Original Article

Association of Elevated C-Reactive Protein with Severe Periodontitis in Hypertensive Patients in Lagos, Nigeria: A Pilot Study

Grace Onyenashia Alade, Patricia Omowunmi Ayanbadejo[1], Kehinde Adesola Umeizudike[1], Janet Ngozi Ajuluchukwu[2]

Department of Preventive and Social Dentistry, Faculty of Dentistry, College of Health Sciences, University of Port Harcourt, Port Harcourt, Rivers State, [1]Department of Preventive Dentistry, Faculty of Dental Sciences, College of Medicine, University of Lagos, [2]Department of Medicine, Cardiology Unit, Faculty of Clinical Sciences, College of Medicine, University of Lagos, Lagos, Nigeria

Abstract

Background: Epidemiological studies have shown that individuals with chronic periodontitis have a significantly higher risk of developing cardiovascular complications, which might be attributed to the increased production of inflammatory cytokines initiated by the complex microbiota in dental biofilm. **Aim:** The study aims to evaluate the association between chronic periodontitis and C-reactive protein (CRP) levels in a group of hypertensive individuals in Nigeria. **Materials and Methods:** The investigator enrolled 50 hypertensive patients with chronic periodontitis into the study from the medical outpatient clinic of a teaching hospital in Lagos, Nigeria. Full-mouth periodontal examination was done to assess the participant's periodontal status, with probing depths and clinical attachment levels of six sites on all teeth. The investigator defined periodontitis as at least one interproximal site with probing depth ≥4 mm. Classification of participants into three groups was done based on their severity of periodontitis; mild (n = 16), moderate (n = 27), and severe (n = 7) periodontitis. Their CRP serum levels were measured, and the association with the severity of periodontitis was determined. P was found to be ≤ 0.05. **Results:** The median CRP levels were 1.0 (0.6, 2.2), 2.4 (1.1, 4.8), and 4.1 mg/L (3.3, 9.4) for mild, moderate, and severe chronic periodontitis, respectively. The association between the serum CRP levels and severity of periodontitis was statistically significant (P = 0.006). **Conclusion:** There was an association of elevated serum CRP level with increased severity of chronic periodontitis in hypertensive individuals. This preliminary finding among Nigerians suggests that chronic periodontal inflammation may contribute to systemic inflammatory burden in hypertensive patients.

Keywords: *C-reactive protein, hypertension, Nigeria, severe chronic periodontitis*

Introduction

Chronic periodontitis is an inflammatory disease of the supporting tissues, characterized by progressive attachment loss and alveolar bone loss.[1] Although plaque biofilm initiates the infection, the immune status of the host and the effectiveness of the host response are critical determinants of disease susceptibility, which influence the progression of periodontitis.[2]

This host response involves both innate and adaptive immunity.[3] While periodontitis is chronic, acute-phase elements such as C-reactive protein (CRP) are released as well as aspects of the natural resistance reflect the systemic burden of inflammation.[4] Previous studies have reported elevated CRP levels in chronic periodontitis following an acute-phase response.[5,6]

CRP is a plasma protein involved in the acute-phase response and is synthesized primarily by the liver in response to the presence of interleukin 1 and 6. It usually is present in minute quantities in human serum but may increase 100–1000-fold within 72 h of tissue injury.[7,8] Its several analytical properties make it attractive as a clinical marker.[9] These include its long half-life with no observable circadian rhythm,[10] rapid changes detected following the course of inflammation,[11] accessible measurement by blood tests, and commercially available high-sensitivity assays that provide similar results in fresh, stored, and frozen plasma.[12] The normal range for serum CRP is 0–10 mg/L.[13]

CRP was hypothesized to increase the risk of developing hypertension,[14] which has been corroborated by studies among individuals with hypertension.[15] Hypertension is the most prevalent risk factor for cardiovascular disease (CVD). Recent data conducted

How to cite this article: Alade GO, Ayanbadejo PO, Umeizudike KA, Ajuluchukwu JN. Association of elevated c-reactive protein with severe periodontitis in hypertensive patients in Lagos, Nigeria: A pilot study. Contemp Clin Dent 2018;9:S95-9.

Address for correspondence:
Dr. Grace Onyenashia Alade, Department of Preventive and Social Dentistry, Faculty of Dentistry, College of Health Sciences, University of Port Harcourt, Port Harcourt, Rivers State, Nigeria.
E-mail: graceochos@yahoo.co.uk

Access this article online

Website: www.contempclindent.org

DOI: 10.4103/ccd.ccd_104_18

Quick Response Code:

among multiple cohorts indicate that in individuals with normal blood pressure at baseline, CRP levels predicted the development of hypertension at follow-up.[16]

Periodontitis has been identified as a potential risk factor for systemic illnesses such as CVD, which is the leading cause of mortality in most developing nations and is predicted to continue till 2020.[17] In periodontitis, the bacterial products of dental biofilm trigger the production of circulating proinflammatory cytokines, interleukin 1, and tumor necrosis factor α. These cytokines typically mediate atherogenesis, thus contributing to the development of atherosclerosis and CVD among patients with periodontitis.[18-20]

CRP, been identified as an important marker of inflammation and an established independent predictor of CVD disease,[21,22] in view of this, the American Heart Association and Centers for Disease Control and Prevention (CDC) have recommended the clinical use of this marker to assess the risk of CVD.[23] Despite the body of evidence supporting an association between periodontitis and elevated CRP levels in people of different races and nationalities,[24] there is a shortage of literature in the Nigerian population. There is a need to investigate further this relationship among Nigerians considering the racial and genetic variations that exist.

The primary aim of this present study was to evaluate the serum CRP levels in individuals with hypertension and determine its relationship to the severity of periodontitis.

Materials and Methods

Study design and study population

This was a descriptive, cross-sectional study in which enrolment of hypertensive adults with chronic periodontitis was from the Cardiology Clinic. The investigator subsequently performed the periodontal assessment on them at the Periodontology Clinic of the Lagos University Teaching Hospital (LUTH). Recruitment of the participants was within a 6-month period. Ethical approval obtained from the Health Research and Ethics Committee (HREC) of the hospital (ADM/DCST/HREC/306). Each participant signed the written informed consent.

Hypertension determination was by persistent blood pressure measurement with systolic/diastolic blood pressure ≥140/90 mmHg. Inclusion criteria were patients above 18 years old, hypertension, patients on antihypertensive medications, diagnosis of chronic periodontitis, and presence of at least 20 natural teeth. Exclusion criteria included patients with systemic-modifying conditions for periodontitis (pregnancy, diabetes mellitus, chronic inflammatory or immunological conditions, i.e., arthritis, gastrointestinal disorder, skin conditions, bronchitis, or other chronic obstructive airway diseases). Also excluded were current smokers, patients who had mechanical/surgical therapy in the preceding 6 months, and those with prior use of gingival tissue modifying medications (oral contraceptives, cyclosporine, and phenytoin). Identification of the participants with chronic inflammatory conditions and concomitant infections were through detailed medical history, drug history, and clinical presentation.

Data collection

Consecutive hypertensive patients who attended the cardiology outpatient clinic of the hospital and met the inclusion criteria were initially selected using the community periodontal index probe, and those with periodontitis enrolled until the required sample size achieved. Interviewer-administered questionnaires were used to record the patient's sociodemographic data: age, gender, occupation, ethnicity, education, marital status, and duration of hypertension.

All the clinical examinations were carried out by a single investigator. The intraexaminer's reliability was 0.8 using kappa statistics. The periodontal clinical parameters utilized in this study were bleeding on probing (BOP), periodontal pocket depth, and clinical attachment level using the Williams periodontal probe.

Classification of periodontitis was performed according to the CDC and American Academy of Periodontology criteria. Moderate periodontitis was characterized by the presence of ≥2 interproximal sites with a clinical attachment loss of ≥4 mm occurring on ≥2 different teeth, or ≥2 interproximal sites with a probing depth of ≥5 mm, on different teeth.[25] Severe periodontitis was characterized by the presence of ≥2 interproximal sites with a clinical attachment loss of ≥6 mm, on different teeth, and the presence of one or more interproximal sites with a probing depth of ≥5 mm on different teeth. The investigator classified periodontitis that did not fit the first two categories into mild periodontitis.

Serum concentration of CRP was measured in milligrams per liter using the immunoturbidimetry method (Roche Hitachi C311 Autoanalyzer) and processed at the AIDS Prevention Initiative of Nigeria Laboratory, LUTH.

Statistical analysis

Data analysis was performed using the Statistical Package for Social Sciences (SPSS) version 20.0 (IBM SPSS for windows, Armonk, New York: IBM Corp).

Categorical variables reported such as frequencies and associations were determined using the Chi-square test. Continuous variables with normal distribution were described by mean ± standard deviation while medians and interquartile ranges were for continuous variables with skewed distribution. Kruskal–Wallis hypothesis testing was used to compare median CRP with the severity of

periodontitis. All $P < 0.05$ was considered statistically significant at the 5% significance level ($\alpha = 0.05$).

Results

Sociodemographics of the participants

The individuals eligible for the study were 50 comprising 11 (22.0%) males and 39 (78.0%) females, with male to female ratio 1:3.5. Mean age was 52.4 ± 6.96 years (range 37–73 years). No significant difference was observed between the mean age of females (52.6 ± 6.36 years) and males (51.8 ± 9.11 years). Nearly half (46%) of the study participants were in the 50–59 age group [Table 1].

The mean systolic and diastolic blood pressures for the participants were 147.4 ± 9.46 mmHg and 94.3 ± 14.66 mmHg, respectively, as shown in Figure 1.

Distribution of chronic periodontitis among participants

There was a steady increase in the mean pocket depth, mean clinical attachment level, and mean BOP sites, from the mild, moderate, to severe forms of chronic periodontitis, as shown in Table 2.

Relationship between C-reactive protein with severity of periodontitis

The median CRP levels of participants with mild, moderate, and severe chronic periodontitis were 1.0 (0.6, 2.2), 2.4 (1.1, 4.8), and 4.1 (3.3, 9.4), respectively. The difference between the three groups was statistically significant ($P = 0.006$) as shown in Table 3.

There was a definite correlation between the median CRP and BOP sites, as shown in Table 4.

Discussion

The study of the relationship between periodontitis and hypertension is poor among Nigerians. Reports from clinical and epidemiological studies have highlighted the role of periodontitis as a risk factor for CVDs.[26-28] However, the mechanisms by which periodontitis is related to CVD are unclear. Periodontitis-induced systemic inflammation through Gram-negative bacteria contributes to the development and maintenance of atherosclerosis through activation of a biochemical reaction cascade, which may, in turn, contribute to the initiation and development of plaque formation and injury to the endothelium.

Hypertensive individuals were the focus of this study because hypertension is no doubt one of the most prevalent CVDs in Nigeria[29] and is also a risk factor for other CVDs such as stroke, heart failure, and ischemic heart disease.[30] Furthermore, hypertension is associated with atherosclerosis which is considered a chronic inflammatory state.[31] Thus, inflammation may contribute to a rise in blood pressure by promoting changes in the endothelium.

Table 1: Sociodemographic characteristics of the participants

	Frequency (%)
Age group (years)	
30-39	1 (2.0)
40-49	18 (36.0)
50-59	23 (46.0)
60-69	7 (14.0)
70-79	1 (2.0)
Total	50 (100.0)
Gender	
Female	39 (78.0)
Male	11 (22.0)
Total	50 (100.0)
Marital status	
Divorced	3 (6.0)
Married	34 (68.0)
Widow (er)	13 (26.0)
Total	50 (100.0)
Ethnicity	
Yoruba	34 (68.0)
Non-Yoruba (Igbo, Calabar)	16 (32.0)
Total	50 (100.0)
Education	
No formal education	3 (6.0)
Primary	14 (28.0)
Secondary	19 (38.0)
Tertiary	14 (28.0)

Table 2: Severity of chronic periodontitis among participants

Severity of chronic periodontitis	*n* (%)	Mean PD (mm)	Mean CAL (mm)	Mean BOP sites
Mild	16 (32.0)	4.14±0.44	0.33±0.91	2.94±3.38
Moderate	27 (54.0)	4.38±1.02	1.74±2.04	3.37±3.34
Severe	7 (14.0)	5.06±0.58	5.89±2.31	4.57±2.82

PD: Pocket depth; CAL: Clinical attachment losses; BOP: Bleeding on probing

Table 3: Comparison of C-reactive protein with severity of periodontitis

Severity of periodontitis	*n* (%)	Median CRP (interquartile range)	*P*
Mild	16 (32.0)	1.0 (0.6-2.2)	0.006*
Moderate	27 (54.0)	2.4 (1.1-4.8)	
Severe	7 (14.0)	4.1 (3.3-9.4)	

CRP: C-reactive protein, *Statistically significant

Table 4: Correlation between median C-reactive protein and mean bleeding on probing sites

	Initial CRP	Mean BOP
Initial CRP	1	0.003
Mean BOP	0.003	1

CRP: C-reactive protein; BOP: Bleeding on probing

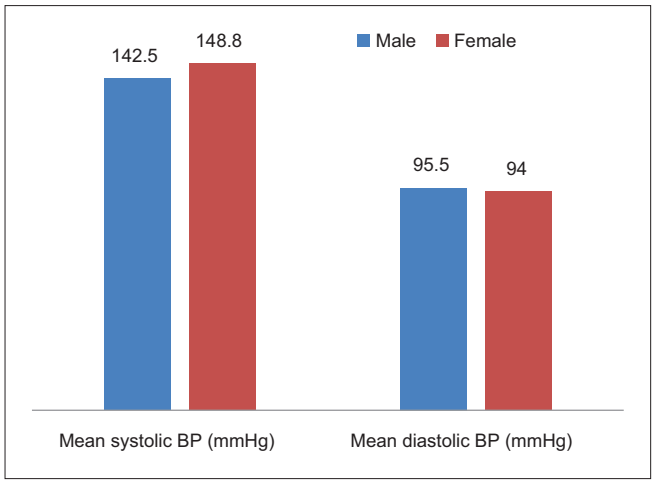

Figure 1: Blood pressure by gender of the participants

In this study, the reported preponderance of female individuals was attributed to the higher prevalence of hypertension in females,[32] hence their presence at the clinic. Other studies have however reported no significant difference between males and females[33,34] or found a higher prevalence of hypertension in men compared with women.[35,36] The more elevated systolic and diastolic blood pressures observed among the female participants in this present study are also ascribed to the menopausal attainment at their age and the reduced effect of the anti-inflammatory (cardioprotective) effect of estrogen (which keeps the blood vessels flexible).[37] This present study also bolsters the prediction by Kearney *et al*.[38] of a higher female predominance with hypertension by the year 2025.

This predominant age group of 50–59 years noticed in the present study supports existing reports of hypertension in older age.[39] This finding may be due to age-related changes in hormone profile, thickening of the walls of arteries, as well as the decreased efficiency of the heart and kidneys.[40,41] The secondary level of education obtained by most of the individuals is consistent with the urban location of the hospital which serves as a referral center for other peripheral clinics.

There was a steady increase in the median CRP level from mild to severe periodontitis. This trend was significant, and the finding is in agreement with the previous studies,[42,43] but contrary to the past research by Baser *et al*.[44] We postulate that there may have been an increased CRP production from the liver in response to the enhanced cytokine production in the stage of severe periodontitis. Furthermore, there was a definite correlation between the number of sites that bled on probing and the CRP levels which signify the presence of an active infection. This finding is similar to a previous study by Salzberg *et al*.[45]

This study is limited however by the number of individuals, which was relatively small; hence, a prospective study using larger sample size is needed to demonstrate the true nature of these relationships.

Conclusion

There was a significant association between the severity of chronic periodontitis in the hypertensive individuals with elevated CRP levels. Thus, increased CRP levels in this category of hypertensive participants may place them at a higher risk for CVD, and this further highlights the need for better collaboration between physicians and dentists.

Recommendations

Hypertensive individuals should receive periodontal screening through regular dental visits or oral health screening at their medical outpatient clinics. CRP monitoring is essential in the management of hypertensive patients, especially those with chronic periodontitis.

Acknowledgment

Mr. Tony Ani is acknowledged for his technical support for the CRP laboratory analysis. Dr. Opeyemi Obilade is acknowledged for his support for the statistical analysis.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Flemmig TF. Periodontitis. Ann Periodontol 1999;4:32-8.
2. Masamatti S, Virdi M, Kumar A. Host modulation therapy: A novel approach in the treatment of periodontal diseases. Internet J Dent Sci 2009;9:1-8.
3. Seymour GJ. Importance of the host response in the periodontium. J Clin Periodontol 1991;18:421-6.
4. Loos BG. Systemic markers of inflammation in periodontitis. J Periodontol 2005;76:2106-15.
5. Buhlin K, Gustafsson A, Pockley AG, Frostegård J, Klinge B. Risk factors for cardiovascular disease in patients with periodontitis. Eur Heart J 2003;24:2099-107.
6. Craig RG, Yip JK, So MK, Boylan RJ, Socransky SS, Haffajee AD, *et al*. Relationship of destructive periodontal disease to the acute-phase response. J Periodontol 2003;74:1007-16.
7. Du Clos TW. Function of C-reactive protein. Ann Med 2000;32:274-8.
8. Claus DR, Osmand AP, Gewurz H. Radioimmunoassay of human C-reactive protein and levels in normal sera. J Lab Clin Med 1976;87:120-8.
9. Libby P, Aikawa M. Stabilization of atherosclerotic plaques: New mechanisms and clinical targets. Nat Med 2002;8:1257-62.
10. Meier-Ewert HK, Ridker PM, Rifai N, Price N, Dinges DF, Mullington JM, *et al*. Absence of diurnal variation of C-reactive protein concentrations in healthy human subjects. Clin Chem 2001;47:426-30.
11. Gabay C, Kushner I. Acute-phase proteins and other systemic responses to inflammation. N Engl J Med 1999;340:448-54.
12. Rifai N, Tracy RP, Ridker PM. Clinical efficacy of an

automated high-sensitivity C-reactive protein assay. Clin Chem 1999;45:2136-41.
13. Ojo A, Jacob SJ, Ayolabi CI. C-reactive protein in tuberculosis and human immunodeficiency virus infection in Abeokuta, Nigeria. Bayero J Pure Appl Sci 2011;4:91-6.
14. Sesso HD, Buring JE, Rifai N, Blake GJ, Gaziano JM, Ridker PM, *et al.* C-reactive protein and the risk of developing hypertension. JAMA 2003;290:2945-51.
15. Lakoski SG, Cushman M, Palmas W, Blumenthal R, D'Agostino RB Jr., Herrington DM, *et al.* The relationship between blood pressure and C-reactive protein in the multi-ethnic study of atherosclerosis (MESA). J Am Coll Cardiol 2005;46:1869-74.
16. Hage FG. C-reactive protein and hypertension. J Hum Hypertens 2014;28:410-5.
17. Celermajer DS, Chow CK, Marijon E, Anstey NM, Woo KS. Cardiovascular disease in the developing world: Prevalences, patterns, and the potential of early disease detection. J Am Coll Cardiol 2012;60:1207-16.
18. Tousoulis D, Charakida M, Stefanadis C. Endothelial function and inflammation in coronary artery disease. Heart 2006;92:441-4.
19. Young JL, Libby P, Schönbeck U. Cytokines in the pathogenesis of atherosclerosis. Thromb Haemost 2002;88:554-67.
20. Geerts SO, Nys M, De MP, Charpentier J, Albert A, Legrand V, *et al.* Systemic release of endotoxins induced by gentle mastication: Association with periodontitis severity. J Periodontol 2002;73:73-8.
21. Ridker PM, Cushman M, Stampfer MJ, Tracy RP, Hennekens CH. Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. N Engl J Med 1997;336:973-9.
22. 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;342:836-43.
23. Pearson TA, Mensah GA, Alexander RW, Anderson JL, Cannon RO 3rd, Criqui M, *et al.* Markers of inflammation and cardiovascular disease: Application to clinical and public health practice: A statement for healthcare professionals from the centers for disease control and prevention and the American heart association. Circulation 2003;107:499-511.
24. Noack B, Genco RJ, Trevisan M, Grossi S, Zambon JJ, De Nardin E, *et al.* Periodontal infections contribute to elevated systemic C-reactive protein level. J Periodontol 2001;72:1221-7.
25. Page RC, Eke PI. Case definitions for use in population-based surveillance of periodontitis. J Periodontol 2007;78:1387-99.
26. Morrison HI, Ellison LF, Taylor GW. Periodontal disease and risk of fatal coronary heart and cerebrovascular diseases. J Cardiovasc Risk 1999;6:7-11.
27. Humphrey LL, Fu R, Buckley DI, Freeman M, Helfand M. Periodontal disease and coronary heart disease incidence: A systematic review and meta-analysis. J Gen Intern Med 2008;23:2079-86.
28. American Academy of Periodontology. Periodontal Disease Linked to Cardiovascular Disease; April, 2012. Available from: http://www.perio.org/consumer/AHA-statement on [Last accessed on 2012 Dec 11].
29. World Health Organization: World Health Report. Reducing Risks, Promoting Healthy Life. Geneva: World Health Organization; 2002. Available from: http://www.who.Int/whr/2002/en/index.html. [Last accessed on 2009 Nov 11].
30. Ogah OS, Okpechi I, Chukwuonye II, Akinyemi JO, Onwubere BJ, Falase AO, *et al.* Blood pressure, prevalence of hypertension and hypertension related complications in Nigerian Africans: A review. World J Cardiol 2012;4:327-40.
31. Libby P, Ridker PM, Maseri A. Inflammation and atherosclerosis. Circulation 2002;105:1135-43.
32. Adedoyin RA, Mbada CE, Balogun MO, Martins T, Adebayo RA, Akintomide A, *et al.* Prevalence and pattern of hypertension in a semiurban community in Nigeria. Eur J Cardiovasc Prev Rehabil 2008;15:683-7.
33. Lawoyin TO, Asuzu MC, Kaufman J, Rotimi C, Owoaje E, Johnson L, *et al.* Prevalence of cardiovascular risk factors in an African, Urban inner city community. West Afr J Med 2002;21:208-11.
34. Amole IO, OlaOlorun AD, Odeigah LO, Adesina SA. The prevalence of abdominal obesity and hypertension among adults in Ogbomosho, Nigeria. Afr J Prim Health Care Fam Med 2011;3:188-92.
35. Sani MU, Wahab KW, Yusuf BO, Gbadamosi M, Johnson OV, Gbadamosi A, *et al.* Modifiable cardiovascular risk factors among apparently healthy adult Nigerian population – A cross sectional study. BMC Res Notes 2010;3:11.
36. Ahaneku GI, Osuji CU, Anisiuba BC, Ikeh VO, Oguejiofor OC, Ahaneku JE, *et al.* Evaluation of blood pressure and indices of obesity in a typical rural community in Eastern Nigeria. Ann Afr Med 2011;10:120-6.
37. Yang XP, Reckelhoff JF. Estrogen, hormonal replacement therapy and cardiovascular disease. Curr Opin Nephrol Hypertens 2011;20:133-8.
38. Kearney PM, Whelton M, Reynolds K, Muntner P, Whelton PK, He J, *et al.* Global burden of hypertension: Analysis of worldwide data. Lancet 2005;365:217-23.
39. Heitz-Mayfield LJ, Schätzle M, Löe H, Bürgin W, Anerud A, Boysen H, *et al.* Clinical course of chronic periodontitis. II. Incidence, characteristics and time of occurrence of the initial periodontal lesion. J Clin Periodontol 2003;30:902-8.
40. Jani B, Rajkumar C. Ageing and vascular ageing. Postgrad Med J 2006;82:357-62.
41. Kosugi T, Nakagawa T, Kamath D, Johnson RJ. Uric acid and hypertension: An age-related relationship? J Hum Hypertens 2009;23:75-6.
42. Pejcic A, Kesic L, Milasin J. Association between periodontopathogens and CRP levels in patients with periodontitis in Serbia. J Dent Res Dent Clin Dent Prospects 2011;5:10-6.
43. Slade GD, Ghezzi EM, Heiss G, Beck JD, Riche E, Offenbacher S, *et al.* Relationship between periodontal disease and C-reactive protein among adults in the atherosclerosis risk in communities study. Arch Intern Med 2003;163:1172-9.
44. Baser U, Oztekin G, Ademoglu E, Isik G, Yalcin F. Is the severity of periodontitis related to gingival crevicular fluid and serum high-sensitivity C-reactive protein concentrations? Clin Lab 2014;60:1653-8.
45. Salzberg TN, Overstreet BT, Rogers JD, Califano JV, Best AM, Schenkein HA, *et al.* C-reactive protein levels in patients with aggressive periodontitis. J Periodontol 2006;77:933-9.