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Research Article

COMPARATIVE EVALUATION OF INTERLEUKIN-18 (IL-18) IN SUBJECTS WITH GINGIVITIS, GENERALIZED CHRONIC PERIODONTITIS AND HEALTHY INDIVIDUAL FOLLOWING NON - SURGICAL PERIODONTAL THERAPY

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ABSTRACT

Background: Interleukin-18 (IL-18) is an important regulatory cytokine in non-oral inflammation. It is a pro-inflammatory and tumor suppressive cytokine, which, due to its structure receptor family, and signal transduction pathways belongs to the IL-1 cytokine family. The aim of the present study was to determine the GCF levels of IL-18 in healthy, Gingivitis and Chronic Periodontitis subject pre and one month post scaling and root planing (SRP).

Materials and Methods: Study consisted of 60 subjectswho were divided into 3 groups i.e. Healthy, Gingivitis & Chronic periodontitis (CP) consisting of 20 subjects in each group.

Results: There was statistical significant difference between the levels of IL-18 in healthy and diseased group. A marked reduction was seen in all the clinical parameters ($p<0.001$) as well as in IL-18 levels ($p<0.001$) following non-surgical periodontal therapy (NSPT) in Gingivitis and Periodontitis group.

Conclusion: IL-18 could be a factor in progression of inflammation because it has chemotactic, pro-inflammatory, and osteoclastic properties. Increased IL-18 levels was seen with severity of the periodontal disease and its levels decreased following successful periodontal treatment.

INTRODUCTION

Periodontitis is a multifactorial disease and several risk components, such as environmental, metabolic, genetic, microbial, factors, aging and poor oral hygiene status are involved in the pathogenesis of the disease.[1]Chronic inflammation and cytokines have been suggested to play a pivotal role in destructive processes occurring in Periodontitis.[2] Many non-microbial factors stimulate (or modulate) synthesis of inflammatory cytokines, including environmental pollutants, shear stress, ultraviolet radiation, thermal injury, and hypoxic conditions. The cytokines, in turn, can induce changes in cellular growth or function, anti-oxidative effectors, heat-shock proteins, sodium excretion, hematopoiesis, and other responses. Thesemechanisms would be activated in direct response to the external stimulus, not as feed-back responses to a change in the internal environment.[3] Cytokine is a term derived from Greek roots meaning "to set cells in motion". Cytokines are intercellular signaling peptides (usually between 8 and 30 kDa in mass) that can act at any range (autocrine, paracrine, endocrine).[4]

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Cytokines are responsible for the maintenance of an intricate communication network between the homotypic and heterotypic cell types. Thus, cytokines play an important role in numerous biological activities including proliferation, development, homeostasis, regeneration, repair, and inflammation. Appropriately activated cells usually synthetize many different cytokines at the same time.[5] It has been postulated that appropriate cytokines production results in protective immunity, while inappropriate cytokine production leads to tissue destruction and disease progression.[6]

MATERIALS AND METHODS

Study Population and Study Group

The study was conducted as an Interventional Study Controlled Trial in 60 subjects, aged between 30-55 years visiting the regular OPD of Department of Periodontology, Subharti Dental College and Hospital, Meerut, Uttar Pradesh. The study was approved by Institutional Ethics Committee. The individuals were enrolled into three groups based on specific inclusion and exclusion criteria. Subjects included were diagnosed as Healthy (group 1), Gingivitis (group 2) and CP (group 3) showing a clinical and radiographic evidence of

bone loss. All participants provided written informed consent prior to their enrolment into the study.

Inclusion Criteria

The following inclusion criteria were used. Patients with1) age ranging from 30-55 years 2) Healthy subjects with no BOP, CAL and PPD ≤ 3 mm 3) CP subjects with PPD of ≥ 4 mm and CAL ≥ 3 mm with radiographic evidence of bone loss 4) Good systemic health.

Exclusion Criteria

Patients with 1) Aggressive Periodontitis (AP) 2) Patients on medications that effect periodontal status 3) Patients who have received periodontal therapy in preceding 6 months 4) Uncooperative patients 5) Medically Compromised patients 6) Pregnancy and lactating mothers.

Clinical Examination

All subjects underwent complete oral examination and full-mouth periodontal investigation was done. Presence of radiographic bone loss was considered to differentiate CP patients from other groups. Periodontal variables were recorded using a University of North Carolina periodontal probe (UNC 15, Hu-Friedy Chicago, IL).GCF sample was collected before SRP & after one month.

The following parameters were recorded at the baseline and one month post SRP:

Oral Hygiene Index – Simplified (OHI-S)
Probing Pocket Depth (PPD)
Clinical Attachment Level (CAL)
Bleeding on Probing (BOP)

GCF Collection

GCF sample was collected on the subsequent day of clinical examination. Only one site (Site with highest score) per subject was selected as sampling sites in Gingivitis and Periodontitis group. In Healthy group, to ensure adequate volume, GCF was pooled from multiple sites. The site selected was gently dried and supragingival plaque removed without touching the marginal gingiva. The area was isolated using cotton rolls to prevent saliva contamination, and GCF was collected by placing the microcapillary pipettes at the entrance of the gingival sulcus, gently touching the marginal gingiva. Each sample collection was allotted a maximum of 10 minutes. The GCF was immediately transferred to an airtight plastic vial and stored at -70°C, and later analyzed for IL-18 by ELISA kit Bostor Biological Technology Ltd, (USA).

Statisical Analysis

The analysis was performed by the Data Analysis software through SPSS 19. Paired 't' test was used to compare the level of IL-18 in group 2 & group 3. Unpaired 't' test was used to compare between different groups. Pearson's correlation test was used to evaluate correlation among GCF level of IL-18 and clinical parameters. P value<0.001 were considered as statistically significant.

RESULTS

During the course of the study there was no post-operative complications in any patient and none of the selected patients dropped out before the termination of the study. The data obtained was subjected to statistical analysis. Mean and standard deviation were estimated in all the 3 groups.The mean level of IL-18 was found to be highest in group 3 (174.2 ± 161.6 pg/ml) pre-operatively (49.9 ± 28.5 pg/ml) post-operatively. Lowest level of IL-18 was found in group 1 (36.8 ± 7.3 pg/ml) followed by group 2(59.7 ± 13.2 pg/ml) pre-operatively (46.9 ± 12.6 pg/ml) post-operatively (Table-1).

Table 1 Biochemical & Clinical comparative evaluation in all 3 groups at baseline & one month post scaling

*=P<0.05, stastistically significant

Variables	Control (n=20)	Gingivitis (n=20)			Chronic Periodontitis (n=20)		
		PRE-OP	POST-OP	P value	PRE-OP	POST-OP	P value
Oral hygiene index simplified OHIS	1.4 ± 0.3	2.8 ± 0.5	1.4 ± 0.2	<0.05*	3.6 ± 0.6	1.5 ± 0.3	<0.05*
Bleeding on Probing BOP (%)	--	35.1 ± 8.4	25.9 ± 5.4	<0.05*	83.3 ± 16.1	30.6 ± 12.7	<0.05*
Probing Pocket Depth PPD (mm)	1.8 ± 0.2	2.4 ± 0.2	1.7 ± 0.1	<0.05*	4.0 ± 0.7	2.5 ± 1.8	<0.05*
Clinical Attachment Loss CAL (mm)	--	--	--	--	4.3 ± 0.8	2.6 ± 0.3	<0.05*
IL-18(pg/ml)	36.8±7.3	59.7±13.2	46.9±12.6	<0.05*	174.2±161.6	49.9±28.5	<0.05*

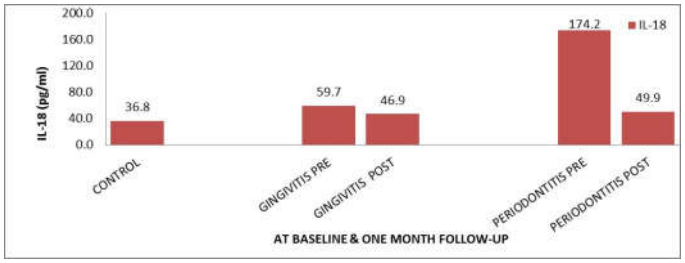

Fig 1 Shows a maximum value of IL-18 in Periodontitis group followed by Gingivitis and least in Healthy group

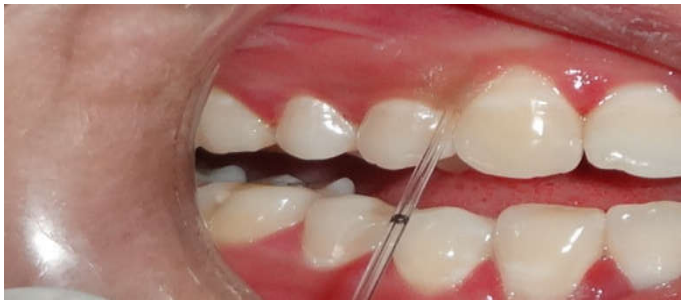

Fig 2 GCF sample collected with micro capillary tube

Fig 3 ELISA reading with ELISA reader

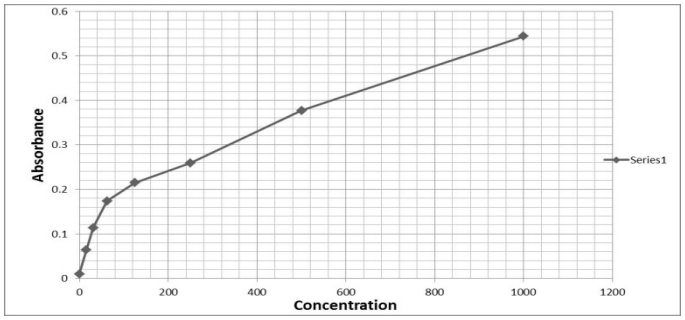

Fig 4 Elisa Kit Graph

DISCUSSION

Periodontal pathogens elicit signals in resident gingival cells or immune cells infiltrating the gingival tissues, resulting in immune responses which lead to either the successful removal of the pathogens or to host-mediated destruction of the periodontal tissues. In this respect, cytokines in inflamed periodontal tissues have been cited as being of major importance in periodontal disease progression.[5]IL-18 is a pro-inflammatory cytokine that belongs to the IL-1 family and plays an important role in inflammation. The uncontrolledrelease of this cytokine is associated with severe chronic inflammatory disease. IL-18 forms a signalling complex with the IL-18 receptor α (Rα) and β (Rβ) chains at the plasma membrane, which induces multiple inflammatory cytokines.[7]

Pradeep *et al*.[8] demonstrated that the IL-18 concentration in GCF increased proportionally with the progression of periodontal disease. In addition, the levels of IL-18 were found to decrease significantly after periodontal therapy (SRP) in the CP group. Also, treatment aimed at arresting periodontal disease progression resulting in a statistically significant reduction of IL-18 concentration in GCF.

They showed 93.34 ± 46.03 pg/µl IL-18 level in gingivitis group and 89.09 ± 66.69 pg/µl in post treatment CP group which is in accordance with the present study IL-18 level in gingivitis group was 59.7 ± 13.2 pg/µl and in post treatment CP group was 49.9 ± 28.5 pg/µl. Thus, IL-18 can be considered an inflammatory biomarker of periodontal disease and deserves further consideration in the development of methods for prevention and therapy.

Figueredo *et al*[9] observed that higher GCF levels of IL-18 were found in inflamed sites from Periodontitis patients regardless of severity of disease when compared with patients with Gingivitis only. Moreover, shallow pockets in Periodontitis patients had a significantly higher total level and concentration of IL-18 when compared with shallow pockets in patients with gingivitis only whereas in the present study PPD positively correlates with IL-18 i.e. level of IL-18 increases with the severity of the disease. Secondly, they also examined the microbial status of microbes in accordance with the severity of the disease i.e. gingivitis sites from Periodontitis patients and Gingivitis sites fromgingivitis patients presented similar levels of the red, orange, and yellow complex species while the present study the disease severity was seen in relation with IL-18 regardless to the microbial status.

Thirumalai *et al*[10] demostrated the mean level of IL-18 was highest in CP group (1160.4 ± 3096.9 pg/µl), followed by AP group (784.3 ± 1834.3 pg/µl) and least in healthy subjects (441.5 ± 1434.2 pg/µl). When CP group was statistically compared with healthy group, the difference was not significant (p=0.068). This result is inconsistent with the findings of the present study which showed statistically significant value (p<0.001) between the two groups. The variation in the result may be due to the difference in study subjects included in the study.

The present study is in accordance with that of Orozco *et al*[11] who found increased local production of IL-18 in GCF Periodontitis compared with gingivitis patients. They also demonstrated that IL-18 concentrations were significantly higher than IL-1 at both Gingivitis and Periodontitis sites, inferring a high significance for this cytokine in periodontal disease.

The present study is accordance with the present study AL-abdallat *et al*[12] who checked the plasma IL-18 levels and found elevated level in diseased as compared to control group i.e. 620 ± 269 pg/ml in diseased and 282 ± 73 pg/ml in control. The results of the present study showed that GCF levels of IL-18 are significantly correlated with each other and show similar result i.e. IL-18 level was higher in diseased condition compared to Healthy group i.e. 174.2 ± 161.6 pg/ml in CP and was 36.8 ± 7.3 pg/ml in control.

The present study is in disagreement with Schallhorn *et al*[13] who found a statistical significant association between plasma IL-18 and the periodontal parameters whereas the relationship between BOP and IL-18 (r=4.32 pg/ml), the indicator of periodontal inflammation in their study was no longer significant when accounting for confounding patient factors in the multiple regression analysis, while the present study show statistical significant relation between IL-18 and BOP, OHIS, PPD and CAL which decreases after the treatment (r=0.102 pg/ml in OHIS, r=0.066 pg/ml in PPD, r= 0.191 pg/ml in BOP and r=0.210 pg/ml in CAL).

The present study is in disagreement with Chitrapriya *et al*[14] who checked the levels of IL-18 in Healthy, Gingivitis and in Chronic mild Periodontitis sites and elevated levels of IL-18 were observed in gingivitis samples followed by healthy and Periodontitis samples i.e. 385.18 ± 71.26 pg/mg in healthy, 1479.42 ± 330.33 pg/mg in gingivitis and 330.24 ± 48.56 pg/ml in CP which contradicts with the present study where higher level of IL-18 seen in CP, followed by Gingivitis and Healthy subjects i.e. 36.8 ± 7.3 pg/ml in Healthy, 59.7 ± 13.2 pg/ml in Gingivitis, 174.2 ± 161.6 pg/ml in CP and 49.9 ± 28.5 pg/ml after NSPT wherein levels of IL-18 have been found to increase with progression of disease from Healthy to Gingivitis to CP. This may explain the reducedlevels of IL-18 in gingival tissues from Periodontitis patients asobserved in their study whereas in present study GCF sample is collected following NSPT.

CONCLUSION

The results demonstrate that there was significant reduction in clinical as well as biochemical parameter. Thus, the following conclusions can be drawn from this study:

1. IL-18 could be a factor in progression of inflammation because it has chemotactic, pro-inflammatory, and osteoclastic properties.
2. Increased IL-18 level was seen with severity of the periodontal disease and its levels decreased following successful periodontal treatment.

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