

# Lipoprotein (a), lipids, and lipoproteins in patients with rheumatoid arthritis

Solbritt Rantapää-Dahlqvist, Solveig Wällberg-Jonsson, Gösta Dahlén

## Abstract

**Lipoprotein (a), (Lp(a)), an independent atherogenic factor, was significantly increased in 93 patients with classical, seropositive rheumatoid arthritis of median disease activity. In the patients with Lp(a) concentrations above the upper reference value of 480 mg/l there was a significant correlation between Lp(a) and the concentration of orosomucoid, erythrocyte sedimentation rate, and the platelet count. The plasma concentrations of cholesterol and high density lipoprotein-cholesterol in both male and female patients were significantly lower than in controls. Apolipoprotein B and apolipoprotein AI in the patients correlated significantly with total cholesterol and high density lipoprotein-cholesterol respectively.**

An increased mortality has been reported in hospital inpatients with rheumatoid arthritis compared with the general population.<sup>1-5</sup> The most common cause of death in patients with rheumatoid arthritis, as in the general population, was cardiovascular disease.<sup>1-5</sup> Some studies found an even higher incidence of cardiovascular disease in patients with rheumatoid arthritis than in controls.<sup>1-6</sup>

Increased concentrations of total cholesterol, low density lipoprotein-cholesterol, and total apolipoprotein B have been found to be associated with an increased risk for cardiovascular disease.<sup>7-9</sup> Even low concentrations of high density lipoprotein-cholesterol and apolipoprotein AI have been found to be risk factors for cardiovascular disease.<sup>7-9</sup>

In patients with inflammatory polyarthritis the serum concentrations of cholesterol and some subfractions of triglycerides have been found to be significantly lower than in controls.<sup>10-12</sup> A significant inverse correlation between inflammatory activity and lipoprotein or lipid concentrations has previously been reported.<sup>12-13</sup> The apolipoprotein AI/apolipoprotein B ratio has been found to be raised in rheumatoid arthritis.<sup>14</sup>

Because lipoprotein (a) (Lp(a)) may exert independent strong atherogenic effects<sup>15-16</sup> and be associated with acute phase reactants<sup>17</sup> we analysed the concentrations of Lp(a) in patients with active rheumatoid arthritis. Apolipoprotein AI, apolipoprotein B, and lipids (cholesterol and triglycerides) were also determined. The concentrations of lipids and Lp(a) in plasma were related to the laboratory data showing disease activity and to drug treatment.

## Patients and methods

### PATIENTS

Ethylenediaminetetra-acetate (EDTA) plasma was collected consecutively from 93 inpatients (75 female, 18 male) with classical, erosive, and seropositive rheumatoid arthritis.<sup>18</sup> All patients had median disease activity (according to the criteria of the Cooperating Clinics Committee of the American Rheumatism Association). Table 1 shows the laboratory data for the patients at the time of the study. The mean age of the patients was 62.8 years (range 25-80), and the mean disease duration 20.9 years (range 0.5-51). All patients were receiving an ordinary hospital diet and the weight/height index was less than 1.1 (weight in kg divided by height in cm minus 100).

Fifty of the patients were receiving corticosteroids (prednisolone 2.5-20 mg daily) and 19 remission inducing drugs (penicillamine, disodium aurothiomalate, sulphasalazine, azathioprine, mitopodozide). Fifty nine were receiving both corticosteroids and remission inducing drugs. Seventy two patients took non-steroidal anti-inflammatory drugs. None of the patients had laboratory or clinical signs of kidney, liver, thyroid, or infectious diseases, diabetes mellitus, or malignancy. Nine patients (10%) were receiving  $\beta$  blockers and eight (9%) thyroxine treatment.

### CONTROLS

Control samples (EDTA plasma) were collected from 67 healthy subjects matched for age (33 female, 34 male) and from the same area as the patients. The controls belonged to a health project (the Norsjö project) that included subjects from a certain area.

### METHODS

Erythrocyte sedimentation rate (Westergren), haptoglobin, orosomucoid, C reactive protein, and platelets were measured by routine methods at the laboratory of clinical chemistry. Cholesterol, high density lipoprotein-cholesterol, and triglycerides were determined enzymatically with reagent kits from Boehringer Mannheim, FRG. Lipoprotein (a) was measured by an enzyme linked immunosorbent assay (ELISA). The detection limit was 10 mg/l and the assay range 10-600 mg/l. Mean intra-assay variation (CV) was 6.6 and 2.3% at Lp(a) concentrations of 40 and 300 mg/l, and interassay variation was 7.7 and 2.7% respectively. The correlation with electroimmunoassay was 0.91.<sup>15</sup> Apolipoprotein

Department of  
Rheumatology,  
University Hospital,  
S-901 85 Umeå, Sweden  
S Rantapää-Dahlqvist  
S Wällberg-Jonsson

Department of Clinical  
Chemistry,  
University Hospital,  
Umeå, Sweden  
G Dahlén

Correspondence to:  
Dr Rantapää-Dahlqvist.

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**Table 1** Laboratory data (mean (SEM) and ranges) in 93 patients with rheumatoid arthritis, and normal values

	ESR* (mm/h)	Orosomuroid (g/l)	Haptoglobin (g/l)	CRP* (mg/l)	Thrombocytes ( $\times 10^9/l$ )
Patients (n=93)	53.1 (17.7) (20–109)	1.8 (0.52) (0.8–3.1)	3.7 (1.1) (1.2–6.3)	25 (20.4) (1–96)	368 (11.4) (131–685)
Reference values	<20	0.1–1.0	0.3–2.5	<5	150–350

\*ESR=erythrocyte sedimentation rate; CRP=C reactive protein.

**Table 2** Plasma concentrations (mean (SEM) and ranges) of lipoprotein (a) (Lp(a)), cholesterol, and triglycerides in 93 patients with rheumatoid arthritis and in 67 controls matched for age from the same area

	Lp(a) (mg/l)	Cholesterol (mmol/l)	Triglycerides (mmol/l)
Patients (n=93)	230.3 (25.20)* (0–1425)	5.49 (0.13)*** (2.45–9.00)	1.42 (0.05) (0.32–2.80)
Controls (n=67)	153.5 (22.13) (0–825)	7.41 (0.21) (4.20–11.60)	1.74 (0.12) (0.70–5.30)

\*\*\*p<0.001; \*\*p<0.01; \*p<0.05 patients v controls.

B and apolipoprotein AI were measured with radioimmunoassay research kits from Pharmacia Diagnostics, Uppsala, Sweden.

#### STATISTICS

All calculations were performed by StatView (Brain Power Inc, Calabasas, Ca, USA). Plasma concentrations of the lipids and lipoproteins in the patients and controls were compared by the Mann-Whitney U test. Correlation between variables was assessed by Pearson product-moment correlation coefficients and tested for two tailed probability values. A two way analysis of variance was used for analysis of two independent groups.

#### Results

The highest concentration of Lp(a) was found in the 50 patients treated with corticosteroids, mean 243.1 mg/l (data not shown); this, however, was not significantly different from the value for untreated patients with rheumatoid arthritis. Consequently, patient data were analysed as one group. Table 2 presents the results. The Lp(a) concentration was significantly increased (p<0.05) in patients with rheumatoid arthritis (mean (SEM) 230.3 (25.2) mg/l) compared with the controls (mean (SEM) 153.5 (22.13) mg/l). In 12 (13%) of the patients with rheumatoid arthritis the Lp(a) concentrations exceeded the upper reference level of 480 mg/l, which was significantly higher than the 2.5% found in a reference group of 653 healthy subjects<sup>16</sup> (p<0.05). For those patients with Lp(a) concentrations greater than 480 mg/l a significant correlation between Lp(a) concentration and orosomuroid (r=0.63, p<0.05), erythrocyte sedimentation rate (r=0.83, p<0.001), and platelet count (r=0.71, p<0.05) was found, and there was a tendency for correlation with haptoglobin (r=0.53, p<0.07) also. In the nine patients with Lp(a) concentrations above 480 mg/l who were receiving corticosteroids the Lp(a) concentration correlated even more significantly with erythrocyte sedimentation rate (r=0.95, p<0.0001), orosomuroid (r=0.68, p<0.05), and platelet count

**Table 3** High density lipoprotein-cholesterol in plasma from 93 patients with rheumatoid arthritis and in 65 controls matched for age from the same area. Results are given as mean (SEM) in mmol/l

Women		Men	
Patients (n=75)	Controls (n=33)	Patients (n=18)	Controls (n=32)
1.40 (0.04)*	1.59 (0.06)	1.09 (0.07)*	1.32 (0.06)

\*p<0.05 patients v controls.

(r=0.73, p<0.05). There was no correlation between C reactive protein and the Lp(a) concentration in any patient group.

The plasma concentration of cholesterol in patients with rheumatoid arthritis (mean 5.49 mmol/l) was significantly lower than in the controls (mean 7.41 mmol/l). The concentration of triglycerides was also decreased (1.42 mmol/l), but not significantly, compared with controls (1.74 mmol/l) (table 2). The mean concentrations (5.63 mmol/l and 1.48 mmol/l respectively) of cholesterol and triglycerides were slightly higher (non-significantly) in the patients treated with corticosteroids. There was no significant difference between patients treated with non-steroidal anti-inflammatory drugs or remission inducing drugs. There was a significant difference in the concentration of high density lipoprotein-cholesterol between patients and controls, and between sexes of both groups. The concentrations of high density lipoprotein-cholesterol were significantly lower both in female patients (1.40 mmol/l; p<0.05) and in male patients (1.09 mmol/l; p<0.05) than in the corresponding controls (table 3). Total apolipoprotein B correlated significantly with total serum cholesterol (r=0.72, p<0.00001); apolipoprotein AI correlated significantly with high density lipoprotein-cholesterol (r=0.78, p<0.00001). The high density lipoprotein-cholesterol/total cholesterol ratio in these patients was 24%—that is, normal.

#### Discussion

In this study the concentration of Lp(a) was significantly increased in patients with rheumatoid arthritis with a median disease activity. As an increased concentration of Lp(a) has been found to be closely associated with cardiovascular disease, Lp(a) may be an important cause of cardiovascular disease in patients with rheumatoid arthritis.

Lipoprotein (a) is a cholesterol-rich lipoprotein with a lipid composition similar to low density lipoprotein. The specific antigen (s) resides in a large protein, apolipoprotein (a), which is attached by a disulphide bridge to apolipoprotein B 100.<sup>19</sup> The plasma concentration of Lp(a) is, to a large extent, genetically determined.<sup>20–21</sup> A single locus with several alleles seems to code both for the apolipoprotein (a) isoforms<sup>22</sup> and for the serum concentration of Lp(a).<sup>21</sup> Sequencing has shown that apolipoprotein (a) has striking homology with plasminogen.<sup>23–24</sup> Studies in vitro suggest that Lp(a) may suppress fibrinolysis and thrombolysis.<sup>25</sup>

Macrophage uptake by scavenger receptors and by phagocytosis of aggregated biologically modified low density lipoprotein is thought to be important in atherogenesis.<sup>26</sup> These mechanisms might be of importance in Lp(a) catabolism as small aggregates have been found to cause cholesterol ester accumulation in macrophages in vitro.<sup>27</sup> As fat elimination through macrophages and the scavenger pathway is thought to be enhanced in patients with active rheumatoid arthritis, in whom the reticuloendothelial system is overstimulated,<sup>12</sup> Lp(a) might be of special atherogenic importance in rheumatoid arthritis. Other early studies in vitro also suggested that Lp(a) is a causative factor for atherogenesis as it binds strongly to glycosaminoglycans<sup>28</sup> and is easily precipitated in the presence of divalent cations.<sup>29</sup>

The significantly higher number of patients with rheumatoid arthritis with Lp(a) concentrations above the upper reference level of 480 mg/l may suggest that Lp(a) is increased as a response to inflammation in these patients. We also found a significant association between high concentrations of Lp(a) (>480 mg/l) and acute phase reactants (erythrocyte sedimentation rate, orosomucoid, platelet count). These results would support the concept that Lp(a) is related to acute phase proteins.<sup>15-17</sup> This correlation was even stronger in patients treated with corticosteroids. No significant correlation was found between high Lp(a) concentrations (>480 mg/l) and clinical complications or severity of the disease. The small number of patients in this study might have obscured such an association, however.

Our results are in line with previous observations made by Rössner and Löfmark,<sup>11</sup> who showed that Lp(a), detected qualitatively as 'sinking pre-beta lipoprotein', was present more often in patients with polyarthritis than in controls.

The plasma concentrations of cholesterol and triglycerides are remarkably high in the population of northern Sweden.<sup>15-16</sup> The decreased plasma concentrations of cholesterol, triglycerides, and high density lipoprotein-cholesterol, with sex differences, found in the patients with rheumatoid arthritis in this study are in agreement with previous findings, however.<sup>10-12, 14-30</sup>

In this study no significant difference was found between the serum concentrations of cholesterol and triglycerides in the untreated patients and those in patients treated with corticosteroids; this is in contrast with another report.<sup>31</sup> All patients in our study, however, had a disease of median activity and none of the patients was inactive or in remission despite treatment with corticosteroids or remission inducing drugs.

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