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Estimation of soluble Triggering Receptor Expressed on Myeloid cells-1 (sTREM-1) and its influence on expression of IL-10 in Periodontal Health and Disease

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ABSTRACT

Aim: To estimate the levels of soluble triggering receptor expressed on myeloid cells-1(sTREM-1) and interleukin-10 (IL-10) and to assess the influence of sTREM-1 on the expression of IL-10 in periodontal health and diseases.

Materials and Methods: Sixty six subjects were allocated into four study groups –clinically Healthy periodontium (H) (n=17), Generalized Plaque induced Gingivitis (GPIG) (n=16), Generalized Chronic Periodontitis (CP) (n=17) and Generalized Aggressive Periodontitis (AP) (n=16). Clinical parameters such as probing pocket depth (PPD), clinical attachment level (CAL), plaque index (PI) and modified sulcular bleeding index (mSBI) were recorded.GCF samples were collected and analysis was done using ELISA for the estimation of IL-10 and sTREM-1 levels.

Results: The mean sTREM-1 level in the GCF was significantly higher in the AP group (600.52 ± 86.57 pg/ml) followed by CP (482.81±84.64 pg/ml) and GPIG (259.64 ±44.99 pg/ml) when compared with H group (152.88±59.28 pg/ml). On the contrary, the highest mean concentration of IL-10 was obtained in GPIG (25.96±5.90 pg/ml) followed by CP (11.78±3.91 pg/ml) andAP (8.23±1.92 pg/ml) and least levels in the H group (8.045±1.58 pg/ml). sTREM-1 levels were negatively correlated with IL-10 levels but not statistically significant.

Conclusions: The GCF sTREM-1 concentration was higher in periodontal diseases when compared to healthy samples. IL-10 levels were negatively correlated withsTREM-1 levels. These results, underscore the pro-inflammatory role of sTREM-1 and the protective anti-inflammatory role of IL-10 in periodontitis.

KEY WORDS*: sTREM-1, Interleukin-10, Pro inflammatory, Anti-inflammatory, Biomarkers, Peridontitis*

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INTRODUCTION

The Toll-like receptors (TLRs) are essential to activate the innate inflammatory response in periodontitis with the consequent coordination of the T-helper (Th) and regulatory T (Treg) cell responses.[1]A significant factor in this orchestration is Triggering receptor expressed on myeloid cells (TREM-1)expressed on the surface of myeloid immune cells such as polymorphonuclear neutrophils and a subset of monocytes.[2]The synergism between the activation of TREM-1 and TLR results in exaggerated release of pro-inflammatory cytokines, including tumor necrosis factor (TNF)-α, interleukin (IL)-1β, and inhibition of anti-inflammatory cytokines such as IL-10.[3]

sTREM-1 is a subtype of secreted TREM-1 which is expressed in the laterstages of myeloid cell differentiation.It can be released either from shedding of surface-expressed TREM-1 molecules, proteolytic cleavage or through the translation of an alternative splice form of TREM-1.[4,5]In the early phase of infection, the engagement of Pattern Recognition Receptors (PRRs) by microbial components induce upregulation of sTREM-1. The activation of sTREM-1 stimulates the production of IL-8 and Monocyte chemotactic protein, thereby inducing neutrophil degranulation and oxidative burst.[6]Since sTREM-1 is released during the course of infection and inflammation, it can be utilized as a potential marker of systemic inflammation.[7]As sTREM-1 can be conveniently measured in various biological fluids including saliva and GCF, it has the potential to serve as a biomarker for the severity of periodontal inflammatory diseases.[8]

IL- 10, a major regulator of innate immune responseis secreted by alternatively activated macrophages, B lymphocytes, and dendritic cells. The Tregs are a further important source of IL-10.[9]It regulates the cytokines expression from myeloid origin, with major functional alterations on the activation and maintenance of immune response. Both over-expression and under-expression of IL-10 have been associated with several inflammatory and autoimmune diseases. Through inhibition ofinterferon-γ (IFN- γ) production, IL-10 drives the Th1/Th2 balance towards the Th2 phenotype.[10]

Periodontal inflammation may be concerned with both increased inflammation-promoting molecules like sTREM-1 andreduced inflammation-protecting molecules like IL-10 and such a dual impact is probably the underlying element in periodontal disease progression. However, the mechanism behind how this balance works in various stages of periodontitisis unclear.[11]Although the systemic distribution of sTREM-1 and its importance have been demonstrated in several systemic diseases, evidence on its association with periodontal disease is limited.[12-14]Also there is insufficient data on the simultaneous changes in “pro-inflammatory” versus “anti-inflammatory” cytokinesin GCF of periodontitis subjects. The study on the influence of these molecules will provide useful insights into periodontal pathogenesis and improve diagnostic and therapeutic approaches for advanced periodontitis.

The current study therefore aimed to assess the levels of sTREM and IL-10, so as to provide a better understanding of these biomolecules, in the immune-inflammatory process in Healthy (H), Generalized Plaque Induced Gingivitis (GPIG), and Generalized Chronic Periodontitis (CP) and Generalized Aggressive Periodontitis (AP) patient cohorts. Understanding this association may

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potentiate our ability, to utilize the levels of these biomolecules in GCF to be either diagnostic or prognostic markers in the management of periodontal disease.

MATERIALS AND METHODS

This cross-sectionalstudy was approved by the ethical committee ofthe institutional review board of SRM University(SRMDC/IRB/2018/MDS/No.501).The study was conducted at the Department of Periodontics, SRM Dental College, Chennai from January 2019 to August 2019. The purpose and procedure of the study were fully explained to all the participants and written informed consent was obtained.

A total of 66 patients were recruited fulfilling theinclusion criteriaand allotted into four study groups asfollows: Group I: Patients having (mSBI) < 0.2 and PPD of < 3 mm and no clinical attachment loss (17 participants)(H); Group II: Patients with PPD <3 mm and no clinical attachment loss (16 participants)(CGIP): GroupIII: Based on American Academy of Periodontology (AAP) 1999 classification- patients with PPD>5mm and clinical attachment loss >3mm(17 participants); Group IV: Based on American Academy of Periodontology (AAP) 1999 classification- patients with rapid attachment loss and bone destruction, amount of microbial deposits inconsistent with disease severity, generalized proximal attachment loss affecting at least 3 teeth other than 1st molars and incisors (16 participants). The protocols followedin the study are given in the flow chart [Figure 1].

Patientswith history of systemic diseases or conditions, history of tobacco usage and alcohol consumption, history of periodontal thearpy in the past 6 months, history of antibiotic usage in the past 6 months, and patients who were not willing to participate in the study were exempted from the study.

COLLECTION OF GCF

Following recruitmentinto the study, clinical parameters were recorded. To prevent contamination of the GCF samples with blood, the samples were collected on the morning of the subsequent day, 3-4 hours after breakfast. The subjects were made to sit comfortably in an upright position and the area to be sampled was isolated, supragingival plaque was gently removed with a curette without disturbing the marginal gingiva and slightly air dried to avoid salivary contamination. (Group I&II- samples were collected from 5 different sites, Group III & IV -sites with ≥ 5 mm PPD with concomitant CAL of ≥ 4mm). Micro-capillary pipettes [5µl micro-capillary pipettes, Sigma Aldrich] were gently inserted into the sulcus, care was taken not to induce bleeding, and the pipettes were placed in the collection sites for a maximum of 10 minutes. The deepest sites were chosen for GCF collection and the samples from those sites were pooled so that 2-3 µl was obtained. The collected GCF was transferred to Eppendorf tubesand stored at -80◦C, until analysis.

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ESTIMATION OF sTREM-1 AND IL-10

The GCF levels of sTREM-1 and IL-10 were estimated using commercially available ELISA kitsprocured from Ray Biotech Inc, USA. The assays were utilized according to manufacturer's instructions.

STATISTICAL ANALYSIS

The Kolmogorov-Smirnov and Shapiro-Wilks tests revealed that the variables did not follow normal distribution. Therefore, non-parametric methods were applied. To compare thevalues between groups Kruskal Wallis test was applied followed by Bonferroni adjusted Mann Whitney post hoc tests for multiple pairwise comparisons. To know the relationship between variables Spearman Rank correlation coefficient was calculated. The collected data were analysed using IBM, SPSS software 23.0 version. Significance level was fixed as 5% ($\alpha = 0.05$).

RESULTS

Among the total study population, 26 (39.4%) were males and 40 (60.6%) were females. Mean age of individuals who participated in the study was 29.85± 11.97 years for males and 31.23 ± 12.69 years for females. The clinical parameters (PI, PPD, CAL, mSBI) recorded among the four groups varied and were statistically significant (Table 1).The correlation between the clinical parameters and the biochemical variables using Spearman Rank correlation co-efficient given in table 2 shows that IL-10 had a negative correlation withPPD and CAL which was statistically significant (0.007* &0.021) and a positive correlation with the PI scores and mSBI scores but not statistically significant (0.193 & 0.615). sTREM-1 had strong positive correlation with PPD, CAL and mSBI scores (0.000*), and a positive correlation with PI scores which was not statistically significant (0.655). Further, sTREM-1 had a negative correlation with IL-10 concentration but not statistically significant (0.377).The inter group comparison of IL-10 and sTREM-1 levels among the 4 study groups in table 3 demonstrates statistically significant difference in both IL-10 and sTREM-1 levels (<0.001*). The mean levels of IL-10 was the highest in Gingivitis (25.96 ± 5.90 pg/ml) followed by Chronic Periodontitis (11.78 ± 3.91pg/ml) and Aggressive Periodontitis group (8.23±1.92 pg/ml) and the lowest concentration was seen in the clinically healthy periodontium group (8.04±1.58 pg/ml). The highest mean levels of sTREM-1 was seen in Aggressive Periodontitis group (600.52±86.57 pg/ml), followed by Chronic Periodontitis (482.81±84.64 pg/ml) and Gingivitis (259.64±44.99 pg/ml) group and the lowest levels were observed inclinically Healthy periodontium group (152.88±59.28 pg/ml).The scatter plot (figure 2) shows that the concentration of sTREM-1 increased with the disease progression with the highest concentration seen in patients withGeneralized Aggressive Periodontitis and least concentration seen in Healthy periodontium.

DISCUSSION

Periodontitis occurs as a collaborative result of multiple etiological and risk factors, with periodontopathogens and host immune response being the paramount elements. A determining factor that co-ordinates periodontal homeostasis as well as the inflammatory changes leading to

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periodontal disease progression is the cytokine network in the periodontium consisting of diverse pro-inflammatory and anti-inflammatory cytokines. It influences the host immuno-inflammatory response as it partakes in the initial wave of response opposed to micro-organisms, acts as a stimuli at gingival barrier to recruit various immune cells, and establishes a link between immune cells and cells in the periodontal micro-environment thereby orchestrating the severity, extent, and nature of immune response.[15]Therefore, it would be appropriate to evaluate the localized pro- and anti-inflammatory cytokines in predicting periodontal disease progression, to aid in diagnosis, and prognosticate therapeutic effects.

The current study primarily aimed at assessing the quantitative levels of pro-inflammatory sTREM-1 and anti-inflammatory IL- 10, their association in healthy periodontium,gingivitis, generalized chronic periodontitis and generalized aggressive periodontitis and to evaluate the influence of sTREM -1 on the expression of IL – 10. sTREM-1 has been widely studied in various systemic disorders as a possible diagnostic and prognostic marker but its data on periodontal disease is scarce.[12-14]Contrarily, IL-10 is a well-established anti-inflammatory cytokine having pronounced effects in the periodontium.[10] Therefore, the present study highlights the significance of analyzing the dynamics that regulate the periodontal homeostasis using sTREM-1 and IL-10 amidst pro and anti-inflammatory cytokines.

All the GCF samples had detectable levels of sTREM-1 and IL-10, as patients were categorized and included asclinically healthy gingiva and did not have pristine gingiva. In the current study, the mSBI values positively correlated with sTREM-1 concentrations among the 4 study groups and this correlation was statistically significant. These findings were in accordance with the study by Chen et al in who found that there was a strong association of TREM-1 expression levels with the levels of “red complex” bacterial accumulation and the associated inflammatory response.[16] Bostanci et al in 2013 also suggested a similar correlation with severity of periodontitis and elevated GCF sTREM-1 levels.[17]

Interestingly, the sTREM-1 levels had no significant correlation with the plaque index values and this finding could be attributed to the bacterial proteolysis of sTREM-1 or dueto the progession towards chronic inflammation which resembles the study by Bisson et al in 2012.[18] The positive correlations with PPD and CAL, also indicate that sTREM-1 levels are associated with the severity of periodontal tissue destruction which was demonstrated in earlier studies.
Recently,Surabhigigras et al in 2017 demonstrated increased GCF sTREM-1 levels with the periodontal disease severity.[19]The results of our study also corroborated this finding as GCF sTREM-1 levels were significantly elevated in chronic and aggressive periodontitis when compared to healthy tissues.Further, even though the Aggressive Periodontitis group had higher levels of sTREM-1 compared to the Chronic Periodontitis group, the difference was statistically insignificant which is in conformity with the study by Willi et al in 2014.[20]

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IL-10 is a pleiotropic molecule known for its immunoregulative properties playing a crucial role in the pro and anti-inflammatory balance of cytokines.Goutoudiet al suggested the role of IL-10, in modulating immune and inflammatory responses, B cell activation and the suppression of tissue destruction.[21]The total levels of GCF IL-10 in the current showed significant negative correlation with PPD and CAL values, and no correlation with PI and mSBI scores which alluded that the levels of IL-10 decreased with the increase in values of PPD and CAL. The IL-10 levels were the highest for gingivitis group followed by chronic periodontitis and aggressive periodontitis groups with the lowest levels in healthy controls. This shows that patients with advanced periodontitishave lesser IL-10 levels compared to less severe groups. Thus the role of IL-10 in periodontitis, can be attributed to the stimulation of protective antibody production and downregulation of the product ion of monocyte derived proinflammatory cytokines.

Further, the correlation of sTREM-1 to IL-10 was explored and the sTREM-1 concentration in our study was seen to be negatively correlated with IL-10 but was not statistically significant which might be due to their antagonistic effect. Wu et al in 2011stated that TREM-1 functions as an inflammatory amplifier by modulating TLR signaling and Th1/Th2 responses. The blockade of TREM-1 inducedreduced Th1 responses (IL-1b, IFNc, IL-6), reduced neutrophil infiltration and TLR activation, but increased Th2 responses (IL-4, -5 and -10).[22]Similarly, in a recent study by Ismo Raisanenet al in2019,positive correlation of TREM-1 with salivary aMMP-8 levels, a pro-inflammatory marker was demonstrated.[23]On the other hand, Schenk et aldemonstrated that upon stimulation with TGF-β and IL-10 monocytes down-regulated the expression of TREM-1 synergistically.[24]The results obtained from our study were in conformity with the above-mentioned studies suggesting the negative correlation of sTREM -1 with IL- 10.

Conjointly, the synergy of TLR and TREM-1 results in potent inflammatory responses. Interestingly, the pro - and anti- inflammatory cytokines affected by TREM-1 also modulated its cell surface expression, suggesting the possible existence of an autocrine loop designed to sustain TREM-1 signaling. A dynamic interplay between pro- and anti- inflammatory cytokines by virtue of mediators of TLR signaling allows for the maintenance of health in periodontium.[25] However, in cases of periodontitis, this equilibrium is lost leading to destruction of periodontium. This fact is braced by the study of Paknejad et al in 2016 where it was suggested that sTREM-1 could be responsible for periodontal breakdown leading to tissue destruction and for this reason it could be a potential diagnostic marker in periodontitis.[26]
Further studies at molecular level as well as assessment of gene expressions should be carried out to have a better perception on the synergism of TLR signaling and sTREM-1 production and its possible association with IL-10. Moreover, assessment of these biomarker levels after periodontal therapy will help us in understanding the prognostic values of these cytokines in various phases of periodontal diseases for the development of new clinical interventions, in

which targeted activation or blockade of TREM-1 and IL-10 may help in maximizing the efficacy of existing treatments.

CONCLUSION

Our findings demonstrated that both sTREM-1 and IL-10 have the potential to be used as diagnostic biomarkers to track the severity of the diseased conditions and their potential implications in the diagnosis of untreated periodontitis. Comprehension of these specific host and bacterial biomarkers using a chair side diagnostic test could allow for easier early identification of susceptible patients to initiate preventive therapeutic intervention before the occurrence of irreversible tissue destruction. Future long-term studies on large and diverse patient population are required to validate these findings for the application of these biomarkers to the clinical arena.

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Conflicts of interest: The authors declare no conflicts of interest
Sources of support: Nil

FIGURE 1

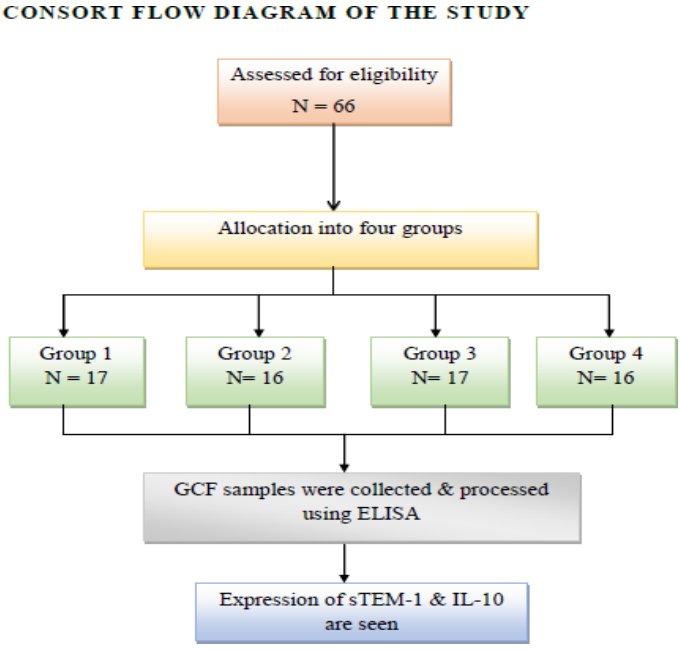

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FIGURE 2: SCATTER PLOT SHOWING CORRELATION BETWEEN IL-10 AND sTREM-1.

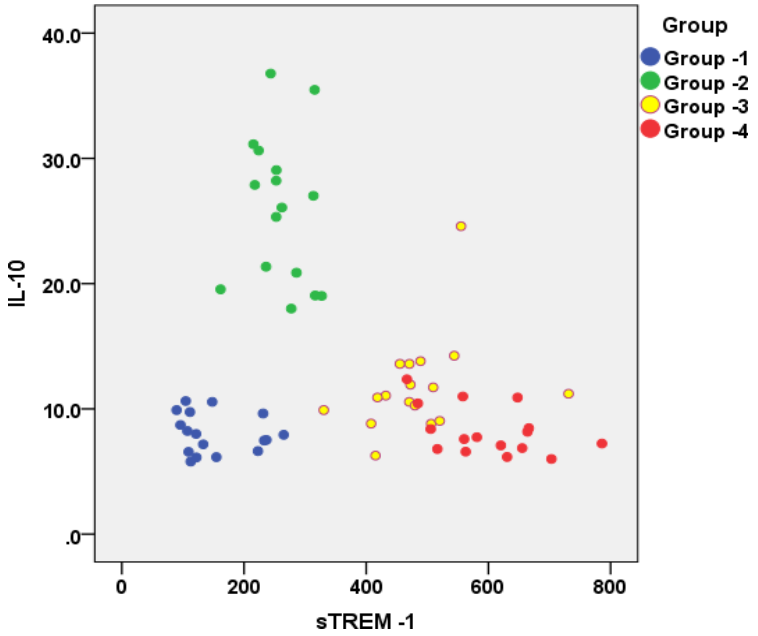

TABLE-1: COMPARISON OF CLINICAL PARAMETERS BETWEEN GROUPS

	PI	PPD (mm)	CAL (mm)	mSBI
P value	<0.001*	<0.001*	<0.001*	<0.001*
GROUP I	1.49±0.21	2.52±0.20	0.00±0.00	0.00±0.00
GROUP II	1.43±0.19	2.42±0.21	0.00±0.00	0.91±0.19
GROUP III	2.42±0.29	5.72±0.40	3.78±0.69	4.15±0.23
GROUP IV	1.28±0.21	6.56±0.36	4.95±0.40	4.01±0.12

TABLE 2: CORRELATION OF THE CLINICAL PARAMETERS WITH THE BIOMARKERS IL-10 AND sTREM-1 (SPEARMAN RANK COORELATIONCOEFFICIENT)

		PI	PPD	CAL	m SBI	IL-10	sTREM -1
PI	Correlation	10	0.046	0.029	0.269	0.162	0.056
	P-Value	-	0.714	0.816	0.029*	0.193	0.655
	N	66	66	66	66	66	66
PPD	Correlation	0.046	10	0.91	0.728	-0.327	0.781
	P-Value	0.714	-	0.000*	0.000*	0.007*	0.000*
	N	66	66	66	66	66	66

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	Correlation	0.029	0.91	10	0.791	-0.285	0.88
	P-Value	0.816	0.000*	-	0.000*	0.021	0.000*
CAL	N	66	66	66	66	66	66
	Correlation	0.269	0.728	0.791	10	0.063	0.81
	P-Value	0.029*	0.000*	0.000*	-	0.615	0.000*
m SBI	N	66	66	66	66	66	66
	Correlation	0.162	-0.327	-0.285	0.063	10	-0.111
	P-Value	0.193	0.007*	0.021*	0.615	-	0.377
IL-10	N	66	66	66	66	66	66
	Correlation	0.056	0.781	0.88	0.81	-0.111	10
	P-Value	0.655	0.000*	0.000*	0.000*	0.377	-
sTREM-1	N	66	66	66	66	66	66

TABLE 3: COMPARISON OF sTREM-1 AND IL-10 LEVELS AMONG GROUPS

Parameter	Group	N	Mean Rank	Mean pg/ml	Std. Dev	Chi Square value	p-Value
IL-10	Group 1	17	18.65	8.045	1.586	45.116	<0.001*
	Group 2	16	58.13	25.964	5.908		
	Group 3	17	37.76	11.783	3.913		
	Group 4	16	20.13	8.235	1.926		
sTREM-1	Group 1	17	10.53	152.887	59.280	55.844	<0.001*
	Group 2	16	23.88	259.644	44.997		
	Group 3	17	44.29	482.811	84.644		
	Group 4	16	56.06	600.520	86.578		