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Effects of Periodontal Therapy on Systemic Markers in Healthy Patients

*Rachana Hegde**

Department of Periodontology, Roseman University of Health Sciences College of Dental Medicine, USA

Abstract

Objectives: Periodontitis is associated with increased in inflammatory markers, especially cytokines and these inflammatory markers in turn have been observed in individuals with various systemic diseases. Periodontal therapy has also been believed to induce bacteremia and is thought to be a risk factor for distant site infections such as infective endocarditis in susceptible individuals. There are also reports of deleterious effects of blood loss following a periodontal surgery. However, there is conflicting data that reflects lack of evidence suggesting strong causal association between periodontal therapy and its effects on inflammatory marker, bacteremia and blood loss. This literature review will assess systemic effects (cytokines, bacteremia and blood loss) of invasive periodontal therapy and dental implants in systemically healthy individuals.

Methods: A comprehensive MEDLINE/PubMed literature search was conducted in January 2012 on systemic effects of surgical periodontal therapy and dental implant therapy. Of the 227 articles identified from literature; 23 articles were identified as highly relevant for the purposes of this literature review and the findings of these selected articles are summarized based on the intervention received.

Results: Inflammatory markers, TNF-α, IL-6, CRP and fibrinogen, significantly increase up to 24 h. After periodontal therapy and reaches its baseline levels after 1 month. Circulating PMNs, erythrocytes and Hemoglobin decreases after therapy and returns to baseline levels at 7 days. Transient bacteremia in the range of 3.3% to 80.9% was found in patients undergoing periodontal therapy. This transient bacteremia was reported to increase significantly during the point of maximum trauma to the soft tissues. Despite individual variation of the extent, invasiveness and duration of periodontal surgery, blood loss after routine periodontal therapy remains below 500 ml.

Conclusion: This literature review identifies anecdotal reports on incidence of cardiovascular and other systemic events following periodontal treatment. It further concludes that the relationship between periodontal treatment, bacteremia and inflammatory markers is dynamic and not completely understood. Further research is required to understand the causative model of post periodontal therapy systemic events.

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Correspondence:
Rachana Hegde, Department of Periodontology, Roseman University of Health Sciences College of Dental Medicine, USA, Tel: (213) 590-6771; Fax: 801-878-1482; E-mail: rhegde@roseman.edu

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Introduction

Chronic periodontitis is defined as an infectious disease resulting in inflammation within the supporting tissues of the teeth, progressive attachment, and bone loss. It is characterized by pocket formation and/or gingival recession [1]. Although it is a disease that is initiated by bacteria and their components like lipopolysaccharide, host defense plays an important role in the pathogenesis and disease progression. Various pathogenic products stimulate a variety of host cells resulting in the expression of inflammatory cytokines. Subsequent cascade of events and alteration in host immune response leads to increased inflammatory cell recruitment and tissue destruction.

It is now known that people with periodontitis have increased systemic levels of acute phase proteins, plasma antibody levels, coagulation factor, total white blood cell count, neutrophils, C reactive protein (CRP), and cytokines such as INF-gamma (Interferon gamma), TNF-α (Tumor necrosis Factor-Alpha), IL (Interleukin)-1β, IL-2 and IL-6 [2-6]. Heightened inflammatory markers have been reported in patients with cardiovascular disease [7,8], adverse pregnancy outcomes [9], diabetes [10] and respiratory disease [11]. Periodontal disease has hence been epidemiologically associated with these adverse systemic outcomes.

Periodontal therapy has also been believed to induce bacteremia, which is considered a risk factor for distant site infections such as infective endocarditis in susceptible individuals. This led to the

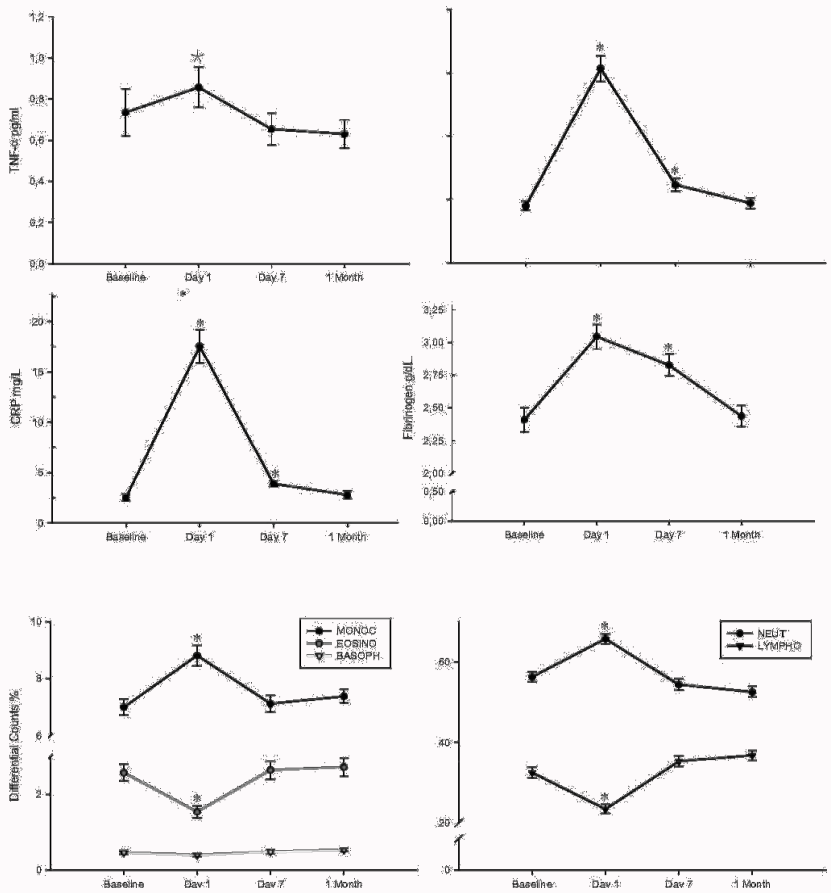

Figure 1: Changes in circulating levels of TNF-a, IL-6, CRP and Fibrinogen and leucocyte differential counts at 1, 7 and 30 days after periodontal therapy [3]. N=55 at each time point. Analysis performed by ANOVA for repeated measures. * P<0.01, * P<0.001.

present American Heart Association recommendations of antibiotic prophylaxis before dental procedures [12]. These recommendations are based on data concerning surrogate measures of risk such as invasiveness of a dental procedure and degree of periodontal disease at surgical site. However, there is conflicting data that reflects lack of evidence suggesting strong causal association between dental procedure-induced bacteremia and infective endocarditis [13]. It is hypothesized that other factors such as host immune and inflammatory response may play a role in determining the systemic effects of invasive dental procedures [14].

The purpose of the present literature review is to assess the systemic effects of invasive periodontal therapy and dental implants in systemically healthy individuals.

Methods

To obtain information on systemic effects of surgical periodontal therapy and dental implant therapy, a comprehensive MEDLINE/PubMed literature search was conducted in January 2017 using the phrases "Systemic effects of periodontal or implant surgery and inflammatory markers or cytokines or plasma proteins" and "Periodontal therapy and Bacteremia". The literature searches yielded 327 articles published to date that were available in English; the author reviewed the abstracts from these 327 articles and selected a subset, attempting to meet the following criteria:

Study design

Randomized clinical trials or prospective studies.

Subjects

Healthy adults with no known systemic complications. Studies that did not report the patients being systemically healthy were not included in this review.

Sample size

More than 10 patients. Articles reporting on single center experience; case reports were not included of the 327 articles identified from literature; there were few articles that were repeated in multiple searches and the actual number of unique articles is less than 327. Based on the above inclusion criteria, 33 articles were identified as highly relevant for the purposes of this literature review and Table 1 and 2 summarizes the findings of these selected articles literature.

Summary of Literature Review

D'Aiuto et al. [3] found that TNF-α, IL-6, CRP and fibrinogen significantly increases and reaches its peak 24 h (Day 1) after periodontal therapy, however it starts decreasing after 24 h and reaches its baseline levels only after 1 month. They also found that the PMNs decreased significantly 24 h after treatment and erythrocytes and hemoglobin level remained lower than normal levels even at day 7 after the treatment. The group later concluded that during the acute response to periodontal therapy, there was a broad concordance between markers of inflammation and endothelial function. Figure 1 summarizes the findings.

Similarly, Ide et al. [26] measured the inflammatory markers immediately after the treatment and found increased levels of both

Table 1: Summary of effects on cytokines after periodontal therapy.

Author	Study design	Sample size	Intervention	Parameter	Follow Up-Time line	Result
Bahrani et al. [14]	Clinical Trial	41	Single and multiple extraction	IL-1 α,IL-1 β, IL-2, IL-4, IL-6, IL-7, IL-8, IL-10, IL-12, GMCSF, IFN-Gamma , and TNF-α	1 hour following single tooth extraction	No significant difference at any time point
					8 and 24 hours following multiple tooth extractions	
Taylor et al. [15]	Randomized Clinical trial	136	Treatment group: Scaling and Root Planing, oral hygiene instructions and extractions	Cardiovascular risk markers: Fibrinogen,CRP, plasminogen activator inhibitor- 1(PAI-1), tissue plasminogen activator, von Willebrand factor (vWF)	8 weeks following treatment	Reduction in fibrinogen in treatment group
				Hematological markers: Hemoglobin(Hb), hematocrit, Red Blood Cells (RBCs), Platelets		Tendency to get lower but not significantly lower levels of CRP, PAI-1and vWF
			Control :no treatment	Inflammatory markers: Lymphocytes, Monocytes,Nuetrophils, White Blood Cells (WBCs)		Hemoglobin, RBCs and hematocrit increased significantly in treatment group and platelets decreasedHDL and total cholesterol also significantly increased in the treatment group compared to the control
				Metabolic Markers: Total cholesterol,HDL,LDL, Triglycerides		
Caúla et al. [16]	Randomized Clinical Trial	64	Test group: Scaling and Root Planing, oral hygiene instructions and extractions	CRP,Erythrocyte Sedimentation Rate(ESR), total cholesterol, HDL,LDL,tryglycerides	2 months and 6months	2 months: Significant reduction of erythrocyte sedimentation rate (ESR) and triglycerides in the test group
			Control :no treatment			6months: Median values of C-reactive protein, ESR, total cholesterol, and triglycerides were reduced
Kamil et al. [17]	Randomized Clinical Trial	36	Test group: Scaling and Root Planing, oral hygiene instructions	CRP, total cholesterol, HDL,LDL,tryglycerides	3 months	Significant reduction in CRP
			Control :no treatment			
Li et al. [18]	Randomized Clinical Trial	50	Test group: Scaling and Root Planing, oral hygiene instructions	Circulating progeniotor cell count (CPCs) and vascular endothelial function, CRP	3 months	No change in CRP, circulating CD34 cells significantly decreased in test group
			Control :no treatment			
Leite et al. [19]	Randomized Clinical Trial	55	Test group: multiple sessions of Scaling and Root Planing, oral hygiene instructions	CRP, total cholesterol, HDL,LDL,tryglycerides and complete blood count	6 months	Decrease in CRP and increase in HDL
			Control :no treatment			
George et al. [20]	Randomized Clinical Trial	45	Test group: Scaling and Root Planing, oral hygiene instructions	IL-6 and CRP	2 months	Decrease in IL-6 and CRP in test group
			Control :no treatment			
D'Aiuto et al. [21]	Randomized Clinical Trial	65	The 3 groups consisted of: 1) an untreated control (24 subjects); 2) a standard regimen of periodontal therapy- subgingival mechanical instrumentation; and 3) an intensive course of periodontal treatment (IPT, 20 subjects), consisting of SPT with adjunctive local delivery of minocycline-HCl	C-reactive protein (CRP), interleukin-6 (IL-6), total cholesterol, and LDL cholesterol	Baseline	Significant reduction in CRP in both treatment groups at 2 months (0.5 ± 0.2 mg/L for SPT, P=0.030 and 0.8 ± 0.2 mg/L for IPT, P=0.001)
						IL-6 also reduced significantly
					2 months	Significant interaction between cigarette smoking and treatment
						Decrease in total and LDL cholesterol after 2 months was found in Intensive Therapy group
D'Auito et al. [3]	Clinical Trial	55	Intensive session of subgingival mechanical instrumentation under local anesthesia (4 h)	TNF-alpha, IL-6, CRP and Fibrinogen	1, 7 and 30 days after treatment	TNF- α levels were significantly raised only after 1 day of therapy
						IL-6 , CRP and Fibrinogen concentration peaked at 24 h and returned to baseline values within one month
						Mild neutrophilia, monocytosis and lymphopenia
D'Auito et al. [22]	Randomized Clinical Trial	94	Subgingival scaling and root planing with subjects under local anesthesia	C-reactive Protein (CRP) and Interleukin-6 (IL-6)]	Baseline	Significant reductions in serum IL-6 (median decrease 0.2 ng/L, 95% CI 0.1-0.4 ng/L)
					2 and 6 months	CRP at 6 months after treatment, (CRP median decrease 0.5 mg/L, 95% CI 0.4-0.7)

D'Aiuto et al. [23]	Single Blind trial	14	Intensive periodontal treatment, consisting of full-mouth subgingival root debridement delivered within a 6-h period	Interleukin-1 receptor antagonist (IL-1Ra), Interleukin-6 (IL-6) and C-reactive protein (CRP)	Baseline	1 day after treatment, mild neutrophilia, monocytosis and lymphopenia
						Sharp increase in IL-1Ra, IL-6,
					1, 3, 5, 7 and 30 days after treatment	A 10-fold increase in CRP at day 1 and remained high upto 1 week.
						At 3–7 days after treatment, mild tendency towards a normocytic anemic state and a degree of lympho-thrombocytosis
Elter et al. [24]		22	Subgingival scaling and root planing with subjects under local anesthesia	CRP, IL-6, total cholesterol, or high-density lipoprotein cholesterol	Baseline	At 1 months significant reduction in, flow-mediated dilation, and serum IL-6and a trend toward reduction in serum CRP
					1 month	no significant changes in nitroglycerinmediated dilation and cholesterol
Forner et al. [25]	Single Center Prospective Study	20	Scaling without local anesthesia	IL-1b, TNF-α, IL-6, IL-8, IL-10 and IL-12p70	Baseline	At 8 hours-IL-6 levels were significantly
					8 hour post scaling	IL-8 was significantly decreased
						No systematic changes occurred in the levels of IL-1b, TNF–α, IL-10 and IL-2p70.
Ide et al. [26]	Clinical Trial	39	Subgingival debridement with ultrasonic and hand instruments	Serum and plasma fibrinogen, C-reactive protein, sialic acid, TNF-α and interleukin -6 and -1b	6 weeks after completion of treatment or after an equivalent 3-month control period	No statistically significant changes in levels of any of the systemic markers
Ide et al. [27]	Clinical Trial	23	Subgingival scaling for 60 minutes	TNF α, IL-6, CRP	0, 15, 30, 60 and 120 minutes	Significant increase in circulating TNF a and IL-6
Rahman et al. [28]	Single Center Prospective Study	10	Tooth extraction followed by Dental Implant	CRP	6 months	At 12 months-Mean CRP levels decreased significantly (from 3.45 to 1.55 mg/dl)
					9 months	6,9, and 12-month post-implant placement mean CRP values were statistically significantly different from the mean pre-operative CRP value
					12 months	
Taylor et al. [29]		67	Full mouth tooth extraction	C-reactive protein, plasminogen activator inhibitor-1 and fibrinogen, and white cell and platelet counts	Baseline	At 12 weeks-CRP and PAI-1 levels fell significantly
					12 weeks	Fibrinogen values decreased significantly
						Total white blood cell count, neutrophils, lymphocytes, and platelets also were significantly reduced
Tonetti et al. [30]	Randomized Clinical Trial	120	Intensive periodontal therapy- SRP + extraction+ arestin	CRP, IL-6, TNF-α, E- selectin, von Willebrand factor, neutrophils	Before treatment and	At 24 hrs.- flow mediated dilatation was significantly lowered in the intensive-treatment group than in the control-treatment group (absolute difference, 1.4%; 95% [CI], 0.5 to 2.30)
					1, 7, 30, 60, and 180 days after treatment	Levels of C-reactive protein, interleukin-6, and the endothelial-activation markers soluble E-selectin and von Willebrand factor were significantly higher for all comparison
						At 60 and 180 days, flow-mediated dilatation was greater and the plasma levels of soluble E-selectin were lower in the intensive-treatment group than in the control group
Ushida et al. [31]	Randomized Clinical Trial	36	Three groups: undergoing Quadrant wise mechanical debridement, single-visit Full mouth debridement with povidone iodine or with water	Serum IL-6 and soluble thrombomodulin were measured by enzyme-linked immunosorbent assay, and serum CRP	Baseline,	Serum IL-6 level increased significantly immediately after debridement in all the three groups
						No significant difference in CRP in any groups at any time points
					Immediately after 1 month	At 1 month-quadrant-wise group, serum IL-6 level decreased significantly compared with baseline.
						Serum-soluble thrombomodulin decreased significantly in the full-mouth groups but not in the quadrant-wise group

Yamazaki et al. [32]		24	Scaling and root planing or periodontal surgery	C-reactive protein (CRP), interleukin-6 and tumor necrosis factor-a (TNF-a)	Baseline and Completion of treatment	No significant difference in level of CRP interleukin-6 TNF-α levels did not change following periodontal treatment

Table 2: Summary of bacteremia after periodontal and implant surgery.

Author	Study design	Sample size	Intervention	Follow up time	Result	Microorganisms identified
Asi et al. [33]	Clinical Trial	30	Modified Widman Flap	Point of maximum trauma-degranulation and SRP	46 % patients without Antibiotic prophylaxis were positive for micro organisms	*Staphylococcus albus* coagulase negative, *Klebsiella*, *Psedomonas aerugenosa*, *Streptococcus viridans*, Alpha hemolytic *Streptococcus*, *Neisseria catarrhalis*
Castillo et al. [34]	Prospective Study	42	Full mouth SRP	Immediately after SRP	Bacteremia was found in 21.4% to 38% of patients immediately after treatment	*P gingivalis* and *A actinomycetemcomitans* were the most frequent organisms seen before and after SRP
				15 min	19%- 28.6% 15 min after the treatment	
				30 min	14.3%-11.9% 30 min after the treatment	
Kinane et al. [35]	Single blinded parallel study	30	Full Mouth Ultrasonic Scaling, Periodontal Probing and Tooth Brushing	Baseline- 1 min after probing	Reported % of Bacteremia using culture techniques	*Streptococcus parasanguis*, *A. naeslundii*, *Eubacterium* sp., *Eubacterium limosum*, *Propionobacterium acnes*
					Ultrasonic scaling 13%	
					Periodontal probing 20%	
				Up to 3 min after tooth brushing	Tooth brushing 3%	
					Reported % of Bacteremia using PCR	
				Immediately after FM ultrasonic	Ultrasonic scaling 23%	
					Periodontal probing 16%	
					Tooth brushing 13%	
Lafaurie et al. [36]	Clinical Trial	42	SRP	Immediately before treatment	80.9% of the patients presented positive cultures after SRP and it occurred more frequently immediately after treatment	Frequently identified *Porphyromonas gingivalis*, *Micromonas micros* and *Actinomyces* spp. Less Frequent *Campylobacter* spp., *Eikenella corrodens*, *Tannerella forsythensis*, *Fusobacterium* spp.and *Prevotella intermedia*
				15 min		
				30 min after treatment	19% of the patients still had microorganisms in the bloodstream 30 min. after the procedure	
Pineiro et al. [37]	RCT	50	Implant	Baseline	Prevalence of bacteremia was 6.7% at 30 s and 3.3% at 15 min	
				30 s after implant placement	No statistically significant differences were found with baseline	
				15 min after suturing		

IL-6 and TNF-alpha within 60 min to 120 min post treatment, but no significant difference in the measured levels were noted by the same group at 6 weeks. Ushida et al. [31] found this effect to be greater in patients treated with full mouth debridement compared to quadrant wise mechanical debridement and hence recommended evaluating the risks and benefits of full mouth debridement in patients with higher circulating levels of these markers i.e., people at high risk for cardiovascular events. However, Bahrani et al. [14] found no significant differences in any of the cytokine levels between baseline and 1 h post extraction. But, they also reported that their subjects had high variability in baseline cytokine levels and their study lacked the power (n=41) to identify the existing differences in cytokine levels.

Summary

Bacteremia occurs when bacteria enter the bloodstream transiently and can be detected by laboratory blood culture techniques. Numerous papers were found in literature citing the incidence of bacteremia after daily procedures including chewing and tooth brushing. However, very few papers were found emphasizing the association between bacteremia and periodontal surgery. Also, it was difficult to differentiate between the treatment groups "scaling and root planning" and "periodontal surgery", since little information was available on the invasiveness of the "scaling and root planning" procedure. For the sake of completeness of this review, non-surgical periodontal procedure like full mouth scaling and root planning with sub gingival curettage are included in this review.

Bacteremia was found in patients undergoing periodontal therapy in the range of 3.3% to 80.9%. However, most studies concluded that this bacteremia is transient in nature and increases significantly during the point of maximum trauma to the soft tissues.

Discussion

Following periodontal therapy, cascade of events occur that include bacteremia, increased circulating inflammatory markers and blood loss. It is empirical to understand the interaction between these factors to identify a new causal model of association between oral therapy and incidence of adverse systemic events like infective endocarditis.

Inflammatory Markers and Bacteremia

While bacteremia does occur as result of periodontal surgery, it is also evident that "everyday" procedures like chewing and tooth

brushing also results in bacteremia [28]. Most of the literature available measures the percentage prevalence of bacteremia and not the intensity. The intensity of the inocula of disseminated bacteria found in humans is lower than the intensity of bacteremia that has been shown to be an important factor in the genesis of experimental animal endocarditis [38]. Hence, argument in the favor of periodontal manipulation being the cause of cardiovascular events still remains unproven.

It is also evident from the current review that there is a transient increase in the inflammatory markers especially IL-6, TNF-α and CRP after periodontal therapy. It is proposed that the mechanisms that lead to this increased systemic inflammatory burden in otherwise healthy individuals include: (a) the local, infection driven production of inflammatory mediators (IL-1, IL-6) "dumped" into systemic circulation [39,40]. (b) the ability of the periodontal pathogens and/or their toxins to disseminate and thus induce a distant inflammatory response [41,42]. (c) a combination of the above.

Bacteremia and Blood Loss

A correlation was found between the duration of oral surgery, amount of blood loss and bacteremia. When the amount of blood loss was more than 50 ml and the duration of surgery exceeded 100 min, the incidence of bacteremia was higher [43]. There was a statistically significant difference in the incidence of blood cultures positive for organisms at both shorter (<3 min, P=0.04) and longer (>6 min, P=0.04) surgery times [44]. On the contrary, Takai et al. [45] found that there was no association between degree of surgical invasion and bacteremia. They concluded in their clinical trial of 237 patients that any transoral incision produces bacteremia, the risk increases if the site is infected.

Conclusion

The results from this literature review indicate that there are anecdotal reports on incidence of cardiovascular and other systemic events following periodontal treatment. The relationship between periodontal treatment, bacteremia and inflammatory markers is dynamic but not completely understood. Further research is required to understand this interplay and its effects on systemic health.

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