

The Association between Serum Procalcitonin and Periodontitis in Type 2 Diabetic Patients on metformin in Baghdad / Iraq

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Abstract

Among the most common conditions that affects teeth, periodontitis leads to destruction of the supporting apparatus of tooth structure. Procalcitonin (PCT) may be a helpful marker to determine the severity of infection, forecast the prognosis, and track the effectiveness of treatment. Aim of the study was to assess the association between the serum PCT level and periodontal infections in diabetic type 2 individuals on metformin treatment of 1000 mg dosage per day and contrasting it with non-diabetic people.

The current study 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 (10 control and 60 patients) with matched age and gender, Control group: Included 10 subjects systemically healthy with clinically healthy periodontium. Generalized Periodontitis group (GP) group: Included 20 patients diagnosed to have generalized periodontitis without chronic systemic disease. Type 2 DM (T2DM) group: Included 20 patients diagnosed to have type 2 DM 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 confirmed by HbA1c test (> 7%) on oral hypoglycemic medication (metformin 1000 mg/day).

Assessment of clinical periodontal parameters (BOP, PLI, PPD, CAL) was done, and five ml of venous blood was taken from each participant for the quantitative determination of serum PCT by ELISA technique.

In this study serum PCT was significantly lower in controls than that in other groups and significantly lower in GP group than that in T2DM+ GP group. There was a significant strong positive correlation between serum PCT and HbA1c % in T2DM+GP group, and a positive significant correlation between serum PCT and BOP % in T2DM+GP group.

In conclusion, an elevated blood PCT 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 diabetic individuals may be mediated by serum PCT, a possible proinflammatory mediator.

Keywords: Diabetes, inflammation, Iraq, periodontitis, Procalcitonin.

العلاقة بين بروكالسيتونين المصل والتهاب اللثة في مرضى السكري من النوع ٢ على علاج الميتفورمين زهراء مؤيد حميد^١ و الاء عمران علي^{*٢}

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الخلاصة

من بين الحالات الأكثر شيوعاً التي تؤثر على الأسنان، يؤدي التهاب اللثة إلى تدمير الجهاز الداعم لبنية الأسنان، قد يكون البروكالسيتونين علامة مفيدة لتحديد شدة العدوى، والتنبؤ بالتشخيص، وتتبع فعالية العلاج. كان الهدف من الدراسة هو تقييم العلاقة بين مستوى البروكالسيتونين في مصل الدم والالتهابات اللثوية لدى الأفراد المصابين بالسكري من النوع الثاني على علاج الميتفورمين بجرعة ١٠٠٠ ملغ يومياً ومقارنتها مع الأشخاص غير المصابين بالسكري.

هذه دراسة حالة رقابية أجريت في قسم اللثة خلال الفترة من شباط إلى ايار ٢٠٢٢. شملت الدراسة ٧٠ شخصاً من نوع حالة مراقبه (١٠ اصحاء و ٦٠ مريض) متطابقة في الجنس والعمر. تم تقسيم المشاركين إلى أربع مجموعات وفقاً لالتهاب دواعم الأسنان والسكري: وهي المجموعة الأولى وتشمل ١٠ اصحاء المجموعة الثانية وهي مجموعة التهاب دواعم الأسنان المعمم وتشمل ٢٠ مريض بأمراض التهاب دواعم الأسنان المعمم بدون امراض جهازية مزمنة. المجموعة الثالثة وهي مجموعة السكر من النوع الثاني وتشمل ٢٠ مريض بالسكر من النوع الثاني حيث نسبة السكر التراكمي أكثر من ٧٪. ويستخدمون عقار الميتفورمين بجرعة ١٠٠٠ ملغم لكل يوم وهذه المجموعة ذات لثة صحية سريريا. المجموعة الرابعة وهي مجموعة السكر من النوع الثاني مع التهاب دواعم الأسنان وتشمل ٢٠ مريض بالتهاب دواعم الأسنان المعمم وبالسكر من النوع الثاني حيث نسبة السكر التراكمي أكثر من ٧٪. ويستخدمون عقار الميتفورمين بجرعة ١٠٠٠ ملغم لكل يوم. تم تسجيل معايير اللثة السريرية وتشمل: مؤشر البلاك، النزف عند التسبير، فحص عمق الجيب اللثوي ومقدار انحسار اللثة ثم تم أخذ خمسة مل من الدم الوريدي من كل مشارك للتحديد الكمي لمستوى البروكالسيتونين في المصل وذلك بطريقة مقايسة الممتز المناعي المرتبط بالانزيم. في هذه الدراسة كان مستوى البروكالسيتونين في المصل في مجموعة (الاصحاء) اقل احصائياً بكثير من المجموعات الأخرى مع وجود دلالة احصائية. وكان اقل احصائياً بكثير في مجموعة (التهاب دواعم الأسنان المعمم) من ذلك في مجموعة (السكر من النوع الثاني مع التهاب دواعم الأسنان) مع وجود دلالة احصائية. وكان هناك ارتباط إيجابي قوي كبير ذو دلالة احصائية بين مستوى البروكالسيتونين في المصل ومستوى السكر التراكمي في مجموعة (السكر من النوع الثاني مع التهاب دواعم الأسنان المعمم).

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وعلاقة إيجابية ذات دلالة إحصائية مع النزف عند التسبير في مجموعة (السكر من النوع الثاني مع التهاب دواعم الأسنان المعمم). في الختام، تم اقتراح ارتفاع مستوى البروكالسيتونين في المصل كعلامة حيوية محتملة لاضطرابات اللثة لأنه يلعب دوراً في التهاب اللثة. بالإضافة إلى ذلك، قد يكون له دور في التوسط في الالتهاب المزمن تحت السريري منخفض الدرجة لدى الأفراد المصابين بالسكري وهو وسيط محتمل سابق للالتهاب.

الكلمات المفتاحية: السكري، التهاب، العراق، التهاب اللثة، بروكالسيتونين.

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 has been one of the important causes of tooth loss worldwide ⁽³⁾. It is a multifactorial inflammatory illness associated with dysbiotic plaque biofilms that causes gradual loss of the tooth-supporting system ⁽⁴⁾. According to estimates, severe periodontitis affected 7.4% of the world's population in 2017. It is also the sixth most prevalent dental disease in the world ⁽⁵⁾. In addition to radiographic evidence of bone degeneration to support the diagnosis, clinical criteria such as bleeding on probing (BOP), clinical attachment loss (CAL), and probing pocket depth (PPD) are assessed to identify cases of periodontitis and gauge the severity of the disease ⁽⁶⁾. A healthy periodontium and balanced subclinical host-microbe interactions may result from the host's immunological response to the subgingival tooth-associated biofilm (tissue homeostasis). A healthy, symptom-free periodontium is preserved by this equilibrium ⁽⁷⁾. Multiple factors, including genetic, epigenetic, in addition to environmental factors (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⁾. Poorly controlled glucose level in the body and T2DM have negative impact on periodontal health ⁽¹⁰⁾. Diabetes mellitus is associated with periodontal ligament destruction which can lead to tooth loss as more periodontal tissue destruction in diabetic patients was found, due to augmented enzymatic activity thus increasing severity of periodontitis ⁽¹¹⁾. Poorly controlled glycemic concentration level can be associated with the initiation and progression of gingivitis, periodontitis, and alveolar bone loss. Early detection of diabetic patients enables for prevention of the progression and complications of this disease ⁽¹²⁾.

Patients with poorly controlled diabetes frequently have deep pockets and attachment loss, and periodontitis affects 34% to 68% of them on average ⁽¹³⁾. Procalcitonin (PCT) is an emerging acute-phase reactant specifically elevated in bacterial infections ⁽¹⁴⁾. It increases in response to bacterial endotoxins and inflammatory cytokines, which is a positive trait in a biomarker for bacterial infection identification, disease severity assessment, patient response assessment, and antibiotic overuse avoidance ⁽¹⁵⁾. In patients with periodontitis compared to those in good periodontal health, serum PCT levels were greater, and a study completed in 2020 found a significant positive correlation between serum PCT levels and periodontal parameters tested in the periodontitis group ⁽¹⁶⁾. The aim of this study is to evaluate relationship of serum PCT level with periodontal bacterial infections in diabetic patients on metformin treatment and compare it with non-diabetic patients.

Materials and 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 ⁽¹⁷⁾. 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 a full examination of clinical periodontal parameters (PI, BOP, PPD, and CAL) and 5 ml of venous blood was harvested from each subject. Then all participants were asked to do thyroid functions tests (T3, T4, TSH), and HbA1c test.

Subjects 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 confirmed by HbA1c test (> 7%) on oral hypoglycemic medication (metformin 1000 mg/day) with clinically healthy periodontium (without periodontitis).
- **Type 2 DM with generalized periodontitis (T2DM + GP group):** Included 20 patients diagnosed to have both generalized periodontitis and T2DM confirmed by HbA1c test (> 7%) on oral hypoglycemic medication (metformin 1000 mg/day).

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

Table 1. Materials

Material	Company and origin
William's periodontal probe	Medesy, Italia
disclosing agent (Guided Biofilm Therapy, biofilm discloser)	Zwingerberg, Germany
Centrifuge	Hettich EBA 200, Germany
ELISA reader device	Human Reader HS, Germany
ELISA kit for PCT	MyBioSource, San Diego, California, USA
Microplate ELISA washer device	Tecan-Switzerland

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 presence or absence of plaque at four surfaces of each tooth (buccal, palatal/lingual, mesial & distal) by using a disclosing agent ⁽²¹⁾. Full mouth bleeding on probing score recorded as present (1) or absent (0) at six sites per tooth ⁽²²⁾. 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) was used to record the presence of supra-gingival plaque on all four tooth surfaces ⁽²¹⁾. For this test, the plaque is disclosed by disclosing agent (Guided Biofilm Therapy, biofilm discloser, Zwingerberg, 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

which attachment loss includes more than 30% of site ⁽²⁰⁾. While Type 2 diabetic patients was confirmed by HbA1c test (> 7%) on oral hypoglycemic medication (metformin 1000 mg/day). Metformin used was from Merck Serono a multinational company based in Darmstadt, Germany, patients used one tablet a day of 1000 mg extended-release metformin.

Exclusion criteria: Any participant with any of the following, was excluded from the study:

Any patient had a history of other chronic, systemic disease with known association with periodontitis as rheumatoid arthritis, cardiovascular disease, 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 (anti-inflammatory or 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.

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 ⁽²²⁾.

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⁾.

Body Mass Index measurement (BMI)

Body Mass Index (BMI) was measured by dividing person's weight in kilograms by the square of height in meters by the equation $\text{weight (kg)} / [\text{height (m)}]^2$ ⁽²³⁾.

Serum sample collection

Five ml of venous blood was taken from each participant from the cubital fossa using 5ml plastic disposable syringe, transferred into jell separating tubes, centrifuged using (Hettich EBA 200 centrifuge) for 20 minutes at (3000 RPM) and then sera were separated, then the tubes were labeled and stored at (-20°C) for later analysis by ELISA for the quantitative determination of serum PCT using ELISA reader device (Human Reader HS)⁽²⁴⁾.

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. HbA1c test was done using a high-performance liquid chromatographic (HPLC) method, which relies on pumps to pass a pressurized liquid and a sample mixture through a column filled with adsorbent, leading to the separation of the sample components, due to their different degrees of interaction with the adsorbent particles⁽²⁵⁾, a GH-900Plus HbA1c analyzer was used.

Estimation of serum procalcitonin (PCT)

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 for PCT, all purchased from (MyBioSource) ELISA kit, from MyBioSource company in San Diego, California, USA, were used for determining PCT levels in serum 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 PCT antibody, when PCT 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 (H₂SO₄) 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. Post hoc tests (least significant difference (LSD)) was used to confirm the differences in mean of PCT between study group. A level of P value <0.05 was considered significant.

Results and Discussion

In this study, there are no statistically significant differences ($P \geq 0.05$) in means of age and BMI, and in gender between study groups and no significant difference between T2DM and GP + T2DM groups in HbA1C level and duration of diabetes. Mean of PCT was significantly higher in T2DM+ GP group than that in other groups (335.1 pg/µl, $P= 0.001$) as shown in (Table 4). Post hoc tests (LSD) were run to confirm the differences occurred in mean of PCT between study groups and showed that mean of PCT was significantly lower in controls than that in other groups. Mean of PCT was significantly lower in GP group than that in T2DM+ GP group; while no significant differences between T2DM and GP + T2DM groups in PCT level as shown in (Table 4).

As shown in (Table 5), significant strong positive correlation detected between PCT and HbA1c% in (T2DM+GP) group ($r= 0.844$, $P= 0.000$). And a positive significant correlation between serum PCT and BOP% in (T2DM+GP) group ($r=0.675$, $P=0.034$), with no statistically significant correlations between PCT and other periodontal parameters.

Table 2. Comparison in certain characteristics between studied groups

Variable	Study group				P – Value
	Control Mean ± SD	GP Mean ± SD	T2DM Mean ± SD	GP + T2DM Mean ± SD	
Age (Year)	43.7 ± 8.7	51.0 ± 7.6	46.7 ± 9.4	51.35 ± 8.9	0.063 *
BMI (Kg/m ²)	24.35 ± 2.9	26.18 ± 2.7	27.16 ± 2.7	26.34 ± 4.6	0.21 *
HbA1C (%)	-	-	8.45 ± 0.85	8.69 ± 1.0	0.429 **
Duration of DM (Year)	-	-	7.61 ± 1.6	8.12 ± 1.2	0.236 **
Gender	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)	

BMI: body mass index, SD: Standard Deviation * Analysis of Variance (ANOVA) (two tailed) . ** Student t test .Non-significant P-value was found for all characteristics

Table 3. Comparison in gender distribution between studied groups

	no. (%)	no. (%)	no. (%)	no. (%)	
Gender	Control	GP	T2DM	GP + T2DM	P - Value
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)	

*** Chi square test .Non-significant P-value

Table 4. Post hoc tests (LSD) to confirm the differences in mean of PCT between studied groups

PCT (pg/μL)	Study group				P – Value
	Control Mean ± SD	GP Mean ± SD	T2DM Mean ± SD	GP + T2DM Mean ± SD	
194.04 ± 45.0	266.92 ± 45.4	-	-	0.002 #	
194.04 ± 45.0	-	324.04 ± 23.3	-	0.001 #	
194.04 ± 45.0	-	-	335.1 ± 98.7	0.001 #	
-	266.92 ± 45.4	324.04 ± 23.3	-	0.048 #	
-	266.92 ± 45.4	-	335.1 ± 98.7	0.042 #	
-	-	324.04 ± 23.3	335.1 ± 98.7	0.961	

P-value is significant .Post hoc tests (LSD) were run to confirm the differences occurred in mean of PCT between study groups

Table 5. Correlations between PCT and certain parameters measured in each group

Groups		PCT (pg/μL)	
		R	P – Value *
Control	PLI%	0.335	0.344
	BOP%	0.058	0.874
GP	PLI%	0.310	0.398
	BOP%	0.300	0.401
	PPD	0.336	0.342
	CAL	0.280	0.410
T2DM	PLI%	0.210	0.501
	BOP%	0.249	0.290
	HbA1c%	0.447	0.082
T2DM+GP	PLI%	0.420	0.065
	BOP%	0.175	0.034 #
	PPD	0.410	0.072
	CAL	0.400	0.075
	HbA1c %	0.844	0.000 ##

#: percentage * Pearson's correlation test (r) # P- value is Significant ## P- value is very significant

Discussion

In this study, periodontitis was hypothesized to act in diabetes as a stimulator for PCT production, since endotoxin is a strong stimulator for PCT synthesis and secretion and can increase the systemic release of calcitonin precursors from almost all types of tissues of the body. According to the current research, the T2DM+GP group had the highest mean serum PCT values, followed by the T2DM group, the GP group, and lastly the control group.

This is agreed with a result found by Wang *et al* study, in which patients with T2DM exhibited increment from baseline serum PCT level ⁽²⁶⁾. This may be explained by the continuous low-grade inflammation, hyperglycemia, and microvascular damage that T2DM patients experience. These pathophysiological traits of T2DM patients may have an impact on a number of immunological processes ⁽²⁷⁾. Therefore, following macrophage-mediated stimulation, that tissue cells, including adipocytes, will secrete PCT ⁽²⁸⁾. Obesity and the increased adipose tissue mass is associated with the development of T2DM ⁽²⁹⁾. Procalcitonin (PCT) secretion is increased because adipose tissues harbor increased numbers of activated macrophages ⁽³⁰⁾. Another agreement noticed with studies conducted by Mohan *et al*, 2021 ⁽¹⁶⁾, and Leira *et al*, ⁽³¹⁾ where patients with periodontitis have significantly higher serum PCT than those with good periodontal health. The increase in serum PCT in periodontitis may be related to the infectious nature of the condition, which causes inflammation in the tissues supporting the teeth and may also trigger a systemic inflammatory response ⁽³²⁾, which leads to production of acute phase proteins systemically, and PCT is one of them. Additionally, serum PCT levels in healthy individuals are undetectable, but they can be found after two hours following bacterial infection, rising rapidly within six hours until reaching its peak level at around 24 hours ⁽³³⁾, because bacterial lipopolysaccharide is found to be a potent inducer of PCT in systemic circulation which is not associated with an increase in calcitonin, that is why PCT has been compared to several markers of sepsis and proven to be more specific and having higher predictive values ⁽³⁴⁾. Although serum PCT mean values increased in the periodontitis groups in the current study when compared to controls, there were significant results when comparing the GP and T2DM+GP groups, but there was no significant difference when comparing the T2DM group with the T2DM+GP groups. Which suggests that periodontitis has less impact on PCT in serum than T2DM does. Serum PCT and HbA1C% showed a robust, statistically significant positive connection in this investigation in (T2DM+GP) group.

These findings may be explained by the biological activity of PCT on calcitonin receptor family

complexes, which affects vascular tone, insulin sensitivity, and insulin secretion by the pancreatic beta cells. This relationship between PCT secretion and insulin resistance in T2DM may be the underlying cause of these findings ⁽²⁸⁾. In addition, increased HbA1c percentage indicates increased adipose tissue which means more activated macrophage therefore more PCT secretion ⁽³⁰⁾. In addition, serum PCT had a positive significant correlation with BOP% in T2DM+GP group, this may be explained by direct and indirect modulation of PCT synthesis, directly by bacterial endotoxins or other toxic metabolite from microbes such as DNA, fimbriae or peptidoglycans and bacterial lipopolysaccharide, as an increase in periodontal parameters severity indicates more pathogenic bacteria and a rise in bacterial load leading to highly complex microbiota producing endotoxins causing the expression of PCT in serum by the peripheral mononuclear cells ⁽³⁵⁾, while for the indirect pathway PCT is a pro-inflammatory and a cytokine-like mediator ⁽³⁶⁾ its expression has been regulated by proinflammatory cytokines such as TNF- α , IL-6 ⁽³⁷⁾. Therefore positive correlation between BOP and PCT levels in serum could be attributed to the recruitment of host inflammatory cells leading to the release of cytokines at tissue-injury sites ⁽³⁸⁾.

Metformin had an important role in reducing HbA1c % by suppression of hepatic glucose production, mainly as a result of reduction in gluconeogenesis ⁽³⁹⁾, and increasing glucose uptake in muscle ⁽⁴⁰⁾. In addition to metformin anti-inflammatory action, by inhibition of advanced glycation endproducts (AGEs) formation ⁽⁴¹⁾, this anti-inflammatory action of metformin may have had a role in reducing the level of serum PCT in T2DM patients.

Conclusion

Serum PCT plays an important role during periodontal inflammation and elevated serum PCT level is suggested as a potential biomarker for periodontal diseases. In addition, serum PCT may act as a potential proinflammatory mediator in subclinical - low grade- chronic inflammation of diabetic patients. The use of serum PCT as a local as well as a systemic biomarker for inflammation and infection may prove useful for future research in this field.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Ethics Statements

All procedures included in this study were in accordance with Helsinki declaration and its later amendments for human researches. The protocol of this study 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 describing the nature and aims of the study.

Author Contribution

study conception and design: Assist. Prof. Alaa Omran Ali. Data collection, analysis, interpretation of results and draft manuscript preparation: Zahraa Moayed Hameed. Both authors reviewed the results and approved the final version of the manuscript.

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