Conventional Lipid Profile and Lipoprotein(a) Concentrations in Treated Patients with Rheumatoid Arthritis

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ABSTRACT. ***Objective.*** Patients with rheumatoid arthritis (RA) have an increased cardiovascular risk not completely explained by traditional cardiovascular risk factors. If the proatherogenic lipid profile observed in active and untreated RA improves by effectively treating RA without the use of a lipid-lowering agent, other nonconventional cardiovascular lipid risk factors may be implicated. We evaluated conventional lipid risk factors and lipoprotein(a) in treated patients with RA.

Methods. This cross-sectional study was conducted in 122 patients with RA. Lipid profiles of patients were compared with a control group, consisting of a population-based study cohort (DRECE study), matched for sex, age, menopausal status, and body mass index. Excess lipoprotein(a) was defined by a serum concentration > 0.3 g/l.

Results. High-density lipoprotein cholesterol (HDL-c) concentrations were higher in pre- and postmenopausal women with RA than in controls ($p = 0.023$ and $p \leq 0.001$, respectively). All RA patients had significantly lower levels of apolipoprotein B and apolipoprotein B/apolipoprotein A-I ratio, and postmenopausal women with RA also had significantly lower low-density lipoprotein cholesterol and total cholesterol levels than their respective controls. No differences were observed in serum levels of apolipoprotein A-I and triglyceride. All RA patients had higher lipoprotein(a) values than controls. Fourteen men (56%) and 10 (53%) and 42 (54%) pre- and postmenopausal women with RA, respectively, had hyperlipoproteinemia(a).

Conclusion. RA patients undergoing antirheumatic therapy display a nonatherogenic conventional lipid profile, i.e., high HDL-c, low apolipoprotein B concentrations, and low apolipoprotein B/apolipoprotein A-I ratio. This may be counteracted by the high prevalence of hyperlipoproteinemia(a) observed in these patients. (J Rheumatol First Release April 15 2009; doi:10.3899/jrheum.080928)

Key Indexing Terms:
RHEUMATOID ARTHRITIS LIPOPROTEINS GLUCOCORTICOIDS CHOLESTEROL

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Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease of unknown etiology affecting ~0.5% of the general adult population of Spain[1]. RA is associated with increased mortality rates[2] that are mostly attributable to cardiovascular disease, primarily coronary heart disease[3], which is a consequence of early atherosclerosis[4]. It has been estimated that patients with RA have a relative risk of cardiovascular disease of roughly 2–3 compared with age- and sex-matched controls[5], not completely explained by traditional risk factors[6]. Numerous factors, such as chronic inflammation, side effects of medication, decreased mobility, undertreatment of conventional cardiovascular risk factors[7], and dyslipidemia may be implicated in the pathogenesis of atherosclerosis of patients with RA. A proatherogenic lipid profile has been reported in patients with active and untreated RA, in the form of low high-density lipoprotein cholesterol (HDL-c) as the most common[8,9]. These lipid abnormalities can be improved by treating RA effectively without the use of a lipid-lowering agent[10]. On the other

hand, high levels of lipoprotein(a) [Lp(a)], a lipoprotein with atherogenic and thrombogenic properties that is increased in patients with coronary artery disease, have been observed in inflammatory diseases[11]. Sparse and contradictory results on Lp(a) levels in RA patients have been reported[12,13]. Our aim was to evaluate conventional lipid profile and Lp(a), a nonconventional lipid risk factor, in RA patients undergoing standard therapy with disease-modifying agents and low-dose glucocorticoids and compare their characteristics with those of the general population.

MATERIALS AND METHODS

Patients. This cross-sectional study was conducted at the rheumatology department of the Hospital Universitari de Bellvitge, a tertiary teaching hospital in Barcelona, Spain. In our area, patients with RA are usually referred to staff members of the rheumatology department for specialized opinion. The department has an established protocol for evaluation and followup of patients with RA.

The study comprised 122 patients (25 men, 19 premenopausal women, and 78 postmenopausal women) consecutively recruited from the outpatient rheumatology clinic. All patients had been diagnosed with RA according to the 1987 revised criteria of the American College of Rheumatology at least 1 year earlier[14]. The study was approved by the Ethics Committee of the Hospital Universitari de Bellvitge.

Patients who agreed to participate were scheduled for an additional appointment. Information on each patient was collected through a self-report questionnaire, structured interview, general physical examination, and blood and urine samples. The laboratory assessments included routine biochemistry, hematologic tests, and lipid and lipoprotein profiles: total cholesterol (TC), triglycerides (TG), low-density lipoprotein-cholesterol (LDL-c), very low-density lipoprotein-cholesterol (VLDL-c), high-density lipoprotein cholesterol (HDL-c), HDL2-cholesterol (HDL2-c), HDL3-cholesterol (HDL3-c), apolipoprotein A-I (apo A-I), apolipoprotein B (apo B), and Lp(a). Creatinine clearance was calculated using the Cockcroft-Gault formula corrected on the basis of body surface area[15].

Current medication use was carefully recorded both from the information provided by the patients and from medical records, including disease-modifying antirheumatic drugs (DMARD) and the dose and type of glucocorticoids. The equivalent dose of prednisone was calculated in each case as follows: 5 mg prednisone = 4 mg methylprednisolone = 7.5 mg deflazacort. Each patient was assessed to determine body mass index (BMI) calculated by dividing weight in kilograms by the square of height in meters, blood pressure (as the average of 2 measurements obtained 5 min apart after subjects had rested in the supine position for at least 10 min); sedentary lifestyle (sedentary defined as not walking for 30 consecutive min at least 3 times a week); disease activity [measured using the Disease Activity Score based on evaluation of 28 joints (DAS28)][16]; and ability to perform daily activities [measured using the Health Assessment Questionnaire (HAQ) with a range from 0 to 3, where 0 represents no functional impairment][17].

Patients were excluded if they had acute infection or showed clinical signs of, or referred to, a known clinical history of neoplastic disease or thyroid dysfunction. No other exclusion criteria were applied to ensure that the group of patients included in this study was representative of the general RA population and also to avoid differences other than RA between our patients and the general population, which renders comparison between them more reliable.

Control group. The control group was selected from a population-based study (DRECE study)[18] and consisted of 2151 subjects (1008 men, 641 premenopausal women, 402 postmenopausal women), matched to the RA group for sex, age, menopausal status, and BMI (unpublished data). Lp(a) was evaluated in a subgroup of subjects from that study (DRECE II)[19].

Determination of serum lipid and lipoprotein concentrations. A venous blood sample was drawn after an overnight fast of at least 12 h for determination of serum lipid and lipoprotein concentrations. Specimens were collected into tubes without anticoagulant and centrifuged at 1200 g for 10 min at room temperature and stored at 4°C until analysis. Serum VLDL were isolated by preparative ultracentrifugation at a density gradient of 1.006 kg/l. TC and TG were measured by an enzymatic colorimetric method (CHOD-PAP and GPO-PAP, respectively; Roche Diagnostics, Basel, Switzerland). Serum HDL-c concentrations were measured by a direct colorimetric enzymatic method (HDL-c plus; Roche Diagnostics). Serum HDL3-c concentrations were measured in the supernatant obtained after precipitation of the HDL2 subfraction through the addition of a 15% polyethylenglycol solution (PEG 20000) at pH 7.5. Serum HDL2-c concentrations were calculated as the difference between concentrations of HDL-c and HDL3-c.

Serum LDL-c concentrations were derived by calculation using the Friedewald equation[20]. LDL-c estimation was considered inaccurate and was not performed when the TG level exceeded 2.3 mmol/l. Apo A-I, apo B, and Lp(a) were quantified by immunoturbidimetric methods (Roche Diagnostics). All procedures were carried out with a modular system analyzer (Roche Diagnostics).

The methods used to measure serum lipid and lipoprotein concentrations in the DRECE study were the same as those used in our study, with the exception of HDL-c. Serum HDL-c concentrations in the DRECE study were obtained after precipitation of apo B-containing lipoproteins with phosphotungstic acid/$MnCl_2$ and their cholesterol concentration was measured in the supernatant with an Advia 1650 (Siemens Healthcare Instruments) and reagents (CHOD-PAP) provided by Biosystems, Barcelona, Spain, after adjusting the sample/reagent ratio for good photometric precision.

For comparison of HDL-c values by the direct method (HDLdir) and the phosphotungstic acid/$MnCl_2$ method (HDL Ptg-Mn) used in the DRECE study, 50 samples with HDL-c values between 14 and 84 mg/dl were cross-analyzed, and results were evaluated using Passing-Bablok regression and the Bland-Altman plot. No significant differences were found ($p = 0.09$) and Passing-Bablok regression yielded an intercept of 1.2 (95% CI 0.97–1.23) and a slope of 0.95 (95% CI 0.925–1.023); HDLdir = 1.232 + 0.951 HDL Ptg-Mn. These data demonstrated that results presented neither systematic nor proportional differences.

Statistical analysis. Data were analyzed using SPSS 12.0 for Windows (SPSS, Chicago, IL, USA). P values less than 0.05 were considered significant. Non-normal lipid variables were analyzed by logarithmic transformation and are expressed by antilogarithmic transformation to facilitate understanding. Results of non-normal descriptive variables are expressed as median (interquartile range), continuous variables as mean ± standard deviation (SD), and categorical and ordinal variables as relative frequency (%). Groups were compared using the chi-square test for categorical variables, Kruskal-Wallis test for non-normal descriptive and ordinal variables, and analysis of variance (ANOVA) for normal continuous variables. Comparisons of lipid and lipoprotein values between RA patients and the control group were analyzed by Student t test. Associations between HDL-c and Lp(a) with disease activity were analyzed by partial correlations. The influence of the antirheumatic therapy on lipid variables between RA patients and controls was analyzed by ANCOVA. The partial correlation and ANCOVA were adjusted for sex, age, and glucocorticoid use.

RESULTS

The main demographic, clinical, and laboratory features of the study participants in relation to sex and menopausal status are shown in Table 1. As expected, the majority had long disease duration, positive rheumatoid factor, and erosive disease. RA men had lower disease activity, according to DAS28 evaluation. Also, in the majority, RA treatment con-

Table 1. Clinical characteristics of patients with RA.

	Male, n = 25	Premenopausal Female, n = 19	Postmenopausal Female, n = 78	p
Age, yrs	61 (12)	43 (6)	65 (8)	< 0.001
Disease duration, yrs	10 (8)	9 (6)	14 (9)	0.035
Morning stiffness > 1 h, %	16	21	5	0.057
Functional class, %				0.095
I	38	32	18	
II	42	47	48	
III	21	21	31	
IV	0	0	3	
Rheumatoid factor +, %	75	89	78	0.466
Rheumatoid factor titer*	79 (24–175)	78 (21–176)	46 (18–118)	0.478
Nodular disease, %	42	37	27	0.339
Erosive disease, %	79	89	82	0.704
Sedentary lifestyle, %	8	16	29	0.061
HAQ 0–3*	0.9 (0.1–1.6)	1 (0.3–1.6)	1.5 (0.9–2.3)	0.005
DAS28	3.8 (1.7)	5.0 (1.3)	4.8 (1.4)	0.012
Current smoker, %	40	10	3	< 0.001
SBP/DBP, mm Hg	154 (17)/90 (10)	132 (21)/82 (11)	156 (23)/86 (9)	< 0.001
Body mass index, kg/m^2	25.6 (3.6)	24.8 (3.5)	28.6 (4.7)	< 0.001
ESR, mm/h	25 (20)	39 (27)	36 (20)	0.066
CRP, mg/l	13 (6–26)	7 (3–31)	10 (4–22)	0.723
Fibrinogen, mg/ml	5.0 (1.3)	4.4 (1.3)	4.7 (1.0)	0.287
Glucose, mmol/l	6.0 (1.9)	5.0 (0.7)	5.3 (0.8)	0.006
Creatinine, µmol/l	101 (33)	78 (17)	82 (19)	< 0.001
Proteinuria, g/24 h*	0.18 (0.14–0.24)	0.09 (0–0.13)	0.11 (0.08–0.16)	< 0.001
Creatinine clearance, ml/h	69 (22)	89 (21)	68 (17)	< 0.001
RA treatment during the study period, %				
Glucocorticoids	84	68	88	0.097
Equivalent dose of prednisone, mg/day	4.1 (2.8)	3.7 (2.9)	4.5 (2.3)	0.422
Methotrexate	44	58	54	0.606
TNF-α blockers	0	31	5	< 0.001
Other disease-modifying antirheumatic drugs	36	26	28	0.718

* Variables not normally distributed are expressed as median (interquartile range). Continuous variables are expressed as mean (SD). SBP: systolic blood pressure; DBP: diastolic blood pressure; HAQ: Health Assessment Questionnaire; DAS: Disease Activity Score; TNF: tumor necrosis factor. ESR: erythrocyte sedimentation rate; CRP: C-reactive protein.

sisted of low-dose glucocorticoids and methotrexate or other DMARD, including tumor necrosis factor-α inhibitor therapy (TNF-α blockers). Regarding conventional cardiovascular risk factors, RA men had a high prevalence of smoking, both RA men and postmenopausal RA women had higher mean blood pressure values than premenopausal women and higher basal glycemia; however, marked hyperglycemia was not observed in any case. Postmenopausal RA women were more sedentary than patients from the other groups, as expected from their worse functional class and HAQ results, and had higher BMI. No patient had severe kidney dysfunction.

Values of serum lipid and lipoprotein metabolism measures are shown in Table 2. The main difference among groups was the lower HDL-c and apo A-I values found in men compared with pre- and postmenopausal women. The lower HDL-c values in men were due to a lower cholesterol of the HDL2 subfraction. Further, men had higher serum concentrations of apo B, the apolipoprotein of LDL, than pre- and postmenopausal women, and higher serum LDL-c concentrations and TG than premenopausal, but not postmenopausal, women. Women had lower values of the atherogenic ratios TC/HDL-c, LDL-c/HDL-c, and apo B/apo A-I than men. Fourteen men (56%), 10 premenopausal RA women (53%), and 42 postmenopausal RA women (54%) had hyperlipoproteinemia(a) defined by a serum Lp(a) concentration > 0.3 g/l. No significant differences in Lp(a) values were found among groups.

Mean serum lipid and lipoprotein concentrations in RA patients and controls from the DRECE study are shown in Table 3. HDL-c was higher in RA patients than in controls, with the differences being significant in pre- and postmenopausal women. All RA patient groups had significantly lower apo B levels and apo B/apo A-I ratios compared

Table 2. Serum lipid, lipoprotein (Lp), and apolipoprotein (Apo) values.

	Male	Premenopausal Female	Postmenopausal Female	p
Total cholesterol, mmol/l	5.59 (0.91)	5.16 (1.03)	5.70 (0.84)	0.063
Triglyceride, mmol/l*	1.43 (1.57)[a]	1.04 (1.53)[b]	1.15 (1.54)[a,b]	0.033
LDL-c, mmol/l	3.75 (0.89)[a]	3.00 (0.85)[b]	3.45 (0.75)[a,b]	0.010
VLDL-c, mmol/l	0.42 (0.29)	0.29 (0.24)	0.31 (0.24)	0.133
HDL-c, mmol/l	1.40 (0.45)[a]	1.86 (0.59)[b]	1.93 (0.42)[b]	< 0.001
Apo A-I, g/l	1.41 (0.22)[a]	1.64 (0.45)[b]	1.72 (0.26)[b]	< 0.001
Apo B, g/l	1.07 (0.25)[a]	0.84 (0.15)[b]	0.92 (0.19)[b]	< 0.001
Lp(a), g/l*	0.32 (3.11)	0.26 (2.58)	0.30 (2.84)	0.796
TC/HDL-c ratio	4.34 (1.43)[a]	3.00 (1.07)[b]	3.09 (0.83)[a,b]	< 0.001
LDL-c/HDL-c ratio	2.96 (1.19)[a]	1.81 (0.95)[b]	1.90 (0.69)[a,b]	< 0.001
Apo B/Apo A-I ratio	0.79 (0.25)[a]	0.55 (0.19)[b]	0.55 (0.16)[a,b]	< 0.001

Data are expressed as mean (SD). [a,b] Two means with different superindex express statistically significant differences ($p < 0.05$ by Bonferroni's contrast). * TG and Lp(a) values analyzed as logarithm and expressed as antilogarithm. LDL-c: low density lipoprotein cholesterol; VLDL-c: very low density lipoprotein cholesterol; HDL-c: high density lipoprotein cholesterol; TC: total cholesterol.

Table 3. Mean serum lipid and lipoprotein concentrations in RA patients and DRECE study subjects.

	Male			Premenopausal Female			Postmenopausal Female		
	RA, n = 25	DRECE*, n = 1008	p	RA, n = 19	DRECE*, n = 641	p	RA, n = 78	DRECE*, n = 402	p
BMI, kg/m^2	26	27	0.092	25	26	0.092	29	29	0.279
TC, mmol/l	5.59	5.59	0.966	5.16	5.10	0.789	5.70	5.99	0.003
TG, mmol/l**	1.44	1.49	0.735	1.04	0.93	0.305	1.16	1.17	0.902
HDL-c, mmol/l	1.40	1.29	0.236	1.86	1.52	0.023	1.93	1.56	< 0.001
LDL-c, mmol/l	3.75	3.58	0.358	3.00	3.12	0.568	3.45	3.83	< 0.001
Apo A-I, g/l	1.41	1.48	0.093	1.64	1.59	0.666	1.72	1.69	0.244
Apo B, g/l	1.07	1.36	< 0.001	0.84	1.08	< 0.001	0.92	1.33	< 0.001
LP(a), g/l**	0.32	0.06	< 0.001	0.26	0.07	< 0.001	0.30	0.07	< 0.001
TC/HDL ratio	4.34	4.74	0.220	3.00	3.55	0.023	3.09	4.01	< 0.001
LDL/HDL ratio	2.96	2.98	0.964	1.81	2.20	0.053	1.90	2.59	< 0.001
Apo B/Apo A-I ratio	0.79	0.95	0.013	0.55	0.71	0.002	0.55	0.81	< 0.001

* Control group selected from a population-based study[18]. Lp(a) was evaluated in a subgroup of subjects from this study, DRECE II (n = 91 males and 18 and 32 pre- and postmenopausal females)[19]. ** TG and Lp(a) values analyzed as logarithm and expressed as antilogarithm. For definitions see Table 2.

with controls, and postmenopausal RA women also had significantly lower LDL-c and TC levels than their respective controls. Serum apo A-I and TG levels did not differ significantly between RA patients and controls. Women RA patients had lower TC/HDL and LDL/HDL ratios than their respective controls, whereas no differences in these ratios were seen between male RA patients and their controls. Control subjects had significantly lower Lp(a) values than all RA patients.

The association of disease activity and antirheumatic therapy (use of glucocorticoid or DMARD or TNF-α blocker) with lipid measures was analyzed. Statistically significant differences were found in HDL-c concentrations among patients taking glucocorticoids and those not taking glucocorticoids and controls, after adjustment for sex and age (1.75, 1.42, and 1.41 mmol/l, respectively; $p < 0.001$). No statistically significant differences were found in relation to DMARD use or TNF-α blocker use, after adjustment for sex, age, and glucocorticoid use (data not shown). A slight negative correlation was found between HDL-c and disease activity (evaluated with DAS28), after adjustment for sex, age, and glucocorticoid use ($r = 0.237$, $p = 0.013$). No relationship was found between Lp(a) values and disease activity and antirheumatic therapy (glucocorticoids or DMARD or TNF-α blocker use).

DISCUSSION

In this study, patients with established RA taking disease-modifying agents and low-dose glucocorticoid therapy were found to have high HDL-c and low apo B concentrations and low apo B/apo A-I ratios, a lipid profile considered to be protective against cardiovascular disease[21,22]. Never-

theless, these patients had high concentrations of serum LP(a), a lipoprotein with atherogenic and thrombogenic properties[23].

Although lipid metabolism in RA has received only modest attention, most studies suggested that, compared with patients with inactive disease, noninflammatory arthritis, or normal controls, patients with active RA have adverse lipid profiles, characterized principally by lower HDL-c and apo A-I levels[9]. In those studies, an inverse correlation between lipid values and the acute-phase response[11] and an improvement in lipid profile after immuno-intervention were observed[10]. In the same way, we found a slight negative correlation between HDL-c and disease activity. However, it must to be noted that almost all our patients were taking disease-modifying and/or glucocorticoid therapy and these therapies may be related to the higher HDL-c levels we observed. We previously reported that low doses of glucocorticoids could have an overall favorable effect on lipid metabolism, consisting of an increase in HDL-c, with no increase in the cholesterol of atherogenic lipoproteins[24,25]. Hence, we believe that the high HDL-c concentrations observed in this group of RA patients taking antirheumatic drugs could be explained by the effect of the low-dose glucocorticoids normally used in patients with RA.

It has been observed that TNF-α blockers may increase HDL-c levels[26]. A small percentage of patients in our study were treated with these agents; however, when HDL-c levels in the group of RA patients not on TNF-α-blocker therapy were compared with those of controls, the differences between them remained unchanged.

RA patients had significantly lower apo B levels and apo B/apo A-I ratios, compared with controls, a situation that protects against atherosclerosis. Apo B is the predominant protein component of LDL and the main determinant of the atherogenicity of these particles. Moreover, the excess of apo B has been related to the atherogenic lipoprotein phenotype, a lipid disorder in which small, dense LDL particles predominate over the larger, buoyant, normal LDL particles[27]. In this respect, Hurt-Camejo, *et al* reported higher levels of small, dense LDL particles in RA patients compared with controls[28]. Several factors may be implicated in the lower apo B levels of these patients, mainly disease activity or chronic inflammation. Inflammation is related to a decreased hepatic lipoprotein production and also to increased catabolism[29]. In humans, inflammation lowers serum cholesterol and this decrease is accompanied by a drop in serum apo B levels. The mechanism by which infection/inflammation lowers cholesterol levels has not been studied in depth and many pathophysiological factors may be involved. In this respect, it has been observed that interleukin 6 both inhibits cholesterol synthesis and decreases cholesterol and apo B secretion, and interferon-ß also decreases apo B synthesis[30].

Our observations concur with the results of studies in which an increase in cardiovascular risk not fully explained by conventional risk factors was reported in patients with RA[6,31,32]. According to this concept, treated RA patients from this study did not show conventional cardiovascular lipid risk factors such as high serum cholesterol, LDL-c, triglycerides, or apo B/apo A-I ratios, or low HDL-c. However, we have seen a high prevalence of hyperlipoproteinemia(a) in patients with RA. Indeed, if 0.3 g/l is considered the upper reference value for Lp(a), more than 50% of patients in this study had this disorder. A similar proportion of hyperlipoproteinemia(a), in a group of RA patients not treated with glucocorticoids or disease-modifying agents, was reported by Dursunoglu, *et al*[11]. Lp(a) is a lipoprotein with atherogenic and prothrombotic properties that is considered a nonconventional cardiovascular risk factor[23,33]. Lp(a) acts as an acute-phase reactant, and some studies have found increased Lp(a) concentrations in RA patients[11,34]. Although it has been reported that conventional lipid profile can be improved by effectively treating RA without using a lipid-lowering agent[10], the effects of RA treatment on metabolism of Lp(a) remain unclear. Indeed, we previously described that low doses of glucocorticoids could have an overall favorable effect on lipid metabolism, consisting of an increase in HDL-c, with no change in the cholesterol of atherogenic lipoproteins[24,25]. However, we found no differences in serum Lp(a) levels between RA patients who were and those who were not undergoing low-dose glucocorticoid therapy. Conversely, higher gluocorticoid doses may decrease Lp(a) concentrations, as reported by Aoki, *et al* in patients with other rheumatic diseases such as systemic lupus erythematosus[35]. Thus, we suggest that effective treatment of RA with low doses of glucocorticoids and/or with disease-modifying agents has no influence on Lp(a) concentrations. This may be explained in part because Lp(a) levels are controlled on a strong genetic basis[36].

It must to be noted that we analyzed lipid metabolism in men and premenopausal and postmenopausal women separately to avoid the marked differences in serum lipid and lipoprotein levels related to sex and hormonal status[37], an issue that was not taken into account in other studies.

We conclude that serum levels of conventional cardiovascular lipid risk factors in patients with RA who are undergoing antirheumatic therapy may be considered as protective against cardiovascular disease. However, this may be counteracted by the high prevalence of hyperlipoproteinemia(a) observed in these patients.

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