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Periodontal health improves systemic inflammatory and haemostatic status in subjects with coronary heart disease

L. Montebugnoli[1], D. Servidio[1], R. A. Miaton[1], C. Prati[1], P. Tricoci[2], C. Melloni[2] and G. Melandri[2]

Departments of [1]Oral Science and [2]Cardiology, University of Bologna, Italy

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Abstract

Objectives: A relationship between poor oral health and coronary heart disease (CHD) and systemic inflammatory and haemostatic factors has been recently documented in an Italian population. The present study was performed to assess whether intensive dental care may produce a periodontal improvement along with a change in systemic inflammatory and haemostatic factors.

Material and Methods: The study population consisted of 18 males aged 40–65 years with proven CHD and elevated values of systemic inflammatory and haemostatic factors. A detailed description of their oral status was given by using two different dental indices (clinical periodontal sum score and clinical and radiographic sum score). Blood samples were taken for measurement of the following systemic markers of inflammation [(C-reactive protein (CRP), leucocytes, fibrinogen)] and haemostatic factors [(von Willebrand factor, fibrin D-dimer and oxidized-low density lipoprotein (Ox-LDL)]. All parameters were determined in each subject at baseline, after 4 months as a control and 3 months after an intensive protocol of scaling and root planing. ANOVA for repeated measures was used for the statistical analysis.

Results: No statistical difference was found between values at baseline and at the 4-month-control. All oral indexes showed a significant decrease ($p < .01$) 3 months after periodontal treatment. All systemic inflammatory indexes decreased but only the decrease in CRP reached statistical significance ($p < .05$). A significant decrease ($p < .01$) was also found as regards Ox-LDL among haemostatic factors.

Conclusions: Preliminary results from the present study suggest an association between poor oral status and CHD, and provide evidence that the improvement of periodontal status may influence the systemic inflammatory and haemostatic situation.

Key words: atherosclerosis; cardiovascular disease; periodontal disease; periodontal treatment

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It is generally accepted that coronary heart disease (CHD) is the result of genetic and environmental risk factors such as diabetes, hypertension, smoking, abnormal serum lipids and age (Stamler 1979), but there is also evidence that high levels of systemic inflammatory and haemostatic factors might possibly accelerate vascular inflammation and promote thrombosis (Danesh et al. 1998, Holvoet et al. 1998b, Dardik et al. 2000, Hamsten et al. 2000, Loos et al. 2000, MacCallum et al. 2000, Ridker et al. 2000, 2001, Sinasalo et al. 2000, Inoue et al. 2001).

More recent data have shown that poor dental health and, in particular, periodontal disease increase 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, Emingil et al. 2000, Slade et al. 2000, Wu et al. 2000, Noack et al. 2001, Genko et al. 2002, Joshipura et al. 2004).

The significant association between poor oral status and CHD has been confirmed in a recent study, which also provided evidence of the important role

played by inflammatory and haemostatic factors in this association (Montebugnoli et al. 2004).

However, to fully confirm that elevated values of systemic predictors for CHD are related to periodontal infections, it is essential to see whether periodontal treatment is effective in reducing such factors.

The present study was performed to assess whether intensive dental care may produce a periodontal improvement in patients with proved CHD along with a change in a series of systemic inflammatory and haemostatic factors related to CHD.

Material and Methods

The study population consisted of 20 non-smoking males (10 had never smoked, the remaining quit at least 2 months before entering the study), aged 40–65 years (mean 49.6 ± 4.5) with proven CHD, randomly extrapolated from those who had participated in a previous epidemiological study (Montebugnoli et al. 2004).

All patients with CHD had suffered a recent history of acute myocardial infarction (less than 6 months prior to the study, but more than 2 months before entering 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.

All subjects were examined blindly by the same doctor, a qualified periodontist, who ignored the study period where the patient to be examined was situated at any time, and all subjects underwent clinical and radiological examinations by means of panoramic tomography.

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

- *Clinical periodontal sum score* (CPSS): the sum of the number of sites with probing pocket depths of 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);
- *Clinical and radiographic sum score* (CRSS): the number of radiographic vertical bone pockets and furcation lesions were added to the respective CPSS (Mattila et al. 2000).

Blood samples were taken from all subjects for measurements of a series of systemic markers of inflammation: C-reactive protein (CRP), leucocytes, fibrinogen; and a series of haemostatic factors: von Willebrand factor, fibrin D-dimer, and oxidized-low density lipoprotein (Ox-LDL).

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). Leukocyte count was measured with automated cell counters. Fibrinogen was determined in citrated samples by the mean of nephelometric assay. D-dimer (ng/ml) and Von Willebrand factor were measured by ELISA (Asserachrom, Stago, France). The quantification of Ox-LDL was performed using an enzyme-immunosorbent linked assay (ELISA) kit (Ox-LDL IgG ELISA test, Biodesign International, Saco, Me, USA)

After baseline data had been recorded, all subjects were reassessed after a 4-month period during which they received no periodontal care (non-treatment control period).

After this, all subjects underwent a non-surgical periodontal treatment consisting of two appointments of intensive oral hygiene instruction, including plaque disclosing, toothbrushing technique, inter-dental cleaning and supragingival scaling and polishing, and four appointments on a weekly basis during which subgingival debridement was carried out on a quadrant-by-quadrant basis using ultrasonic scalers and hand instruments.

All dental indexes and all systemic inflammatory and haemostatic factors were re-examined 3 months after completion of treatment (treatment period).

After fitting a general linear model, multiple regression ANOVA for repeated measures was used to evaluate differences between the three periods (baseline, non-treatment and treatment periods); The method used to discriminate between the means was Fisher's least significant difference procedure.

Results

Two subjects were lost to follow-up, reducing the numbers involved and completing the study with 18 subjects.

Table 1 illustrates the findings of dental indexes and systemic inflammatory and haemostatic factors at each study period (baseline, non-treatment and treatment periods). In all cases, the

Table 1. Mean values ± SD, range and 95%CI of dental indexes (CPSS and CRSS) and systemic inflammatory and haemostatic factors at each study period (baseline, non-treatment period as a control, and treatment period)

	Baseline			Non-treatment period			Treatment period		
	mean ± SD	range	95% CI	mean ± SD	range	95% CI	mean ± SD	range	95% CI
CPSS	75.9 ± 45.6	158	53.3–98.6	57.5 ± 39.0	141	38.1–76.9	26.3 ± 21.1**	79	15.7–36.8
CRSS	91.5 ± 49.3	175	66.9–116.0	70.8 ± 45.0	164	48.4–93.2	38.9 ± 24.8**	97	26.5–51.2
C-reactive protein	4.33 ± 2.0	5.9	3.3–5.3	4.32 ± 2.1	7.1	3.2–5.4	3.42 ± 2.3*	7.0	2.2–4.5
Fibrinogen	375.3 ± 65.4	252	342–407	377.5 ± 71.4	266	341–412	352.3 ± 61.6	203	322–383
Leucocytes	7885 ± 1164	4100	7306–8464	7928 ± 1308	4480	7278–8579	7581 ± 1310	4960	6929–8232
von Willebrand	102.8 ± 64.6	128.4	82.4–123.1	110.2 ± 23.0	85.9	98.7–121.6	112.1 ± 24.8	89.0	99.8–124.4
D-dimer	365.0 ± 250.9	960	240–489	362.5 ± 220.1	829	253–472	314.4 ± 136.2	538	247–382
Ox-LDL	542.8 ± 597	2136	245–839	514.5 ± 632	2323	200–829	444.5 ± 567**	1965	162–726

CRSS, clinical and radiographic sum score; CPSS, clinical periodontal sum score; Ox-LDL, oxidized low-density lipoprotein; CI, confidence interval. *$p<.05$; **$p<.01$: significance between values recorded after non surgical periodontal treatment and values at baseline and at non-treatment period.

standardized skewness and the standardized kurtosis values were within the range expected for data from a normal distribution (values of these statistics never outside the range of -2 to $+2$).

No significant difference in any of the dental indexes and the systemic inflammatory and haemostatic factors were detected at the control (non-treatment) period with respect to baseline.

Both oral indexes showed a significant decrease after the treatment period ($F = 14.1$, $p < 0.01$ for CPSS; $F = 15.3$, $p < 0.01$ for CRSS).

All systemic inflammatory indexes also decreased after the treatment period, but only the decrease in CRP reached statistical significance ($F = 3.22$, $p < 0.05$).

A significant decrease was also found as regards Ox-LDL among the haemostatic factors ($F = 5.18$, $p < .01$).

Discussion

To our knowledge this is the first study, which has investigated the effects of a periodontal therapy on a series of systemic inflammatory and haemostatic factors in patients with proven CHD.

Particular care was taken to choose a well-selected population of patients with CHD, consisting of only males to avoid any influence by gender, aged between 40 and 65 years to avoid any possible bias because of 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.

Further, to avoid any time-related interference on the results obtained at the end of the periodontal treatment, both dental indexes and inflammatory and haemostatic markers were reassessed after a 4-month period during which all patients received no periodontal care, the entire group of subjects acting as a non-treatment control group.

The efficacy of periodontal treatment was confirmed in the present study by the significant reduction in both dental indexes chosen as indicators of the periodontal status (Mattila et al. 2000).

The results obtained 3 months after the non-surgical periodontal treatment showed a reduction in all systemic inflammatory and haemostatic factors, except for von Willebrand factor, even though only the decrease in CRP among inflammatory factors and Ox-LDL among haemostatic factors reached statistical significance.

Our data obtained in patients with proven CHD are in agreement with other studies conducted in normal subjects with adult periodontitis, which have shown a positive effect of periodontal treatment on systemic inflammatory factors.

In 2002 Mattila et al. demonstrated a reduction in both fibrinogen and CRP 6 weeks after the completion of a non-surgical periodontal treatment, although only the CRP decrease reached statistical significance.

Similar results were obtained by Iwamoto et al. in 2003 who showed a significant reduction in PCR and TNF-α in periodontitis patients non-surgically treated with topical application of antibiotics and mechanical debridement of calculus once a week for 1 month.

A significant reduction in white blood cell count 3 months after the completion of a subgingival scaling was recently reported by Christian et al. in 2002.

Other studies which have failed to confirm such results should, however, be mentioned (Ebersole et al. 1997, Ide et al. 2003).

The negative role of elevated blood levels of CRP, leucocytes, fibrinogen and other inflammatory factors in contributing to atheroma formation and promoting thrombosis is well known (Danesh et al. 1998, Loos et al. 2000, Ridker et al. 2000, Ridker et al. 2001) and the positive effect of a non-surgical periodontal treatment in reducing such factors should be welcome in the prevention of cardiovascular disease. A recent statement for healthcare professionals from the Center for Disease Control and Prevention and the American Heart Association has recognized a dose–response relationship between the level of CRP and risk of incident coronary disease, the cut-point of high risk being a level more than 3 mg/l (Pearson et al. 2003). In the present study, the number of subjects with CRP level more than 3 mg/l shifted from 13 before periodontal treatment to six after periodontal treatment, and nine patient reached values less than 1.8 mg/l which is related to a very low risk of CHD.

As far as the relationship between CHD and systemic haemostatic factors is concerned, it has been widely demonstrated that rheological variables are consistently associated with cardiovascular diseases and approximately half the predictive value of plasma viscosity for cardiovascular events can be attributed once again to plasma fibrinogen or white blood cells (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, tissue plasminogen activator antigen, circulating tissue plasminogen activator, D-dimer, and Phrothrombinic fragment F1.2 have been associated with a risk of ischaemic heart disease (Merlini et al. 1994, Thompson et al. 1995, Lowe 1997, Ridker 1997, Smith et al. 1997, Lowe et al. 1998, Cushman et al. 1999).

An association between LDL oxidation and atherogenesis was first suggested by experiments showing that ox-LDL caused injury to endothelial cells (Penn & Chisolm 1994) and was further supported by studies showing higher plasmatic levels in patients with CHD and with cerebral artery disease (Holvoet et al. 1998a, Inoue et al. 2001, Lehtimaki et al. 1999) and a protective effect of antioxidants against progression of atherosclerosis (Steinberg 1995).

Further, a relationship between the extent of CHD in heart transplant patients and plasma levels of ox-LDL was recently established, suggesting that ox-LDL may be a marker of CHD (Holvoet et al. 1998a).

Contrary to what is discussed about CRP and other inflammatory markers, there are no data in the literature concerning the role of periodontal health in reducing systemic haemostatic factors and the present study is the only one revealing a significant reduction in ox-LDL plasmatic values as a consequence of periodontal treatment.

In conclusion, although our results should be considered preliminary because of the relatively small number of patients, non-surgical periodontal therapy seems to affect systemic markers of inflammation and haemostasis and could have the potential to influence cardiovascular diseases. It would be interesting in the light of this group of subjects to see whether or not a further progression of the arterial stenosis could occur in the next future.

Long-term longitudinal studies are needed to confirm the role of continuous periodontal care to keep inflammatory

and haemostatic factors low and to reduce the risk of CHD.

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Address:
L. Montebugnoli
Department of Oral Science
University of Bologna
Italy
E-mail: montebu@alma.umibo.it