


A Case–Control Study of Type 2 Diabetes Mellitus and Periodontitis in Saudi Arabian Adults

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Mir Faeq Ali Quadri ¹
Hamam I Fageeh²
Wael Ibraheem²
Abbas Jessani³

¹Department of Preventive Dental Sciences, Division of Dental Public Health, College of Dentistry, Jazan University, Jazan, Saudi Arabia;

²Department of Preventive Dental Sciences, Division of Periodontology, College of Dentistry, Jazan University, Jazan, Saudi Arabia; ³College of Dentistry, Schulich School of Medicine & Dentistry, Toronto, Canada

Objective: The relationship between type 2 diabetes mellitus (T2DM) and periodontitis is bidirectional and has been investigated. However, the evidence from the middle-eastern region is sparse. The current report assessed the association between uncontrolled T2DM and periodontal status from a sample of the Saudi Arabian adult population.

Methods: A case–control study was carried out. Cases were adults diagnosed with periodontitis (clinical attachment loss ≥ 1 mm) and controls were patients from the same dental setting with no gum conditions matched with age, sex, and location. Diabetes was recorded using HbA1c readings. The other health conditions including hypertension, epilepsy, bronchitis, thyroid disorders, and arthritis were obtained from medical records. Data on the use of tobacco and related products (smoking, khat/qat, sheesha, shammah) were gathered using a self-perceived questionnaire. Frequencies, percentages, p-values, crude and adjusted odds ratios (OR) with 95% confidence intervals were computed.

Results: Overall sample comprises 166 cases and 332 controls with a mean age of 37.5 years. Multivariable analysis indicated uncontrolled T2DM as an important predictor for periodontitis among Saudi Arabian adults, and they had nearly three times greater odds (OR: 2.779; 95% CI: 1.425–5.419; $p=0.003$) of being diagnosed with periodontitis in contrast to non-diabetics. Secondary findings revealed that cigarette ever-users were two times more likely to be suffering from periodontitis than never-users, and those brushing once per day or less had five times greater odds of developing periodontitis as compared to those brushing twice daily.

Conclusion: To conclude, the current evidence from Saudi Arabia is supportive of earlier studies and an awareness of this association is warranted among all healthcare providers and patients in the region for early detection of periodontitis.

Keywords: type-2 diabetes mellitus, adult periodontitis, case–control study, association, Saudi Arabia

Plain Language Summary

The current study is the first to gather evidence from Jazan region of Saudi Arabia to demonstrate the relationship between T2DM and periodontitis. Findings reveal that the individuals with uncontrolled type-2 diabetes mellitus (T2DM) are more likely to develop periodontitis in comparison to the non-diabetic population. As the relationship between diabetes and periodontitis is bidirectional, selection of appropriate study design while establishing the relationship is essential. The idea is to address temporality by demonstrating that diabetes precedes periodontitis. The HbA1c level indicates uncontrolled blood sugar level for the past few months and one could assume that the people with higher than normal HbA1c level may have been suffering from uncontrolled T2DM for many months. However, the current study do not specify the likely number of months that are needed to develop periodontitis for an individual suffering from uncontrolled T2DM and also the plausible

Correspondence: Mir Faeq Ali Quadri
Department of Preventive Dental Sciences, Division of Dental Public Health, College of Dentistry, Jazan University, Jazan City 45142, Saudi Arabia
Tel +00966 5989 59409
Email dr.faeq.quadri@gmail.com

mechanism. An awareness of this association among healthcare providers and patients is essential as it may contribute towards early detection and prevention of periodontitis among the diabetics.

Introduction

Periodontitis is one of the most prevalent oral diseases in the adult population worldwide.^{1,2} A common clinical sign of periodontitis is loss of dental connective tissue and bone, caused by inflammatory host response secondary to bacterial infection.³ There are certain pathophysiological conditions that have the ability to disrupt the symbiotic equilibrium of microbes in the oral cavity, ultimately leading to periodontitis.⁴⁻⁶ One such debilitating physiologic condition is diabetes, which is shown to be associated with periodontitis.⁷ Among the two broad categories of diabetes, epidemiological studies have classified type 2 diabetes mellitus (T2DM) as a widespread condition, with current reports indicating approximately 285 million people with this disease, and estimating an increase of 50% by the year 2030.⁸ Reports indicate that blood sugar levels caused by diabetes may trigger a bacterial imbalance leading to a cascade of inflammatory reactions in the periodontal apparatus, causing loss of teeth, decreased chewing ability, nutritional imbalance, and eventually, a reduced oral health-related quality of life.^{9,10}

The certainty of association is agreed upon by many experts, and systematic review and meta-analysis have been performed to demonstrate and evaluate the effect of diabetes on periodontitis.¹¹ There are findings that report otherwise. For instance, a systematic review had stated that patients with diabetes had the same extent of periodontal disease compared with non-diabetics.¹² The contrast in findings is largely attributed to the quality of methodology adopted by the included studies in the reviews. A recent systematic review had revealed an increased heterogeneity ($I^2 = 89.7\%$, $p < 0.001$) among the included reports especially in terms of their study design.¹³ In line with this, another systematic review that demonstrated a significant association between diabetes and periodontitis showed that out of the 49 cross-sectional and 8 longitudinal studies about 26 could have demonstrated better and precise findings if the assessment of variables was standardized, sample recruitment process was robust, and if the findings were adjusted for confounding variables.¹⁴

The Center for Evidence-Based Medicine (CEBM) specifies that proper study design and methodology and judgmental intuition of other potential factors are highly

important to estimate an effect between the exposure and the outcome.¹⁵ Till date, there has been no evidence provided from an ethnically similar population of Saudi Arabian adults to substantiate the association of uncontrolled diabetes and periodontitis by utilizing the gold standard glycated hemoglobin (HbA1c) test reports and clinical attachment loss, respectively. It is proclaimed that epidemiological studies are appropriate to investigate the association; among them, cross-sectional studies exhibit limited causal inference as the exposure and outcomes are examined concurrently.¹⁶ Cohort studies provide better evidence but are not always feasible due to the huge enrollment required to demonstrate an effect, and the likely loss of follow-up data for some participants.¹⁷ Due to these reasons, it is put forth that a case-control study design satisfies the criteria of temporality and is a more feasible approach in determining the association. With this, the current study aimed to investigate the association between uncontrolled T2DM (exposure) and periodontitis (outcome) among Saudi Arabian adult population; and it is hypothesized that the odds of developing periodontitis in participants with uncontrolled T2DM are higher than in their non-diabetic counterparts.

The rationale for this investigation is the plausible influence of pathogenic mechanism in the individuals who have uncontrolled diabetes in comparison to non-diabetic,^{18,19} and the data from the Saudi Arabian population are limited.

Methods

Study Design and Study Location

A hospital-based case-control study was designed following the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines.^{20,21} The current study was conducted in the Jazan province of Saudi Arabia, which is located in the south-western part of the Arabian Peninsula, bordering Yemen. The site of data collection was the Dental Center affiliated with Jazan University. It is the largest oral health service provider in the region, catering to the needs of more than 1.5 million citizens, with the complete oral health cost borne by the Government of Saudi Arabia.

Sample Size Estimation

In a previous nationwide study, the age-specific prevalence of T2DM among Saudi Arabian residents was reported to be 40.6%, with the Jazan region contributing to around

9.4% of the cases.²² Due to lack of prevalence estimates of periodontitis directly from this region, the sample size calculation was based on data from the most recent available study performed in another region of Saudi Arabia.²³ This included 80% power, 95% precision, and an assumption of 0.5% of controls being exposed to the risk factor. The sample, was inclusive of two controls for each case (1:2). The estimated sample size required to reject the null hypothesis, with a 10% addition for dropouts was determined to be 66 cases and 132 controls. However, to attain a better precision all the available cases ($n = 166$) and twice ($n = 332$) the number of controls in the months from August to October of 2018 were recruited.

Selection Criteria

Saudi Arabian adults confirming their identity by displaying the national card were recruited as cases and controls for the current study. This was done to ensure similar ethnic backgrounds and cultural habits of study participants. Patients presenting with physical and mental disabilities, or patients who did not provide signed consent, were excluded.

Defining the Cases and Controls

Cases were defined as clinically diagnosed periodontitis patients who underwent oral health examinations at the Dental Center affiliated with Jazan University by two calibrated specialists using the method prescribed by the American Academy of Periodontology (2014).²⁴ Controls were adults selected from the same Dental Center, who had not been diagnosed with periodontitis, and adjusted for age (± 5 years), sex, and location.

Assessment of Outcome Variable

Assessment of outcome was conducted using the standardized classification system for periodontal diseases and conditions.^{24,25} A Williams' periodontal probe (Hu-Friedy® PW6) was used to measure clinical parameters, including clinical attachment loss (CAL) and probing depths (PD). Six sites per tooth were assessed, and a diagnosis of periodontitis was made when subjects presented with at least two sites with a $PD \geq 4$ mm and a $CAL \geq 1$ mm (one on each tooth).²⁵

Assessment of Exposure Variables

Medical reports were checked to confirm the history of T2DM, based on the date of first diagnosis confirmed through glycated hemoglobin (HbA1c) tests. Then,

patients with the current HbA1c level higher than $HbA1c \geq 7\%$; ≥ 53 mmol/mol were defined as those having uncontrolled diabetes.^{26–28} A medical history of hypertension, epilepsy, bronchitis, thyroid disorders, and arthritis was confirmed from the participant's medical records, and responses were dichotomized (yes/no). Oral hygiene practice was recorded by asking the participants if they preferred brushing their teeth twice a day, once a day, or less than once a day. The response received was dichotomized, and "twice per day" was considered as a good oral hygiene practice, while the other options were considered as a fair/poor oral hygiene practice. Data on tobacco and related products (smoking, khat/qat, sheesha, and shammah) commonly used in the region were gathered through a patient-evaluation questionnaire, and responses were subsequently dichotomized to classify the patients as ever-users and never-users. Previous users of the mentioned products who had abstained for more than 5 years were also considered as never-users.

Specialist Calibration

Periodontitis among the study participants was diagnosed independently by two American board-certified periodontists who were part of the current study. The first 10% of the recruited cases were cross-examined to assess the calibration. The inter-examiner reliability was calculated as Kappa (unweighted Kappa), and the result obtained ranged between 0.75 and 0.90 with an average of 0.84 ± 0.03 for the eight patients, achieving a satisfactory calibration agreement.²⁹

Data Collection Process

The data collection process involved a clinical examination of the suspected cases and a total of 166 cases were recruited. Twice the number of controls ($n = 332$) were recruited from other departments of the same dental setting. Both cases and controls were subsequently assessed for uncontrolled T2DM and other exposure variables using the parameters mentioned earlier. History of periodontitis and diabetes was verified using the available electronic health records of the patients to observe that the outcome followed the exposure.

Statistical Analyses

Relationship between periodontitis and T2DM, as well as other covariates, were first identified using the Chi-square or Fisher's exact test, as appropriate. The associations were explored further with binary and multiple logistic regression

analyses, after adjusting for confounders. Data were presented as frequencies, percentages, p-values, crude OR and adjusted OR; with their 95% CI. Data entry and statistical analyses were performed using the Statistical Package for the Social Sciences v.24 (SPSS, IBM Statistics). A p-value of <0.05 was considered as significant.

Results

The sample consisted of 166 cases and 332 controls (1:2) from the available pool of patients. The mean age of the study sample was 37.5 years (SD = 5.1). None were mentally or physically challenged or had gestational diabetes, renal disorders, HIV-infection, cancers, or kidney disorders. Estimates for hypotension, T1DM, pregnancy, epilepsy, thyroid, and shammah (smokeless tobacco, could not be computed as these conditions were only present in either the cases or controls, and were even excluded from the multivariable models.

Findings from the relationship of periodontitis with general health conditions are reported in Table 1. T2DM, hypertension, diabetes, epilepsy, allergic conditions, asthma, and bronchitis were the reported general health conditions in the study sample. Among them, T2DM was more common in the cases and the controls. A significant relationship of T2DM and hypertension with periodontitis was observed. Hypertension was reported in 4.8% of the cases and in 0.6% of the controls (p = 0.003), while T2DM was reported in 28.9% of the cases and 5.7% of the controls (p < 0.001) (Table 1).

Findings from the relationship of periodontitis with oral hygiene habits and substance use are reported in Table 2. Brushing once per day or less as opposed to twice daily was observed significantly more in cases

(39.1%) compared to controls (11.4%) (p < 0.001). Smoking (p = 0.006) and khat/qat (p = 0.002) use was also found to be significantly higher in patients with periodontitis (Table 2).

The findings from the binary and multiple logistic regression analyses are presented in Table 3. The crude analysis identified T2DM and hypertension as significantly associated with periodontitis. Patients with T2DM and hypertension had six times (OR: 6.701; 95% CI: 3.783–11.872) and eight times (OR: 8.354; 95% CI: 2–39.799) higher odds, respectively, of being diagnosed with periodontitis. The multivariate analyses were adjusted for asthma, bronchitis, and sheesha use. Adjusted analysis revealed that T2DM patients had nearly three times greater odds (OR: 2.779; 95% CI: 1.425–5.419; p = 0.003) of being diagnosed with periodontitis than their non-T2DM counterparts (Table 3).

Cigarette smoking, khat use, and oral hygiene practice were significantly associated with periodontitis in the crude analysis. The adjusted analysis however revealed that patients with the habit of cigarette smoking were two times (OR: 2.088; 95% CI: 1.013–4.305; p = 0.046) more likely to have periodontitis. Khat use was not significantly related. Finally, patients brushing only once per day or less had a five times greater chance of developing periodontitis as compared to patients brushing twice daily (Table 3).

Discussion

Epidemiologic studies in Arab nations, including Saudi Arabia suggest a consistent rise in the T2DM cases that need immediate attention.^{22,30} The Center for Disease Control (CDC) has reported that individuals diagnosed with diabetes are more likely to suffer from severe inflammation

Table 1 General Health Conditions and Their Relationship with Periodontitis (N= 498)

General Health Conditions	Cases (N=166) n (%)	Controls (N=332) n (%)	Total n (%)	p-value
T2DM	48(28.9)	19(5.7)	67(13.4)	<0.001*
T1DM	1(0.6)	0(0)	1(0.2)	0.333†
Hypertension	8(4.8)	2(0.6)	10(2.0)	0.003*†
Hypotension	0(0)	2(0.6)	2(0.4)	0.555†
Asthma	5(3.0)	13(3.9)	18(3.6)	0.611
Pregnancy	0(0)	2(0.6)	2(0.4)	0.555†
Epilepsy	1(0.6)	0(0)	1(0.2)	0.333†
Arthritis	3(1.8)	5(2.7)	8(1.6)	1.000†
Allergies	1(0.6)	9(2.7)	10(2)	0.176†
Thyroid disorders	1(0.6)	0(0)	1(0.2)	0.333†
Bronchitis	1(0.6)	3(0.9)	4(0.8)	1.000†

Notes: *Statistically significant (p<0.05), † Fishers' test.

Table 2 Relationship of Oral Hygiene Practice and Substance Use with Periodontitis (N= 498)

Habits	Cases (N=166) n (%)	Controls (N=332) n (%)	Total n (%)	p-value
Cigarette ^a	27(16.2)	27(8.1)	54(10.8)	0.006*
Khat/qat ^a	20(12.0)	15(4.5)	35(7.0)	0.002*
Sheesha ^a	1(0.6)	1(0.3)	2(0.4)	1.000 [†]
Shammah ^a	1(0.6)	0(0)	1(0.2)	0.333 [†]
Brushing once a day or less [§]	65(39.1)	38(11.4)	103(20.6)	<0.001*

Notes: *Statistically significant (p<0.05); [†]Fishers' test; [§]Reference category: brushing twice a day; ^aEver-users vs never-users.

Table 3 Binary and Multivariate Logistic Regression Analysis Demonstrating the Effect Various Exposure Variables on Periodontal Status (N= 498)

Risk Factors	Crude			Adjusted [†]		
	OR	95% CI	p-value	OR	95% CI	p-value
T2DM	6.701	(3.783–11.872)	<0.001*	2.779	(1.425–5.419)	0.003*
Hypertension	8.354	(2–39.799)	0.003*	3.279	(0.507–21.191)	0.212
Arthritis	1.204	(0.284–5.099)	1.000	0.459	(0.095–2.230)	0.334
Allergies	0.218	(0.027–1.731)	0.176	0.268	(0.029–2.474)	0.245
Cigarette	2.194	(1.241–3.880)	0.006*	2.088	(1.013–4.305)	0.046*
Khat/qat	2.895	(1.441–5.816)	0.002*	2.206	(0.922–5.279)	0.075
Brushing once a day [§]	4.979	(3.144–7.885)	0.000*	5.630	(3.514–9.021)	<0.001*

Notes: *Statistically significant (p<0.05); [†]Adjusted for asthma, bronchitis, and sheesha; [§]Reference category: brushing twice a day.

Abbreviation: OR, odds ratio.

and inadequate white blood cell functions, which can subsequently lead to destruction of periodontal tissues.³¹ However, to properly study the effect of diabetes on periodontitis, it was important to distinguish diabetic patients with uncontrolled blood sugar levels from those with controlled blood sugar levels. This is because the degree of glycemic control may determine the vulnerability of the immune defense mechanism, which ultimately leads to the damage of periodontal tissues. Further, there are reports that suggest that T2DM, in particular, has the ability to remain undiagnosed for a long time as the affected patients retain their capacity to produce insulin, and the symptoms are usually missed.³² Thus, gold-standard measures as opposed to subjective measures were required to confirm the glycemic control in the diabetic patients.

Although the relationship between diabetes mellitus and periodontitis is well studied, the current study is the first in Saudi Arabia to investigate the effect of uncontrolled T2DM on periodontal status using a case-control study design. After adjusting for other variables like systemic diseases, substance used (Khat, sheesha, and shammah), and socio-demographic characteristics (age, sex, location, and ethnicity), it is observed that the subjects with uncontrolled diabetes (T2DM) had nearly three

times greater likelihood of developing periodontitis. A recent research in Saudi Arabia with a different study design aiming to compare the levels of Advance Glycation End-products in the gingival crevicular fluids of patients suffering from chronic periodontitis, with and without T2DM, supported the findings of the current study.³³ However, the stated limitation was the inclusion of patients with controlled diabetes mellitus along with uncontrolled diabetes mellitus. In addition, one group of patients with uncontrolled diabetes was prescribed with medications and were still reported as having abnormal glycemic control, indicating that other risk factors or covariates that could have led to this uncontrolled state of blood sugar level were not considered.³³

A longitudinal study among the Gullah African Americans also showed that uncontrolled T2DM relates to a nearly two times higher magnitude of periodontal tissue destruction compared to their counterparts (controlled diabetics and non-diabetics).³⁴ The results are further substantiated by other investigations from the United Kingdom,³⁵ United States of America,³⁶ India,³⁷ and Spain.³⁸ A systematic review and meta-regression of longitudinal studies also confirms this association. However, these findings from meta-regression indicated a 25% variability

between the published studies with respect to their sample size.¹³ It further reiterated that some of the included studies did not have a representative sample,¹³ and evidence suggest that a small sample size often overestimates the association between the exposure and the outcome.³⁹

Secondary findings from the current study revealed that the patients who brushed their teeth once per day or less had a five times greater chance of developing periodontitis than patients who brushed twice per day. Affirming this, Han et al (2017) suggested that maintaining a good personal oral hygiene through brushing, flossing, and professional oral prophylactic treatment is an important strategy to prevent gingival diseases, including periodontitis.⁴⁰ Similarly, other studies have also unequivocally stated that poor oral hygiene practices increase the risk of periodontitis by nearly fivefold, and that the risk substantially reduces with regular tooth brushing and dental visits.⁴¹

The multivariable model in the current study also indicated that cigarette ever-users have nearly double the likelihood of being diagnosed with periodontitis than never-users. This association between cigarette smoking and periodontitis is well established.^{42,43} However, the use of khat (*Catha edulis*), which is reported to be responsible for periodontal diseases among a section of Arab populations living in the Southern border of the Arabian peninsula and Yemen,⁴⁴ did not demonstrate a significant relationship with the incidence of periodontitis in the current study. We suggest that there may have been a collinear effect of cigarette use and khat (*Catha edulis*) use. In support of our finding, the latest systematic review conducted by Al-Maweri et al in 2018 also reported that the available evidence suggesting the effect of khat on periodontal tissues is weak.⁴⁵

The strength of the current study lies in the use of gold-standard measures for the exposure (T2DM) and the outcome (periodontitis) variables. The cases and controls from the sample of Arab adults were further matched with important covariates such as, age, sex, and location. The current report was also unique in relation to some of the earlier studies as it specifically considered patients with uncontrolled T2DM, as recommended by experts.⁴⁶ The data collection process of this study focused towards temporality by confirming that the outcome among patients followed their exposure to risk factors. The study also prevented selection bias by recruiting all the eligible cases. Lastly, multivariable analysis with cluster effect of common risk factors was computed to obtain the findings after taking potential confounders into account.

However, the results should be interpreted carefully, as a case-control study is not the best approach to demonstrate

a cause and effect relationship. While we acknowledge that a prospective cohort study design would be preferable for the demonstration of causal association, this was not advisable in the present scenario due to the lack of a sufficiently large sample of uncontrolled T2DM patients. Also, in a prospective study, a concern of attrition bias could have arisen when the two groups (with and without uncontrolled T2DM) had taken physician consultations for their T2DM condition. Thereby, leading to a controlled state of blood sugar level. In addition, the findings of the current study may not be completely generalizable as the study was based on data gathered from a single hospital. However, the study was performed at the largest Dental Center in the region that caters free oral health care to the residents.

Despite the limitations, the current study gives directions to the future research and provides evidence of association from a population that has not been studied earlier. Thus, the findings from this study endorse routine periodontal assessment for patients with diabetes in Saudi Arabia, especially those with a history of uncontrolled blood sugar levels. Additionally, as patients with T2DM are often not aware of their medical condition, oral healthcare providers are also advised to refer patients with diagnosed generalized periodontitis and without self-reported diabetes to general practitioners. In future, more evidences of such relationship from the Saudi Arabian population is needed. Subsequently, the definitive relationship between oral and general health should be enhanced among the researchers and clinicians across Saudi Arabia by exploring and presenting the associations of oral health problems with other conditions such as the cardiovascular disease.⁵

Conclusion

To conclude, the current case-control study is the first from the Jazan region of Saudi Arabia to indicate that uncontrolled T2DM denoted by increased HbA1c level is associated with greater odds of periodontitis. An awareness of this association among the healthcare providers and patients in this region will contribute towards the overall prevention of periodontitis in Saudi Arabia.

Abbreviations

T2DM, type-2 diabetes mellitus; HbA1C, hemoglobin A1C; CAL, clinical attachment loss; CDC, Center for Disease control; CEBM, Center for Evidence-Based Medicine.

Data Sharing Statement

The dataset of the current study will be made available upon request.

Ethics Approval and Consent to Participate

This study was approved by the Research Unit (RU), College of Dentistry, Jazan University. Written and signed consent was obtained from each participant recruited in the study. The study abides by the Helsinki Declaration presented by the World Medical Association.

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Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

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Disclosure

The authors do not have any competing interests to report with regards to the current research.

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