 2009–2010

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Abstract

Aim—We investigated the relationship between periodontal disease, a clinical manifestation of periodontal infection, and prediabetes.

Methods—The National Health and Nutrition Examination Survey, 2009–2010 enrolled 1,165 diabetes-free adults (51% female) aged 30–80 years (mean $\pm$ SD=50 $\pm$ 14) who received a full-mouth periodontal examination and an oral glucose tolerance test. Participants were classified as having none/mild, moderate or severe periodontitis and also according to mean probing depth $\geq$ 2.19 mm or attachment loss $\geq$ 1.78 mm, (respective 75th percentiles). Pre-diabetes was defined according to ADA criteria as either: i) impaired fasting glucose (IFG) or impaired glucose tolerance (IGT). In multivariable logistic regression models, the odds of IFG and IGT were regressed on levels of periodontitis category.

Results—The odds ratios and 95% confidence intervals for having IGT among participants with moderate or severe periodontitis, relative to participants with none/mild periodontitis were 1.07[0.50,2.25] and 1.93[1.18,3.17], $P=0.02$. The ORs for having IFG were 1.14[0.74, 1.77] and

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1.12[0.58, 2.18], $P=0.84$. PD 75th percentile was related to a 105% increase in the odds of IGT: OR[95% CI] =2.05[1.24, 3.39], $P=0.005$.

Conclusions—Periodontal infection was positively associated with prevalent impaired glucose tolerance in a cross-sectional study among a nationally representative sample.

INTRODUCTION

There is evidence that chronic infections might increase the risk for diabetogenesis. For example, clinical indicators of periodontal infection were reported to be associated with a 2-fold increase in the risk of diabetes development during 20-years of prospective follow-up (Demmer et al., 2008) and more recently, serological evidence of *H. pylori* infection was found to be associated with a 2.7-fold increase in risk for incident diabetes (Jeon et al., 2012).

Studies have also examined the relationship between infection and early markers of impaired glucose metabolism to advance our understanding of the natural history of associations. Most research on this topic arises from designs using periodontal infection models to study the general hypothesis of microbial-induced diabetes risk. Periodontal infection models are useful because minimally invasive clinical measures are manifestations of adverse subgingival microbial exposures (Demmer et al., 2010b). Accordingly, clinical periodontal measures have been reported to be associated with increased risk for accelerated five-year progression of hemoglobin A1c (A1c) (Demmer et al., 2010a) as well as elevated levels of insulin and insulin resistance (Demmer et al., 2012b).

Periodontal infections have also been linked to increased risk for prediabetes defined as either impaired fasting glucose (Zadik et al., 2010, Choi et al., 2011) or impaired glucose tolerance (Saito et al., 2004). The initial reports linking periodontal infections to prediabetes have provided helpful insights but some important limitations exist such as: i) lack of full-mouth clinical periodontal exams (Zadik et al., 2010, Choi et al., 2011, Saito et al., 2004) that can more accurately reflect the extent and severity of infection; ii) exclusion of women (Saito et al., 2004, Zadik et al., 2010); and/or iii) the use of old criteria for defining prediabetes (Saito et al., 2004). Moreover, no previous study has provided results comparing the relative strength of association between infection and both impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) in separate analyses from the same study population. Comparative studies of these outcomes would be meaningful as IFG and IGT are believed to each portend different levels of risk for future diabetes and cardiovascular disease. IFG and IGT might also represent a different underlying pathophysiology and diabetes risk phenotype (Nathan et al., 2007, Blake et al., 2004).

We studied the association between clinical measures of periodontal infection and prediabetes. Periodontal infections were assessed using full-mouth periodontal examinations and prediabetes was defined using both fasting glucose and 2-hour post-challenge glucose levels. Participants were adult men and women enrolled in the Continuous NHANES 2009–2010, a randomly sampled, population-based study of noninstitutionalized US residents.

METHODS

The Continuous National Health and Nutrition Examination Survey (NHANES) 2009–2010 is a nationally representative, stratified, multistage probability sample of the civilian noninstitutionalized U.S. population. The current analysis includes men and women aged 30–80 years of age who received a periodontal examination and an oral glucose tolerance test (OGTT). Individuals were excluded if they had diabetes as determined via: i) Self-reported, diabetes diagnosis; or ii) HbA1c levels $\geq 6.5\%$; or iii) fasting glucose $\geq 126\text{mg/dl}$. Individuals were also excluded if they: i) were not fasting for ≥ 9 hours at the time of the first OGTT blood collection; or ii) were missing important covariate data collection. The final sample size for the current analysis is $n=1,165$.

Periodontal Examination

Periodontal probing depth (PD) and clinical attachment loss (AL) measurements were made by trained, registered hygienists in the full-mouth (excluding 3rd molars) at 6 sites per tooth (Eke et al., 2012). Periodontal examiners received intense training followed by periodic monitoring and recalibration against a reference examiner. The reference examiner made 3 visits to each dental examination team per year to observe field operations and to replicate 20 to 25 oral health examinations.

Oral Glucose Tolerance Test (OGTT)

Plasma was collected after a minimum 9-hour fast. Immediately after the initial venipuncture, participants were then asked to drink a calibrated 75 gram dose of glucose solution (Trutol™). A second venous plasma collection was performed 2 hours after the glucose challenge (http://www.cdc.gov/nchs/data/nhanes/nhanes_09_10/OGTT.pdf). Plasma specimens were processed, stored and shipped to Fairview Medical Center Laboratory at the University of Minnesota, Minneapolis, Minnesota for analysis. Glucose concentration was determined by a hexokinase method (Demmer et al., 2012b).

Prediabetes Definitions

Impaired fasting glucose (IFG) and Impaired glucose tolerance (IGT) were defined in accordance with the American Diabetes Association (ADA) criteria (2012) as follows: IFG=fasting plasma glucose $\geq 100\text{ mg/dl}$ and $<126\text{ mg/dl}$; IGT=2-hour post-challenge glucose values $\geq 140\text{ mg/dl}$ and $<200\text{ mg/dl}$.

Risk Factor Assessment

Comprehensive questionnaires to assess risk factors relevant to both periodontal disease and prediabetes were administered as previously described (Demmer et al., 2012b). The demographic variables age, race/ethnicity, sex, education ($<$ high school, completed high school, some college, college graduate) and poverty-income-ratio (calculated by dividing family income by the poverty guidelines, specific to family size, as well as the appropriate year and state according to Department of Health and Human Services guidelines) were collected. Behavioral risk factor assessments included physical activity level (none, moderate and vigorous based on occupational and recreational related physical activity performed in a typical week), cigarette smoking, alcohol consumption and caloric intake.

Height, weight and blood pressure measures were made by trained research assistants according to standardized protocols. BMI was calculated as weight (kilograms)/height (meters)² and participants were categorized as underweight/normal weight (<25 kg/m²), overweight (25–29.9 kg/m²), or obese (≥ 30 kg/m²). Triglycerides, total cholesterol and HDL-cholesterol, C-reactive protein (CRP) and white blood cell count (WBC) were measured from fasting blood samples.

Statistical Analysis

SAS Survey procedures (version 9.3) were used for data analysis. Analysis of variance and categorical analysis methods were used to obtain descriptive statistics according to both periodontal and prediabetes status for important demographic, behavioral, dental and cardiometabolic variables. P-values presented arise from F-statistics or chi-square statistics. The odds of prediabetes defined as any-IFG (irrespective of IGT) or any-IGT (irrespective of IFG) were regressed across categories of periodontal disease in multivariable logistic regression models. Periodontal infection was defined using three separate approaches based on measures of PD and AL. First, participants were categorized as having non/mild, moderate or severe periodontitis according to the Centers for Disease Control and Prevention/American Academy of Periodontology (CDC/AAP) definition (Page and Eke, 2007). A second definition was created by categorizing participants as being either ≥ 75th percentile or <75th percentile for mean PD at interproximal sites (2.19 mm). The third periodontal definition was based on being either ≥ 75th percentile or <75th percentile for mean AL at interproximal sites (1.78 mm). For the latter two definitions, supplemental analyses were conducted using cutpoints derived from all periodontal sites (i.e., including mid-facial and mid-buccal sites). For regressions modeling the CDC/AAP definition of periodontitis as the primary exposure we additionally report the p-value for linear trend derived from the ordinal three-level periodontitis variable (none/mild, moderate or severe).

Additionally, multivariable generalized logistic regression models examined the association between CDC/AAP defined periodontitis and a polytomous prediabetes outcome which categorized participants as having either: i) no prediabetes; ii) isolated-IFG; iii) isolated-IGT; or iv) combined IFG & IGT. NHANES survey weights, cluster and strata variables were included in the analysis to account for the complex survey design as previously described (Demmer et al., 2012b). In addition to odds ratios and 95% confidence intervals, we report the p-value for any difference in the odds of the polytomous prediabetes outcome according to level of periodontitis derived from Wald chi-square tests.

A series of multivariable models were developed to better assess the influence of confounding. Based on data availability, we focus on confounding by socio-demographic indicators (age, sex, race/ethnicity and educational level), health behaviors (smoking status, caloric intake, alcohol consumption and physical activity) and adiposity (body mass index). We also consider variables that might mediate the association between periodontal infection and prediabetes (blood pressure, cholesterol profile, WBC and CRP). Models were additionally informed by two Directed Acyclic Graphs (DAGs) constructed using Dagitty (Textor et al., 2011). Figure 1A assumes more complex causal structures in which potential socio-demographic confounders relate to periodontal infection and prediabetes

through multiple mechanisms (e.g., confounding can act through health behaviors and adiposity but also through other mechanisms not represented in our data); this causal structure necessitates adjustment for all sociodemographic variables. Alternatively, the DAG in Figure 1B assumes that all confounding effects act through either health behaviors or adiposity; this causal structure does not require adjustment for sociodemographic variables if health behaviors and adiposity adjustments are made.

The following multivariable models were considered. Model 2 adjusted for only health behaviors (smoking status, caloric intake, alcohol consumption and physical activity) and a marker of adiposity (body mass index) based on assumptions inherent in Figure 1B. Model 3 adjusted for only the socio-demographic variables age, sex, race/ethnicity and educational level. Model 4 adjusted for health behaviors and socio-demographic variables. Model 5 adjusted for socio-demographics, health behaviors and adiposity. Finally, model 6 expanded model 5 by additionally adjusting for variables that could be considered as either a confounder or mediator of associations between periodontal infection and prediabetes depending on the causal structure hypothesized; this model included adjustment for systolic blood pressure, total cholesterol-to-HDL ratio, WBC and CRP as previous reports suggest periodontal infection as a possible risk factor for these outcomes (D'Aiuto et al., 2006, Desvarieux et al., 2010, Demmer et al., 2013). Unless otherwise stated, ORs reported in the main text were derived from model 5 as we believe this provides the best combination of parsimony and validity.

To provide additional information regarding the magnitude and direction of confounding by the aforementioned variables considered individually, we also constructed tables summarizing the difference between parameter estimates from logistic models with more vs. less covariable adjustment using a “change-in-estimate” approach (Mickey and Greenland, 1989); change-in-estimate was defined as: $[(\text{LN}(\text{more adjusted OR}) - \text{LN}(\text{less adjusted OR})) / \text{LN}(\text{adjusted OR})] \times 100$, yielding the percent change in the OR resulting from lack of adjustment. The approach uses 13 model selection iterations (the number of possible covariables). Iteration 1 started with the unadjusted parameter estimate for periodontal infection and then ran 13 separate regressions considering the influence of all potential confounders on the unadjusted parameter estimate. The confounder that produced the greatest change-in-estimate was added to the regression to form an “intermediate” model and another modeling iteration was repeated; each modeling iteration increases the number of independent variables in the intermediate model by 1 and decreases the number of remaining confounders by 1. Four variables hypothesized as possible mediators were assessed in the last four iterations. Results from our change-in-estimate analysis did not suggest that the aforementioned models 1 – 6 would be inappropriate.

RESULTS

General Characteristics

Participants had a mean $\pm$ SD age of 50 ± 14 years and 51% were women. Hispanics, Whites and Blacks represented 31%, 49% and 15% of the sample (5% reported other race/ethnicity). Mean PD was (mean $\pm$ SD) 1.63 ± 0.58 mm and mean AL was 1.59 ± 1.05 mm. The prevalence of moderate and severe periodontitis was 33% and 10%, respectively, and the remaining

participants had no/mild periodontitis. Periodontitis was associated with adverse levels of several risk factors for cardiometabolic disease such as age, education smoking status, HDL-cholesterol and systolic blood pressure (Supplemental Table 1). Body mass index and obesity prevalence did not vary according to levels of periodontitis (Supplemental Table 1). Supplemental table 1 also summarizes periodontal clinical characteristics across periodontitis status to better inform the severity of disease in this population-based sample. For example, mean PD and AL among individuals with severe periodontitis were 2.5 mm and 3.4 mm, respectively. In comparison, mean PD and AL values among individuals with PD or AL 75th percentile were 2.4 mm and 2.9 mm, respectively.

Variation in levels of cardiometabolic risk factors across levels of mean AL or PD were similar to what was observed for periodontitis. However, participants with mean AL 75th vs. <75th percentile were 7 years older on average ($p<0.0001$) while those with PD 75th vs. <75th percentile were only 1 year older ($p=0.18$) which is consistent with previous report from NHANES (Demmer et al., 2012b).

The mean $\pm$ SD values for two-hour post-challenge glucose and fasting plasma glucose were 109 $\pm$ 32 mg/dl and 98 $\pm$ 9 mg/dl (Supplemental Table 1). The respective prevalence estimates for isolated-IFG, isolated-IGT and combined IFG+IGT were 33%, 6% and 10%; the prevalence estimates of any IFG and any IGT were 43% and 16%. Among participants with vs. without IGT, 65% and 39% also had IFG (26% risk difference, $P<0.0001$). In comparison, among participants with vs. without IFG, 25% vs. 10% also had IGT (15% risk difference, $P<0.0001$).

As compared to participants without prediabetes or with isolated-IFG, participants with isolated-IGT tended to be older, female, have higher CRP and WBC levels but intermediate fasting insulin and HOMA-IR values; they were also less likely to smoke or participate in vigorous activity (Table 1). Fasting glucose levels were similar among participants without any prediabetes and those with isolated-IGT (1.5 mg/dl difference, $P=0.11$). In contrast, two-hour post-challenge glucose levels were higher in isolated-IFG vs. no prediabetes: 105 $\pm$ 1.3 vs. 93 $\pm$ 0.9, $P<0.0001$ (Table 1). Relative to participants without any IGT/IFG, or those with isolated-IFG, those with isolated-IGT were older, had lower indicators of socio-economic status and higher levels of inflammatory biomarkers but were less likely to be ever smokers Table 1.

Periodontal Status and Prediabetes

After multivariable adjustment, including smoking status and BMI, the odds ratios for any-IGT among participants with moderate or severe periodontitis, relative to those with no/mild periodontitis, were 1.07[0.50,2.25] and 1.93[1.18,3.17] (Table 2, model 5). In contrast, the ORs[95%CI] for any-IFG among participants with moderate or severe periodontitis, respectively, were 1.14[0.74,1.77] and 1.12[0.58,2.18] (Table 2, model 5).

The odds for any-IGT were increased by 105% when comparing 4th quartile vs. 1st-3rd quartiles of mean PD: OR[95%CI]=2.05[1.24,3.39] (Table 3, model 5). The ORs summarizing the relationship between mean AL and any-IGT were attenuated as were results for any-IFG (Table 3). Findings were similar when modeling PD and AL

continuously (Supplemental Table 2) and also when PD and AL were derived from all periodontal sites, including mid-facial and mid-buccal sites (Supplemental Table 3). Additional adjustment for potential mediators did not meaningfully change observed ORs or the interpretation of results (Tables 2 & 3, model 6).

Results from change-in-estimate analyses to quantify the magnitude and direction of confounding revealed important patterns (Supplemental Tables 4–6). For the probing depth exposure, education level, smoking status, race/ethnicity, age and activity level were the strongest confounders. For the AL exposure age, smoking status and education adjustments produced meaningful changes in the odds ratio; the age related confounding was substantial. Confounding patterns for the CDC/AAP defined periodontitis exposure were similar to those for mean AL. In all analyses smoking status, race/ethnicity and activity level demonstrated patterns of negative confounding in which adjustment for these variables strengthened, rather than attenuated, the association between periodontal infection and prediabetes. Negative confounding was also observed for sex adjustments although the magnitude of sex related confounding was minimal (Supplemental Tables 4–6).

When considering the relationship between periodontal status and either isolated-IFG, isolated-IGT or combined IFG+IGT in generalized logistic regression models, the observed ORs were notably larger for the isolated-IGT outcome than for isolated-IFG (Table 4). After full multivariable adjustment (as in Model 6, tables 2 and 3), when comparing individuals with mean PD 75th vs. <75th percentile, the respective ORs[95%CI] for isolated-IFG, isolated-IGT or combined IFG+IGT were: 0.91[0.57,1.45], 1.85 [0.73,4.66] and 2.06[0.91,4.66] (also shown in Table 4). Respective ORs[95%CI] when modeling mean AL 75th vs. <75th percentile were: 1.13[0.70,1.84], 1.11[0.57,2.16], 1.45[1.01, 2.08]; these results were adjusted for all variables in table 4 with the exception of mean PD. The fact that the OR for mean AL predicting combined IFG+IGT was statistically significant while the same OR for mean probing depth was not – despite a larger OR – is due to a greater NHANES design effect for the PD vs. the AL parameter estimate.

Results summarizing the observed relationships between several other putative prediabetes risk factors including age, gender, educational level, alcohol consumption, body mass index, systolic blood pressure and cholesterol levels are presented in Table 4.

CONCLUSION

We have found clinical measures of periodontal infection to be associated with the prediabetic state. Severe periodontitis was associated with a 93% increase in the odds of impaired glucose tolerance after multivariable adjustment. Findings were similar for mean PD. In contrast, associations between measures of periodontal infection and IFG were weak and not statistically significant.

These findings advance our understanding of the relationship between diabetes and clinical periodontal disease. Most research in this area hypothesizes that associations between clinical periodontal disease and diabetes status are due to a causal contribution of diabetes to periodontal tissue destruction (Lalla and Papapanou, 2011, Taylor, 2001, Taylor et al.,

1998a, Taylor et al., 1998b, Demmer et al., 2012a). While biologically plausible, and supported by strong findings in several studies (Lalla and Papapanou, 2011, Taylor, 2001), the interpretation of results from most studies has been limited in a variety of ways, such as by small sample sizes and/or lack of comprehensive confounder adjustment as previously discussed (Demmer et al., 2012a). Recent findings arising from a longitudinal, population-based cohort with the data collection necessary to perform comprehensive covariate adjustments have reported evidence to support the hypothesis of diabetes as a causal risk factor for periodontitis, although findings were much weaker than previous studies and only uncontrolled diabetes was observed to predict worsening periodontal status (Demmer et al., 2012a).

It has also been proposed that associations between periodontal infection and diabetes might be bidirectional. For example, an impaired immune response to dysbiotic subgingival biofilms among people with diabetes might contribute to a chronic inflammatory state and subsequently to both clinical periodontal disease as well as heightened insulin resistance and reduced glycemic control. The ensuing uncontrolled glycemia could further exacerbate periodontal destruction via the formation of advanced glycation end products (Lalla and Papapanou, 2011).

More recently, the hypothesis of bidirectional relationships between periodontal infection and diabetes has been extended to consider adverse subgingival microbial exposures as a causal risk factor for diabetogenesis (Demmer et al., 2008, Demmer et al., 2012b, Demmer et al., 2010a). The current findings bolster this hypothesis by building on previous research and demonstrating an association between periodontal infection and prediabetes. Although the temporality of associations cannot be established in cross-sectional data, it is unlikely that IFG or IGT could have been a driving causal factor in the development of severe periodontitis as most previous research suggests that severe dysglycemia observed in uncontrolled diabetes is necessary to have a meaningful influence on periodontal tissue destruction (Taylor et al., 1998a, Demmer et al., 2012a, Tsai et al., 2002). Nevertheless, it is possible that hyperglycemia in the prediabetic state might contribute to compositional shifts in the subgingival microbiome and incipient gingival inflammation.

The hypothesis that infection might contribute to diabetogenesis is biologically plausible and fits logically into the larger framework regarding host inflammatory phenotype as a risk factor for insulin resistance and diabetes development (Demmer et al., 2008, Demmer et al., 2010a, Demmer et al., 2012b). Chronically elevated systemic inflammation has been shown to predict insulin resistance (Park et al., 2009, Pradhan et al., 2003) impaired glucose metabolism (Chakarova et al., 2009) and incident T2DM (Pradhan et al., 2001, Hu et al., 2004). Accordingly, several exogenous inflammatory stimuli such as air pollution (Kramer et al., 2010), tobacco smoke (Foy et al., 2005) and pollutants (Lee and Jacobs, 2006, Lee et al., 2010, Lee et al., 2007) have also been linked to T2DM risk. Regarding the potential for periodontal infections to trigger a chronic inflammatory response, it has been suggested that “keystone” pathogens such as *P. gingivalis* might possess the ability to evade and/or subvert the host immune system in a manner that enables keystone organisms to persist in the subgingival space, subsequently shifting the microbial community composition towards a state of dysbiosis and chronic inflammation (Hajishengallis et al., 2012, Hajishengallis et al.,

2011). Accordingly, there is a large body of research reporting that individuals with clinical evidence of current periodontal inflammation also have elevated levels of systemic inflammation and randomized controlled trials have shown that anti-infective periodontal treatment can lead to reductions in systemic inflammation (Lockhart et al., 2012, Demmer et al., 2013).

In these data, after multivariable adjustment (excluding potential mediators), the ORs summarizing associations between periodontal infection and outcomes that included impaired glucose tolerance (i.e., IGT with or without IFG) ranged from ~1.4–2.0 depending on the exposure modeled. In contrast, ORs summarizing associations between infection and IFG ranged from 0.98 – 1.05. This suggests that IGT outcomes might be more relevant vis-à-vis infection and potentially supports the mechanistic involvement of inflammation. Previous studies have demonstrated increased CRP levels to be more strongly linked to IGT than IFG outcomes (Chakarova et al., 2009, Muntner et al., 2004, Capaldo et al., 2013) and our own current results also show higher CRP levels among participants with isolated-IGT vs. isolated-IFG. Although, we did not observe strong attenuation of our findings after adjustment for inflammation, findings of this nature are not uncommon among studies of periodontal infection and diabetes risk. As previously discussed, it is possible that CRP and WBC might be sufficient but not necessary mediators in the causal pathway from microbial exposures to impaired glucose regulation and a larger set of inflammatory biomarkers might be required to adequately consider mediation hypotheses (Demmer et al., 2012b). Future studies with more comprehensive biomarker assessments during longitudinal follow-up will be necessary to better inform the potential for inflammatory mediation.

ORs were generally larger for analyses modeling either mean PD or CDC/AAP periodontitis as the primary exposure when compared to mean AL. This is likely due to the fact that mean AL was notably lower among participants in the upper 25th percentile of AL as compared to participants with severe periodontitis. In contrast, mean PD was similar among individuals with severe periodontitis and those in the upper 25th percentile of PD.

Our apparently null results for the IFG outcome are in contrast to positive findings among >12,000 participants in NHANES III (Choi et al., 2011) in which both AL and PD were related to an ~20%–50% increase in odds of IFG. However, the previous NHANES III publication did not measure IGT and it is possible that the finding was driven by a higher prevalence of combined IFG & IGT relative to our current sample.

Periodontal infection was associated with impaired glucose tolerance after comprehensive multivariable adjustment. The strongest confounders in these data appeared to be age, smoking, race/ethnicity, education level and activity level. After adjustment for these variables, further adjustment did not meaningfully change the strength of association. Importantly, adjustment for body mass index – the strongest known risk factor for prediabetes – also had only marginal influence on the strength of associations. The fact that smoking was a negative confounder (i.e., smoking adjustment strengthened rather than attenuated results) is notable as smoking has frequently been suspected as a prominent source of positive confounding (i.e., smoking adjustment attenuates results) in studies concerning periodontal infection and nonperiodontal outcomes such as cardiovascular

disease and cancer(Hujoel et al., 2002). Therefore, the pattern of negative confounding substantially minimizes the potential for our reported ORs to be overestimated due to residual confounding related to tobacco exposure. The pattern of negative confounding by smoking arises from the fact that smoking is often inversely related to metabolic outcomes while it is positively related to periodontal disease; in our current report, the odds of isolated-IGT were lower among current smokers relative to never smokers (see results). Similarly, previous studies found smoking to be a negative confounder of the relationship between periodontal infection and five-year change in hemoglobin A1c level. That pattern was the result of inverse associations between baseline smoking status and longitudinal A1c change(Demmer et al., 2010a).

We have found clinical indicators of periodontal infection to be associated with impaired glucose tolerance among a nationally representative sample of U.S. adult men and women. The exact temporality of associations cannot be determined in these cross-sectional data nor are there sufficient data to carefully explore the role of inflammation as an underlying biological mechanism. Longitudinal studies that collect broader panels of inflammatory biomarkers will be important for answering these questions. Nevertheless, the findings are suggestive of a potential role for periodontal infections in the etiology of impaired glucose regulation. If replicated in future studies, the public health implications would be substantial given the high prevalence of inflammatory periodontal infections in the general population(Demmer and Papapanou, 2010).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This research was supported by NIH grants R00 DE-018739 and R21 DE-022422 to Dr. Demmer. Additional funding support was provided by a Pilot & Feasibility Award to Dr. Demmer from the Diabetes and Endocrinology Research Center, College of Physicians and Surgeons, Columbia University (DK-63608); Dr. Desvarieux also receives support from R01 DE-13094 and a Chair in Chronic Disease, École des Hautes Études en Santé Publique, France.

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Clinical Relevance

Scientific Rationale for Study: Periodontal infections have been hypothesized as a potential risk factor for poor metabolic outcomes but limited data are available exploring whether periodontal infections are differentially associated with impaired glucose tolerance or impaired fasting glucose among diabetes-free individuals.

Principal Findings: Periodontitis was associated with increased odds of impaired glucose tolerance but not impaired fasting glucose.

Practical Implications: Future research studies are merited to understand whether periodontal infections are more strongly associated with specific glucose metabolism phenotypes and whether the observed associations are causal or confounded.

Figure 1.

A. Directed Acyclic Graph (DAG) representing one possible underlying causal structure of interrelationships among periodontal infection, prediabetes and several mediators or confounders of the association. This causal structure assumes potential socio-demographic confounders relate to periodontal infection and prediabetes through multiple mechanisms (e.g., confounding by socio-demographic variables can act through health behaviors and adiposity but also through other mechanisms not represented in our data); this causal structure would necessitate adjustment for all sociodemographic variables. A similar argument can be made for more proximal variables in the causal chain such as health behaviors and adiposity. Only statistical adjustment for all potential confounders will provide the least confounded estimate.

B. Directed Acyclic Graph (DAG) representing one possible underlying causal structure of interrelationships among periodontal infection, prediabetes and several mediators or confounders of the association. This causal structure assumes that all confounding effects of sociodemographic variables act entirely through effects on either health behaviors or adiposity (two constructs which are measured in our data); this causal structure does not require adjustment for sociodemographic variables so long as health behaviors and adiposity adjustments are made.

Characteristics of participants according to prediabetes status. 1,165 men and women 30–80 years old, enrolled in The Continuous National Health and Nutrition Examination Survey (NHANES) 2009 – 2010.

Table 1

	No Prediabetes n=598 (51%)	Isolated IFG n=379 (33%)	Isolated IGT n=66 (6%)	Combined IFG & IGT n=122 (10%)	P-value
Age (years)	46.9 ± 0.6	48.9 ± 0.8 ^a	55.2 ± 2.7 ^{a,b}	57.3 ± 1.5	<0.0001
Male (%)	38%	66% ^a	26% ^b	57%	<0.0001
Race/Ethnicity					0.99
% Hispanic	30%	31%	32%	31%	
% Non-Hispanic White	49%	49%	47%	50%	
% Non-Hispanic Black	16%	14%	15%	13%	
% Other	5%	6%	6%	6%	
Education					0.004
% Less than high school	22%	26% ^a	36% ^a	31%	
% Completed High School	21%	25%	20%	25%	
% Some college or AA degree	29%	26%	27%	26%	
% College graduate and above	29%	24%	17%	17%	
Family Poverty Income Ratio	3.3 ± 0.1	3.3 ± 0.1	2.9 ± 0.2 ^{a,b}	3.1 ± 0.2	0.11
Smoking Status					0.09
% Never	60%	53%	68% ^b	54%	
% Former	23%	26%	18%	29%	
% Current	17%	21%	14%	17%	
CDC BMI category					<0.0001
<25 kg/m ²	36%	18% ^a	21% ^a	20%	
25 – 29.9 kg/m ²	37%	41%	38%	32%	
30 kg/m ²	27%	42%	41%	48%	
BMI (kg/m²)	27.3 ± 0.5	29.9 ± 0.3 ^a	29.8 ± 1.1 ^a	30.9 ± 0.8	0.0004
Alcohol use (grams/day)	10.9 ± 1.4	10.0 ± 1.33	4.9 ± 2.8	9.9 ± 2.4	0.28
Physical Activity in a typical week				0.004	

	No Prediabetes n=598 (51%)	Isolated IFG n=379 (33%)	Isolated IGT n=66 (6%)	Combined IFG & IGT n=122 (10%)	P-value
None	28%	26%	44% ^{a,b}	41%	
Moderate activity	35%	33%	35%	34%	
Vigorous activity	37%	41%	21%	25%	
Kilocalories consumed in previous 24 hrs.					
21118.9±45	2419.8±81 ^a	1957.3±132 ^b	2120.7±94	0.04	
Periodontal Status					
Mean Probing Depth (mm)	1.47±0.03	1.60±0.04 ^a	1.56±0.09	1.68±0.09	0.004
Mean Attachment Loss (mm)	1.31±0.04	1.51±0.08 ^a	1.46±0.12	1.90±0.14	0.003
Periodontal Disease (CDC AAP definition)				<0.0001	
Healthy	64%	53% ^a	52%	40%	
Moderate	29%	36%	38%	37%	
Severe	7%	11%	11%	23%	
Blood Pressure					
Systolic BP (mmHg)	116±0.9	121±0.8 ^a	125±1.8 ^a	124±1.9	<0.0001
Diastolic BP (mmHg)	68±1.0	71±1.0 ^a	70±1.8	70±1.6	0.1
HDL-Cholesterol	58±0.6	50±1.0 ^a	56±3.2	52±2.0	<0.0001
LDL-Cholesterol	122±0.8	124±2.8	127±3.9	117±3.1	0.25
Total Cholesterol-to-HDL-Cholesterol Ratio	3.7±0.04	4.3±0.08 ^a	4.1±0.2	4.1±0.2	<0.0001
WBC Count (cellsx10⁹/L)	6.2±0.09	6.5±0.13	6.7±0.26	6.9±0.2	0.01
hs-C-Reactive Protein (mg/L)	2.6±0.2	4.4±0.6 ^a	5.4±0.7 ^a	5.0±0.8	<0.0001
American Heart Association hs-CRP Categories					
<1.0 mg/L	36%	30% ^a	27% ^{a,b}	25%	<0.0001
1.0 – 3.0 mg/L	36%	36%	23%	27%	
>3.0 mg/L	28%	34%	50%	48%	
Plasma Fasting Glucose (mg/dl)	91.7±0.3	105.8±0.4 ^a	93.2±1.0 ^b	109.1±0.8	<0.0001
Two Hour Glucose(OGTT) (mg/dl)	93±0.9	105±1.3 ^a	158±3.2 ^{a,b}	166±1.7	<0.0001

	No Prediabetes n=598 (51%)	Isolated IFG n=379 (33%)	Isolated IGT n=66 (6%)	Combined IFG & IGT n=122 (10%)	P-value
Insulin levels (µU/ml)	9.8±0.4	15.3±0.6 ^a	12.7±1.1 ^a	17.4±1.4	<0.0001
HOMA-IR	2.2±0.1	4.0±0.17 ^a	2.9±0.3 ^{a,b}	4.7±0.4	<0.0001
HbA1c % (mmol/mol)	5.3± 0.01 (34±0.1)	5.5±0.02 (37±0.2) ^a	5.6±0.07 (38±0.8) ^a	5.7±0.05 (39±0.5)	<0.0001

^a P<0.05 for any comparison with the no prediabetes group

^b P<0.05 for comparisons between IFG and IGT

Table 2

Odds ratios (95% CI) for prevalent prediabetes according to periodontal status. 1,165 men and women 30–80 years old, enrolled in The Continuous National Health and Nutrition Examination Survey (NHANES) 2009–2010.

	Healthy/Mild periodontitis (n=665)	Moderate Periodontitis (n=383)	Severe Periodontitis (n=117)	P for Linear trend
Prediabetes Outcome Defined as Any Impaired Glucose Tolerance				
IGT prevalence	12%	18%	31%	
Model 1	Ref.	1.70 (0.88–3.3)	2.56(1.65–3.98)	<0.0001
Model 2	Ref.	1.67 (0.85–3.28)	2.90 (1.80–4.68)	<0.0001
Model 3	Ref.	1.04 (0.52–2.06)	1.75 (1.16–2.62)	0.012
Model 4	Ref.	1.04 (0.49–2.20)	2.01(1.27–3.20)	<0.01
Model 5	Ref.	1.07 (0.50–2.25)	1.93 (1.18–3.17)	0.02
Model 6	Ref.	1.04 (0.51–2.11)	1.87(1.10–3.16)	0.04
Prediabetes Outcome Defined as Any Impaired Fasting Glucose				
IFG prevalence	38%	48%	59%	
Model 1	Ref.	1.54 (1.12–2.14)	2.01(1.28–3.14)	0.004
Model 2	Ref.	1.62 (1.11–2.37)	1.99 (1.17–3.38)	0.01
Model 3	Ref.	1.14 (0.79–1.65)	1.14 (0.68–1.90)	0.78
Model 4	Ref.	1.11 (0.73–1.69)	1.15 (0.65–2.01)	0.86
Model 5	Ref.	1.14 (0.74–1.77)	1.12 (0.58–2.18)	0.84
Model 6	Ref.	1.08 (0.70–1.68)	1.05 (0.56–1.99)	0.94

Model 1: Crude; Model 2: smoking, total calorie intake, total alcohol intake, physical activity, BMI; Model 3: age, sex, race/ethnicity, education level, Model 4 model 3 + smoking, total caloric intake, total alcohol intake, physical activity; Model 5: model 4 + BMI; Model 6: model 5 + systolic blood pressure, total cholesterol/hdl ratio, total WBC count and CRP.

Table 3

Odds ratios for prevalent prediabetes according to mean probing depth and mean attachment loss levels. 1,165 men and women 30–80 years old, enrolled in The Continuous National Health and Nutrition Examination Survey (NHANES) 2009–2010.

	Mean Probing Depth*			Mean Attachment Loss*		
	<75 th percentile (n=873)	75 th percentile (n=292)	P-value	<75 th percentile (n=874)	75 th percentile (n=291)	P-value
Prediabetes Outcome Defined as Any Impaired Glucose Tolerance (IGT)						
IGT prevalence	14%	23%		14%	24%	
Model 1	Ref.	2.06 (1.31–3.21)	0.002	Ref.	1.95 (1.24–3.07)	0.004
Model 2	Ref.	2.26 (1.43–3.58)	<0.001	Ref.	2.09 (1.39–3.16)	<0.001
Model 3	Ref.	1.97 (1.26–3.07)	0.003	Ref.	1.31 (0.85–2.01)	0.22
Model 4	Ref.	2.23 (1.37–3.62)	0.001	Ref.	1.43 (0.91–2.24)	0.12
Model 5	Ref.	2.05 (1.24–3.39)	0.005	Ref.	1.41 (0.90–2.22)	0.14
Model 6	Ref.	1.99 (1.17–3.38)	0.01	Ref.	1.32 (0.84–2.09)	0.23
Prediabetes Outcome Defined as Any Impaired Fasting Glucose (IFG)						
IFG prevalence	39%	55%		39%	55%	
Model 1	Ref.	1.62 (1.16–2.27)	0.005	Ref.	1.64 (1.10–2.45)	0.02
Model 2	Ref.	1.42 (0.91–2.20)	0.12	Ref.	1.63 (1.04–2.58)	0.03
Model 3	Ref.	1.22 (0.80–1.85)	0.35	Ref.	1.10 (0.68–1.78)	0.69
Model 4	Ref.	1.15 (0.73–1.81)	0.55	Ref.	1.06 (0.61–1.83)	0.84
Model 5	Ref.	1.03 (0.59–1.81)	0.91	Ref.	1.04 (0.59–1.81)	0.90
Model 6	Ref.	0.98 (0.55–1.75)	0.94	Ref.	0.96 (0.56–1.63)	0.87

* Mean probing depth and attachment loss values are based on interproximal sites from all teeth present excluding 3rd molars.

Model 1: Crude; Model 2: smoking, total calorie intake, total alcohol intake, physical activity, BMI; Model 3: age, sex, race/ethnicity, education level, Model 4 model 3 + smoking, total calorie intake, total alcohol intake, physical activity; Model 5: model 4 + BMI; Model 6: model 5 + systolic blood pressure, total cholesterol/hdl ratio, total WBC count and CRP.

Table 4

Predictors of prevalent prediabetes in multivariable logistic regression models among 1,165 men and women aged 30–80 years, enrolled in The Continuous National Health and Nutrition Examination Survey (NHANES) 2009–2010.

	Isolated-IFG	Isolated-IGT	Combined IFG+IGT	P-value*
Periodontal Status				0.05
Mean PD 75 th percentile	0.91 [0.57,1.45]	1.85 [0.73,4.66]	2.06 [0.91,4.66]	
Age (10 year increase)	1.25 [1.07,1.46]	1.40 [0.99,1.98]	2.13 [1.65,2.75]	<0.0001
Male vs. female	2.59 [1.78,3.77]	0.54 [0.22,1.28]	2.40 [1.08,5.30]	<0.0001
Race/Ethnicity				0.57
Hispanic vs. White	1.13 [0.60,2.11]	0.73 [0.26,2.04]	1.08 [0.41,2.86]	
Black vs. White	0.95 [0.49,1.84]	0.71 [0.23,2.25]	0.69 [0.31,1.56]	
Other vs. White	2.23 [0.78,6.36]	0.91 [0.36,2.28]	2.12 [0.40,11.1]	
Education Level				0.001
College grad vs. <HS	1.03 [0.57,1.85]	0.62 [0.13,2.89]	0.99 [0.54,1.84]	
Some college vs. <HS	0.86 [0.47,1.58]	0.64 [0.27,1.50]	0.81 [0.47,1.40]	
HS grade vs. <HS	1.26 [0.69,2.30]	0.70 [0.17,2.88]	1.33 [0.74,2.39]	
Smoking Status				0.12
Former vs. Never	1.02 [0.66,1.58]	0.75 [0.32,1.79]	0.71 [0.35,1.42]	
Current vs. Never	0.95 [0.55,1.64]	0.26 [0.09,0.75]	0.71 [0.32,1.59]	
Alcohol Consumption				0.01
1–3 drinks/day vs. none	0.81 [0.62,1.05]	0.89 [0.39,2.06]	0.69 [0.31,1.54]	
4 drinks/day vs. none	0.67 [0.32,1.40]	0.15 [0.01,1.67]	1.35 [0.51,3.62]	
Caloric Intake (500 Kcal/day increase)	1.10 [0.97,1.25]	1.05 [0.84,1.31]	1.01 [0.81,1.27]	0.43
Physical Activity Level				0.10
Moderate vs. none	1.20 [0.76,1.88]	0.68 [0.29,1.59]	0.69 [0.41,1.58]	
Vigorous vs. none	1.19 [0.65,2.19]	0.44 [0.14,1.34]	0.63 [0.36,1.11]	
Body Mass Index				<0.0001
Overweight vs. normal	1.76 [1.16,2.68]	1.18 [0.50,2.80]	2.12 [1.26,3.58]	
Obese vs. normal	2.29 [1.17,4.48]	0.92 [0.33,2.58]	3.56 [2.23,5.70]	
Systolic blood pressure (10 mm Hg increase)	1.12 [1.00,1.24]	1.22 [1.03,1.45]	1.05 [0.85,1.32]	0.04
Total cholesterol-to-HDL cholesterol ratio (1 unit increase)	1.15 [1.05,1.26]	1.27 [1.07,1.51]	1.12 [0.87,1.45]	0.002
CRP Level 1–3 mg/L	0.78 [0.59,1.03]	0.82 [0.29,2.33]	0.63 [0.26,1.15]	<0.001
>3 mg/L	1.41[0.88,2.25]	1.91[0.97,3.76]	1.61[0.79,3.26]	
White Blood Cell Count (1 × 10⁹ cells increase)	1.07 [0.94,1.21]	1.12 [0.88,1.42]	1.11 [0.88,1.41]	0.78

IFG=Impaired fasting glucose

IGT = Impaired glucose tolerance

* P-value derived from Wald chi-square values used to test the null hypothesis of no difference in the odds of prediabetes across levels of exposure.

PD=Probing Depth