Potential association between prediabetic conditions and gingival and/or periodontal inflammation

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ABSTRACT
Aims/Introduction: Prediabetic conditions, which include impaired fasting glucose (IFG) and impaired glucose tolerance (IGT), might be associated with chronic gingival and/or periodontal inflammation. However, the occurrence of this oral inflammation in prediabetic conditions is poorly understood. The present study aimed to assess the association between prediabetes and gingival and/or periodontal inflammation.

Materials and Methods: A total of 94 Puerto Rican men and women aged 40–65 years, who were residents of San Juan, Puerto Rico, and free of diabetes, were included in the study. All participants had at least one tooth site with clinical attachment loss ≥3 mm. Fasting and 2-h plasma glucose were collected. Gingival/periodontal inflammation was assessed by bleeding on gentle probing of the sulcus at six sites per tooth.

Results: Participants with the percentage of teeth with bleeding on probing (BOP) equal to or greater than the median were compared with those with the percentage of teeth with BOP less than median. Participants with high BOP tended to present higher IFG (odds ratio [OR] 5.5, 95% confidence interval [CI] 1.2–25.3) and/or prediabetic condition (OR 3.6, 95% CI 1.0–13.2) than those with a low percentage of BOP, adjusting for age, sex, smoking, alcohol consumption, waist circumference and number of missing teeth. Using the continuous form of the outcome, the corresponding adjusted least squares means of percentage of BOP were 26.8 (standard error of the mean [SEM] 2.3) and 43.8 (SEM 6.0) in normal and IFG, respectively (P = 0.01), and 27.0 (SEM 2.4) and 39.0 (SEM 5.3) among healthy and prediabetic individuals, respectively (P = 0.05).

Conclusion: IFG and/or prediabetes are strongly associated with BOP, a marker of chronic gingival/periodontal inflammation.

INTRODUCTION
Bleeding on probing (BOP) is highly prevalent, and is a major component of routine periodontal examinations carried out in clinical settings and dental clinical research. However, its clinical relevance in the disease progression from chronic gingivitis to severe periodontal disease remains unclear. BOP is a classic sign of periodontal inflammation, and has been observed to be highly correlated to active periodontal disease. Thus, it could serve as an indicator of disease activity1. In contrast, although there is a strong correlation between BOP and gingival inflammation2,3, BOP might have limited predictability in terms of periodontal disease progression4,5. Nevertheless, if this measurement is carried out properly, BOP could be an additional useful clinical tool to detect the presence and monitor the development of acute or chronic inflammatory processes, regardless of the stage of the disease progression. In individuals with extensive periodontal disease, this parameter could be highly pertinent to their chronic inflammatory status and could, therefore, serve as an additional screening or monitoring tool for disease progression.

Studies have suggested that diabetes is a systemic disease well documented as a risk factor for the development of periodontal disease6. As such, diabetes is an ideal model to study the
natural history of this oral disease and its progression. Still, the mechanisms underlying the transition from chronic gingivitis to periodontal disease among people with diabetes are not known. Nor is it clear whether the transition rate is higher among those with type 2 diabetes or those presenting with prediabetic conditions compared with individuals in the general population showing no evidence of systemic disease. Therefore, comparing BOP, in addition to probing depth (PD) and clinical attachment loss (CAL), between individuals with or without prediabetic conditions is important. The findings of such a study could suggest means for prevention and control of both periodontal disease and diabetes among high-risk populations. Indeed, the association between chronic gingival and/or periodontal disease and diabetes among high-risk populations. The present study aimed to evaluate the potential association between prediabetes (presence of impaired fasting glucose [IFG] and/or 2-h impaired glucose tolerance [IGT]), and the occurrence of gingival and/or periodontal inflammation and prediabetic conditions is poorly understood and has rarely been studied.

The present study aimed to evaluate the potential association between prediabetes (presence of impaired fasting glucose [IFG] and/or 2-h impaired glucose tolerance [IGT]), and the occurrence of gingival and/or periodontal inflammation among Hispanics consisting of Puerto Rican adults residing in the San Juan, Metropolitan area.

MATERIALS AND METHODS

Study Population

A cross-sectional study including 100 Puerto Rican overweight or obese adults aged 40–65 years and residing in the San Juan, Puerto Rico, metropolitan area was carried out in November 2008. Participants were excluded if they had diagnosis of diabetes (type 1 or 2, or others) and metastatic cancer, or had less than four natural teeth (to allow periodontal examination). Other exclusion criteria included: (i) taking either insulin or oral antidiabetic agents; (ii) having braces or orthodontic appliances that might make the periodontal measurements difficult; (iii) being pregnant; (iv) diagnosis of hypoglycemia; (v) history of coronary heart disease, congenital heart murmurs, heart valve disease, congenital heart disease, endocarditis, stroke, rheumatic fever and hemophilia or bleeding disorders; (vi) undergoing current dialysis treatment; (vii) undergoing current anticoagulation therapy; or (viii) requiring antibiotic prophylaxis before a dental procedure.

A total of 141 Puerto Rican adults originally responded to the recruitment. Of these, 27 were not eligible, two refused to participate in the study, 11 participants did not appear for their appointments, and one participant, who had a medical problem during the study procedure, dropped out. Among the remaining 100 participants who successfully completed all the study procedures, five participants who had fasting plasma glucose (FPG ≥126 mg/dL) and/or oral glucose tolerance test (2-h postprandial glucose ≥200 mg/dL) indicative of diabetes, and one participant who was later found to be ineligible (older than 65 years) were excluded from the analysis. Therefore, the final sample for statistical analysis included 94 overweight or obese Puerto Rican adult participants. The pilot study was approved by the institutional review board at the University of Puerto Rico, and all participants provided signed informed consent before any study procedures.

Measurements of Glucose, Insulin, Homeostasis Model Assessment and Other Serum Lipid Levels

Participants were asked to fast for 10 h before their appointments, and up to the last blood drawing on that appointment. After signing the informed consent, FPG was collected. The 1- and 2-h postprandial blood samples were subsequently gathered after glucose beverage consumption (296 mL of glucola containing 75 g of dextrose). Participants’ fasting glucose level is determined to be impaired if it is between 100–125 mg/dL, the 1-h glucose tolerance level is impaired if it is ≥155 mg/dL (1-h IGT) and the 2-h glucose tolerance is impaired if the level is between 140 and 199 mg/dL (2-h IGT). The cut-off point of 155 mg/dL for the 1-h oral glucose tolerance test is associated with obesity, and can be used to identify individuals who are at risk for type 2 diabetes and vascular atherosclerosis. More detailed information on the assessment of glucose, fasting insulin, homeostasis model assessment (HOMA) and serum lipid levels, such as triglyceride and high-density lipoprotein (HDL) cholesterol is described in our previous article. The prediabetic condition is defined as having either IFG or 2-h IGT.

Periodontal Examination

Periodontal examination, carried out by one of three trained and calibrated dental examiners, included measures of PD, gingival recession, CAL and BOP. PD is the depth of the periodontal pocket measured as the distance in millimeters between the free gingival margin (FGM) and the base of the pocket. Gingival recession is the distance in millimeters between the FGM and the line of the cemento-enamel junction (CEJ). CAL is clinically presented by the total denudation of the root surface of the tooth, and computed as the difference in millimeters between the measure of PD and the gingival recession (CEJ to FGM distance). BOP, which indicates the presence or absence of bleeding at any of six sites per tooth during periodontal probing procedures, was recorded as follows: the probe was gently inserted to the base of the sulcus or pocket with a probing force of no more than 20 g, and BOP was considered positive when the probed site bled within 20s after removal of the probe tip. The severity of the BOP was determined by the percentage of the number of teeth with any site bleeding during the periodontal probing.

Other Data Collection

Participants had three consecutive blood pressure measurements. Anthropometric measures, such as weight, height, and waist and hip circumferences, were collected during the interview, and the body mass index (BMI) and waist-to-hip ratio were computed. Briefly, an in-person interview gathered information on demographic and socioeconomic variables, such as age, sex, marital status and total years of education. Health-related lifestyle habits included smoking status (ever smoked vs
never smoked) and history of alcohol consumption (current vs
never or former).

Statistical Analysis
We categorized the participants as high or low BOP (percentage
age of teeth with BOP greater than or equal to the median and percentage of teeth with BOP less than the median). The two
groups were compared using the mean or median and standard
deviation for continuous variables, and the frequency and per-
centage for categorical variables. In our analyses, we computed
the odds ratios (OR) and 95% confidence intervals (CI) of the
association between both impaired fasting glucose, and prediab-
etes and BOP. The estimates were adjusted for potential con-
founding factors based on the literature. The association
between BOP and fasting glucose was assessed using linear
regression, and the adjusted mean percentages of BOP (least-
squares means) observed among participants with impaired gly-
cose levels or the prediabetic condition were compared with
those of participants with a normal range of glucose levels or
no prediabetic condition using generalized linear models. The
association between IFG or prediabetes and percentage of
bleeding on probing within specific characteristics of the pop-
ulation was also assessed using linear regression.

RESULTS
The general characteristics of the study population by BOP are
shown in Table 1. The mean age of participants with a per-
centage of BOP greater than or equal to the median (n = 51)
was 50 years (standard deviation [SD] 7.5) and 52 years (SD
6.9) among participants with a percentage of BOP less than the
median (n = 43). Approximately 35% of the participants with
high BOP were male, compared with 26% among participants
with low BOP. Among participants with high BOP, approxi-
mately 63% were never smokers, 20% former smokers and 18%
current smokers; the corresponding numbers were similar
among participants with low BOP (63%; 21 and 16%, respec-
tively).

Participants with high BOP were significantly more likely to
be current alcohol drinkers (53% vs 30%) than those with low
BOP. In addition, the groups with high and low BOP were
similar with respect to hypertension (63% vs 61%), body mass
index (mean 34, SD 6.9 vs mean 32, SD 5.1) and high waist
circumference (82% vs 86%).

Participants with high BOP had insignificantly higher mean
levels of fasting glucose (91.3 mg/dL, SD 9.4 vs 89.5 mg/dL, SD
7.5), insulin (16.1 μU/mL, SD 9.3 vs 14.0 μU/mL, SD 7.1)
and 1-h oral glucose tolerance test (143.9 mg/dL, SD 43.6 vs
128.6 mg/dL, SD 34.6) than participants with low BOP. Partici-
pants with high BOP were more likely to have IFG (19.6% vs
7%), 1-h IGT (41.2% vs 18.6%), 2-h IGT (7.8% vs 7%) and
prediabetic condition (23.5% vs 11.6%) as compared with those
with low BOP; however, only the 1-h IGT was significant.

All participants had at least one tooth site with CAL ≥3 mm
(data not shown). Compared with participants with low BOP,
Table 1 | General characteristics of the study population by bleeding on probing

| Characteristics                           | % BOP <median (n = 43) | % BOP ≥median (n = 51) |
|-------------------------------------------|------------------------|------------------------|
| Age (years)                               | Mean ± SD or n (%)      | Mean ± SD or n (%)      |
| Male                                      | 52.2 ± 6.9              | 50.0 ± 7.5              |
| Years of education                       | 11 (25.6)               | 18 (35.3)               |
| Never smoked                              | 64 ± 24                 | 65 ± 22                 |
| Former smokers                           | 27 (62.8)               | 32 (62.8)               |
| Current smokers                          | 9 (20.9)                | 10 (19.6)               |
| Current alcohol consumption              | 7 (16.3)                | 9 (17.7)                |
| Body mass index (height/weight²)          | 32.2 ± 5.1              | 340 ± 6.9               |
| Hypertension                              | 26 (60.5)               | 32 (62.8)               |
| Waist circumference                       | 37 (86.1)               | 41 (82.0)               |
| Glucose abnormalities (continuous)        | 89.5 ± 7.5              | 91.3 ± 9.4              |
| Fasting glucose (mg/dL)                   | 128.6 ± 34.6            | 143.9 ± 43.6            |
| OGTT (mg/dL)                              | 103.9 ± 24.5            | 1089 ± 27.3             |
| Fasting insulin (μU/mL)                   | 14.0 ± 7.1              | 161.1 ± 9.3             |
| Glucose abnormalities (categories)        |                        |                        |
| Impaired fasting glucose:                 |                        |                        |
| IFG (100–125 mg/dL)                       | 3 (7.0)                 | 10 (19.6)               |
| 1-h impaired glucose tolerance:          | 8 (18.6)                | 21 (41.2)*              |
| IGT (≥155 mg/dL)                          | 3 (7.0)                 | 4 (7.8)                 |
| 2-h impaired glucose tolerance:          | 5 (11.6)                | 12 (23.5)               |

*P-value ≤0.05. BOP, bleeding on probing; IFG, impaired fasting glu-
cose; IGT, impaired glucose tolerance; OGTT, oral glucose tolerance test; SD, standard deviation.

those with high BOP had insignificantly fewer tooth sites with
CAL of at least 4 mm or CAL of at least 5 mm. However,
participants with high BOP also tended to have insignificantly
more tooth sites with deep PD of at least 5 mm than those
with low BOP (data not shown).

Table 2a shows the results of the logistic regression models
for the association between glucose metabolic components and
BOP. No significant association between fasting glucose level
and higher prevalence of BOP was observed; the age-adjusted
OR was 1.4 (95% CI 0.8–2.3) for a 10 mg/dL increment. The
estimate remained non-significant after adjustment for age, sex,
smoking status, alcohol consumption, waist circumference (in
category) and number of missing teeth (OR 1.5, 95% CI 0.9–
2.6). Also, no significant association between 2-h glucose toler-
ance level and BOP was observed. In contrast, the association
was significant and similar in both crude and full adjustment
of estimates for the association between 10 mg/dL increment of
1-h glucose level and BOP (OR 1.1, 95% CI 1.0–1.3). The crude
The association between impaired fasting glucose and high BOP was 4.0 (95% CI 1.0–16.4). Multivariate analyses increased the OR to 5.5 (95% CI 1.2–25.3). The association between 1-h impaired glucose tolerance and a high prevalence of BOP was also significant (adjusted OR 3.7, 95% CI 1.3–10.6). The associations between 2-h impaired glucose tolerance, fasting insulin or HOMA and high percentage of BOP were not statistically significant. Prediabetes was associated with increased BOP, with an adjusted OR of 3.6 (95% CI 1.0–13.2).

When analysis of covariance was used to assess the association between plasma glucose levels, presence of IFG or prediabetic conditions and the increase in percentage of teeth with BOP (continuous form), results were generally similar to those of the logistical regression models (Table 2b). The age-adjusted least squares mean of percentage of BOP among participants with normal fasting glucose was lower compared with that of participants with impaired fasting glucose (normal FG: least squares mean 27.0 vs IFG 43.2). The association was significant after full adjustment of the estimate (normal FG: least squares mean 26.8 vs IFG 43.8). A similar pattern occurred for the association between 1- and 2-h IGT, high insulin level, and percentage of BOP, but the associations were not significant. The percentage of BOP (least squares mean adjusted for age, sex, smoking status, alcohol consumption, waist circumference and number of missing teeth) was 27.0 for 1-h normal GT vs 34.1 for 1-h IGT; 29.1 for 2-h normal GT vs 29.8 for 2-h IGT and 28.2 for normal insulin (<14: median) vs 30.1 for high insulin.

The percentage of BOP was 30.1 for normal HOMA (<3: median) vs 28.4 for high HOMA. The association between prediabetes (IFG or 2-h IGT) and percentage of BOP was significant (normal: mean percentage of BOP 27.0 vs prediabetic 39.0).

We also assessed the association between the prediabetic condition and the percentage of BOP by certain characteristics (Table 3). The association between the prediabetic condition and BOP was stronger and significant among older participants (β = 17.7, P = 0.03), participants who ever smoked (β = 25.9, P = 0.02), participants with severe PD, obesity, low triglycerides or high HDL cholesterol.

**DISCUSSION**

Findings from the present study suggested a potential association between impaired fasting plasma glucose level and prediabetes, and gingival and/or periodontal bleeding on gentle probing of the periodontal tissues. Higher BOP was observed among overweight or obese adult Puerto Ricans with impaired fasting glucose or prediabetes. Only a few studies have assessed the possible link between early-stage diabetes and BOP indicating current gingival/periodontal inflammation. A study by Noack et al. did not find a significant difference in the percentage of sites showing BOP between individuals with IGT and individuals with normal glucose levels. However, that study did not assess the link between BOP and prediabetes. Similarly, a non-significant greater percentage of sites with gingival bleeding was observed across type 2 diabetic patients and patients with impaired glucose tolerance as compared with a normal population. Nevertheless, it was not clear whether the gingival bleeding indicated in the other study used BOP or gingival index. A recent study by Javed et al. found higher severe
Table 3 | Association between prediabetic conditions and percentage of bleeding on probing by certain characteristics (age, smoking, periodontal status, alcohol consumption, obesity)

| Characteristics | n     | β (SE)† | P-value |
|-----------------|-------|---------|---------|
| Age             |       |         |         |
| <51 years       | 43    | −39 (8.1) | 0.05*  |
| ≥51 years       | 50    | 177 (7.6) | 0.07   |
| Smoking status  |       |         |         |
| Never smoked    | 58    | −0.6 (6.6) | 0.93   |
| Ever smoked     | 35    | 259 (10.4) | 0.02*  |
| Periodontal status |     |         |         |
| PD <5 mm        | 50    | 0.07 (7.6) | 0.99   |
| PD ≥5 mm        | 43    | 212 (9.5)  | 0.03*  |
| Alcohol consumption |   |         |         |
| Never or former | 53    | 7.6 (7.1)  | 0.29   |
| Current         | 40    | 166 (11.5) | 0.16   |
| Obesity         |       |         |         |
| Overweight      | 34    | 184 (16.3) | 0.27   |
| Obese           | 59    | 10.3 (6.3) | 0.11   |
| Triglycerides   |       |         |         |
| <150 mg/dL      | 62    | 19.1 (8.4)  | 0.03*  |
| ≥150 mg/dL      | 31    | 1.5 (8.7)   | 0.86   |
| HDL cholesterol |       |         |         |
| ≥40 mg/dL (0)   | 53    | 16.8 (8.1)  | 0.04*  |
| <40 mg/dL (1)   | 40    | 5.6 (10.4)  | 0.59   |

*P-value ≤ 0.05. The total number of participants in this analysis was reduced to n = 93, as one participant did not have information on waist circumference. †Adjusted for age, sex, smoking status (never vs ever), alcohol consumption (never or former vs current), waist circumference (category) and number of missing teeth, correspondingly. HDL, high-density; PD, probing depth; SE, standard error.

The association between prediabetes and the percentage of BOP was assessed by the level of the characteristics of the study population (shown in Table 3), there were significant associations among older individuals and those who had ever smoked or had deep pocket depth, low triglycerides and high HDL cholesterol. No significant associations were observed among the remaining specific characteristics, such as alcohol consumption and obesity. Whether the significant observed association between IFG or prediabetes and a higher percentage of BOP among participants with low triglycerides or high HDL cholesterol was real or by chance still remains to be further investigated in an adequately large and prospective study.

We did not find any association between the continuous form of fasting glucose level and the presence of BOP. Other than the possible interpretations resulting from the limitations of the present study, our findings might indicate threshold effects only with high glucose levels, parallel to the findings commonly observed among individuals with established diabetes.20–22

Although BOP measures are routinely carried out at dental clinical examination, BOP has not been given much attention. Gingival bleeding after stimulation of the gingival sulcus or pocket has been found to be associated with periodontal inflammation in clinical3,38–40, histopathological2,41 and bacteriological3,42 aspects of the disease. Regarding the inherent ability of BOP to distinguish the disease condition, previous studies have reported a low sensitivity, but high specificity, of this measurement.43 These findings could depend on the prevalence of the disease to be measured in the study population. BOP is frequently encountered in individuals at high risk of developing chronic systemic inflammatory diseases20–22. As previously stated, the present findings suggested that BOP is more frequently found in participants with impaired fasting glucose or prediabetes among those with the presence of deep pocket depths (PD ≥5 mm) than without.

The sample size and cross-sectional design of the present study limited the interpretation of the present findings. We did not collect data related to oral hygiene status, such as Plaque

self-perceived gingival bleeding and clinical signs of periodontal inflammation, such as bleeding on probing, in patients with prediabetes as compared with non-prediabetic controls.

Prediabetes has been associated with periodontal disease measures, such as alveolar bone loss.18,19 A higher percentage of BOP was found among individuals with type 2 diabetes as compared with non-diabetic individuals.20–22 Other recent studies have reported positive or non-significant associations mostly between BOP and established type 2 diabetes.23–26

Multiple studies have postulated different mechanism pathways explaining the potential association between established diabetes and periodontal diseases.27–32 Patients with diabetic mellitus have a higher risk for periodontitis development, probably because of vascular changes, neutrophil dysfunction, altered systemic inflammatory responses33, altered collagen synthesis, microbiotic factors or genetic predisposition 34,35.

In contrast, the potential biological mechanisms explaining the association between moderate glycemic intolerance and periodontal status have been scarcely studied. It is important to assess early stages to better understand the natural history and interrelationships between the two diseases. Previous studies have assessed the potential role of reactive oxygen species in the association. Impaired glycemic status is associated with an increased production and accumulation of reactive oxygen species in the body tissues including the periodontium.36,37

The present study evaluated and controlled for biologically meaningful potential confounders, such as age, sex, smoking status, alcohol consumption, waist circumference and number of missing teeth, for the estimates of the association between pre-diabetic conditions and BOP. We also assessed obesity, as expressed by waist circumference (categorical form was used as it was a stronger confounder) and BMI as confounders. We assessed the amount of smoking as a potential residual confounding factor in the model, but it did not contribute to a significant change in the estimates. For example, the adjusted OR with FPG was 5.5 (95% CI 1.2–25.3) without adjusting for the variable ‘amount of smoking’ vs OR: 5.9 (95% CI 1.2–28.2) adjusting for ‘amount of smoking’.
Index and Gingival Index. Thus, the potential confounding effect of supra-gingival plaque with the presence of bleeding of the marginal gingiva might have masked the BOP measurement as well.

In contrast, as previously mentioned, the present study has some strength in that it assessed the potential connection between early-stage diabetes and oral health status. Specifically, the association between impaired fasting glucose and prediabetes and BOP, as a parameter of gingival/periodontal disease, was observed. More studies need to be carried out, because this measurement, in conjunction with other periodontal parameters, such as PD and CAL, could give a more complete picture of an individual’s current inflammatory status. In the present study, the significance of the association between impaired fasting glucose and periodontal disease, defined by the presence of deep pocket depth and a high prevalence of BOP, is borderline (P = 0.08). Thus, if our preliminary association between prediabetes and gingival/periodontal inflammation are supported by large prospective studies, this could ultimately yield substantial benefits, as the use of these measurements in additional screening or monitoring would provide a tool for the early prevention or control of chronic inflammatory development of periodontal disease, and for predicting diabetes development among high-risk populations.

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