Evaluation of serum IL-17A levels in chronic periodontitis patients with or without diabetes

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Abstract

Chronic periodontitis is a poly-microbial immune-inflammatory disease which causes the destruction of supporting structures of the tooth. Prevalence of periodontitis in the global population is 10 % with severe periodontitis and these levels have not changed in the past 20 years. There was a recognized close association between diabetes mellitus (DM) and chronic periodontitis (CP). Diabetes is considered as a risk factor to develop periodontitis and those with untreated periodontitis leads to poorer glycemic control. Both diseases are proposed to have an inflammatory mechanism that links common pathways for pathophysiological processes. The pathways which link inflammatory processes include altered polymorphonuclear cell (PMN) function, increased adipokine production and altered apoptosis. This could lead to activation of inflammatory reactions causing the release of increased inflammatory cytokines production in patients with chronic periodontitis and diabetes mellitus with bidirectional influences.

Keywords: Chronic periodontitis; Polymorphonuclear; Type 1 & 2 diabetes mellitus

Introduction

Chronic periodontitis is a poly-microbial immune-inflammatory disease which causes the destruction of supporting structures of the tooth. Prevalence of periodontitis in the global population is 10% with severe periodontitis and these levels have not changed in the past 20 years [1]. There was a recognized close association between diabetes mellitus (DM) and chronic periodontitis (CP) [2]. Diabetes is considered as a risk factor to develop periodontitis and those with untreated periodontitis leads to poorer glycemic control. Both diseases are proposed to have an inflammatory mechanism that links common pathways for pathophysiological processes. The pathways which link inflammatory processes include altered polymorphonuclear cell (PMN) function, increased adipokine production and altered apoptosis [3]. This could lead to activation of inflammatory reactions causing the release of increased inflammatory cytokines production in patients with chronic periodontitis and diabetes mellitus with bidirectional influences.

Chronic Periodontitis and diabetes can be considered as a reservoir of infection and inflammation in which the pro inflammatory cytokines such as Tumor necrosis factors (TNF-α), Interleukin-1 (IL-1), IL-6, IL-17 and IL-18 were associated with various complications [4-6]. These cytokines were disseminated to other parts of body organs or vice versa causes directly or indirectly to systemic diseases such as Rheumatoid arthritis and Multiple Sclerosis. IL-17A cytokine is a most studied member of the IL-17 cytokine family and its increased production was associated with autoimmune disease and chronic inflammation including periodontitis [7-9]. The significant high level of IL-17A cytokine has been demonstrated in the gingival crevicular fluids and serum. IL-17A cytokine suggested being involved in host response of CP when correlating gingival tissue supernatants at sites with moderate to severe CAL [10].

IL-17A cytokines are involved in triggering Type 1 & 2 diabetes mellitus through autoimmune and inflammatory mechanisms respectively. IL-17A suggested being involved in two pathways of autoimmune destruction of β –cells in pancreas [11]. First pathway, involving T cells through effector Th1, Th2 and Th17 cells and its cytokine production could lead to breakdown of immune balance which causes autoimmune destruction. Another pathway suggested was through direct effects of proinflammatory cytokines (IL-1β, TNF-α, IL-6) and chemokines on islets of β-cell survival and apoptosis [12]. Consequently, IL-17A cytokines participated in both pathways of inflammation which causes β-cell destruction (T1DM) in synergy with proinflammatory cytokines. In type 2 diabetes, dysregulation of IL-17A production is considered to be influencing the proinflammatory cytokine expression and chronic inflammation (β-cells apoptosis and β-cell failure) with insulin resistance leads to development of type 2 diabetes. Previous studies showed that serum IL-17A protein level was enhanced in both types of diabetes (type I & II) compared with healthy individuals [13].

Despite the role of IL-17A in inflammation has been studied and also recent studies reported conflicting results in chronic periodontitis and diabetes, the association of IL-17A and diabetes is still sparse. Although they presented the distinct pattern of diseases regardless of the different clinical parameters, association of serum IL-17A levels in chronic periodontitis with or without diabetes has to be determined. This study was aimed to evaluate the serum IL-17A levels in chronic periodontitis patients with or without diabetes.

Materials and Methods

The study was approved by the Institutional Ethics Committee, Department of Research, JKKN Dental College and Hospital (34F/04/2018/IEC/JKKDC) and informed consent was obtained from all the study participants. Inclusion Criteria for Periodontitis patients were cases diagnosed based on AAP criteria for Generalized Chronic periodontitis with presence of clinical attachment loss more than 3 mm in at least six sites and pocket probing depth (ppd) more than 4 mm at least six sites, bleeding on probing must be there in more than 30% of sites. Exclusion Criteria were smokers, existing orthodontic therapy, Aggressive periodontitis, General Health problems (Hepatitis, HIV infection, Chemotherapy), pregnancy, lactation, and non-Indian races. For Type 1 & 2 diabetes patients, both male and female patients, age group between 30 -44 years, those who have already been diagnosed with Type 1 or Type 2 diabetic patients irrespective of controlled or uncontrolled glycemic status were taken for the study. For the diabetic patients the following parameters were recorded such as the presence of clinical symptoms (such as polyuria, polydipsia and weight loss), biochemical parameters (Levels of glycemic, glycated hemoglobin (HbA1c), and body mass index).

The study was carried out in 168 subjects and consists of 6 groups wherein group 1 consists of 28 Type 1 diabetes patients with periodontitis, group 2 consists of 28 Type 1 diabetes patients without periodontitis, group 3 consists of 28 Type 2 diabetes patients with periodontitis, group 4 consists of 28 Type 2 diabetes patients without periodontitis, group 5 consists of 28 Non-diabetic patients with chronic periodontitis, group 6 consists of 28 Non-diabetic patients without periodontitis (control group). The Sample of 3 ml venous blood was collected from cubital fossa of each subject under strict

sterile conditions and transferred to the laboratory by using standard blood collection tubes after centrifuge for 15 minutes at 2200-2500 RPM.

Methodology

The analysis is done based upon the Enzyme Linked Immunosorbent Assay (ELISA) by sandwich Elisa kit principle and the procedure consists of following steps. The IL-17A Elisa kit (Proteintech, Human IL-17A ELISA Kit) was used to detect and quantify protein levels of serum IL-17A. The antibody specific for IL-17A has precoated into the microwells. After incubation, IL-17A protein in the sample was captured by the coated antibody. Following extensive washing, another antibody specific IL-17A was added to identify the captured IL-17A protein. In signal development, horseradish peroxide (HRP)-conjugated antibody was added followed by Tetramethy-benzidine (TMB) reagent. The stop solution containing sulfuric acid was added to stop color development. The color intensity proportional to quantity of bound protein was measured at 450 nm with the correction wavelength set at 630 nm.

Statistical Analysis

The statistical comparison of all the variables between the groups was done by Kruscal Wallis ANOVA and the correlation of serum IL-17A levels with Clinical parameters was done by Pearson correlation test . The p value <0.05 was considered as statistically significant. All the Statistical analysis was done using the SPSS version 21.

Results

A total of 168 patients (mean age of 37) in six groups were included in the study for the analysis of serum IL 17 levels. Overall comparison of IL-17A level in between the groups showed that there was a significant difference (p value < 0.001) among the groups with highest mean level (5.02±0.45) for group-3 (T2DM+CP) followed by group-5 (only CP) and lowest (1.21±0.49) in group-6 (healthy) as shown in table 1. In the pairwise comparison, group 1 (T1DM+ CP) versus group 2 (T1DM) there was no significant difference in IL-17 Levels, whereas group-3 versus groups- 4, group 3 had significantly high levels of serum IL 17 and group-5 versus group-6, group 5 had had significantly high levels (p>0.05). When IL 17 levels were compared between group 2 (T1DM) and group 4 (T2DM), group 4 showed significantly high serum IL-17A levels (p>0.001) as shown in table 2. The type 2 diabetes with periodontitis group (group 3) had significantly high levels of IL-17A when compared with the only diabetes group (group 4) (Table 2).

On evaluating the clinical parameters, there was a significant difference in probing pocket depth (PPD) between the groups (Table 3), with group-5 (CP) had significantly high mean value of PPD (7.48±1.03) followed by group-3 (T2DM+CP) (6.63±0.90) and lowest in group-4 (2.75±0.16) (only T2DM) with p value (p<0.001) as shown in Table 3. When comparing the clinical attachment level (CAL), group-1 (T1DM+CP) had significantly high mean value (3.54±0.49) followed by group-5 (only CP) (6.63±0.90) and lowest in group-2 (2.75±0.16) (T1DM) with p value (p<0.001) as shown in Table 4. While comparing the gingival index (GI) there was a significant difference between the groups (p value <0.001) with group-1, 3 & 5 (T1DM+CP, T2DM+CP & CP) had high mean value as compared to group- 2 & 4 (Table 5).

The present study evaluated the correlation between IL-17A levels and periodontal clinical parameters such as PPD, CAL and BI. The results revealed that there was no significant correlation with any of the clinical parameters except for group-2 (T2DM) showed nearly significant correlation p value 0.059 with r value of 0.360 (Table 6). (Table 1-6) (Figure 1,2)

Discussion

The present study evaluated the serum IL-17A levels in type 1 and type 2 diabetic patients with and without chronic periodontitis patients. The results revealed that there was a significant difference in the IL 17 levels between the six groups with the highest level in Overall comparison of IL-17A levels showed that comparable mean IL-17A proteins were seen in type 2 diabetes and CP. IL-17A levels were seen higher in group 3 (T2DM+CP, 5.02±1.32) and group-5 (only CP, 3.5±1.20) (Table 1) compared with all other groups. Group-3 (T2DM+CP) and group 5 (only CP) had high levels of mean IL-17A proteins which could explain the accumulation of advanced glycation end products (AGEs) in gingiva and exacerbated immune response and impaired tissue integrity makes patients more vulnerable to chronic periodontitis [14]. But both types of diabetes (type 1&2) had significantly more mean levels of IL-17A (2.98±1.30, 1.44±0.47) when compared with healthy groups. T2DM (2.98±1.30) had high mean IL-17A levels compared with T1DM (1.44±0.47) with or without periodontitis. In this study, mean IL-17A level was less in T1DM

Table 1: Comparison serum IL-17A levels between the groups using Kruscal Wallis ANOVA.

	Groups	Mean (pg/mL)	Std. Deviation	Mean Rank	Chi-Square	p value
IL-17A	T1DM+ CP (Group 1)	1.30	0.45	46.02	112.13	0.001
	T1DM (Group 2)	1.44	0.47	53.98		
	T2DM+ CP (Group 3)	5.02	1.34	143.75		
	T2DM (Group 4)	2.98	1.30	104.75		
	CP (Group 5)	3.5	1.20	118.43		
	control (Group 6)	1.21	0.49	40.07		

Table 2: Inter group Comparison of IL-17A using Mann-Whitney U test.

IL-17A	N	Mean Rank	Sum of Ranks	Mann-Whitney U	Z	p value
T1DM with CP (G1)Versus T1DM (G2)	28	26.29	736	330	-1.02	0.308
	28	30.71	860			
T2DM + CP (3)versus T2DM(G4)	28	38.34	1073.5	116.5	-4.518	0.001
	28	18.66	522.5			
CP versus (G5) control(G6)	28	41.75	1169	21	-6.087	0.001
	28	15.25	427			
T1DM+CP(G1) Versus T2DM+CP(G3)	28	14.98	419.5	13.5	-6.21	0.001
	28	42.02	1176.5			
T1DM(G2) Versus T2DM(G4)	28	17.82	499	93	-4.905	0.001
	28	39.18	1097			

Table 3: Comparison of PPD between the groups using Kruscal Wallis ANOVA.

	Groups	Mean (pg/mL)	Std. Deviation	Mean Rank	Chi-Square	p value
PPD	T1DM+ CP (Group 1)	6.15	0.93	110.02	123.48	0.001
	T1DM (Group 2)	2.76	0.21	44.73		
	T2DM+ CP (Group 3)	6.63	0.90	122.86		
	T2DM (Group 4)	2.75	0.16	38.93		
	CP (Group 5)	7.48	1.03	141.96		
	control (Group 6)	3.19	1.39	48.50		

Table 4: Comparison of CAL between the groups using Kruscal Wallis ANOVA.

	Groups	Mean (pg/mL)	Std. Deviation	Mean Rank	Chi-Square	p value
CAL	T1DM+ CP (Group 1)	3.54	0.49	130.20	126.72	0.001
	T1DM (Group 2)	0.36	0.27	41.98		
	T2DM+ CP (Group 3)	3.27	0.60	120.86		
	T2DM (Group 4)	0.36	0.27	41.98		
	CP (Group 5)	3.47	0.37	128.45		
	control (Group 6)	0.38	0.27	43.54		

Table 5: Comparison of Gingival Index between the groups using Kruskal Wallis.

	Groups	Mean (pg/mL)	Std. Deviation	Mean Rank	Chi-Square	p value
Gingival Index	T1DM+ CP (Group 1)	2.36	0.27	126.50	126.51	0.001
	T1DM (Group 2)	0.36	0.27	41.04		
	T2DM+ CP (Group 3)	2.36	0.27	126.50		
	T2DM (Group 4)	0.36	0.27	41.04		
	CP (Group 5)	2.36	0.27	126.50		
	control (Group 6)	0.42	0.32	45.43		

Table 6: Correlation between serum IL-17A and Clinical parameters (Pearson correlation coefficient).

Group		IL-17A		
		PPD	CAL	Gingival Index
T1DM +CP (Group 1)	r value	0.095	-0.2	-0.202
	p value	0.632	0.307	0.303
T1DM (Group 2)	r value	0.111	-0.307	-0.307
	p value	0.573	0.112	0.112
T2DM+CP (Group 3)	r value	0.172	0.061	-0.036
	p value	0.383	0.759	0.855
T2DM (Group 4)	r value	0.36	-0.085	-0.085
	p value	0.059	0.665	0.665
CP (Group 5)	r value	0.269	-0.161	-0.164
	p value	0.167	0.412	0.403
control (Group 6)	r value	0.238	-0.203	-0.223
	p value	0.224	0.299	0.253

and T1DM+CP (group 1 & 2) when compared with CP (3.5±1.20, group-5) and in group 3 (T2DM+CP). This could be the reason for less synergistic effects in autoimmune condition (T1DM) compared with inflammation condition of T2DM and also in CP patients as shown in table 1. In contrast to our study, a previous study by Honkanen J et al, demonstrated the detrimental effects of IL-17 on human islet cells, providing a link between Th17 immunity and β cell damage (type 1 diabetes) in mice [15].

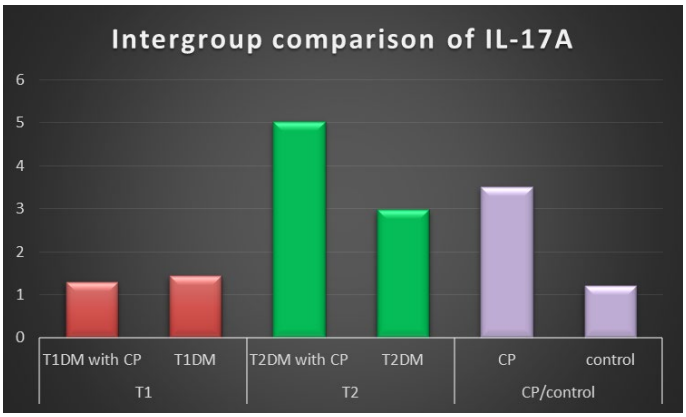

Figure 1: Inter group comparison of IL-17A protein.

Comparing between T1DM & T2DM groups, serum IL-17 level was statistically significant and also seen in comparison between T1DM+CP (group-1) versus T2DM+CP (Group-3, Table 2). In comparison with CP and diabetes, serum IL-17 Level was significantly seen in T2DM+CP group than T1DM+CP as shown in table 2. This could be both characteristic features of chronic inflammatory conditions which have common links with inflammatory mediators and pathogenesis. In contrast to our study, Techatanawat S et al, studied the relationship between serum IL-17A and type 2 DM or periodontitis showed that there was no statistical correlation [2].

In our study, the CP group had significant correlation with IL-17A protein when compared with healthy groups. This was agreed with Ozcave et al, found significant correlation of IL-17A level between CP and healthy groups [16].

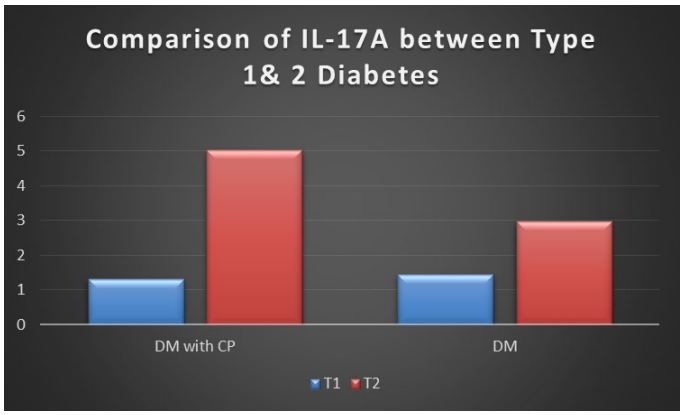

Figure 2: Inter group comparison of IL-17A protein.

Another study which was done by Oda et al, suggested that higher levels of IL-17A seen in patients with CP than gingivitis [17]. We had expected to see synergistic effects of CP & DM on the level of IL-17A cytokine; however both diabetes (T1DM & T2DM) without periodontitis had low levels of mean IL-17A protein when compared with CP plus diabetes. Although the role of IL-17A in chronic periodontitis has been proved in recent studies, our study showed no significant correlation with or without diabetes or with or without periodontitisas shown in table 2. IL-17A levels showed statistically significant ($p<0.05$) when compared between intergroups (Group -1 versus Group-3 and Group-2 versus Group-4) as shown in table 2. In contrast to our study, Roohi A et al, studied the serum IL-17 and IL-23 levels in type 1 & 2 diabetes patients and demonstrated that there was no association with type 1 and type 2 diabetes but TGF- levels were lower in type 1 diabetic patients [18].

Clinical parameters of chronic periodontitis (PPD, CAL and Gingival Index) were statistically significant when compared between the groups (Table 2,3&4). In our study, correlation of clinical parameters of all groups showed no statistically difference except for the mean of PPD (probing pocket depth) in group-2 ($r=0.360$). Clinical attachment level and gingival index were not correlated with IL-17A protein in all groups. This was consistent with a study done by Ozcaka et al., reported that clinical parameters (CAL, PPD) were not correlated with serum IL-17A level of CP patients [19]. In contrast to our study, Lester et al demonstrated that tissue concentration of IL-17A cytokine was correlated with mean CAL of CP patients [20]. They explained that it could be due to IL-17A production more locally adjacent to inflamed sites in response to bacterial challenge; this made a positive correlation compared with systemic (serum or plasma) level.

The Limitation of our study was less numbers of patients included in each group. Secondly, either controlled or uncontrolled diabetes patients were included in this study. This could lead to the serum IL-17A variation bias with glycemic status in both diabetes groups. Third, the patients were selected from the same zone of location; this could mislead the genetic variation. However, within the limitations, our study showed significant levels of serum IL-17A cytokine seen in chronic periodontitis with type 2-diabetes and also in CP patients, indicating the possible importance of serum IL-17A in disease pathology of chronic periodontitis with diabetes.

Conclusion

The present study demonstrated that there was a significant level of serum IL-17A in chronic periodontitis with type 2-diabetes and also in chronic periodontitis of the south Indian population. Further studies with large sample size might address this issue to give an evidence based overview of this serum IL-17A and chronic periodontitis.

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