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Physio-Pathological Relationship between Periodontal and Cardiovascular Diseases

SUMMARY

Several recent studies have demonstrated epidemiological association between periodontal and cardiovascular diseases. Chronic periodontal lesions may be the site from which lipopolisacharides and pro-inflammatory citokines may reach the bloodstream and foster atherosclerotic plaque rupture by different mechanisms. The purpose of this study was to compare the plasma levels of established risk markers for atherosclerosis, such as lipoproteins and C-reactive protein and fibrinogen in periodontitis cases to those in healthy, non-periodontitis cases.

Significant positive correlation was found between cholesterol levels and probing depths, as well as low-density lipoprotein levels and probing depths. We also found a significant negative correlation between high-density lipoprotein levels and probing depths, however not for fibrinogen and C-reactive protein.

Keywords: Periodontitis; Cardiovascular disease; Cholesterol; Lipoproteins; Inflammatory Markers

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Introduction

Several studies have recently demonstrated epidemiological associations between periodontal and cardiovascular diseases[1,2]. Possible overestimation may result from insufficient compensation for lifestyle differences and common risk factors (smoking and diabetes) in the statistical models[1]. Another possible mechanism accounting for the reported association between periodontal and cardiovascular diseases could be the release of lipopolisacharides (LPS) and pro-inflammatory citokines from the chronic periodontal lesions into the blood stream[3-6].

Almost all of the cells of the immune system are capable of producing pro-inflammatory citokines. In periodontitis, the major triggers of their synthesis are the LPS of the Gram-negative bacteria of the bacterial plaque[7,8]. The pro-inflammatory citokines may play a role in increasing the inflammation of the atherosclerotic plaques by:

Stimulating the invasion of macrophages in the plaque and the activation of matrix metal proteinases (MMP)[7-8];

Stimulating the synthesis of intercellular adhesion molecule-1 (ICAM-1) from the endothelial cells[7-8];

Stimulating the synthesis of C-reactive protein (CRP) from the hepatic cells, as well as of fibrinogen - CRP binds to the C1q fraction of complement at the surface of damaged endothelial cells[4,6,9-13].

IL-1β and TNF-α can also affect the lipid metabolism[7,14-17].

Although DNA from oral bacteria has been found in atherosclerotic plaques, a bacterial contribution to the plaque formation has yet to be demonstrated. [1,2,18,19]

Atherosclerosis, a relatively benign condition, can be transformed to a life threatening condition due to its rupture. Why some atherosclerotic plaques are more susceptible to rupture than the others? This is determined by the thickness of the fibrous cap[7,8,15,20-22]. Inflammation may enhance the risk of atherosclerotic plaque for rupture because it puts the collagen fibril of the fibrous cap under a double attack of low synthesis from the smooth muscle cells and high degradation from macrophages[7,8,15,20-22]. Plaque rupture is followed by coronary thrombosis, which clinically is expressed as the acute coronary syndrome.

The **aim** of this study was to compare the plasma levels of the established risk markers for atherosclerosis (such as lipoproteins, C-reactive protein and fibrinogen) in patients with periodontal disease and healthy patients (non-periodontitis cases).

Materials and Methods

The periodontitis group consisted of 26 subjects, non-periodontitis group of 25 subjects. The period of study lasted 5 months. Those with known cardiovascular diseases or diabetes were excluded from the study.

Clinical Examination for Periodontal Disease

All patients underwent a comprehensive periodontal examination[23,24], including radiographs and clinical examination. Probing depth and attachment loss were calculated using a calibrated periodontal probe (from 1.5mm-11.5mm; every 1 mm - TPS Vivacare), which enabled control of probing forces up to 200 N/cm^2 (when both markings of the handle and probe correspond to one another). Probing depths >3mm were considered pathologic. Data were collected into the periodontal chart designed according to Basle, modified by Gressly.

Plaque was evaluated using the Plaque Index (PI) of Silness and Löe, whereas gingival status was evaluated using the Gingival index (GI) of Silness and Löe.

Individual radiographs of the sites with the largest pocket depths, as well as panoramic radiographs, were used to establish a correct diagnosis.

Blood Lipid and Inflammatory Indices Analysis

Plasma was obtained after centrifugation at 1500 g for 10 min and stored at -70°C until analysis.

Cholesterol levels were measured using the enzymatic colorimetric method (510 nm). Normal values of this method are: 150 - 330 mg/dl. High-density lipoprotein (HDL) levels were measured by using the precipitation method. Normal values of this method are: 35 - 55 mg/dl. Low-density lipoprotein (LDL) levels were measured by using the indirect method (Friedewald formula). Normal values of this method are: <180 mg/dl. Fibrinogen levels were measured by using the classic turbidimetric method. Normal values of this method are: 200 - 400 mg/dl. CRP levels were measured by using the slide latex agglutination test. When CRP was present in the sample, presence of agglutination indicated a content of CRP equal or greater than 6 mg/l, without previous sample dilution. Normal value of method: <6 mg/l.

Statistical Methods

Parametric and non-parametric data were analysed using the Student-t test or Mann Whitney U-test, respectively. Associations between the periodontal and serological parameters were evaluated using the Spearman Rank order correlation coefficient.

Results

The characteristics of the study and control groups are given in table 1. Table 2 gives the average levels of cholesterol, HDL, LDL, fibrinogen and CRP in periodontitis and non-periodontitis group, respectively.

Table 1. The characteristics of the patient and comparison groups

	Periodontitis n=26	Non-Periodontitis n=25
Gender (F/M)	16/10	17/8
Mean age (years.)	58.3	33.5
No. of cigarettes per day	2.82	2.8
BMI(kg/m2)	24.7	23.6
Mean no. of teeth	15.5	28.5
Mean no. of pocket sites>3mm	14.75	-
Mean depth of pathological pockets (mm)	4.16	-
Mean attachment loss (mm)	4.59	-

Table 2. The average levels of cholesterol, HDL, LDL, fibrinogen and CRP in periodontitis and non-periodontitis group

	Periodontitis	Non-Periodontitis
Cholesterol (mg/dl)	234.7	195.3
LDL (mg/dl)	175	129
HDL (mg/dl)	37.7	39
Fibrinogen (mg/dl)	333	293
CRP (mg/l)	<6	<6

Total cholesterol levels were higher in patients of the study group than in the controls (p=0.04). We found a strong significant positive correlation between cholesterol and probing depths (R=0.79) and attachment loss (R=0.9). LDL levels were also higher in the study group than in the controls (p=0.01). We found a strong significant positive correlation between LDL and probing depths (R= 0.75) and attachment loss (R=0.9). HDL levels were lower in the study group than in the controls (p=0.04). Weak, but significant negative correlation between HDL and probing depths (R= 0.25) and attachment loss (R= 0.58) was apparent.

Although plasma fibrinogen levels were higher in patients, the differences were not significant. CRP levels were less than 6mg/l in both groups.

Discussion

In agreement with previous studies[1], this study has reported significant correlation between periodontal disease and low levels of HDL. A weak, but statistically significant relationship between HDL and probing depth has been observed. Albeit not very strong, we think that this correlation is important as it suggests that periodontal disease might influence blood lipid concentrations and

thereby the risk of cardiovascular disease. Mortality in individuals with low levels of HDL is higher than in individuals with higher levels of HDL, regardless of total cholesterol levels[15]. This might be explained with the fact that HDL participates in the reverse transport of cholesterol[17], it is a carrier of antioxidant enzymes[17] and has anti-inflammatory properties by decreasing the adhesivity of endothelial cells[1].

Our explanation for this association is that chronic inflammation in periodontium leads to the release of lipopolisacharides and pro-inflammatory citokines (IL-1β and TNF-α), which have the capacity to affect lipid metabolism.

In agreement with other studies[1,2,14], we found significant differences in total cholesterol and LDL levels between periodontitis and non-periodontitis cases, which may account for the correlation between periodontal and cardiovascular diseases, to which high cholesterol and LDL levels are known risk factors.

In our study we did not found significant differences in fibrinogen levels. Contradictory reports of literature, however, emphasise the need for further research in this context[6,18,19].

Unlike previous studies[1,2,6,9-11], we found no detectable difference in CRP levels between periodontitis and non-periodontitis cases: both groups had <6mg/l. Our explanation for this is that we have used a low sensitivity test, whereas the high sensitivity test can detect levels of plasma CRP as low as 1 mg/l. Therefor, we should recommend the use of high sensitivity CRP test in further studies.

Conclusions

In this study we have found serological differences of some parameters, known to be risk factors for atherosclerosis, between patients with periodontal disease and healthy patients. These findings can provide a physio-pathological explanation for the epidemiological associations between periodontal and cardiovascular diseases, as observed in many recent studies.

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