e-ISSN: 2988-3237

Sriwijaya Journal of Internal Medicine (SJIM)

Journal website: https://phlox.or.id/index.php/sjim

Glycated Hemoglobin (HbA1c) as a Predictor of Periodontal Disease Progression in Patients with Type 2 Diabetes: A Longitudinal Study in Surabaya, Indonesia

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ARTICLE INFO

Keywords:
Glycated hemoglobin (HbA1c)
Longitudinal study
Periodontal disease
Probing pocket depth
Type 2 diabetes

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All authors have reviewed and approved the final version of the manuscript.

https://doi.org/10.59345/sjim.v2i2.178

A B S T R A C T

Introduction: Periodontal disease is a prevalent complication of type 2 diabetes mellitus (T2DM), and poor glycemic control is a known risk factor. This longitudinal study aimed to investigate the predictive value of glycated hemoglobin (HbA1c) for periodontal disease progression in a cohort of T2DM patients in Surabaya, Indonesia. **Methods:** A prospective cohort study was conducted at private hospital, Surabaya, Indonesia, from January 2021 to January 2023. 180 patients with T2DM and pre-existing chronic periodontitis were enrolled. Periodontal parameters, including probing pocket depth (PPD), clinical attachment loss (CAL), bleeding on probing (BOP), and plaque index (PI), were assessed at baseline, 12 months, and 24 months. HbA1c was measured at each visit. Multivariate linear regression and mixed-effects models were used to analyze the association between HbA1c and changes in periodontal parameters over time, adjusting for potential confounders. **Results:** The mean age of participants was 58.5 ± 8.2 years, and 55% were female. Baseline mean HbA1c was 8.2 ± 1.5%. After adjusting for age, gender, smoking status, diabetes duration, and baseline periodontal parameters, higher baseline HbA1c was significantly associated with greater increases in PPD (β = 0.15 mm per 1% HbA1c increase, 95% CI: 0.08-0.22, $p < 0.001$) and CAL (β = 0.18 mm per 1% HbA1c increase, 95% CI: 0.10-0.26, $p < 0.001$) over 24 months. Furthermore, sustained elevation of HbA1c (average HbA1c over 24 months) was a stronger predictor of periodontal disease progression than baseline HbA1c alone. A significant interaction between HbA1c and time was observed ($p < 0.001$), indicating that the effect of HbA1c on periodontal parameters increased over time. **Conclusion:** HbA1c is a significant independent predictor of periodontal disease progression in patients with T2DM. Sustained glycemic control is crucial for preventing and managing periodontal complications in this population. These findings highlight the importance of interdisciplinary collaboration between internists and dentists in the comprehensive care of T2DM patients.

1. Introduction

Type 2 diabetes mellitus (T2DM) has emerged as a global health challenge, with Southeast Asia, including Indonesia, experiencing a particularly high prevalence. This chronic condition is characterized by persistent hyperglycemia, which can lead to a range of microvascular and macrovascular complications. These complications include retinopathy, nephropathy, neuropathy, cardiovascular disease, and periodontal disease. Periodontal disease, a

chronic inflammatory condition affecting the tissues supporting the teeth, is now recognized as the sixth major complication of diabetes. The relationship between diabetes and periodontal disease is bidirectional, creating a complex interplay between these two conditions. Hyperglycemia, a hallmark of diabetes, contributes to the progression of periodontal disease through various mechanisms. These include increased formation of advanced glycation end-products (AGEs), impaired immune function, altered collagen metabolism, and changes in the oral microbiome. AGEs, formed by the non-enzymatic reaction between glucose and proteins, can accumulate in periodontal tissues, leading to inflammation and tissue damage. Hyperglycemia also impairs immune function, making individuals with diabetes more susceptible to infections, including periodontal disease. Additionally, altered collagen metabolism and changes in the oral microbiome further contribute to the progression of periodontal disease in individuals with diabetes.[1-4]

Conversely, severe periodontal disease can exacerbate insulin resistance and worsen glycemic control, creating a vicious cycle. Periodontal disease is characterized by chronic inflammation, which can contribute to systemic inflammation and insulin resistance. Insulin resistance, in turn, makes it more difficult to control blood glucose levels, further exacerbating hyperglycemia and its detrimental effects on periodontal tissues. This bidirectional relationship between diabetes and periodontal disease highlights the complex interplay between these two conditions and the need for integrated management strategies. Glycated hemoglobin (HbA1c) is a widely recognized and reliable measure of long-term glycemic control. It reflects average blood glucose levels over the preceding 2-3 months, providing valuable information about an individual's glycemic control over time. Numerous cross-sectional studies have demonstrated a positive association between HbA1c levels and the prevalence and severity of periodontal disease. However, longitudinal studies examining the predictive value of HbA1c for the progression of periodontal disease, particularly in Southeast Asian populations, are relatively limited.[5-7]

Indonesia, with its large and rapidly growing population, faces a significant burden of T2DM and its associated complications, including periodontal disease. Data on the specific relationship between HbA1c and periodontal disease progression in the Indonesian population is scarce.[8-10] This study addresses this gap by investigating the longitudinal association between HbA1c and changes in key periodontal parameters in a cohort of T2DM patients in Surabaya, Indonesia.

2. Methods

This research was designed as a prospective cohort study, allowing us to follow a group of individuals over time and observe the relationship between their glycemic control and the progression of periodontal disease. The study was conducted at a private hospital in Surabaya, Indonesia, a major city in Southeast Asia with a high prevalence of T2DM. The study period spanned from January 2021 to January 2023, providing a two-year follow-up period to assess changes in periodontal parameters.

The study population consisted of patients attending the outpatient endocrinology clinic at the private hospital. To be eligible for inclusion in the study, patients had to meet the following criteria; Diagnosis of T2DM: Patients had to have a confirmed diagnosis of T2DM according to the American Diabetes Association criteria; Age ≥ 35 years: This age criterion was chosen to focus on the adult population at higher risk of developing T2DM and its complications; Diagnosis of chronic periodontitis: Patients had to have a diagnosis of chronic periodontitis, defined as having at least four teeth with one or more sites with probing pocket depth (PPD) ≥ 4 mm and clinical attachment loss (CAL) ≥ 3 mm; Ability to provide informed consent: Patients had to be able to understand the study procedures and provide voluntary informed consent. Patients were excluded from the study if they met any of the following criteria; Type 1 diabetes: This study focused specifically on T2DM, as it is the most prevalent form of diabetes and has a different pathophysiology compared to type 1 diabetes; Pregnancy or lactation: Hormonal changes during pregnancy and lactation can significantly affect

periodontal health, potentially confounding the relationship between glycemic control and periodontal disease progression; Current use of systemic antibiotics or immunosuppressants: These medications can influence periodontal inflammation and healing, potentially interfering with the study outcomes; History of periodontal surgery or scaling and root planing within the past six months: Recent periodontal treatment can significantly alter periodontal parameters, making it difficult to assess the natural progression of periodontal disease; Severe systemic diseases: Patients with severe systemic diseases, such as uncontrolled hypertension, end-stage renal disease, or active malignancy, were excluded as these conditions could significantly affect periodontal status or study participation; Any condition that contraindicated periodontal probing: Patients with conditions that contraindicated periodontal probing, such as bleeding disorders or acute oral infections, were excluded to ensure the safety and accuracy of periodontal assessments.

Potentially eligible patients were identified through electronic medical records and invited to participate during their routine clinic visits. This recruitment strategy ensured that the study population was representative of the typical T2DM patient population attending the clinic. After providing written informed consent, participants underwent a comprehensive oral examination and baseline data collection. The oral examination was performed by calibrated periodontists who were blinded to the patients' HbA1c levels to ensure objectivity in periodontal assessments.

Data were collected at three time points: baseline (January 2021), 12 months (January 2022), and 24 months (January 2023). This longitudinal data collection allowed us to assess changes in periodontal parameters over time and their association with HbA1c levels. The following data were collected at each visit; Demographic and Medical History: Age, gender, ethnicity, smoking status (current, former, never), duration of diabetes, diabetes medications (oral hypoglycemic agents, insulin), and presence of other comorbidities were recorded using a standardized questionnaire. This information allowed us to adjust for potential confounding factors in the analysis; Anthropometric Measurements: Height and weight were measured, and body mass index (BMI) was calculated (kg/m²). BMI was included as a potential confounder in the analysis, as it is associated with both diabetes and periodontal disease; Glycemic Control: HbA1c was measured using a standardized laboratory method (high-performance liquid chromatography [HPLC]) at each visit. The average HbA1c over the 24-month period was also calculated to assess long-term glycemic control; Periodontal Examination: A comprehensive periodontal examination was performed by two calibrated periodontists who were blinded to the patients' HbA1c levels. The following parameters were assessed at six sites per tooth for all teeth except third molars; Probing Pocket Depth (PPD): Measured in millimeters from the gingival margin to the base of the pocket using a manual periodontal probe (UNC-15 probe); Clinical Attachment Loss (CAL): Measured in millimeters from the cementoenamel junction (CEJ) to the base of the pocket. If the CEJ was covered by the gingiva, the distance from the gingival margin to the CEJ was estimated and subtracted from the PPD; Bleeding on Probing (BOP): Recorded as present or absent within 30 seconds of probing; Plaque Index (PI): Assessed using the Silness and Löe plaque index, scored on a scale of 0-3. Inter-examiner reliability was assessed using the Kappa statistic for BOP and intraclass correlation coefficient (ICC) for PPD and CAL. Kappa values for BOP were consistently above 0.85, and ICC values for PPD and CAL were above 0.90, indicating excellent agreement between examiners.

Data were analyzed using SPSS version 27.0 and R version 4.2.2. Descriptive statistics were used to summarize baseline characteristics. Continuous variables were presented as mean ± standard deviation (SD) or median (interquartile range [IQR]) as appropriate, and categorical variables were presented as frequencies (percentages). Baseline comparisons were performed to assess differences in baseline characteristics between groups defined by HbA1c quartiles or tertiles. One-way ANOVA or Kruskal-Wallis tests were used for continuous variables, and chi-square tests or Fisher's exact tests were used for

categorical variables. Longitudinal analysis was performed using linear mixed-effects models to examine the association between HbA1c (both baseline and average HbA1c over 24 months) and changes in PPD, CAL, BOP, and PI over time. These models account for the correlation between repeated measurements within the same individual. Time (0, 12, and 24 months) was treated as a categorical variable, and an interaction term between HbA1c and time was included to assess whether the effect of HbA1c on periodontal parameters changed over time. Models were adjusted for potential confounders, including age, gender, smoking status, diabetes duration, baseline periodontal parameters, and BMI. Pre-specified subgroup analyses were performed based on smoking status (never vs. ever smokers) and diabetes duration (<5 years vs. ≥5 years) to explore potential effect modification. Sensitivity analyses were conducted to assess the robustness of the findings. These included; Excluding participants who received periodontal treatment (other than routine oral hygiene instructions) during the follow-up period; Using different cut-points for HbA1c (e.g., <7%, 7-9%, >9%) to define glycemic control categories. A p-value < 0.05 was considered statistically significant.

3. Results

Table 1 presents the baseline characteristics of the 180 study participants stratified by HbA1c quartiles. The mean age of participants was 58.5 years, with no significant differences across HbA1c quartiles. 55% of participants were female, with a similar distribution across quartiles. The majority of participants were Javanese (70%), followed by Madurese (20%), with no significant differences between HbA1c groups. The mean BMI was 27.3 kg/m², indicating overweight. No significant differences were observed across HbA1c quartiles. A significant difference was found (p=0.021), with higher waist circumference in the highest HbA1c quartile, suggesting a link between central obesity and poorer glycemic control. A significant association was seen (p=0.042), with a higher proportion of never-smokers in the lowest HbA1c quartile. This suggests smoking may negatively impact glycemic control. A significant difference was observed (p=0.003), with participants in the lowest HbA1c quartile reporting more physical activity, highlighting the importance of exercise in diabetes management. A significant difference was found (p=0.018), with longer diabetes duration in the highest HbA1c quartile. This is expected, as glycemic control often worsens over time. A significant association was seen (p<0.001), with a higher proportion of participants on oral hypoglycemic agents only in the lowest HbA1c quartile, while those on insulin or combination therapy were more common in higher quartiles, reflecting the progression of diabetes management. As expected, HbA1c levels increased significantly across quartiles (p<0.001). Similar to HbA1c, fasting glucose levels increased significantly across quartiles (p<0.001). While not statistically significant (p=0.087), there was a trend towards higher prevalence of hypertension in higher HbA1c quartiles. A significant association was found (p=0.035), with higher prevalence in higher HbA1c quartiles, indicating a link between poor glycemic control and lipid abnormalities. Similar to dyslipidemia, a significant association was seen (p=0.048), with higher prevalence in higher HbA1c quartiles. PPD, CAL, BOP, PI parameters showed significant differences (p<0.001) across HbA1c quartiles, with worse periodontal health observed in higher quartiles, suggesting a strong link between glycemic control and periodontal status. A significant difference was found (p=0.008), with fewer teeth in the highest HbA1c quartile, indicating potential tooth loss associated with poorer glycemic control; Antihypertensives: No significant association was found (p=0.235); Lipid-Lowering Agents: A significant association was observed (p=0.001), with higher use in higher HbA1c quartiles, reflecting the link between poor glycemic control and dyslipidemia.

Table 1. Baseline characteristics of study participants (n=180) stratified by HbA1c quartiles.

Characteristic	Overall (n=180)	HbA1c Quartile 1 (<7.0%) (n=40)	HbA1c Quartile 2 (7.0-7.9%) (n=50)	HbA1c Quartile 3 (8.0-8.9%) (n=55)	HbA1c Quartile 4 (≥9.0%) (n=35)	p-value	Statistical test used
Demographics							
Age (years), mean ± SD	58.5 ± 8.2	56.8 ± 7.9	58.2 ± 8.5	59.1 ± 8.0	60.2 ± 8.1	0.214	One-way ANOVA
Female, n (%)	99 (55.0)	22 (55.0)	28 (56.0)	30 (54.5)	19 (54.3)	0.987	Chi-square test
Ethnicity, n (%)							
Javanese	126 (70.0)	28 (70.0)	35 (70.0)	39 (70.9)	24 (68.6)	0.975	Chi-square test
Madurese	36 (20.0)	8 (20.0)	10 (20.0)	11 (20.0)	7 (20.0)		
Other	18 (10.0)	4 (10.0)	5 (10.0)	5 (9.1)	4 (11.4)		
Anthropometrics							
BMI (kg/m²), mean ± SD	27.3 ± 3.5	26.9 ± 3.2	27.1 ± 3.4	27.5 ± 3.6	27.8 ± 3.8	0.653	One-way ANOVA
Waist Circumference (cm), mean ± SD	92.5 ± 8.7	89.8 ± 7.5	91.2 ± 8.2	93.7 ± 9.1	95.6 ± 9.0	0.021	One-way ANOVA
Lifestyle Factors							
Smoking Status, n (%)							
Never	108 (60.0)	28 (70.0)	33 (66.0)	30 (54.5)	17 (48.6)	0.042	Chi-square test
Former	45 (25.0)	8 (20.0)	12 (24.0)	15 (27.3)	10 (28.6)		
Current	27 (15.0)	4 (10.0)	5 (10.0)	10 (18.2)	8 (22.9)		
Physical Activity (min/week), median (IQR)	90 (60-150)	120 (90-180)	100 (60-150)	80 (45-120)	60 (30-90)	0.003	Kruskal-Wallis test
Diabetes-Related Characteristics							
Diabetes Duration (years), mean ± SD	7.8 ± 4.5	6.5 ± 3.8	7.2 ± 4.2	8.1 ± 4.7	9.2 ± 5.1	0.018	One-way ANOVA
Diabetes Medication, n (%)							
Oral Hypoglycemic Agents Only	105 (58.3)	32 (80.0)	35 (70.0)	28 (50.9)	10 (28.6)	<0.001	Chi-square test
Insulin Only	27 (15.0)	2 (5.0)	5 (10.0)	8 (14.5)	12 (34.3)		
Combination (Oral + Insulin)	48 (26.7)	6 (15.0)	10 (20.0)	19 (34.5)	13 (37.1)		
HbA1c (%), mean ± SD	8.2 ± 1.5	6.5 ± 0.4	7.4 ± 0.3	8.4 ± 0.3	9.8 ± 0.7	<0.001	One-way ANOVA
Fasting Plasma Glucose (mmol/L), mean ± SD	9.5 ± 2.8	7.2 ± 1.5	8.8 ± 2.1	10.1 ± 2.5	11.9 ± 3.2	<0.001	One-way ANOVA
Comorbidities, n (%)							
Hypertension	81 (45.0)	15 (37.5)	20 (40.0)	25 (45.5)	21 (60.0)	0.087	Chi-square test
Dyslipidemia	72 (40.0)	12 (30.0)	18 (36.0)	22 (40.0)	20 (57.1)	0.035	Chi-square test
Cardiovascular Disease	18 (10.0)	2 (5.0)	4 (8.0)	5 (9.1)	7 (20.0)	0.048	Fisher's exact test
Periodontal Parameters							
PPD (mm), mean ± SD	4.8 ± 1.2	4.2 ± 0.9	4.6 ± 1.1	5.0 ± 1.2	5.4 ± 1.3	<0.001	One-way ANOVA
CAL (mm), mean ± SD	5.5 ± 1.4	4.8 ± 1.1	5.3 ± 1.3	5.8 ± 1.4	6.2 ± 1.5	<0.001	One-way ANOVA
BOP (%), mean ± SD	68.5 ± 15.2	58.2 ± 12.5	65.7 ± 14.8	72.3 ± 15.5	78.1 ± 16.2	<0.001	One-way ANOVA
PI (score), mean ± SD	1.8 ± 0.6	1.5 ± 0.5	1.7 ± 0.6	1.9 ± 0.6	2.1 ± 0.7	<0.001	One-way ANOVA
Number of Teeth, mean ± SD	24.5 ± 3.2	25.8 ± 2.8	24.9 ± 3.1	24.1 ± 3.3	23.2 ± 3.5	0.008	One-way ANOVA
Medications (other than diabetes), n (%)							
Antihypertensives	75 (41.7)	14 (35.0)	18 (36.0)	23 (41.8)	18 (51.4)	0.235	Chi-Square test
Lipid-Lowering Agents	68 (37.8)	10 (25.0)	16 (32.0)	20 (36.4)	22 (62.9)	0.001	Chi-Square Test

SD: Standard Deviation; IQR: Interquartile Range; BMI: Body Mass Index; PPD: Probing Pocket Depth; CAL: Clinical Attachment Loss; BOP: Bleeding on Probing; PI: Plaque Index; Statistically significant ($p < 0.05$).

Table 2 shows the longitudinal changes in periodontal parameters over the 24-month study period for the 180 participants. There's a clear trend towards worsening periodontal health over time. This is evidenced by the statistically significant increases in Probing Pocket Depth (PPD) and Clinical Attachment Loss (CAL) from baseline to 24 months. These increases indicate deepening periodontal pockets and greater attachment loss, signifying the progression of periodontal disease; PPD: Increased by an average of 0.4 mm (95% CI: 0.3 to 0.5) over 24 months. This is a statistically significant change ($p<0.001$), suggesting a gradual worsening of pocket depths; CAL: Showed a statistically significant increase ($p<0.001$) of 0.6 mm (95% CI: 0.5 to 0.7) over the 24 months, indicating progressive destruction of the tooth-supporting structures; BOP: Decreased by 10.4% (95% CI: -12.8 to -8.0) from baseline to 24 months. This statistically significant reduction ($p<0.001$) could be attributed to improved oral hygiene practices among participants due to their awareness of being monitored during the study; PI: Also decreased significantly ($p<0.001$) by 0.3 (95% CI: -0.4 to -0.2) over the study period, likely for the same reasons as the BOP reduction; Number of Teeth: Showed a small but statistically significant decrease ($p=0.003$) of 0.3 teeth (95% CI: -0.5 to -0.1). This suggests potential tooth loss associated with the progression of periodontal disease.

Table 2. Longitudinal changes in periodontal parameters over 24 months (n=180).

Parameter	Baseline (Mean ± SD)	12 Months (Mean ± SD)	24 Months (Mean ± SD)	Change from Baseline to 24 Months (Mean (95% CI))	p-value (Time Effect)
Probing pocket depth (PPD)					
PPD (mm)	4.8 ± 1.2	5.0 ± 1.3	5.2 ± 1.4	0.4 (0.3, 0.5)	<0.001
Clinical attachment loss (CAL)					
CAL (mm)	5.5 ± 1.4	5.8 ± 1.5	6.1 ± 1.6	0.6 (0.5, 0.7)	<0.001
Bleeding on probing (BOP)					
BOP (%)	68.5 ± 15.2	62.3 ± 14.8	58.1 ± 14.5	-10.4 (-12.8, -8.0)	<0.001
Plaque index (PI)					
PI (score)	1.8 ± 0.6	1.6 ± 0.5	1.5 ± 0.5	-0.3 (-0.4, -0.2)	<0.001
Number of teeth	24.5 ± 3.2	24.4 ± 3.2	24.2 ± 3.3	-0.3 (-0.5, -0.1)	0.003

SD: Standard Deviation; CI: Confidence Interval; PPD: Probing Pocket Depth; CAL: Clinical Attachment Loss; BOP: Bleeding on Probing; PI: Plaque Index; p-value (Time Effect): Determined using linear mixed-effects models, testing the overall change in the parameter over time (across all groups combined).

Table 3 presents the results from multivariate linear mixed-effects models, which were used to analyze the association between HbA1c (both baseline and average over 24 months) and changes in periodontal parameters over time; HbA1c and Periodontal Disease Progression: Both baseline HbA1c and average HbA1c were significantly associated with increases in Probing Pocket Depth (PPD) and Clinical Attachment Loss (CAL) over the 24-month period. This indicates that higher HbA1c levels, reflecting poorer glycemic control, are linked to a worsening of periodontal disease; Magnitude of Association: For every 1% increase in baseline HbA1c, PPD increased by 0.15 mm (95% CI: 0.10 to 0.20) and CAL increased by 0.18 mm (95% CI: 0.13 to 0.23). The association was stronger for average HbA1c: for every 1% increase, PPD increased by 0.21 mm (95% CI: 0.16 to 0.26) and CAL increased by 0.25 mm (95% CI: 0.20 to 0.30). This suggests that sustained poor glycemic control has a greater impact on periodontal health than a single baseline measurement; Interaction with Time: The significant interaction terms (HbA1c x Time) for both PPD and CAL indicate that the effect of HbA1c on these parameters increased over time. This means that the detrimental impact of high HbA1c on periodontal tissues becomes more pronounced with longer durations of exposure; No Significant Association with BOP and PI: No significant associations were found

between HbA1c (baseline or average) and changes in Bleeding on Probing (BOP) or Plaque Index (PI). This could be due to several factors, such as improvements in oral hygiene practices among participants due to study participation, or the fact that BOP and PI are more susceptible to short-term fluctuations and less specific indicators of disease progression compared to PPD and CAL.

Table 3. Association between HbA1c and changes in periodontal parameters: results from multivariate linear mixed-effects models (n=180).

Periodontal parameter	HbA1c Predictor	β (95% CI)	p-value
Probing pocket depth (PPD)			
	Baseline HbA1c	0.15 (0.10, 0.20)	<0.001
	Average HbA1c	0.21 (0.16, 0.26)	<0.001
	HbA1c x Time (Baseline)	0.05 (0.03, 0.07)	<0.001
	HbA1c x Time (Average)	0.07 (0.04, 0.10)	<0.001
Clinical attachment loss (CAL)			
	Baseline HbA1c	0.18 (0.13, 0.23)	<0.001
	Average HbA1c	0.25 (0.20, 0.30)	<0.001
	HbA1c x Time (Baseline)	0.06 (0.04, 0.08)	<0.001
	HbA1c x Time (Average)	0.09 (0.06, 0.12)	<0.001
Bleeding on probing (BOP)			
	Baseline HbA1c	0.02 (-0.03, 0.07)	0.456
	Average HbA1c	0.03 (-0.02, 0.08)	0.231
	HbA1c x Time (Baseline)	-0.01 (-0.04, 0.02)	0.512
	HbA1c x Time (Average)	-0.02 (-0.05, 0.01)	0.198
Plaque index (PI)			
	Baseline HbA1c	-0.01 (-0.05, 0.03)	0.678
	Average HbA1c	0.00 (-0.04, 0.04)	0.982
	HbA1c x Time (Baseline)	0.01 (-0.02, 0.04)	0.489
	HbA1c x Time (Average)	0.00 (-0.03, 0.03)	0.915

β: Beta coefficient, representing the estimated change in the periodontal parameter (in mm for PPD and CAL, in percentage points for BOP, and in score units for PI) for every 1% increase in HbA1c; 95% CI: 95% Confidence Interval for the beta coefficient; HbA1c x Time: Interaction term between HbA1c and time, representing the change in the effect of HbA1c on the periodontal parameter over time; Adjusted for: Age, gender, smoking status (never, former, current), diabetes duration, baseline value of the respective periodontal parameter, and BMI.

Table 4 presents the results of subgroup analyses examining the association between average HbA1c and changes in Probing Pocket Depth (PPD) and Clinical Attachment Loss (CAL), stratified by smoking status and diabetes duration; Smoking Status: In both never-smokers and ever-smokers (former/current), average HbA1c was significantly associated with increases in PPD and CAL. This confirms that the link between glycemic control and periodontal disease progression holds true regardless of smoking status. However, the magnitude of the association was greater in ever-smokers. For every 1% increase in average HbA1c, PPD increased by 0.27 mm in ever-smokers compared to 0.18 mm in never-smokers. Similarly, CAL increased by 0.31 mm in ever-smokers compared to 0.22 mm in never-smokers. This suggests that smoking may exacerbate the detrimental effects of poor glycemic control on periodontal tissues. This

effect modification by smoking status was statistically significant for both PPD (p=0.021) and CAL (p=0.038); Diabetes Duration: Average HbA1c was significantly associated with increases in PPD and CAL in both subgroups (<5 years and ≥5 years of diabetes duration). This indicates that the link between glycemic control and periodontal disease progression is present regardless of how long someone has had diabetes. Although the beta coefficients were slightly higher in the ≥5 years subgroup, the differences were not statistically significant (p=0.185 for PPD and p=0.247 for CAL). This suggests that while longer diabetes duration might lead to slightly greater periodontal damage for the same increase in HbA1c, the effect is not substantially different.

Table 4. Subgroup analyses: association between average HbA1c and changes in PPD and CAL, stratified by smoking status and diabetes duration.

Periodontal parameter	Subgroup	β (95% CI) for average HbA1c	p-value (HbA1c Effect)	p-value (Interaction)
Probing Pocket Depth (PPD)				
	Smoking Status			
	Never Smokers	0.18 (0.12, 0.24)	<0.001	0.021
	Ever Smokers (Former/Current)	0.27 (0.20, 0.34)	<0.001	
	Diabetes Duration			
	< 5 years	0.19 (0.11, 0.27)	<0.001	0.185
	≥ 5 years	0.23 (0.17, 0.29)	<0.001	
Clinical Attachment Loss (CAL)				
	Smoking Status			
	Never Smokers	0.22 (0.16, 0.28)	<0.001	0.038
	Ever Smokers (Former/Current)	0.31 (0.24, 0.38)	<0.001	
	Diabetes Duration			
	< 5 years	0.23 (0.15, 0.31)	<0.001	0.247
	≥ 5 years	0.28 (0.22, 0.34)	<0.001	

β: Beta coefficient, representing the estimated change in PPD or CAL (in mm) for every 1% increase in average HbA1c within the specified subgroup; 95% CI: 95% Confidence Interval for the beta coefficient; p-value (HbA1c Effect): Tests the significance of the association between average HbA1c and the periodontal parameter within each subgroup; p-value (Interaction): Tests the significance of the difference in the HbA1c effect between the subgroups (e.g., Never Smokers vs. Ever Smokers). A significant p-value for interaction indicates effect modification; Adjusted for: Age, gender, baseline value of the respective periodontal parameter, and BMI. (Smoking status and diabetes duration are not adjusted for in these models, as they are the stratification variables).

Table 5 outlines the results of various sensitivity analyses conducted to assess the robustness of the main findings regarding the association between average HbA1c and changes in Probing Pocket Depth (PPD) and Clinical Attachment Loss (CAL); Main Analysis (from Table 3): This refers to the primary analysis presented earlier, showing a significant association between average HbA1c and increases in both PPD and CAL over 24 months. This serves as the reference point for comparison with the sensitivity analyses; Sensitivity Analysis 1: This analysis excluded participants who received any periodontal treatment (other than routine oral hygiene instructions) during the follow-up period. The results remained largely consistent with the main analysis, with significant associations still observed between average HbA1c and changes in PPD and CAL. This suggests that the main findings were not significantly influenced by any potential confounding effects of periodontal treatment; Sensitivity Analysis 2: Instead of using average HbA1c as a continuous variable, this analysis categorized participants into three groups

based on HbA1c levels (<7.0%, 7.0-8.9%, ≥9.0%). Comparisons between these groups revealed significant differences in PPD and CAL changes, with the highest HbA1c group (≥9.0%) showing the greatest increases. This supports the main findings that higher HbA1c levels are associated with greater periodontal disease progression; Sensitivity Analysis 3: This analysis used a different statistical model (Generalized Estimating Equations [GEE] with an exchangeable correlation structure) to assess the association between average HbA1c and changes in PPD and CAL. The results were again consistent with the main analysis, showing significant associations. This indicates that the main findings were not dependent on the specific statistical model used.

Table 5. Sensitivity analyses: association between average HbA1c and changes in PPD and CAL.

Analysis	Periodontal parameter	β (95% CI) for average HbA1c	p-value
Main analysis (from Table 3)			
(All participants, adjusted for age, gender, smoking status, diabetes duration, baseline periodontal parameter, and BMI)	PPD (mm)	0.21 (0.16, 0.26)	<0.001
	CAL (mm)	0.25 (0.20, 0.30)	<0.001
Sensitivity analysis 1:			
(Excluding participants who received periodontal treatment other than routine oral hygiene instructions during follow-up, n=165)	PPD (mm)	0.20 (0.15, 0.25)	<0.001
	CAL (mm)	0.24 (0.19, 0.29)	<0.001
Sensitivity analysis 2:			
(Using HbA1c categories: <7.0%, 7.0-8.9%, ≥9.0%)	PPD (mm)		
- <7.0% vs. ≥9.0%		0,35 (0.27, 0.43)	<0.001
- 7.0-8.9% vs. ≥9.0%		0.18 (0.11, 0.25)	<0.001
(Using HbA1c categories: <7.0%, 7.0-8.9%, ≥9.0%)	CAL (mm)		
- <7.0% vs. ≥9.0%		0.41 (0.33, 0.49)	<0.001
- 7.0-8.9% vs. ≥9.0%		0,22 (0.15, 0.29)	<0.001
Sensitivity analysis 3:			
(Using a different model: Generalized Estimating Equations [GEE] with an exchangeable correlation structure)	PPD (mm)	0.22 (0.17, 0.27)	<0.001
	CAL (mm)	0.26 (0.21, 0.31)	<0.001

β: Beta coefficient, representing the estimated change in PPD or CAL (in mm) for every 1% increase in average HbA1c (except for Sensitivity Analysis 2, where it represents the difference between HbA1c categories); 95% CI: 95% Confidence Interval for the beta coefficient; Adjusted for: All analyses are adjusted for age, gender, smoking status, diabetes duration, baseline value of the respective periodontal parameter, and BMI unless otherwise specified.

4. Discussion

The primary finding of this study, the significant association between HbA1c and the progression of periodontal disease, aligns with a growing body of evidence from various populations, further solidifying the understanding of this crucial relationship. This study, however, provides a unique contribution by focusing on an Indonesian cohort, a population grappling with a high prevalence of type 2 diabetes mellitus (T2DM) yet lacking extensive data on the

intricate interplay between diabetes and periodontal disease. This research sheds light on the specific dynamics of this relationship within the Indonesian context, adding valuable insights to the global understanding of this issue. A key strength of this study lies in its longitudinal design, which allowed for the observation of changes in periodontal health over time in relation to HbA1c levels. This approach provides a more nuanced understanding compared to cross-sectional studies, which can only capture a snapshot of the relationship at a single point in time. By following participants over 24 months, this study was able to track the progression of periodontal disease and its correlation with both baseline and average HbA1c levels, offering a dynamic view of the disease process. The stronger association observed between average HbA1c over 24 months and periodontal disease progression compared to baseline HbA1c alone underscores the critical role of long-term glycemic control in maintaining periodontal health. A single HbA1c measurement, while informative, represents only a momentary glimpse of an individual's glycemic status. In contrast, the average HbA1c over a longer period provides a more comprehensive picture of the cumulative exposure to hyperglycemia, which is a key driver of the chronic inflammatory processes that underpin periodontal disease. This finding has significant implications for clinical practice, emphasizing the need for sustained and consistent glycemic control in individuals with T2DM. It suggests that achieving target HbA1c levels at a single point in time is not sufficient to protect against periodontal complications. Rather, it is the long-term maintenance of good glycemic control that plays a crucial role in mitigating the risk of periodontal disease progression. This highlights the importance of ongoing monitoring and management of blood glucose levels, along with patient education and support to facilitate adherence to treatment regimens. The observed interaction between HbA1c and time further strengthens the argument for early and sustained intervention to achieve optimal glycemic control. This interaction suggests that the detrimental effects of hyperglycemia on periodontal tissues accumulate over time, leading to a more pronounced impact with prolonged exposure. Therefore, early intervention to establish and maintain good glycemic control is crucial to prevent or delay the onset and progression of periodontal complications. This finding underscores the importance of proactive diabetes management, particularly in younger individuals with T2DM. By intervening early and maintaining consistent glycemic control, healthcare providers can help minimize the long-term risks of periodontal disease and its associated complications, ultimately contributing to improved oral and systemic health outcomes.[11-15]

The association between hyperglycemia and periodontal disease progression is a complex interplay influenced by several interconnected mechanisms. Understanding these mechanisms is crucial for developing targeted interventions to mitigate the risk and progression of periodontal disease in individuals with diabetes. One of the key mechanisms linking hyperglycemia to periodontal disease is the increased formation of advanced glycation end-products (AGEs). AGEs are formed through a non-enzymatic reaction between glucose and proteins, lipids, or nucleic acids. In the context of hyperglycemia, the excess glucose in the bloodstream leads to an elevated production of AGEs. These AGEs can accumulate in various tissues, including periodontal tissues, and contribute to inflammation and tissue damage. AGEs exert their detrimental effects through several pathways. They can bind to specific receptors on cells, called RAGE (receptor for advanced glycation end-products), triggering the activation of various signaling pathways that promote inflammation, oxidative stress, and apoptosis. This inflammatory response can lead to the destruction of periodontal tissues, including the gingiva, periodontal ligament, and alveolar bone. Furthermore, AGEs can alter the structure and function of collagen, a major component of periodontal tissues. Collagen provides structural support and integrity to the periodontium, and its modification by AGEs can impair its ability to withstand mechanical stress and resist degradation. This can lead to the weakening of periodontal tissues and increased susceptibility to breakdown. Hyperglycemia can also impair immune function, making individuals with diabetes more susceptible to infections, including

periodontal disease. The immune system plays a crucial role in defending the body against pathogens, and its dysfunction can compromise the host's ability to control bacterial infection and inflammation in the periodontium. Hyperglycemia can affect various aspects of immune function, including the activity of neutrophils, macrophages, and lymphocytes. Neutrophils are the first line of defense against bacterial infection, and their ability to phagocytose and kill bacteria is impaired in individuals with hyperglycemia. Macrophages are also important for clearing pathogens and regulating inflammation, and their function is similarly compromised in the presence of high glucose levels. Lymphocytes, including T cells and B cells, are essential for adaptive immunity, which provides long-term protection against specific pathogens. Hyperglycemia can disrupt lymphocyte function, impairing the host's ability to mount an effective immune response against periodontal pathogens. Collagen, as mentioned earlier, is a crucial component of periodontal tissues, providing structural support and integrity. Hyperglycemia can disrupt collagen metabolism, leading to alterations in its synthesis, degradation, and turnover. High glucose levels can increase the production of reactive oxygen species (ROS), which can damage collagen fibers and impair their function. Additionally, hyperglycemia can activate enzymes called matrix metalloproteinases (MMPs), which break down collagen. The imbalance between collagen synthesis and degradation can lead to the weakening of periodontal tissues and increased susceptibility to breakdown. The oral microbiome, the complex community of microorganisms that inhabit the oral cavity, plays a crucial role in maintaining oral health. However, hyperglycemia can disrupt the balance of the oral microbiome, leading to an increase in pathogenic bacteria and a decrease in beneficial bacteria. Studies have shown that individuals with diabetes tend to have a higher prevalence of periodontal pathogens, such as Porphyromonas gingivalis and Aggregatibacter actinomycetemcomitans, in their oral microbiome. These pathogens are known to contribute to periodontal inflammation and tissue destruction. Furthermore, hyperglycemia can create a more favorable environment for the growth of these pathogens by providing them with an abundant source of glucose. The altered oral microbiome can further exacerbate periodontal inflammation and contribute to the progression of periodontal disease. It is important to note that these mechanisms are not mutually exclusive but rather interconnected and influence each other. For example, AGEs can activate immune cells, leading to increased inflammation and further tissue damage. Impaired immune function can also contribute to changes in the oral microbiome, favoring the growth of pathogenic bacteria. The complex interplay between these mechanisms highlights the multifactorial nature of the relationship between hyperglycemia and periodontal disease progression. Addressing these mechanisms through a combination of glycemic control, periodontal therapy, and lifestyle modifications is crucial for preventing and managing periodontal disease in individuals with diabetes.[16-20]

5. Conclusion

This study has provided clear evidence that HbA1c serves as a significant independent predictor of periodontal disease progression in patients with T2DM. The findings underscore the critical role of sustained glycemic control in preventing and managing periodontal complications in this population. The study highlights the importance of interdisciplinary collaboration between internists and dentists in the comprehensive care of T2DM patients. By effectively managing HbA1c levels, healthcare professionals can contribute to improved periodontal health outcomes and overall well-being for individuals with T2DM. The insights gained from this research emphasize the need for ongoing monitoring and management of blood glucose levels, along with patient education and support, to facilitate adherence to treatment regimens and mitigate the risk of periodontal disease progression.

6. References

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