Association of Endodontic Infection with Detection of an Initial Lesion to the Cardiovascular System

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Abstract

Introduction: Dental infections might predispose toward the onset of cardiovascular disease (CVD). To date, only a few studies, yielding inconclusive findings, have investigated the potential correlation between apical periodontitis (AP) and CVD. The aim of this study (as the first part of a prospective study) was to evaluate, in the absence of CV risk factors, whether subjects with AP were more exposed to the pathogenetic indices of an atherosclerotic lesion. **Methods:** Forty men between the ages of 20 and 40 years who were free from periodontal disease, CVD, and traditional CV risk factors were enrolled in the study; 20 subjects had AP, and 20 acted as controls. All subjects underwent dental examination and complete cardiac assessment: physical examination, electrocardiogram, conventional and tissue Doppler echocardiography, and measurement of endothelial flow reserve (EFR). The following laboratory parameters were tested: interleukins -1, -2, and -6 (IL-1, IL-2, IL-6), tumor necrosis factor alpha, and asymmetrical dimethylarginine (ADMA). Data were analyzed by using the 2-tailed Student's *t* test, Pearson *t* test (or Spearman *t* test for nonparametric variables), and multivariate linear regression analysis. **Results:** Echocardiography revealed no abnormalities in any of the subjects studied. ADMA levels were inversely correlated with EFR ($P < .05$) and directly correlated with IL-2 ($P < .001$). Patients with AP presented with significantly greater blood concentrations of IL-1 ($P < .05$), IL-2 ($P < .01$), IL-6 ($P < .05$), and ADMA ($P < .05$) and a significant reduction of EFR ($P < .05$). **Conclusions:** Increased ADMA levels and their relationship with poor EFR and increased IL-2 might suggest the existence of an early endothelial dysfunction in young adults with AP. *(J Endod 2011;37:1624–1629)*

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Key Words

Apical periodontitis, cardiovascular disease, endodontic infection

It is an acknowledged fact that the equilibrium in the circulatory system is maintained by normal functional endothelium that, by inhibiting platelet aggregation, monocyte adhesion, and vascular smooth muscle cell proliferation, maintains the physiological balance between procoagulant and anticoagulant forces (1). Cardiovascular diseases (CVDs) are known to originate from endothelial inflammatory dysfunction (2) and are influenced by well-known CV risk factors, including smoking, diabetes, hypertension, and dyslipidemia (3). Chronic inflammation plays a crucial role in the pathogenesis and progression of atherosclerosis and at the same time promotes acute CV events such as plaque rupture and coronary thrombosis (4).

In recent years, a number of studies have demonstrated the possible association between CVD and periodontal disease (5). Apical periodontitis (AP) is an inflammatory and frequently chronic disorder of the periapical tissues caused by the persistence of a microbial infection within the endodontic system of the affected tooth (6, 7). The scientific literature has failed to provide unequivocal interpretation of the potential connection between endodontic infection and CV risk (8). Therefore, it would be of great interest, both from a scientific point of view and from a public health perspective, to ascertain whether the presence of AP is associated with indices of CV function and biological markers associated with systemic inflammation.

A prospective study was designed to investigate whether the state of low-grade chronic inflammation that accompanies AP is capable of significantly altering cardiac endothelial function. In the initial part of the study the first 40 subjects, 20 with AP and 20 controls, all of whom were men younger than the age of 40 and were free from CVD and CV risk factors, were studied. In future studies the sample size will be increased, and evaluation will be extended to women and older people.

Materials and Methods

Study Design and Patient Population

The present study represents the first part of an observational cross-sectional trial conducted on young men observed at the Diagnostic Section of the Dental Clinic at the University of Cagliari during 2009. Subjects were divided into 2 groups, patients affected by AP and healthy controls. The study protocol was approved by the Institutional Ethics Committee (Azienda Ospedaliero-Universitaria, University of Cagliari). Written informed consent was obtained from all subjects.

Inclusion criteria were the following:

1. Male patients
2. Age 20–40 years
3. Presence of at least 1 radiographically assessed endodontic lesion
4. Presence of at least 25 teeth
5. Echocardiographic left ventricle ejection fraction (LVEF) value ≥55%
6. Hepatic and renal function within normal limits (bilirubin ≤1.5 mg/dL, creatinine ≤2.0 mg/dL)

Exclusion criteria were as follows:

1. Presence of localized or diffuse periodontal disease
2. Presence of non-endodontic lesions in the maxillary bones
3. Presence of CV risk factors (arterial hypertension, dyslipidemia, diabetes mellitus, obesity, history of smoking)
4. LV hypertrophy at echocardiography
5. Previous and/or current CV or cerebrovascular disease
6. Presence of chronic inflammatory conditions in other districts involving systemic health

Forty consecutive patients who registered for a dental check-up at the School of Dentistry were enrolled; 20 were affected by AP (age ± standard deviation [SD], 35 ± 5 years; range, 22–40 years), and 20 were control subjects matched for age and physical characteristics (27 ± 3 years; range, 21–33 years). All patients underwent a complete CV assessment: medical history, physical examination, blood pressure measurement, 12-lead electrocardiogram, and conventional and tissue Doppler (TDI) echocardiographic analysis. In addition, blood samples were collected for the assessment of circulating levels of interleukin-1, -2, and -6 (IL-1, IL-2, IL-6), tumor necrosis factor alpha (TNF-α), and asymmetrical dimethylarginine (ADMA).

Dental Examination

A complete dental examination was performed on each patient. A panoramic radiograph was examined and used as initial screening and was followed by selected periapical radiographs taken on teeth suspected of presenting AP and in all teeth with root canal treatments or presenting extensive restorations (including prosthetic restorations) with or without previous endodontic treatment. Periapical radiographs were taken with a radiographic unit (Castellini, Castelmaggiore, Italy) by using a long cone paralleling technique (70 Kv; 10 Ma; film-focus distance, 28 cm) and Ultra Speed film (Eastman Kodak, Rochester, NY). Radiographs were examined in a darkened room by an expert endodontist by using an illuminated viewer box with 3.5× magnification to assess the presence of a periapical lesion involving at least 1 root of a given tooth. To reduce interobserver variability all radiographs were randomly evaluated by a second expert observer, and an average of each observation was calculated. Intraoral examination was then completed. By using both radiographic and intraoral evaluations the following parameters were recorded:

1. Number of teeth present
2. Number and location of restored teeth
3. Number of endodontically treated teeth
4. Number and location of teeth affected by carious processes
5. Soft tissue assessment (presence and location of swelling/sinus tracts)
6. Periodontal probing
7. Number and location of teeth with AP
8. State of the upper and lower jaws

Conventional and TDI Echocardiography

Echocardiographic images were recorded by using a commercially available system equipped with TDI and SR imaging (Toshiba APLIO CV ultrasound system-SSA 770A/CV; Toshiba Corp, Tochigi, Japan). LVEF was obtained from the apical 4- and 2-chamber views according to Simpson's rule and was considered abnormal when less than 55%. Pulsed wave Doppler examination of the LV inflow from the 4-chamber view was performed with the sample volume placed between the mitral leaflet tips and early (E) and late (A) diastolic peak velocities; E deceleration time (DecT) was measured, and E/A ratio was subsequently derived (9). Longitudinal function was evaluated by using pulsed TDI at the mitral annulus, placing the sample volume in the basal segment of the interventricular septum from the apical 4-chamber view; peak velocities in systole, isovolumic relaxation time, and early and late diastole were measured. For more accurate measurements TDI curves were obtained from raw data analysis. LV longitudinal function was evaluated from raw data; myocardial Strain and Strain rate were also quantified in the interventricular septum. All examinations were performed by the same experienced echocardiographer who was unaware of patients' clinical status and therapeutic regimen. A simultaneous electrocardiographic tracing was also obtained. To reduce interobserver variability, all echocardiographic data were randomly read by a second experienced observer, and an average value for each measurement was calculated. Reproducibility of TDI parameters in our laboratory had been previously documented (9).

Inflammatory Stress Markers

Blood samples were collected in tubes with clot activating factors and centrifuged immediately after collection; serum was stored at −20°C until assay. Levels of IL-1, IL-2, IL-6, and TNF-α were determined by enzyme-linked immunosorbent assay (Immunotech, Marseille, France). Results are expressed in picograms per milliliter.

ADMA

Plasma ADMA was analyzed by high-performance liquid chromatography coupled with laser-induced fluorescence detection. In all subjects a blood sample was obtained by venipuncture of the antecubital vein at 8 AM after overnight fasting. Blood samples were collected into serum tubes, centrifuged, and extracted by serum protein electrophoresis at room temperature. After derivatization, ADMA was quantified by the chromatographic method.

Endothelial Function

Endothelial flow reserve (EFR) was measured at the level of the distal extremity in the upper limbs by means of peripheral arterial tonometry (PAT), a non–operator-dependent method providing a reproducible index of endothelial-dependent vasodilation (10). We used the ENDO-PAT2000 model (Itamar Medical, Caesarea, Israel), an apparatus measuring changes to vasal tone influenced by the endothelium in the fingers through biosensors. Modifications of vasal tone are produced by occlusion of the brachial artery for 5 minutes with consequent hyperemic response; the contralateral arm was used as control.

Statistical Analysis

Data are reported as mean ± SD. Differences between values assessed in AP patients and healthy controls were calculated by the Student's 2-tailed t test for unpaired data. Correlation between instrumental (EFR) and laboratory variables was assessed by Pearson t test. P values were considered as significant when $P \leq .05$.

Results

Table 1 summarizes the basic dental features of the patients in the study group (AP).

In case of multirooted teeth, they were simply classified as having AP whether they exhibited 1 or more periapical lesions. There were no appreciable differences in anthropometric, clinical, and chemical parameters between AP subjects and controls. All patients in the study sample presented at least 1 lesion of endodontic origin. Neither