AGGRESSIVE AND SLOWLY-PROGRESSIVE PERIODONTITIS IN PATIENTS WITH CORONARY ARTERY DISEASES. LEVELS OF C-REACTIVE PROTEIN, FIBRINOGEN, AND IL-6

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ABSTRACT

Objectives: The purpose of this study was to investigate the incidence of aggressive (AP) or slowly-progressive (SP) periodontitis in patients diagnosed with coronary artery disease (CAD) and to assess the severity of periodontitis in relation to levels of pro-inflammatory molecules, C-reactive protein (CRP), fibrinogen, and IL-6.

Materials and Methods: 27 CAD patients and 33 age- and sex-matched controls were enrolled in this case-control study. Diagnosis of CAD was done by clinical examination, case history, ECG, echocardiography, and significant changes in serial cardiac specific enzymes. Comprehensive periodontal examination in the form of periodontal pocket depth (PPD), clinical attachment level (CAL), bleeding on probing (BOP), and a panoramic x-ray were done to every patient. Serum levels of highly sensitive CRP (hs-CRP), IL-6, fibrinogen, total cholesterol (TC), LDL, HDL, and triglycerides (TG) were analyzed for each subject.

Results: Number of AP patients was higher in CAD (26.1%) than in control (11.5%), and SP was 56.5% and 30.8% respectively with no significant difference between the two groups. The PPD, CAL, and BOP scores were statistically significantly higher in CAD than in control group. The hs-CRP, and IL-6 was very highly significantly elevated (p <0.001) and fibrinogen was significantly elevated (p <0.05) in CAD than in control patients. These values showed no significant differences in edentulous patients of both groups. Highly positive statistically significant correlations were observed between hs-CRP levels and severity of periodontitis represented by elevated PPD, CAL, and BOP scores.

Conclusions: CAD patients had higher non-significant percentage of both AP and SP forms of periodontitis. Severity, and not the type, of periodontitis were positively correlated to the elevated serum levels of hs-CRP, IL-6, and fibrinogen in CAD patients. These correlation was very high significant only with hs-CRP serum levels.


INTRODUCTION

Cardiovascular diseases (CVD) still represent the major cause of death in industrialized countries. Although the traditional risk factor concept has been well established, it doesn’t fully account for the risk of cardiovascular disease (Kullo et al 2000, Hackam & Anand 2003). Inflammation plays an important role in atherothrombogenesis and its clinical complications, so research has aimed to identify potential causes of chronic inflammation (Danesh et al 1997, Hoffmeister et al 2000). The role of chronic infections on atherosclerotic cardiovascular disease is now supported by a bulk of validating evidence that has also generated a series of antimicrobial intervention trials to establish causality in the association (Fong 2000, Kiechl et al 2001, Espinola-Klein et al 2002).

Periodontitis is characterized by chronic infection and inflammation in the periodontal tissue leading to the destruction of the alveolar bone with subsequent tooth loss (Page et al 1997). Periodontitis has high prevalence in the general population and is associated mainly with gram-negative bacteria (Sheiham & Netuveli 2002, Brown & Löe 1993).

Several studies have investigated the association between periodontal disease and atherosclerosis or its major clinical complication, the coronary heart disease (Spahr et al 2006, Demmer and Desvarieux 2006, D’Aiuto et al 2004a). Early studies suggest that poor dental health and periodontal bone loss may be associated with coronary heart disease events, even after adjustment for established cardiovascular risk factors (Mattila et al 1989, Beck et al 1996). Recently, Discussions have focused on the divergent results that different groups have obtained after analysis of material from the same study (Beck & Offenbacher 2001, Genco et al 2002, Hujoel et al 2002). Critics have underlined the fact that both periodontitis and atherosclerosis share common risk factors, and that the association, even if established, could be spurious. While the debate on the strength and nature of association between periodontitis and cardiovascular disease will continue for some time, recent evidence has changed the definition of periodontitis. Subjects affected by this disease share common polymorphisms in specific genes considered important in the regulation of inflammatory response (Kornman et al 1999, Kornman & Duff 2001). Furthermore, patients with severe periodontitis have increased levels of serum C-reactive protein (CRP), hyperfibrinogenemia, moderate leukocytosis, as well as increased serum levels of IL-1 and IL-6 when compared with unaffected control populations (Kweider et al 1993, Ebersol & Capelli 2000, Loos et al 2000, Noak et al 2001, Fredriksson et al 2002).

Two mechanistic hypotheses have been proposed regarding the etiological pathways of the association between periodontitis, systemic inflammation and cardiovascular disease; direct and indirect pathways. In the direct pathways, oral microbes and their byproducts can gain systemic access via circulatory system. Geerts and colleagues (2002) showed that gentle mastication can induce endotoxemia, and this risk was elevated according to an increased severity of periodontal disease. Other investigators (Kinane et al 2005, Rajasuo et al 2004, Forner et al 2006) have shown that dental procedures and tooth brushing can induce bacteremias. Recent research indicates that the magnitude of bacteremia after scaling was amplified among patients with periodontitis as opposed to patients with gingivitis or healthy control patients (Forner et al 2006). Common periodontal pathogens have been detected in carotid endarterectomy samples (Haraszthy et al 2000, Chiu 1999).

The indirect pathways considered the diseased periodontium as a source of systemic inflammatory mediators. Atherosclerosis has a strong inflammatory component (Ross 1999, Libby 2000), and epidemiologic evidence suggests that increased levels of systemic inflammation are predictive of cardiovascular events (Ridker et al 1997, Ridker et al 2000). People with periodontal disease have elevated levels of systemic inflammatory markers, such as CRP (Slade 2003), and treatment of periodontal disease has been reported to

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decrease systemic inflammation levels (D’Aiuto et al 2004b). In this respect, CRP is considered as the most sensitive marker of the acute phase response to infectious burdens and/or inflammation (Gabay & Kushner 1999). Liver production of CRP is usually elicited by an inflammatory stimulus and mediated through a complex network of cytokines (mainly IL-6) (de Maat & Kluft 2001). Systemic low-grade infections with their moderate acute phase responses may accelerate the formation of atheromatous plaques with consequent increased risk of future cardiovascular events (Danesh et al 2000).

Most of the previously mentioned studies focused on the role of periodontal disease as a risk factor for different forms of cardiovascular diseases, as well as the increased rate of CVD among patients with periodontitis or with history of periodontal diseases. On the other hand, the incidences of periodontal disease among patients with existent coronary artery disease (CAD) have not deeply investigated. The purpose of this study was to investigate the incidence of slowly- or rapidly- progressive periodontitis in patients diagnosed with coronary artery disease (CAD) and to assess the severity of periodontitis with levels of pro-inflammatory molecules C-reactive protein (CRP), fibrinogen, and IL-6.

**Materials and Methods:**

**Patients and study design:**

A total of 60 patients were enrolled in this prospective case-control study. Patients were recruited from those attending Department of Cardiology, at the Faculty of Medicine, Mansoura University. All patients were subjected to thorough history taking with stress on analysis of chest pain, presence of traditional coronary risk factors, and clinical examination especially for left ventricular failure. ECG were analysed for site, extent of ischemic changes and arrhythmias. Echocardiography was performed for all patients and control with special stress on the left ventricular systolic and diastolic functions and resting segmental wall motion abnormalities.

Patients were classified into two groups, study group represented patients with coronary artery disease (27 patients, 17 males and 10 females), and control group (33 patients, 19 males and 14 females) of non-coronary artery disease. A detailed medical history was taken from each patient. History taking was including the following:

1. Electrocardiography (ECG): a standard 12-leads ECG were taken at speed of 25 mm/sec, and a sensitivity of 1 mv/cm using Hellige simplicrcriptor EK31. ECG was analyzed for signs of myocardial ischemia and/or infarction, observation of any arrhythmia or conduction defect, and signs of chamber enlargement.

2. Echocardiography, for measuring left ventricle ejection fraction percentage (LVEF %).

The diagnosis of coronary artery disease was made by the presence of two or more of the following findings: 1) clinical history of typical ischemic chest pain. 2) characteristic ECG changes (ST-T wave changes). 3) significant changes in serial cardiac specific enzymes. Exclusion criteria include valvular heart disease, congenital cardiac lesions, cardiomyopathy, heart failure, renal failure, liver cirrhosis, and pulmonary hypertension.

**Periodontal examination:**

All patients were referred to Department of Oral Medicine & Periodontology, Faculty of Dentistry, Mansoura University, for periodontal evaluation. All individuals were examined in a standardized way in a dental unit under optimum conditions. All periodontal examination and scores were performed by one examiner. Every patient was subjected to comprehensive periodontal examination in the form of periodontal pocket depth (PPD), clinical attachment level (CAL), bleeding on probing (BOP), and a panoramic x-ray. A color-coded periodontal probe (PCP-12 screening probe, Hu-Friedy, Chicago, IL, USA) was used for scoring. Each score was taken at six different sites of each tooth in the mouth (midbuccal, mesio-buccal, disto-buccal, midlingual, mesio-lingual, and disto-lingual). The mean of six
was calculated for each tooth, the mean of all present teeth was then recorded for each patient and used as a statistical unit for each patient in the study. Edentulous patients were diagnosed separately and reasons for teeth losses were taken. Patients were classified into either: slowly-progressive periodontitis, rapidly-progressive periodontitis, gingivitis, or edentulous patients.

Biochemical analysis:

Eight ml of venous blood was withdrawn from every patient after fasting of at least 12 hours. Each blood sample was divided into two tubes, 1ml of blood was delivered into plastic specimen tube containing 50 µl Di-K-EDTA solution for performing complete blood picture using automated cell counter (Celldyne 1700, USA). The other 7 ml of blood sample were left to clot in a plain polypropylene tube at 37˚C for 30 minutes, centrifuged at 4000 rpm for 4 minutes, and serum was separated for laboratory assessments. Serum glucose level, liver function tests, renal function tests, and coagulation profile were routinely done for each patient (Human, Wiesbaden, Germany). For lipid profile assessment, serum low-density lipoprotein (LDL) cholesterol was calculated after determining serum total cholesterol concentration (TC), high density lipoprotein (HDL) and the triglycerides (TG) concentration according to the equation of Friedewald et al (1972), provided that TG does not exceed 400 mg/dl:

\[
LDL = \text{Serum Cholesterol (SC)} - \left( \frac{1}{5} \times TG + HDL \right)
\]

A 1.5 ml Eppendorf tubes were used for preserving serum samples at -80˚C for subsequent specific laboratory investigations of serum levels of highly-sensitive CRP (hs-CRP) and IL-6.

The serum level of hs-CRP was measured using ELISA technique (Diasyslab Inc.; Webster, USA) was an enzymatically amplified “two-steps” sandwich-type immunoassay in which standard samples, controls and unknown samples were incubated in micro-titration wells which have been coated with hs-CRP antibody. After incubation and washing, the wells were with another anti-hs-CRP detection antibody labeled with the enzyme horseradish peroxidase (HRP). After a second incubation and washing step, the wells were incubated with the substrate tetra-methyl-benzidine (TMB). An acidic stopping solution was then added and the degree of enzymatic turnover of the substrate was determined by measurement at 450 nm. The absorbance measured was directly proportioned to the concentration of hs-CRP present. The data were entered into computer program capable of performing many functions of data plotting and curve fitting for calculation of the results which were expressed in ng/ml. Results of these samples were multiplied by 500 to correct for additional dilution.

The serum level of IL-6 was detected with ELISA (Cytimmune Science Inc.; Rockville, Europe). A goat anti-rabbit antibodies were used to capture a specific IL-6 complex in each sample consisting of IL-6 antibody, bio-tinylated IL-6, and sample-standard. The assay was visualized using a streptavidin alkaline phosphatase conjugate and a chromogenic substrate reaction. The amount of IL-6 detected in each sample was compared to an IL-6 standard curve which demonstrated an inverse relationship between optical density (O.D.) and cytokine concentration (i.e. the higher the O.D., the lower the IL-6 concentration in the sample, and vice-versa).

Statistical Analysis

The statistical of data was done by using SPSS program (Statistical Package for Social Science, Version10). Data description was done in the form of mean ± standard division and frequency proportion. Analysis of data was done to test statistical significance between groups. For parametric data, student-t test was used to compare between the two groups, paired sample t test was used to compare within one group at different follow up times, and LSD (least significant difference) was used to test inter-group difference. For non-parametric data, chi-square test was used to compare between the two groups. Pearson 2-tailed correlation was used to correlate between different parameters in both groups.
RESULTS

Characteristics of Study Population:

The demographic data of both the study and control groups are displayed in Table 1. A total of 27 patients with coronary artery disease (CAD) and another 33 age and sex-matched patients with no CAD were enrolled in this case-control study. The percentage of male subjects in the study group was slightly higher (62.9%) than in the control group (57.6%) even if it represented non-significant difference (p = 0.67). In the CAD (study) group, 67% demonstrated dyslipidemia which was statistically significant different when compared to control group (51%) at p value of 0.05. Hypertensive patients in the study group represented 85.2%, while they were 54.5% in the control group. Number and percentage of patients with diabetes mellitus in both study and control groups were 14 (51.9%) and 16 (48.5%) respectively with no statistically significant different between the two groups.

Periodontal Evaluation:

As shown in Table 1, number of edentulous patients in study and control groups were 4 (14.8%) and 7 (21.2%) respectively which was non-significant between the two groups. The total number of patients with gingivitis were 23 (85.2%) and 26 (78.7%) for both study and control groups respectively. The mean PPD was very statistically significant higher in study group (4.60±1.6 mm) when compared to the mean PPD in control group (2.96±1.8 mm) at p value 0.002 (Table 2). These findings were parallel to CAL measurements that showed very high statistically significant difference when comparing study (4.38±1.5 mm) and control (2.94±1.8 mm) groups (p = 0.005). The mean BOP of study group was 2.38±0.52 which was very highly statistically higher (p <0.001) than in control group (1.48±0.7). Figure 1 shows the different periodontal parameters (CAL, PPD, and BOP) of both groups.

When data were analysed regarding the periodontal examination, CAD group demonstrated higher number of both slowly progressive and aggressive periodontitis (13 and 6 patients) represented 56.5% and 26.1% respectively, when compared to control group (8 and 3 patients represented 30.8% and 11.5% respectively). When calculating the number of CAD patients with periodontitis, Table 3, (both SP and AG) it was 19 patients represented 71.3% which was highly statistically different when compared to control group (only 11 patients represented 33.3%).

<table>
<thead>
<tr>
<th>TABLE (1) Demographic Data of Both Case (Study) and Control Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
</tr>
<tr>
<td>---------</td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>p</td>
</tr>
</tbody>
</table>

**SP** slowly-progressive periodontitis  **RP** rapidly-progressive periodontitis  **M** mean  **SD** standard deviation  *** very high significant  ** high significant  * significant
**Table (2) Clinical Parameters of Dentulous Patients of Both Groups**

<table>
<thead>
<tr>
<th></th>
<th>Study Group (Mean±SD)</th>
<th>Control Group (Mean±SD)</th>
<th>Student t-test</th>
<th>t</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPD</td>
<td>4.60±1.6</td>
<td>2.96±1.8</td>
<td>3.295</td>
<td>0.002***</td>
<td></td>
</tr>
<tr>
<td>CAL</td>
<td>4.38±1.5</td>
<td>2.94±1.8</td>
<td>2.978</td>
<td>0.005**</td>
<td></td>
</tr>
<tr>
<td>BOP</td>
<td>2.38±0.52</td>
<td>1.48±0.7</td>
<td>4.883</td>
<td>&lt;0.001***</td>
<td></td>
</tr>
</tbody>
</table>

PPD: periodontal pocket depth  
CAL: clinical attachment level  
BOP: bleeding on probing

Table (3) Numbers and percentages of total Periodontitis patients among Study and Control Groups

<table>
<thead>
<tr>
<th></th>
<th>Number of Patients</th>
<th>Number &amp; % of Periodontitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study Group</td>
<td>27</td>
<td>19 (70.3%)</td>
</tr>
<tr>
<td>Control Group</td>
<td>33</td>
<td>11 (33.3%)</td>
</tr>
<tr>
<td><strong>p</strong></td>
<td></td>
<td>&lt;0.05**</td>
</tr>
</tbody>
</table>

** high significant

**Biochemical Analysis:**

Table 4, shows the biochemical parameters of both study and control group. The patients in study group showed very high significant elevated levels of hs-CRP (3385.5±896.7) when compared to level in control patients (1804.3±333.5) at p value of <0.001***. For the mean IL-6 level, it showed a very high significant increase in study group (6.18±1.26) than in control one (2.96±1.73). The mean fibrinogen level among study group was 73.74±9.24, and for the control group was 44.66±15.31, the differences between the two values were statistically significant at p value of <0.05. Levels of hs-CRP, IL-6 and fibrinogen of both study and control groups are shown in Figure 3. The other mean biochemical values of TC, LDL, and TG showed also elevated levels in study group which were highly significantly different when compared to those of control group. The HDL showed significantly lower values in CAD patients in comparison to the controls.

**Fig. (1) Periodontal parameters among study (cases) and control groups.**

CAL: clinical attachment level  
APD: average periodontal depth  
BOP: bleeding on probing

**Fig. (2) Different lipid profiles of study (CAD) and control groups**

TC: total cholesterol  
LDL: low-density lipoprotein  
HDL: high density lipoprotein  
TG: triglycerides
### TABLE (4) Biochemical Parameters of Dentulous Patients of the Two Groups.

<table>
<thead>
<tr>
<th></th>
<th>Study Group (Mean±SD)</th>
<th>Control Group (Mean±SD)</th>
<th>Student t-test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>t</td>
</tr>
<tr>
<td>hs-CRP</td>
<td>3385.5±896.7</td>
<td>1804.3±833.5</td>
<td>7.065</td>
</tr>
<tr>
<td>IL-6</td>
<td>6.18±1.26</td>
<td>2.96±1.73</td>
<td>8.041</td>
</tr>
<tr>
<td>Fibgen</td>
<td>73.74±9.24</td>
<td>44.66±15.31</td>
<td>8.651</td>
</tr>
<tr>
<td>TC</td>
<td>241.44±24.6</td>
<td>176.87±10.8</td>
<td>13.55</td>
</tr>
<tr>
<td>LDL</td>
<td>166.88±4.45</td>
<td>121.15±6.46</td>
<td>31.217</td>
</tr>
<tr>
<td>HDL</td>
<td>29.81±2.28</td>
<td>40.36±2.51</td>
<td>-16.84</td>
</tr>
<tr>
<td>TG</td>
<td>194.81±31.5</td>
<td>146.69±23.9</td>
<td>6.71</td>
</tr>
</tbody>
</table>

*hs-CRP: highly sensitive C-reactive protein (normal mean = 1917 ng/ml).*

*Fibgen: fibrinogen (normal 25-60 µg/dl)*

*IL-6: interleukin-6 (normal mean =2.16 ng/ml).*

*TC: total cholesterol (normal up to 200 mg/dl)*

*LDL: low-density lipoprotein (normal < 130 mg/dl)*

*HDL: high-density lipoprotein (normal > 35 mg/dl)*

*TG: triglycerides (normal < 150 mg/dl)*

**high significant**

***very high significant***

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**Fig. (3) Levels of C-reactive protein (CRP), Fibrinogen, and IL-6 in study (cases) and control groups**

### TABLE (5) Biochemical parameters of Edentulous Patients in both Groups

<table>
<thead>
<tr>
<th></th>
<th>Number</th>
<th>CRP</th>
<th>IL-6</th>
<th>Fibgen.</th>
<th>TC</th>
<th>LDL</th>
<th>HDL</th>
<th>TG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study</td>
<td>4</td>
<td>1539±947</td>
<td>3.65±1.06</td>
<td>43.75±8.6</td>
<td>193.5±33.6</td>
<td>141.8±2.75</td>
<td>28.5±1.73</td>
<td>164±24.6</td>
</tr>
<tr>
<td>Control</td>
<td>7</td>
<td>1442±627</td>
<td>2.67±1.6</td>
<td>38.71±13.2</td>
<td>182.9±4.91</td>
<td>119.7±2.36</td>
<td>30.1±2.71</td>
<td>145±21.9</td>
</tr>
<tr>
<td>P</td>
<td>0.14</td>
<td>0.58</td>
<td>0.61</td>
<td>0.88</td>
<td>0.17</td>
<td>0.78</td>
<td>0.26</td>
<td></td>
</tr>
</tbody>
</table>

*non-significant
Analysis of data of edentulous patients showed marked reduction in all biochemical values than dentulous patients in both groups. Table 5, showed non significant differences of the tested biochemical parameters between study and control groups.

Correlation between the different biochemical parameters and the periodontal scores are shown in Table 6. A highly significant positive correlation was observed between hs-CRP levels and the mean PPD, CAL, and BOP of the study group. This meant that elevated clinical periodontal scores were highly significantly associated with elevated serum levels of hs-CRP. These correlations between hs-CRP and each periodontal score of both study and control groups are demonstrated in Figures 4, 5, and 6. A positive but non-significant correlation could be observed between the periodontal parameters and IL-6, and fibrinogen.

**TABLE (6) Correlation Between Clinical Parameters of Patients with Periodontitis and Different Biochemical Parameters in both Study and Control Groups**

<table>
<thead>
<tr>
<th></th>
<th>CAL</th>
<th>PPD</th>
<th>BOP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Study</td>
<td>Control</td>
<td>Study</td>
</tr>
<tr>
<td>CRP</td>
<td>r +0.69</td>
<td>-0.47</td>
<td>+0.82</td>
</tr>
<tr>
<td></td>
<td>p 0.001***</td>
<td>0.14</td>
<td>0.001***</td>
</tr>
<tr>
<td>IL-6</td>
<td>r +0.44</td>
<td>+0.08</td>
<td>+0.31</td>
</tr>
<tr>
<td></td>
<td>p 0.05</td>
<td>0.82</td>
<td>0.19</td>
</tr>
<tr>
<td>Fibgen.</td>
<td>r +0.17</td>
<td>+0.13</td>
<td>+0.45</td>
</tr>
<tr>
<td></td>
<td>p 0.47</td>
<td>0.70</td>
<td>0.05</td>
</tr>
<tr>
<td>LDL</td>
<td>r +0.05</td>
<td>-0.08</td>
<td>-0.12</td>
</tr>
<tr>
<td></td>
<td>p 0.84</td>
<td>0.80</td>
<td>0.59</td>
</tr>
<tr>
<td>HDL</td>
<td>r -0.13</td>
<td>+0.28</td>
<td>+0.78</td>
</tr>
<tr>
<td></td>
<td>p 0.59</td>
<td>0.39</td>
<td>0.75</td>
</tr>
<tr>
<td>TG</td>
<td>r -0.38</td>
<td>-0.09</td>
<td>-0.18</td>
</tr>
<tr>
<td></td>
<td>p 0.11</td>
<td>0.79</td>
<td>0.43</td>
</tr>
</tbody>
</table>

\(r\) correlation coefficient  
*** very high significant  
** high significant  
+ positive correlation  
- negative correlation

**Fig. 4 (A) Significant positive correlation between CRP & CAL of Study Group. (B) Non-significant positive correlation of Control Group.**
A negative non-significant correlation was observed between the triglyceride (TG) and the clinical periodontal parameters. For the LDL, positive non-significant correlation was observed only between it and CAL and BOP, while a negative correlation occurred at the PPD.

**DISCUSSION**

There is a growing evidence of a strong relationship between chronic infection and atherosclerosis as well as specific link between periodontal infection and coronary heart disease (Spahr et al 2006). Over the past 15 years, a substantial number of population-based clinical and laboratory studies reported findings providing support for a possible relationship between periodontal disease and cardiovascular disease (Demmer & Desvarieux 2006, Nakib et al 2004, Joshipura et al 2004, Desvarieux et al 2003, Emingil et al 2000, Genco et al 1999).

In the present case-control study, we investigated the potential association between coronary artery disease (CAD) and periodontal disease, focusing on the prevalence of different forms of periodontitis (either slowly or aggressive) among patients with confirmed diagnosis of coronary artery disease (CAD) compared with sex- and age-matched non-CAD control patients. Based on clinical measures of different periodontal parameters (BOP, PPD, and CAL), as well as radiographic evaluation of panoramic radiographs, patients were diagnosed as either slowly progressive, or aggressive...
periodontitis. Edentulous patients were statistically evaluated separately in relation to CAD. We found significantly higher number of patients with periodontitis (slowly progressive and aggressive) among patients with CAD \( (p < 0.05) \) when compared to control patients. The CAD patients (study group) showed increased severity of periodontal disease as represented by significantly higher PPD \( (p < 0.002) \), CAL \( (p < 0.005) \) and BOP \( (p < 0.001) \) in comparison to control group values. There was no significant difference between CAD and control patients regarding the number of slowly progressive or aggressive periodontitis. This indicated that it was the severity, not the type, of periodontitis which had a positive association to CAD.

Our results demonstrated very highly statistically elevated levels of the systemic inflammatory markers hs-CRP, and IL-6, as well as total cholesterol, and LDL in CAD patients when compared to non-CAD control \( (p < 0.001) \). The HDL was highly significantly lower in CAD than control patients. Fibrinogen level was statistically elevated at \( p < 0.05 \). These finding were in consistence with the findings of Noack et al (2001) who observed statistically significant increase in CRP levels in 109 patients with moderate to severe periodontitis when compared with 65 periodontally healthy controls \( (p = 0.036) \). Also CRP levels were reported to be higher in 50 CVD patients with severe periodontitis \( (>4 \text{ mm-deep pockets}) \) than in 46 healthy cases (Buhlin et al 2003). Meurman et al (2003) have reported that both CRP and fibrinogen concentrations were significantly higher in CVD patients than in controls. Our study showed marked decrease of these markers in the edentulous patients of both CAD and control groups, which support the hypothesis that periodontitis is associated with hyperinflammatory status represented by increased serum levels of CRP, IL-6, and fibrinogen, as well as increased lipid profiles.

In the present study, a positive highly significant correlation \( (p = 0.001) \) was observed between the elevated levels of CRP in CAD patients and the severity of periodontitis represented by the increased PPD and CAL as well as BOP, while a non-significant correlations were noticed at the control group patients. This positive significant correlation between the severity of periodontitis and the serum concentration of CRP indicated that the effect of periodontitis on systemic inflammation seems to be dose-dependent. These findings are in agreement with the hypothesis that the periodontal burden (infection plus associated inflammatory responses) acts on individual susceptibility profile that amplifies the systemic inflammatory responses and, in turn, may play a role in systemic inflammatory diseases such as atherosclerosis (D’Aiuto et al 2004b).

Studies by Wu et al (2000), and Slade et al (2003, & 2000) provided evidence that periodontal disease is associated with cardiovascular risk factors, including acute-phase proteins, CRP, and plasma fibrinogen. There are extensive literatures associating CRP and fibrinogen, among other inflammatory factors, with coronary heart disease. Meta analysis of theses studies (Danesh et al 1998 and 2000) are consistent with highly statistically significant associations of the acute-phase proteins, CRP and fibrinogen, as well as elevated white blood cell counts, with subsequent risk of CVD (Liuzzo et al 1994, Pietila et al 1993) and that CRP is an independent risk factor for CVD. A detailed mechanism by which CRP participates in the pathogenesis of atheromas is lacking. In a recent randomized clinical trial (D’Aiuto et al 2006), intensive periodontal treatment reduced systemic inflammatory markers and systolic blood pressure and improved lipid profiles. Participants of the intensive periodontal treatment group experienced significant reductions in white blood cell count, CRP, IL-6, total cholesterol, and low density lipoprotein cholesterol at 1, 2, and/or 6 months compared to participants in the standard periodontal therapy group. Joshipura et al (2004) have published cross-sectional data from the prospective male health-professionals follow-up study, where self-reported periodontal disease was analyzed in a sample of 468 men with respect to a variety of biomarkers of CVD. Their results showed that periodontal disease was associated with higher levels of CRP and LDL. However, these findings could not support our results because diagnosis of periodontitis in Joshipura et al study was a self-reported one and not made through periodontal examination and scoring as done in our study.
In the present study, we demonstrated overall increase in the total cholesterol, LDL, and triglycerides in patients with CAD than in control patients. Also the level of HDL was lower in study (CAD) group than in control one. These changes in lipid profiles in CAD patients were correlated to the severity of periodontitis represented by increased periodontal parameter measures, even these correlations did not reach statistical significance. In the study of Buhlin’s group (2003), a relationship was found between periodontitis and low concentration of HDL, the analysis was adjusted for age, gender, and smoking. These findings support the earlier results of Katz et al (2002) indicating that periodontal disease may also influence blood lipid concentration. Our study showed a reversed (negative) correlation between the low level of HDL and CAL in CAD patients, while positive non-significant correlations were detected between HDL level and PPD and BOP in both CAD and control groups.

In conclusions, the preset study showed that CAD patients had higher non-significant percentage of both AP and SP forms of periodontitis. Severity, and not the type, of periodontitis were positively correlated to the elevated serum levels of hs-CRP, IL-6, and fibrinogen in CAD patients. These correlation was very high significant only with hs-CRP serum levels.

REFERENCES


