Original Paper

Pathophysiology of Haemostasis and Thrombosis

Pathophysiol Haemost Thromb 2009–10;37:49–54
DOI: 10.1159/000318189

Received: March 9, 2010
Accepted after revision: April 26, 2010
Published online: July 3, 2010

Levels of C-Reactive Protein and Protein C in Periodontitis Patients with and without Cardiovascular Disease

Ezgi Malali[a] Isik Basar[c] Ebru Emekli-Alturfan[b] Eser Elemek[d] Sehkar Oktay[b] Faruk Ayan[c] Nesrin Emekli[b] Ulku Noyan[a]

Departments of [a]Periodontology and [b]Biochemistry, Faculty of Dentistry, Marmara University, and [c]Department of Cardiology, Cerrahpasa Medical Faculty and [d]Department of Immunology, Institution of DETAE, Istanbul University, Istanbul, Turkey

Key Words
Periodontitis · Community Periodontal Index of Treatment Needs · Cardiovascular disease · C-reactive protein · Protein C

Abstract
Since periodontitis is a chronic and inflammatory disease, a number of hypotheses have proposed that it has an etiological or modulating role in cardiovascular disease (CVD). This study aimed to ascertain the changes in the plasma levels of C-reactive protein (CRP) and protein C (PC), a natural anticoagulant also having an anti-inflammatory effect, in patients who have mild-to-severe periodontitis with or without CVD. The test group consisted of 26 patients with CVD and chronic periodontitis and the control group consisted of 26 patients with chronic periodontitis and no systemic disease. In both groups Community Periodontal Index of Treatment Needs scores were recorded and blood samples were collected. CRP levels were significantly high and PC activity was significantly low in the test group compared to the control group ($p < 0.001$). There was a negative correlation between tooth loss and PC and between CRP and PC. How PC is affected by the inflammatory events and its association with CRP is an active area of investigation.

Introduction

Since cardiovascular disease (CVD) is one of the leading causes of death in developed countries, understanding the risk factors for atherosclerosis and CVD has been a very active area of investigation. In the last decade researches have shifted their focus from classic causes to alternative risk factors. Now it is well known that atherosclerosis occurs in response to an injury of the vascular endothelium and that it is an inflammatory process [1]. A hypothesis of the contribution of chronic infections to atherogenesis led scientist to investigate the relationship between oral hygiene and CVD [2]. Epidemiological studies suggest a link between periodontal infections and an increased risk for CVD, and associations are observed between the severity of periodontitis and coronary atherosclerosis [3, 4].

Periodontitis is a chronic infection affecting the tissues surrounding and supporting the teeth, caused by the bacteria of the dental plaque and the inflammatory response of the host. Periodontal diseases are initiated by the accumulation of plaque bacteria, such as *Porphyromonas gingivalis* and *Treponema denticola*, around teeth and in the gingival sulcus [5, 6]. As a response to the presence of bacteria and bacterial products, such as li-

KARGER

Fax +41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

1424–8832/10/0371–0049$26.00/0

Accessible online at:
www.karger.com/pht

Ezgi Malali
Marmara University, Faculty of Dentistry, Department of Periodontology
Guzelbahce Buyukciftlik, Sok. No:6 Kat:4
TR–34365 Nisantasi/Istanbul (Turkey)
Tel. +90 532 437 56 58, E-Mail ezgimalali@hotmail.com

popolysaccharides, cell-mediated inflammation is triggered and a number of proinflammatory cytokines (tumor necrosis factor (TNF)-α, interleukin (IL)-1, and IL-8) are synthesized [7–9].

Like the inflammatory process of CVD, systemic inflammation primed by periodontal infection and the release of lipopolysaccharides into the periphery also activates both inflammatory cells and endothelial cells, and cytokines are carried to the liver where they induce the production of acute-phase proteins such as C-reactive protein (CRP). It has been shown that CRP is not only a predictor of CVD but also an active mediator of atherogenesis and that it affects endothelial cells and monocytes/macrophages [8, 10].

Protein C (PC), a precursor of activated PC (APC), is a vitamin K-dependent plasma glycoprotein synthesized by the liver and obtained by the effect of thrombin in plasma; PC has a crucial effect on coagulation by suppressing the formation of fibrin. The normal range (70–140%) of circulating levels of PC has been well established by several epidemiological studies and in healthy humans a positive correlation between PC and APC was found. The PC pathway is the most important mechanism in preventing microvascular thrombosis [11, 12], and along with endothelial PC receptor it also regulates coagulation in large vessels [13]. Besides this anticoagulant property, APC is also thought to have potent anti-inflammatory properties. APC dampens inflammation by inhibiting monocyte/macrophage expression, cytokine signaling, the upregulation of cell surface leukocyte adhesion molecules, and leukocyte-endothelial cell interactions. But when there is a more profound injury or inflammatory stimulus, cytokines such as IL-1 and TNF-α from activated leukocytes suppress the PC pathway and reduce the levels of APC [14].

Since periodontitis and CVD share the same inflammatory pathogenesis, we aimed to ascertain whether there is an association between the severity of periodontitis and CVD by determining the levels of CRP, an inflammatory marker, and PC, an anti-inflammatory, anticoagulant marker.

Patients and Methods

Patients admitted to the Cardiology Department of Cerrahpasa Medical Faculty, who were hospitalized with a diagnosis of CVD and were in the subacute phase, were dentally examined and their Community Periodontal Index of Treatment Needs (CPITN) scores were recorded. In the dental clinic of the Periodontology Department systemically healthy patients were clinically examined and their CPITN scores were recorded as well (table 1).

Table 1. Patient demographics of the groups

	Study patients	Test group	Control group
Male	29	17	12
Female	23	9	14
Mean age (range), years	54.21 (40–85)	57.26 (40–85)	51.15 (40–75)
Tooth loss (mean ± SD)	10.59 ± 7.38	13.69 ± 7.74	7.50 ± 5.59[a]

SD = Standard deviation.
[a] Test group versus control group, $p < 0.003$.

Blood samples were collected from both groups to determine CRP levels and PC activity. CRP was evaluated using the quantitative turbidimetric method (Futura System, Rome, Italy) and functional PC activity was determined by quantitative sandwich enzyme immunoassay (Hyphen BioMed, France). Ethical approval for the study was obtained from the local committee of ethics of Istanbul University, and informed written consent was provided by each participant.

Results

Twenty-six patients (17 male and 9 female) and 26 control patients (12 male and 14 female) participated in our study. Thirty-one patients were examined in the Cardiology Department; 5 fully edentulous patients were not included in the study. To equally distribute the CPITN scores, 45 systemically healthy patients were examined in the dental clinic and 26 of them were included in the study. The mean age of the patients included in the study was 54.21 years for the test group and 57.26 years for the control group. In each group there were 10 patients with CPITN score 2, 11 patients with CPITN score 3, and 5 patients with CPITN score 4. In the test group the mean tooth loss was 13.69 and in the control group it was 7.50; the difference between the groups was statistically significant ($p < 0.003$) (table 1).

In the test group the CRP level was 6.32 ± 9.76 mg/l and in the control group it was 0.98 ± 1.06 mg/l; PC activity was 79.38 ± 18.99% in the test group and 110.31 ± 17.05% in the control group. The difference between the test and control groups was statistically significant ($p < 0.001$) (table 2). There was a negative correlation between tooth loss and PC ($r = -0.295$) and between CRP and PC ($r = -0.467$) (table 3).

Table 2. PC and CRP levels in the test and control groups

	Test group	Control group	p
CRP (mean ± SD), mg/l	6.32 ± 9.76	0.98 ± 1.06	<0.001
PC (mean ± SD), %	79.38 ± 18.99	110.31 ± 17.05	<0.001

SD = Standard deviation.

Table 3. Correlations between CRP, PC and tooth loss

Correlation	r
CRP-PC	–0.467[a]
Tooth loss-PC	–0.295[b]
Tooth loss-CRP	0.265

[a] Spearman correlation is significant at the 0.01 level.
[b] Spearman correlation is significant at the 0.05 level.

Discussion

Although a number of studies have been performed recently on the possible association between CVD and periodontitis, this association is not thoroughly understood yet [15, 16]. In our study, we aimed to ascertain the levels of CRP and PC in blood in patients who have mild-to-severe periodontitis with or without CVD.

Among all the acute phase reactants, CRP in particular has been the focus of attention as a key marker of atherosclerosis, and elevated levels constitute a risk predictor for CVD [17–20]; since the levels of CRP rise earlier than those of other reactants, CRP has been used as an early marker of tissue damage [21]. The casual link between CRP and CVD remains to be established. The association of CRP with CVD may be attributed to its association with other reactant proteins that promote thrombosis [22, 23]. There are several mechanisms suggesting that CRP promotes CVD, including binding to partly degraded low-density lipoprotein in atherosclerotic plaques, proinflammatory effects, and an increasing macrophage production of tissue which may promote thrombosis [24, 25]. Similar to the findings of other studies [26–29], in the present study we also found that the CRP level in the CVD group was significantly higher ($p < 0.001$) than that in the healthy controls, indicating a role of CRP in CVD.

Against periodontal infection, hosts respond with both innate and adaptive immunity. Although periodontitis has a chronic nature, acute-phase elements are also a part of the innate immunity in periodontitis and confirm that, in periodontitis, a systemic inflammation is present [30, 31]. There are a number of studies which compare periodontal infections and the systemic markers of inflammation, particularly CRP [32–35]. Bizzarro et al. [35] compared the CRP levels of periodontitis patients to those of periodontally healthy patients and found a statistically significant difference. In agreement with Bizzarro et al. [35], most studies have shown a relationship between CRP and periodontal disease severity [34, 36, 37]. On the contrary, there are some studies that have found no relationship between healthy and periodontitis patients [8, 33]. According to our study design, the control group consisted of systemically healthy but periodontally diseased individuals and we did not find a correlation between CRP levels and periodontal disease severity. Different results were reported by the studies performed using CPITN scores. Accordingly, Wakai et al. [36] found a statistically significant elevation of CRP levels between groups, while Furuichi et al. [8] did not find a significant difference between periodontal groups. In the present study we did not find a correlation between CRP levels and periodontal disease severity. These contradictory results about the relationship between CRP and periodontal disease can be due to the unstable character of CRP, the influence of many conditions in the body [38, 39], and the variety of tests performed to measure CRP levels [8].

Since CVD is closely related to both coagulation and the inflammatory system, PC may be an important marker for determining the host response. Many studies conducted on sepsis cases revealed that the PC pathway played an important role in the clinical outcome of the patients [40–42]. According to an animal study, the amount of APC determines the response of baboons to *Escherichia coli* infusion, independently of the amount of bacteria [43]. Numerous studies have demonstrated that decreased circulating levels of PC in septic patients are associated with increased morbidity and mortality [11, 44–46], and the development of PC deficiency within approximately 1 day of diagnosis of sepsis has been correlated with early death [47]. The present study revealed statistically significantly lower amounts of PC in CVD patients compared to those in healthy controls. This decrease could be due to the regular consumption of PC according to the chronic characteristic of CVD. Another possibility could be the deficiency in PC production,

which can lead to impaired anticoagulation, thrombus formation, and thus CVD. The relationship between CVD and PC is still unknown and needs to be clarified with larger study groups.

When considering the relationship between poor oral hygiene and CVD, tooth loss is one important marker that is investigated and there are still controversies as to whether it is related or not [39, 48, 49]. The test group had a higher (almost double) amount of tooth loss than the healthy controls (13.69 and 7.50, respectively) ($p < 0.003$), although the severity of periodontal disease between the groups was equally distributed. This statistically and clinically significant result might indicate that tooth loss can be related to an increased risk for CVD.

There are studies showing that CRP levels increase as the amount of tooth loss increases [39, 50, 51] and 1 study showing no relationship [52]. In the present study we did not find a correlation between CRP and tooth loss. You et al. [51] and Linden et al. [39] found high levels of CRP in the high-tooth-loss group (17–32 mg/l, tooth loss >14). The mean tooth loss of the test group in the present study was 10.59 ± 7.38, which is relatively low; this could be the reason we did not find a correlation between CRP and tooth loss.

When the PC levels of this study were analyzed considering dental data, the level of PC was not correlated with the severity of the periodontitis, but there was a statistically significant negative correlation between tooth loss and PC levels. PC is an important marker in sepsis [14, 53] and this means that when the bacteria invade the circulation, PC and its pathway react to that invasion. According to this knowledge it is thought that there could be a relationship between PC and periodontitis because it is well known that periodontal bacteria from the subgingival biofilm may enter the systemic circulation and colonize the coronary endothelium and may constantly cause small amounts of bacteremia [54]. Since this study is the first one to investige the relationship between periodontitis and PC levels, there is not enough data to make a decision, but this negative correlation with tooth loss could indicate that PC levels may reflect the effect of long-term inflammation in the entire body.

Recent studies have shown that the PC pathway is in many ways downregulated by proinflammatory cytokines, and that cytokines such as IL-6 and TNF are present in high amounts in CVD [12, 55]. According to the study of Nan et al. [12] CRP was also found to downregulate both EPCR and thrombomodulin, which are critical in the activation of the PC pathway. This finding supports the idea that CRP promotes CVD and is in agreement with the strong negative correlation between CRP and PC levels in the present study.

Periodontitis has been proposed as playing an etiological or modulating role in CVD. In this study, the levels of CRP and PC were statistically significantly different in the test and control groups, but how PC might impact the inflammatory systems and the association between the PC pathway and CRP remains an active area of investigation.

Acknowledgement

In addition to the support of the authors' institutions, this study was partially supported by project number 25-DPT-070401 from the Commission of Scientific Investigations Projects of Yıldız University.

References

1 Tonetti MS: Periodontitis and risk for atherosclerosis: an update on intervention trials. J Clin Periodontol 2009;36:15–19.

2 Mattila KJ, Pussinen PJ, Paju S: Dental infections and cardiovascular diseases: a review. J Periodontol 2005;76:2085–2088.

3 Andriankaja OM, Genco RJ, Dorn J, Dmochowski J, Hovey K, Falkner KL, Trevisan M: Periodontal disease and risk of myocardial infarction: the role of gender and smoking. Eur J Epidemiol 2007;22:699–705.

4 Bahekar AA, Singh S, Saha S, Molnar J, Arora R: The prevalence and incidence of coronary heart disease is significantly increased in periodontitis: a meta-analysis. Am Heart J 2007;154:830–837.

5 Page RC, Kornman KS: The pathogenesis of human periodontitis: an introduction. Periodontol 2000 1997;14:9–11.

6 Lalla E, Lamster IB, Hofmann MA, Bucciarelli L, Jerud AP, Tucker S, Lu Y, Papapanou PN, Schmidt AM: Oral infection with a periodontal pathogen accelerates early atherosclerosis in apolipoprotein E-null mice. Arterioscler Thromb Vasc Biol 2003;23:1405–1411.

7 Espinola-Klein C, Rupprecht HJ, Blankenberg S, Bickel C, Kopp H, Rippin G, Victor A, Hafner G, Schlumberger W, Meyer J: Impact of infectious burden on extent and long-term prognosis of atherosclerosis. Circulation 2002;105:15–21.

8 Furuichi Y, Shimotsu A, Ito H, Namariyama Y, Yotsumoto Y, Hino Y, Mishige Y, Inoue M, Izumi YJ: Associations of periodontal status with general health conditions and serum antibody titers for *Porphyromonas gingivalis* and *Actinobacillus* actinomycetemcomitans. J Periodontol 2003;74:1491–1497.

9 Desvarieux M, Demmer RT, Rundek T, Boden-Albala B, Jacobs DR Jr, Sacco RL, Papapanou PN: Periodontal microbiota and carotid intima-media thickness: The Oral Infections and Vascular Disease Epidemiology Study (INVEST). Circulation 2005;111:576–582.
10 Paraskevas S, Huizinga JD, Loos BG: A systematic review and meta-analyses on C-reactive protein in relation to periodontitis. J Clin Periodontol 2008;35:277–290.
11 Yan SB, Helterbrand JD, Hartman DL, Wright TJ, Bernard GR: Low levels of protein C are associated with poor outcome in severe sepsis. Chest 2001;120:915–922.
12 Nan B, Yang H, Yan S, Lin PH, Lumsden AB, Yao Q, Chen C: C-reactive protein decreases expression of thrombomodulin and endothelial protein C receptor in human endothelial cells. Surgery 2005;138:212–222.
13 Fukudome K, Ye X, Tsuneyoshi N, Tokunaga O, Sugawara K, Mizokami H, Kimoto M: Activation mechanism of anticoagulant protein C in large blood vessels involving the endothelial cell protein C receptor. J Exp Med 1998;187:1029–1035.
14 Van De Wouwer M, Collen D, Conway EM: Thrombomodulin-protein C-EPCR system: integrated to regulate coagulation and inflammation. Arterioscler Thromb Vasc Biol 2004;24:1374–1383.
15 Emingil G, Buduneli E, Aliyev M: Association between periodontal disease and acute myocardial infarction. J Periodontol 2000; 71:1882–1886.
16 Genco R, Offenbacher S, Beck J: Periodontal disease and cardiovascular disease: epidemiology and possible mechanisms. J Am Dent Assoc 2002;133:14–22.
17 Danesh J, Collins R, Appleby P, Peto R: Association of fibrinogen, C-reactive protein, albumin, or leukocyte count with coronary heart disease: meta-analyses of prospective studies. JAMA 1998;279:1477–1482.
18 Blake GJ, Ridker PM: High sensitivity C-reactive protein for predicting cardiovascular disease: an inflammatory hypothesis. Eur Heart J 2001;22:349–352.
19 Ridker PM, Brown NJ, Vaughan DE, Harrison DG, Mehta JL: Established and emerging plasma biomarkers in the prediction of first atherothrombotic events. Circulation 2004; 109:6–19.
20 Ridker PM, Silvertown JD: Inflammation, C-reactive protein, and atherothrombosis. J Periodontol 2008;79:1544–1551.
21 Lowe GD: The relationship between infection, inflammation, and cardiovascular disease: an overview. Ann Periodontol 2001;6: 1–8.
22 Mendall MA, Strachan DP, Butland BK, Ballam L, Morris J, Sweetnam PM, Elwood PC: C-reactive protein: relation to total mortality, cardiovascular mortality and cardiovascular risk factors in men. Eur Heart J 2000; 21:1584–1590.
23 Lowe GD, Yarnell JW, Rumley A, Bainton D, Sweetnam PM: C-reactive protein, fibrin D-dimer, and incident ischemic heart disease in the Speedwell study: are inflammation and fibrin turnover linked in pathogenesis? Arterioscler Thromb Vasc Biol 2001;21:603–610.
24 Lagrand WK, Visser CA, Hermens WT, Niessen HW, Verheugt FW, Wolbink GJ, Hack CE: C-reactive protein as a cardiovascular risk factor: more than an epiphenomenon? Circulation 1999;100:96–102.
25 Pepys MB, Berger A: The renaissance of C reactive protein. BMJ 2001;322:4–5.
26 Tracy RP, Lemaitre RN, Psaty BM, Ives DG, Evans RW, Cushman M, Meilahn EN, Kuller LH: Relationship of C-reactive protein to risk of cardiovascular disease in the elderly: results from the Cardiovascular Health Study and the Rural Health Promotion Project. Arterioscler Thromb Vasc Biol 1997;17: 1121–1127.
27 Ridker PM, Hennekens CH, Buring JE, Rifai N: C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. N Engl J Med 2000; 342:836–843.
28 Ridker PM, Stampfer MJ, Rifai N: Novel risk factors for systemic atherosclerosis: a comparison of C-reactive protein, fibrinogen, homocysteine, lipoprotein(a), and standard cholesterol screening as predictors of peripheral arterial disease. JAMA 2001;285:2481–2485.
29 Albert CM, Ma J, Rifai N, Stampfer MJ, Ridker PM: Prospective study of C-reactive protein, homocysteine, and plasma lipid levels as predictors of sudden cardiac death. Circulation 2002;105:2595–2599.
30 Ebersole JL, Cappelli D: Acute phase reactants in infections and inflammatory diseases. Periodontology 2000;23:19–49.
31 Loos BG: Systemic markers of inflammation in periodontitis. J Periodontol 2005;76:2106–2115.
32 Buhlin K, Gustafsson A, Pockley AG, Frostegard J, Klinge B: Risk factors for cardiovascular disease in patients with periodontitis. Eur Heart J 2003;24:2099–2107.
33 Craig RG, Yip JK, So MK, Boylan RJ, Socransky SS, Haffajee AD: Relationship of destructive periodontal disease to the acute-phase response. J Periodontol 2003;74: 1007–1016.
34 Joshipura KJ, Wand HC, Merchant AT, Rimm EB: Periodontal disease and biomarkers related to cardiovascular disease. J Dent Res 2004;83:151–155.
35 Bizzarro S, Van Der Velden U, Ten Heggeler JM, Leivadaros E, Hoek FJ, Gerdes VE, Bakker SJ, Gans RO, Ten Cate H, Loos BG: Periodontitis is characterized by elevated PAI-1 activity. J Clin Periodontol 2007;34:574–580.
36 Wakai K, Kawamura T, Umemura O, Hara Y, Machida J, Anno T, Ichihara Y, Mizuno Y, Tamakoshi A, Lin Y, Nakayama T, Ohno Y: Associations of medical status and physical fitness with periodontal disease. J Clin Periodontol 1999;26:664–672.
37 Amar S, Gokce N, Morgan S, Loukideli M, Van Dyke TE, Vita JA: Periodontal disease is associated with brachial artery endothelial dysfunction and systemic inflammation. Arterioscler Thromb Vasc Biol 2003;23: 1245–1249.
38 Sattar N, Lowe GD: High sensitivity C-reactive protein and cardiovascular disease: an association built on unstable foundations? Ann Clin Biochem 2006;43:252–256.
39 Linden GJ, McClean K, Young I, Evans A, Kee F: Persistently raised C-reactive protein levels are associated with advanced periodontal disease. J Clin Periodontol 2008;35: 741–747.
40 Fisher CJ, Yan SB: Protein C levels as a prognostic indicator of outcome in sepsis and related diseases. Crit Care Med 2000;28:49–56.
41 Faust SN, Levin M, Harrison OB, Goldin RD, Lockhart MS, Kondaveeti S, Laszik Z, Esmon CT, Heyderman RS: Dysfunction of endothelial protein C activation in severe meningococcal sepsis. N Engl J Med 2001;345: 408–416.
42 Liaw PC, Esmon CT, Kahnamoui K, Schmidt S, Kahnamoui S, Ferrell G, Beaudin S, Julian JA, Weitz JI, Crowther M, Loeb M, Cook D: Patients with severe sepsis vary markedly in their ability to generate activated protein C. Blood 2004;104:3958–3964.
43 Taylor F, Chang A, Ferrell G, Mather T, Catlett R, Blick K, Esmon CT: C4b-binding protein exacerbates the host response to *Escherichia coli*. Blood 1991;78:357–363.
44 Fourrier F, Chopin C, Goudemand J, Hendrycx S, Caron C, Rime A, Marey A, Lestavel P: Septic shock, multiple organ failure, and disseminated intravascular coagulation: compared patterns of antithrombin III, protein C, and protein S deficiencies. Chest 1992;101:816–823.
45 Fijnvandraat K, Derkx B, Peters M, Bijlmer R, Sturk A, Prins MH, van Deventer SJ, ten Cate JW: Coagulation activation and tissue necrosis in meningococcal septic shock: severely reduced protein C levels predict a high mortality. Thromb Haemost 1995;73:15–20.
46 Mesters RM, Helterbrand J, Utterback BG, Yan B, Chao YB, Fernandez JA, Griffin JH, Hartman DL: Prognostic value of protein C concentrations in neutropenic patients at high risk of severe septic complications. Crit Care Med 2000;28:2209–2216.
47 Lorente JA, Garcia-Frade LJ, Landin L, De Pablo R, Torrado C, Renes E, Garcia-Avello A: Time course of hemostatic abnormalities in sepsis and its relation to outcome. Chest 1993;103:1536–1542.

48 Mucci LA, Hsieh CC, Williams PL, Arora M, Adami HO, De Faire U, Douglass CW, Pedersen NL: Do genetic factors explain the association between poor oral health and cardiovascular disease? A prospective study among Swedish twins. Am J Epidemiol 2009; 170:615–621.
49 Syrjälä AM, Ylöstalo P, Hartikainen S, Sulkava R, Knuuttila ML: Number of teeth and myocardial infarction and stroke among elderly never smokers. J Negat Results Biomed 2009;8:6.
50 Slade GD, Offenbacher S, Beck JD, Heiss G, Pankow JS: Acute-phase inflammatory response to periodontal disease in the US population. J Dent Res 2000;79:49–57.
51 You Z, Cushman M, Jenny NS, Howard G, REGARDS: Tooth loss, systemic inflammation, and prevalent stroke among participants in the reasons for geographic and racial difference in stroke (REGARDS) study. Atherosclerosis 2009;203:615–619.
52 Ylöstalo PV, Järvelin MR, Laitinen J, Knuuttila ML: Self-reported gingivitis and tooth loss poorly predict C-reactive protein levels: a study among Finnish young adults. J Clin Periodontol 2008;35:114–119.
53 Esmon CT: Protein C anticoagulant pathway and its role in controlling microvascular thrombosis and inflammation. Crit Care Med 2001;29(suppl):S48–S52.
54 Tuter G, Kurtis B, Serdar M, Aykan T, Okyay K, Yucel A, Toyman U, Pinar S, Cemri M, Cengel A, Walker SG, Golub LM: Effects of scaling and root planing and sub-antimicrobial dose doxycycline on oral and systemic biomarkers of disease in patients with both chronic periodontitis and coronary artery disease. J Clin Periodontol 2007;34:673–681.
55 Esmon CT: New mechanisms for vascular control of inflammation mediated by natural anticoagulant proteins. J Exp Med 2002; 196:561–564.