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High-sensitivity serum C-reactive protein levels in subjects with or without myocardial infarction or periodontitis

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Abstract

Background: Serum high-sensitivity C-reactive protein (hsC-rp) is a non-specific marker of inflammation. Elevated hsC-rp levels are found in subjects with cardiovascular diseases (CVDs). Periodontitis may influence hsC-rp levels.

Objectives: To assess periodontal status and hsC-rp serum levels in consecutive subjects hospitalized and diagnosed with acute myocardial infarction (AMI) ($n = 85$) and in a group of carefully matched subjects (gender, age social, ethnic, and smoking habits) without clinical evidence of CVD ($n = 63$).

Methods: hsC-rp levels, other routine serum values, and clinical periodontal conditions were studied.

Results: Subjects with AMI had higher hsC-rp levels than control subjects ($p < 0.001$, Mann–Whitney *U*-test). The odds that subjects in the control group with periodontitis (30% or more sites with > 4.0 mm loss of alveolar bone) had serum hsC-rp > 1.8 mg/l was 1.5 (95% CI: 1.1–7.3, $p < 0.05$). Stepwise linear regression analysis failed to include periodontal parameters in an explanatory model to hsC-rp values. Only the serum leucocyte (white blood cell (WBC)) counts were explanatory to hsC-rp values (β standard coefficient = 0.45, $t = 3.2$, $p < 0.001$). Serum WBC counts were significantly higher in control subjects with periodontitis ($p < 0.03$) but not in subjects in the AMI group ($p < 0.57$).

Conclusions: (1) As expected, elevated serum hsC-rp concentration and serum WBC counts are associated with acute coronary heart disease. (2) Elevated serum hsC-rp values are associated with radiographically defined periodontitis in subjects with no evidence of CVD. (3) Periodontal parameters are not explanatory to elevated serum hsC-rp values if serum WBC and low-density lipoprotein counts are included in the regression model.

Key words: acute infarct; healthy; high-sensitivity C-reactive protein; periodontitis; WBC

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Traditional risk factors only partly account for the occurrence of cardiovascular disease (CVD) (EUROASPIRE Study Group 1997). Several biological markers have been considered in assessing the risk for myocardial infarction, stroke, and peripheral arterial disease. Elevated serum levels of high-sensitivity serum C-reactive protein (hsC-rp), an acute-phase reactant and a marker of underlying systemic inflammation, have been studied in several case–control studies (i.e. Pietila et al. 1993, Ridker et al. 1997, 2002, Arenillas et al. 2003, De Beer et al. 2000, Ridker 2002, Stone et al. 2002). Serum hsC-rp levels > 2.0 mg/l appear to reflect inflammation and an elevated risk for CVD in combination with other risk profile factors (Ridker et al. 2002). Elevated C-reactive protein values have also been associated with other diseases (i.e. Kop et al. 2002, Stehouwer et al. 2002, Tamakoshi et al. 2003).

Recent studies have suggested that periodontitis may induce elevated serum C-reactive protein levels (Ebersole et al. 1997, Loos et al. 2000, Noack et al. 2001, Amar et al. 2003, Buhlin et al. 2003, Craig et al. 2003). In addition, the presence of pathogens associated with periodontitis has been associated with elevated hsC-rp values (Noack et al. 2001, Craig et al. 2003). Studies of hsC-rp levels in gingival fluid at sites with

evidence of periodontitis are inconclusive (Sibraa et al. 1991). No clinically significant effects on serum C-reactive protein levels have been reported as a result of periodontal therapy (Ide et al. 2003, Iwamoto et al. 2003), whereas others have found that periodontal therapy result in lowering of serum hsC-rp values (Mattila et al. 2002, D'Aiuto et al. 2004). In these two studies of subjects with advanced periodontitis, the baseline median serum hsC-rp levels were lower than 2.0 mg/l and decreased, on average, with 0.5 mg/l after therapy. The consequence of periodontal therapy on the potential reduction of risk for CVD using serum hsC-rp values as a substitute endpoint is unclear.

The association between coronary heart disease and periodontitis has been suggested in several studies (DeStefano et al. 1993, Mattila 1993, Beck et al. 1996, Morrison et al. 1999, Persson et al. 2002, 2003). A recent systematic review has demonstrated that most studies on the relationship between CVDs and periodontal diseases lack confirmed information on medical and/or oral conditions (Madianos et al. 2002). This fact further complicates the interpretation of data on the relationships between periodontitis and CVD, including the effects of periodontitis and treatment of periodontitis in relation to changes in hsC-rp values as an effect of therapy.

Subjects who are asymptomatic for CVD often have serum hsC-rp values below 3.0 mg/l hsC-rp assays (Dinant et al. 1994, Rifai et al. 1999). A large number pf factors including both inflammatory diseases including arthritis have an impact on serum hsC-reactive protein levels. Thus, lower serum hsC-rp levels are reported in subjects who exercise frequently (Dinant et al. 1994) while hormonal replacement therapy may increase serum hsC-rp levels (Abramson & Vaccarino 2002). The population based on National Health and Nutrition Examination Survey also demonstrated that serum hsC-rp levels are highly skewed (range: 0.1–156.0 mg/l and with median values of 1.6 mg/l for men) (Davison & Davis 2003). This suggests that the statistical analysis of data on the relationship between periodontitis and CVD must take into account many factors other than the periodontal conditions alone.

The purpose of the present study was to assess the relationship between periodontal status and hsC-rp serum levels in consecutive hospitalized subjects with confirmed acute myocardial infarction (AMI) and in a group of carefully matched subjects (gender, age social background, ethnicity, and smoking habits) without clinical evidence of CVD as confirmed by a cardiologist, including assessment of periodontal status as confirmed by periodontists.

Materials and Methods

The study was approved by the Institutional Review Board (IRB), University of Lund, Sweden. Two groups of subjects were included. The first group consisted of consecutive and consenting subjects admitted to the Kristianstad Regional Central Hospital, Sweden with a diagnosis of AMI. The diagnosis was based on chest pain associated with typical electrocardiogram (ECG) changes (ST elevation, and/or non ST elevation and T-wave inversion), combined with a typical serial pattern of cardiac markers (i.e. creatinine kinase isoenzyme and troponin T) as assessed according to local laboratory standards. The initial ECG was considered diagnostic for myocardial infarction if there was ST segment elevation of 2 mm or more in a chest lead, or ST segment elevation of 1 mm or more in a limb lead. Non-ST elevation and T-wave inversion changes combined with typical serial pattern of cardiac markers were also considered diagnostic for myocardial infarction. Left bundle block was considered diagnostic for myocardial infarction if chest pain combined with typical serial pattern of cardiac markers were present. As previously described, all subjects were clinically examined by a cardiologist (Persson et al. 2003, Renvert et al. 2004).

Once the subjects had recovered from their myocardial infarction and had been released from the hospital, they received a periodontal examination at the University of Kristianstad Dental Clinic. The periodontal examination included a full-mouth radiographic assessment, and a routine clinical examination for the extent of bleeding on probing (BOP), probing depths (PPDs), and attachment levels. Information regarding previous dental treatments was also collected. None of the subjects had received periodontal therapy during the preceding year. Medical records were further reviewed for information on a history of other chronic inflammatory conditions.

A control group consisting of subjects matched by gender, age, social factors, and smoking status was then identified. For details on enrollment strategies and clinical measures, see Persson et al. (2003). Briefly, each subject with AMI was asked to bring a friend of the same gender, age, and social background to a cardiovascular and periodontal examination. Only subjects who were found free from clinical evidence of CVD were enrolled in the study as control subjects. To supplement the number of control subjects, a registry of research subjects in Kristianstad, Sweden was screened and the appropriate number of matching subjects were enrolled. Approximately, 50% of the control subjects came from this registry. These subjects also underwent a thorough medical examination. Control subjects with a past history of a diagnosed or unclear cardiovascular condition were excluded.

The extent of alveolar bone loss (ABL) was measured from the cement–enamel junction (CEJ) to the bone level (BL) on radiographs as described elsewhere using a distance CEJ–BL $\geqslant$ 4.0 mm as the disease cutoff levels. Periodontitis was defined as the proportion of readable radiographic inter-proximal sites with a distance CEJ–BL $>$ 4.0 mm $\geqslant$ 30%. (Persson et al. 2003, Renvert et al. 2004).

Analysis of hsC-rp serum levels

In the AMI group, hsC-rp levels in serum were assessed from 85 subjects (62 males) and available from 63 control subjects (52 males). Serum samples from the subjects were analysed at the same medical chemical laboratory as the samples from the subjects with AMI. A blood sample of 5 ml from each subject was centrifuged at 1400 *g* for 10 min. and the serum was stored for blood chemistry analysis following the hospital blood chemistry laboratory routine protocol. A total of 300 µl per sample was analysed in a Beckman Coulter IMMAGE automatic analyser (Beckman Coulter, Fullerton, CA, USA) for hsC-rp levels. The IMMAGE assay protocol included the use of a polyclonal anti-Crp antibody coated to latex particles and rate nephelometric measurements. The IMMAGE nephelometer made a 1:36 dilution for values up to 80 mg/l and a 1:216 dilution for higher concentrations.

Statistics

Descriptive statistics were used to assess the distribution of hsC-rp serum

levels. Non-parametric Wilcoxon's signed rank test was used to compare hsC-rp and white blood cell (WBC) serum levels between the two matched groups. Mann–Whitney *U*-test was used for within-group comparisons. Correlation coefficients (Pearson's and Spearman's rank) were studied to identify factors correlated with hsC-rp levels. Linear and binary logistic regression analysis was used to identify which of the included factors could be associated with coronary heart status. Receiving operating characteristic (ROC) curves were evaluated to assess the utility of serum hsC-rp concentrations to concur with the diagnosis of AMI and to that of periodontitis. Odds ratios (Mantel–Haenszel common odds) were calculated for different serum hsC-rp cutoff levels and periodontitis. Data analysis was performed using the SPSS 11.5 statistical software program for PC (SPSS Inc., Chicago, IL, USA).

Results

The mean ages of the AMI ($n = 85$) and control ($n = 63$) groups were 63.1 (SD ± 9.4) years and 61.9 (SD ± 9.4) (NS), respectively. In the AMI group, 71.4% and in the control group 79.3% of the subjects had a history of smoking with an estimated average numbers of smoke/years of 23 years and 18 years (NS, $p < 0.27$), respectively.

As anticipated, serum WBC counts were significantly higher in the subjects with AMI ($p < 0.001$). In neither group did the hsC-rp values show a normal distribution pattern. The distributions of hsC-rp values in serum are presented in a box-plot diagram for the two groups (Fig. 1). The hsC-rp serum values in subjects with AMI had a mean value of 18.4 mg/l (SD ± 8.6, median: 8.6 mg/l, range: 0.3–109.0). An hsC-rp serum value > 2.0 mg/l was found in 78.8% of these subjects. In the control group, the mean hsC-rp value was 2.5 mg/l (SD ± 3.3, median: 1.5 mg/l, range: 0.2–6.4). An hsC-rp serum value > 2.0 mg/l was found in 41.3% of these subjects. The difference between hsC-rp serum values in subjects with or without AMI was highly significant ($p < 0.0001$, n-par test). These results were also valid when hsC-rp serum values were dichotomized as < 2.0 or > 2.0 mg/l ($p < 0.001$) (Fig. 2).

The proportional distributions of routine periodontal measurements in both groups (BOP, PPD ⩾6.0 mm, and ABL defined as CEJ–BL⩾4.0 mm) between the two groups demonstrated no differences for the extent of PPD whereas the proportions of BOP and ABL were significantly higher in the AMI group ($p < 0.001$).

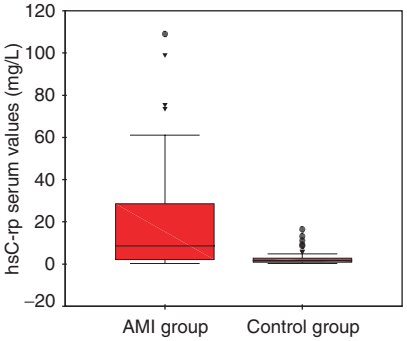


Fig. 1. Distribution of serum C-reactive protein levels in subjects with ($n = 85$) or without ($n = 63$) history of myocardial infarction (• represents extreme outliers; ▼ represents outlier values).

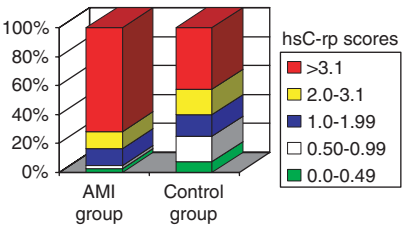


Fig. 2. Distributions of serum high-sensitivity serum-reactive protein (hsC-rp) values in subjects with or without a history of acute myocardial infarction.

Control subjects

The ABL measures demonstrated that 12.9% of the control subjects had no evidence of ABL whereas 56.3% of them had ⩾30% of inter-proximal sites identified on intra-oral radiographs with distances CEJ–BL⩾4.0 mm. No evidence of probing depth ⩾6.0 mm was found in 54.3% of the control subjects. The mean proportion of sites with BOP in these control subjects was 24.2% (SD ± 11.9). The analysis of the serum hsC-rp values in relation to proportional bleeding index failed to demonstrate differences in hsC-rp serum values as an effect of gingivitis classification ($p < 0.95$) (Fig. 3) or for the proportion of probing depth ⩾6.0 mm ($p < 0.10$), or the number of remaining teeth ($p < 0.53$) using the hsC-rp 1.8 mg/l cutoff level as the grouping variable.

Analysis by Wilcoxon's signed rank test failed to demonstrate differences in hsC-rp serum values between control

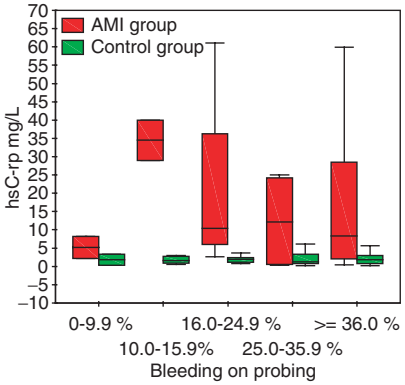


Fig. 3. Box plot diagram demonstrating serum high-sensitivity serum-reactive protein (hsC-rp) levels in control subjects ($n = 63$) with varying degrees of gingival inflammation.

subjects with or without periodontitis using ABL at ⩾30% as the cutoff level (p value < 0.74). An hsC-rp serum level > 10.0 mg/l considered to be at a pathological level (Davison & Davis 2003) was found in 33.3% of the control subjects with significant bone loss. The serum WBC counts were significantly higher in subjects with a diagnosis of periodontitis (ABL⩾30%) ($p < 0.03$, Mann–Whitney *U*-test).

Correlation coefficients (Pearson's correlation and Spearman's rank correlation) were studied to assess significant correlations between study parameters and hsC-rp serum values. No significant correlations between hsC-rp serum concentrations and any of the 35 other serum parameters or for any of the periodontal variables studied were found in subjects belonging to the control group. The association between % BOP with no evidence of periodontitis (r^2 value: 0.02) or with periodontitis (ABL⩾30% of sites) (r^2 value: 0.02) and hsC-rp serum values was insignificant.

Stepwise linear regression analysis failed to include any of the periodontal parameters in an explanatory model to hsC-rp values. The only explanatory variable was serum WBC counts (β standard coefficient = 0.36, $t = 2.35$, $p < 0.02$). The common odds ratio of having hsC-rp value ⩾1.8 mg/l and periodontitis with ABL⩾30% was 1.5 (95% CI; 0.6–3.7, $p < 0.61$). Changing the hsC-rp cutoff level to 2.0 mg/l changed these odds only marginally.

Subject with myocardial infarction

All subjects with AMI had evidence of ABL and 94% of them had more than

30% of sites with ABL ⩾ 4.0 mm. One or more sites with a probing depth ⩾ 6.0 mm was found in 59.5% and BOP were found in 56.2% of the subjects. Serum hsC-rp concentrations ⩾ 1.8 mg/l were found in 83.5% of the subjects with AMI. Only 5.9% of the AMI subjects had hsC-rp serum concentration ⩽ 1.0 mg/l. Statistical analysis failed to demonstrate differences in hsC-rp serum values as an effect of gingivitis classification ($p < 0.23$), also illustrated in a boxplot diagram presenting hsC-rp values at different severity levels of gingival bleeding (Fig. 3). Similarly, statistical analysis failed to demonstrate differences in the proportional distribution of sites with BOP ($p < 0.20$), probing depth ⩾ 6.0 mm ($p < 0.71$), or the number of remaining teeth ($p < 0.95$) based on the hsC-rp values below or above the 1.8 mg/l cutoff level as the grouping variable.

Correlation coefficients (Pearson's correlation and Spearman' rank correlation coefficients) were studied to assess significant correlation between a series of study parameters and hsC-rp serum values. Those variables that were significantly correlated with the actual hsC-rp value or the dichotomized < 1.8 mg/l/ > 2,0 mg/l values were included in linear stepwise or in binary logistic Wald forward-regression analysis. Stepwise linear regression analysis failed to include any of the periodontal parameters in an explanatory model to hsC-rp values while serum WBC counts and low-density lipoproteins counts were explanatory (Table 1). In subjects with AMI serum WBC counts failed to differentiate between those with or without periodontitis defined as ABL ⩾ 30% ($p < 0.57$, Mann–Whitney *U*-test).

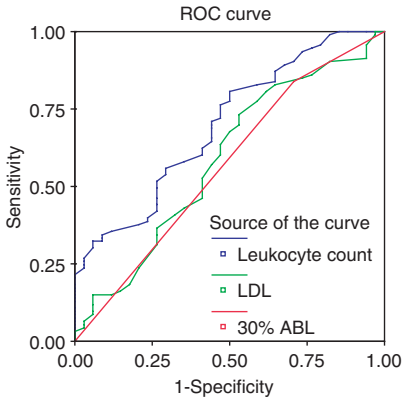
All cases

Stepwise linear regression analysis failed to include any of the periodontal parameters in an explanatory model to hsC-rp values. Only the serum WBC counts remained in the explanatory model analysis to hsC_rp values (β standard coefficient = 0.45, $t = 3.2$, $p < 0.001$). Serum WBC counts were correlated with both the proportion of bleeding ($r = 0.46$, $p < 0.001$) and the number of sites with a distance CEJ–BL ⩽ 4.0 mm ($r = 0.39$, $p < 0.001$). None of the other serum assay results could be correlated with periodontal parameters. ROC curve analysis confirmed that only the WBC counts were predictive for the hsC-rp 1.8 mg/l cutoff level (Fig. 4). Serum low-density lipoprotein levels and the extent of ABL approached significance.

Table 1. Results from linear regression analysis in defining explanatory factors to serum hsC-rp levels in subjects with myocardial infarction (AMI)

Model		Unstandardized coefficients		Standardized coefficients	*t*	Significance
		B	SE	β		
1	Constant	0.041	7.530		0.005	0.996
	WBC counts	2.032	0.830	0.274	2.449	0.017
2	Constant	− 8.125	8.410		− 0.966	0.337
	WBC counts	2.751	0.887	0.371	3.100	0.003
	Low-density lipids	0.146	0.072	0.242	2.023	0.047

Dependent variable: hsC-rp mg/l. hsC-rp, high-sensitivity serum C-reactive protein; WBC, white blood cell.



Area Under the Curve

Test Result Variable(s)	Area	Std. Error	Asymptotic Sig.	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
30% ABL	.566	.059	.253	.450	.683
LDL	.586	.059	.139	.470	.702
Leucosyre Leucocyte count	.698	.052	.001	.596	.799

Fig. 4. Utility of periodontal and other serum assays to predict serum high-sensitivity serum-reactive protein concentrations > 1.8 mg/l and illustrated by receiving operating characteristic curve analysis including serum white blood cell, low-density lipoprotein (LDL) levels and 30% alveolar bone loss (ABL) periodontitis definition as variables.

Discussion

In the present study, subjects with AMI had elevated hsC-rp values. This is consistent with reports that hsC-rp concentration can increase rapidly in response to acute coronary heart disease (Bogarty et al. 2001). Peak serum hsC-rp values after infarction normally reach peak values within 48 h and high peak values can be a predictor of future AMI risk and mortality (Suleiman et al. 2003). Data also suggest that a serum hsC-rp > 1.4 mg/l may be an independent predictor of a first ever transient ischaemic stroke event (Mattila 1993) and that hsC-rp serum values > 1.8 mg/l appear to be a predictor of future cardiovascular events (Liede et al. 1998). The high hsC-rp serum values in the present study for the AMI group can be explained by the fact that the serum used for the analysis was taken at the time of hospital admission and during the initial acute phase of myocardial infarction.

A significant association between evidence of periodontal infection and elevated hsC-rp serum values has previously been reported for the 2.1 mg/l threshold value (Sibraa et al. 1991). In the present study, the threshold value for serum hsC-rp was studied both at 2.0 and 1.8 mg/l as threshold values in relation to having a diagnosis of perio-

dontitis ($\geqslant$30% distance CEJ–BL > 4.0 mm). However, the data failed to demonstrate that periodontal infection (the extent of gingivitis, probing depth $\geqslant$6.0 mm, or extent of ABL) was significantly associated with a risk of having serum hsCrp levels > 1.8 mg/l. The hypothetical explanation for this might be that only the long-term chronic effects of periodontitis reflected as ABL and noticeable on radiographs are explanatory to elevated serum hsC-rp values, whereas current clinical evidence of gingivitis and/or an elevated proportion of increased probing depths may be a current low-grade expression of inflammation not directly reflected by elevated hsC-rp values.

In the present study, however, all subjects with an hsC-rp serum value $\geqslant$10.0 mg/l defined as pathological (Alvarez-Garcia et al. 2003) had evidence of significant ABL (periodontitis). Most importantly, we could demonstrate elevated hsC-rp values in subjects who, following a cardiovascular examination, were found free from clinical signs of coronary heart disease but who had periodontitis defined as evidence of ABL. This finding suggests that the assessment of hsC-rp serum levels in subjects with periodontitis could provide important guidance in order to identify subjects also at AMI risk. Furthermore, the present finding also suggests that having chronic periodontitis may trigger a systemic response as expressed by upregulated hsC-rp values.

The accumulated effects of periodontitis identifiable as ABL may be more representative of the total systemic impact of periodontitis than a measure of current periodontal status defined by current probing depth and/or gingival assessments.

Several mechanisms may influence hsC-rp levels in serum. Thus, hsC-rp serum levels decrease after anti-inflammatory and antibiotic treatment of subjects with severe CVD (Gurfinkel et al. 1997, Ridker et al. 1997, Munford 2001), or following periodontal therapy (Mattila et al. 2002, D'Aiuto et al. 2004)

Assuming that serum hsC-rp values in the range of 0.8–2.0 mg/l in 55–74-year-old subjects suggest risk for CVD (Rifai & Ridker 2003) it might be of clinical importance to lower serum hsC-rp by periodontal therapy. If periodontal therapy could lower hsC-rp values by 0.4 mg/l, the present study data suggest that 13.4% of the control subjects and 11.9% of the AMI subjects would experience such reduction/improvement of serum hsC-rp levels below 1.8 mg/l. Thus, 30.0% of the subjects in the control group and 54.3% of the subjects in the AMI group would still have hsC-rp levels significantly above that threshold. Hence, it appears possible that for a segment of the population periodontal therapy may contribute to a reduced risk for CVDs assuming that serum hsC-rp levels can predict cardiovascular events. This hypothesis must be tested in well-controlled clinical trials. Such studies would have to specifically study subjects with periodontitis who have serum hsC-rp values that are above the 1.6–1.8 mg/l range excluding subjects with extreme values (Ford et al. 2003).

In the present study, subjects in the control group with periodontitis defined by the extent of ABL$\geqslant$30% had significantly higher serum WBC counts whereas the same relationship could not be identified among subjects with AMI. This can be explained by the fact that few subjects in the AMI were periodontally healthy and the statistical analysis thereby lacked statistical power. Alternatively elevated WBC counts as an effect of periodontitis may be masked by the high serum WBC counts usually found in subjects with AMI. Given the limited data on a relationship between WBC counts and periodontal status, the present study findings of an association between the severity of periodontitis and elevated serum WBC are of interest and should be further studied. Few studies have explored this relationship and the conclusions are controversial (Gustafsson & Asman 1996, Fredriksson et al. 1998, Christian et al. 2002, Loos et al. 2000).

In conclusion: (1) elevated serum hsC-rp concentration is associated with acute coronary heart disease, (2) elevated serum WBC counts are associated with AMI, and (3) although elevated serum hsC-rp values are associated with periodontitis defined radiographically also in subjects with no evidence of CVD periodontal parameters are not included in an explanatory model to elevated serum hsC-rp values if serum WBC, and low-density lipoprotein counts are included in the regression model.

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