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ORIGINAL ARTICLE

SAA and PLTP activity in plasma of periodontal patients before and after full-mouth tooth extraction

S Vuletic[1], BA Taylor[2], GH Tofler[3], A Chait[1], SM Marcovina[1], K Schenck[4], JJ Albers[1]

[1]*Department of Medicine, University of Washington, Seattle, Washington, United States;* [2]*Sydney Dental Hospital, New South Wales, Australia;* [3]*Royal North Shore Hospital, New South Wales, Australia;* [4]*Department of Oral Biology, University of Oslo, Oslo, Norway*

OBJECTIVE: To assess whether treatment of advanced periodontal disease affects plasma levels of serum amyloid A (SAA) and phospholipid transfer protein (PLTP) activity.
DESIGN: We measured the levels of SAA and PLTP activity in plasma of 66 patients with advanced periodontal disease before and after treatment by full-mouth tooth extraction (FME).
RESULTS: At baseline, median SAA levels in our study population were within the normal range (2.7 μg ml^{-1}) but SAA was elevated (>5 μg ml^{-1}) in 18% of periodontitis patients. Three months after FME, SAA levels were significantly reduced ($P = 0.04$). SAA did not correlate with any of the periodontal disease parameters. PLTP activity was elevated in patients with periodontitis, compared to the PLTP activity reference group (age-matched systemically healthy adults, $n = 29$; 18 μmol ml^{-1} h^{-1} *vs* 13 μmol ml^{-1} h^{-1}, respectively, $P = 0.002$). PLTP activity inversely correlated with average periodontal pocket depth (PPD) per tooth ($r_s = -0.372$; $P = 0.002$). Three months after FME, median PLTP activity did not change significantly.
CONCLUSIONS: Full-mouth tooth extraction significantly reduces SAA, a marker of inflammation, while it does not affect plasma PLTP activity. However, the inverse correlation between PLTP activity and average PPD suggests that increased PLTP activity may limit periodontal tissue damage.
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Keywords: periodontitis; SAA; PLTP

Introduction

Serum amyloid A (SAA) is a high density lipoprotein (HDL)-associated protein, synthesized by the liver. Increased SAA is a systemic marker of both acute and chronic inflammatory conditions and also affects HDL composition and function (Clifton *et al*, 1985; Cabana *et al*, 1996; Chait *et al*, 2005). SAA levels have been shown to positively correlate with the development of atherosclerosis (Chait *et al*, 2005). SAA is thus both an indicator and potentially also a mediator of inflammation in tissue (Chait *et al*, 2005).

Plasma phospholipid transfer protein (PLTP) is a multifactorial lipid transfer protein. PLTP transfers phospholipids, modulates α-tocopherol content of lipoprotein particles and cells, and facilitates lipid efflux and lipoprotein particle remodeling (Tollefson *et al*, 1988; Jauhiainen *et al*, 1993; Kostner *et al*, 1995; Rao *et al*, 1997; Desrumaux *et al*, 1999; Wolfbauer *et al*, 1999). PLTP belongs to a family of proteins involved in binding and neutralization of bacterial lipopolysaccharide (LPS), and its levels have been shown to increase in states associated with increased inflammatory responses, such as sepsis, diabetes, metabolic syndrome and cardiovascular disease (Barlage *et al*, 2001; Cheung *et al*, 2005; Tan *et al*, 2005). PLTP-deficient mice have decreased mean size of atherosclerotic plaques in comparison to mice expressing normal levels of PLTP and it has been suggested that these effects are resulting from the alterations in lipid metabolism, reduction in levels of plasma IL-6, and decreased IL-6 production induced by TNF-α (Jiang *et al*, 2001; Yan *et al*, 2004; Schlitt *et al*, 2005). Furthermore, transgenic mice over-expressing human PLTP exhibit an increase in atherosclerotic mean plaque size (van Haperen *et al*, 2003; Yang *et al*, 2003; Lie *et al*, 2004). A recent report shows that PLTP deficiency in macrophages leads to decreased atherosclerotic plaque size (Vikstedt *et al*, 2007). These studies suggested that PLTP may have both pro-atherogenic and pro-inflammatory properties *in vivo*. However, another recently published study suggests that the presence of active PLTP in macrophages *in vivo* is mainly atheroprotective (Valenta *et al*, 2006).

Periodontitis is a chronic inflammatory condition caused by oral pathogens, characterized by the loss of

Correspondence: S Vuletic, MD, University of Washington, Northwest Lipid Metabolism and Diabetes Research Laboratories, 401 Queen Anne Ave N, Seattle, WA 98109, USA. Tel.: +1-206-543-5534, Fax: +1-206-685-3279, E-mail: simona@u.washington.edu
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the bone and connective soft tissues supporting the teeth. The disease process is localized to a relatively small part of the body, but may affect an area of as much as 60 cm^2. It has been suggested that protracted exposure to the mildly to moderately increased levels of systemic inflammatory mediators can be the basis for an increased cardiovascular risk in patients with periodontitis (Kweider *et al*, 1993; Morrison *et al*, 1999; Wu *et al*, 2000; Rutger Persson *et al*, 2003; Taylor *et al*, 2006).

Plasma phospholipid transfer protein activity has been shown to be elevated in patients with periodontitis (Pussinen *et al*, 2004) while SAA levels are reported to be raised in persons with both periodontitis and cardiovascular disease (CVD), but not in persons with periodontitis only (Glurich *et al*, 2002). Presently, we measured the levels of SAA and PLTP activity in plasma of PERICAR (PERIodontal disease and CARdiovascular risk study) participants in an interventional model before and after full-mouth tooth extraction (FME) to establish the effect of removal of all of the remaining teeth on these parameters in patients with periodontitis. Differential white blood cell analyses were also conducted in a subset of the patients in order to evaluate the contribution of numbers of various types of leukocytes to the measured inflammatory markers.

Methods

Study group

The PERICAR study recruited adult participants over the age of 40 years with advanced periodontitis (Taylor *et al*, 2006). Patients with general health complaints or symptoms that were consistent with active systemic inflammation or infection were excluded from the study. Participants' characteristics are presented in Table 1.

Study design

The model chosen was a longitudinal cohort study with observations made before and after treatment of advanced periodontitis in cases where FME was indicated. The design could not be randomized because allocation of patients to experimental and control groups would have delayed treatment of advanced periodontitis for several months for some patients. This was considered to be unethical and unlikely to be accepted by the patients.

The study was approved by the Ethics Review Committee of the Sydney Dental Hospital, and written informed consent was obtained from all study participants.

Table 1 Population characteristics ($n = 66$)

Age (Mean ± s.d.)	57 ± 11 years
Gender (*n* female /*n* male)	23 /43
Smoking ($n = 29$)	43.9%
Cigarettes per day (mean ± s.d.)	33.2 ± 11.6
Years smoking (mean ± s.d.)	20.8 ± 11.8
Number of teeth (mean ± s.d.)	8 ± 4
Family history of coronary heart disease ($n = 16$)	24.2%
Reported history of diabetes ($n = 8$)	12.1%
Reported history of hypertension ($n = 18$)	27.3%
Reported history of hyperlipidemia ($n = 25$)	37.9%

At the initial visit, 27 of the 67 patients presented with loose teeth, 17 presented with pain, and 23 presented with various other symptoms. Fifty two participants had one or more extractions on the day of the initial visit, and one patient received oral antibiotics. The medical history of the participants was recorded and a medical and dental examination was carried out prior to FME. The history focused on cardiovascular risk factors, including diabetes mellitus, hypertension, hyperlipidemia, smoking, and any history of cardiac, cerebral, or peripheral vascular disease. The medical examination included the patients' height, weight, temperature, blood pressure, heart rate, and ECG recording. The dental examination included charting of probing pocket depth (PPD) and recession at six sites around each tooth. Loss of attachment (LOA) was considered to be the sum of PPD and recession, if both were present, or PPD more than 2 mm in the absence of recession. The average of PPD and LOA was calculated for each participant. The average of the highest PPD and LOA measurement from each of the teeth in a participant's dentition was also calculated to give the average highest PPD /tooth and average highest LOA/tooth.

Most FME ($n = 42$) were completed within 1–4 weeks of initial presentation. Another 15 participants had all their teeth extracted between 4 and 8 weeks after presentation, and a further 10 patients took more than 8 weeks to complete FME. All participants completed FME within 14 weeks. No provisional dentures were provided to participants. Approximately, 3 months after FME, the medical history was repeated and a medical examination was performed. An oral examination was conducted at the same time, mainly to confirm the absence of teeth, tooth fragments, or oral ulceration. No such complications were detected. One blood sample was lost in transfer, leaving 66 samples in total for the analyses.

Blood sampling and analyses

Peripheral blood samples were obtained between 9 AM and 11:30 AM on the day of the initial presentation, prior to any oral manipulation, and 3 months after completion of FME. Blood was drawn using a standard venepuncture technique and collected in 4.5 cc EDTA tubes. Samples were centrifuged and plasma was collected and frozen at −70°C until analysis.

Plasma phospholipid transfer protein-mediated phospholipid transfer activity was assessed as previously reported (Cheung *et al*, 1996). Briefly, plasma samples ($V = 1\ \mu l$) were assayed for the ability to transfer C^{14}-labeled phospholipid from donor liposome particles to the acceptor particles (plasma HDL without measurable PLTP activity) at 37°C. Upon incubation, the reaction was stopped by immersion of tubes in ice and addition of TSE buffer at 4°C (10 mM Tris, 150 mM NaCl, 1 mM EDTA, pH 7.4). Donor particles were precipitated by dextran sulfate magnesium (Warnick *et al*, 1982) and centrifugation at 4°C, $1800 \times \boldsymbol{g}$ for 30 min in a swing-bucket centrifuge (Sorvall RT6000,

DuPont, Wilmington, DE, USA). Radioactivity of the supernatant was measured in a scintillation counter (Beckman Coulter LS6500, Beckman Coulter, Fullerton, CA, USA), corrected for the background transfer, and phospholipid transfer activity was expressed as micromole of radioactive phospholipid transfer per milliliter of sample per hour. The analyses were performed twice in triplicate. Plasma PLTP activity values in PERICAR study participants were compared with those measured in the reference group of healthy adults from the Northwest Lipid Metabolism and Diabetes Research Laboratories database (n = 29, 14 females and 15 males, age range 35–66 years old).

Plasma SAA concentration was assayed using a commercial enzyme-linked immunosorbent assay kit (Anogen, Mississauga, ON, Canada).

Differential white blood cell analyses were conducted in a subset of 39 patients.

Statistical analyses

Statistical analyses were performed with Statistica for Windows (StatSoft Inc., 2000, Tulsa, OK, USA), using Mann–Whitney U-test and Spearman Rank Order Coefficient Correlation tests. P-values <0.05 were considered statistically significant, except in multiple comparison analyses where P-values ≤ 0.01 were considered statistically significant.

Results

Median periodontal variables at baseline and median concentrations of SAA and PLTP activity in plasma of the 66 PERICAR study participants before and after treatment are presented in Table 2.

Serum amyloid A concentration and PLTP activity in plasma of the patients with periodontitis varied widely between the subjects. Median baseline PLTP activity in the patients (17.6 μmol ml^{-1} h^{-1}) was significantly higher as compared with median activity in a systemically healthy reference group (13.0 μmol ml^{-1} h^{-1}; P = 0.002). In contrast, median baseline SAA in the patients (2.56 μg ml^{-1}) was comparable with the previously published values in a systemically healthy reference group (2.2 μg ml^{-1}) (Tannock *et al*, 2005), while 12 patients (18%) had elevated baseline SAA concentration (>5 μg ml^{-1}).

At baseline, SAA and plasma PLTP activity in the present periodontitis patients did not differ significantly based on gender, current smoking status, diabetes, hypertension or hyperlipidemia (data not shown). In our study group, baseline C-reactive protein (CRP) (data published by Taylor *et al*, 2006; used with permission) and SAA concentrations significantly correlated with each other (r_s = 0.389, P = 0.001; Figure 1). At baseline, PLTP activity did not correlate with either CRP or SAA concentrations (r_s = 0.171 and r_s = 0.168, respectively, ns).

Baseline PLTP activity was significantly negatively correlated with the average and average high PPD

Table 2 Periodontal variables, SAA concentration and plasma PLTP activity in PERICAR study participants (n = 66)

	Median [25–75%]	
Variable	*Baseline*	*Post-Treatment*
Average PPD (mm)	4.3 [3.8–4.9]	N/A
High PPD[a] (mm)	5.8 [5.0–6.6]	N/A
Average LOA[b] (mm)	7.5 [6.5–8.9]	N/A
High LOA[c] (mm)	9.5 [8.2–10.8]	N/A
SAA (μg ml^{-1})	2.7 [1.0–4.3]	2.1* [0.5–3.7]
PLTP activity (μmol ml^{-1} h^{-1})	17.6 [16.2–18.7]	17.7 [16.3–19.4]

PPD: probing pocket depth.
LOA: loss of attachment.
[a]The mean PPD for the dentition calculated using the deepest PPD at each tooth.
[b]The mean LOA for the dentition using the LOA at six sites for each tooth.
[c]The mean LOA for the dentition derived using the single site with the most LOA for each tooth.
*P = 0.04.

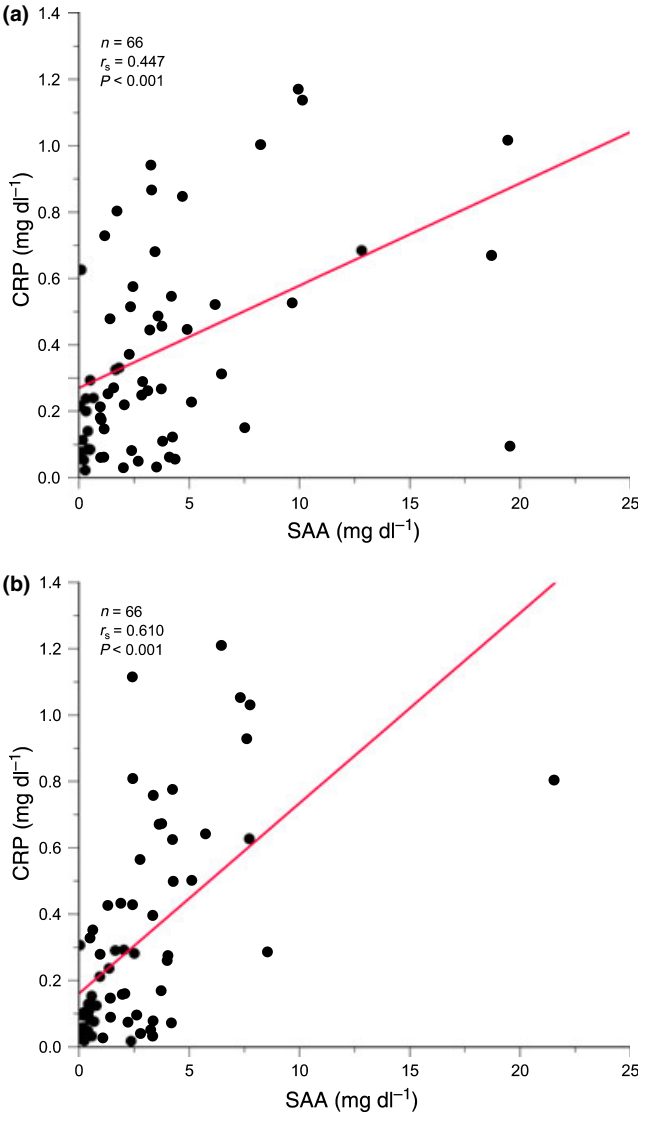

Figure 1 Correlation between serum amyloid A (SAA) and C-reactive protein (CRP) at baseline (**a**) and post-treatment (**b**)

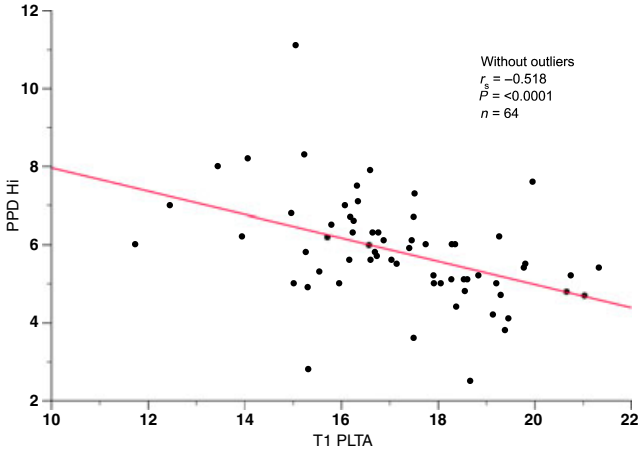

Figure 2 Correlation between PLTP activity (PLTA) and average high periodontal pocket depth (PPD Hi). Two participants with PLTP activity values above 27 μmol ml^{-1} h^{-1} were excluded (n = 64)

(r_s = –0.372; P = 002 and r_s = –0.518; P < 0.001, respectively; Figure 2). SAA levels did not statistically significantly correlate with any of the pre-treatment periodontal disease parameters.

Three months after FME, SAA levels moderately, but statistically significantly, decreased (P = 0.04), while plasma PLTP activity did not change significantly as compared to baseline (Table 2). In those patients who had elevated baseline SAA levels (n = 12), there was a significant reduction in SAA three months after the intervention (11.15 μg ml^{-1} *vs* 4.77 μg ml^{-1}, P = 0.004).

Post-treatment CRP and SAA values highly correlated with each other (r_s = 0.531, P < 0.001, Figure 1), but post-treatment PLTP activity did not correlate with either of these two inflammatory markers (r_s = 0.235 for CRP and r_s = 0.034 for SAA, ns).

None of the post-treatment variables were affected by gender, current smoking status, reported family history of coronary heart disease, reported hypertension or hyperlipidemia (data not shown), but post-treatment PLTP activity was significantly higher in study participants with reported history of diabetes compared with those without (n = 8; 21.0 ± 5.2 *vs* 17.5 ± 2.3 μmol ml^{-1} h^{-1}, respectively; P = 0.023).

Post-treatment PLTP activity significantly correlated with the baseline WBC and neutrophil count (r_s = 0.412, P = 0.01; and r_s = 0.434, P = 0.006, respectively). In study participants who had elevated baseline WBC and neutrophil counts (data published by Taylor *et al*, 2006; used with permission), post-treatment PLTP activity was significantly higher (Table 3). In contrast, PLTP activity in patients whose WBC and neutrophil counts were normal at baseline did not change after the treatment (Table 3).

Post-treatment SAA levels were not affected by the baseline WBC or neutrophil counts (data not shown).

Table 3 The effects of treatment on PLTP activity (PLTA) based on baseline leukocyte (WBC) and neutrophil counts

PLTA	*Baseline PLTA* (μmol ml^{-1} h^{-1})	*Post-Treatment* (μmol ml^{-1} h^{-1})
Baseline WBC		
$< 7.3 \times 10^{-9}$ l^{-1} (n = 20)	16.6 ± 3.1	16.5 ± 1.8
$> 7.3 \times 10^{-9}$ l^{-1} (n = 19)	17.2 ± 1.8	18.5 ± 1.8*
Baseline neutrophils		
$< 5.0 \times 10^{-9}$ l^{-1} (n = 21)	16.6 ± 3.0	16.4 ± 1.7
$> 5.0 \times 10^{-9}$ l^{-1} (n = 18)	17.2 ± 1.8	18.6 ± 1.7*

*$P \leq 0.002$.

Discussion

Periodontitis is a common chronic localized inflammation caused by oral pathogens. Multiple studies indicate that people with periodontal disease are at higher risk of atherosclerosis and cardiovascular disease (Kweider *et al*, 1993; Morrison *et al*, 1999; Wu *et al*, 2000; Rutger Persson *et al*, 2003; Taylor *et al*, 2006). It has been suggested that the positive correlation between periodontitis and cardiovascular disease is caused by chronic systemic elevation of inflammatory mediators caused by periodontal infection (Slade *et al*, 2000; Noack *et al*, 2001; Schillinger *et al*, 2005).

Cross-sectional studies can indicate statistically significant associations between variables, but those can be caused by confounding background factors. Interventional models, however, can reveal cause–effect relationships. Presently, we detected a statistically significant decrease in SAA levels after treatment of our patients. SAA levels have been shown to positively correlate with the development of atherosclerosis (Clifton *et al*, 1985), suggesting that long-term raised SAA levels induced by periodontitis may directly or indirectly contribute to the development of CVD. SAA, which resides on HDL particles, may be involved in the retention of lipoproteins in the vessel wall, thus contributing to lipoprotein oxidation and development of atherosclerotic lesions (O'Brien *et al*, 2005). Therefore, elevated levels of SAA found in a subset of our patients may indicate elevated risk for CVD, compared to periodontitis patients who had normal SAA levels.

A previous study failed to show decreased SAA levels after treatment of patients with periodontitis following a conventional periodontal treatment (Glurich *et al*, 2002). It is possible that after a conventional treatment, patients are left with some inflammation because all teeth are not extracted and this might explain the different outcomes in the two studies. We previously measured CRP levels in the present group of patients and found that CRP levels also statistically significantly decreased after FME (Taylor *et al*, 2006), in accord with the presently observed SAA decrease. Taken together, our findings show that SAA levels in patients with periodontitis are at least partly determined by the presence or absence of periodontitis. Furthermore, a significant reduction in SAA levels by FME suggests that removal of the source of inflammation in periodontitis may reduce the risk of CVD in those periodontitis patients who had elevated both CRP and SAA.

Plasma phospholipid transfer protein belongs to a protein family that includes lipopolysaccharide-binding protein (LBP) and bactericidal permeability-increasing

protein (BPI) (Bingle and Craven, 2004). Although LBP and BPI are better known for LPS neutralization function, it is likely that one of PLTP's physiological roles is reduction of bacteria-induced damage in the tissues (Bingle and Craven, 2004). Our study confirms previously published findings of elevated PLTP activity in periodontitis (Pussinen *et al*, 2004), as PERICAR study participants, as a group, had higher values of plasma PLTP activity compared to the average PLTP activity values in healthy population. However, we did not observe any significant decrease in plasma PLTP activity levels 3 months after FME, while SAA and CRP levels significantly decreased. Moreover, PLTP activity in our patients did not statistically significantly correlate with either CRP or SAA concentrations before or after treatment. These observations may mean that the regulation of PLTP activity level in plasma is more complex, requiring larger systemic changes for its reduction.

Data from the present study indicate that plasma PLTP activity inversely correlates with the extent of periodontal tissue damage in periodontitis. An increase in tissue damage is a sign of incomplete or abnormal resolution of the inflammatory process (Levy *et al*, 2001; Kadl and Leitinger, 2005; Serhan and Savill, 2005). In the initial stages of inflammation, neutrophils produce and release reactive oxygen species (ROS) in a process that is essential for oxidative damage of pathogens and subsequent phagocytosis (reviewed by Hampton *et al*, 1998). Resolution of inflammation is tightly associated with the presence of neutrophils in the tissue at the beginning of the inflammatory process, suggesting that normal formation and release of ROS and subsequent phagocytosis regulate the final stages of inflammation and potentially limit tissue damage. Several recent reports suggest that resolution of inflammation is critical for limiting tissue damage in periodontitis, and that defects in intracellular lipid signaling in neutrophils are associated with aggressive tissue damage in periodontitis (van Dyke and Serhan, 2002; Gronert *et al*, 2004). In our study, the baseline neutrophil count was significantly positively correlated with PLTP activity in plasma after treatment, suggesting that neutrophils during the inflammatory process may determine PLTP activity during the resolution phase of inflammation. These findings, combined with the observed inverse correlation between PLTP activity and the extent of the tissue damage, suggest a functional link between PLTP and processes involved in resolution of the inflammatory process, implying that pre-treatment conditions affect post-treatment resolution of the inflammation in periodontitis. However, because we did not measure neutrophil ROS formation, as a direct measure of neutrophil activity, this potential link between PLTP activity and neutrophil function needs to be verified by subsequent studies. Alternatively, lower plasma PLTP activity may reflect a larger extent of tissue damage due to inflammation, suggesting a potential effect of pro-inflammatory cytokines on PLTP activity.

In conclusion, our study has shown that therapeutic intervention in periodontitis that removes the source of inflammation significantly reduces SAA, and consequently may reduce the risk of CVD. It is possible that periodontitis patients who have increased both CRP and SAA represent a specific subgroup in terms of their risk for atherosclerosis and CVD compared to periodontitis patients whose plasma SAA levels are normal. Furthermore, the present results suggest that individuals who have higher plasma PLTP activity values may be better protected against tissue damage than those whose plasma PLTP activity is low despite the presence of inflammation. The results support the contention that an increase in PLTP phospholipid transfer activity, often found in systemic diseases and states associated with inflammation, may be relevant for limiting tissue injury during inflammatory processes by its involvement in the resolution of inflammation.

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