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Lipoprotein Subclasses Determined by Nuclear Magnetic Resonance Spectroscopy and Coronary Atherosclerosis in Patients with Rheumatoid Arthritis

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Abstract

Objective—Patients with rheumatoid arthritis (RA) are at increased risk of atherosclerosis, but routine lipid measurements differ little from those of people without RA. We examined the hypothesis that lipid subclasses determined by nuclear magnetic resonance spectroscopy (NMR) differed in patients with RA compared to controls and are associated with disease activity and the presence of coronary-artery atherosclerosis.

Methods—We measured lipoprotein subclasses by NMR in 139 patients with RA and 75 control subjects. Lipoproteins were classified as large LDL (diameter range: 21.2–27.0 nm), small LDL (18.0–21.2 nm), large HDL (8.2–13.0 nm), small HDL (7.3–8.2 nm), and total VLDL (≥ 27 nm). All subjects underwent an interview and physical examination; disease activity was quantified by the 28 joint disease activity score (DAS28) and coronary artery calcification (CAC) was measured with electron beam computed tomography.

Results—Concentrations of small HDL particles were lower in patients with RA (18.2 ± 5.4 nmol/L) than controls (20.0 ± 4.4 nmol/L), $P=0.003$. In patients with RA, small HDL concentrations were inversely associated with DAS28 ($\rho=-0.18$, $P=0.04$) and CRP ($\rho=-0.25$, $P=0.004$). Concentrations of small HDL were lower in patients with coronary calcification (17.4 ± 4.8 nmol/L) than in those without (19.0 ± 5.8 nmol/L), $P=0.03$. This relationship remained significant after adjustment for the Framingham risk score and DAS28 ($P=0.025$). Concentrations of small LDL particles were lower in patients with RA (1390 ± 722 nmol/L) than in control subjects (1518 ± 654 nmol/L), $P=0.05$, but did not correlate with DAS28 or CAC.

Conclusions—Low concentrations of small HDL particles may contribute to increased coronary atherosclerosis in patients with RA.

Dyslipidemia, as determined by conventional measurements of total cholesterol, triglycerides and HDL and LDL cholesterol, is a widely-recognized cardiovascular risk factor in the general population.(1;2) Because cardiovascular risk is increased in patients with rheumatoid arthritis (RA), substantial interest has been focused on the role of abnormal lipid concentrations. Concentrations of low density lipoprotein (LDL) cholesterol are

generally not elevated in RA,(3) but in some studies high density lipoprotein (HDL) cholesterol concentrations are decreased,(1) even before RA becomes clinically apparent.(2) Nevertheless, conventional HDL and LDL cholesterol concentrations have limited capacity to predict cardiovascular risk in RA(3) and, as we have previously shown, are not associated with coronary artery atherosclerosis in these patients.(4)

Recent evidence suggests that concentrations of specific lipid subfractions, as determined by NMR, are important in the initiation and progression of atherosclerosis,(5) and measurement of these subfractions may improve the prediction of coronary risk.(6) Individuals with similar conventional lipid profiles could have significant differences in the distribution of specific VLDL, LDL, and HDL lipoprotein subfractions, possibly resulting in differences in cardiovascular risk.(6;7) The mechanisms underlying individual differences in lipid subfraction concentrations and size are not clear, but inflammation is one factor that can modify lipid subfractions and result in a more atherogenic profile.(8)

We examined the hypothesis that lipid subclasses differed in patients with RA compared to control subjects and that these differences were associated with disease activity and with the presence of coronary artery atherosclerosis.

Methods

Patients

The subjects studied are part of a cohort participating in ongoing studies to characterize the relationship between RA and atherosclerosis.(9) One-hundred and thirty-nine patients who met the classification criteria for RA,(10) and 75 control subjects without any inflammatory disease, were included in this study. All subjects were older than 18 years of age and were not taking lipid lowering agents.

As previously described,(9;11;12) patients were recruited from clinical RA cohorts, an early RA registry, local rheumatologists, and by advertisements. Control subjects did not have RA or inflammatory arthritis and were recruited from patients' acquaintances, by advertisement, and from a database of volunteers maintained by the Vanderbilt General Clinical Research Center. Patients with RA and control subjects were frequency-matched for age, sex and race. The study was approved by the Institutional Review Board of Vanderbilt University Hospital. All subjects gave written informed consent.

Clinical assessment

Patient assessment included a structured interview, self-report questionnaires, physical examination, laboratory tests, and electron-beam computed tomography (CT), and in patients, review of medical records. Height and weight were measured and body mass index calculated. Blood pressure was determined as the average of two measurements obtained 5 minutes apart after subjects had rested for at least 10 minutes. Hypertension was defined as current use of anti-hypertensive agents, or a systolic blood pressure of 140 mmHg or higher, or a diastolic pressure of 90 mmHg or higher. In patients, disease activity was measured using the Disease Activity Score based on 28 joints (DAS28).(13) Functional capacity was measured using the modified health assessment questionnaire (MHAQ). (14)

Lipoprotein subclasses

After an overnight fasting period, blood was drawn. Plasma samples, stored at -70°C, were analyzed by commercial proton NMR spectroscopy assay at Liposcience Inc. (Raleigh, NC). Quantitation is based on the spectral signals emitted by the amplitudes of the characteristic lipid methyl group NMR signals that they emit.(15) Concentrations of large

LDL (diameter range: 21.2-27.0 nm), small LDL (18.0-21.2 nm), large HDL (8.2-13.0 nm), small HDL (7.3-8.2 nm), and total VLDL (≥ 27 nm) and mean particle size (in nanometer diameter units) were measured.

Coronary artery calcification

All subjects underwent imaging with an Imatron C-150 scanner (Imatron, South San Francisco, CA), in order to derive an Agatston score as described previously.⁽¹⁶⁾ This is a non-invasive imaging technique to detect coronary-artery calcification as a measure of coronary atherosclerosis burden. An investigator (PR), blinded to any clinical information, read all the scans and provided an overall calcium score for each subject based on the sum of the scores of each individual coronary artery.

Other laboratory tests

Total cholesterol, HDL and LDL cholesterol and triglycerides were measured in all subjects. Insulin concentrations were measured using multiplex ELISA (Lincoplex, Millipore, St. Louis, MO) and the homeostasis model assessment (HOMA) index, defined as the fasting glucose [mmol/L] x fasting insulin (uU/ml)/22.5, was calculated to quantify insulin sensitivity. C-reactive protein (CRP) was measured in patients with RA.

Statistical methods

Demographic characteristics are presented as mean and standard deviation (SD) for continuous variables, and as frequency and percent for categorical variables. The differences among cases and controls were determined by Wilcoxon rank sum or Fisher's exact test, as appropriate. Analysis was performed in two steps: first, lipid subparticle concentrations and size were compared by Wilcoxon rank sum test in patients with RA and control subjects, and in RA patients with and without coronary artery calcification. Spearman correlations were calculated to examine the association between lipoprotein subfractions and metabolic and inflammatory variables. Second, in patients with RA, a multivariate logistic regression was modeled to examine the association between small HDL concentrations and coronary calcification after adjustment for the Framingham risk score and disease activity. All analyses used a two-sided significance level of 5 percent and were performed with STATA 10.0 (STATA Corp, Texas).

Results

Patients and control subjects

Patients with RA and control subjects were of similar age (54 ± 12 years, and 52 ± 12 years, respectively, $P=0.23$) and sex (70.5 and 65.0 percent female, respectively, $P=0.44$). There were no significant differences between the groups in cumulative pack-years of smoking, diabetes, BMI, total, HDL or LDL cholesterol or triglyceride concentrations. More patients with RA were current smokers (23% compared to 11%), and there was a trend towards higher systolic and diastolic blood pressure in patients with RA (Table 1). The mean disease duration of RA was 10.3 ± 11.1 years and the mean DAS28 was 3.7 ± 1.6 . There were 77 (55.4%) patients taking corticosteroids, 98 (71%) taking methotrexate, and 28 (20%) taking anti-TNF drugs. The median (IQR) Agatston score for patients with a calcium score greater than zero was 129 (32-425).

Lipoprotein subclasses in patients with RA and control subjects

Table 2 and Figure 1 show the concentrations of lipoprotein subclasses among patients with RA and control subjects. Concentrations of small HDL particles were significantly lower in patients with RA (18.2 ± 5.4 nmol/L) than control subjects (20.0 ± 4.4 nmol/L), $P=0.003$.

Concentrations of small LDL particles were lower in patients with RA (1390 ± 722 nmol/L) than in control subjects (1518 ± 654 nmol/L), $P=0.05$. There were no other significant differences in lipid subclasses among patients with RA and control subjects.

Association between NMR lipoprotein subclasses and metabolic variables and markers of inflammation

Table 3 shows the associations between NMR lipoprotein subclass and the traditional lipid profile with body mass index, HOMA index, CRP, disease activity and coronary calcium score in patients with RA. Small LDL concentrations were positively correlated with BMI and insulin resistance, whereas large LDL concentrations were negatively correlated with these variables. Neither small nor large LDL concentrations were significantly correlated with DAS28, MHAQ, or CRP. Small HDL concentrations were inversely associated with DAS28 ($\rho=-0.18$, $P=0.04$), MHAQ ($\rho=-0.18$, $P=0.04$) and CRP ($\rho=-0.25$, $P=0.004$).

Association between NMR lipoprotein measurements and coronary calcium in patients with RA

Small HDL concentrations were the only lipid subfraction correlated with the coronary calcium score and there was a weak inverse relationship ($\rho=-0.18$, $P=0.03$) (Table 3). In patients with RA who had coronary calcification, concentrations of small HDL (17.4 ± 4.8 nmol/L) were significantly lower than in those without coronary calcification (19.0 ± 5.8 nmol/L) ($P=0.03$) (Table 4, Figure 2). This association remained significant after adjustment for Framingham risk score and disease activity ($P=0.025$). A sensitivity analysis that excluded individuals with diabetes yielded results that were similar to those of the main analysis.

Patients with coronary calcification also tended to have lower HDL cholesterol concentrations (47 ± 14 mg/dL) than those without calcification (51 ± 26 mg/dL) ($P=0.07$). There were no other statistically significant differences in lipid subclasses among RA patients with and without coronary calcification.

Lipid concentrations measured by conventional methods were not associated with coronary calcium score (Table 3), nor was the total cholesterol /HDL ratio ($\rho=0.06$, $P=0.48$).

Association between NMR lipoprotein measurements and disease specific treatment in patients with RA

Patients with RA taking prednisone had higher concentrations of large LDL (470 ± 180 nmol/L vs. 400 ± 159 nmol/L, $p=0.02$) and lower concentration of small LDL (1225 ± 640 nmol/L vs. 1607 ± 797 nmol/L, $p=0.005$) than those who were not. Small (17.8 ± 5.5 vs. 18.9 ± 5.1 nmol/L, $p=0.22$) and large HDL (11.4 ± 5.1 nmol/L vs. 9.8 ± 4.2 nmol/L, $p=0.08$) concentrations did not differ significantly among patients taking or not taking prednisone. However, no significant differences in lipoprotein subclasses were found among patients receiving anti-TNF therapy, conventional DMARDs, and both therapies in combination (all $p>0.40$).

Discussion

This study shows that patients with RA have lower concentrations of small HDL cholesterol, and to the best of our knowledge is the first to suggest that in these patients, lower concentrations of small HDL cholesterol are associated with increased risk of atherosclerosis as measured by coronary calcification.

Clinical screening for traditional cardiovascular risk includes measurement of total cholesterol, triglycerides and HDL cholesterol.(17) In the general population coronary artery disease risk is associated with both high concentrations of LDL and low concentrations of HDL cholesterol. However, concentrations of LDL cholesterol generally have not been found to be elevated in RA.(18) In our study, LDL concentrations were marginally lower in patients with RA than controls whereas HDL cholesterol concentrations did not differ. Some have reported lower HDL cholesterol concentrations in RA; for example, a recent study comparing patients with and without RA in a US national sample aged 60 years or older found that HDL cholesterol was approximately 2.5 mg/dL lower in patients with RA meeting 3 or more ACR criteria, and 8.8 mg/dL lower in those meeting 4 or more criteria. (19) However, despite minor differences in HDL cholesterol reported, changes in the traditional cholesterol profile does not account for the increased atherosclerosis in patients with RA.(9)

Recent evidence suggests that the significant variation in cardiovascular risk observed in individuals with similar lipid profiles by conventional testing may be explained in part by variations in the distribution of lipid subclass concentrations.(6;7) Each individual lipoprotein class is comprised of particles of different diameter, density, and composition. The concentration of these subparticle fractions is associated with different cardiovascular risk. Higher concentrations of small LDL have been associated consistently with increased risk of atherosclerosis and coronary heart disease in many studies,(20) but less information is available regarding the clinical significance of HDL particle size. Studies have yielded conflicting results with higher concentrations of small HDL associated with both increased and decreased risk of coronary heart disease. (21;22)

Our results, demonstrating differences in LDL and HDL cholesterol subclasses in RA, are partially concordant with a previously reported study in patients with RA. In a cross-sectional study, Hurt-Camejo and colleagues (23) found that patients with RA (n=31) and controls (n= 28) had similar concentrations of triglycerides and total and HDL cholesterol, whereas concentrations of small dense LDL were higher, and small HDL lower, in patients with RA. Also, Rizzo et al,(24) reported increased concentrations of small dense LDL in 25 patients with untreated RA but did not measure HDL subclasses. In contrast, we found that concentrations of small LDL tended to be lower in patients with RA compared to controls. It is difficult to explain the lower concentration of small LDL in our patients with RA. They had relatively well-controlled RA with a median DAS28 score of 3.7 ± 1.6 whereas patients in the studies of both Hurt-Camejo (23) (mean ESR 65 mm/hour, mean number of swollen joints =13) and Rizzo,(24) (average DAS28 score 6.2) had more active disease. Nevertheless, one would expect that the concentration of small LDL in patients with well-controlled RA would be at least equivalent to that of controls. However, the effects of prednisone on lipoprotein subclasses are unclear; we found that current use of prednisone was associated with lower concentrations of small LDL. Both our study, and that of Hurt-Camejo (23), found that concentrations of small HDL cholesterol were lower in patients with RA than controls. Our study extends these observations and suggests that HDL particle size may be a more informative marker for atherosclerosis than traditional lipids in RA.

Several possible mechanisms may explain the association of low concentrations of small, dense HDL with increased atherosclerosis. First, since small HDL is a potent antioxidant, then low levels might inadequately prevent oxidation of LDL and thus promote atherogenesis.(25) Second, the inverse association between small HDL concentrations and markers of active inflammation such as CRP and DAS28 suggests that this subfraction may link inflammation and vascular disease in patients with RA. A potential mechanism for this could be serum amyloid A, which is increased by inflammation, and impairs cellular cholesterol efflux to small HDL. (26) Third, small HDL may be the major subfraction

mediating the anti-inflammatory and antioxidant effects of HDL.(26) HDL is usually anti-inflammatory, but can become pro-inflammatory under certain circumstances. In support of this idea, Mc Mahon et al. reported that patients with RA have higher concentrations of pro-inflammatory HDL than control subjects.(27) It is thus possible that a contraction of the pool of small HDL signals a switch to a pro-inflammatory phenotype. However, possible relationships between pro-inflammatory HDL and particular lipoprotein subfractions remains poorly characterized. Fourth, complement regulatory proteins, protease inhibitors, and acute phase response proteins have been identified in HDL, suggesting common pathways between this lipoprotein, inflammation, and the innate immune system. (28)

Some limitations of this study should be considered. First, we used samples that were frozen at -70°C for a period ranging between 6 and 36 months. However, previous studies showed stable concentrations of lipoprotein particles over 6 years under the same conditions.(6) Second, although some significant associations were seen, differences in the lipid profiles between patients and controls were small. Further, the significant differences among patients with and without coronary calcification were also small. Thus, the findings provide clues for further research rather than an explanation for the increased cardiovascular morbidity and mortality in RA. Third, this was a cross-sectional study and thus, the temporal sequence of the events is unknown. Fourth, hyperglycemia and drugs to control diabetes could influence the HDL size. However, a sensitivity analysis that excluded individuals with diabetes yielded results that were similar to those of the main analysis. Fifth, given the number of different regimens of anti-inflammatory and disease modifying drugs used by patients, the individual effect of these on lipid profiles could not be examined in this study. Finally, NMR lipid analysis does not provide information about the function of lipoproteins.

In conclusion, low concentrations of small HDL particles may contribute to increased coronary atherosclerosis in patients with RA.

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Figure 1.
Small HDL cholesterol concentrations in patients with RA and control subjects
Error bars represent mean and SD; P=0.003

Figure 2.
Small HDL cholesterol concentrations in RA patients with (+) and without (-) coronary artery calcification
Error bars represent mean and SD; P=0.03
CAC coronary artery calcification

Table 1

Clinical characteristics of 139 patients with RA and 75 controls

	RA (n=139)	Control subjects (n=75)	P-value
General characteristics			
Age (years)	54±12	52±12	0.23
Female (%)	98 (70.5)	49 (65)	0.44
Caucasian (%)	122 (87.8)	63 (84.0)	0.23
Traditional cardiovascular risk factors			
Systolic blood pressure (mm Hg)	133±20	128±17	0.05
Diastolic blood pressure (mm Hg)	75±11	72±9	0.07
Body mass index (kg/m ²)	28.7±6.1	28.1±5.4	0.54
Cumulative smoking (Pack-years)	12.9±22.0	10.9±23.3	0.29
Diabetes (%)	11 (7.9%)	3 (4%)	0.39
Traditional Lipid profile			
Total cholesterol (mg/dl)	188±40	192±34	0.31
High-density lipoprotein (mg/dl)	49±21	47±13	0.86
Low-density lipoprotein (mg/dl)	114±33	122±30	0.06
Triglycerides (mg/dl)	135±183	115±62	0.37
Glucose (mg/dl)	90±16	93±38	0.69

Data are presented as n (%) or mean ± SD

Table 2

NMR lipoprotein particle concentration and size in patients with RA and control subjects

	RA (n=139)	Control subjects (n=75)	P-value
LDL particles			
Large LDL particles (nmol/L)	442±175	397±157	0.10
Small LDL particles (nmol/L)	1390±722	1518±654	0.05
LDL size (nm)	21.0±0.7	20.8±0.7	0.10
HDL particles			
Large HDL particles (μmol/L)	10.7±4.8	10.7±5.3	0.88
Small HDL particles (μmol/L)	18.2±5.4	20.0±4.4	0.003
HDL size (nm)	9.1±0.5	9.0±0.4	0.11
VLDL particles			
Total VLDL (nmol/L)	65.7±38.1	63.4±25.9	0.86
VLDL size (nm)	50.4±8.9	49.2±6.9	0.58

Data are presented as mean ± SD

Spearman correlation analyses between NMR lipoprotein measurements and metabolic and clinical variables and coronary artery calcification in patients with RA

Table 3

	BMI	HOMA &	CRP	DAS28	MHAQ	Coronary calcium
Lipid subfractions						
Large LDL	-0.22 [¶]	-0.19 [¶]	0.001	-0.05	-0.09	0.09
Small LDL	0.21 [¶]	0.26 [¶]	0.16	0.12	-0.06	0.02
Large HDL	-0.13	-0.15	0.01	0.04	0.15	-0.07
Small HDL	0.20 [¶]	-0.12	-0.25 [¶]	-0.18 [¶]	-0.18 [¶]	-0.18 [¶]
Traditional lipid profile						
Total cholesterol	-0.06	-0.01	-0.03	-0.06	-0.17 [¶]	0.08
LDL cholesterol	-0.003	0.07	0.01	-0.01	-0.21 [¶]	0.16
HDL cholesterol	-0.29 [‡]	-0.24 [¶]	-0.12	-0.16	0.02	-0.03
Triglycerides	0.12	0.06	0.01	0.07	-0.01	-0.05

& HOMA (homeostasis model assessment index)= fasting glucose [mmol/L] x fasting insulin (uU/ml)/22.5

[¶] P<0.05,

[‡] P<0.001

Table 4

NMR lipoprotein particle concentration and size in patients with RA with and without coronary calcification

	With coronary calcification (n=68)	Without coronary calcification (n=71)	P-value
LDL particles			
Large LDL particles (nmol/L)	458±185	426±164	0.44
Small LDL particles (nmol/L)	1411±712	1370±736	0.60
LDL size (nm)	21.0±0.7	21.0±0.7	0.85
HDL particles			
Large HDL particles (μmol/L)	10.7±4.9	10.7±4.7	0.71
Small HDL particles (μmol/L)	17.4±4.8	19.0±5.8	0.03
HDL size (nm)	9.1±0.5	9.1±0.5	0.67
VLDL particles			
Total VLDL (nmol/L)	63.2±31.2	68.1±43.7	0.63
VLDL size (nm)	50.8±9.4	50.1±8.4	0.92
Conventional lipid profile			
Total cholesterol (mg/dl)	190±38	186±43	0.31
High-density lipoprotein (mg/dl)	47±14	51±26	0.07
Low-density lipoprotein (mg/dl)	119±33	109±33	0.67
Triglycerides (mg/dl)	121±66	148±248	0.87
Total cholesterol/HDL ratio	4.2±1.3	4.1±1.6	0.40

Data are presented as mean ± SD