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THE ASSOCIATION BETWEEN SALIVARY PROCALCITONIN AND PERIODONTITIS IN TYPE 2 DIABETIC PATIENTS

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Abstract

One of the most prevalent conditions that affects teeth, periodontitis causes the surrounding and supporting tooth structure to be destroyed. Procalcitonin may be a helpful marker to determine the severity of infection, forecast the prognosis, and track the effectiveness of treatment.

The study aims to assess the association between the salivary procalcitonin level and periodontal bacterial infections in diabetic individuals and contrasting it with non-diabetic people.

This is a case control study conducted at the department of periodontics during a period from February to May 2022. It included 70 subjects divided into four groups according to periodontitis and diabetes. Salivary sample was taken from each participant for the quantitative determination of salivary procalcitonin.

The mean of salivary procalcitonin was significantly higher in GP + T2DM group than that in other groups. It was significantly lower in controls than that in other groups and significantly lower in T2DM group than that in GP + T2DM group. There were significant positive correlations between salivary procalcitonin and all of bleeding on probing, probing pocket depth, and clinical attachment loss.

In conclusion, an elevated salivary procalcitonin level has been proposed as a possible biomarker for periodontal disorders because it plays a role in periodontal inflammation. Additionally, subclinical, low grade chronic inflammation in diabetes individuals may be mediated by salivary procalcitonin, a possible proinflammatory mediator.

Keywords: Periodontitis, procalcitonin, diabetes, salivary, inflammation, Iraq.

Introduction

The term "periodontitis" refers to a group of inflammatory illnesses that affect the teeth's supporting tissues (the gingiva, bone, and periodontal ligament), with potential consequences for tooth loss and systemic inflammation [1]. It affects about 20-50% of the population around the globe [2]. Periodontitis is one of the leading causes of tooth loss worldwide [3]. It is a multifactorial inflammatory condition characterized by dysbiotic plaque biofilms that gradually destroys the mechanism supporting the teeth [4]. Worldwide, 7.4% of people were estimated to have severe periodontitis in 2017. Additionally, it is the sixth most common disease worldwide [5]. Clinical criteria such bleeding on probing (BOP), clinical attachment loss (CAL), and probing pocket depth (PPD) are evaluated to identify cases of periodontitis and determine the severity of the illness in addition to radiographic evidence of bone degradation to support the diagnosis [6]. The host's immune response to the subgingival tooth-associated biofilm may result in a healthy periodontium and balanced subclinical host-microbe interactions (tissue homeostasis). This equilibrium protects a periodontium that is sound and symptom-free [7]. Multiple factors, including genetic, epigenetic, environmental (such as smoking, stress, and food), aging, and systemic illnesses, all appear to affect periodontitis resistance or susceptibility (such as diabetes (DM)), and may alter the host's response in a beneficial or harmful way [8]. Periodontitis has been accepted as the sixth complication of DM [9]. Type 2 DM and poorly controlled glucose level in the body have negative impact on periodontal health [10]. As DM is associated with periodontal ligament destruction which can lead to tooth loss as more periodontal tissue destruction in diabetic patients was observed due to augmented enzymatic activity thus increas-

ing severity of periodontitis [11]. Consequently, poorly controlled glycemic concentration level can be associated with the initiation and progression of gingivitis, periodontitis, and alveolar bone loss. Therefore, early detection of diabetic patients may enables for prevention of the progression and complications of this disease [12]. The prevalence of T2DM in Iraq reached epidemical proportions in 2007, impacting about two million people [13]. Periodontitis typically affects 34% to 68% of them [14]. Procalcitonin (PCT) is an emerging acute-phase reactant specifically elevated in bacterial infections [15]. It rises in reaction to bacterial endotoxins and inflammatory cytokines, which is a beneficial characteristic in a biomarker for identifying bacterial infections, gauging the severity of disease, gauging patient response, and avoiding antibiotic abuse [16]. In patients with periodontitis compared to those in good periodontal health, salivary PCT levels were greater, and a study completed in 2020 found a significant positive correlation between salivary PCT levels and periodontal parameters tested in the periodontitis group [17]. The aim of this study is to evaluate relationship of salivary PCT level in the body with periodontal bacterial infections in diabetic and compare it with non-diabetic patients.

Aim of study

To assess the association between the salivary procalcitonin level and periodontal bacterial infections in diabetic individuals and contrasting it with non-diabetic people.

Patients & Methods

Study design, setting, and time: This was a case-control study, which was conducted at the department of periodontics at AL-Shaheed Nawar Mousa Specialized Dental Center and General Dental Unit at Al-Kindy Hospital during a period from February to May 2022 in Baghdad/ Iraq. All procedures included in this study were in accordance with Helsinki declaration and its later amendments for human researches. The protocol was approved by the Ethics Committee, College of Dentistry, University of Baghdad (project No. 446622). Each patient was asked to sign an informed consent form after providing all information fully describing the nature and aims of the study. A questionnaire was used to record the background information, dental and medical history of the participants, then saliva was taken from each participant using passive drooling technique, followed by a full examination of clinical periodontal parameters (PI, BOP, PPD, and CAL). Then all participants were asked to do thyroid functions tests (T3, T4, TSH), and HbA1c test.

Study Population and sample size: The study included 70 subjects divided into four groups:

• *Control group:* Included 10 subjects systemically healthy with clinically healthy periodontium. This group represents a baseline data for the level of serum PCT.

• *Generalized Periodontitis group (GP group):* Included 20 patients diagnosed to have generalized periodontitis and didn't have any chronic systemic disease.

• *Type 2 DM (T2DM group):* Included 20 patients diagnosed to have type 2 DM and confirmed by HbA1c test (> 7%) on oral hypoglycemic medication (metformin 1000 mg/day) with clinically healthy periodontium.

• *Type 2 DM with generalized periodontitis (T2DM + GP group):* Included 20 patients diagnosed to have both generalized periodontitis and T2DM.

Healthy periodontium was considered as bleeding on probing less than 10%, probing pocket depth of ≤ 3 mm with intact periodontium (no probing attachment loss) [18].

A periodontitis case is defined by interdental CAL which is detectable at ≥ 2 non-adjacent teeth, or buccal or lingual/palatal CAL ≥ 3 mm with pocketing > 3 mm is detectable at ≥ 2 teeth [19]. All periodontitis cases are generalized periodontitis in which attachment loss includes more than 30% of site. Exclusion criteria included any patient had a history of other chronic, systemic disease with known association with periodontitis as rheumatoid arthritis, cardiovascular disease, etc., previous history of organ transplant or cancer therapy, immunocompromised patients, pregnant, on contraceptive pills and lactating women, smoking or alcohol drinking, patients with medication intake (antimicrobial therapy) within previous three months, renal or thyroid disease, patients who have undergone or currently under extensive periodontal treatment, , patients with corona virus infection, and patients refusing to participate.

The clinical periodontal parameters: Assessment of the periodontal status was performed for

all participants. Full mouth examination was performed using the periodontal probe of William's (marking at 1,2,3,5,7,8,9 and 10 mm). Full mouth plaque score by O'Leary is used to detect the presence or absence of plaque at four surfaces of each tooth (buccal, palatal/lingual, mesial & distal) by using a disclosing agent [20]. Full mouth bleeding on probing score recorded as present (1) or absent (0) at six sites per tooth [21]. Probing pocket depth and clinical attachment level were recorded, PPD was measured from the gingival margin to the base of the pocket while CAL is the distance measured from CEJ to the base of the pocket/sulcus at six sites per tooth [19]. Scores were given according to the criteria of the following indices:

• *Plaque index (PI):* Plaque Control Record (PCR) by O'Leary et al [20] was used to record the presence of supra-gingival plaque on all four tooth surfaces. For this test, the plaque is disclosed by disclosing agent (Guided Biofilm Therapy, biofilm discloser, Zwingenberg, Germany). The stain was smeared on all the teeth surfaces then the patient was asked to gargle with water to remove unbounded and excess staining material. The purple-stained surfaces were recorded score 1 and the unstained surfaces were recorded as 0 in a simple chart.

• *Bleeding on probing (BOP):* The periodontal probe was inserted with gentle force into the sulcus/pocket until minimal resistance was felt. The probing force presumably was ranging between 20 to 25g. The examination started from the distal surface of the right upper 7 moving mesially to measure all the existing teeth. For each tooth, six surfaces were examined; the surface that displayed bleeding on probing within 15-30 seconds was scored 1 and the surface with no bleeding was scored 0 [21].

• *Periodontal pocket depth (PPD):* The distance from the margin of the gingiva to the pocket's bottom was determined by gently inserting a periodontal probe into the pocket until resistance was felt at the pocket's base. The PPD measurement has been performed using the periodontal probe of William's, six sites were measured [19].

• *Clinical attachment loss (CAL):* By gently inserting a periodontal probe into the periodontal pocket until resistance is felt when the probe stops at the base of the pocket, it was possible to measure the clinical attachment level, which is the distance from the CEJ to the base of the pocket. If there is no gingival recession, CEJ can be felt with the probe. The sites of measurement were six sites [19].

Salivary sample collection Salivary samples were collected from the study subjects between 9:00 am to 1:00 pm. They were collected before oral examination was performed. Passive saliva drooling method was used for the collection of the whole saliva. Each subject was given a plastic cup and asked to let the saliva poured into the cup in a quite secluded environment without any stimulation or spitting for 5 minutes. A micropipette was used to aspirate saliva into a plastic tube, after collection, samples were centrifuged at 3000 rpm for 20 minutes to separate the cellular debris from the salivary supernatants. The salivary fluid, after being centrifuged and separated from the cellular debris, a measured volume of 500µl was aspirated again using a micropipette and stored into a clean Eppendorf tube then frozen at -20ºC until analyzed by ELISA.

Then all participants were asked to do thyroid functions tests (T3, T4, TSH), in order to exclude any thyroid disorder, and HbA1c test, to confirm that HbA1c being > 7% to be included in the study.

Immunological assays

Laboratory procedure: After the completion of the sampling procedure, the samples were thawed and left for a few minutes to reach room temperature. Commercially available ELISA kits, all purchased from (MyBioSource) ELISA kit California, USA, were used for determining PCT levels in salivary samples. The analysis was done following the manufacturer's instructions. The ELISA procedure for this study was the sandwich ELISA technique, the wells come with the kit was coated with the tested PCT antibody, when the protein captured by antigen a solution also contains antibody applied to the wells to form the captured complex. After the captured complex is formed, 50µl of chromogen solution A is added to every well, and 50µl of chromogen solution B is then added to every well. With a complete protection from light. After 15 minutes, the wells were checked for color change. The color was changed to light blue with different saturation degrees, after 15-20 minutes 50 µL of stop solution (H_2SO_4) was added to each well, the color of the liquid in the wells directly changed to yellow. The tray then was placed in the plate reader device within 15 minutes after adding the stop solution. The concentrations of the PCT were

measured by passing a light beam and measuring the absorbance of the light passing through the solution, the measurements were performed at 450 nm which is the wave length of the yellow color.

Statistical analysis: The data analyzed using Statistical Package for Social Sciences (SPSS) version 26. The data presented as mean, standard deviation and ranges. Categorical data presented by frequencies and percentages. Analysis of Variance (ANOVA) (two tailed) was used to compare the continuous variables between study groups. Chi square test was used to assess the association between categorical variables, while fisher exact test was used instead when the expected frequency was less than 5. Pearson's correlation test (r) was used to assess correlation between continuous variables accordingly. A level of P – value less than 0.05 was considered significant.

Results

In this study, no statistically significant differences ($P \geq 0.05$) in means of age and BMI, and in gender between study groups. Mean of salivary PCT was significantly higher in GP + T2DM group than that in other groups (334.83 pg/µl, P= 0.001) as shown in Table (1).

Table (1): Comparison in certain characteristics between study groups

Variable	Study group				
	Control	GP	T2DM	GP + T2DM	P – Value
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	
Age (Year)	43.7 ± 8.7	51.0 ± 7.6	46.7 ± 9.4	51.35 ± 8.9	0.063
BMI (Kg/m2)	24.35 ± 2.9	26.18 ± 2.7	27.16 ± 2.7	26.34 ± 4.6	0.21
Salivary PCT (pg/µL)	150.99 ± 10.3	268.83 ± 99.6	242.53 ± 20.9	334.83 ± 45.5	0.001
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
Male	4 (40.0)	15 (75.0)	8 (40.0)	13 (65.0)	0.082
Female	6 (60.0)	5 (25.0)	12 (60.0)	7 (35.0)	

Post hoc tests (LSD) were run to confirm the differences occurred in mean of salivary PCT between study group and showed that mean of salivary PCT was significantly lower in controls than that in other groups. Mean of salivary PCT was significantly lower in T2DM group than that in GP + T2DM group; while no significant differences between GP + T2DM group and GP groups in salivary PCT as shown in Table (2).

Table (2): Post hoc tests (LSD) to confirm the differences in mean of salivary PCT between study group

	Study group				
	Control	GP	T2DM	GP + T2DM	P – Value
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	
Mean of salivary PCT (pg/µL)	150.99 ± 10.3	268.83 ± 99.6	-	-	0.022
	150.99 ± 10.3	-	242.53 ± 20.9	-	0.001
	150.99 ± 10.3	-	-	334.83 ± 45.5	0.001
	-	268.83 ± 99.6	242.53 ± 20.9	-	0.641
	-	268.83 ± 99.6	-	334.83 ± 45.5	0.055
	-	-	242.53 ± 20.9	334.83 ± 45.5	0.001

As shown in Table (3), significant strong positive correlation detected between salivary PCT and PPD (r= 0.752, P= 0.001); while weak positive correlations detected between salivary PCT and both of BOP (r= 0.523, P= 0.027) and CAL (r= 0.442, P= 0.045). No statistically significant correlations between salivary PCT and both of PI and HbA1c.

Table (3): Correlations between salivary PCT and certain parameters

Variable	Salivary PCT (pg/µL)	
	R	P - Value
Plaque Index (%)	0.332	0.312
Bleeding on probing (%)	0.523	0.027
Periodontal pocket depth	0.752	0.001
Clinical attachment loss	0.442	0.045
HbA1c (%)	0.381	0.278

Discussion

Since endotoxin is a strong stimulator for PCT formation and can encourage the systemic release of calcitonin precursors from almost all tissues of the body, we hypothesized that periodontitis in diabetes may act as a stimulation for PCT production.

According to the current research, the T2DM+GP group had the highest mean salivary PCT values, followed by the GP group, then T2DM group, and lastly the control group. The significant increase in the mean value of salivary PCT in periodontitis groups was in agreement with a number of studies conducted by Hendek MK et al, 2015 [22], and Mohan R et al, 2021 ([17]) when they noticed significantly increased mean value of salivary PCT in periodontitis groups when compared with periodontally healthy individuals, while disagreed with Bassim CW et al, 2008 [23] and Yousefimanesh H et al 2015 [24] studies. This may be explained that PCT is a notable biomarker of the acute phase proteins [25] that are produced by the liver in response to pro-inflammatory cytokines, that originate at the periodontal sites due to the activation of the signal transduction pathway of both innate and adaptive immunity by the interaction of gram-negative bacteria endotoxin's with Toll like receptors present on the surface of polymorphonuclear leukocytes and monocytes [26].

In addition, in this study there was a significant increased mean value of salivary PCT in T2DM group when compared with control group, and this disagreed with study conducted by Bassim CW et al, 2008 who found no significant difference in salivary PCT between diabetic group and healthy control group [23]. This disagreement may be attributed to duration of the diseases, differences in sample size, and the differences in age and sex of the studied groups. A number of mechanisms are thought to be responsible for the inflammatory state in T2DM, including hypoxia and cell death of expanding adipose tissue, activation of the JUN N-terminal kinase pathway, activation of interleukin-1, and recruitment and activation of immune cells. These mechanisms may all contribute to the significant increase in salivary PCT in T2DM patients [27], which leads to an increase in mediators of systemic inflammation, and PCT has been proven to be a potential mediator of inflammations and this explains its increased concentration in body fluids like saliva. In addition to the fact that the action of (CRGP) and PCT on insulin secretion has been shown to inhibit insulin secretion by signaling through (CRLR) consequently, PCT may play a role in the pathogenesis of T2DM [28]. Although the significant increase of salivary PCT mean values in diabetic groups when compared with controls in the current study, but there were significant results when comparing T2DM and T2DM + GP groups, with no significant result when comparing GP group with T2DM + GP groups; which indicates that generalized periodontitis has more influence on PCT in saliva than diabetes does.

This study showed a positive correlation of salivary PCT with periodontal parameters in agreement with that found by Yousefimanesh H et al,

2015 [24], Hendek MK et al, 2015 [22], Mohan R et al, 2021 [17], and Bassim CW et al 2008 [23] studies. These results may be explained by PCT role as a pro-inflammatory and a cytokine-like mediator [29]. Its expression has been regulated by proinflammatory cytokines such as TNF-α, IL-6 [30]. Therefore, positive correlations between clinical parameters and PCT levels could be attributed to the release of cytokines at tissue-injury sites [22]. Additionally, a rise in the severity of periodontitis is associated with a rise in the number of pathogenic bacteria and bacterial load, which results in a complex microbiota that causes PCT expression in peripheral mononuclear cells. because, as was already mentioned, bacterial lipopolysaccharide and endotoxins are two of the primary factors that stimulate PCT secretion [31]. This indicates that when destruction process progressed, PCT level was increased. In conclusion, salivary PCT plays a role during periodontal inflammation and elevated salivary PCT level is suggested as a potential biomarker for periodontal diseases. In addition, salivary PCT may act as a potential proinflammatory mediator in subclinical - low grade- chronic inflammation of diabetic patients. The use of salivary PCT as a local as well as a systemic biomarker for inflammation and infection may prove useful for future research in this field.

Authership & conflect of interest

This is to verify authership of this article and there is no conflect of interest in any way.

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