

Evaluation of the Salivary Levels of Interleukin-17 and Galectin-3 in Patients with Periodontitis and Type 2 Diabetes Mellitus

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Abstract

Background: Periodontitis and type 2 diabetes mellitus are both considered as a chronic disease that affect many people and have an interrelationship in their pathogenesis. **Objective:** The aim is to evaluate the salivary levels of interleukin-17 (IL-17) and galectin-3 in patients with periodontitis and type-2 diabetes mellitus. **Materials and Methods:** The samples were gathered from 13 healthy (control group) and 75 patients split into 3 groups, 25 patients with type 2 diabetes mellitus and healthy periodontium (T2DM group), 25 patients with generalized periodontitis (P group), and 25 patients with generalized periodontitis and type 2 diabetes mellitus (P-T2DM group). Clinical periodontal parameters were documented. The concentration of IL-17 and galectin-3 in salivary samples was estimated using enzyme-linked immunosorbent assay. **Result:** The concentration of IL-17 in the T2DM group (388.612 ± 120.111 pg/mL), the P group (443.887 ± 69.188 pg/mL), and the P-T2DM group (532.769 ± 137.673 pg/mL) showed higher values than the control group (292.079 ± 62.356 pg/mL) with a significant difference at ($P < 0.05$). Also, the P-T2DM group showed higher values than the P group and the T2DM group with a significant difference ($P < 0.05$). The concentration of galectin-3 in the T2DM group (2.409 ± 0.147 ng/mL), the P group (2.699 ± 0.386 ng/mL), and the P-T2DM group (2.568 ± 0.285 ng/mL) showed higher values than the control group (1.888 ± 0.356 ng/mL) with a significant difference ($P < 0.05$). The P group showed a higher value than the T2DM group with a significant difference ($P < 0.05$). **Conclusion:** Salivary IL-17 and galectin-3 levels might be used as a biomarker for periodontitis.

Keywords: Periodontitis, galectin-3, interleukin-17, type 2 diabetes mellitus

INTRODUCTION

Periodontitis is a chronic inflammatory condition that causes inflammation of the tissues surrounding the teeth that eventually ends with loss of the tissue-supporting structure.^[1] Diabetes mellitus type II (T2DM) is a global disease characterized by insulin secretion defects and/or a decrease in insulin sensitivity.^[2] Individuals' poor glycemic controls are more susceptible to a variety of short- and long-term problems.^[3,4]

Interleukin-17 (IL-17) is a cytokine that is produced by T helper 17 (Th17) cells and serves a variety of roles. IL-17 family is categorized as a unique family because the receptor of IL-17 lacks a homologous structure to another type of protein.^[5] Although Th17 cells are the most likely to produce IL-17, they can also produce by

neutrophils, macrophages, dendritic cells, natural killer cells, gamma delta T cells, and mast cells.^[6] Furthermore, Th17 cells also produce other cytokines like tumor necrosis factor alpha, IFN- γ , IL21, and IL22.^[7]

IL-17 has been linked to the pathogenesis of periodontitis in a variety of ways. IL-17 may stimulate the expression of receptor activator of nuclear factor kappa-B ligand (RANKL) that promotes osteoclastogenesis.^[8] Inducing

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inflammatory responses by activating other mediators released by macrophages, epithelial, dendritic, and fibroblastic cells.^[9] The activation of certain matrix metalloproteinases can contribute to periodontal tissue damage.^[10] Also, studies suggested that IL-17 may have a significant effect on the pathogenesis of T2DM.^[11]

Galectin-3 (Gal-3) is a glycoprotein that belongs to the lectin family, and it considers a single member of the chimera type of galectin made up of three structurally different domains 1) short N-terminal domains, 2) collagen- α -like domain, and 3) the carbohydrate recognition domain.^[12] Gal-3 is found in a variety of human tissues, including immune cells.^[13] This biomolecule is present in the cytoplasm and can be transferred to the nucleus and released to the periphery or out of the cell. As a result of these properties, Gal-3 achieves biological activities that vary depending on its position. Gal-3 contributes to the chemoattraction of macrophages and monocyte to the tissue and promotes the generation of proinflammatory mediators.^[12,14] Gal-3 might have a role in periodontal disease pathogenesis, which is attributed to its higher concentrations in periodontitis.^[15] This study aims to evaluate the salivary levels of IL-17 and galectin-3 in patients with periodontitis and type-2 diabetes mellitus.

MATERIALS AND METHODS

This study was an observational case-control study conducted at Al-Kindi Teaching Hospital and Al-Elwya Specialist Dental Center at a time frame from January 2022 to April 2022. All participants were given information about the goals of the study and agree to participate. To calculate sample size, IL-17 was used as a primary outcome of the study. Sample size was conducted using G*Power version 3.0.10 basis on data retrieved from a previous study^[16] at 95% confidence interval and 5% error margin.

Selection of groups

This study includes 88 individuals with ages between 35 and 65 years. They were split into:

Control group: included 13 periodontally and systemically healthy individuals (bleeding on probing (BOP) <10%, probing pocket depth (PPD) of ≤ 3 mm).^[17]

Type 2 diabetes mellitus (T2DM) group: included 25 patients with healthy periodontium and had been diagnosed by a specialist as T2DM patients and their current glycated hemoglobin HbA1c test $\geq 7\%$. The diagnosis of T2DM was performed on the basis of the recommended criteria by American diabetes association.

Periodontitis (P) group: included 25 nondiabetic patients with generalized periodontitis (>30% of teeth involved), a patient considered periodontitis if interdental clinical

attachment loss (CAL) is detectable at two or more non-adjacent teeth, or buccal or oral CAL ≥ 3 mm with pocketing >3 mm is detectable at ≥ 2 teeth, unstable (PPD ≥ 4 mm with BOP or PPD >5 mm).^[18]

Periodontitis—type 2 diabetes (P-T2DM) group: included 25 patients with the same criteria mentioned.

Exclusion criteria: patients with systemic diseases rather than T2DM, pregnant women, antibiotic treatment, smoker patients, previous periodontal therapies less than 3 months, patients who are not willing to participate, patients receiving insulin treatment, and patients with diabetic complications.

Unstimulated saliva samples were essential for estimating the level of IL-17 and Gal-3. The saliva samples were gathered by using a passive method from all groups at a time (9 a.m.–11 a.m.). Samples were centrifuged at approximately 3000 rpm for 20 minutes by a centrifuge machine (Hettich, Germany) in order to separate the clear supernatant. Then the samples were saved at -20°C till the enzyme-linked immunosorbent assay was accomplished.

Clinical periodontal parameters were recorded by using William's periodontal probe for all subject to assess plaque index (PLI), the presence of plaque for each surface of the tooth received a score of 1, and the absence of dental plaque received a score of 0.^[19] Assessment of BOP, by inserting a periodontal probe with a gentle force into the bottom of the gingival sulcus or periodontal pocket if there is bleeding within 15–30 seconds, the surface was given a score of 1 and a score of 0 for nonbleeding surfaces.^[20] Assessment of PPD, the distance extending from the gingival margin to the deepest point where the periodontal probe goes into the pocket or/sulcus and assessment of CAL, and the distance extending from the cemento-enamel junction to the base of the pocket.

The calibration was made to achieve examiner accuracy and repeatability by measuring the clinical periodontal parameters for five volunteers until reach the level of agreement >0.75.

Using MyBioSource enzyme-linked immunosorbent assay test kit/USA (96-wells) for quantitative measurement of salivary levels of IL-17 and Gal-3, the measurements were applied according to the instruction provided by the manufacturer. The absorbance was measured using a spectrophotometry plate reader (HumaReader HS, Germany) at 450 nm.

Statistics

Using statistical package for social science, SPSS version 24. Test normality by the Shapiro–Wilk test, data descriptive and inferential statistics were used. One way analysis of variance (ANOVA) followed by Games-Howell or Tukey HSD post hoc tests for parametric variable,

independent sample *t*-test, and Pearson correlation (*r*). The level of significance of *P*-value was <0.05.

Ethical approval

The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki. It was carried out with patients' verbal and analytical approval before the sample was taken. The study protocol and the subject information and the consent form were reviewed and approved by a local ethics committee according to the document number 456 (including the number and the date in (19-1-2022) to get this approval.

RESULTS

The data were normally distributed by using the Shapiro-Wilk test. Age ranged from 35 to 65 years, with a total mean and standard deviation of 52.863 and 8.028, respectively. While in gender distribution, there were 51 men and 37 women among the participants, as shown in Table 1. Concerning clinical periodontal parameters, P-T2DM recorded the highest mean value of PLI (73.731 ± 13.314), BOP (64.068 ± 9.965), PPD (5.097 ± 0.601), and CAL (3.992 ± 0.978) as described in Table 2. Regarding PLI and BOP, there was a statistically significant difference among groups at ($P < 0.05$) by using ANOVA followed by

post hoc test Tukey HSD and Games-Howell, respectively. The result showed a statistically significant difference between all pairgroups regarding PLI and BOP except when compared the control group with the T2DM group in PLI there was a statistically nonsignificant difference at ($P > 0.05$). However, a statistical analysis using the independent sample *T*-test for PPD and CAL showed no significant difference between the P-T2DM group and the P group.

The mean concentrations of IL-17 were highest in the P-T2DM group (532.769 ± 137.673 pg/mL). Statistical analysis by using the ANOVA test showed significant differences among groups at $P < 0.05$. Following multiple comparisons, using Games-Howell post hoc test, the only nonsignificant result was found when comparing the P group with the T2DM group, while other findings were a statistically significant difference [Table 3]. Regarding the mean concentrations of Gal-3 were highest in the P group (2.699 ± 0.386 ng/mL), the ANOVA analysis showed a significant difference among groups at ($P < 0.05$). Following multiple comparisons using the Games-Howell post hoc test, a nonsignificant result was found when comparing the P-T2DM group with the p group and T2DM group, while other findings were a statistically significant difference [Table 3].

For correlation of IL-17 with clinical periodontal parameters showed a significant moderate positive

Table 1: Distribution of age and gender among study group

	Control	T2DM	P	P-T2DM	Total	<i>P</i> -value
Age (Mean $\pm$ SD)	49.000 $\pm$ 8.621	55.280 $\pm$ 7.797	51.440 $\pm$ 7.730	53.880 $\pm$ 7.655	52.863 $\pm$ 8.028	0.089*
Gender						
Male (N)	7	15	16	13	51	0.832*
Percentage	53.85	60	64	52	57.95	
Female (N)	6	10	9	12	37	
Percentage	46.15	40	36	48	42.05	

* One-way ANOVA, * Chi-Square, $P > 0.05$ = nonsignificant, bold value indicates $P < 0.05$ = significant

Table 2: Means value of clinical periodontal parameters (PLI, BOP, PPD, CAL) and biomarkers

	Control	T2DM	P	P-T2DM	<i>P</i> -value
	Mean $\pm$ SD	Mean $\pm$ SD	Mean $\pm$ SD	Mean $\pm$ SD	
Clinical parameter					
PLI	24.641 $\pm$ 11.864	32.374 $\pm$ 10.213	64.112 $\pm$ 15.046	73.731 $\pm$ 13.314	0.000*
BOP	4.531 $\pm$ 2.506	7.111 $\pm$ 1.419	55.922 $\pm$ 10.449	64.068 $\pm$ 9.965	0.000*
PPD	–	–	4.792 $\pm$ 0.501	5.097 $\pm$ 0.601	0.058*
CAL	–	–	3.579 $\pm$ 0.918	3.992 $\pm$ 0.978	0.130*
Biomarker					
IL-17 pg/mL	292.079 $\pm$ 62.356	388.612 $\pm$ 120.111	443.887 $\pm$ 69.188	532.769 $\pm$ 137.673	0.000*
Gal-3 ng/mL	1.888 $\pm$ 0.356	2.409 $\pm$ 0.147	2.699 $\pm$ 0.386	2.568 $\pm$ 0.285	0.000*

*One-way ANOVA, *independent sample *T*-test, $P > 0.05$ = nonsignificant, PLI = plaque index, BOP = bleeding on probing, PPD = probing pocket depth, CAL = clinical attachment loss, bold value indicates $P < 0.05$ = significant

Table 3: Intergroup multiple comparisons of IL-17, Gal-3, and clinical periodontal parameters (PLI, BOP) between all pairs of study groups by using post hoc tests

		IL-17 pg/mL [§]	Gal-3 ng/mL [§]	PLI [†]	BOP [§]
Control	T2DM	0.012	0.001	0.300	0.016
	P	0.000	0.000	0.000	0.000
	P-T2DM	0.000	0.000	0.000	0.000
P	T2DM	0.208	0.007	0.000	0.000
	P-T2DM	0.032	0.528	0.047	0.034
P-T2DM	T2DM	0.001	0.081	0.000	0.000

[§]Games-Howell, [†]Tukey HSD (honestly significant difference), PLI = plaque index, BOP = bleeding on probing, $P > 0.05$ = nonsignificant, bold value indicates $P < 0.05$ = significant

Table 4: Correlation of salivary IL-17, Gal-3 with clinical periodontal parameters among study group using Pearson correlation (r)

Groups	Markers	PLI		BOP		PPD		CAL	
		r	P-value	r	P-value	r	P-value	r	P-value
Control	IL-17	0.389	0.189	0.450	0.123				
	Gal-3	0.045	0.885	-0.009	0.976				
T2DM	IL-17	0.204	0.327	0.149	0.477				
	Gal-3	0.306	0.136	0.109	0.605				
P	IL-17	0.233	0.263	0.281	0.173	0.408	0.043*	0.637	0.001*
	Gal-3	0.382	0.060	-0.017	0.937	0.228	0.273	0.133	0.527
P-T2DM	IL-17	0.600	0.002*	0.501	0.011*	0.567	0.003*	0.240	0.248
	Gal-3	0.505	0.010*	0.266	0.198	0.354	0.082	0.167	0.426

* Significant $P < 0.05$, PLI = plaque index, BOP = bleeding on probing, PPD = probing pocket depth, CAL = clinical attachment loss, bold value indicates $P < 0.05$ = significant

correlation of IL-17 with PPD and CAL in the P group. While for the P-T2DM group, there was a significant moderate positive correlation of IL17 with PLI, BOP, and PPD [Table 4]. For correlation of Gal-3 with clinical periodontal parameters, it showed a significant moderate positive correlation of PLI with Gal-3 in the P-T2DM group [Table 4].

DISCUSSION

The mean concentrations of IL-17 in the P group were higher than in the control group, with a significant difference between them. This result agrees with other studies by Yang *et al.* [21] and Mushtaq *et al.* [22] Conversely, Özçaka *et al.* [23] reported a lower level of IL-17 in the P group compared to the control group. Isaza-Guzmán *et al.* [24] recognized a zero concentration of IL-17 in saliva. These variations in salivary cytokine levels may be attributable to differences in ethnicities, flow rate, quantity, contents of saliva, and whether the saliva is stimulated or unstimulated which may impact cytokine concentrations. [25]

The increase in IL-17 levels in periodontitis may be related to the cells of periodontal tissues producing IL-17 locally in response to microbial challenges. IL-17 action directly or indirectly on host tissues. [26] First, increased IL-17 intensifies inflammatory responses and causes tissue

damage by promoting the synthesis of inflammatory and osteoclastogenic mediators by gingival resident cells. Second, IL-17 may act on osteoblasts, resulting in prostaglandin2 (PGE2) generation and expression of RANKL on B cells, T cells, and gingival fibroblasts. This stimulates osteoclast progenitor cells to differentiate into mature osteoclasts, leading to the resorption of alveolar bone. [8]

This study also showed a significant increase of IL-17 levels in the T2DM group compared with the control group, this result comes in agreement with other study by Ding *et al.* [27]. IL-17 in co-operates with other cytokines seen to play a risk factor for the development of T2DM. [28]

The salivary level of IL-17 was revealed to be the highest value in the P-T2DM group. Whereas hyperglycemia has been linked to the production of oxygen-free radicals, activation of oxidative stress, and secretion of inflammatory cytokines. [29] Furthermore, the release of these inflammatory factors can stimulate osteoclasts, causing damage to periodontal and bone tissue and exacerbating periodontal diseases. Therefore, poor glycemic control can induce an inflammatory response and affect periodontal health. The result was similar to another study by Ding *et al.* [27]

This study showed a higher mean concentration of salivary Gal-3 in periodontitis than in control with a statistically

significant difference between them. Also, Isola *et al.*^[30] found the same result in the salivary sample. While Karsiyaka *et al.*^[31] found the same results in their study comparing the level of Gal-3 in gingival crevicular fluid (GCF). The results disagree with Wu *et al.*^[32] who found a lower level of salivary Gal-3 in periodontitis patients than in the healthy group. The possible explanation for this increase is that Gal-3 plays essential roles during the inflammatory process including activation of neutrophils, monocytes differentiation into macrophages, mast cells activation,^[33] stimulation of proinflammatory cytokines production (IL-6, tumor necrosis factor alpha)^[34] induce leukocyte recruitment during inflammation.^[35]

The result showed a significant difference between the T2DM group, and the control group this result was in agreement with Li *et al.*^[36] Who detected the presence of Gal-3 in saliva and found that a higher level of the marker in diabetes in comparison with the control group.

Poor glycemic control in diabetic individuals predisposes to the accumulation of advanced glycation end product.^[37] Gal-3, which acts as a scavenging receptor for advanced glycated end-product advanced glycation end products, is elevated in diabetes mellitus and is considered a possible biomarker for this condition.^[38]

The result showed that the P group has a higher level of Gal-3 compared with the P-T2DM group with a nonsignificant difference. Li *et al.*^[36] suggested in their study that the Gal-3 level decreased when periodontitis worsen in type 2 diabetic patients. The authors attributed their results to the decompensation of bone tissues associated with accelerated bone destruction in diabetes with severe periodontitis and found the primary origin of Gal-3 in bone is osteoblasts.

Concerning clinical periodontal parameters, there was a significant difference between the P group and the P-T2DM group concerning PLI and BOP, and these results agree with the previous study by Abdul-Wahab and Ahmed.^[39] Because increased glucose levels in the saliva of diabetic patients may contribute to an increase in plaque accumulation and a change in the response of periodontal tissue to local factors.^[40] COVID-19 pandemic made it difficult to recruit subjects to enlarge the sample size that limited the ability to consider the staging and grading of periodontitis and also the correlation between these biomarkers with blood sugar did not studied, so it is suggested for future researches.

CONCLUSION

Form the results, we conclude that an increase in the salivary level of IL-17 and Gal-3 in diabetic and periodontitis patients could be utilized as a biomarker for diagnosing these diseases.

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Conflicts of interest

There are no conflicts of interest.

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