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Poor oral health is associated with coronary heart disease and elevated systemic inflammatory and haemostatic factors

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Abstract

Objectives: To assess the relationship between poor oral health and coronary heart disease (CHD) and systemic inflammatory and haemostatic factors in an Italian population.

Material and Methods: The study population consisted of 63 males aged 40–65 years with proven CHD and 50 controls matched for age, geographic area, and socioeconomic status. A detailed description of their oral status was given using four different dental indices (total dental index (TDI), panoramic tomography score, clinical periodontal sum score (CPSS), and clinical and radiographic sum score (CRSS)). Blood samples were taken for measurement of the following CHD risk factors: serum total cholesterol, triglycerides, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, and glucose; a series of systemic markers of inflammation (C-reactive protein, leucocytes, fibrinogen, homocysteine) and a series of haemostatic factors (von Willebrand factor, fibrin D-dimer, prothrombinic fragment F1.2, plasminogen activator inhibitor type I (PAI-1), and serum antibodies) against oxidized LDL (anti-Ox-LDL).

Results: Multiple logistic regression adjusted for all risk factors for CHD showed statistically significant relationships ($p < 0.01$) between all dental indices and CHD. Significant relationships (p always < 0.01) were found between CPSS and CRSS and leucocyte count. Significant relationships (p always < 0.05) were also found between TDI and the von Willebrand factor, and between CPSS and the von Willebrand factor, anti-Ox-LDL, and PAI-1.

Conclusions: The present study suggests an association between poor oral status and CHD, and provides evidence that inflammatory and haemostatic factors could play an important role in this association.

Key words: cardiovascular disease; epidemiology; odds ratio; periodontal disease; risk factor

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It is well known that coronary heart disease (CHD) can be the result of genetic and environmental risk factors such as diabetes, hypertension, smoking, abnormal serum lipids, and age (Stamler 1979).

There is also extensive evidence that associates CHD with high levels of systemic inflammatory factors such as C-reactive protein (CRP), leucocytes, fibrinogen and homocysteine, and haemostatic factors such as von Willebrand factor, fibrin D-dimer, phrothrombinic fragment F1.2, plasminogen activator inhibitor type I (PAI-1) and serum antibodies against oxidized low-density lipoprotein (LDL) (Danesh et al. 1998, Dardik et al. 2000, Hamsten et al. 2000, Loos et al. 2000, MacCallum et al. 2000, Ridker et al. 2000, 2001, Inoue et al. 2001).

More recent data have shown that poor dental health and, in particular, periodontal disease increases the risk of occurrence of CHD, providing evidence that dental diseases have a number of risk factors in common with CHD such as high levels of serum lipids, inflammatory, and haemostatic factors (DeStefano et al. 1993, Mattila et al. 1995, Beck et al. 1996, Lowe et al.

1998, Morrison et al. 1999, Wu et al. 2000, Emingil et al. 2000, Noack et al. 2001).

These data have not, however, been supported by all authors who have studied the issue (Joshipura et al. 1996, Hujoel et al. 2001, Mattila et al. 2000, Howell et al. 2001).

Some possible reasons for these inconsistent findings could include the differences in ages and sex of the subjects in the studies, the differences in describing CHD, and in the variety of measures that have been used to describe the oral status (Genco et al. 2002), suggesting that the role of dental infections as a coronary risk factor could vary according to the characteristics of the population studied (Mattila et al. 2000).

The purpose was to investigate (1) if poor oral health can be associated with CHD and, (2) if high levels of a series of systemic inflammatory and haemostatic factors are involved in the pathogenesis of atherosclerosis.

Material and Methods

In the present study, particular care was taken to control as many variables as possible, considering only males living in a well-defined area of Italy, aged between 40 and 65 years to avoid bias due to age, and with proven CHD; a detailed description of their oral status is also given using four different dental indices relating to different aspects of their oral health.

The study population consisted of 63 males aged 40–65 years (mean 52.3 ± 4.9 years) with proven CHD, who were referred to the Institute of Cardiology of the University of Bologna for coronary angiography, and of 50 controls (mean 54.5 ± 6.1), matched for geographic area and socioeconomic status, and randomly selected from the official records of inhabitants of Bologna, Italy.

All patients with CHD had suffered a recent history of acute myocardial infarction (less than 6 months prior to the study) as verified by hospitalization and with at least 50% diameter stenosis in one or more coronary arteries as diagnosed by coronary angiography.

All subjects enrolled in the study gave informed consent to participate and the study was approved by the institutional review board.

A structured questionnaire was administered to all participants by trained interviewers to elicit information about smoking (never, current, quit), hypertension, diabetes mellitus, education (university, secondary, elementary), social class (1 = salaried employees, higher level; 2 = salaried employees, lower level; 3 = specialized blue collar workers; 4 = non-specialized blue collar workers), and body mass index (BMI defined as weight/height^2).

Blood samples were taken from all subjects for measurements of a series of risk factors for CHD: serum total cholesterol, triglycerides, high-density lipoprotein cholesterol (HDL-cholesterol), LDL-cholesterol, and glucose; a series of systemic markers of inflammation: CRP, leucocytes, fibrinogen, homocysteine; and a series of haemostatic factors: von Willebrand factor, fibrin D-dimer, prothrombinic fragment F1.2, PAI-1, and serum antibodies against oxidized LDL (anti-Ox-LDL).

Serum total cholesterol (mg/dl), triglyceride (mg/dl), and glucose (mg/dl) levels were determined by automated enzymatic assays. LDL-cholesterol was assayed by enzymatic measurement, and HDL-cholesterol was determined by the precipitation method.

The CRP serum level was quantified using a commercial high-sensitivity kit for human CRP (Nanorid ''LL'', The Binding Site Limited, Birmingham, UK): the lower and upper detection limits of this kit are 0.18 and 8.5 mg/l, respectively. A kit for elevated CRP levels was used for assaying samples with CRP concentration > 8.5 mg/l (Noack et al. 2001).

Leucocyte count was measured with automated cell counters. Fibrinogen was determined in citrated samples by means of nephelometric assay. The total plasma fasting homocysteine was determined in EDTA samples using high-performance liquid chromatography (HPLC) as previously described Legnani et al. 1997).

PAI-1 antigen concentrations (ng/ml) were qualified by enzyme-linked immunosorbent assays (TintElize PAI-1, Biopool, Umea, Sweden).

Prothrombin fragment F1.2 (nm) was measured by ELISA (Behringwerke ag, Marburg, Germany).

D-dimer (ng/ml) and the von Willebrand factor were also measured by ELISA (Asserachrom, Stago, France).

The quantification of anti-Ox-LDL was performed using an enzyme-immunosorbent linked assay (ELISA) kit (Ox-LDL IgG ELISA test, Biodesign International, Saco, ME, USA).

All subjects were examined blindly by the same doctor, a qualified periodontist, and all underwent clinical and radiological examinations by means of panoramic tomography.

Following the results of the clinical and radiological examinations, four dental indices were used in the study:

- TDI (total dental index): the arithmetic sum of the points given to each subject according to the severity of their caries, periodontal, periapical, and pericoronitis lesions (Mattila et al. 1993)
- PTS (panoramic tomography score): the sum of radiolucent periapical lesions, third-degree caries lesions, vertical bone pockets, radiolucent lesions in furcation areas (Mattila et al. 2000)
- CPSS (clinical periodontal sum score): the sum of the number of sites with probing pocket depths 4 mm or greater, number of gingival sites with bleeding after probing, visible suppuration on probing, number of furcation lesions exceeding grade 1 (Mattila et al. 2000)
- CRSS (clinical and radiographic sum score): the number of radiographic vertical bone pockets and furcation lesions were added to the respective CPSS (Mattila et al. 2000)

Statistical analysis

Each dental index was dichotomized at the mean value and multiple logistic regression was used to estimate the odds ratios between each oral index variable and CHD, with the following confounding factors forced into the model: age, smoking, hypertension, diabetes, education, social class, BMI, serum total cholesterol, triglycerides, LDL-cholesterol and HDL-cholesterol cholesterol, and glucose.

Multiple logistic regression was also used to estimate the odds ratios, adjusted for CHD, between each dental index variable and the systemic markers of inflammation (CRP, leucocytes, fibrinogen, homocysteine), and the haemostatic factors (von Willebrand factor, phrothrombinic factor F1.2, fibrin D-dimer; PAI-1 and anti-Ox-LDL).

Here also, multiple logistic regression was used to estimate the odds ratios between CHD and the systemic markers of inflammation and haemostatic factors.

The unpaired Student's *t*-test and Mann–Whitney *U*-test were also applied

to demonstrate whether the CHD group and control groups differed and if there were differences for the dichotomous periodontal indices

Results

The results from the multiple logistic regression adjusted for all risk factors for CHD showed statistically significant relationships (p always <0.01) between all dental indices and CHD. The significant differences between the CHD group and the control group as regards all dental indices were confirmed by independent t-test and non-parametric Mann–Whitney test (Table 1).

As far as inflammatory markers were concerned, significant relationships (p always <0.01) were only found between CPSS and CRSS and leucocyte count; the OR adjusted for CHD as a confounding factor was 1.01 (95% CI = 1.00–1.02) for both associations between CPSS and CRSS and leucocytes.

As regards haemostatic factors, significant relationships (p always <0.05) were found between TDI and the von Willebrand factor (OR adjusted for CHD = 1.04; 95% CI = 1.01–1.09) and between CPSS and the von Willebrand factor (OR adjusted for CHD = 1.04; 95% CI = 1.01–1.09), anti-Ox-LDL (OR adjusted for CHD = 1.01; 95% CI = 1.00–1.02), and PAI-1 (OR adjusted for CHD = 1.01; 95% CI = 1.00–1.02).

Significant relationships were also found between CHD and a series of systemic markers of inflammation and haemostatic factors (Table 2).

Table 1. Dental scores (mean ± SD) in CHD patients and in controls; odds ratios were adjusted for all risk factors for CHD; significance was always less than 0.01

	CHD	Controls	Odds ratio (95% CI)	Unpaired Student's t-test, Mann–Whitney U-test*
CPSS	41.0 ± 39.8	14.6 ± 14.7	4.61 (1.00–23.20)	4.47
CRSS	50.7 ± 44.4	18.9 ± 18.7	4.70 (1.01–22.70)	4.69
PTS	11.4 ± 7.3	5.6 ± 4.9	5.14 (1.07–24.53)	4.89
TDI	5.2 ± 1.1	3.7 ± 1.5	20.81 (1.01–50.93)	6.22*

Table 2. Systemic inflammatory (*) and haemostatic (**) factors in CHD patients and in controls

	CHD	Controls	Odds ratio (95% CI)	Unpaired Student's t-test	p
Fibrinogen*	309.7 ± 94.1	264.0 ± 73.7	1.01 (1.00–1.02)	2.17	<0.05
Leucocytes*	7457 ± 1353	6532 ± 1450	1.01 (1.00–1.02)	2.92	<0.01
C-reactive protein*	5.02 ± 6.0	1.96 ± 2.1	1.61 (1.13–2.28)	2.27	<0.01
F1.2**	11.98 ± 13.8	6.06 ± 10.8	1.04 (1.00–1.08)	3.05	<0.01
Von Willebrand**	82.53 ± 13.9	72.57 ± 16.5	1.04 (1.01–1.07)	2.10	<0.05

CHD, coronary heart disease; CI, confidence interval.

Discussion

The results of the present study showed a significant association between poor oral status and CHD regardless of the dental index used.

The reported association was carefully controlled for a series of cardiovascular risk factors as confounders, including age, smoking, BMI, serum cholesterol and LDL levels, blood pressure, diabetes and glucose blood levels, social status and education, and the data are in agreement with other studies that have shown a positive association between poor health status or periodontitis and the risk of cardiovascular disease events (DeStefano et al. 1993, Paunio et al. 1993, Mattila et al. 1989, Beck et al. 1996, Arbes et al. 1999, Morrison et al. 1999, Emingil et al. 2000, Wu et al. 2000).

There are, however, other studies in the literature that have not found any significant association between the two pathologies after adjusting for potential confounders, and which give rise to a number of legitimate concerns about this issue (Joshipura et al. 1996, Hujoel et al. 2001, Mattila et al. 2000, Howell et al. 2001).

It should be considered that the results from all the above studies could be affected by the way they were conducted, and by a series of variables that could have interfered with the outcomes.

Age, for example, is an important variable that may have a big impact on periodontitis-associated CHD; coronary atherosclerotic plaque is a common finding in old subjects and the age of the participants is the most likely reason for underestimating a positive association between CHD and poor oral status (DeStefano et al. 1993, Mattila et al. 1993, 2000).

Other factors that could affect the outcomes include differences in the way of measuring CHD (some studies were conducted on the basis of CHD reported by questionnaire), or dental status (the measures used to assess the oral status seem to be related to the strength and significance of the associations reported) (Genco et al. 2002, Mattila et al. 2000).

In the present study, we investigated a carefully selected population that consisted of subjects living in a well-defined area of Italy, aged between 40 and 65 years to avoid any possible bias due to the presence of CHD related to physiological changes in old patients or any interference by congenital disease in young patients, and with a proven CHD demonstrated by clinical evidence of recent myocardial infarction along with the presence of atherosclerotic plaque in at least one coronary artery.

Furthermore, a significant relationship between poor oral status and CHD was demonstrated by using four dental indices, blindly investigated, which included some related to the general oral status (TDI, PTS) and others particularly to the periodontal status (CPSS, CRSS). These indices have been used in the past by other authors and their repeatability and validity carefully attested (Grau et al. 1997, Mattila et al. 2000).

The biological basis for the hypothetical association between oral diseases and, in particular, periodontal diseases and the development of atherosclerotic diseases is still unclear.

What is well known is that atherosclerosis results from a multifactor aetiology and, together with traditional factors such as obesity, hyperlipidaemia, diabetes, hypertension, and smoking, infectious agents could be responsible for atherosclerotic diseases, via an alteration of the systemic haemostasis.

There is now an extensive body of literature associating a series of systemic inflammatory and haemostatic factors with CHD. Elevated blood levels of CRP, leucocytes, fibrinogen, and other inflammatory factors have been frequently related to a subsequent risk of cardiovascular disease, suggesting that high levels of inflammatory factors could contribute to atheroma formation

(Danesh et al. 1998, Loos et al. 2000, Ridker et al. 2000, 2001).

Concerning the relationship between CHD and systemic haemostatic factors, it has been widely demonstrated that rheological variables are consistently associated with cardiovascular diseases. Approximately half the predictive value of plasma viscosity for cardiovascular events can be attributed once again to plasma fibrinogen, but other studies have shown that white blood cells are also a predictor of ischaemic heart disease via an increase in blood viscosity (Lowe 1994).

In addition to these two variables, several other blood variables related to both haemostasis and thrombosis have been consistently identified with cardiovascular disease and in several prospective studies, the coagulation von Willebrand factor complex has been associated with risk of ischaemic heart disease (Thompson et al. 1995, Ridker 1997).

Tissue plasminogen activator antigen is, like von Willebrand, released from endothelial cells, and it is the major physiological activator of plasminogen. Circulating tissue plasminogen activator is rapidly inactivated by its inhibitor, PAI-1, and plasma levels of PAI-1 have also been related to a risk of CHD (Juhan-Vague and Alessi 1993, Lowe 1997, Smith et al. 1997). D-dimer is a marker that originates from cross-linked fibrin and its levels are predictive of future cardiovascular events in healthy males (Ridker et al. 1994, Lowe et al. 1998) and the elderly (Cushman et al 1999).

Phrothrombinic fragment F1.2 cleaves from phrothrombin during the latter's conversion to thrombin by activating factor X, and elevated concentrations have been described in patients after an uncomplicated acute myocardial infarction (Merlini et al. 1994).

Finally, high levels of serum antibodies against oxidized LDL (anti-Ox-LDL) have been detected in patients with CHD as well as in patients with cerebral artery disease (Salonen et al. 1992, Puurunen et al. 1994, Lehtimaki et al. 1999).

The results of the present study are in agreement with the above studies, showing a positive association between the presence of CHD and high levels of a series of systemic markers of inflammation such as CRP, fibrinogen and leucocytes, and haemostatic factors such as prothrombinic fragment F1.2 and von Willebrand factor. These results are highly significant if we consider that all patients with CHD were on medication with aspirin, which could have affected the various haemostatic and systemic inflammatory factors investigated.

Moreover, what emerged from the present study is the presence of a relationship between poor dental health and systemic inflammatory and haemostatic factors.

We were unable to find positive associations between all dental indices and all inflammatory or haemostatic factors. Nevertheless, statistically significant relationships were found, even after adjusting the data for the presence of CHD, between CPSS and CRSS values and blood levels of leucocyte count, and between CPSS and von Willebrand factor antigen, PAI-1 and anti-Ox-LDL, and between TDI and the von Willebrand factor.

These findings could further support the possibility of an interactive component between the presence of infections inside the oral cavity and a perturbation of systemic haemostatic mechanisms that may affect coronary artery diseases. They also confirm the data of previous studies conducted on patients with periodontal disease, which showed that periodontitis is associated with high CRP and fibrinogen levels, high white blood cells counts and high levels of von Willebrand factor antigen (Mattila et al. 1995, Lowe et al. 1992, Loos et al. 2000, Slade et al. 2000, Wu et al. 2000).

In conclusion, the present study confirms the findings of other recent reports that suggest an association between poor oral status and CHD, and provide evidence that inflammatory and haemostatic factors could play an important role in this association.

However, our results should be interpreted cautiously because of the moderate level of some associations.

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