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Research Article

Evaluation of Serum IL-17A Levels in Diabetes with Chronic Periodontitis Patients

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Abstract: IL-17A cytokine is a most studied member of the IL-17 cytokine family and its increased production is associated with autoimmune disease and chronic inflammation including periodontitis. This study was aimed to evaluate the serum IL-17A levels in chronic periodontitis patients with or without diabetes. The study was carried out in 168 subjects and consisted of 6 groups wherein group 1 consisted of 28 Type 1 diabetes patients with periodontitis, group 2 consisted 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 and analyzed by using ELISA kit. 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). The serum IL-17A is significantly high in chronic periodontitis and type 2 diabetes with chronic periodontitis.

Keywords: Serum IL-17A, Chronic Periodontitis, Type 1 Diabetes, Type 2 Diabetes.

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1. 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.

2. 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.

Inclusion Criteria	Exclusion Criteria
Periodontitis patients	**Periodontitis patients**
1. Clinical attachment loss more than 3 mm in at least six sites	1. Smokers
2. Pocket probing depth (ppd) more than 4 mm at least six sites	2. Existing orthodontic therapy
3. Bleeding on probing must be there in more than 30% of sites	3. Aggressive periodontitis, General Health problems (Hepatitis, HIV infection, Chemotherapy), pregnancy, lactation, and non-Indian races.
Type 1 & 2 diabetes	**Type 1 & 2 diabetes**
1.Both male or female patients, age group between 30 -44 years	1. Above 50 years of Age
2. Those who have already been diagnosed with Type 1 or Type 2 diabetic irrespective of controlled or uncontrolled glycemic status were taken for the study	2. Excluding of other systemic diseases

For the diabetic patients, the following parameters were recorded such as the presence of clinical symptoms (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.

2.1 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.

3. STATISTICAL ANALYSIS

The statistical comparison of all the variables between the groups was done by Kruskal 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.

4. 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 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).

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 1 Comparison serum IL-17A levels between the groups using Kruscal Wallis ANOVA. Overall comparison of IL-17A levels were significantly seen with p value of >0.001. Group 3 (T2DM+CP) patients had a high mean value (5.02±1.34) of IL-17A. (T1DM=Type 1 diabetes, CP=Chronic periodontitis, T2DM=Type 2 diabetes, Control=healthy patients (No diabetes and periodontitis).

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

Group & Sample total numbers		IL-17A Mean Rank	Sum of Ranks	Mann-Whitney U	z	P value
T1DM +CP (Group 1) vs Group 2	28	26.29	736	330	-1.02	0.308
		30.71	860			
T2DM+CP vs (Group 4)	28	38.34	1073.5	116.5	-4.518	0.001
		18.66	522.5			
Group 5 vs Group 6	28	41.75	1169	21	-6.087	0.001
		15.25	427			
CP (Group 1 vs (Group 3)	28	14.98	419.5	13.5	-6.21	0.001
		42.02	1176.5			
Group 2 vs Group 4	28	17.82	499	93	-4.905	0.001
		39.18	1097			
Group 1 vs Group 6	28	30.21	846	344	-0.791	0.429
		26.79	750			
Group 2 vs Group 6	28	32.39	907	283	-1.795	0.073
		24.61	689			
Group 3 Vs Group 6	28	42.13	1179.5	10.5	-6.26	0.001
		14.88	416.5			
Group 4 Vs Group 6	28	40.45	1132.5	57.5	-5.49	0.001
		16.55	463.5			
Group 5 Vs Group 6	28	41.75	1169	21	-6.087	0.001
		15.25	427			

Table 02: Inter group Comparison of IL-17A using Mann-Whitney U test. When subgroup analysis, there was significant level of serum IL-17A levels except T1DM +CP (Group 1) vs Group 2, Group 1 vs Group 6 and Group 2 vs Group 6. Type 1 diabetes with or without CP had no significant level of IL-17A. (T1DM=Type 1 diabetes, CP=Chronic periodontitis, T2DM=Type 2 diabetes, Control=healthy patients (No diabetes and periodontitis.

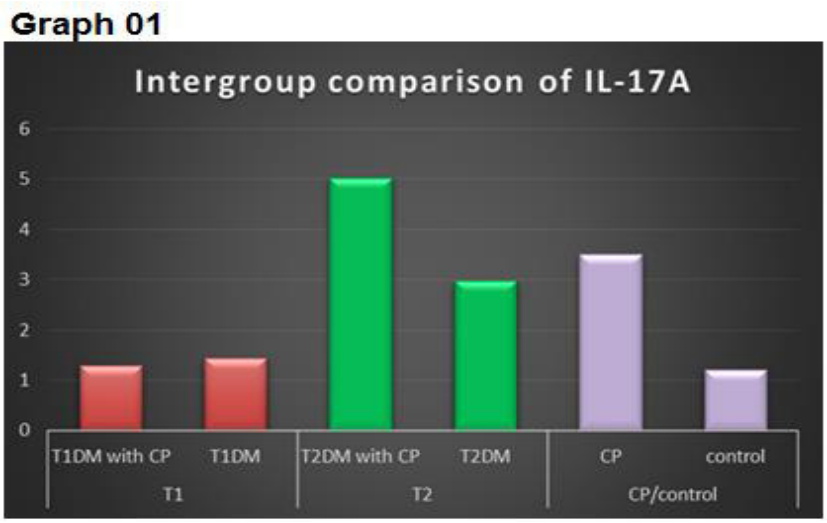
On evaluating the clinical parameters, there was a significant difference in probing pocket depth (PPD) between the groups (table 3), with group-5 (CP) had significantly high mean value of PPD (7.48±1.03) followed by group-3 (T2DM+CP) (6.63±0.90) and lowest in group-4 (2.75±0.16) (only T2DM) with p value (p<0.001). 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). 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 3: Correlation between serum IL-17A and Clinical parameters (Pearson correlation coefficient

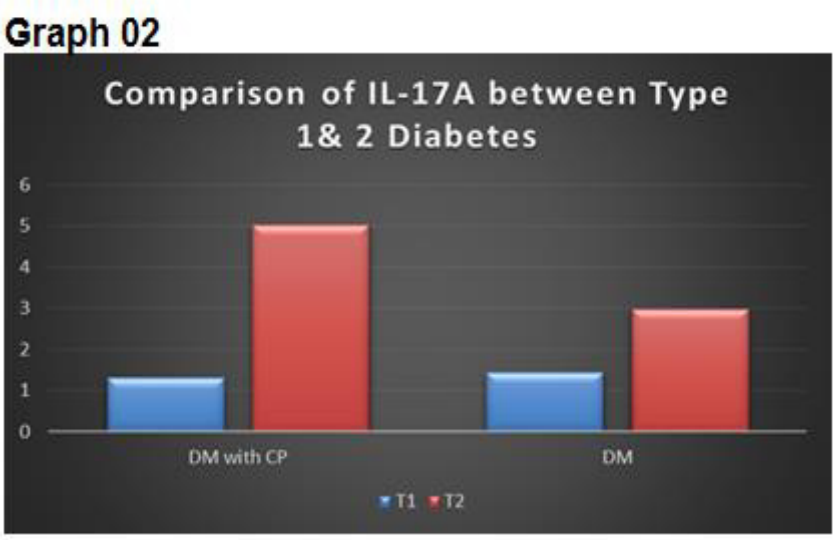
Group		IL-17A		
		PPD	CAL	Gingival Index
T1DM +CP (Group 1)	r value	0.095	-0.2	-0.202
	p value	0.632	0.307	0.303
T1DM (Group 2)	r value	0.111	-0.307	-0.307
	p value	0.573	0.112	0.112
T2DM+CP (Group 3)	r value	0.172	0.061	-0.036
	p value	0.383	0.759	0.855
T2DM (Group 4)	r value	0.36	-0.085	-0.085
	p value	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

Table 3 Correlation between serum IL-17A and Clinical parameters (Pearson correlation coefficient). When comparing the correlation of IL-17A cytokine with clinical parameters (PPD=Probing pocket depth, CAL=Clinical attachment level, GI=Gingival index) only group 4 (T2DM) had significant association. (T1DM=Type 1 diabetes, CP=Chronic periodontitis, T2DM=Type 2 diabetes, Control=healthy patients (No diabetes and periodontitis).

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 3).



Graph 1: Inter group comparison of IL-17A protein showed group 3 and 4 (T2DM+CP) and only T2DM had significant mean level. (T1DM=Type 1 diabetes, CP=Chronic periodontitis, T2DM=Type 2 diabetes, Control=healthy patients (No diabetes and periodontitis)



Graph 2: Inter group comparison of IL-17A protein between type 1 and 2 diabetes showed that type 2 diabetes had significant levels of IL-17A. (T1DM=Type 1 diabetes, CP=Chronic periodontitis, T2DM=Type 2 diabetes, Control=healthy patients (No diabetes and periodontitis)

5. DISCUSSION

The present study evaluated the serum IL-17A levels in type 1 and type 2 diabetic patients with and without chronic periodontitis. The results revealed that, there was a significant difference in the IL 17 levels between the six groups with the highest level in Type 2 diabetic patients with chronic periodontitis followed by chronic periodontitis and type 2 diabetic patients without chronic periodontitis. The lowest levels were observed in type 1 diabetic patients with or without periodontitis and the healthy controls. The results revealed that, Type 2 diabetic patients with chronic periodontitis have significantly higher serum IL 17A than type 2 diabetic patients without chronic periodontitis. Similar to our results, Techatanawat et al[2] have reported that diabetic patients with chronic periodontitis had significantly higher salivary IL 17 A levels than diabetics without chronic periodontitis. On the contrary, they couldn't find any significant difference in the serum IL 17 between diabetes with and without periodontitis. Periodontitis is considered as one of the complications of type 2 diabetes. Though diabetes is considered as a metabolic disorder; inflammation is also playing a key role in its complications. Roohi et al[13], when comparing the salivary IL 17 levels between type 2 diabetic patients with and without complications, also observed that the levels were significantly high in diabetic patients with complications. Similar results were reported by Parhi et al in a study done in the Indian population as well[14]. On the contrary Afzal et al [15]reported significantly less serum IL 17 level in diabetic patients with complications (retinopathy) as compared to healthy controls. The cells in periodontal tissues, including macrophages, mast cells, neutrophils, natural killer T (NKT) cells, gamma-delta (γ δ) T-cells, and periodontal ligament cells can also produce this IL-17A cytokine. Therefore, periodontal inflammation could also induce increased IL-17 levels. It has been reported that, diabetes influences dysbiosis of periodontal microflora through the IL 17 mediated pathway (Xiao et al)[16]. They have observed that blockage IL 17 with IL 17 antibody reduces the pathogenic potential periodontal pathogens in diabetic animal models. The increased level of IL17 observed in the present study also supports the role of IL17 in the dual relationship between type 2 diabetes and periodontitis. As per the results of the present study, as compared to healthy controls the serum IL17 levels were significantly higher in type 2 diabetic patients but not with type 1 diabetics. Similar to our results Chen et al[17] observed an elevated serum IL 17 levels in type 2 diabetic patients as compared to healthy controls. IL 17 is found to have an important role in pathogenic mechanisms of diabetes by many researchers. Bradshaw et al, showed that monocytes isolated from T1DM patients induced more IL-17 producing T cells compared with healthy controls[18]. They also observed significantly increased IL-17 producing T cells in peripheral blood of patients with long standing T1DM. 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[19]. Our results are not fully corroborating with previous results. The possible explanation could be that, most of the previous studies are either in vitro or animal studies. There can be multiple factors influencing the serum cytokines levels and needs further research in deducing these contradictory observations. The results of the present study also revealed that, there was significantly high serum levels IL 17 in patients with chronic periodontitis as compared to healthy controls. This is in agreement with Ozcave et al[20] who found a significantly high IL-17A level in chronic periodontitis as compared to healthy groups. Arief et al[21] and Vernal et al[9] also reported similar results. Another study which was done by Oda et al[22] reported higher levels of IL-17A in patients with CP than gingivitis. In our study, the CP group had significant correlation with IL-17A protein when compared with healthy groups. Takahashi et al[23] have reported that IL 17 is produced at the periodontal tissues and it plays an important role in the pathogenesis of periodontitis. In the present study, when the IL 17 levels were correlated with clinical parameters such as PPD, CAL and BI there was no significant correlation with any of the clinical parameters. This was consistent with a study done by Ozcaka et al[20] and Arief et al[21] who reported that the clinical parameters (CAL, PPD) were not correlated with serum IL-17A level of CP patients. In contrast to our study, Nainee et al[24] demonstrated that Gingival Crevicular fluid (GCF) concentration of IL-17A cytokine was correlated with clinical parameters of chronic periodontitis patients. The local

production of IL-17 A by the cells from the inflammatory periodontal tissues in response to microbial challenge at the local site might be the possible reason for these contradictory observations between serum and GCF. An interesting observation of the present study was that, there was no significant difference in the serum IL 17 levels between type 1 diabetes with and without periodontitis. Even Though the chronic periodontitis patients showed higher serum IL levels, the patients with type 1 diabetes with chronic periodontitis had only low levels IL 17 similar to healthy controls. IL 17, which is an immunologist modulators cytokine, is reported to have an important role in type 1 diabetes as well as chronic periodontitis. Surprisingly the present study showed that, type 1 diabetes with or without periodontitis did not have any significant difference in the serum IL17 levels in comparison with healthy controls. But the present study showed contradictory results and it needs further research to explain the possible mechanisms. It may suggest that, inflammatory changes are not well reflected in the serum in case of type 1 diabetes. Further studies are warranted in this direction. While comparing the IL 17 serum levels between type 1 and type 2 diabetes the present study revealed that it is significantly high in type 2 as compared to type 1. On the contrary Roohi et al[14] could not find any significant difference in the serum IL 17 levels between type 1 and type 2 diabetes. In diabetes mellitus there is an imbalance between Th17 and Treg cells leading to an increase in the Th17 cell content and IL-17 level (Zak et al)[25]. The serum IL 17 level is significantly high in type 2 diabetic patients with chronic periodontitis as compared to type 1 diabetic patients with chronic periodontitis. Inflammation is considered as one of the factors in the pathogenesis of both type 1 and type 2 diabetes[26]. Our results point out that systemic inflammation may not be prominent in type 1 diabetes as compared to type 2 diabetes. Even though IL17 is considered as a key cytokine in the pathophysiology of type 1 and type 2 diabetes, the contradictory observations with respect to its serum level points towards the different pathogenic mechanisms involved in both the diseases. Highest level of IL17 was observed in type 2 diabetes with chronic periodontitis followed by chronic periodontitis. These results suggest that chronic periodontitis is one of the major factors leading to systemic inflammation and the chronic periodontitis along with type 2 diabetes can exaggerate the inflammatory systemic burden. Both the diseases have characteristic features of chronic inflammation and have common links with inflammatory mediators. The major limitation of our study was the fewer numbers of patients included in each group. Secondly, both controlled and uncontrolled diabetes patients were included in this study. This could lead to the serum IL-17A variation with glycemic status in both diabetes groups. Moreover this could also have resulted in inclusion of patients with other un noticeable complications of diabetes. Since serum level of the cytokine was estimated, while interpreting the results these factors also need to be considered. Third, the patients were selected from the same zone of location; this could mislead the genetic variation. However, within the limitations, the present study showed significantly high levels of serum IL-17A cytokine in type 2 diabetes with and without chronic periodontitis as well as in chronic periodontitis patients, indicating the possible importance of serum IL-17A in disease pathology of chronic periodontitis and type 2 diabetes.

6. CONCLUSION

The serum IL-17A was significantly high in type 2 diabetes with chronic periodontitis patients. These results suggested that chronic periodontitis is one of the major factors leading to systemic inflammation and chronic periodontitis along with type 2 diabetes can exaggerate the inflammatory systemic burden. Both the diseases have characteristic features of chronic inflammation and have common links with inflammatory mediators. Further studies with large sample size are required to elucidate the role of this cytokine in interrelationships of chronic periodontitis and diabetes mellitus

7. AUTHOR CONTRIBUTION STATEMENT

Dr. P.K. Sasikumar, conceptualized and gathered the data with regard to this work. Dr.Sheeja S Varghese, Guided the study and Dr.Sakthisaranya Devi analyzed these data and necessary inputs were given towards the designing of the manuscript. All other authors discussed the methodology and results and contributed to the final manuscript

8. CONFLICT OF INTEREST

Conflict of interest declared none.

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