

Dursun Dursunoğlu · Harun Evrengül · Bülent Polat  
Halil Tanrıverdi · Veli Çobankara · Asuman Kaftan  
Mustafa Kılıç

## Lp(a) lipoprotein and lipids in patients with rheumatoid arthritis: serum levels and relationship to inflammation

Received: 26 March 2003 / Accepted: 12 December 2003 / Published online: 31 July 2004  
© Springer-Verlag 2004

**Abstract Objectives:** Changes in lipid profiles, Lp(a) lipoprotein, and acute phase reactants are associated with early atherosclerosis in rheumatoid arthritis (RA). The associations of Lp(a) levels with atherosclerotic disorders, diabetes, RA, and renal diseases suggest that Lp(a) might be involved in autoimmune reactions. **Methods:** Eighty-seven women with RA diagnosed according to American Rheumatism Association criteria (mean age  $45.4 \pm 9.4$  years) were recruited and 50 healthy women (mean age  $44 \pm 10.7$  years) included as a control group. Serum Lp(a), total cholesterol (TC), triglyceride (TG), LDL cholesterol (LDL-C), HDL cholesterol (HDL-C), and C-reactive protein levels were analyzed. **Results:** In the RA and C groups, serum Lp(a) levels were  $39.2 \pm 20.6$  mg/dl and  $14.8 \pm 9.7$  mg/dl, respectively ( $P < 0.001$ ). The TC levels were  $188.4 \pm 41.8$  mg/dl and  $185.3 \pm 19.3$  mg/dl ( $P > 0.05$ ), TG levels were  $124.5 \pm 50.1$  mg/dl and  $94.6 \pm 24.9$  mg/dl ( $P < 0.01$ ), HDL-C levels were  $40.0 \pm 7.4$  mg/dl and  $52.8 \pm 4.8$  mg/dl ( $P < 0.01$ ), and LDL-C levels were  $123.4 \pm 24.6$  mg/dl and  $113.3 \pm 21.1$  mg/dl ( $P > 0.05$ ). While serum CRP levels showed a positive correlation with Lp(a), they correlated negatively with HDL-C levels ( $r = 0.83$  and  $P < 0.0001$ ,  $r = -0.49$  and  $P < 0.0001$ , respectively). It was meaningful that Lp(a) correlated negatively with serum HDL-C level ( $r = -0.36$ ,  $P < 0.001$ ). **Conclusions:** It is suggested that higher serum Lp(a), lower HDL-C, higher TG level, and a high ratio of TC/

HDL-C might show high risk of atherosclerosis. Inflammation in RA may cause changes in HDL-C and Lp(a) metabolisms.

**Keywords** Inflammation · Lipids · Lp(a) lipoprotein · Rheumatoid arthritis

### Introduction

Although it is not yet known exactly, changes in lipid profiles, Lp(a) lipoprotein, and acute phase reactants are associated with early atherosclerosis in rheumatoid arthritis (RA). Coronary atherosclerosis and acute myocardial infarction are the most common causes of death in patients with RA [1, 2, 3, 4, 5]. Several complex mechanisms are responsible for dyslipidemia in these patients. Chronic inflammation process, immobilization, gastrointestinal and liver diseases, systemic complications, several inflammatory mediators, and drugs may affect the lipid metabolism [6, 7]. In recent years, associations of Lp(a) with insulin release, RA, and renal diseases have suggested that Lp(a) might be involved in immunologic mechanisms [8]. The aim of this study was to evaluate the relations of serum lipids and Lp(a) levels with inflammation in RA patients.

### Material and methods

#### Patients

Eighty-seven female patients with RA diagnosed according to American Rheumatism Association criteria [9] (mean age  $45 \pm 9.4$  years) and 50 healthy women (mean age  $44 \pm 10.7$  years) as a control group were studied in the Pamukkale University Medical Faculty departments of internal medicine and cardiology between January 2001 and December 2002. None of the patients with RA had been taking corticosteroids or

D. Dursunoğlu · H. Evrengül · B. Polat · H. Tanrıverdi  
A. Kaftan · M. Kılıç  
Department of Cardiology,  
Pamukkale University Medical Faculty, Denizli, Turkey

V. Çobankara  
Department of Internal Medicine,  
Pamukkale University Medical Faculty, Denizli, Turkey

D. Dursunoğlu (✉)  
Yunus Emre Mah. 6402 sk. No: 12, Kınıklı, Denizli, Turkey  
E-mail: ddursunoglu@tnn.net  
Tel.: +90-258-213 67 62

**Table 1** Characteristics of the patients and healthy subjects

	Patients ( <i>n</i> = 87)	Healthy subjects ( <i>n</i> = 50)	<i>P</i>
Mean age (years)	45 ± 9.4	44 ± 10.7	NS*
Lp(a) level (mg/dl)	39.2 ± 20.6	14.8 ± 9.7	< 0.001
TC level (mg/dl)	188.4 ± 41.8	185.3 ± 19.3	NS
TG level (mg/dl)	124.5 ± 50.1	94.6 ± 24.9	< 0.001
HDL-C level (mg/dl)	40.0 ± 7.4	52.8 ± 4.8	< 0.001
LDL-C level (mg/dl)	123.4 ± 24.6	113.3 ± 21.1	NS
TC/HDL-C ratio	4.7 ± 1.5	3.5 ± 0.7	< 0.01
LDL-C/HDL-C ratio	3.1 ± 1.2	2.1 ± 0.7	< 0.05
CRP (mg/L)	7.1 ± 4.2	0.03 ± 0.01	< 0.001
ESR (mm/h)	52.2 ± 18.1	12.3 ± 8.2	< 0.001

\**P* > 0.05

disease-modifying antirheumatic drugs, and all of them were in the active phase of illness at the time of hospital admission. Some of the patients were diagnosed with RA for the first time at admission, and most had given up the drugs by themselves for unknown reasons and had taken none for at least 2 months. None of the RA patients had a history of angina pectoris, myocardial infarction, or interventional management for coronary artery disease. Also, their resting electrocardiograms were normal. As a control group, healthy subjects without hypertension, diabetes mellitus, or signs or symptoms of any heart disease or any known chronic disease were chosen. Their physical examinations and resting electrocardiograms were also normal.

#### Assays

Serum Lp(a), total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and C-reactive protein (CRP) were measured after an overnight fast (at least 12 h), and TC/HDL-C and LDL-C/HDL-C ratios were calculated.

Serum TC, HDL-C, TG, and CRP levels of patients and controls were analyzed with commercial kits (Abbott, USA) using an autoanalyzer (Aeroset, USA). Also, serum very low-density lipoprotein cholesterol (VLDL-C) was measured as TG/5. LDL-C was calculated with the Friedewald formula ( $LDL-C = TC - HDL-C - VLDL-C$ ), if the serum TG level was under 400 mg/dl. Serum Lp(a) was analyzed by the nephelometric method using a Beckman kit, and normal range was 0–30 mg/dl.

#### Statistics

Statistics were performed with the version 10.0 Statistical Package for Social Sciences program for Windows. Normality of variables was tested by the Kolmogorov-Smirnov test. Distribution of TC, TG, HDL-C, LDL-C, Lp(a), and CRP levels were not normal. Thus, a log transformation before statistical analyses of means was performed, and then Student's *t*-, Pearson's chi-squared, linear-by-linear association, and Pearson's correlation tests were performed.

#### Results

The characteristics of the patients with RA are compared with those of healthy subjects in Table 1. Mean age was similar in the RA and control groups (45 ± 9.4 years and 44 ± 10.7 years, respectively) (*P* > 0.05). In patients, serum Lp(a) levels were higher than in healthy subjects (39.2 ± 20.6 mg/dl and 14.8 ± 9.7 mg/dl, respectively) (*P* = 0.001). Serum TC and LDL-C levels were not significantly different between the two groups—188.4 ± 41.8 mg/dl and 185.3 ± 19.3 mg/dl (*P* > 0.05), and 123.4 ± 24.6 mg/dl and 113.3 ± 21.1 mg/dl (*P* > 0.05) in patients and healthy subjects, respectively.

Serum TG levels were significantly higher in patients (124.5 ± 50.1 mg/dl) than healthy subjects (94.6 ± 24.9 mg/dl, *P* < 0.001), while serum HDL-C levels were significantly lower (40.0 ± 7.4 mg/dl) than in controls (52.8 ± 4.8 mg/dl, *P* < 0.001). In both patients and healthy subjects, the TC/HDL-C ratios were 4.7 ± 1.5 and 3.5 ± 0.7 (*P* < 0.01) and LDL-C/HDL-C ratios were 3.1 ± 1.2 and 2.1 ± 0.7 (*P* < 0.05), respectively.

Serum CRP levels were 7.1 ± 4.2 mg/dl and 0.03 ± 0.01 mg/dl in patients and healthy subjects and differed significantly (*P* < 0.001). Erythrocyte sedimentation rates were 52.2 ± 18.1 mm/h and 12.3 ± 8.2 mm/h in patients and controls, and also significantly different (*P* < 0.001).

Subgroups of serum Lp(a) and lipid ratios in patients and healthy subjects are shown in Table 2. Fifty-five patients (63.2%) and nine healthy subjects (18%) had Lp(a) levels of > 30 mg/dl (*P* < 0.001). Numbers of patients and healthy subjects were significantly different in subgroups of the TC/HDL-C ratio (*P* < 0.001). In 11 patients with RA (12.6%) and 24 healthy subjects (48%), the TC/HDL-C ratios were under 3.5 (*P* < 0.001) and in 52 patients (59.8%) and eight healthy subjects (16%) greater than 4.5 (*P* < 0.001). Twenty-four patients (27.6%) and 18 healthy subjects (36%) showed these ratios between 3.5 and 4.5 (*P* < 0.001). However, the numbers of patients and healthy subjects were similar according to the subgroups of the LDL-C/HDL-C ratio (*P* > 0.05).

**Table 2** Groups of serum Lp(a) levels and lipid ratios in patients and healthy subjects. *TC* total cholesterol, *HDL-C* high-density lipoprotein cholesterol, *LDL-C* low-density lipoprotein cholesterol, *Df* degree of statistical freedom, *NS* not significant

	Patients ( <i>n</i> =87)		Healthy subjects ( <i>n</i> =50)		<i>P</i>	$\chi^2$	<i>Df</i>
	<i>N</i>	Percent of total	<i>N</i>	Percent of total			
Lp(a) (mg/dl) subgroups							
≤ 30	32	36.8	41	82.0	<0.001	26.082	1
> 30	55	63.2	9	18.0			
TC/HDL-C ratio subgroups							
< 3.5	11	12.6	24	48.0	<0.001	29.895	1 <sup>a</sup>
3.5–4.5	24	27.6	18	36.0			
> 4.5	52	59.8	8	16.0			
LDL-C/HDL-C ratio subgroups							
< 3	46	52.9	30	60.0	NS*	0.293	1 <sup>a</sup>
3–6	37	42.5	17	34.0			
> 6	4	4.6	3	6.0			

<sup>a</sup> Linear-by-linear association test

\**P* > 0.05

## Correlations

Correlations between serum CRP and Lp(a) and HDL-C levels are shown in Fig. 1 and Fig. 2. Serum CRP levels correlated positively with Lp(a) ( $r=0.83$ ,  $P=0.0001$ ) and negatively with HDL-C ( $r=-0.49$ ,  $P=0.0001$ ). Serum CRP levels did not correlate with serum TC or TG levels ( $r=-0.05$ ,  $P>0.05$  and  $r=-0.17$ ,  $P>0.05$ , respectively). The correlation between serum Lp(a) and HDL-C levels is shown in Fig. 3. Serum Lp(a) correlated negatively with HDL-C ( $r=-0.36$ ,  $P=0.001$ ).

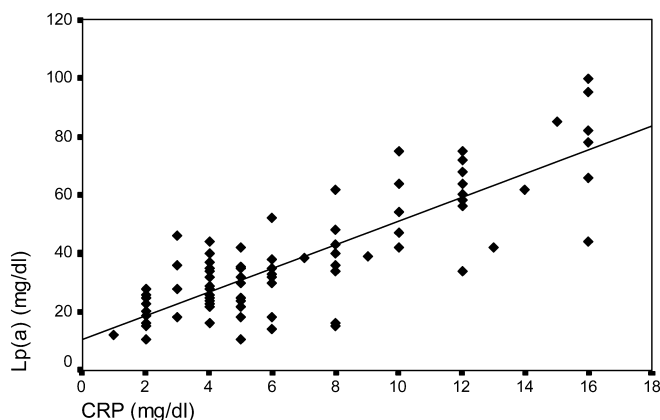
## Discussion

Coronary atherosclerosis and acute myocardial infarction are the most common causes of death in patients with RA. Changes in lipid profiles, Lp(a), and acute phase reactants are associated with early atherosclerosis in RA. In addition to high TC and LDL-C levels, it is well known that high Lp(a) and low HDL-C levels are independent determinants of atherosclerosis. In recent years, meta-analytic studies have shown that high serum

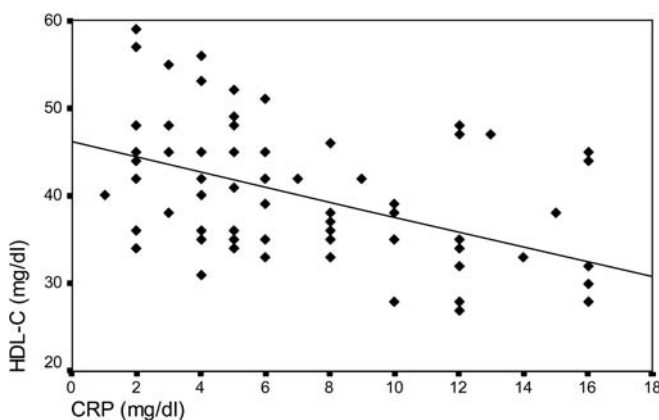
TG was an independent atherogenic factor for coronary heart disease (CHD) [10].

The results of several studies on Lp(a) levels in RA patients are different and incompatible. Rantapää-Dahlqvist et al. found that the Lp(a) level in RA patients was higher than in healthy subjects; however, they did not establish any correlation between Lp(a) and CRP [8]. Lakatos et al. found higher TC and LDL-C levels and lower HDL-C and TG levels in RA patients than in healthy subjects [11]. Other investigators found that not only serum HDL-C and TG levels, but also TC and LDL-C levels were lower in RA patients than healthy subjects [12, 13, 14, 15, 16].

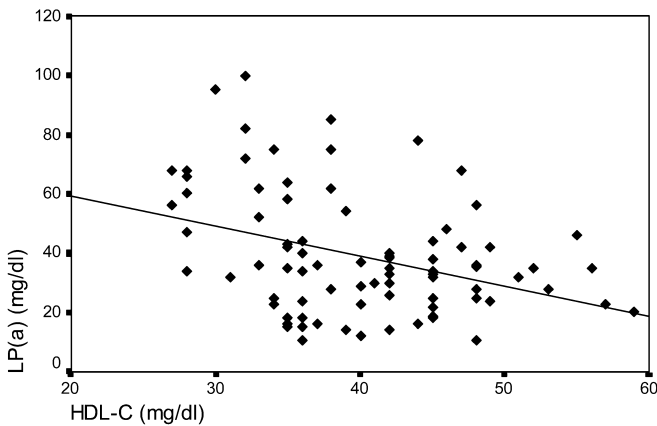
The mechanisms of dyslipoproteinemia in RA are not well known, and several hypotheses have been suggested [17, 18, 19, 20, 21, 22, 23, 24]. The chronic inflammation process, immobilization, gastrointestinal and liver diseases, systemic complications of chronic diseases, several inflammatory mediators, and drugs may effect lipid metabolism. In myocardial infarction, acute infectious disease, and in heavily burned subjects, Lp(a) levels were found lower, suggesting that Lp(a) metabolism might be responsible for the inflammation. Lp(a) was found to be involved in carbohydrate metabolism, and increased Lp(a) levels have been described in diabetic patients



**Fig. 1** Correlation between Lp(a) and CRP ( $r=0.83$ ,  $P=0.0001$ )



**Fig. 2** Correlation between HDL-C and CRP ( $r=-0.49$ ,  $P=0.0001$ )



**Fig. 3** Correlation between Lp(a) and HDL-C ( $r = -0.36$ ,  $P = 0.001$ )

having clinical complications [25, 26]. It was shown that the rapidity of protein synthesis was decreased in active RA patients, and this decrease may depend on either liver response to inflammatory mediators or increased synthesis and secretion of acute phase reactants from the liver [27]. These mechanisms may change lipoprotein metabolism, as the liver is the organ most important to Lp(a) metabolism.

The effects of the inflammatory process on Lp(a) metabolism are unclear. It was suggested that increased synthesis and/or decreased destruction of Lp(a) or changes in Lp(a) distribution between intravascular and extravascular regions may cause dyslipoproteinemia in RA [25]. The Lp(a) contained sixfold more sialic acid than LDL-C, so it was suggested that in inflammation, Lp(a) synthesis increased in liver like the other acute phase reactants. Since the lipid contents of Lp(a) and LDL-C were similar, they might have similar mechanisms in atherogenesis. It is suggested that the reticulo-endothelial system became overstimulated in active RA and then lipid elimination by scavenger receptors of macrophages increased. For that reason, Lp(a) may have a role as an important atherogenic factor [26, 28, 29, 30].

Rössner et al. found that the Lp(a) (settled pre-beta lipoprotein) level was higher in polyarthritis patients than a control group [31]. Lazarevic et al. established that serum TC, LDL-C, and HDL-C levels were lower and TG was higher in RA patients having antilipoprotein antibodies; and they explained that this dyslipoproteinemia might be due to the antilipoprotein antibodies [32]. Wallberg-Jonsson et al. showed that von Willebrand's factor, plasminogen activator inhibitor-1, and also haptoglobin and triglycerides were significantly increased in patients with RA who later suffered from thromboembolic events registered in a 2-year follow-up period [33]. In our study, there were relatively higher levels of TG in the patient group, in contrast to most of the other studies. None of the subjects was taking any anti-inflammatory drug that could affect lipid metabolism at the time of the study, so those lipid anomalies might be directly effected by RA and the inflammatory

process. Additionally, the different HDL-C levels between RA patients and healthy subjects might be due to physical inactivity in the former, because all of our study patients had active-phase RA and various degrees of physical inactivity.

In recent years, several studies have established that atherosclerosis is an inflammatory disease and associated with high serum CRP levels (especially high-sensitive CRP), which is a predictor of coronary heart disease (CHD) [26, 30]. However, mechanisms of the inflammatory process in atherosclerosis are complex and not known exactly. In our study, although we found no correlation between CRP and TC and TG, we showed the positive correlation between CRP and Lp(a) and also the negative correlation between CRP and HDL-C levels. As a result, the association between RA and atherosclerosis is strong, because both diseases are inflammatory systemic and metabolic disorders. Dyslipoproteinemia in RA includes lower HDL-C, higher Lp(a), and higher TG and is related to atherosclerosis. Since increased serum CRP levels correlated with higher Lp(a) and lower HDL-C, our study convinces us that atherosclerosis is an inflammatory disease.

## References

1. Isomaki HA, Mutru O, Koota K (1975) Death rate and causes of death in patients with rheumatoid arthritis. *Scand J Rheumatol* 4:205–208
2. Abruzzo JL (1982) Rheumatoid arthritis and mortality. *Arthritis Rheum* 25:1020–1023
3. Prior P, Symmons DPM, Scott DL, Brown R, Hawkins CF (1984) Causes of death in rheumatoid arthritis. *Br J Rheumatol* 23:92–99
4. Mutro O, Laakso M, Isomaki H, Koota K (1985) Ten year mortality and causes of death in patients with rheumatoid arthritis. *BMJ* 290:1811–1813
5. Wallberg-Jonsson S, Cederfelt M, Rantapää-Dahlqvist S (2000) Hemostatic factors and cardiovascular disease in active rheumatoid arthritis: an 8 year follow up study. *J Rheumatol* 27:71–75
6. Scanu AM (1992) Lipoprotein (a): a genetic risk factor for premature coronary heart disease. *JAMA* 267:3326–3329
7. Gordon T, Castelli WP, Hjortland MC, Kannel WB, Dawber TR (1977) High density lipoprotein as a protective factor against coronary heart disease. *Am J Med* 62:707–714
8. Rantapää-Dahlqvist S, Wallberg-Jonsson S, Dahlen G (1991) Lipoprotein (a), lipids and lipoproteins in patients with rheumatoid arthritis. *Ann Rheum Dis* 50:366–368
9. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, Healey LA, Kaplan SR, Liang MH, Luthra HS et al (1988) The American Rheumatism Association 1987 revised criteria for classification of rheumatoid arthritis. *Arthritis Rheum* 31:315–324
10. Assmann G, Schulte H, Cullen P (1997) New and classical risk factors—the Munster Heart study (PROCAM). *Eur J Med Res* 2:237–242
11. Lakatos J, Harsanyi A (1988) Serum total HDL, LDL cholesterol and triglyceride levels in patients with rheumatoid arthritis. *Clin Biochem* 21:93–96
12. Svensson K, Lithel H, Hallgren R, Selinus I, Vesby B (1987) Serum lipoprotein in active rheumatoid arthritis and other chronic inflammatory arthritides: I. Relativity to inflammatory activity. *Arch Intern Med* 147:1912–1916

13. Lorber M, Aviram M, Linn S, Scharf Y, Brook JG (1985) Hypocholesterolemia and abnormal high density lipoprotein in rheumatoid arthritis. *Br J Rheumatol* 24:250–255
14. Park YB, Lee SK, Lee WK, Suh CH, Lee CW, Lee CH, Song CH, Lee J (1999) Lipid profiles in untreated patients with rheumatoid arthritis. *J Rheumatol* 26:1701–1704
15. Asanuma Y, Kawai S, Aoshima H, Kaburaki J, Mizushima Y (1999) Serum lipoprotein(a) and apolipoprotein(a) phenotypes in patients with rheumatoid arthritis. *Arthritis Rheum* 42:443–447
16. Seriole B, Accardo S, Cutolo M (1996) Lipoprotein (a) and other risk factors for thrombosis in rheumatoid arthritis. *J Rheumatol* 23:194–196
17. Seriole B, Accardo S, Fasciolo D, Bertolini S, Cutolo M (1996) Lipoproteins, anticardiolipin antibodies and thrombotic events in rheumatoid arthritis. *Clin Exp Rheumatol* 14:593–599
18. Seriole B, Accardo S, Fasciolo D, Sulli A, Bertolini S, Cutolo M (1995) Lipoprotein (a) and anticardiolipin antibodies as risk factors for vascular disease in rheumatoid arthritis. *Thromb Haemost* 74:799–800
19. Dahlen GH, Boman J, Birgander LS, Lindblom B (1995) Lp(a) lipoprotein, IgG, IgA and IgM antibodies to *Chlamydia pneumoniae* and HLA class II genotype in early coronary artery disease. *Atherosclerosis* 114:165–174
20. Dahlen GH (1994) Indications of an autoimmune component in Lp(a) associated disorders. *Eur J Immunogenet* 21:301–312
21. Lee YH, Choi SJ, Ji JD, Seo HS, Song GG (2000) Lipoprotein (a) and lipids in relation to inflammation in rheumatoid arthritis. *Clin Rheumatol* 19:324–325
22. Banks MJ, Kitas GD (1999) Lipoprotein (a) levels and atherosclerosis in rheumatoid arthritis: comment on the article by Asanuma et al. *Arthritis Rheum* 42:2491–2492
23. Wallberg-Jonsson S, Uddhammar A, Dahlen G, Rantapää-Dahlqvist S (1995) Lipoprotein (a) in relation to acute phase reaction in patients with rheumatoid arthritis and polymyalgia rheumatica. *Scand J Clin Lab Invest* 55:309–315
24. Dahlen GH (1994) Lp (a) lipoprotein in cardiovascular disease. *Atherosclerosis* 108:111–126
25. Ehnholm C, Garoff H, Renkonen O, Simons K (1972) Protein and carbohydrate composition of Lp(a) lipoprotein from human plasma. *Biochemistry* 11:3229
26. Ross R (1999) Atherosclerosis: an inflammatory disease. *N Engl J Med* 340:115–126
27. Magaro M, Altomonte L, Zoli A, Mirone L, Ruffini MP (1991) Serum lipid pattern and apolipoproteins (A-I and B-100) in active rheumatoid arthritis. *Z Rheumatol* 50:168–170
28. Gianturco SH, Bradley WA (1994) Atherosclerosis: cell biology and lipoproteins. *Curr Opin Lipidol* 5:313–315
29. Svensson K, Lithell H, Hallgren R, Selinus I, Vessby B (1987) Altered serum lipoproteins and enhanced lipoprotein elimination in patients with rheumatoid arthritis and other chronic inflammatory arthritides. I. Relationship to the inflammatory activity. *Arch Intern Med* 147:1912–1916
30. Hansson GK (2001) Immune mechanisms in atherosclerosis. *Arterioscler Thromb Vasc Biol* 21:1876–1890
31. Rossner S, Lofmark C (1977) Dyslipoproteinemia in patients with active chronic polyarthritis: a study on serum lipoproteins and triglycerides clearance (intravenous fat tolerance test). *Atherosclerosis* 28:41–52
32. Lazarevic MB, Vitic J, Myones BL, Mladenovic V, Nanusevic N, Skosey JL, Swedler WI (1993) Antilipoprotein antibodies in rheumatoid arthritis. *Semin Arthritis Rheum* 22:385–391
33. Wallberg-Jonsson S, Dahlen GH, Nilsson TK, Ranby M, Rantapää-Dahlqvist S (1993) Tissue plasminogen activator, plasminogen activator inhibitor-1 and von Willebrand factor in rheumatoid arthritis. *Clin Rheumatol* 12:318–324