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ORIGINAL ARTICLE

Serum levels of oncostatin M (a gp 130 cytokine): an inflammatory biomarker in periodontal disease

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Abstract

Objective: Periodontitis is considered to be a risk factor for systemic diseases such as atherosclerosis, diabetes, etc., and cytokines play a key role. The present study was carried out to measure the level of serum oncostatin M (OSM) in patients with chronic periodontitis, and to evaluate the effect of non-surgical periodontal therapy on the serum OSM concentration.

Materials and methods: Sixty subjects were divided into three groups (each group $n = 20$) based on the gingival index (GI), probing pocket depth (PPD) and clinical attachment level (CAL): group I healthy; group II gingivitis; and group III chronic periodontitis. Group III patients were followed for 8 weeks after non-surgical periodontal therapy as the after-treatment group (group IV). Estimation of serum OSM was done using an enzyme-linked immunosorbent assay.

Results: The mean OSM concentrations in serum were highest in the chronic periodontitis group (mean 68.05 pg ml^{-1}) and decreased following treatment (39.65 pg ml^{-1}) while OSM was undetectable in healthy subjects or in patients with gingivitis.

Conclusion: Increased serum OSM concentration in patients with chronic periodontitis and its positive correlation with PPD and CAL, suggest its role as an inflammatory biomarker in periodontal disease and it may exaggerate other systemic conditions such as atherosclerosis and rheumatoid arthritis.

Keywords: *Oncostatin M; cytokines; serum; gingivitis; periodontitis; inflammatory biomarker*

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Introduction

Periodontal diseases are chronic inflammatory diseases triggered in response to periodontopathogens and its clinical outcome is highly influenced by the host immune response. Components of microbial dental plaque have the capacity to activate the local host response by infiltrating inflammatory cells, including T lymphocytes, macrophages and polymorphonuclear leukocytes (PMNs), plasma cells (Kornman et al. 2000), endothelial cells and fibroblasts (Gemmell & Seymour 2000), which are responsible for the production of various cytokines. These cytokines have important proinflammatory effects and are related to the periodontal tissue destruction that involves the stimulation of bone resorption and induction of tissue-degrading proteinases (Abbas & Lichtman 2003). Recent evidence indicates that patients with periodontitis present increased systemic inflammation, as indicated by raised serum levels of various inflammatory markers (cytokines) when compared with controls (Ebersole et al. 1997, Loos et al. 2000). This increase in systemic inflammation has been reported to have a modulating role in cardiovascular disease (Beck et al. 2005), diabetes mellitus (Iacopino 2001) and respiratory disease (Katancik et al. 2005) and to have an adverse effect on pregnancy outcome (Sanchez et al. 2004). Taking into consideration the major role of these cytokines in systemic diseases, it is important to study the levels of these markers in the peripheral circulation of subjects with periodontal disease.

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Oncostatin M (OSM), a member of the interleukin (IL)-6 family of cytokines, which has been demonstrated to fulfil Koch's postulates as an inflammatory mediator (Modur et al. 1997). In the cascade of periodontal inflammation, human T cells and monocyte lineages can synthesize and secrete large amounts of OSM and IL-6 in response to bacterial products and play a key role in regulating periodontal bone resorption, by acting on both osteoblast and osteoclast receptor activator of nuclear factor-κ B ligand (RANKL) regulation (Lu et al. 2006). OSM induces expression of P-selectin, E-selectin, intercellular adhesion molecule-1 and vascular cell adhesion molecule-1 in human endothelial cells, which play an important role in recruiting leukocytes to inflammatory sites (Modur et al. 1997, Yaoet al. 1996). OSM may stimulate the production of IL-6, or may act synergistically with IL-6 or tumour necrosis factor (TNF)-α to upregulate the production of metalloproteinases (MMPs) or augment IL-6 production (Manicourt et al. 2000, Brown et al. 1991). A recent study by Lin et al. (2005) demonstrated the increased amount of OSM and IL-6 in the gingival crevicular fluid (GCF), which was positively correlated to the severity of periodontitis. Increased OSM expression and its role in the pathogenesis of various systemic diseases, such as rheumatoid arthritis (Hui et al. 1997), multiple myeloma (Halin et al. 2000), atherosclerosis (Modur et al. 1997), wound biology (Goren et al. 2006), obesity (Song et al. 2007) and Kaposi's sarcoma (Cai et al. 1994), has been evaluated.

It has been reported that periodontal disease is interrelated with systemic health in important ways, and oral conditions, such as periodontal infections, and may serve as risk factors or indicators for important medical outcomes (Page 1998). Recent evidence suggests that periodontal infection may significantly enhance the risk for certain systemic diseases or alter the natural course of systemic conditions. Conditions in which the influence of periodontal infection is documented include coronary heart disease (CHD) and CHD-related events such as angina and infarction, atherosclerosis, stroke, diabetes mellitus, preterm labour, low-birth-weight delivery and respiratory conditions such as chronic obstructive pulmonary disease (Mealey 1999, Page & Beck 1997). Therefore the possibility that, morbidity and mortality from systemic diseases may be reduced by improving periodontal health makes it imperative to explore the effect of periodontal disease on systemic levels of inflammatory mediators.

To date, no study has reported the serum OSM levels in various stages of periodontal disease, such as gingivitis and chronic periodontitis or with periodontal health, nor correlated OSM levels before and after periodontal therapy. Thus, in view of the aforementioned findings, this clinicobiochemical study was carried out to estimate the serum OSM levels in subjects with clinically healthy periodontium, gingivitis or chronic periodontitis and subsequently, after non-surgical periodontal therapy, scaling and root planning (SRP), which is a conventional periodontal therapy or non-surgical periodontal therapy, to remove or eliminate the aetiological agents such as dental plaque and calculus, which cause inflammation, in periodontitis subjects.

Materials and methods

The study population consisted of 60 subjects (30 men and 30 women; age range 25–40 years) attending the outpatient clinic of the Department of Periodontics, Government Dental College and Research Institute, Bangalore, Karnataka, India. Written informed consent was obtained from those who agreed to participate voluntarily and ethical clearance was obtained from the institution's ethical committee. Inclusion criteria included subjects within the age group 25–40 years, who had not received periodontal therapy within the preceding 6 months and who had at least 20 natural teeth. Subjects with systemic diseases, such as rheumatoid arthritis, diabetes or hypertension, or those with a body mass index >26 kg m^{-2}, tumours, gross oral pathology, etc., postmenopausal and pregnant women, aggressive periodontitis patients, subjects who had taken any medication such as antibiotics/anti-inflammatory drugs or had received periodontal therapy in the preceding 6 months, and smokers were excluded.

Each subject underwent full mouth periodontal probing and charting, along with periapical radiographs using the long-cone technique. Radiographic bone loss was recorded dichotomously (presence or absence) to differentiate chronic periodontitis patients from other subjects. No delineation was attempted within the chronic periodontitis group based on the extent of alveolar bone loss.

Based on the gingival index (GI) (Loe and Silness, 1963), probing pocket depth (PPD), clinical attachment level (CAL) and radiographic evidence of bone loss, subjects were categorized into three groups. Group I (healthy) consisted of 20 subjects with clinically healthy periodontium, with a gingival index of 0, a PPD of ≤3 mm and clinical attachment loss of 0, with no evidence of bone loss on radiograph. Group II (gingivitis) consisted of 20 subjects who showed clinical signs of gingival inflammation, a gingival index of >1, a PPD of ≤3 mm and had no attachment loss or radiographic bone loss. Group III (chronic periodontitis) consisted of 20 subjects who had signs of clinical inflammation, a gingival index of >1, a PPD of ≥5 mm and attachment loss ≥3 mm with radiographic evidence of bone loss. Patients with chronic periodontitis (group III) were treated with a non-surgical approach, i.e. SRP, and serum samples were collected

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8 weeks after the treatment to constitute group IV (the after-treatment group). Descriptive statistics of the study groups is given in Table 1.

Serum collection

Two millilitres of blood was collected from the antecubital fossa by venipuncture using a 20-gauge needle with 2-ml syringe and immediately transferred to the laboratory. The blood sample was allowed to clot at room temperature and, after 1 h serum was separated from blood by centrifuging at 3000*g* for 5 min. The extracted serum was immediately transferred to a plastic vial and stored at –70°C until the time of assay.

OSM assay

The serum samples were then assayed for OSM levels by using the Human OSM enzyme-linked immunosorbent assay (ELISA) Kit obtained from KRISHJEN BioSystems, Mumbai, India (catalogue no. KB 100-H Oncostatin-M). Samples were analysed at the Department of Microbiology, Kempegowda Institute of Medical Sciences, Bangalore, India.

All reagents were allowed to warm to room temperature for at least 30 min prior to opening. Reagents are prepared according to the manufacturer's instructions immediately before use and mixed thoroughly without foaming. Standards and samples of 100 µl per well were added to the plate and six twofold serial dilutions were performed on the 2000 pg ml^{-1} top standard. Thus, the human OSM standard concentrations obtained were 2000, 1000, 500, 250, 125, 62.5 and 31.2 pg ml^{-1}. After appropriate dilution, serum samples or the standard-containing plates were incubated at room temperature for 2 h with shaking. All subsequent washes were performed as per the manufacturer's instructions. One hundred microlitres of biotin antibody solution was added to each well; the plate was sealed and incubated at room temperature for 2 h with shaking. One hundred microlitres of diluted streptavidin–HRP conjugate solution (1:1000 in diluents) was added to each well; the plate was sealed and incubated at room temperature for 30 min with shaking. One hundred microlitres of freshly mixed TMB substrate solution was added and the plate incubated at room temperature in the dark for 15 min. Positive wells turned a bluish colour. The reaction was stopped by adding 100 µl of 2 N H_2SO_4 to each well. Positive wells turned from blue to yellow. Results were read immediately on a spectrophotometer using 450 nm as the primary wave length. The concentration of OSM in the tested samples was estimated using the standard curve.

Statistical analysis

All data were analysed using a software program (SPSS® version 10.5, SPSS Inc., Chicago, IL, USA). A test for the validity of normality assumption using standardized range statistics was carried out and it was found that the assumption was valid. Accordingly parametric tests were carried out for comparing the means of OSM concentration in different groups. The paired '*t*' test was used to compare OSM concentrations in serum in groups III and IV. Pair-wise comparison using Scheff's test for serum OSM was carried out to explore which pair or pairs differed significantly at the 5% level of significance. Pearson's correlation test was used to observe any correlation between the serum OSM concentration and clinical parameters.

Results

All the tested samples were found to be positive for the presence of OSM. The mean OSM concentration in serum was found to be highest in group III (chronic periodontitis) (68.05 pg ml^{-1}). The mean serum OSM concentration in group IV (after treatment) was 39.65 pg ml^{-1}. However, in group I (healthy) and group II (gingivitis), the serum OSM concentration was below

Table 1. Descriptive statistics of the study population showing mean, standard deviation and range for the age, GI, CAL, PPD and Serum OSM concentrations.

Groups		Age (years)	GI	CAL (mm)	PPD (mm)	Serum OSM (pg/ml) Mean ± SDRange (min, max)
Group I	Mean ± SD	28.20 ± 4.31	0	0	1.9 ± 0.73	0.00
(n=20)	Range (min, max)	(25,39)	–	–	(1, 3)	
Group II	Mean ± SD	26.90 ± 2.84	1.9 ± 0.53	0	2.6 ± 0.51	0.00
(n=20)	Range (min, max)	(25,34)	(1.1, 2.8)	–	(2, 3)	
Group III	Mean ± SD	34.30 ± 6.61	2.15 ± 0.43	5.8 ± 1.13	7.5 ± 1.84	68.05 ± 13.42
(n=20)	Range (min, max)	(25,42)	(1.40, 2.8)	(5, 8)	(6, 11)	(50.00, 87.50)
Group IV	Mean ± SD	34.30 ± 6.61	0.33 ± 0.49	2.9 ± 1.85	3.9 ± 2.51	39.65 ± 16.67
(n=20)	Range (min, max)	(25,42)	(0.0, 1.4)	(1, 6)	(2, 8)	(0.00, 68.50)

(For Group I and Group II it was below the detectable limit of the kit, sensitivity 5 pg/ml)

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the detection limit of the kit (sensitivity 5 pg ml^{-1}), thus approximately corresponding to 0.00 pg ml^{-1} (Table 1).

To test the hypothesis of equality of means among the four groups ANOVA was carried out, which indicated that the means differ significantly among the groups (F: 45.43, $F < 0.05$; Table 2). Scheff's test was carried out to find out which pair or pairs differ significantly. The results showed that the difference was statistically significant between group III and groups IV (p <0.005; Table 3). When group III and IV (after treatment) were compared with the paired 't' test, the difference in the serum concentrations of OSM was statistically significant suggesting that after scaling and root planning, OSM levels decreased considerably (Table 4).

Pearson's correlation coefficient test was carried out to find correlations between clinical variables, i.e. GI, PPD, CAL and OSM concentration in serum. Again, reduction in these clinical variables after the treatment in group IV, showed a positive correlation with serum OSM concentration (Table 5). The confidence interval was calculated for differentiating the limits of serum OSM values in group III and group IV to consider OSM as an inflammatory biomarker. Differentiating values with a probability 0.95 for chronic periodontitis is ≥41.00 pg ml^{-1} (Table 6).

Table 2. Results of ANOVA comparing the mean serum oncostatin M (OSM) concentration (in pg ml^{-1}) between group III and group IV.

Study group	Serum OSM (pg ml^{-1})Mean ± SDRange (min–max)	F-value	p-Value
Group III (n=20)	68.05 ± 13.42 (50.00–87.50)	96.0844	<0.001*
Group IV (n=20)	39.65 ± 16.67 (0.00–68.50)		

For group I and group II it was below the detectable limit of the kit, sensitivity 5 pg ml^{-1}.

Table 3. Pair-wise comparison using Scheff's test for serum oncostatin M (OSM) concentration (pg ml^{-1}).

Study groups	Mean difference	Standard error	p-Value
Group I & group II	0.0000	114.5903	1.0000
Group I & group III	-68.0500	114.5903	<0.001*
Group I & group IV	-39.6500	114.5903	<0.001*
Group II & group III	-68.0500	114.5903	<0.001*
Group II & group IV	-39.6500	114.5903	<0.001*
Group III & group IV	28.4000	114.5903	<0.001*

*The mean difference is significant at 0.05 level.

Discussion

OSM is a gp 130 family, multifunctional unique cytokine that plays an important role in various biological systems such as inflammatory response, haematopoiesis, tissue remodelling and development (Orozco et al. 2007). Periodontitis is an inflammatory disease of the periodontium caused mainly by microbial plaque and host interaction, and leads to increased inflammatory cytokines at the diseased site (Kornman et al. 2000). Cytokines produced by various cells such as macrophages/monocytes, dendritic cells, lymphocytes, PMNs, endothelial cells and fibroblasts (Abbas & Lichtman 2003) are of major importance in periodontal disease progression. Numerous cytokines are produced in response to microbes and other antigens and stimulate diverse responses (Orozco et al. 2007).

In periodontitis, OSM alone may stimulate the production of IL-6, or it may act synergistically with IL-6 or TNF-α to upregulate the production of MMPs or augment IL-6 production (Katancik et al. 2005). IL-6 may act on both the osteoblasts and osteoclasts through autocrine and paracrine RANKL regulation (Beck & Offenbacher 2005) causing bone resorption. In the present study it has been found that there was an increased serum OSM concentration in the chronic periodontitis patients (68.05 pg ml^{-1}), suggesting increased local concentration of OSM with respect to the severity of the disease. Also, there was a decreased serum concentration of OSM after non-surgical periodontal therapy (from 68.05 to 39.65 pg ml^{-1}). Differentiating values with probability 0.95 shows that a serum OSM concentration ≥41.00 pg ml^{-1} may indicate chronic periodontitis. Again, it was not detected in the serum of gingivitis patients perhaps because a lower concentration of OSM was secreted at the disease site compared with the periodontitis site, in which soft as well as hard tissue (alveolar bone) destruction takes place. These findings indicate OSM as an inflammatory and bone resorptive biomarker of periodontal disease. Longitudinal prospective studies involving larger population are needed to confirm these findings and to improve understanding of the role of OSM cytokines in the pathogenesis of periodontal diseases.

Table 4. Paired t-test to compare group III and group IV with all the variables.

Variable		Mean	Std.Dv.	Mean Diff.	SD Diff.	Paired t value	p-value
Serum OSM conc. (in pg/ml)	Group III (n=10)	68.05	13.42	28.40	10.88	8.25	< 0.001*
	Group IV (n=10)	39.65	16.67				

*Significant at < 0.05 level

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Table 5. Pearson's correlation coefficient test comparing serum oncostatin M concentration (in pg ml^{-1}) with gingival index (GI), probing pocket depth (PPD) and clinical attachment level (CAL).

Groups	Serum and GI	Serum and PPD	Serum and CAL
Group III ($n=20$)	0.6906*	0.8195*	0.7626*
Group IV ($n=20$)	0.6676*	0.6707*	0.6693*

*Significant at 0.05 level ($p<0.05$).

Table 6. Differentiating values for different groups for serum oncostatin M concentration in pg ml^{-1}.

Study group	Mean	SD	Mean ± 2 SD		Differentiating values with $p<0.95$
GroupIII ($n=20$)	68.0500	13.4235	41.2029	94.8971	>41 pg ml–1

Lin et al. (2005) measured gp 130 cytokines (OSM and IL-6) in the GCF of patients with mild, moderate and severe chronic periodontitis and demonstrated that increased amounts of OSM and IL-6 in the GCF were positively correlated to the severity of periodontitis. However, the present study is the first to report increased serum OSM levels in patients with chronic periodontitis (68.05 ± 13.42 pg ml^{-1}).

In the present study, the influence of age and gender of the subjects on the serum OSM concentration was minimized by including an equal number of men and women in each group and selecting the subjects within the specified age group of 25–40 years. Having four groups (healthy, gingivitis, chronic periodontitis and chronic periodontitis after treatment) in our study helped us to evaluate the role of OSM in periodontal disease and the effect of periodontal therapy on serum OSM concentrations.

It is well established that chronic periodontitis may indicate potential risk factors for systemic conditions and can affect their onset and progression by various mechanisms. Studies have demonstrated a moderate association between cardiovascular diseases and periodontal diseases (Malthaneret et al. 2002, Scannapieco et al. 2003), and periodontal disease has been considered to be a sixth complication of diabetes (Loe 1993). Offenbacher et al. (1996) found that women giving birth to low-birth-weight infants had greater clinical attachment loss than women giving birth to normal-weight infants, showing a 7.5-fold increased risk of having a low-birth-weight infant. Studies have also reported a reduced preterm birth rate in women who received mechanical periodontal therapy (SRP) during gestation (Jeffcott et al. 2003, Lopez et al. 2002). In diabetic patients with periodontitis, periodontal therapy (SRP) showed beneficial effects on glycaemic control and resulted in decreased insulin demand (Mealey 1999). Recently, Friedewald et al. (2009) in an editors' consensus report mentioned two meta-analyses showing that, the periodontal disease is a risk factor of coronary artery disease (CAD) with a relative risk ranging from 1.24 to 1.35, raising the possibility that periodontitis independently predicts CAD. A systematic review and meta-analysis by Paraskevas et al. (2008) concluded that, periodontal therapy reduces the C-reactive protein level, which is a risk predictor of cardiovascular disease.

Several studies explained the role OSM in the formation of atherosclerotic plaque through production of various inflammatory mediators by recruitment of macrophages (Tanimura et al. 1986, Shioi et al. 2002). Also, the association of OSM with rheumatoid arthritis, multiple myeloma, Kaposi's sarcoma and atherosclerosis has been studied (Modur et al. 1997, Hui et al. 1997, Halin et al. 2000, Cai et al. 1994). An increase in serum OSM levels in periodontitis patients may increase the risk for atherosclerosis and other above-mentioned diseases or conditions. Although not proven, the possibility of increased risk of other diseases due to increased levels OSM in serum could pave the way to future studies to correlate OSM levels in serum and GCF, and to explore the actual potential risk associated with this.

In conclusion, based on the findings of the present study, a role of OSM in the progression of periodontal disease is proposed. Further, longitudinal prospective studies are needed to confirm the findings of our study.

Limitations and future work

The small number of subjects enrolled into this preliminary study limits the strength of our conclusion. Further work is needed to examine the relationship between serum OSM concentration in patients with chronic periodontitis and other systemic diseases such as atherosclerosis, rheumatoid arthritis and multiple myeloma. Moreover, measurement of serum OSM in well-characterized epidemiological populations or clinical cohorts will be necessary to determine whether there is any prognostic value in serum OSM. In future, exploring the use of OSM as an inflammatory and bone resorptive biomarker and a novel therapeutic target in periodontal and systemic diseases could be interesting fields of research.

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Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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