

Estimation of Salivary Creatine Kinase Level and Periodontal Health Status among Type II **Diabetic and Nondiabetic Patients with Chronic** Periodontitis

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Abstract	

Objectives This study was conducted to determine the periodontal health status and the level of creatine kinase (CK) of the study and control groups and to correlate the level of this enzyme with clinical periodontal parameters in the study and control groups.

Materials and Methods This study included 80 male participants aged 35 to 55 years, divided into four groups: poorly controlled type 2 diabetes mellitus with chronic periodontitis (G1), well-controlled type 2 diabetes mellitus with chronic periodontitis (G2), chronic periodontitis without diabetes (G3), and periodontally healthy controls (G4). Clinical periodontal parameters (plaque index, gingival index, periodontal pocket depth [PPD], and clinical attachment loss) and salivary CK levels (measured using enzyme-linked immunosorbent assay) were compared between groups.

Keywords

- ► chronic periodontitis
- clinical periodontal parameters
- creatine kinase
- saliva
- ► type 2 diabetes mellitus

Results All clinical periodontal parameters and CK levels were highest in poorly controlled type 2 diabetes mellitus with chronic periodontitis patients, and the enzyme level revealed highly significant differences between all pairs of the study and control groups. There were nonsignificant weak correlations of CK with all clinical parameters in all groups except a significant moderate positive correlation with PPD in the nondiabetic with chronic periodontitis group.

Conclusion It was concluded that poor glycemic control negatively impacts periodontal health status. CK is considered a good biochemical marker of periodontal tissue destruction and is useful in the diagnosis, monitoring, and management of periodontal diseases.

Introduction

Chronic periodontitis (CP) is chronic inflammatory disease, initiated by the accumulation of a pathogenic dental plaque biofilm above and below the gingival.^{1,2} Key periodontal pathogens, such as Porphyromonas gingivalis, Tannerella

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forsythia, and Aggregatibacter actinomycetemcomitans, produce potent virulence factors that directly damage periodontal tissues and modulate the host immune response, leading to the breakdown of collagen, bone resorption, and the formation of periodontal pockets. It represents a consequence of local infections in the oral cavity resulting in

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irreversible destruction of the tooth-supporting apparatus such as alveolar bone, cementum, and the periodontal ligament. The clinical presentation of CP varies, with disease severity characterized by probing pocket depths (PDs), clinical attachment loss (CAL), and radiographic bone loss,³ often leading to tooth mobility and eventual tooth loss if left untreated. Genetic susceptibility, along with environmental factors such as smoking and systemic diseases, significantly influences the progression and severity of CP. The extent and severity of the disease are modified by host response, genetics, and lifestyle factors such as smoking, obesity, age, race, hormonal changes, and diabetes.^{4,5}

Diabetes mellitus (DM) is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin action, insulin secretion, or both.^{6,7} Diabetes is a condition primarily defined by the level of hyperglycemia giving rise to risk of micro-vascular damage, nephropathy, retinopathy, and neuropathy. It is associated with reduced life expectancy, significant morbidity due to specific diabetes-related microvascular complications, increased risk of macrovascular complications, stroke and peripheral vascular disease, and diminished quality of life.⁸ A close relationship between DM and PD has been well recognized in several clinical and epidemiological studies.⁹⁻¹¹ DM is believed to promote periodontitis through an exaggerated inflammatory response to the periodontal microflora.¹² It has been shown that poorly controlled DM has a greater incidence of severe PD compared with those patients who are well controlled or have no DM, which has been more prevalent in persons with type 2 DM (T2DM).¹³

Saliva, a complex biological fluid with diverse functions, is essential for maintaining oral health.^{14–16} It consists of water, electrolytes, proteins (including immunoglobulins, enzymes such as amylase and lysozyme, and growth factors), and various antimicrobial compounds.¹⁷ Saliva plays crucial roles in lubrication, buffering, and the clearance of microorganisms and food debris from the oral cavity. It also contributes to maintaining oral pH and provides a protective barrier against infections.¹⁸ Increasingly, saliva is being recognized as a rich source of biomarkers for detecting and monitoring various health conditions.^{16,45} Its noninvasive collection method and the presence of proteins, nucleic acids, and other molecules reflecting both local oral and systemic processes make it a promising diagnostic fluid.¹⁹

Creatine kinase (CK), also known as creatine phosphokinase or phosphocreatine kinase, is 82 kDa enzyme that is found mainly in tissue with high energy demands, especially brain, skeletal muscle, and myocardium. The CK isoenzyme MM-CK is predominantly found in skeletal muscle, and its presence in other bodily fluids, such as saliva and gingival crevicular fluid (GCF), typically indicates cellular damage and tissue injury.²⁰ The increased levels of CK were associated with muscle disruption, cell damage, and necrosis. It was also used to detect periodontal diseases and determine the success of periodontal treatment.²¹ Creatinine phosphokinase catalyzes the conversion of creatine and consumes adenosine triphosphate to create phosphocreatine and adenosine diphosphate. Creatine phosphokinase is stored in specific granules and secretory vesicles of the neutrophils and is mainly released during their migration to the site of infection. It is also present in bacteria within dental plaque. Intracellular enzyme (CK) is increasingly released from the damaged cells of periodontal tissues into the GCF. The enzymatic action changes reflect metabolic changes in the periodontium in inflammation.²² Because there is no information about CK levels in the saliva of type II diabetic patients with CP, and it is important in the assessment of periodontal tissue destruction, for these reasons, this study was conducted.

Materials and Methods

Study Design

A cross-sectional approach was employed. The subjects consisted of 80 males with an age range of 35 to 55 years and body mass index (BMI) between 18.50 and 24.99 kg/m². Sample collection occurred from November 2022 to February 2023. Ethical approval for this study, which involved human participants, was granted by the local ethical committee (reference number 4871) of Kufa University/Najaf - IRAQ. The study adhered to the principles of the Helsinki Declaration of 1975, as revised in 2013.²³ The subjects recruited for the study were patients attending the Specialized Center for Endocrinology and Diabetes in Najaf and patients from the Department of Periodontics at a teaching hospital, College of Dentistry, University of Kufa. All the individuals were informed about the purposes of the investigation and consented to its protocol. The subjects were divided into:

- Group 1 (G1): consists of 20 males with CP and T2DM, poorly controlled, and the glycated hemoglobin (HbA1c) was >9%.
- Group 2 (G2): consists of 20 males with CP and T2DM, well controlled, and HbA1c was <7%.
- Group 3 (G3): consists of 20 males with CP and without a history of any systemic diseases.
- Group 4 (G4): consists of 20 males without a history of any systemic diseases and with healthy periodontium; this was defined by gingival index (GI) scores <0.5²⁴ and without periodontal pockets or CAL. This group represents baseline data for the level of salivary CK.

Inclusion criteria include T2DM patients (\geq 5 years) on oral hypoglycemic medication, BMI ranges between 18.5 and 24.9 kg/m2,²⁵ all subjects presenting at least 20 teeth, and CP in patients defined as the presence of at least four sites with PPD \geq 4 mm and CAL of 1 to 2 mm or greater; this was made according to the international classification system for PD.²⁶

Exclusion criteria include T1 and T2 diabetic patients taking insulin therapy, presence of systemic diseases other than diabetes, presence of retinopathy, neuropathy, or diabetic foot, patients who have undergone periodontal treatment and a course of anti-inflammatory or antimicrobial therapy 3 months prior to the study, a history of smoking, and a history of alcohol abuse or dependence.

Sample Size Determination

The sample size was determined using a power analysis conducted with G*Power software (version 5.1). With an

alpha level of 0.05, a power of 0.80, and an expected moderate effect size (f = 0.25), the analysis indicated a minimum sample size of 16 participants per group. To account for potential dropouts and increase in statistical power, we recruited 20 participants per group, resulting in a total sample size of 80. A sample size of 20 per group might be sufficient to detect the difference with acceptable statistical power (typically set at 0.80 or higher).

Sample Preparation

An unstimulated saliva sample was taken from each patient. Following this, a complete examination of clinical periodontal parameters [plaque index (PLI), GI, periodontal PD [PPD], and CAL] was done. Saliva was centrifuged at 2,000 rpm. For 10 minutes, the resultant supernatant was aspirated, put into an Eppendorf tube, and kept frozen at –20°C until analyzed. The salivary CK level was determined by enzyme-linked immunosorbent assay (ELISA; Human CK-MB ELISA kit) in the Al-Mustafa Laboratory in Karbala.

Hypotheses: this study was conducted based on the premise that poorly controlled type II diabetes negatively influences periodontal health and elevates salivary CK levels. Specifically, we hypothesized that:

- · Patients with poorly controlled T2DM and CP will exhibit poorer periodontal health status (higher PLI, GI, probing PD, and CAL) compared to well-controlled T2DM patients and nondiabetic individuals with CP.
- Salivary CK levels will be significantly higher in patients with poorly controlled T2DM and CP compared to wellcontrolled T2DM patients, nondiabetic CP patients, and periodontally healthy controls.

Statistical Analysis

Statistical analysis was done using mean, standard deviation, ANOVA (analysis of variance) test, t-test, and Pearson correlation coefficient (r). The level of significance (S) was accepted at *p*-value \leq 0.05, highly significant (HS) at *p*-value \leq 0.01, and nonsignificant (NS) at p-value >0.05.

Results

Clinical Periodontal Parameter Analysis

The highest mean values of the clinical periodontal parameters were recorded in G1, followed by G2, then G3 and G4 in terms of PLI, GI, PPD, and CAL. Inter-study group comparisons regarding all clinical periodontal parameters revealed highly significant differences between G1 versus G2 and G3, as well as between G2 and G3 (►Table 1 and ►Fig. 1).

Biochemical Parameter Analysis

The biochemical analysis (**-Table 2** and **-Fig. 2**) of the salivary CK revealed that the highest concentration was in G1 (8.154 U/L), followed by G2 (5.229 U/L), then G3 (3.083 U/L) and finally the G4 (1.609 U/L). Furthermore, highly significant differences in the mean values of the salivary CK concentration were revealed among the study and control groups. The results of the comparisons for all pairs of the study and control groups in **-Table 2** and **-Fig. 2** about

Parameters	5	G2 (mean \pm SD)	G3 (mean \pm SD)	G1 vs. G2	<i>p</i> -Value	G1 vs. G3	<i>p</i> -Value	G2 vs. G3	<i>p</i> -Value
	(mean±SD)			(t-test)		(t-test)		(t-test)	
PLI	0.281 ± 2.767	0.229 ± 1.972	0.271 ± 1.497	10.426	0.000 HS	16.227	0.000 HS	5.931	0.000 HS
GI	0.331 ± 2.473	0.197 ± 1.938	0.361 ± 1.565	6.391	0.001 HS	8.054	0.000 HS	4.097	0.000 HS
PPD (mm)	$\textbf{0.717}\pm\textbf{6.966}$	0.454 ± 5.491	0.324 ± 4.949	8.098	0.002 HS	11.688	0.000 HS	3.549	0.000 HS
CAL (mm)	0.416 ± 2.914	0.241 ± 2.151	0.261 ± 1.809	6.446	0.001 HS	11.364	0.000 HS	4.019	0.000 HS
Abbreviation: CAL, cl	inical attachment loss; (GI, gingival index; HS, high	ly significant; PLI, plague ii	ndex; PPD, periodo	ntal pocket depth;	SD, standard devia	tion.		

groups

parameters and the intergroup comparisons between all pairs of the study

Mean values of the clinical periodontal

-

Table

Note: p < 0.05; significant difference



Fig. 1 Clinical periodontal parameters across study groups.

Table 2 Mean values of salivary creatine kinase (U/L) and the significance of difference among the study and control groups

Parameter	G1 (mean \pm SD)	G2 (mean ± SD)	G3 (mean ± SD)	G4 (mean \pm SD)	F-test	<i>p</i> -Value
Creatine kinase pg/mL	8.154 ± 2.049	5.229 ± 1.965	$\textbf{3.083} \pm \textbf{1.518}$	1.609 ± 0.943	5.791	0.001 HS

Abbreviation: HS, highly significant; SD, standard deviation. Note: p < 0.05; significant difference.



Fig. 2 Salivary creatine kinase (U/L) in difference among the study and control groups.

biochemical parameter levels revealed highly significant differences between the control group and all of the study groups, between G1 and G2, as well as between G2 and G3, and finally, between G1 and G3.

Correlations of Salivary Creatin Kinase with Clinical Periodontal Parameters

As seen in **►Table 3** and **►Fig. 3**, CK enzyme generally demonstrated nonsignificant weak correlations with all

Parameter	G1 (R)	p-Value	G2 (R)	p-Value	G3 (R)	p-Value	G4 (R)	p-Value
PLI	-0.109	0.647 NS	0.328	0.159 NS	-0.047	0.844 NS	-0.134	0.573 NS
GI	0.006	0.980 NS	0.294	0.208 NS	0.198	0.404 NS	-0.367	0.111 NS
PPD	0.249	0.289 NS	0.063	0.793 NS	0.463	0.040 S	Х	Х
CAL	0.037	0.876 NS	-0.232	0.325 NS	0.360	0.119 NS	Х	Х

Table 3 Correlations between the levels of salivary creatin kinase (IU/L) with the clinical parameters at each study and control groups

Abbreviation: CAL, clinical attachment loss; GI, gingival index; NS, not significant; PLI, plaque index; PPD, periodontal pocket depth; R, correlation coefficient; S, significant; X, not applicable.

Note: p > 0.05; no significant difference.

clinical parameters at all groups except a significant moderate positive correlation with probing PD in G3.

Discussion

The results demonstrate that patients with poorly controlled T2DM and CP exhibited significantly higher mean values for all periodontal parameters (PLI, GI, probing PD, and CAL) compared to the other groups. This aligns with previous research indicating a strong association between poorly controlled diabetes and increased periodontal disease severity.^{27,28} The hyperglycemic state in poorly controlled T2DM contributes to several detrimental effects on periodontal health. Decreased salivary volume and buffering capacity, coupled with alterations in the oral microbiota, lead to increased plaque accumulation.²⁹ Furthermore, the detrimental effects of advanced glycation end-products (AGEs) and their interaction with the receptor for AGEs within the periodontium impair wound healing, increase vascular permeability, and contribute to periodontal tissue destruction.³⁰ Diabetes also dysregulates inflammatory and immune responses, leading to an accumulation of pro-inflammatory cytokines in gingival tissues and further tissue breakdown.³¹ Impaired neutrophil function and hyperactivity of monocytes and macrophages contribute to the increased prevalence and severity of periodontal pockets observed in diabetic patients.³² Poor glycemic control, associated with elevated AGEs,³³ significantly increases susceptibil-



Fig. 3 Correlation between clinical parameters and salivary creatine kinase.

ity to infection and periodontal tissue damage, resulting in greater attachment loss—a characteristic finding in diabetic patients who are twice as likely to experience this compared to nondiabetic individuals.³⁴

This study also reveals significantly higher salivary CK levels in the poorly controlled T2DM with CP group compared to all other groups ($p \le 0.01$). CK, an intracellular enzyme, is released into the saliva and GCF during periodontal tissue destruction and inflammation. Its increased activity reflects metabolic changes and the degree of cellular damage within the periodontium.^{12,35} The release of CK is likely mediated by several mechanisms, including necrosis, apoptosis, and membrane disruption caused by the inflammatory cascade involving cytokines and reactive oxygen species.³⁶ CK in saliva is likely derived primarily from GCF, which is in direct contact with the inflamed periodontal tissues. The contribution of different cell types, such as neutrophils, fibroblasts, and epithelial cells, to CK release warrants further investigation.³⁷ While this study showed only a weak, nonsignificant correlation between salivary CK and periodontal parameters, except for a moderate positive correlation with probing PD in the nondiabetic CP group, the significant difference in CK levels between groups suggests that it may serve as a useful adjunct biomarker.³⁸ However, further research is needed to establish its sensitivity and specificity compared to other established periodontal biomarkers (e.g., interleukin [IL]-1β, IL-6, tumor necrosis factor- α , matrix metalloproteinases). The ease of salivary CK measurement via ELISA is an advantage, but factors such as sample collection and storage protocols need to be standardized to minimize variability.

The clinical implications of these findings are significant. Salivary CK could potentially serve as a valuable noninvasive marker for assessing periodontal tissue destruction, particularly in T2DM patients.³⁹ Future research should focus on longitudinal studies to monitor CK levels during disease progression and treatment response in larger, more diverse populations, including female participants. Investigating the combined use of salivary CK with other biomarkers might enhance diagnostic accuracy. Furthermore, research should examine the potential of CK levels to predict response to various therapeutic interventions. In summary, while further research is needed to fully elucidate the clinical utility of salivary CK, our findings provide preliminary evidence supporting its potential role as a marker for periodontal damage in individuals with T2DM.

Conclusion

The current outcomes may provide evidence of an association between CP and DM. Patients with CP and poorly controlled T2DM had significantly higher activity levels of the salivary CK enzyme than other groups. Subsequently, the CK enzyme can be utilized as a marker to determine the amount of destruction of periodontal tissues.

Limitations

This study's limitations include its single-center design and the exclusive inclusion of male participants. The latter was due to concerns about the confounding influence of hormonal fluctuations on salivary CK levels and periodontal parameters in females, limiting generalizability to women. Furthermore, although a power analysis was conducted, a larger sample size could have increased statistical power, potentially revealing more subtle relationships. BMI was collected but not analyzed in the study. Future multicenter studies with larger, more diverse participant groups are needed to validate these findings and explore gender-specific differences.

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Conflicts of Interest None declared.

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