

# The Acute Phase Response Does Not Fully Predict the Presence of Insulin Resistance and Dyslipidemia in Inflammatory Arthritis

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**ABSTRACT. Objective.** Rheumatoid arthritis (RA) is associated with an increased mortality rate from cardiovascular disease. This may relate to insulin resistance and dyslipidemia, which were both reported to correlate with the acute phase response in RA. We investigated whether insulin resistance and dyslipidemia could be explained by the acute phase response as well as excess weight in inflammatory arthritis.

**Methods.** We investigated 87 patients, 38 with RA, 29 with spondyloarthritis, 20 with undifferentiated inflammatory arthritis. Thirty age, sex, and race matched healthy volunteers served as controls. Fasting blood samples were taken for determination of erythrocyte sedimentation rate (ESR), plasma glucose, serum insulin, and total cholesterol (chol), low density lipoprotein cholesterol (LDL-chol), high density lipoprotein cholesterol (HDL-chol), and triglycerides. Insulin resistance was estimated by the homeostasis model assessment for insulin resistance (HOMA) and the quantitative insulin sensitivity check index (QUICKI).

**Results.** In controls the mean (SD) HOMA ( $\mu\text{U}\cdot\text{mmol}/\text{ml}\cdot\text{l}$ ), QUICKI, body mass index (BMI,  $\text{kg}/\text{m}^2$ ), and ESR (mm/h) were 1.1 (0.5), 0.393 (0.048), 22.9 (2.8), and 13 (8) in patients; they were 1.9 (1.3), 0.357 (0.037), 26.5 (4.2), and 26 (18) in controls, respectively. Each of these differences was highly significant ( $p < 0.001$ ). HDL-chol concentrations were lower ( $p = 0.002$ ) and chol/HDL-chol ratios and triglyceride levels were higher ( $p < 0.001$  and  $p = 0.004$ , respectively) in patients compared to controls. A high ESR predicted insulin resistance and dyslipidemia, while a high BMI similarly predicted insulin resistance but not dyslipidemia. After controlling for ESR and BMI, insulin sensitivity was no longer different between patients and controls, while HDL-chol concentrations remained lower ( $p = 0.015$ ) and chol/HDL-chol ratios remained higher ( $p = 0.003$ ) in patients compared to controls.

**Conclusion.** Insulin resistance and dyslipidemia were highly prevalent in patients with inflammatory arthritis. The acute phase response and excess weight could fully explain the insulin resistance but only partially explain the dyslipidemia. These findings have important implications for the management of inflammatory arthritis. (J Rheumatol 2002;29:462–6)

## Key Indexing Terms:

INFLAMMATORY ARTHRITIS  
DYSLIPIDEMIA

INSULIN RESISTANCE  
ERYTHROCYTE SEDIMENTATION RATE

An increased mortality from cardiovascular disease (CVD) in rheumatoid arthritis (RA) has been reported by several investigators<sup>1-4</sup>. Recently, a prevalence of 49% of ischemic heart disease was reported in RA<sup>5</sup>. Potential risk factors

include the presence of insulin resistance<sup>6</sup> and dyslipidemia<sup>7</sup>. Svenson, *et al*<sup>6</sup> documented insulin resistance in RA, and this correlated with elevated serum C-reactive protein (CRP) levels. Treatment with disease modifying agents (DMARD) was followed by normalization of insulin sensitivity<sup>6</sup>. Subsequently, Park, *et al*<sup>7</sup> found elevated cholesterol (chol)/high density lipoprotein (HDL)-chol and apolipoprotein B/A1 ratios in RA, and CRP concentrations correlated inversely with apolipoprotein A1 and HDL-chol levels. The authors postulated that dyslipidemia induced by the acute phase response could explain the reported excess CVD mortality in RA<sup>7</sup>.

The acute phase response is indicative of disease activity in RA<sup>4</sup>. This condition is also associated with obesity<sup>8</sup> that could similarly contribute to insulin resistance<sup>9</sup> and dyslipidemia<sup>10</sup>.

We sought to confirm the presence of insulin resistance

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and dyslipidemia in RA, as well as in spondyloarthritis (SpA) and undifferentiated inflammatory arthritis (UIA). We investigated whether the acute phase response and excess weight could fully explain insulin resistance and dyslipidemia in inflammatory arthritis.

## MATERIALS AND METHODS

Eighty-seven consecutive nondiabetic patients who visited our clinic for the first time were enrolled. Their mean age (SD) was 49 (13.5) years (range 18–81). Eighty were Caucasian and 7 were Asian. Fifty-four were women, of which 26 had RA (FRA), 14 SpA (FSpA), and 14 UIA (FUIA). Of the 33 men, 12 had RA (MRA), 15 SpA (MSPA), and 6 UIA (MUIA). The mean (SD) disease duration was 4.8 (7.8) years. RA patients met the 1987 American Rheumatism Association criteria for RA<sup>11</sup> and SpA patients met the European Spondylarthropathy Study Group criteria<sup>12</sup> for SpA. UIA patients had swelling of at least 2 joint areas for a minimum of 6 weeks without meeting the criteria for either RA or SpA. Patients who had used glucocorticoids over the previous 2 months or were taking agents known to affect insulin sensitivity of lipid metabolism were excluded. Twenty-six patients were taking no medication. Agents taken were nonsteroidal anti-inflammatory agents (n = 51), low efficacy opioid agonists (n = 7), paracetamol (n = 6), methotrexate (n = 5), sulfasalazine (n = 4), misoprostol (n = 3), lansoprazole (n = 2), clonazepam (n = 2), mianserin (n = 2), alendronate (n = 1), and amitriptyline (n = 1). All patients had clinically active disease. The majority were referred to us by general practitioners, thereby explaining the low frequency of DMARD usage. Twenty-three (26%) patients smoked, 35 (45%) used alcohol, and 7 (13%) of the female patients were taking estrogen. The disease duration, family history of coronary artery disease at age < 65 years, and blood pressure were recorded and the body mass index (BMI) was calculated in each patient. Fasting blood samples (between 8:00 and 10:00 AM) were taken for determination of erythrocyte sedimentation rate (ESR), total chol, HDL-chol, triglycerides (Olympus Diagnostics, Co. Clare, Ireland), LDL-chol (Randox Laboratories Ltd., Grumlin, United Kingdom), plasma glucose, and serum insulin (Abbott, Chicago, IL, USA). Laboratory testing was done using autoanalyzers, enzymatic methods (for lipids), and microparticle enzyme immunoassay on the AxSYM system (for insulin). The intraassay and interassay coefficients of variance for insulin were 2.6% and 2.9%, respectively. Insulin resistance was estimated by the homeostasis model assessment for insulin resistance (HOMA)<sup>13</sup> using the formula = fasting serum insulin ( $\mu\text{U/ml}$ )  $\times$  fasting plasma glucose (mmol/l)/22.5; and the quantitative insulin sensitivity check index (QUICKI)<sup>14</sup> using the formula =  $1/\log$  insulin ( $\mu\text{U/ml}$ ) + log glucose (mg/dl).

Fasting serum lipids and insulin, plasma glucose, and ESR were determined in 30 healthy controls matched for age [mean (SD) 47.4 (13.9) yrs, range 19–83], sex (21 women, 9 men), and race (27 Caucasians, 3 Asians). Similarly to the patients, 7 (23%) controls smoked, 35 (40%) used alcohol, and 3 (14%) female controls were taking estrogen. The highest HOMA value and the lowest QUICKI value obtained in controls were 2.29  $\mu\text{U}\cdot\text{mmol/ml}\cdot\text{l}$  and 0.337, respectively. These levels were chosen as thresholds for insulin resistance.

Statistical analyses were conducted using the Statistical Package for Social Sciences (SPSS) program. The BMI, insulin, glucose, HOMA, QUICKI, ESR, and lipid values were compared between patients and controls using one-way analysis of variance (ANOVA). Associations between the presence of inflammatory arthritis and cardiovascular risk factors (dyslipidemia and family history of coronary artery disease at age < 65 yrs) were analyzed by chi-squared test. Multiple intergroup (FRA, FSpA, FUIA, MRA, MSPA, and MUIA) comparisons were by one-way ANOVA and the Bonferroni post hoc test. The dependencies of the HOMA, QUICKI, and dyslipidemia on the ESR and BMI were analyzed using simple linear regression analysis and analysis of covariance (ANCOVA). Results were expressed as mean (SD). A p value < 0.05 was considered significant.

## RESULTS

**Metabolic variables and ESR.** Comparisons between the metabolic variables and ESR in controls and patients are represented in Table 1. The BMI was above normal (> 25 kg/m<sup>2</sup>) in 57 (65%) patients and 8 (25%) controls. The fasting serum insulin and plasma glucose, HOMA, chol/HDL-chol ratio, and triglycerides were significantly higher, while the HDL-chol and QUICKI were significantly lower, in patients compared to controls, respectively. Sixteen (18%) patients were hypertensive.

Multiple comparisons of age, disease duration, metabolic variables, and ESR between the different patient groups revealed no significant differences apart from an older age in MRA than in FSpA (p = 0.042), a higher HDL-chol in FRA than in MUIA (p = 0.045), and a higher ESR in FRA than in FUIA (p = 0.043) and MUIA (p = 0.012).

The disease duration did not correlate with the BMI, HOMA, QUICKI, or any of the lipid values (p > 0.05).

**Associations between inflammatory arthritis and CVD risk factors.** According to the National Cholesterol Education Program (NCEP)<sup>15</sup>, 48 (55%) patients and 8 (22%) controls were dyslipidemic (p < 0.001). Of the 39 (45%) patients with normal total chol and LDL-chol according to the NCEP, 13 (15%) still had a total chol/HDL-chol > 5. Inflammatory arthritis was associated with dyslipidemia, including an increased total chol/HDL-chol ratio, and a positive family history for premature coronary artery disease, as shown in Table 2.

**ESR and BMI as predictors of inflammatory arthritis and dyslipidemia.** The contributions of the ESR and BMI to the variances of inflammatory arthritis and dyslipidemia, respectively, are represented in Table 3. ESR made a small but significant contribution to the variance of inflammatory arthritis, chol/HDL-chol ratio, and HDL-chol. BMI made a small but significant contribution to the variance of inflammatory arthritis, but did not predict lipid values. As shown

Table 1. Comparisons between metabolic variables and ESR in controls and patients with inflammatory arthritis [mean (sd)].

Variable	Controls, n = 30	Patients, n = 87	p
BMI, kg/m <sup>2</sup>	22.9 (2.8)	26.5 (4.2)	< 0.001
Insulin, $\mu\text{U/ml}$	5.2 (2.3)	8.2 (4.7)	0.002
Glucose, mmol/l	4.5 (0.4)	5.0 (0.9)	0.009
HOMA, $\mu\text{U}\cdot\text{mmol/ml}\cdot\text{l}$	1.1 (0.5)	1.9 (1.3)	< 0.001
QUICKI	0.393 (0.048)	0.357 (0.037)	< 0.001
Total chol, mmol/l	5.3 (1.1)	5.8 (1.1)	0.058
LDL-chol, mmol/l	3.2 (1.0)	3.6 (0.9)	0.051
HDL-chol, mmol/l	1.4 (0.3)	1.2 (0.3)	0.002
Total chol/HDL-chol	3.9 (0.8)	5.3 (1.6)	< 0.001
Triglycerides, mmol/l	1.1 (0.5)	1.7 (1.2)	0.004
ESR, mm/h	13 (8)	26 (18)	< 0.001

HOMA: homeostasis model assessment for insulin resistance; QUICKI: quantitative insulin sensitivity check index; chol: cholesterol.

Table 2. Cardiovascular disease risk factors in patients and controls.

CVD Risk Factor	Control, n = 30 (%)	Patients, n = 87 (%)	p
Dyslipidemia, NCEP	8 (22)	48 (55)	< 0.001
Total chol/HDL-chol > 5	2 (7)	39 (45)	< 0.001
Positive CAD family history	3 (10)	30 (34)	< 0.003

NCEP: National Cholesterol Education Program; chol: cholesterol; CAD: coronary artery disease.

Table 3. Contributions of ESR and BMI to the variances of insulin resistance and dyslipidemia, respectively.

Variable	ESR, mm/h		BMI, kg/m <sup>2</sup>	
	R <sup>2</sup>	p	R <sup>2</sup>	p
QUICKI	0.060	0.012	0.107	0.001
HOMA, $\mu$ U·mmol/ml <sup>-1</sup>	0.059	0.012	0.052	0.017
Chol/HDL-chol ratio	0.051	0.017	0.003	0.273
HDL-chol, mmol/l	0.032	0.048	0.001	0.319
Triglycerides, mmol/l	0.017	0.113	0.030	0.055

QUICKI: quantitative insulin sensitivity check index; HOMA: homeostasis model assessment for insulin resistance; chol: cholesterol.

in Table 4, after controlling for both the BMI and ESR, insulin sensitivity was similar in patients and controls, while the total chol/HDL-chol ratio remained higher and the HDL-chol remained lower in patients compared to controls.

## DISCUSSION

We confirmed that RA is associated with insulin resistance and dyslipidemia, as reported<sup>6,7</sup>. We found that these metabolic disturbances are present to a similar extent in other subsets of inflammatory arthritis, namely SpA and UIA. As in reports by Svenson, *et al*<sup>6</sup> and Park, *et al*<sup>7</sup>, the acute phase response predicted insulin resistance and dyslipidemia. However, the contributions of the ESR to the variances in insulin resistance and dyslipidemia were rather small, and ESR could not fully account for the respective metabolic

Table 4. Significances of differences in insulin resistance and lipids in patients compared to controls after controlling for ESR or BMI, and ESR and BMI.

Variable	Variable Controlled for		
	ESR, mm/h	BMI, kg/m <sup>2</sup>	ESR and BMI
	p	p	p
QUICKI	0.051	0.102	0.143
HOMA, $\mu$ U·mmol/ml <sup>-1</sup>	0.012	0.010	0.092
HDL-chol, mmol/l	0.007	0.003	0.015
Total chol/HDL-chol	0.001	< 0.001	0.003
Triglycerides, mmol/l	0.012	0.040	0.125

QUICKI: quantitative insulin sensitivity check index; HOMA: homeostasis model assessment for insulin resistance; chol: cholesterol.

disturbances. In patients with higher disease activity (mean ESR was 26 mm/h in the present cohort), the contribution of the acute phase response to inflammatory arthritis and dyslipidemia may be larger. Our aim was to investigate the respective relationships in the population with inflammatory arthritis at large. Therefore, rather than a selected group with high disease activity, we enrolled consecutive patients who visited our clinic for the first time, excluding only those who had diabetes or who were taking glucocorticoids, lipid lowering agents, or agents affecting insulin sensitivity.

A high prevalence of obesity has been reported in RA<sup>8</sup>, and obesity may even be a risk factor for the development of inflammatory arthritis<sup>16</sup>. The BMI was higher in our patients compared to controls and contributed to the variance of insulin resistance but not dyslipidemia. When we controlled for the BMI in addition to ESR, the differences in insulin resistance between patients and controls disappeared, but chol/HDL-chol ratios still remained higher and HDL concentrations still remained lower in the patients.

The high prevalence of insulin resistance (29%) and particularly dyslipidemia (70%) in our patients and the reported 60–80% excess CVD mortality in RA<sup>1-3</sup> stresses the need for considering these and other CVD risk factors in the management of patients with inflammatory arthritis. A similar approach is strongly recommended in lupus<sup>17</sup>, another rheumatic disorder associated with an up to 50-fold increased prevalence of CVD<sup>18</sup>. In a cohort study on 211 patients with RA followed for 17 to 21 years, a high last-registered ESR prior to CVD events, in addition to hypertension, high haptoglobin and age at disease onset, increased the risk for CVD<sup>4</sup>. The authors suggested a positive effect of disease activity-reducing treatment on CVD risk and survival<sup>4</sup>. The coincident beneficial effect of efficacious DMARD therapy on insulin resistance, in RA, is of interest in this context<sup>6</sup>. Also, in a recent 10 year followup study on 622 patients with RA, most of whom were treated with intensive DMARD therapy soon after disease onset, no excess CVD mortality was recorded<sup>19</sup>. However, the latter outcome was recently attributed to the respective study design, i.e., the enrolment of patients with shorter disease duration and milder disease<sup>20</sup>. Our results further suggest increased CVD risk in patients with inflammatory arthritis, even in the absence of excess weight or active disease.

Elevated CRP is now recognized as a useful predictor of CVD in the population at large<sup>21</sup>. The lower detection level of routine CRP testing (e.g., immunoturbidimetric assay on Olympus AU600, Olympus Diagnostics, may be too high for assessment of CVD risk<sup>21</sup>, particularly when overall disease activity is mild, as in our patient cohort. In 21 (24%) of our patients, the CRP concentrations were < 5 mg/l. Ultrasensitive CRP testing (e.g., Tina 'quant CRP latex particle enhanced immunoturbidimetric assay on Hitachi 917, Roche Diagnostics, Rotkreutz, Switzerland) was not

available to us at the time of study. The ESR has been shown to predict cardiovascular events<sup>4</sup> and dyslipidemia<sup>7</sup> in RA. In view of the above, we decided to use the ESR as an acute phase response marker, rather than CRP.

Our finding of an independent association between inflammatory arthritis and low HDL-cholesterol concentrations as well as high cholesterol/HDL-cholesterol ratios is in keeping with the paradigm that CVD and inflammatory arthritis may share similar predisposing factors<sup>22</sup>. Also, a family history of coronary artery disease<sup>15</sup>, which is another cardiovascular risk factor, was 3.4 times more common in patients with inflammatory arthritis compared to controls. This warrants confirmation in a prospective study. In a prospective study on 52,800 subjects, total cholesterol predicted rheumatoid factor (RF) positive RA among women and RF negative RA among men<sup>23</sup>. Total cholesterol and LDL-cholesterol were higher in our women but not men with inflammatory arthritis, compared to controls (results not shown). All except 3 (8%) of our RA patients (all women) were RF positive.

Insulin resistance, excess weight, high triglyceride and low HDL-cholesterol concentrations, high cholesterol/HDL-cholesterol ratios, and hypertension were commonly encountered in our patients and are all features of the metabolic syndrome<sup>9,24</sup>. The Pima Indians experience the highest prevalence of obesity and insulin resistance so far reported<sup>25</sup>, while the prevalence of RA in this population is 5.3 as compared to the figure of 0.5–1% worldwide<sup>26</sup>. How these metabolic disturbances may contribute to the onset and perhaps the persistence of inflammatory arthritis requires elucidation<sup>22</sup>. Insulin resistance is associated with decreased stress responsiveness of the hypothalamic-pituitary-adrenal axis<sup>27,28</sup>, endothelial dysfunction<sup>29</sup>, an acute phase response<sup>30</sup>, increased levels of plasminogen activator inhibitor-1<sup>9</sup>, and decreased antioxidant concentrations<sup>31</sup> and (presumably compensatory) increased nitric oxide levels<sup>32</sup>. Each of these phenomena is implicated in the etiopathogenesis of inflammatory arthritis<sup>33</sup>. Pivotal disease mechanisms in both inflammatory arthritis and CVD are activation of the proinflammatory gene transcription factor nuclear factor  $\kappa$ B<sup>34,35</sup>, monoclonal expansion of CD4+CD28<sup>null</sup> T cells<sup>36,37</sup>, the presence of an acute phase response<sup>21,30,33</sup>, and endothelial dysfunction<sup>29,33</sup>.

A limitation of our study is that we used the HOMA<sup>13</sup> and QUICKI<sup>14</sup> to estimate insulin resistance while the gold standard for assessment of insulin sensitivity is the euglycemic hyperinsulinemic clamp technique. However, in a recent population study on 888 subjects, insulin resistance as measured by the insulin clamp correlated strongly with the HOMA ( $r_s = 0.813$ ,  $p < 0.0001$ ), confirming its validity as a surrogate marker for insulin resistance<sup>13</sup>. The QUICKI was found to be even more accurate and reproducible in this regard<sup>14</sup>. The limitation is also mitigated when a large number of subjects, as in our study, is investigated. Also, physical activity and dietary composition can influence

insulin sensitivity and lipid metabolism<sup>38</sup>. None of our patients were disabled to the extent that they could not exercise and, in general, their disease activity was relatively mild (mean ESR 26 mm/h). It is our experience and that of others that subjects with inflammatory arthritis tend to lead a healthier lifestyle with regard to diet<sup>16</sup> and exercise<sup>39,40</sup>. Park, *et al*<sup>7</sup> found no significant correlations between daily activities of patients with RA and HDL-cholesterol concentrations. In view of the above, we do not believe that differences in exercise and/or food intake between our patients and controls explain our findings. Finally, we chose healthy volunteers rather than patients with “degenerative” arthritis, i.e., osteoarthritis, as controls since the latter condition is also independently associated with dyslipidemia<sup>41</sup> and insulin resistance<sup>42</sup>.

Insulin resistance and dyslipidemia are common in inflammatory arthritis. Together with the reported increased CVD event rate in this disease<sup>1-4,20</sup>, this suggests the need for CVD risk factor assessment and treatment in inflammatory arthritis. Adequate treatment of disease activity and weight control not only in RA, but also SpA and UIA, may decrease CVD risk and events. This deserves confirmation in a controlled study.

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