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Increased plasma levels of IL-6 in bacteremic periodontis patients after scaling

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Abstract

Bacteremia frequently occurs after dental treatment. Periodontal inflammation may influence the incidence, magnitude and duration of bacteremia. The presence of circulating oral bacteria or bacterial components may induce cytokine synthesis in blood cells, which may contribute to the development or exacerbation of atherosclerosis. The present study tested the hypothesis that bacteremia occurring after scaling in periodontitis patients results in altered plasma levels of cytokines. Twenty periodontitis patients were subjected to scaling. Blood samples at baseline and at 0.5, 10 and 30 minutes postscaling were examined for bacteremia whereas baseline and eight-hour postscaling blood samples were examined for the levels of IL-1β, TNF-α, IL-6, IL-8, IL-10 and IL-12p70. IL-6 levels were significantly increased eight hours after scaling, while IL-8 was significantly decreased. No systematic changes occurred in the levels of IL-1β, TNF–α, IL-10 and IL-2p70. IL-6 levels may be increased while IL-8 may be decreased due to scaling, which may have implications for general health.

Key words: bacteremia; cytokine; periodontitis

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Bacteremia frequently occurs after dental treatment, the magnitude of the episodes usually being within a range of a few CFU/ml (Heimdahl et al. 1990). As a result of bacteremia, which is detected in 13–70% of periodontitis patients after scaling, cytokine synthesis by stimulated blood leukocytes is likely to occur (Heimdahl et al. 1990, Kinane et al. 2005).

Although bacteremia with oral bacteria is eliminated in less than 1 h (Lockhart et al. 2004), detrimental systemic effects may follow as a consequence of bacterial invasion of endothelial cells and coronary artery smooth muscle cells (Dorn et al. 1999). Thus, DNA from several periodontal pathogens has been demonstrated in surgically removed atherosclerotic plaques (Haraszthy et al. 2000, Okuda et al. 2001). The presence of invading bacteria or their products may result in destabilization of atheromas because of cytokine-induced release of matrix metalloproteinases, which, in turn, increases the risk of rupture and infarction (Ross 1999, Becker et al. 2001). Also, the atheromatous plaque may be enlarged as a result of exposure to cytokines, including IL-6 (Huber et al. 1999).

Endotoxin injections in humans is followed by increased levels of soluble tumour necrosis factor (TNF) (Michie et al. 1988, Cannon et al. 1990, Martich et al., 1991, Wilson et al. 2001), IL-1β (Michie et al. 1988, Cannon et al. 1990), IL-6 (Martich et al. 1991) and IL-8 (Martich et al. 1988), whereas binding of cytokine to cell surface receptors is decreased (Van der Poll et al. 1995). The advantage of endotoxin infusion studies is that the evaluation of the host response may be more standardized as opposed to a study of occasional bacteremias with larger variation. However, endotoxin infusion studies do not reflect the clinical situation.

Various virulence factors of the invading bacteria appear to affect cytokine synthesis. It was recently reported that *Porphyromonas gingivalis* fimA type II induced a prolonged cytokine response by macrophages in vitro compared with *P. gingivalis* fimA type I and *Actinomyces naeslundii* (Sugano et al. 2004). In addition, selected nucleotide sequences from *P. gingivalis* fimbrillin induced IL-6 production in human monocytes in vitro (Ogawa & Uchida 1995). Not only Gram-negative but also Gram-positive bacterial components such as streptococcal cell wall structures and culture supernatants induced expression of IL-1β, TNF-α and IL-8 in whole-blood cells in vitro (Hanage & Cohen 2002). Correspondingly, increased circulating levels of IL-6, but not TNF-α were detected after injection of *Streptococcus mutans* into mice (Chia et al. 2002).

The aim of the present study was to assess changes in plasma levels of IL-1β, TNF-α, IL-6, IL-8, IL-10 and IL-12p70 8 h after scaling in periodontitis patients, and to associate such changes

with the magnitude of bacteremia induced by scaling.

Material and Methods

Patient selection

Twenty systemically healthy individuals with untreated periodontitis were recruited at the School of Dentistry, University of Copenhagen. The participants were also included in a study of bacteremia after chewing, toothbrushing and scaling in individuals with varying severity of periodontal inflammation. The regional ethical committee approved the study. All participants were informed about procedures and informed consent was obtained in writing.

Exclusion and inclusion criteria

The exclusion criteria were antibiotic treatment within the latest 6 months, any other pharmacological treatment than oral contraceptives, systemic diseases and chronic infections other than periodontitis. Furthermore, patients with prosthetic heart valves, previous endocarditis, transplants, pregnant or lactating women, and individuals with pulpal or periapical infections were excluded. The inclusion criteria were severe periodontitis, defined as at least 10 sites with probing pocket depth (PPD) > 5 mm. Eleven patients had an initial diagnosis of aggressive periodontitis (clinical attachment level (CAL) > 4.3 mm at age younger than 45) and nine had an initial diagnosis of chronic periodontitis (CAL > 2.98 at ages 46–63) (Armitage 2000). Table 1 shows patient data.

Clinical examination

A thorough patient history was obtained regarding systemic health and intake of medication. Smoking habits were registered (number of cigarettes/day, years of smoking). Full-mouth periodontal registration was performed, including the following clinical variables: PPD, gingival index (GI) (Löe & Silness 1963), plaque index (PI) (Silness & Löe 1966), bleeding on probing (BOP) and CAL. All PPD measurements were added in order to

Table 1. Patient data ($n = 20$)

Age (years)	
Mean	43.75
Min.	28
Max.	63
Gender	
Men	5
Women	15
Smoking (number of persons)	
Smokers	11
Non-smokers	9
Time used for scaling (minutes)	
Mean	27.5
Min.	25
Max.	30
Number of teeth	
Mean	27
Min.	21
Max.	28
Mean clinical attachment loss (mm)	
Mean	5.37
Min.	2.98
Max.	6.73
Gingival index	
Mean	1.66
Min.	0.86
Max.	2.18
Plaque index	
Mean	1.12
Min.	0.23
Max.	2.29
Bleeding on probing (%)	
Mean	60
Min.	19.4
Max.	100
Bleeding on probing (number of sites)	
Mean	94.4
Min.	30
Max.	168
Number of pockets > 5 mm	
Mean	47.2
Min.	15
Max.	111
Pocket sum score (mm)	
Mean	756.9
Min.	464
Max.	1083

Max., maximum; Min., minimum.

Table 2. Incidence of bacteremia after scaling in periodontitis patients

	Incidence	Mean magnitude in positive samples (CFU)	Range (CFU)
Baseline	0	0	
0.5 min.	15/20	0.78	[0.11–2.67]
10 min.	7/20	0.22	[0.11–0.67]
30 min.	2/20	0.11	[0.11–0.11]

Incidence data represent number of bacteremic participants out of the total number of participants, while magnitude data represent the number of colony forming units/ml blood.
CFU, colony-forming units.

Table 3. Microorganisms obtained from blood samples of the 15 bacteremic participants

	0.5 min. (CFU)	10 min. (CFU)	30 min. (CFU)	Total (CFU)
Streptococci (13)	32	**7**	**2**	41
Streptococcus anginosus (1)		2		2
Streptococcus australis (1)	1			1
Streptococcus crista (1)	6			6
Streptococcus gordonii (1)	1			1
Streptococcus infantis (1)	1			1
Streptococcus mitis biovar 1 (4)	6	1	1	8
Streptococcus oralis (3)	4			4
Streptococcus parasanguis (2)	2		1	3
Streptococcus salivarius (3)	1	2		3
Streptococcus sanguis (3)	3			3
Streptococcus vestibularis (1)	1			1
Streptococcus spp. (4)	6	2		8
Gram-positive rods (3)	10			10
Actinomyces spp. (1)	5			5
Lactobacillus spp. (1)	1			1
Corynebacterium spp. (1)	2			2
Others (1)	2			2
Gram-negative rods (16)	55	2		57
Porphyromonas gingivalis (2)	8	1		9
Prevotella intermedia (7)	24			24
Prevotella buccae (1)	2			2
Fusobacterium nucleatum (6)	10	1		11
Others (2)	11			11
Unidentifiable (2)	8	7		15
Total (15)	105	16	2	123

Numbers in rows represent the number of isolates, while numbers in parentheses represent number of participants harbouring the strain.
CFU, colony-forming units.

estimate the area of the pocket epithelium, expressed as pocket sum score (PSS).

Experimental procedure

Scaling was performed according to individual need by a combination of hand instruments and airscaler (Sonicflex, KaVo, Denmark). The time used for scaling was recorded. Local anaesthesia was not used in order to avoid bacteremia during injection. All participants were examined and treated by the same dentist (L.F.).

Blood sampling

After thorough disinfection of the skin at the site of venipuncture with 0.5% chlorhexidine ethanol, an indwelling catheter was placed in the antecubital vein. The catheter was rinsed with sterile, isotonic saline after insertion and after obtaining each blood sample. The site of venipuncture was covered by a sterile pad to avoid contamination. Two millilitres of blood was discarded before drawing the blood for the bacteremia analysis in order to avoid addition of saline from the previous flush. Blood samples at baseline and at 0.5, 10 and 30 min postscaling were examined for bacteremia whereas baseline and 8 h postscaling blood samples were collected in heparinized Vacuette® tubes (Hettich Lab Instruments, Hvidovre, Denmark) and examined for levels of cytokines. The blood samples for the bacteremia analyses were collected in tubes containing 1.86 ml of 0.35% sodium polyanaethol sulphonate (SPS). The analyses were performed using the lysis-filtration method (Heimdahl et al. 1990).

Characterization of the bacteremia study

The investigation of an association of alterations in plasma cytokine levels with the magnitude of bacteremia is based on a substudy in an investigation of bacteremia after chewing, toothbrushing and scaling in periodontitis patients, gingivitis patients and periodontally healthy individuals (Forner et al. 2006). Bacteremia after scaling occurred in 15 (75%) of the 20 periodontitis patients. The magnitude decreased considerably within the 30 min. A total of 123 isolates were collected from the 15 bacteremic patients. The majority of isolates was streptococci and Gram-negative rods, but also Gram-positive rods were identified (Tables 2 and 3).

Cytokine analyses

Plasma was separated by centrifugation. Analyses were performed on undiluted samples by means of Cytometric Bead Array Inflammation Kit (Becton Dickinson, Copenhagen, Denmark) and the corresponding software. The intra- and inter-assay variabilities are lower than 10%. (Khan et al. 2004, Jimenez et al. 2005). To this end, a FACScalibur flowcytometer (Becton Dickinson) was employed.

Statistical analyses

A 5% level of significance was used in the statistical analyses. The analyses were performed using the statistical analysis system (SAS) for pc (SAS

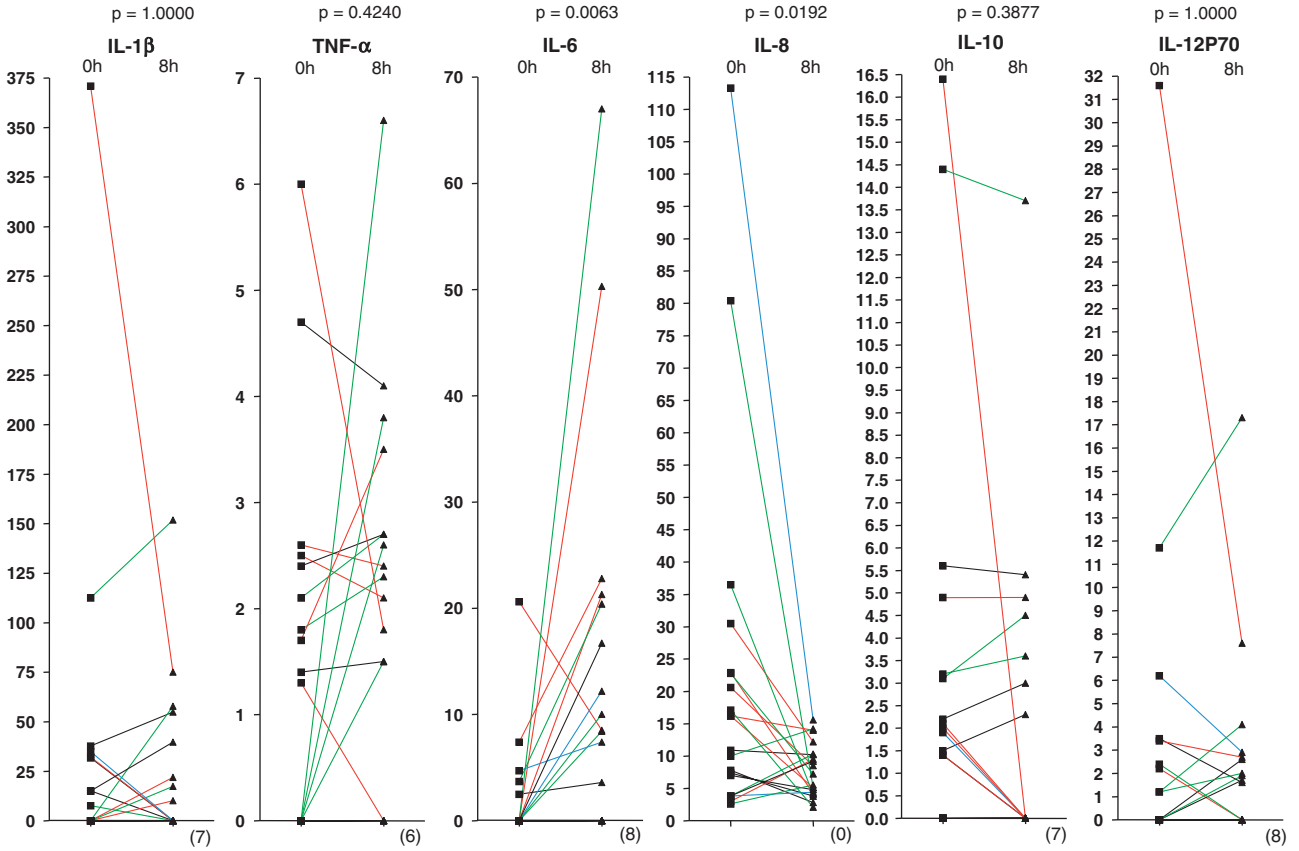

Fig. 1. Plasma cytokine levels before (0) and 8 h after scaling (note different scales for each cytokine). The participants are divided in no bacteremia (black) and duration of bacteremia 0.5 min. (red), 10 min. (green) and 30 min. (blue). Numbers in parenthesis represent the number of patients maintaining a cytokine level of 0 pg/ml throughout the 8 h. pg, picogram; IL, interleukin; TNF, tumour necrosis factor; n, number of participants.

Institute 1987) SAS/STAT guide for personal computers, sixth edition, SAS Institute Inc., Cary, NC). Cytokine levels before and 8 h after scaling were compared by sign statistics. Correlations between bacteremia, cytokine levels and clinical variables were analysed by Spearman's correlation coefficients.

Results

Changes in plasma cytokine levels before and after scaling

Plasma IL-6 was significantly increased ($p = 0.0049$) and plasma IL-8 was significantly decreased ($p = 0.0192$) 8 h after scaling as compared with baseline values. No systematic change was detected in plasma IL-1β, TNF-α, IL-10 and IL-12p70 (Fig. 1).

Effect of bacteremia on plasma cytokine levels

Changes in cytokine levels during the 8-h period were not associated with magnitude, duration or bacterial species of bacteremia. Neither were the baseline cytokine levels or cytokine changes during the 8-h period associated with any clinical variables.

Dependence on other factors

The baseline plasma cytokine levels and changes in plasma cytokines during the 8-h period were independent of age, gender, smoking, periodontal diagnosis (chronic or aggressive periodontitis) and time used for scaling. (Fig. 1 and 2)

Discussion

In the present study, plasma IL-6 was increased and IL-8 was decreased, while levels of IL-1β, TNF-α, IL-10 and IL-12p70 were unaffected by bacteremia. The changes in plasma cytokine levels were not associated with the magnitude of bacteremia. Several factors may account for this finding. Primarily, the magnitude of bacteremia is difficult to determine because of incomplete antiphagocytic, anticomplement and antilysozymal activity of SPS and consequently reduced bacterial recovery. Secondly, there may be an unknown cytokine production by non-vital and uncultivable (Paster et al. 2001) bacteria, which are not detected when analysing blood cultures. Cultivable taxa of oral bacteria have a range of growth requirements and no single isolation medium satisfies all bacteria. Therefore, it is conceivable that the results of this study represent only a fraction of the bacteremias that develop after various manipulations of the oral cavity. In addition, the composition of bacteremias in the present study varied considerably, as both uni and polymicrobial bacteremias were found and with varying magnitude and bacterial spectrum. Conceivably, this complexity influences the cytokine levels, as each strain has an individual impact on cytokine synthesis in vitro (Shapira et al. 1998). Induction of cytokine production by bacterial components is most extensively studied for *P. gingivalis*. However, *P. gingivalis* was not commonly found in our population, which should be taken into consideration when interpreting the results.

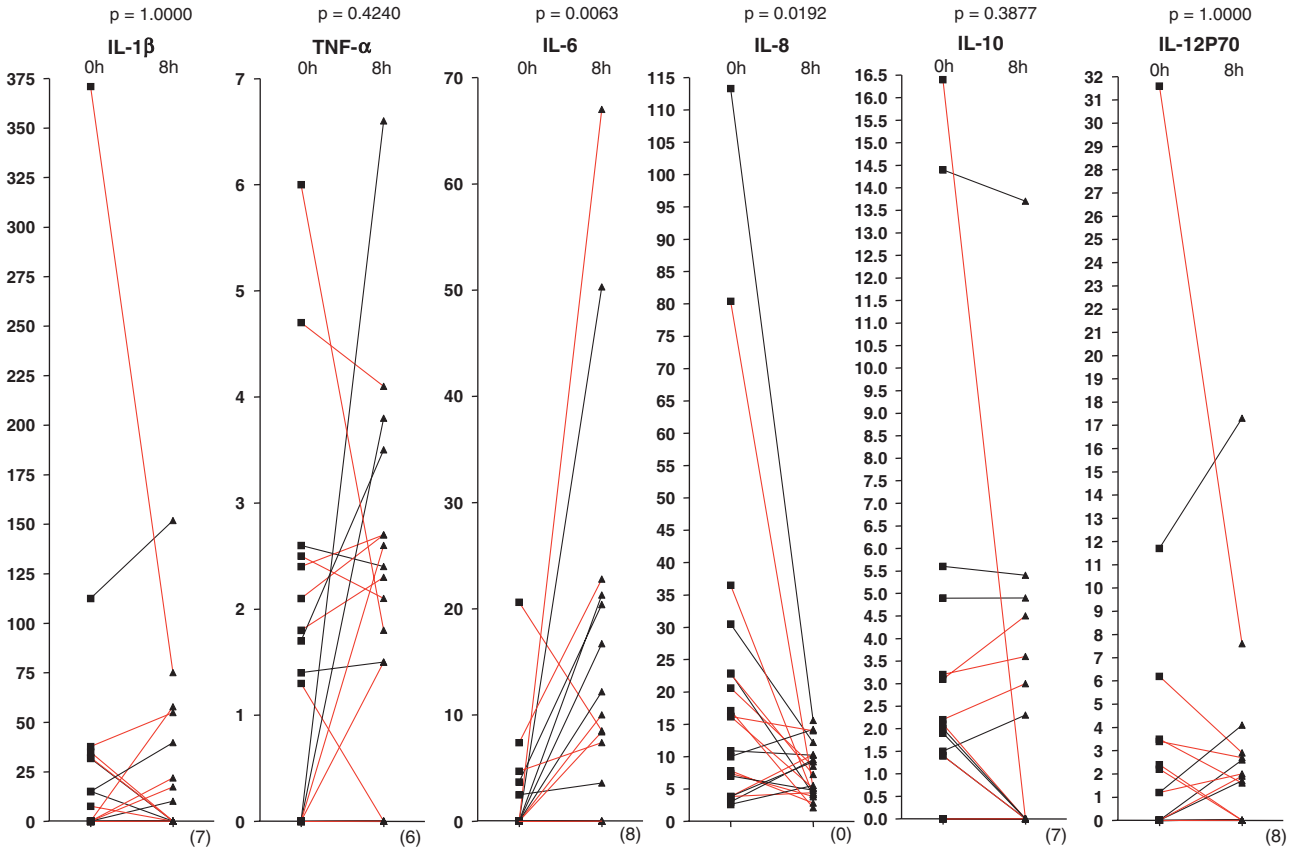

Fig. 2. Plasma cytokine levels before (0) and 8 h after scaling (note the different scales for each cytokine). The participants are divided in chronic (black) and aggressive (red) periodontitis. Numbers in parenthesis represent the number of patients maintaining a cytokine level of 0 pg/ml throughout the 8 h. pg, picogram; IL, interleukin; TNF, tumour necrosis factor; n, number of participants.

Changes in IL-6 levels may have been influenced by the lack of *P. gingivalis*. Thirdly, IL-6 may have been induced locally in the tissues during scaling, which may have contributed to increased plasma levels of IL-6. Finally, differences in host response may account for the observed variation among the 20 participants. For instance, peripheral blood monocytes from individuals with a hyperinflammatory phenotype secrete 3–10-fold greater amounts of IL-1β and TNF-α than do normal individuals (Hernichel-Gorbach et al. 1994).

The increase in plasma IL-6 is consistent with prevous findings by Ide et al. (2004), who demonstrated endotoxinemia and elevated levels of TNF-α and IL-6 after scaling. A reduction in plasma IL-8 has not been previously reported. Apart from a reduced production, the decreased levels could also be due to an increased cellular binding of IL-8 as a result of activation of polymorphonuclear leucocytes by bacterial antigens. In contrast to the findings by Ide et al. (2004), we found no systematic change in plasma TNF-α. Likewise, there were no changes in plasma levels of IL-1β, IL-10 and IL-12p70. It is possible that the investigation of the concentrations and functions of the patients' PMNs would have provided a basis for a more accurate interpretation of the results of the changes in the cytokine levels.

Periodontitis has been shown to be associated with increased circulating levels of IL-6 (Mengel et al. 2002, Buhlin et al. 2003). This increase appears to be correlated with disease severity (Mengel et al. 2002). Furthermore, periodontal treatment is followed by a decrease in circulating inflammatory mediators, which is related to inflammation control (D'Aiuto et al. 2004, 2005). Our study supports this and previous results from in vivo endotoxin infusion studies by concluding that translocation of bacteria from the periodontal pockets gives rise to a systemic inflammatory response. Thus, maintaining healthy periodontal conditions is crucial in order to avoid negative consequences of bacteremia.

The present study may be considered as a step in exploring systemic effects of oral bacteria. Future research should be directed at determining the individual role of single bacterial species and components with regard to cytokine inducing effects.

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Clinical Relevance

Scientific rationale for study: Bacteremia with oral bacteria may induce cytokine synthesis in white blood cells.

Principal findings: Plasma IL-6 was significantly increased 8 h after scaling as compared with baseline values, while plasma IL-8 was significantly decreased. The changes in cytokine concentrations were unaffected by the nature of bacteremia and the clinical characteristics of the participants.

Practical implications: As IL-6 appears to be involved in the pathogenesis of atherosclerosis, bacteremia with oral bacteria may be important for the course of cardiovascular disease. Owing to different abilities of oral bacteria to induce cytokine synthesis, the role of bacteremia with various bacteria in systemic inflammation should be investigated further.