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Original Article

Inflammatory cytokine levels in patients with periodontitis and/or coronary heart disease

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Abstract: The purpose of this study was to investigate systemic and local levels of four classic inflammatory cytokines (IL-1β, MCP-1, VEGF, PDGF) in patients with periodontitis and coronary heart disease (CHD). 109 volunteers were enrolled and the condition of their periodontal tissue and coronary artery were assessed. The patients were then divided into four distinct groups: periodontitis only, CHD only, periodontitis with CHD, and healthy controls. Gingival crevicular fluid (GCF) and venous blood were collected. The concentrations of cytokines were detected meanwhile by specific ELISA. The IL-1β and MCP-1 concentrations in the serum and GCF of the three disease groups were significantly higher than those in the control group ($P \leq 0.05$). Serum VEGF concentrations of the patients with existing disease was lower than that of the controls. VEGF levels in the GCF of all disease groups were significantly higher than that of the control group ($P \leq 0.05$).

Keywords: Interleukin-1β (IL-1β), monocyte chemoattractant protein-1 (MCP-1), vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), periodontal disease, coronary heart disease

Introduction

Growing clinical and animal evidence suggests that periodontal disease is associated with cardiovascular problems. The link between periodontal disease and cardiovascular disease may be related to inflammatory processes. The link between periodontal disease and cardiovascular disease is probably inflammation [1]. Periodontal disease has been found to be correlated with increased plasma levels of mediators of inflammation, such as C-reactive protein (CRP) and interleukin 6, which are associated with atherosclerosis and an increased risk of acute cardiovascular events [2]. Inflammatory cytokines may also indicate the presence of different stages of atherothrombosis and could be useful in predicting the risk and severity of Coronary Heart Disease (CHD) [3]. For example, MCP-1 and VEGF present in atherosclerotic plaques regulate the recruitment of monocytes and endothelial adhesion molecules [4, 5]. Increased plasma VEGF levels in patients with coronary artery disease may indicate that the coronary lesion is at a critical stage and VEGF increase in patients with established coronary artery disease may be used as an indicator of the need for revascularization [6]. Platelet-derived growth factor (PDGF) is a potent mitogen for vascular smooth muscle cells and is implicated in the vascular response to injury and the pathogenesis of atherosclerosis [7]. Therefore, the study of inflammatory mediators may be helpful in developing a diagnostic test or risk assessment for both periodontal and cardiovascular diseases.

Interleukin-1β (IL-1β) is an inflammatory cytokine, one of the central mediators in the cytokine network and is known to control important functions both in the immune system and in inflammation. Monocyte chemoattractant protein-1 (MCP-1) is a well-known chemotactic cytokine that regulates mononuclear inflammatory cell recruitment. Vascular endothelial growth factor (VEGF) promotes normal and pathological angiogenesis, and Platelet-derived growth factor (PDGF) is one of the most potent serum mitogens and promotes cell migration and proliferation, synthesis of collagen, and regulates angiogenesis [8-10].

Table 1. Age and gender of the investigated groups (mean ± SD). Untreated periodontitis without CHD (group P), CHD without periodontitis (group C), both CHD and untreated periodontitis (group P/C), and general good health with no clinical evidence of CHD and periodontitis (H)

Group	Gender	Number	Age (years)
P	male	13	44.40 ± 2.80
	female	14	48.20 ± 3.50
C	male	11	41.50 ± 4.40
	female	15	47.40 ± 4.60
P/C	male	15	42.60 ± 3.80
	female	13	46.50 ± 3.50
H	male	12	40.20 ± 2.50
	female	16	39.80 ± 3.50

The enzyme-linked immunosorbent assay (ELISA) is commonly used to measure individual cytokine levels, whereas the multiplex assay is a new rapid and sensitive approach of simultaneously measuring levels of multiple cytokines in small samples by capturing them on spectrally distinct beads mounted on microchips [11]. To our knowledge, this assay has so far not been used to compare the expression of multiple inflammatory cytokines between patients with CHD and chronic periodontitis. In this pilot study, we used a multiplex bead assay to simultaneously measure the concentration of four classic inflammatory cytokines, (IL-1β, MCP-1, VEGF, PDGF), in gingival crevicular fluid (GCF) and serum of Chinese patients with or without CHD or chronic periodontitis.

Materials and methods

Study population

This study was approved by the Institutional Review Board of Zhejiang University and informed consent was obtained from each participant. 109 patients attending the University teaching hospitals were enrolled in the study according to the following four diseases states: untreated periodontitis without CHD (group P), CHD without periodontitis (group C), both CHD and untreated periodontitis (group P/C), and general good health with no clinical evidence of CHD and periodontitis (H) (**Table 1**). Periodontitis was defined as a mean probing pocket depth (PPD) of greater than 4 mm and bleeding on probing (BOP) [12]. CHD was diagnosed by coronary angiography. Group P and H participants were from the Department of Periodontology, Zhejiang University, and had no history of systemic diseases and had not received any medication in the previous 4 weeks. Group C and P/C participants were from the Department of Cardiovascular Medicine, Zhejiang University, and had angiographically proven atherosclerosis without evidence of diabetes mellitus, stroke, or other systemic diseases. Patients had no declared history of smoking, or drinking alcohol.

Clinical examination

All participants underwent a comprehensive periodontal examination. PPD, clinical attachment levels (CAL) and BOP were assessed with a Michigan-O-style periodontal probe at six sites per tooth. The CAL was measured from the cementoenamel junction, to the most apical penetration of the periodontal probe.

Sampling of gingival crevicular fluid and serum

GCF was collected as described previously by Lamster *et al*. [13]. Briefly, before GCF sampling, the tooth surfaces were dried gently by an air syringe and were isolated by cotton rolls. Supragingival plaque was gently removed. Paper strips (Periopaper; Harco, Tustin, CA, USA) were carefully inserted into the crevice until mild resistance was felt and left there for 30s. Care was taken to avoid mechanical injury. Strips contaminated with blood were discarded. For the P and P/C group, GCF samples were collected from one site per quadrant with the deepest PPD. For the C and H group, GCF samples were collected from the mesio-buccal site of the first molar per quadrant. Papers were weighed before and after sampling. The strips were separately placed into 1.5 ml Eppendorf tubes and maintained at -20°C until further analysis. During the same appointment, 3 ml of blood was taken from the cubital vein of each participant. The whole blood samples were incubated at 37°C for 30 min and centrifuged at 2000 rpm for 2 min. The serum was removed carefully and stored at -70°C.

Cytokine assay

Stored GCF and serum samples were defrosted at room temperature. GCF was extracted from the paper strips by adding 150 µL buffer (40

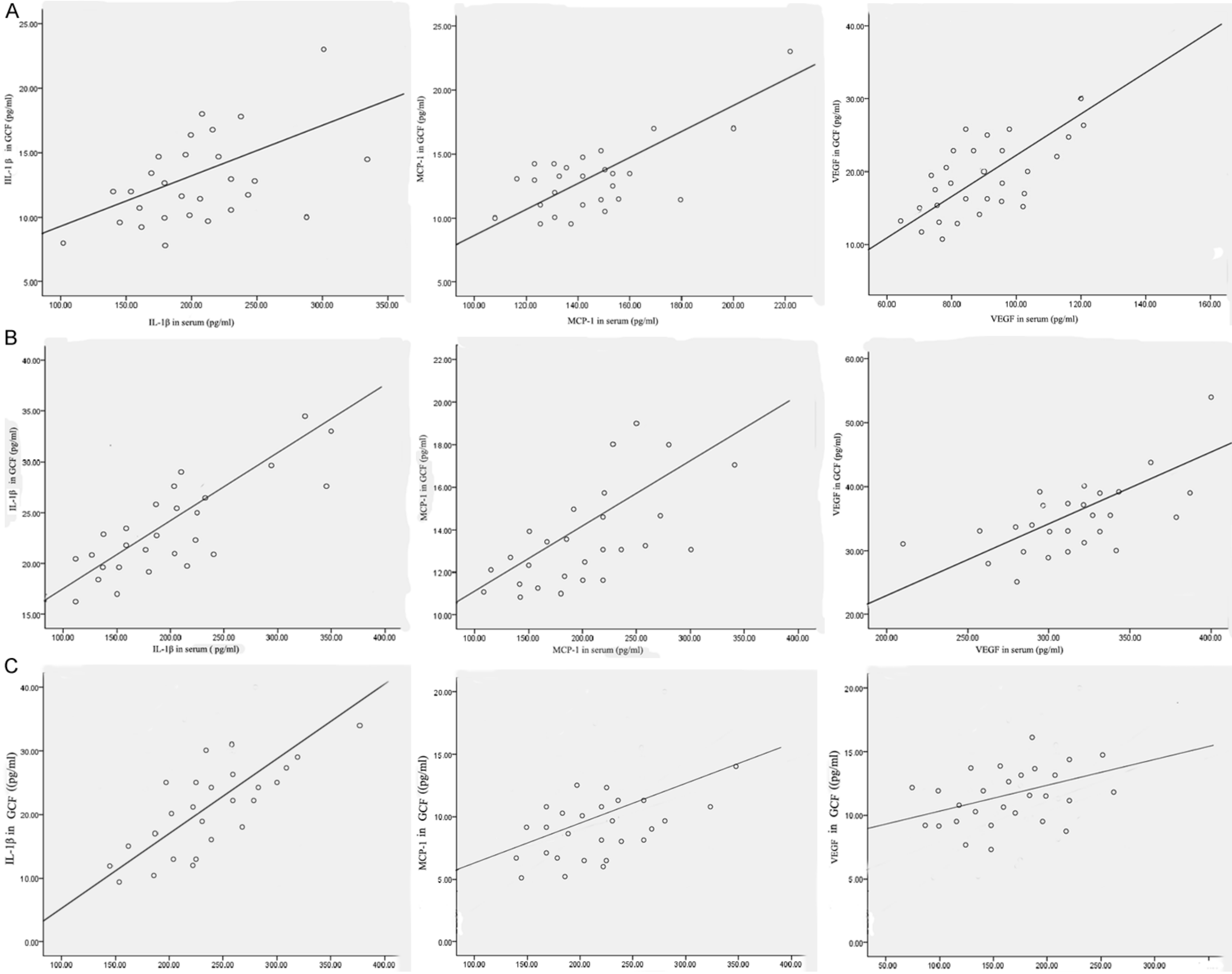
A
IIL-1β in GCF (pg/ml)
IL-1β in serum (pg/ml)
MCP-1 in GCF (pg/ml)
MCP-1 in serum (pg/ml)
VEGF in GCF (pg/ml)
VEGF in serum (pg/ml)
B
IL-1β in GCF (pg/ml)
IL-1β in serum (pg/ml)
MCP-1 in GCF (pg/ml)
MCP-1 in serum (pg/ml)
VEGF in GCF (pg/ml)
VEGF in serum (pg/ml)
C
IL-1β in GCF ((pg/ml)
MCP-1 in GCF ((pg/ml)
VEGF in GCF ((pg/ml)

Figure 1. Correlation analysis between IL-1β, MCP-1, and VEGF levels in serum (pg/ml) and GCF (pg/sample; pg/μl) for (A) the P group (r = 0.857, $P \leq 0.001$, r = 0.838, $P \leq 0.001$ and r = 0.717, $P \leq 0.001$, respectively), (B) P/C group (r = 0.830, $P \leq 0.001$, r = 0.901, $P \leq 0.001$ and r = 0.874, $P \leq 0.001$, respectively), and (C) the C group (r = 0.632, $P \leq 0.001$, r = 0.874, $P \leq 0.001$ and r = 0.748, $P \leq 0.001$, respectively).

Table 2. Oral clinical parameters of the investigated groups (Mean ± SD)

Group	Number	PD (mm)	CAL (mm)	BOP (%)	PLI	SUL (%)
P	27	5.01 ± 1.24$^{*,\#}$	5.79 ± 1.45$^{*,\#}$	63.45 ± 11.54*	2.87 ± 0.69*	25.45 ± 9.57*
C	26	4.78 ± 0.98$^{*,\#}$	4.98 ± 1.14$^{*,\#}$	57.24 ± 13.34*	2.71 ± 0.32*	21.24 ± 11.24*
P/C	28	2.68 ± 0.21	0.00	51.27 ± 18.47*	2.68 ± 0.28*	23.14 ± 5.78*
H	28	2.54 ± 0.35	0.00	8.02 ± 6.57	1.37 ± 0.54	6.87 ± 3.24

*Statistically significant difference to the healthy controls (Dunnett's two-sided t-test, $P \leq 0.05$); $^{\#}$Statistically significant difference to group C (Dunnett's two-sided t-test, $^{*}P \leq 0.05$, $^{**}P \leq 0.01$).

Table 3. Gingival crevicular of fluid (GCF) level of four inflammatory cytokines in the investigated patient groups and healthy controls (Mean ± SD, pg/ml)

	P	C	P/C	H
IL-1β	25.12 ± 13.72**	18.17 ± 8.05*	23.70 ± 11.71**	7.62 ± 0.85
MCP-1	16.07 ± 5.45*	15.45 ± 3.94*	15.85 ± 4.57*	8.74 ± 1.47
VEGF	54.42 ± .12.87*	41.80 ± 10.29*	32.09 ± 9.54*	22.82 ± 7.93
PDGF	39.32 ± 7.95	42.65 ± 11.32	50.31 ± 10.50	42.60 ± 10.92

*Means that compared with Healthy control group, the aggregation rate increased significantly, $^{*}P \leq 0.05$, $^{**}P \leq 0.01$.

mM phosphate-buffered saline, pH 7.2) to each vial, which was then shaken at 4°C for 1 hour and centrifuged at 10,000 rpm for 10 min at 4°C. Each serum sample was mixed with 100 mL standard buffer from the multiplex human cytokine bead array kit (Bio-Rad Laboratories, Hercules, CA, USA) and centrifuged at 3000 rpm for 5 min at 4°C. The supernatant was collected. A sandwich immunoassay based protein array system (Biosource International, Camarillo, CA, USA), which contains dyed microspheres conjugated with a monoclonal antibody specific for a target protein, was used. Antibody coupled beads were incubated with the serum or GCF sample (antigen), after which they were incubated with biotinylated detection antibody before finally being incubated with streptavidin-phycoerythrin. A broad sensitivity range of standards (Biosource International, Camarillo, CA, USA) ranging from 1.95 to 32000 pg/ml were used to help enable the quantification of a dynamic wide range of cytokine concentrations and provide the greatest sensitivity. The immunoassay was read by the Bio-Plex array reader (Bio-Rad Laboratories, Hercules, CA, USA) which uses Luminex fluorescent-bead-based technology (Luminex Corporation Austin, TX, USA) with a flow-based dual laser detector with real-time digital signal processing to facilitate the analysis of up to 100 different families of color-coded polystyrene beads and allow multiple measurements of the sample ensuing in the effective quantification of cytokines.

Statistical analysis

For the comparison of cytokine concentrations between patient groups, group means and standard deviations were calculated and differences were assessed for statistical significance by one-way analysis of variance (ANOVA) initially and then data comparisons were performed with Dunnett's two-sided t-test. The level of statistical significance was set at 0.05. All statistical procedures were performed with SPSS software (version 18.0, SPSS Inc, Chicago, IL, USA).

Results

Periodontal parameters

The clinical parameters in each group are shown in **Table 2**. The mean PD and CAL in the P/C + and the P group were significantly higher than the values in the C group and the H group ($P \leq 0.05$). The mean PD in the C group was slightly increased compared to the healthy controls. The bleeding scores in P/C group were significantly higher than the scores in the C group ($P \leq 0.05$) and the H group ($P \leq 0.05$). BOP in the P group was significantly increased compared to the BOP scores of group C (P =

Table 4. Serum level of four inflammatory cytokines in three investigated patient groups and healthy controls (mean ± SD, pg/ml)

	P	C	P/C	H
IL-1β	225.12 ± 43.72*	208.17 ± 58.15*	323.70 ± 42.70*	77.52 ± 31.05
MCP-1	216.07 ± 45.15*	175.45 ± 43.04*	301.85 ± 44.27*	58.44 ± 22.44
VEGF	24.32 ± . 2.47*	31.80 ± 4.29*	22.07 ± 5.24*	52.82 ± 15.73
PDGF	111.52 ± 17.95	92.75 ± 17.37	90.41 ± 10.55	102.68 ± 10.97

*Means that compared with Healthy control group, the aggregation rate increased or decreased significantly ($P \leq 0.05$).

0.001) and the control group ($P \leq 0.05$). Statistically significant differences were also observed for BOP between the CHD group and the healthy control group ($P \leq 0.05$).

Serum concentration of cytokines

There were no significant differences in levels of the IL-1β, MCP-1, VEGF and PDGF assayed among the P, C, and P/C groups ($P > 0.05$). The mean serum concentrations of IL-1β and MCP-1 in the patients with periodontitis and/or CHD were significantly higher than those in the healthy ($P \leq 0.05$). In contrast, there were no significant differences in these values among the P, C, and P/C groups ($P \geq 0.05$). The serum concentration of VEGF was significantly higher in the healthy controls than the other three groups. The serum concentration of PDGF showed no significant difference in the four groups ($P \geq 0.05$) (**Table 3**).

GCF concentrations of cytokines

The mean level of IL-1β was significantly higher in the two groups with chronic periodontitis than the other two groups lacking the condition ($P \leq 0.05$). The mean level of MCP-1 was significantly higher in the three disease groups than the healthy group ($P \leq 0.05$). The mean amounts of VEGF were significantly higher in the C, P, C/P groups than H group ($P \leq 0.05$). The mean amounts of PDGF showed no significant differences among the four groups ($P \geq 0.05$) (**Table 4**).

Four inflammatory cytokines levels in GCF compared to serum

For the C group, the IL-1β, MCP-1, and VEGF levels in serum (pg/μl) and in GCF (pg/μl), a significant positive correlation was found (r = 0.632, $P \leq 0.001$ r = 0.874, $P \leq 0.001$ and r = 0.748, $P \leq 0.001$, respectively) as well as for the P group (r = 0.857, $P \leq 0.001$, r = 0.838, $P \leq 0.001$ and r = 0.717, $P \leq 0.001$, respectively) and for the P/ C group (r = 0.830, $P \leq 0.001$, r = 0.901, $P \leq 0.001$ and r = 0.874, $P \leq 0.001$, respectively) (**Figure 1**). No significant correlation was observed in the three patients groups for the PDGF concentration in serum or GCF (not illustrated in the **Figure 1**) in healthy individuals, the IL-1β, MCP-1, and VEGF levels in serum and GCF showed no obvious correlations (not illustrated in the **Figure 1**).

Discussion

The application of a multiplex cytokine array system may become a powerful tool to extensively describe the cytokine profile and to assess the role of these molecules in the pathogenesis of the oral diseases [14]. With the novel, advanced multiplex cytokine array system, a distinct CHD and PD-related serum and GCF cytokine pattern has been revealed that discriminated between patients and healthy individuals. The amount of information obtained from the multiplex cytokine assay is considerable and gives a new description of the pathogenic cytokines in this condition, and is therefore both powerful and represents a good cost-benefit.

IL-1β in patients with chronic periodontitis can reach high systemic concentrations [15, 16]. An increased plasma concentration of some cytokines is also associated with atherosclerosis and acute cardiovascular events [17, 18]. Furthermore, Mazzone *et al*. demonstrated that IL-1β and MCP-1 could be the causal link between periodontitis and CHD. Our findings indicate that serum concentrations of both IL-1β and MCP-1 among patients in the three disease groups (P, C, P/C) were significantly higher than those in the healthy controls is consistent with published findings [21, 22].

An alternative hypothesis for the link between periodontitis and CHD is that periodontal pathogens could enter the bloodstream, exert atherogenic effects, and directly invade blood vessel walls and atherosclerotic plaques [19, 20]. The results of this study demonstrate that

elevated IL-1β and MCP-1 concentrations in serum could serve as a direct marker of inflammatory activity in patients at risk for CHD and chronic periodontitis. These findings also support the hypothesis that inflammatory cytokines are involved in the pathogenesis of CHD and chronic periodontitis.

The glycoprotein VEGF has attracted attention as a potential inducer of angiogenesis. It is detectable in periodontal tissues within endothelial cells, plasma cells and macrophages, and in junctional, sulcular, and gingival epithelium. VEGF levels in GCF increased in periodontitis compared to levels in healthy controls, and periodontal treatment resulted in a reduction in VEGF concentration. These data indicate that VEGF plays a key role in periodontal disease progression and can be considered a biomarker of the disease [21, 22]. However, in the study, the serum concentration of VEGF in the healthy control group was higher than the three disease groups, conversely the VEGF levels in the GCF of patients with periodontitis and/or coronary heart disease were significantly higher than the healthy controls. Clearly, the magnitude of VEGF concentrations in the serum among the four groups was much lower than those in the GCF. A.R. Pradeep found that GCF and serum VEGF levels increased progressively with the disease severity and decreased after treatment of periodontal disease [23]. VEGF may have a local role in the development of chronic periodontitis through paracrine effects, rather than systemic effects after secretion into the blood circulation. VEGF indeed accumulates at local infected sites and helps mediate inflammation, such as initiate capillary proliferation and increase permeability of blood vessels [24].

In our study, the PDGF concentration in both serum and GCF of the four groups showed no significant differences. The identification of homology between the simian sarcoma virus oncogene, v-sis, and the B-chain of PDGF, as well as the frequent over-expression of both the ligands and receptors in various tumors and stroma led to the proposal of PDGF-mediated autocrine and paracrine regulation [25].

Our findings suggest that the inflammatory cytokines IL-1β, MCP-1, and VEGF could play a key role and can be considered a biomarker in the progression of coronary heart disease and chronic periodontitis, but the role of PDGF is still unclear. It also remains to be determined whether markers of inflammation actually have a causal relationship with cardiovascular disease or simply reflect the underlying disease process. Such information is important, as there is the potential to use these markers in targeting preventive therapies and in routine practice [26].

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Disclosure of conflict of interest

None.

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