Research article

Cardiovascular risk in rheumatoid arthritis versus osteoarthritis: acute phase response related decreased insulin sensitivity and high-density lipoprotein cholesterol as well as clustering of metabolic syndrome features in rheumatoid arthritis

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Abstract

Rheumatoid arthritis (RA) patients experience a markedly increased frequency of cardiovascular disease. We evaluated cardiovascular risk profiles in 79 RA patients and in 39 age-matched and sex-matched osteoarthritis (OA) patients. Laboratory tests comprised ultrasensitive C-reactive protein (CRP) and fasting lipids. Insulin sensitivity (IS) was determined by the Quantitative Insulin Sensitivity Check Index (QUICKI) in all OA patients and in 39 of the RA patients. Ten RA patients were on glucocorticoids. RA patients exercised more frequently than OA patients ($\chi^2 = 3.9$, $P < 0.05$). Nine RA patients and one OA patient had diabetes ($\chi^2 = 4.5$, $P < 0.05$). The median CRP, the mean QUICKI and the mean high-density lipoprotein (HDL) cholesterol were 9 mg/l (range, 0.5–395 mg/l), 0.344 (95% confidence interval [CI], 0.332–0.355) and 1.40 mmol/l (95% CI, 1.30–1.49 mmol/l) in RA patients, respectively, as compared with 2.7 mg/l (range, 0.3–15.9 mg/l), 0.369 (95% CI, 0.356–0.383) and 1.68 mmol/l (95% CI, 1.50–1.85 mmol/l) in OA patients. Each of these differences was significant ($P < 0.05$). After controlling for the CRP, the QUICKI was similar in RA and OA patients ($P = 0.07$), while the differences in HDL cholesterol were attenuated but still significant ($P = 0.03$). The CRP correlated with IS, while IS was associated with high HDL cholesterol and low triglycerides in RA patients and not in OA patients. A high CRP (≥8 mg/l) was associated with hypertension ($\chi^2 = 7.4$, $P < 0.05$) in RA patients. RA glucocorticoid and nonglucocorticoid users did not differ in IS and lipids ($P > 0.05$). Excess cardiovascular risk in RA patients as compared with OA patients includes the presence of decreased IS and HDL cholesterol in RA patients. The latter is only partially attributable to the acute phase response. The CRP, IS, HDL cholesterol, triglycerides and hypertension are inter-related in RA patients, whereas none of these relationships were found in OA patients.

Keywords: cardiovascular risk, osteoarthritis, rheumatoid arthritis

Introduction

Rheumatoid arthritis (RA) patients experience a markedly increased frequency of cardiovascular disease (CVD) as compared with osteoarthritis (OA) patients and the general population [1–3]. The mortality rate from CVD is also increased in RA patients [2–4].

Adequate cardiovascular risk assessment comprises both determination of the low-density lipoprotein (LDL) cholesterol target in the individual patient as well as identification of the metabolic syndrome, a cluster of cardiovascular risk factors [5]. LDL cholesterol concentrations were found to be similar in inflammatory arthritis (IA) patients as compared with age-matched, sex-matched and race-matched controls [6].

Other workers, besides us, have previously documented the presence of insulin resistance in IA [6,7]. Insulin resistance is the key defect in the metabolic syndrome [8,9]. In patients with IA, insulin resistance is associated with obesity, inflammation, low HDL cholesterol and high triglycerides [8–10]. These relationships reflect pathophysiological interactions [8–10]. The use of the IS

CHD = coronary heart disease; CI = confidence interval; CRP = C-reactive protein; CVD = cardiovascular disease; DMARD = disease-modifying agent; HDL = high-density lipoprotein; IA = inflammatory arthritis; IS = insulin sensitivity; LDL = low-density lipoprotein; OA = osteoarthritis; QUICKI = Quantitative Insulin Sensitivity Check Index; RA = rheumatoid arthritis.

enhancing agents, namely thiazolidinediones, results in an increase in HDL cholesterol and in a reduction in triglycerides [9].

In the present study, we assessed cardiovascular risk profiles comprehensively in RA patients and in OA patients to test two hypotheses. First, that RA patients experience excess cardiovascular risk as compared with OA patients. Second, that cardiovascular risk factors in RA patients cluster as reported in the metabolic syndrome.

Materials and methods

Patients and investigations

Seventy-nine consecutive patients (66 women, 13 men; 69 Caucasian, 10 Asian), meeting the American College of Rheumatology criteria for classification of RA [11], were enrolled from our outpatient clinic. Their mean age and disease duration were 52 years (95% CI, 49–55 years) and 8.5 years (95% CI, 6.6–10.4 years), respectively. Thirty-nine age-matched (mean, 56 years; 95% CI, 52–59 years), sex-matched (33 women, 6 men) and race-matched (35 Caucasian, 4 Asian) consecutive OA patients [12], from our outpatient clinic, also participated.

Patients on lipid-lowering agents were excluded. None of the patients were following dietary advice at the time of the study. We recorded the medication taken at the time of the study, the quantities of alcohol and cigarettes consumed daily, the number of hours they exercised per week, and their family history for premature coronary heart disease (CHD) (in male and female first-degree relatives aged <55 and <65 years, respectively). Their body mass index (kg/m^2) was calculated, and the waist circumference (cm) measured at the umbilical level. Patients with a blood pressure $>140/90$ mmHg (measured on three occasions) in the sitting position or on antihypertensive agents were considered hypertensive.

Fasting blood samples (between 08:00 and 10:00 hours) were taken in all patients for determination of the ultrasensitive CRP (Tina' quant C-reactive protein latex particle enhanced immunoturbidimetric assay on a Hitachi 917; Roche Diagnostics, Rotkreuz, Switzerland), of total cholesterol, HDL cholesterol and triglycerides (Olympus Diagnostics, County Clare, Ireland), of LDL cholesterol (Randox Laboratories Ltd., Crumlin, UK), and of plasma glucose. Fasting serum insulin (Abbott, Chicago, IL, USA) was determined in all 39 OA patients and in the last 39 of the 79 consecutive RA patients (33 women, 6 men; 34 Caucasian, 5 Asian; median age, 49 years [95% CI, 45–53 years]). Laboratory testing was carried out using autoanalyzers, enzymatic methods (for lipids) and a microparticle enzyme immunoassay on the Axsym system (for insulin).

The intra-assay and interassay coefficients of variance for CRP and insulin were 0.43% and 1.34%, and 1.9% and 1.2%, respectively. The IS was estimated using the QUICKI using the formula: 1 / log insulin (uU/ml) × log glucose (mg/dl) [13]. The one patient who was using insulin was excluded from this part of the study. In accordance with our findings in a recent study on healthy volunteers investigated by the same laboratory [6], we used a threshold QUICKI value of 0.337 for identification of decreased IS.

Statistical analyses

Statistical analyses were performed by Student *t* tests for comparisons of means, linear regression analyses, chi-square tests and analyses of covariance, as appropriate. Clustering of the metabolic syndrome features was evaluated using the paradigm proposed by Timar *et al.* [8], Fonseca [9] and Nishimura and Murayama [10], in which decreased IS is associated with obesity, inflammation, low HDL cholesterol and high triglycerides.

The respective associations were evaluated by simple linear regression analyses (the dependent variable was the QUICKI) since significant colinearity between variables (e.g. HDL cholesterol correlated with triglycerides [$R^2 = 0.223$, $P = 0.002$], and CRP correlated with HDL cholesterol [$R^2 = -0.057$, $P = 0.034$]) precluded evaluation by multiple regression analysis.

Results were expressed as the mean (95% CI) except for prednisone doses, which were expressed as the median (range). Since the distribution of CRP was not normal, the respective results were also expressed as the median (range). The CRP concentrations in OA patients versus RA patients were compared using the Mann–Whitney U test.

Results

Medications taken by OA patients and by RA patients

Medications taken by OA patients and RA patients (all 79 RA patients, as well as the subgroup of 39 in whom the QUICKI was determined) are presented in Table 1. Many of the patients were seen for the first time at our clinic, thereby explaining why only 42 (53%) of the RA cases were on disease-modifying agents (DMARDs). Patients on DMARDs (data not shown) and/or glucocorticoids had similar ($P > 0.05$) QUICKI and lipid values as compared to those not on the respective agents (see later).

Cardiovascular risk factors that were similar in frequency or extent in OA patients and in RA patients

Cardiovascular risk factors that were similar in frequency or extent in OA patients and in RA patients are presented in Table 2. The subgroup of 39 RA patients in whom IS was determined was representative of all 79 RA patients. Apart from similar frequencies in alcohol usage and smoking in OA patients and RA patients, the number of units of alcohol taken per week and cigarettes smoked per

Table 1

Medications taken by osteoarthritis (OA) patients ($n = 39$), by all rheumatoid arthritis (RA) patients ($n = 79$) and by RA patients in whom insulin sensitivity was determined ($n = 39$)

Medication	OA ($n = 39$)	RA ($n = 79$)	RA ($n = 39$)
Antihypertensives	10 (26)	18 (23)	8 (21)
Estrogen	6 (15)	6 (8)	2 (5)
NSAID	14 (36)	33 (42)	17 (44)
Low efficacy opioids	3 (8)	5 (6)	2 (5)
Paracetamol	3 (8)	4 (5)	3 (8)
Thyroxine	2 (5)	2 (3)	0 (0)
Glucosamine	2 (5)	3 (4)	0 (0)
Omeprazole	1 (3)	0 (0)	0 (0)
DMARD	0 (0)	42 (53)*	19 (49)
Prednisone	0 (0)	10 (13)**	6 (15)
Amitryptiline	0 (0)	2 (3)	0 (0)
Zopiclone	0 (0)	3 (4)	0 (0)
Metformin	0 (0)	1 (1)	0 (0)
Gliclazide	0 (0)	3 (4)	2 (5)
Insulin	0 (0)	1 (1)	0 (0)
Fluoxetine	0 (0)	1 (1)	1 (3)
Clonazepam	0 (0)	3 (4)	0 (0)

Data presented as *n* (%). NSAID, nonsteroidal anti-inflammatory agents; DMARD, disease-modifying agents. * Agents were methotrexate ($n = 37$), chloroquine ($n = 17$), minocyclin ($n = 6$), sulphasalazine ($n = 4$), azathioprine ($n = 4$), and myocrysin ($n = 2$). ** Median dose was 5 mg daily (range, 3–20 mg).

Table 2

Cardiovascular risk factors that were similar ($P > 0.05$) in frequency or extent in osteoarthritis (OA) patients ($n = 39$), in all rheumatoid arthritis (RA) patients ($n = 79$) and in RA patients in whom insulin sensitivity was determined ($n = 39$)

Risk factor	OA ($n = 39$)	RA ($n = 79$)	RA ($n = 39$)
Smoking	10 (26)	18 (23)	12 (31)
Alcohol	20 (51)	25 (32)	13 (33)
Family history for CHD	10 (26)	29 (37)	20 (51)
Estrogen usage	6 (15)	6 (8)	2 (5)
Hypertension	23 (59)	39 (50)	20 (51)
Body mass index (kg/m^2)	26.4 (25.0–27.8)	26.9 (25.6–28.2)	25.3 (23.7–26.8)
Waist (cm)	91.6 (88.0–95.3)	90.5 (87.3–93.7)	93.5 (88.7–98.2)
Total cholesterol (mmol/l)	5.72 (5.34–6.10)	5.58 (5.33–5.84)	5.69 (5.35–6.03)
LDL cholesterol (mmol/l)	3.32 (3.10–3.55)	3.34 (3.00–3.69)	3.5 (3.2–3.8)
Triglycerides (mmol/l)	1.71 (1.25–1.96)	1.63 (1.40–1.86)	1.66 (1.28–2.05)

Data presented as *n* (%) or as mean (95% confidence interval). CHD, coronary heart disease; LDL, low-density lipoprotein.

Table 3

Cardiovascular risk factors that differed ($P < 0.05$) in frequency or extent between osteoarthritis (OA) patients ($n = 39$) as compared with all rheumatoid arthritis (RA) patients ($n = 79$) and RA patients in whom insulin sensitivity was determined ($n = 39$)

Risk factor	OA ($n = 39$)	RA ($n = 79$)	RA ($n = 39$)
Exercise[a]	13 (33)	42 (53)	18 (46)
Diabetes[a]	1 (3)	9 (11)	4 (10)
QUICKI[b]	0.369 (0.356–0.383)	N/A	0.344 (0.332–0.355)
HDL cholesterol (mmol/l)[b]	1.68 (1.50–1.85)	1.40 (1.30–1.49)	1.40 (1.30–1.50)
C-reactive protein (mg/l)[c]	2.7 (0.3–15.9)	9 (0.5–395)	10 (0.5–146)

QUICKI, Quantitative Insulin Sensitivity Check Index; HDL, high-density lipoprotein. [a]Data presented as *n* (%). [b]Data presented as mean (95% confidence interval). [c]Data presented as median (range).

day were not different between the two diseases ($P > 0.05$) (data not shown). The mean body mass index was in the overweight range in both diseases.

Cardiovascular risk factors that differed in frequency or extent between OA patients and RA patients

Cardiovascular risk factors that differed in frequency or extent between OA patients and RA patients are presented in Table 3. The subgroup of 39 RA patients in whom the QUICKI was determined was representative of all 79 RA patients. The number of hours exercised per week did not differ in OA exercising cases and RA exercising cases ($P > 0.05$).

The QUICKI, total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides were 0.349 (95% CI, 0.327–0.370), 4.89 mmol/l (95% CI, 4.09–5.68 mmol/l), 2.73 mmol/l (95% CI, 2.11–3.34 mmol/l), 1.52 mmol/l (95% CI, 1.16–1.88 mmol/l) and 1.26 mmol/l (95% CI, 0.95–1.57 mmol/l) in the glucocorticoid users, respectively, and were 0.343 (95% CI, 0.330–0.356), 5.63 mmol/l (95% CI, 5.37–5.90 mmol/l), 3.41 mmol/l (95% CI, 3.16–3.65 mmol/l), 1.37 mmol/l (95% CI, 1.26–1.48 mmol/l) and 1.68 mmol/l (95% CI, 1.43–1.94 mmol/l) in the nonglucocorticoid users. In RA patients, glucocorticoid and nonglucocorticoid users had similar IS and lipids ($P > 0.05$).

One RA patient had type 1 diabetes. The OA patient and two of the RA diabetic patients were not on medication for diabetes. The onset of diabetes had not been precipitated by the use of glucocorticoids in any of the patients, and at the time of the study none of the diabetic patients were taking glucocorticoids. The IS was below normal in 11 (28%) OA patients and in 16 (41%) RA patients ($\chi^2 = 2.04$, $P > 0.05$), and decreased HDL cholesterol concentrations were found in six (15%) OA patients and in 32 (40%) RA patients ($\chi^2 = 28.1$, $P < 0.001$), respectively.

IS and HDL cholesterol in OA patients versus RA patients after controlling for differences in CRP

As in our previous study [6], the acute phase response was associated with decreased IS ($R^2 = -0.147$, $P = 0.016$) and low HDL cholesterol ($R^2 = -0.057$, $P = 0.034$). After controlling for CRP, the QUICKI was no longer different ($P = 0.07$) but the HDL cholesterol remained lower ($P = 0.03$) in RA patients as compared with OA patients.

Relationships among waist circumference, CRP, QUICKI, HDL cholesterol and triglycerides in OA patients and RA patients

The relationships among waist circumference, CRP, QUICKI, HDL cholesterol and triglycerides in OA patients and RA patients are presented in Fig. 1. In OA patients, the waist circumference contributed to the variance of the QUICKI while the CRP did not. Also, the QUICKI was not significantly associated with HDL cholesterol and triglyceride concentrations in OA patients.

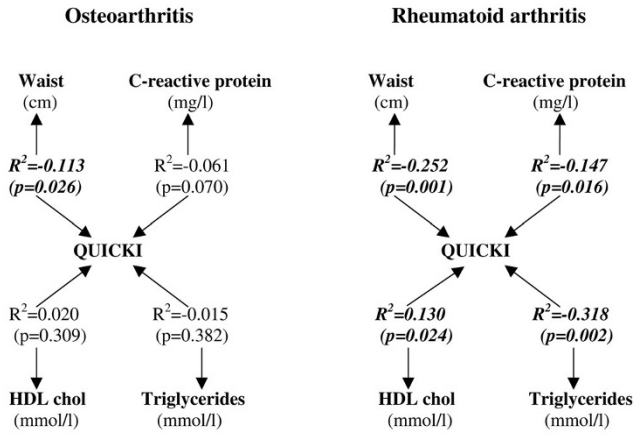
By contrast, in RA patients the CRP similarly contributed to the variance of IS, and the latter was associated with both HDL cholesterol and triglyceride concentrations. Also, 27 (59%) RA patients with a CRP ≥ 8 mg/l ($n = 46$) were hypertensive, as compared with only 10 (30%) RA patients with a CRP < 8 mg/l ($n = 33$). A high CRP was associated with the presence of hypertension ($\chi^2 = 7.4$, $P < 0.05$) in RA patients. The CRP was ≥ 8 mg/l in only three (8%) OA patients.

Discussion

A CHD prevalence rate of 49% in RA patients as compared with 27% in OA patients [1] and a fourfold increased incidence of cardiovascular events in RA patients as compared with the general population [2] were recently reported. Raised total cholesterol and other traditional cardiovascular risk factors did not account for the respective findings [2]. RA patients also experience a 1.3-fold to 2.4-fold increased mortality rate from CHD [4].

In the present study, cardiovascular risk assessment revealed that RA patients exercised more frequently, but they had diabetes more often and their IS and HDL cholesterol concentrations were lower, as compared with

Figure 1



Relationships among waist circumference, C-reactive protein, Quantitative Insulin Sensitivity Check Index (QUICKI), high-density lipoprotein cholesterol (HDL chol) and triglycerides in osteoarthritis patients ($n = 39$) and rheumatoid arthritis patients ($n = 39$). Significant associations are printed in bold italic.

OA patients. As expected, the CRP levels were also higher in RA patients as compared with OA patients. Inflammation, as reflected by the acute phase response, is implicated in CVD in its own right both in the general population [14] and in RA patients [15]. CRP may also directly contribute to atherosclerosis. CRP is localized in atheromatous lesions and stimulates macrophages to produce tissue factor, an important procoagulant found in atherosclerotic plaques [2]. In the present study, the CRP was also significantly associated with decreased IS and HDL cholesterol concentrations. Although elevated CRP levels could explain the difference in IS between RA patients and OA patients, they could only partially account for the low HDL cholesterol concentrations.

These findings confirm our previous study [6], suggest that RA may select for subjects with low HDL cholesterol, and suggest that RA and CVD may share a common predisposition as previously reported [6,16,17]. Further genetic linkage studies may be worthwhile to confirm whether HDL cholesterol concentrations are intrinsically low in RA patients.

Both determination of the LDL cholesterol target in the individual patient as well as identification of metabolic syndrome features, particularly comprising the presence of abdominal obesity, low HDL cholesterol, elevated triglycerides and plasma glucose, and hypertension, are recommended in cardiovascular risk assessment [5]. Insulin resistance constitutes an established pivotal pathogenetic mechanism in the metabolic syndrome [8–10,18]. Although OA is associated with insulin resistance [19] and dyslipidemia [19,20], both IS and HDL cholesterol

concentrations were still significantly lower in RA patients as compared with OA patients. Also, eight RA patients and one OA patient had type 2 diabetes. In a recent study, diabetes was identified in 38 out of 236 (16.1%) RA patients, as compared with 442 out of 4635 (9.5%) non-RA subjects ($P \leq 0.0001$) [2]. Also, type 2 diabetes is a late complication of the metabolic syndrome [8,9] and its occurrence in our patients was not related to the use of glucocorticoids. The high frequency of diabetes in the present RA cohort may not be a chance finding.

In view of the high prevalence of insulin resistance in IA [6], the pathogenetic role of insulin resistance in the metabolic syndrome and its relationship to the acute phase response in IA [6], we analyzed the relationships among abdominal obesity, CRP, IS, HDL cholesterol and triglycerides in both OA patients and RA patients. In OA patients, the waist circumference contributed to the variance in IS but no other associations could be identified. By contrast, in RA patients, all of the respective risk factors were interdependent. Also, a high CRP was associated with the presence of hypertension.

In the present study, we found inflammation and abdominal obesity to be associated with decreased IS in RA patients. Insulin resistance and the other metabolic syndrome features also relate to psychosocial stress and other environmental factors' related abnormalities in cortisol, sex steroid and growth hormone secretion [21]. The role of psychosocial stressors in decreased IS in RA patients requires further study.

The biochemical disturbances clustering in the metabolic syndrome may participate in the onset and persistence of IA [6]. With regard to cardiovascular risk, our findings suggest that identification of the metabolic syndrome may be particularly important in this condition. RA patients in a recent study were found to have high levels of small, dense LDL particles, and this was related to the acute phase response [22]. High circulating levels of small, dense LDL particles constitute another characteristic feature of the metabolic syndrome [5]. Furthermore, the acute phase response may contribute to atherosclerosis through endothelial activation and interaction with procoagulant factors [3,23]. The high prevalence of CVD in RA patients [1,2] also implicates that this condition should be considered a CHD equivalent when determining the LDL cholesterol target (i.e. the latter may be as low as 2.6 mmol/l) [5]. Indeed, mildly deranged LDL cholesterol concentrations, LDL/HDL ratios and triglyceride concentrations mediate the accelerated atherosclerosis in RA patients [3]. In 58 (73%) of our RA patients, the LDL cholesterol was >2.6 mmol/l.

A limitation of the present study, as applies to other reports on CVD in RA patients [2,3], is that most patients were on drug treatment. Only patients on lipid-lowering agents were excluded. However, excluding patients on drug treatment may have yielded results that do not represent the situation in the clinic. Also, patients on glucocorticoids and/or DMARDs experienced no differences in IS or lipid values as compared with those patients who were not on these agents. Of interest, in this regard, both glucocorticoids and DMARDs were shown to attenuate insulin resistance in IA, an effect that was attributed to acute phase response suppression [24].

Conclusion

Excess cardiovascular risk in RA patients includes the acute phase response and decreased IS and HDL cholesterol, while the respective risk factors are closely interlinked in this condition. How inflammation and other cardiovascular risk factors interact in the pathogenesis of enhanced atherosclerosis in RA patients requires further elucidation. In the meantime, our findings implicate the need for evaluating cardiovascular risk profiles comprehensively in these patients.

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