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Lipoprotein-associated phospholipase A_2 and plasma lipids in patients with destructive periodontal disease

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Abstract

Objectives: Periodontitis is believed to be an independent risk factor of cardiovascular disease (CVD) and to be associated with a moderate systemic inflammatory reaction and hyperlipidaemia. Lipoprotein-associated phospholipase A_2 (Lp-PLA_2) is an enzyme that has been shown to be a risk factor of CVD and that is involved in the degradation of the phospholipid mediator platelet-activating factor (PAF), a potent mediator of inflammation.

Material and Methods: In the present study, we measured concentrations of plasma lipids and plasma activity of Lp-PLA_2 in 32 patients (mean age 43 ± 11 years) with moderate-to-severe periodontitis before and 3 months after local treatment.

Results: Periodontal therapy resulted in a significant reduction of local inflammation and tissue destruction as reflected in reduced pocket depths and reduced bleeding indices. Pre- and post-treatment plasma lipid levels were (median and range, mmol/l): total cholesterol (C) 5.01 (3.94–7.15) and 4.91 (3.32–8.01); low-density lipoprotein-cholesterol (LDL-C) 3.14 (2.40–4.84) and 2.96 (1.39–5.04); HDL-C 1.27 (0.73–2.17) and 1.25 (0.74–2.55); triglycerides 1.37 (0.48–5.11) and 1.14 (0.38–792). Using the Wilcoxon's rank test, neither parameter showed a significant change. In contrast to the lacking response of plasma lipids, we observed a significant reduction in the activity of Lp-PLA_2. Local treatment lowered the enzyme activity by about 10% from 3.61 ± 0.99 to 3.29 ± 0.94 μmol/ml/h (mean ± SD; $p < 0.001$). The pre-treatment values of Lp-PLA_2 and LDL-C significantly correlated with clinical parameters of inflammation and periodontal destruction.

Conclusion: This study indicates that treatment of periodontitis significantly reduces the serum activity of Lp-PLA_2, which is believed to be an independent cardiovascular risk factor.

Key words: cardiovascular disease; periodontitis; phospholipid-asscoiated phospholipase A_2; plasma lipids; risk factors

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Periodontal disease is an infectious disease caused by a small group of predominantly anaerobic Gram-negative bacteria present on the tooth surface as microbial biofilms. Lipopolysaccharides and other microbial substances gain access to the gingival tissue and initiate and perpetuate an inflammatory reaction, which leads to the destruction of the periodontal ligament and alveolar bone. Numerous case control and cohort studies have indicated that patients with periodontitis have an increased risk of cardiovascular disease (CVD), i.e. myocardial infarction, stroke and peripheral arterial disease, when compared with subjects with a healthy periodontium (Hujoel 2002, Haynes & Stanford 2003). On the one hand, the association between periodontitis and CVD may be because of common risk factors such as smoking, diabetes mellitus, aging, male gender and social-economic factors. On the other hand, there is good evidence of periodontitis being an independent risk factor of CVD (Mattila et al. 1989, DeStefano et al. 1993, Joshipura et al. 1996, Arbes et al. 1999, Desvarieux et al. 2003, 2004, Hung et al. 2003, Persson et al. 2003). Disturbances in the

plasma lipoprotein metabolism, systemic inflammatory reactions as well as local inflammation of the artery wall are considered to contribute to the development of early atherosclerotic lesions in CVD (Ross 1999, Khovidhunkit et al. 2000, Blake & Ridker 2002, Zebrack & Anderson 2003; Schwahn et al. 2004). Recently, it has been shown that periodontitis is often associated with endotoxaemia and mild systemic inflammatory reactions, such as an increase in C-reactive protein and other acute phase reactants, while periodontal pathogens have been identified in early atherosclerotic lesions (Kweider et al. 1993, Haraszthy et al. 2000, Loos et al. 2000, Wu et al. 2000, Noack et al. 2001, Geerts et al. 2002). Periodontitis has also been shown to be associated with increased levels of pro-atherogenic plasma lipoproteins, i.e. cholesterol, in particular, low-density lipoprotein (LDL) cholesterol, and triglycerides (Lösche et al. 2000a, Noack et al. 2000, Katz et al. 2002, Cutler & Iacopino 2003, Craig et al. 2003).

Plasma lipoprotein-associated phospholipase A_2 (Lp-PLA_2), also known as platelet-activating factor (PAF) acetylhydrolase (PAF-AH), is a member of the serine-dependent class of A_2 phospholipases that hydrolyse phospholipids at sites where atherosclerotic plaques are forming. Lp-PLA_2 traffics with LDL in the circulation and can hydrolyse oxidized LDL (the most atherogenic form of LDL) into the products, lysophosphatidyl choline and oxidized fatty acid, which are pro-inflammatory mediators and may contribute to the development of atherosclerotic lesions. Indeed, Lp-PLA_2 has been proved to be an independent risk factor of CVD (Ostermann et al. 1988, Packard et al. 2000, Prescott et al. 2000, Blankenberg et al. 2003, Caslake & Packard 2003).

The aim of the present study was to evaluate whether a local therapy in patients with periodontitis may have any influence on Lp-PLA_2 activity and plasma lipids.

Patients and Methods

Patients

Thirty-two patients with periodontitis (15 females and 17 males, age 23–69 years. mean age 42.8 ± 10.6 years) participated in the study. After being informed on the purpose of the study, the patients signed informed consent forms. The study protocol was approved by the local ethical committee. Exclusion criteria were any dental treatment during the past 6 months and a medical history for cancer, rheumatoid arthritis, pregnancy, diabetes mellitus and CVD. Seventeen of the patients were non-smokers, 12 were current smokers and three were ex-smokers.

Dental variables

All dental variables were assessed at six different sites around each tooth before and 3 months after periodontal treatment.

- *Bleeding on probing*: If bleeding occurred immediately after probing for pocket depth it was reported as positive.
- *Probing pocket depth* was measured with a standard periodontal probe (Ainamo et al. 1982) within 1 mm limits.
- *Attachment loss* was measured with a standard periodontal probe within 1 mm limits.

Periodontal treatment

At the initial visit records of the oral hygiene and of the dental variables were made. Oral hygiene instruction was given at the end of this visit and included a demonstration of the Bass brushing technique, a demonstration of the use of inter-dental brushes and a demonstration on the use of dental floss. Patients were recalled at 2-weekly intervals. When optimum oral hygiene had been obtained, supra-gingival scaling and polishing, followed by quadrant root planing were commenced under local anaesthetic. Once hygiene phase therapy was completed, each patient was reviewed 6–8 weeks later. At this visit the dental variables detailed above were recorded again.

Lp-PLA_2 and plasma lipids

A first venous blood samples was taken at the initial visit and a second sample at 6–8 weeks after the periodontal therapy was completed. The samples were obtained after a 12 h fasting period from an antecubital vein. Cell-free serum samples were kept at -75°C until the analysis. Activity of Lp-PLA_2 was determined as the release of [^{3}H]-acetate from 1-O-alcyl-2-[^{3}H]-acetyl-sn-glycero-3-phosphocholine (New England Nuclear Corp, Boston, MA, USA) according to a method described by Stafforini et al. (1990), and the results are given as nmol/ml/h. Plasma lipids, i.e. total cholesterol, LDL and high-density lipoprotein (HDL) cholesterol, and triglycerides were determined using routine enzymatic methods.

Statistical analysis

All data are on a patient basis and are expressed either as mean ± standard deviation or, if the data were not normally distributed, as median and range. Differences between means obtained before and after periodontal treatment were proved for significance using the Student's *t*-test for paired samples or the non-parametric Wilcoxon's rank test. Pearson's correlation coefficient was used to describe correlations between dental and biochemical variables. *p*-values below 0.05 were considered to indicate significance.

Results

The effects of the periodontal treatment on the dental variables are indicated in Table 1. Bleeding on probing, pocket depth and attachment loss were reduced by about 60%, 40% and 15%, respectively. It is shown in Table 2 that the mean value for the activity of Lp-PLA_2 was significantly reduced after periodontal treatment by about 10%. Table 2 also shows median values (and ranges) for the concentrations of plasma lipids that were not normally distributed. Median values of LDL-cholesterol and triglycerides were slightly lower after periodontal treatment when compared with pre-treatment values (about 6% and 16%, respectively), but the changes were not significant.

Table 1. Dental variables (mean ± SD) before and after periodontal treatment

	Before treatment	After treatment	*p*
Bleeding on probing	0.65 ± 0.20	0.24 ± 0.18	< 0.00001
Pocket depth (mm)	3.88 ± 0.72	2.48 ± 0.42	< 0.00001
Attachment loss (mm)	4.75 ± 1.03	4.06 ± 1.13	< 0.00001

Table 2. Activity of Lp-PLA_2 and levels of plasma lipids before and after periodontal treatment

	Before treatment	After treatment	
Lp-PLA_2 (nmol/ml/h)	3.606 ± 986	3.295 ± 945	$p < 0.001$
Total cholesterol (mmol/l)	5.01 (3.94–7.15)	4.91 (3.32–8.01)	NS
LDL-cholesterol (mmol/l)	3.14 (2.40–4.84)	2.96 (1.39–5.04)	NS
HDL-cholesterol (mmol/l)	1.27 (0.73–2.17)	1.25 (0.74–2.55)	NS
Triglycerides (mmol/l)	1.36 (0.48–5.11)	1.14 (0.38–7.92)	NS

Data are given as mean ± SD or median (range).
Lp-PLA_2, Lipoprotein-associated phospholipase A_2; LDL, low-density lipoprotein; HDL, high-density lipoprotein; NS, not significant.

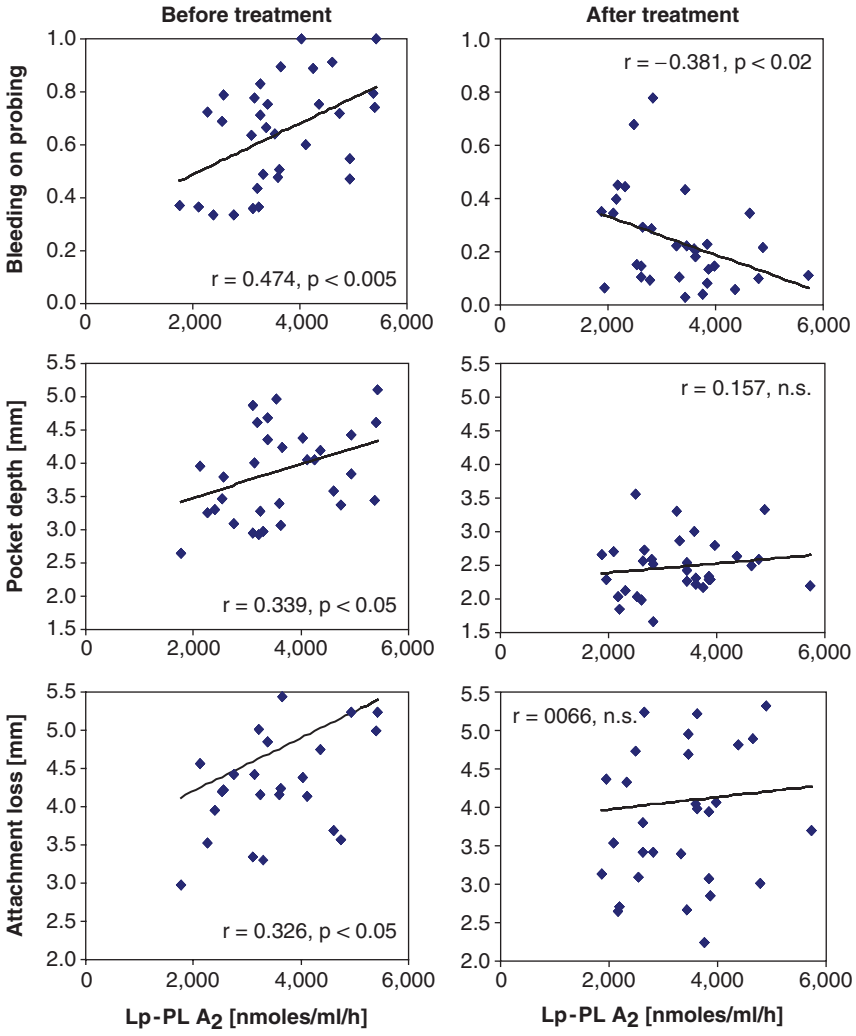

Fig. 1. Correlation between activity of lipoprotein-associated phospholipase A_2 (Lp-PLA_2) and dental variables before and after periodontal treatment. n.s., not significant.

Figure 1 indicates that the pre-treatment activities of the Lp-PLA_2 significantly correlated with the parameters of periodontal inflammation and breakdown, i.e. bleeding on probing, pocket depth and attachment loss. The correlation with pocket depth and attachment loss was completely lost after periodontal treatment, whereas the correlation between the activity of the Lp-PLA_2 and bleeding on probing became negative. In contrast to Lp-PLA_2 activity, the concentrations of plasma lipids, i.e. total, LDL and HDL cholesterols, as well as triglycerides, did not show any significant correlation with the clinical measures, neither prior nor post periodontal treatment.

Lp-PLA_2 activity was not significantly associated with age and the sex of the patients. Despite the correlation between Lp-PLA_2 and some of the clinical measures we could not observe significant correlation when individual changes were considered (data not shown).

Discussion

It has been recently shown that Lp-PLA_2 is an independent risk factor of CVD (Blankenberg et al. 2003, Caslake & Packard 2003). There is also good evidence that Lp-PLA_2 is an acute-phase reactant whose mRNA expression and biological activity is upregulated during the host response to infection and inflammation (Memon et al. 1999, Prescott et al. 2000, Wu et al. 2004). In patients with systemic inflammation a close correlation between Lp-PLA_2 activity and other acute-phase reactants such as C-reactive protein, tumour necrosis factor-α (TNF-α) and pro-inflammatory interleukins has been described (Endo et al. 1994, Dohrn 2000). However, such correlation was not observed when Lp-PLA_2 and C-reactive protein were measured to determine the risk for CVD. In a large community-based study it was shown that Lp-PLA_2 and C-reactive protein have about the same power to indicate the risk of coronary heart disease but there was no significant correlation between both. Thus, the authors concluded that Lp-PLA_2 and C-reactive protein may be complementary in identifying individuals at high CVD risk (Ballantyne et al. 2004).

Recently we have shown that moderate periodontitis is also associated with an enhanced activity of Lp-PLA_2. When compared with healthy controls the increase in patients amounted to about 10% (Lösche et al. 2000b). In the present paper, it is demonstrated that clinical measure of periodontitis such as bleeding on probing, pocket depth or attachment loss was positively correlated with the serum activity of Lp-PLA_2 and that local periodontal treatment resulted in a significant decrease in the enzyme activity by about 10%. In case-control studies in which Lp-PLA_2 was proved to be an independent risk factor for CVD, the differences in the plasma levels of the enzyme between cases and controls were found to be about 5% (Packard et al. 2000, Blankenberg et al. 2003). Thus, the 10% difference between the post- and pre-treatment activities of phospholipid-associated PLA_2 that are observed in

the present study is in the significant range for CVD risk reduction.

Despite the significant reduction in Lp-PLA_2 activity after periodontal treatment and the significant correlations between the pre-treatment values of the enzyme activity with the clinical measure, we could not observe any correlation between the individual changes in Lp-PLA_2 activity and the degree of clinical improvement. The strongest correlation between Lp-PLA_2 activity with clinical measure was in those with bleeding on probing before treatment. The correlation was not only lost after treatment but also shifted to a negative one. Bleeding on probing is a sign of an acute inflammation in the gingival tissue, and a study on Lp-PLA_2 activity in patients with systemic inflammation indicated that an increased activity is frequently associated with local infection and inflammation (Dohrn 2000). Thus, the shift from positive to negative correlation between Lp-PLA_2 activity and bleeding on probing in our patients could be a result of the positive effect of the treatment on the acute periodontal infection and inflammation.

So far one can only speculate whether the decrease in Lp-PLA_2 activity after periodontal treatment was because of a diminution of the systemic inflammatory response in consequence to the successful periodontal therapy. However, effects of periodontal treatment on well-established markers of systemic inflammation have been reported elsewhere. Studying the effect of periodontal treatment of 35 patients with adult periodontitis without a history of cardiovascular or other systemic disease, Mattila et al. (2002) observed a significant decrease in the plasma level of C-reactive protein. A decrease in C-reactive protein as well as in the pro-inflammatory cytokine TNF-α was reported by Iwamoto et al. (2003) after local antimicrobial treatment of 15 periodontitis patients diagnosed with CVD and/or diabetes mellitus.

It has been reported that periodontitis is often associated with enhanced concentrations of pro-atherogenic plasma lipids, i.e. total and LDL cholesterol as well as triglycerides (Lösche et al. 2000a, Wu et al. 2000, Katz et al. 2002). In the study presented here periodontal treatment did not significantly change the plasma levels of the different lipid fractions. This is in contrast to a recent report by Pussinen et al. (2003) who could show that periodontitis is associated with a reduction of the HDL cholesterol level and that periodontal therapy results in an increase in this anti-atherogenic lipid fraction.

In summary, our data presented here add to the evidence that periodontal therapy has an effect on those markers of systemic inflammation, which are believed to indicate an enhanced risk for and to contribute to the development of CVD.

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