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Original Article

Three-Year Influence of Impaired Glucose Metabolism on the Advancement of Periodontitis

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ABSTRACT

This study investigated how disturbances in glucose metabolism relate to periodontitis among overweight and obese adults. A total of 870 diabetes-free participants aged 40–65 years completed a three-year follow-up as part of the San Juan Overweight Adults Longitudinal Study. Prediabetes was defined according to ADA criteria using fasting glucose, 2-hour post-load glucose, and HbA1c levels. Periodontal status was determined using NHANES protocols. To explore the association between initial glucose regulation indicators and periodontal outcomes after three years, multivariable linear regression analyses were performed while controlling for potential confounders. The findings revealed no significant link between impaired glucose metabolism and average pocket depth (PD), clinical attachment loss (CAL), or the proportion of sites with PD ≥5 mm. Interestingly, individuals with impaired glucose tolerance (IGT) showed a lower average percentage of sites with CAL ≥5 mm ($\beta = -1.6$, $p = 0.037$). Both prediabetes and impaired fasting glucose (IFG) correlated with a reduction in the mean percentage of sites exhibiting PD ≥5 mm ($\beta = -1.4$, $p = 0.022$; $\beta = -1.6$, $p = 0.032$, respectively). Additionally, IFG and IGT were linked to decreased percentages of sites with CAL ≥5 mm ($\beta = -1.6$, $p = 0.038$; $\beta = -1.9$, $p = 0.020$, respectively). Overall, these results indicate that neither prediabetes nor insulin resistance at baseline consistently predicted periodontitis progression over the three-year observation period.

Keywords: Cohort study, Pre-diabetic state, Periodontal disease, Obesity, Insulin resistance

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Introduction

Existing research has consistently highlighted a two-way interaction between diabetes and periodontitis [1-3]. Inflammation triggered by periodontal microorganisms promotes cytokine activity, elevates inflammatory markers, disrupts lipid metabolism, and induces endothelial dysfunction—all of which may contribute to glucose imbalance, insulin resistance, and an elevated likelihood of type 2 diabetes [1, 4-6]. Conversely, chronic hyperglycemia characteristic of diabetes enhances innate immune activation, increases pro-inflammatory cytokine production, and stimulates adhesion molecule expression, alongside the accumulation of advanced glycation end products that collectively accelerate periodontal tissue destruction [1, 4].

Long-term studies investigating the association between diabetes [7–12] and the risk of periodontal disease have generally demonstrated a positive relationship. For example, in the Health Professionals Follow-Up Study, men with self-reported diabetes exhibited significantly higher rates of self-reported periodontitis and tooth loss [10]. Moreover, a meta-analysis of prospective cohort data revealed that diabetes raises the likelihood of periodontitis development or progression nearly twofold (RR = 1.86, 95% CI: 1.3–2.8) [13]. Nonetheless, these investigations had notable weaknesses, including brief

observation periods, limited participant numbers, and dependence on the Community Periodontal Index, which inadequately captures periodontal disease severity.

Research examining the early or prediabetic stages of type 2 diabetes in relation to periodontal health has mostly relied on cross-sectional designs [14–23], with some studies reporting no observable link [14, 24–26]. Only a few longitudinal analyses—two extensive [7, 27] and one small-scale [28]—identified associations between prediabetes, insulin resistance, and periodontal or gingival inflammation. Additional longitudinal evidence [29–31] indicated that individuals with metabolic syndrome face a heightened risk of developing or worsening periodontitis and tooth loss, whereas findings from Nascimento *et al*. [32] did not support an association between metabolic syndrome markers and periodontal outcomes.

Due to these conflicting results and the scarcity of long-term data, the San Juan Overweight Adults Longitudinal Study (SOALS) was designed to provide a clearer understanding of how metabolic alterations that precede type 2 diabetes relate to the initiation and progression of periodontitis, as well as to identify potential mediating biological mechanisms in this connection [33].

Materials and Methods

Data source and study population

The SOALS cohort, initiated in 2011, followed participants from baseline through a three-year reassessment period. Details regarding recruitment procedures and participant retention have been reported elsewhere [23, 34, 35]. Briefly, adults aged 40–65 years living in the San Juan region of Puerto Rico were invited to participate if they met the criteria for being overweight or obese (BMI ≥ 25 kg/m²) and had no clinical diagnosis of diabetes. Exclusion criteria included conditions that could interfere with valid periodontal assessment (such as having fewer than four teeth or wearing orthodontic devices) and medical issues posing safety concerns (e.g., cardiovascular disease or bleeding disorders).

Among 1206 diabetes-free individuals enrolled, 255 failed to attend the follow-up examination. Of those who completed the study (n = 951; 79% retention), 81 participants were excluded due to missing information, resulting in a final analytical group of 870 participants **(Figure 1)**. Ethical approval for the study was obtained from the Institutional Review Board of the University of Puerto Rico Medical Sciences Campus (IRB #A4840109, approved on February 7, 2010). All research procedures adhered to the principles of the Helsinki Declaration (1975, revised 2013), and written informed consent was secured from all participants prior to data collection.

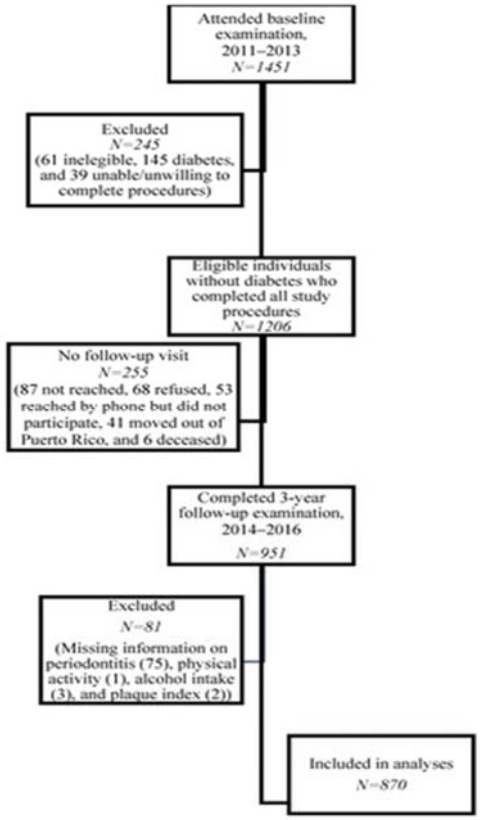

Figure 1. Flow of participants through the study (*N* = 870).

Definition of periodontitis as the study outcome

Comprehensive periodontal examinations were conducted at both baseline (2011) and after a three-year interval (2014). Assessment of periodontitis followed the standardized protocol established by the National Health and Nutrition Examination Survey (NHANES) [36, 37] and was carried out by one of three trained and calibrated dental examiners [23, 34, 35]. Periodontal evaluation included clinical measurements of pocket depth (PD) and gingival recession at six points per tooth, excluding third molars. PD represented the distance from the base of the gingival sulcus or pocket to the free gingival margin (FGM), while gingival recession was defined as the distance from the FGM to the cemento-enamel junction (CEJ). The sum of these two measurements was used to calculate clinical attachment loss (CAL).

At the three-year follow-up, periodontitis was expressed through several indicators: mean PD, mean CAL, and the mean percentages of sites with PD ≥ 5 mm and CAL ≥ 5 mm. Changes over time were determined by subtracting baseline values from follow-

up values; thus, positive differences indicated progression or worsening, whereas negative values reflected improvement. To ensure data reliability, 40 participants were examined by two different evaluators at both time points. Based on data from all examiners, the pooled intra-class correlation coefficients for mean CAL and mean PD at interproximal sites were 0.89 (95% CI: 0.81–0.94) and 0.93 (95% CI: 0.88–0.96), respectively. Agreement between examiners for the number of teeth present was perfect.

Definition of baseline glucose and insulin resistance measures (Exposures)

Participants were instructed to fast for ten hours before their baseline and follow-up visits. Blood glucose and insulin levels were measured at fasting and at 30, 60, and 120 minutes following the administration of a 75-gram oral glucose load. Glucose concentration was analyzed using the Vitros System 250 analyzer, yielding intra-assay and inter-assay coefficients of variation of 1.21% and 3.06%, respectively. Plasma insulin was quantified through an immuno-enzymometric technique using a TOSOH analyzer, with corresponding intra- and inter-assay variations of 1.49% and 4.42%. HbA1c levels were determined through latex immunoagglutination inhibition using a monoclonal antibody-based Siemens Kit compatible with the DCA 2000 and DCA Vantage Analyzer systems.

According to the American Diabetes Association (ADA) criteria [38], participants who were not under antihyperglycemic medication and lacked a clinical diabetes diagnosis were classified as follows:

- Type 2 diabetes mellitus (T2DM): fasting glucose ≥126 mg/dL, 2-hour post-load glucose (2hPG) ≥200 mg/dL, or HbA1c ≥6.5%.
- Prediabetes: impaired fasting glucose (IFG, 100–125 mg/dL), impaired glucose tolerance (IGT, 140–199 mg/dL), or elevated HbA1c (5.7–6.4%).
- Normal glycemia: values below the prediabetes thresholds.

Insulin resistance was assessed using the Homeostatic Model Assessment for Insulin Resistance (HOMA-IR), computed as:

fasting glucose (mg/dL) × fasting insulin (mg/dL)]/405

Because there is no universally accepted cutoff for HOMA-IR, the study used the 75th percentile (≥3.13) of its own population distribution to define elevated insulin resistance.

Ascertainment of covariates

Data were collected through in-person interviews, physical examinations, and laboratory assessments. Demographic and lifestyle information included age, sex, educational attainment (less than high school, high school or higher), smoking status (never, past, current), cigarette use per week, alcohol intake (grams per week), and physical activity quantified as metabolic equivalent of task (MET) hours per week based on frequency and type of activity. Dietary intake was evaluated by the number of weekly servings of fruits and vegetables, and family history of diabetes was recorded.

Anthropometric measurements such as height, weight, waist, and hip circumferences were obtained two to three times following NHANES protocols and averaged for analysis [39]. Oral health behaviors were also recorded, including the frequency of dental visits in the preceding year, tooth brushing, flossing, mouthwash use, and periodontal treatments received during follow-up [40, 41]. Oral hygiene was objectively assessed using the Silness and Löe Plaque Index at six predetermined teeth [42].

Blood pressure was measured three times at 1–2 minute intervals [43], and the mean of the readings was calculated. Participants were then categorized as:

- Hypertensive: physician-diagnosed hypertension, use of antihypertensive medication, or average systolic BP ≥140 mmHg or diastolic BP ≥90 mmHg.
- Pre-hypertensive: systolic BP between 120–139 mmHg or diastolic BP between 80–89 mmHg.
- Normotensive: systolic BP <120 mmHg and diastolic BP <80 mmHg.

Finally, HDL cholesterol (HDL-C) and triglyceride levels were analyzed in a certified local laboratory using commercial enzymatic assays (Roche Diagnostics, Indianapolis, IN, USA).

Statistical analysis

Baseline demographic and clinical features were categorized by glycemic condition (normoglycemia vs. prediabetes). To explore associations between baseline indicators of altered glucose metabolism (prediabetes, IFG, IGT, elevated HbA1c, and HOMA-IR) and periodontal outcomes, separate multivariable linear regression analyses were conducted. These outcomes included average PD, mean CAL, and the proportion of periodontal sites with PD or CAL ≥ 5 mm, with baseline periodontal data considered in the models. Comparable regression analyses were performed to evaluate three-year changes in periodontal indices—mean PD, mean CAL, the percentage of sites with PD ≥ 5 mm, CAL ≥ 5 mm, and mean tooth count.

Potential confounders were chosen according to prior evidence and conceptual assumptions describing the

possible causal relationship between impaired glucose metabolism and periodontal disease. The first adjusted model incorporated age, sex, smoking, and differences in follow-up duration [44, 45]. The expanded model further adjusted for socioeconomic and lifestyle variables, including educational level, physical activity, alcohol intake, waist circumference, fruit and vegetable consumption, plaque index, and baseline periodontal values (except when evaluating three-year change). A significance threshold of $p < 0.05$ and a 95% confidence interval (CI) were applied to interpret the findings. Statistical analyses were carried out using Stata version 15 (StataCorp LP, College Station, TX, USA) for Windows.

Results and Discussion

Baseline characteristics of SOALS participants by glycemic status

The median follow-up period for participants was 2.96 years (interquartile range: 2.88–3.01 years). Individuals classified with prediabetes were generally older ($p < 0.001$), had greater waist circumference ($p < 0.001$), elevated triglyceride ($p < 0.001$) and glucose levels ($p < 0.001$), and reduced HDL-C concentrations ($p = 0.013$). They also exhibited higher rates of moderate or severe periodontitis ($p = 0.037$), hypertension ($p < 0.001$), and insulin resistance ($p < 0.001$), while being less likely to smoke ($p = 0.012$) than normoglycemic participants **(Table 1)**.

Table 1. Baseline characteristics of SOALS participants across glycemic status (n = 870) *.

	Prediabetes (n = 492)	**Normoglycemia (n = 378)**	***p*-Value**
Age (years)	51.6 ± 6.7	49.1 ± 6.6	<0.001
Male sex	26.6	26.7	0.975
High school education or more	90.5	89.4	0.616
Annual income ≥ $20,000	47.8	47.9	0.973
Smoking			0.012
Never	65.5	62.7	0,15
Past smoker	18.3	14.3	0,251
Current smoker	16.3	23.0	0,16
Alcohol intake (grams/day)	2.2 ± 5.2	2.4 ± 6.5	0.585
Physical activity (METS/week)	22.5 ± 44.0	23.4 ± 37.8	0.754
Fruit and vegetable intake (servings/week)	7.0 ± 4.0	7.5 ± 4.1	0.084
Waist circumference (cm)	107.4 ± 14.5	103.9 ± 13.6	<0.001
BMI (kg/m^2)	33.8 ± 6.3	32.5 ± 6.1	0.003
Plaque index	0.79 ± 0.60	0.81 ± 0.60	0.568
Periodontitis status			0.037
None/Mild	33.1	41.5	0,07
Moderate	43.1	38.4	0,216
Severe	23.8	20.1	0,09
Number of teeth	23.4 ± 4.3	24.1 ± 4.1	0.026
Number of teeth in categories			0.216
25–28	48.8	55.3	
17–24	43.3	39.2	0,07
11–16	6.3	4.2	0,117
4–10	1.6	1.3	0,03
Dentist visits in past 12 months	61.2	63.2	0.537
Tooth brushing more than once day	91.1	92.1	0.598
Dental flossing more than once a day	40.8	46.3	0.108
Any mouthwash use	51.8	55.0	0.349
Periodontal treatment	53.9	61.1	0.032
HDL-C (mg/dL)	47.2 ± 11.9	49.3 ± 13.1	0.013
Triglycerides (mg/dL)	157.9 ± 90.3	129.3 ± 58.2	<0.001
Blood pressure classification			<0.001
Normal	17.1	29.9	
Pre-hypertension	30.9	30.2	
Hypertension	52.0	40.0	
Fasting glucose (mg/dL)	96.3 ± 8.8	87.4 ± 5.8	<0.001
2-hr post load glucose (mg/dL)	124.5 ± 32.3	101.2 ± 19.6	<0.001
Fasting insulin (mIU/L)	12.1 ± 7.5	8.5 ± 5.1	<0.001
HbA1c (%)	5.9 ± 0.3	5.5 ± 0.2	<0.001

HOMA-IR	2.9 ± 1.9	1.9 ± 1.2	<0.001

*Data are expressed as mean ± standard deviation or as frequency (percentage). Abbreviations: BMI, Body Mass Index; HDL-C, high-density lipoprotein cholesterol; HbA1c, glycated hemoglobin; HOMA-IR, homeostatic model assessment for insulin resistance.

Baseline and three-year follow-up of mean pocket depth and clinical attachment loss by glucose metabolism status

Among participants with prediabetes, the average PD and CAL were 2.1 ± 0.8 mm and 2.0 ± 1.3 mm, respectively, whereas those with normal glucose levels had slightly lower values of 2.0 ± 0.6 mm and 1.8 ± 1.1 mm **(Table 2)**. Small reductions in PD and CAL were observed over the three-year period in most subgroups with abnormal glucose indicators (for example, mean PD change in IFG: p = 0.041; in HOMA-IR: p = 0.032). The mean proportion of sites with PD ≥ 5 mm was marginally higher in the prediabetes group (4.2 ± 11.3%) compared with normoglycemic participants (3.1 ± 7.8 percent) (data not shown), and a similar trend was seen for CAL ≥ 5 mm (7.5 ± 15.5% vs. 5.6 ± 11.7%). Overall, the data suggest that individuals with abnormal glucose metabolism experienced slight improvements in PD and CAL over the follow-up period [46].

Table 2. Mean levels of pocket depth (PD) and clinical attachment loss (CAL) at baseline and follow-up visits according to impaired glucose metabolism measures.

	Mean PD (mm)			Mean CAL (mm)		
	Baseline	**Follow-Up**	***p*-Value**	**Baseline**	**Follow-Up**	***p*-Value**
Prediabetes						
Yes (n = 492)	2.1 ± 0.8	2.0 ± 0.7	0.143	2.0 ± 1.3	1.9 ± 1.2	0.553
No (n = 378)	2.0 ± 0.6	2.0 ± 0.7		1.8 ± 1.1	1.8 ± 1.2	
	p = 0.223	*p* = 0.995		*p* = 0.042	*p* = 0.105	
IFG						
Yes (n = 183)	2.2 ± 0.8	2.0 ± 0.7	0.041	2.1 ± 1.3	2.0 ± 1.2	0.161
No (n = 687)	2.0 ± 0.7	2.0 ± 0.7		1.9 ± 1.2	1.9 ± 1.2	
	p = 0.020	*p* = 0.494		*p* = 0.010	*p* = 0.110	
IGT						
Yes (n = 156)	2.1 ± 0.7	2.0 ± 0.6	0.202	2.0 ± 1.1	1.8 ± 0.9	0.139
No (n = 714)	2.1 ± 0.7	2.0 ± 0.7		1.9 ± 1.2	1.9 ± 1.2	
	p = 382	*p* = 0.846		*p* = 0.600	*p* = 0.601	
Elevated HbA1c						
Yes (n = 496)	2.1 ± 0.8	2.0 ± 0.7	0.78	2.0 ± 1.2	1.9 ± 1.2	0.706
No (n = 374)	2.1 ± 0.7	2.0 ± 0.7		1.9 ± 1.1	1.8 ± 1.2	
	p = 0.610	*p* = 0.441		*p* = 0.273	*p* = 0.171	
HOMA-IR						
Yes (n = 189)	2.2 ± 0.9	2.1 ± 0.7	0.032	2.1 ± 1.3	2.0 ± 1.2	0.196
No (n = 681)	2.0 ± 0.7	2.0 ± 0.7		1.9 ± 1.2	1.9 ± 1.2	
	p < 0.001	*p* = 0.030		*p* = 0.017	*p* = 0.136	

Note: Prediabetes was classified as having impaired fasting glucose (IFG, 100–125 mg/dL), impaired glucose tolerance (IGT, 140–199 mg/dL), or elevated HbA1c (5.7–6.4%). HOMA-IR was defined using the 75th percentile specific to the study population (≥3.1). Abbreviations: IFG, impaired fasting glucose; IGT, 2-hour impaired glucose tolerance; HbA1c, glycated hemoglobin; HOMA-IR, homeostatic model assessment for insulin resistance.

Relationship between baseline glucose dysregulation and follow-up periodontal measures

Regression analyses accounted for age, smoking, sex, educational level, physical activity, alcohol consumption, waist circumference, intake of fruits and vegetables, plaque index, baseline periodontal status, and follow-up duration. In general, measures of impaired glucose metabolism did not show a significant link with mean PD, mean CAL, or the proportion of sites with PD ≥ 5 mm at follow-up **(Table 3)**. However, participants with IGT had a lower mean percentage of sites with CAL ≥ 5 mm (β = −1.64, p = 0.037), whereas IFG showed a marginal association (β = −1.4, p = 0.063).

Table 3. Multivariable linear regression models for the relationship between baseline glucose metabolism measures and periodontitis measures at follow-up.

	Mean PD, mm		Mean CAL, mm		Mean Percent of Sites with ≥5 mm PD		Mean Percent of Sites with ≥5 mm CAL	
	β (SE)	***p* Value**	**β (SE)**	***p* Value**	**β (SE)**	***p* Value**	**β (SE)**	***p* Value**

Prediabetes								
Model 1	0.0 (0.0)	0.995	0.1 (0.1)	0.105	−0.1 (0.6)	0.81	0.8 (1.0)	0.424
Model 2	0.0 (0.0)	0.645	0.0 (0.1)	0.761	−0.6 (0.5)	0.244	−0.5 (0.6)	0.422
Model 3	0.0 (0.0)	0.704	0.0 (0.1)	0.97	−0.5 (0.5)	0.3	−0.8 (0.6)	0.203
IFG								
Model 1	0.0 (0.1)	0.494	0.2 (0.1)	0.11	0.1 (0.7)	0.919	0.5 (1.2)	0.7
Model 2	0.0 (0.0)	0.309	0.0 (0.1)	0.577	−0.8 (0.6)	0.158	−1.5 (0.8)	0.057
Model 3	0.0 (0.1)	0.314	0.0 (0.1)	0.595	−0.8 (0.6)	0.164	−1.4 (0.8)	0.063
IGT								
Model 1	0.0 (0.1)	0.846	−0.1 (0.1)	0.6	−0.3 (0.7)	0.679	−1.7 (1.3)	0.192
Model 2	0.0 (0.0)	0.522	−0.1 (0.1)	0.324	−0.4 (0.6)	0.525	−1.9 (0.8)	0.016
Model 3	0.0 (0.0)	0.585	0.0 (0.1)	0.534	−0.3 (0.6)	0.593	−1.6 (0.8)	0.037
High HbA1c								
Model 1	0.0 (0.0)	0.441	0.1 (0.1)	0.171	−0.8 (0.6)	0.149	0.9 (1.0)	0.379
Model 2	0.0 (0.0)	0.963	0.0 (0.1)	0.385	−0.6 (0.5)	0.221	0.2 (0.6)	0.702
Model 3	0.0 (0.0)	0.822	0.0 (0.1)	0.711	−0.5 (0.5)	0.286	−0.2 (0.6)	0.754
HOMA-IR								
Model 1	0.1 (0.1)	0.03	0.1 (0.1)	0.136	0.7 (0.7)	0.307	1.6 (1.2)	0.182
Model 2	0.0 (0.0)	0.622	0.0 (0.1)	0.833	−0.4 (0.6)	0.521	−0.3 (0.7)	0.655
Model 3	0.0 (0.0)	0.708	0.0 (0.1)	0.915	−0.3 (0.6)	0.637	−0.4 (0.8)	0.589

Note: For prediabetes, IFG, and IGT, the reference group was participants with normal glycemia; for elevated HbA1c, it was normal HbA1c; and for HOMA-IR, the reference comprised the lower three quartiles combined. Model 1 represents the unadjusted analysis; Model 2 adjusts for age, smoking, sex, and follow-up duration; Model 3 further adjusts for education, physical activity (METs), weekly alcohol intake (grams), waist circumference, fruit and vegetable consumption, total number of teeth, plaque index, and baseline periodontal values. Abbreviations: IFG, impaired fasting glucose; IGT, 2-hour impaired glucose tolerance; HbA1c, glycated hemoglobin; HOMA-IR, homeostatic model assessment for insulin resistance.

Impact of baseline impaired glucose metabolism on three-year periodontal changes

Over the three-year follow-up, baseline glucose metabolism abnormalities were not significantly linked to changes in mean PD or mean CAL **(Table 4)**. However, participants with prediabetes or IFG showed modest decreases in the proportion of sites with PD ≥ 5 mm (β = −1.4, p = 0.02; β = −1.6, p = 0.032, respectively). Reductions in the proportion of sites with CAL ≥ 5 mm were observed in those with IFG (β = −1.6, p = 0.038) and IGT (β = −1.9, p = 0.020), while prediabetes demonstrated a near-significant trend (β = −1.1, p = 0.078). Given that advanced periodontitis may contribute to tooth loss, especially in adults aged 40 and above [47, 48], changes in mean tooth number and new tooth loss were also examined as secondary outcomes, yet no significant relationships were detected (data not shown).

Table 4. Results from multivariable linear regression models for the relationship between glucose metabolism measures and three-year changes in periodontitis.

	Change in Mean PD (mm)		**Change in Mean CAL (mm)**		**Change in Mean Percent of Sites with ≥5 mm PD**		**Change in Mean Percent of Sites with ≥5 mm CAL**	
	β (SE)	***p* Value**	**β (SE)**	***p* Value**	**β (SE)**	***p* Value**	**β (SE)**	***p* Value**
Prediabetes								
Model 1	−0.1 (0.0)	0.143	0.0 (0.1)	0.553	−1.3 (0.6)	0.029	−1.1 (0.6)	0.104
Model 2	−0.1 (0.0)	0.167	0.0 (0.1)	0.685	−1.4 (0.6)	0.022	−0.8 (0.7)	0.197
Model 3	−0.1 (0.0)	0.177	0.0 (0.1)	0.465	−1.4 (0.6)	0.022	−1.1 (0.6)	0.078
IFG								
Model 1	−0.1 (0.1)	0.041	−0.1 (0.1)	0.161	−1.7 (0.7)	0.018	−1.9 (0.8)	0.013
Model 2	−0.1 (0.1)	0.071	−0.1 (0.1)	0.337	−1.7 (0.8)	0.025	−1.7 (0.8)	0.031
Model 3	−0.1 (0.1)	0.097	−0.1 (0.1)	0.387	−1.6 (0.7)	0.032	−1.6 (0.8)	0.038
IGT								
Model 1	−0.1 (0.1)	0.202	−0.1 (0.1)	0.139	−0.8 (0.8)	0.323	−2.5 (0.8)	0.003
Model 2	−0.1 (0.1)	0.23	−0.1 (0.1)	0.244	−0.8 (0.8)	0.313	−2.1 (0.8)	0.011
Model 3	−0.1 (0.1)	0.298	−0.1 (0.1)	0.332	−0.7 (0.8)	0.387	−1.9 (0.8)	0.02
High HbA1c								
Model 1	0.0 (0.0)	0.8	0.0 (0.1)	0.706	−0.6 (0.6)	0.299	0.0 (0.6)	0.992

Model 2	0.0 (0.0)	0.801	0.0 (0.1)	0.727	−0.8 (0.6)	0.214	0.0 (0.7)	0.943
Model 3	0.0 (0.0)	0.813	0.0 (0.1)	0.877	−0.8 (0.6)	0.204	−0.4 (0.7)	0.528
HOMA-IR								
Model 1	−0.1 (0.0)	0.032	−0.1 (0.1)	0.196	−1.4 (0.7)	0.044	−1.0 (0.8)	0.216
Model 2	−0.1 (0.0)	0.031	−0.1 (0.1)	0.225	−1.4 (0.7)	0.056	−0.8 (0.8)	0.273
Model 3	−0.1 (0.1)	0.128	−0.1 (0.1)	0.316	−1.0 (0.8)	0.168	−0.9 (0.8)	0.251

Note: For prediabetes, IFG, and IGT, the reference group comprised individuals with normal glycemia; for elevated HbA1c, the reference was normal HbA1c; and for HOMA-IR, it was the lower three quartiles combined. Model 1 represents the unadjusted analysis; Model 2 adjusts for age, smoking, sex, and follow-up duration; Model 3 further adjusts for education, physical activity (METs), weekly alcohol intake (grams), waist circumference, fruit and vegetable consumption (servings/week), total number of teeth, and plaque index. Abbreviations: IFG, impaired fasting glucose; IGT, 2-hour impaired glucose tolerance; HbA1c, glycated hemoglobin; HOMA-IR, homeostatic model assessment for insulin resistance.

Additional adjustment for baseline factors such as dental visits in the previous year, oral hygiene practices (tooth brushing, flossing, and mouthwash use), blood pressure category, total teeth, medication usage, and periodontal treatment during follow-up did not materially affect the results, so these variables were excluded from the final models. Subgroup analyses stratified by smoking status and tooth count were conducted for each impaired glucose metabolism measure (data not shown), showing consistent directions of association across tooth categories and no evidence of effect modification. Potential mediators—including HDL-C, LDL-C, and triglycerides—were also tested individually in the final models for outcomes where impaired glucose metabolism was linked to periodontitis progression, but inclusion of these factors did not alter the effect estimates, indicating no mediation (data not shown).

This longitudinal study is among the first to examine standard indicators of impaired glucose metabolism and insulin resistance as predictors of periodontitis onset or progression. Our findings did not show a significant positive association between baseline prediabetes or insulin resistance and periodontitis progression over three years, independent of major known confounders, with the exception of genetic factors, which remain a limitation in most epidemiologic research. The results were also consistent among non-smokers, suggesting that residual confounding from smoking did not drive the findings.

Relatively few longitudinal studies have investigated whether hyperglycemia or insulin resistance increases periodontal disease risk among non-diabetic adults, and some have methodological limitations in periodontal assessment. Chiu *et al.* [7] reported a slightly higher five-year risk of periodontal disease (defined as a Community Periodontal Index score ≥3) in individuals with prediabetes (fasting plasma glucose ≥100 mg/dL; HR = 1.25, 95% CI: 1.00–1.57), after controlling for confounders. However, this index does not capture clinical attachment loss or recession and focuses only on PD thresholds, which may underestimate disease severity. Timonen *et al.* [28] evaluated insulin resistance and beta-cell function in relation to four-year periodontal disease development (pockets ≥4 mm), but sample size was small, PD was measured at only four selected sites, and only the deepest site per tooth was recorded, potentially underestimating true disease burden.

In prior analyses within the same cohort, we examined insulin resistance and gingival/periodontal inflammation using the number of sites with bleeding on probing (BOP) and teeth with PD ≥4 mm plus BOP [27]. Participants in the highest HOMA-IR tertile had more sites with BOP (RR = 1.19, 95% CI: 1.03–1.36) and more teeth with PD ≥4 mm plus BOP (RR = 1.39, 95% CI: 1.09–1.78) after adjusting for confounders. The number of sites with BOP indicates active status of both reversible gingivitis and periodontitis, while teeth with PD ≥4 mm plus BOP specifically reflect potential active periodontitis [27]. These findings highlight the need to clarify how impaired glucose metabolism may influence periodontitis over time.

However, the current results contrast with our previous cross-sectional study in the same cohort, which showed a significant association between impaired glucose metabolism and severe periodontitis [23], as well as other longitudinal studies reporting positive associations [7, 27, 28]. The discrepancy may be due to the slow progression of periodontal disease, resulting in minimal detectable changes over a three-year period [48, 49]. For example, a Swedish longitudinal study reported a mean annual progression of 0.06 mm over three years, with individual rates ranging from 0.04 to 0.07 mm depending on age [49]. It remains unclear whether progression rates differ by glycemic status over such a period.

The SOALS study benefits from a longitudinal design, a relatively large sample, and high-quality data. Standardized measures—including fasting glucose, oral glucose tolerance tests, insulin, and HbA1c—were used to assess diabetes precursors. Periodontal assessments followed the NHANES oral health

protocol, considered the gold standard, with six sites examined per tooth. Key potential confounders were measured and accounted for in analyses.

However, several limitations should be acknowledged. The study population consisted primarily of overweight and obese adults, most of whom had at least a high school education, had visited a dentist prior to baseline, and reported prior periodontal treatment, which may limit generalizability. Focusing on this high-risk group may partly explain the lack of observed positive associations, although no known biological mechanism would suggest an inverse relationship. Non-probability sampling was used, limiting broader generalizability, though internal validity within the cohort remains unaffected. Additionally, different examiners were often used between baseline and follow-up due to logistical constraints, which could have introduced some random error or bias.

One possible explanation for the slight inverse associations observed is that participants with baseline impaired glucose metabolism were informed about their prediabetes and its potential link to periodontitis, potentially motivating healthier oral or lifestyle behaviors. Yet, follow-up data showed no substantial differences between participants with prediabetes and those with normoglycemia in terms of tooth brushing, flossing, periodontal treatment, dental visits, plaque score reduction, lipid or inflammatory marker changes, or increased physical activity. Changes in the oral microbiome, which could reflect a shift toward fewer pathogenic bacteria, were not assessed.

Overall, this three-year follow-up does not provide consistent evidence supporting the hypothesis that prediabetes or insulin resistance contributes to PD progression in overweight or obese adults. In fact, some non-significant improvements in pocket depth and significant improvements in clinical attachment loss were observed, potentially reflecting lifestyle changes. It should be noted that PD can remain stable or inactive without bleeding, while gingival recession may continue unnoticed, ultimately resulting in attachment loss and tooth loss over time.

Future studies with larger sample sizes, longer follow-up, and diverse populations are needed to clarify the relationship between glucose abnormalities and periodontitis.

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