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Original Article

Potential Role of NLRP3 Inflammasome Activation in the Pathogenesis of Periodontitis Patients with Type 2 Diabetes Mellitus

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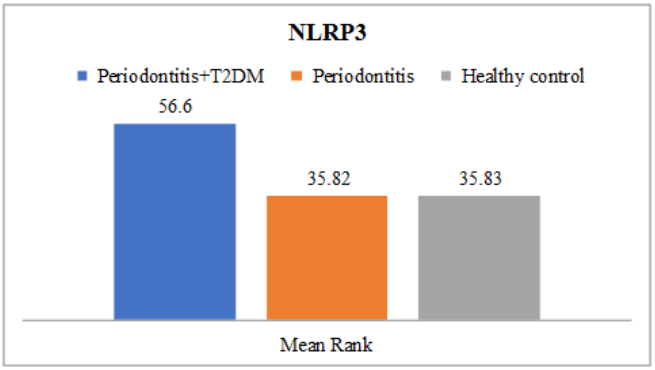
ABSTRACT

In response to microbial infection and cellular injury, the NLRP3 inflammasome, an essential part of the innate immune system, causes caspase-1 activation and the release of the proinflammatory cytokines IL-1 β and IL-18. However, various inflammatory diseases, including periodontal disease have been linked to the abnormal activation of the NLRP3 inflammasome. This study was conducted to investigate the crucial role of NLRP3 inflammasome activation and IL-18 in the pathogenesis of periodontitis patients with type 2 diabetes mellitus. This case control study included eighty-five participants and their age range was (23-55) years old. They were divided into three groups: two groups had periodontitis one of them with type two diabetic mellitus and the other one systemically healthy, the third group was the control group with clinically healthy periodontium and systemically healthy. Serum samples from both patients and controls were analysed by using an ELISA kit designed to detect NLRP3 inflammasome activity and interleukin-18. The elevated NLRP3 and IL-18 levels in PD +T2DM patients and their positive correlation with clinical parameters suggested a critical role in the PD pathogenesis with and without diabetes. A significant positive correlation was also noticeable between NLRP3 and each of (GI, PPD, CAL, and BOP) in PD+T2DM patients. Regarding the group of PD patients, there was no significance correlation between NLRP3 and clinical parameters. In addition, IL-18 was discovered to have a positive correlation with GI, PPD, CAL, and BOP in PD+T2DM patients. Meanwhile, there was a significant correlation between NLRP3 and interleukin-18 in patients with and without type 2 diabetic mellitus. Elevated NLRP3 and IL-18 levels in PD +T2DM patients and their positive correlation with clinical parameters suggested a critical role in the PD pathogenesis with and without diabetes.

GRAPHICAL ABSTRACT



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Introduction

Periodontitis (PD) has been defined as a chronic multifactorial inflammatory disease associated with dysbiotic dental biofilms [1].

Proliferation of bacterial biofilm increases during changed homeostasis inside of the mouth [2]. Periodontitis is an illness that causes progressive destruction of the tooth-supporting tissues. It is distinguished by the absence of periodontal tissue support, as evidenced by clinical attachment loss and radiographically assessed alveolar bone loss, as well as the presence of periodontal pocketing and gingival bleeding [1].

Periodontitis is the most prevalent health disease that impairs aesthetic and social life and can result in tooth loss [3].

Diabetes mellitus (DM) is among the most prevalent metabolic diseases that around the world are growing at an alarming rate. The two main types of diabetes mellitus are: type 1 diabetes mellitus (T1DM) which caused by complete insufficiency in insulin secretion and type II diabetes mellitus (T2DM) which is more widespread and occurred by an incorporation between impedance to insulin action and an insufficient insulin secretion as a compensatory response [4].

Type 2 non-insulin dependent diabetes mellitus (NIDDM) is the most common and mildest type of diabetes, involving 90% of people with diabetes worldwide. It usually appears after the age of 40, which is why it is called adult diabetes [5].

An estimated, (171) million individuals were afflicted by DM globally; in 2011, that number had risen to more than (366) million, with the number anticipated to rise to more than (552) million by 2030.

The DM is regarded as a hyperglycaemia and T2DM is susceptible to oral complications such as periodontal disease (PD), dry mouth, and abscesses [6, 7] which is caused by insulin resistance, decreased function of pancreatic beta cells, and increased production of glucose by the liver [8].

Human immune systems recognize foreign substances and responds in a helpful manner to them. When a pathogen component enters the human body as a defensive mechanism, an immunological reaction is elicited [9]. The activation of the innate immune system is closely associated with the activation of the adaptive side. A number of studies have shown that inflammasome plays a key role in affecting this relationship [10]. Biomarkers play an essential role since they are good predictor factors for several diseases [3].The inflammasome is a multiprotein complex in the cytoplasm that includes a sensor protein, inflammatory caspases and, in some cases, an adapter protein that connects the two. Different stimuli, both internal and external, can set them off, leading to the enzymatic activation of caspases like canonical caspase-1 and noncanonical caspase-11 (or the equivalent caspase-4 and caspase-5 in humans), or caspase-8, leading to apoptosis and pyroptotic cell death, as well as the secretion of IL-1 and IL-18 [10]. There are 22 members of the NLR protein family in humans, with Nod-like receptor protein 3 (NLRP3) being one of the best understood inflammasomes. [11, 12]. Given that NLRP3 responds to various PAMPs and/or DAMPs, both infectious and endogenous, it is not surprising that alterations in NLRP3 function are linked to the pathogenesis of a number of inflammatory diseases [13, 14].

The three constituents of this protein complex are: a caspase-1 component, the apoptosis-associated speck-like protein (ASC), a PYCARD (PYD and CARD Domain) adaptor called NLRP3, and the NLRP3 scaffold [15]. The cytokine interleukin 18 (IL 18) is a sensitive marker of inflammation with a wide range of regulatory roles in immune and inflammatory responses. Th1 cell proliferation and Th1-type immune responses can be boosted by IL-18, and the secretion of inflammatory cytokines and chemokines can be induced as well. IL-18 can also increase cytotoxicity mediated by the Fas/Fas ligand (FasL) system. [16, 17]. IL-8 can activate the secretion of other pro-inflammatory cytokines such as TNF-α, IL-1β, IL-8, and granulocyte-macrophage colony-stimulating factor which promote the expansion, migration, and activation of PMNs during infections [18]. A number of studies have revealed that people with periodontitis have higher IL-18 levels than

healthy people. This study was conducted to investigate the role of NLRP3 inflammasome activation and IL-18 in the pathogenesis of patients with periodontitis and type 2 diabetes mellitus.

Martials and Methods

Subject

In total, 85 participants participated in the case-control study (44 males and 41 females) in the age range of (23-55) years old. They were among the attendants to Taji Primary Healthcare centres from November 2021 to January 2022. A questionnaire was used to record special notes regarding these subjects. The College of Dentistry/University of Baghdad's Ethical Review Board authorized this research (Ref. No. 379 in 21/11/2021).

Inclusion criteria

In order to be included in this study, participants had to fulfil the following conditions: Type 2 DM patients on oral hypoglycaemic therapy only, the presence of at least 20 or more natural teeth, and patients with periodontitis had periodontal pockets equal or greater than 3 mm in two or more non-adjacent teeth, with loss of attachment more than 3 mm.

Oral examination

Periodontal health status was recorded through the examination of clinical periodontal parameters by using a periodontal probe of William's graduation.

Blood sample collection

Under aseptic conditions, three millilitres from each participant will have a vein punctured to collect blood. Serum was separated by centrifugation at 3000 rpm for 10 minutes after blood was transferred to a sterile plain tube, and then it was divided into small aliquots and stored at -20 °C until analysis.

Measurement of NLRP3 inflammasome and IL-18

The levels of NLRP3 and IL-18 were determined by the ELISA kit (Shanghai/China).

Statistical analysis

Was carried out by using SPSS version 24. Smirnov-Kolmogorov test was used to test the normality of distribution of the data, ANOVA parametric test was used to determine and find the difference between 3 or more independent groups, and Tukey honestly significant difference (HSD)/post hoc test was employed to check if there is a connection between two datasets as statistically significant (intergroup comparison). Likewise, for non-parametric data, Kruskal-Wallis and Mann-Whitney tests were utilized. The correlation among different parameters was calculated by the Spearman correlation coefficient test.

Results and Discussion

No differences of statistical significance were found in the current study. ($P>0.05$) was found among three study groups according to the age and sex, as represented in Table 1. In addition, Figure 1 displays the differences in clinical markers between patient groups and controls group.

An increase of statistical significance was found in the present study. ($P<0.05$) was found in the mean rank of serum NLRP3 levels among PD+T2DM group (56.60 pg/ml) compared with the PD group (35.82 pg/ml) and the control group was (35.83 pg/ml), as observed in Figure 2. As listed in Table 2, the comparisons between groups revealed a significant difference between PD+T2DM and control group. On the other hand, the control group did not show a significant difference with PD group.

Moreover, Figure 3 displays the mean rank values of IL-18 for the study and control groups. Quite dissimilarities are existed. Through ($P<0.05$) between groups, PD + T2DM had the greatest mean value of IL-18 among the three groups, with a mean value of (58.73 pg/mL), followed by PD patients group with a mean value of (43.8 pg/mL), and control group with a mean value of (23.16 pg/mL).

Table 1: Case-control differences in age and sex

Demographic Characteristics	Study groups			*P*-value
	Periodontitis+T2DM n=30	Periodontitis n=30	Healthy control n=25	
Age (years)				
Range	(23-56)	(23-52)	(24-50)	0.227^{NS}
Mean ± SD	40.0±8.80	38.50±7.50	36.88±6.50	
Sex				
Female	15 (50%)	14 (47%)	14 (56%)	0.785^{NS}
Male	15 (50%)	16 (53%)	11 (44%)	

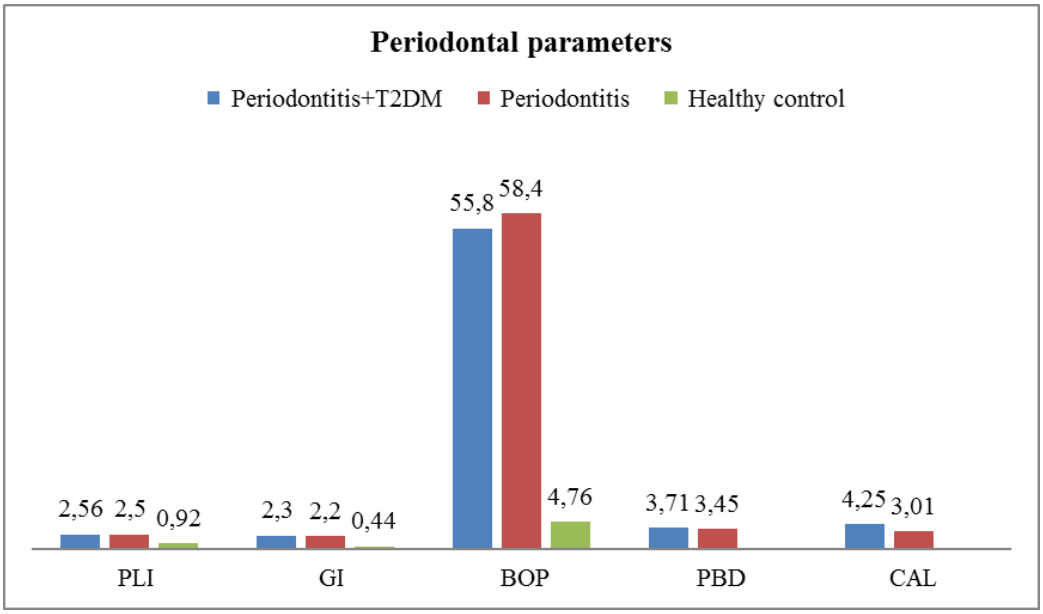

Figure 1: The difference in the mean values of periodontal parameters among three groups

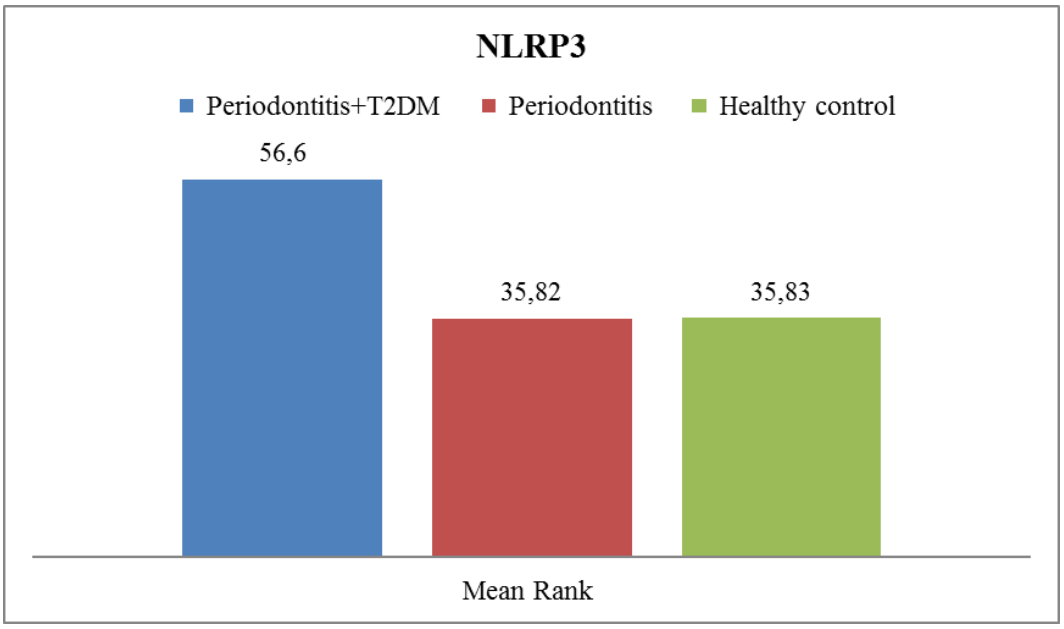

Figure 2: The difference in the mean rank values of serum NLRP3 among study groups

Table 2: Inter groups comparisons of the mean rank values of NLRP3 between all pairs of groups

Grouping	Mean Rank difference	Mann Whitney Test (*P*-value)
NLRP3		
Periodontitis +T2DM vs. Periodontitis	20.87	0.001**
Periodontitis +T2DM vs. Control	21.03	0.001 **
Periodontitis vs. Control	0.51	0.938NS

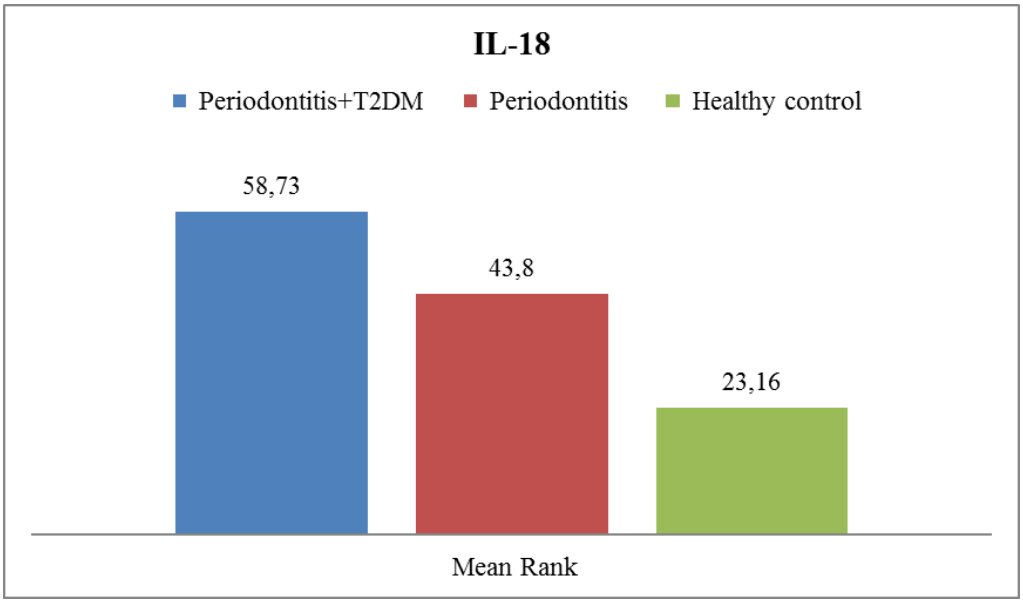

Figure 3: The difference in the mean rank values of serum IL-18 among study groups

According to Table 3, intergroup comparisons of IL-18 levels was done across all pairs of groups. The differences were very noticeable. (P<0.05) was found between the PD+T2DM group and the PD group, and also between PD group and control group, but it was not found between PD +T2DM and control.

The present results revealed positive significant correlations between IL-18 and NLRP3 in PD+ T2DM patients and PD only, as depicted in Table 4.

The correlation between IL-18 levels and clinical parameters is demonstrated in Table 5. There are positive correlations with GI, PPD, CAL, and BOP in PD+T2DM patients, but a non-significance correlation was found with PI. Moreover, there are no correlation between IL-18 and each of PI, GI, CAL and BOP, while there is a significant correlation with PPD among PD patients.

Table 5 showed a significance correlation between the NLRP3 level and each of GI, PPD, CAL, and BOP in PD+T2DM patients, while no significance correlation was observed with PI. Regarding PD patients group, this study indicates no significance correlation of NLRP3 with all parameters.

Serum and salivary NLRP3 inflammasome levels in patients with periodontitis and type 2 diabetes do not appear to be a reliable biomarker of disease risk. The present study showed an increase in the serum NLRP3 level in PD+T2DM group compared with PD patients group and control subjects. This consistent with Kim *et al.* [19] who approved that increased NLRP3 levels are related to micro- and macro-vascular endothelial cell dysfunctions in type 2 diabetes, confirming the regulatory effects induced by NLRP3 on these cell functions. It is worth to note that hyperglycaemia during T2DM is responsible for the upregulation of reactive oxygen species, which can stimulate the expression of the inflammasome [20] and, when combined with periodontitis, can potentially cause endothelial dysfunction and metabolic disease. [21]. In addition, bacterial components like LPS cause depressive symptoms by activating the NLRP3 inflammasome and producing LPS-reactive immunoglobulins [22, 23].

The current study does not show any significant difference in NLRP3 levels between PD and control group. However, increase in NLRP3 in PD patients with T2DM, but not in PD patients compared with controls may be due to sterile inflammation caused by DAMP release that prepares the brain and body for an eventual immune response [24]. DAMPs alert the immune system via PRRs [25]. Inflammasomes are subsequently activated, causing the release of IL-1β, IL-18, and IL-33 [26]. Furthermore, stress exposure activating IL1β and TNF-mediated pathways by promoting NLRP3 signalling [27, 28].

Table 3: Inter groups comparisons of the mean rank values of NLRP3 between all pairs of groups

Grouping	Mean Rank difference	Mann Whitney Test (*P*-value)
IL-18		
Periodontitis +T2DM vs. Periodontitis	14.93	0.019*
Periodontitis +T2DM vs. Control	35.75	1.022NS
Periodontitis vs. Control	20.64	0.002**

Table 4: Correlation between IL-18 level and clinical periodontal parameters in periodontitis patients with T2DM

Periodontitis patients +T2DM	R-value	*P*-value
PI	0.221	0.239NS
GI	0.785	0.000**
PPD	0.537	0.002**
CAL	0.536	0.002**
BOP	0.431	0.017*
Periodontitis patients		
PI	0.161	0.393NS
GI	0.019	0.919 NS
PPD	0.478	0.007**
CAL	0.014	0.937 NS
BOP	0.235	0.209 NS

Table 5: Correlation between NLRP3 level and clinical periodontal parameters in periodontitis patients with T2DM

Periodontitis patients +T2DM	R-value	*P*-value
PI	0.093	0.623NS
GI	0.794	0.000**
PPD	0.592	0.0005**
CAL	0.491	0.005**
BOP	0.447	0.013*
Periodontitis patients		
PI	0.100	0.598NS
GI	0.120	0.525NS
PPD	0.249	0.182NS
CAL	0.040	0.833 NS
BOP	0.190	0.312 NS

Furthermore, the present study indicated a significant positive correlation between NLRP3 and periodontal parameters, and these results are consistent with Aral *et al.* [29] who found a positive correlation between NLRP3 and clinical periodontal parameters. Altogether, these data demonstrated that NLRP3 plays a significant role during periodontal disease pathogenesis. Shahbeik *et al.* showed that concerning the possible relationship between NLRP3 levels and clinical parameters, it may be a potential predictor of periodontal tissue degeneration [30].

Two patient groups were found to have statistically significant elevations in IL-18 serum levels in the current study. (PD+T2DM and PD) compared with the control group. IL-18 is considered to be a pro-inflammatory cytokine which plays an important part in the process of regulation of inflammation and metabolism [31, 32]. This may explain the increased levels of IL-18 in the serum of PD + T2DM and PD patients as observed in present study. This result was in agreement with other studies [33, 34]. The elevation in IL-18 levels among T2DM patients supports previous evidence of a chronic inflammatory state in metabolic disease [35]. Cheng *et al.* [36] reported that the IL-18 has been proposed to be biomarkers for periodontitis. In contrast to this study, Chitapriya *et al.* [37] and Abbas [38] found the elevated serum levels of IL-18 in healthy subjects compared with periodontitis samples.

Considering the correlation of serum IL-18 with clinical periodontal parameters, there was a significant correlation in both patient groups and this was in agreement with Wang *et al.* [39] who observed IL 18 exhibited strong positive correlations with every periodontal clinical index. Other Iraqi study found significant correlation with PPD in the chronic periodontitis group and IL 18 expression was found to have a significant correlation with periodontal destruction [38]. According to the results of this investigation, NLRP3 and IL-18 were significantly positively correlated in patient groups. This could be explained by the increased expression and production of inflammatory cytokines like IL-1β and IL-18, which are inflammatory interleukins involved in the periodontitis occurrence and whose unbalanced production causes tissue degradation [40]. The current result is similar with the observations made by Yamasaki *et al.* who found that NALRP3 and IL-18 expression are positively correlated in periodontitis [41]. On the other hand, Shahbeik *et al.* [30] found no evidence of a significant relationship between IL-18 and NLRP3 and indicated that IL-18 might not be a reliable signal for assessing the inflammatory status of periodontal tissue.

Conclusion

The levels of NLRP3 and IL-18 were elevated in PD +T2DM patients, and their positive correlation with clinical parameters indicated a critical role in the PD pathogenesis with and without diabetes.

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Disclosure Statement

No potential conflict of interest was reported by the authors.

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Authors' contributions

All authors contributed to data analysis, drafting, and revising of the paper and agreed to be responsible for all the aspects of this work.

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