Inflammation, Insulin Resistance, and Aberrant Lipid Metabolism as Cardiovascular Risk Factors in Rheumatoid Arthritis

Several investigators have reported an excess cardiovascular (CV) morbidity and mortality in rheumatoid arthritis (RA)\(^1,2\). For example, del Rincon, et al\(^3\) confirmed a 3.96-fold (95% confidence interval 1.86–8.43) increased incidence rate ratio of CV events in 236 consecutive patients with RA followed for one year. Banks, et al\(^4\) evaluated 67 patients with RA and 37 controls with osteoarthritis (OA), who were matched for all traditional risk factors and use of nonsteroidal antiinflammatory agents. The Rose questionnaire in combination with resting electrocardiography and adenosine-stressed myocardial perfusion imaging revealed a prevalence of ischemic heart disease of 49% in RA and 27% in OA (\(p = 0.03\))\(^4\). An increased prevalence of ischemic changes on 24 hour electrocardiographic Holter monitoring was also reported in RA\(^2\).

EXCESS CARDIOVASCULAR RISK IN RA — A CONSEQUENCE OF SYSTEMIC INFLAMMATION?

Well recognized CV risk factors in the general population comprise elevated low density lipoprotein (LDL) cholesterol, insulin resistance, and systemic inflammation\(^5,9\). The mechanisms whereby systemic inflammation may cause excess CV disease in RA were recently reviewed\(^1\). Indeed, ample evidence has been reported that systemic inflammation predicts CV events in this disease. Thus, a raised erythrocyte sedimentation rate (ESR), the number of swollen joints, and sustained disease activity were each found to predict CV event rates\(^1,2\). In a recent report\(^10\), the use of methotrexate (MTX) was associated with a 70% (95% CI 0.2–0.7) reduction in CV disease related deaths, and this was attributed to the potent antiinflammatory effects of the respective agent.

Subclinical atherosclerosis as estimated by ultrasonographically determined carotid intima media thickness was also documented in RA, and this correlated with measures of disease severity (disease activity accumulated over time since disease onset) rather than traditional risk factors\(^11,12\). However, in multiple regression models, disease severity explained only 21 to 42% of the variance in carotid intima media thickness, indicating the presence of other CV risk factors in RA\(^11\).

ACUTE PHASE RESPONSE RELATED INSULIN RESISTANCE AND ABERRANT LIPID METABOLISM AS POTENTIAL CV RISK FACTORS IN RA

We recently investigated the potential role of insulin resistance as a CV risk factor in RA\(^6,7\). In the Quebec Study\(^13\), an 18% increase in fasting insulin concentrations was independently associated with a 1.7-fold increased risk for ischemic heart disease. We found that insulin concentrations in inflammatory arthritis were 57% higher than in age and sex matched healthy controls\(^6\) and 41% higher than in age and sex matched patients with OA\(^7\). Moreover, high C-reactive protein (CRP) concentrations were associated with insulin resistance and hypertension, while insulin resistance was a statistical predictor of low HDL-cholesterol and high triglycerides\(^7\). Cardiovascular risk factors were therefore interlinked in RA as they are in the insulin resistance or metabolic syndrome\(^7,8\). Active RA and insulin resistance have several atherogenic features in common\(^6,7\), as summarized in Table 1. Low HDL-cholesterol and elevated triglyc-

<table>
<thead>
<tr>
<th>Table 1. Atherogenic features shared by active RA and the insulin resistance syndrome(^6,7).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased cytokine production</td>
</tr>
<tr>
<td>Increased adhesion molecule production</td>
</tr>
<tr>
<td>Elevated acute phase response</td>
</tr>
<tr>
<td>Reduced fibrinolysis</td>
</tr>
<tr>
<td>Reduced HDL-cholesterol</td>
</tr>
<tr>
<td>Increased small dense LDL-particles</td>
</tr>
</tbody>
</table>
erides were reported to mediate subclinical atherosclerosis in RA\textsuperscript{14}. Acute phase response related insulin resistance and aberrant lipid metabolism might play a pivotal role in CV disease in RA. We are currently investigating the role of insulin resistance in atherosclerosis in this disease.

Disease activity in RA is associated with both low LDL and HDL cholesterol and both lipoproteins increase upon suppression of disease activity\textsuperscript{1}. Decreased HDL cholesterol constitutes a potent and independent CV risk factor\textsuperscript{15,16}. Park and colleagues\textsuperscript{16} evaluated serum lipids at baseline and after one year of treatment with corticosteroids or disease modifying antirheumatic drugs (DMARD). In patients experiencing improvement in disease activity, a significant 21\% increase in HDL cholesterol and an insignificant increase in LDL cholesterol were recorded. By contrast, nonresponders experienced no change in HDL cholesterol. We recently evaluated the effects of DMARD and dietary intervention on dyslipidemia, insulin resistance, and the acute phase response in inflammatory arthritis patients with insulin resistance and/or dyslipidemia over a 3 month period\textsuperscript{15}. Dietary intervention was aimed at decreasing insulin resistance\textsuperscript{17}. It consisted of moderate calorie and carbohydrate restriction and replacing saturated with monounsaturated (canola and olive oil/margarine, avocados, peanuts, almonds and macadamia nuts) and n-3 (fish) fatty acids. DMARD had divergent effects on lipoprotein metabolism, as reported\textsuperscript{1}, decreased the acute phase response as expected, and notably, reduced the median insulin resistance by 36\% (interquartile range 26–61\%). A beneficial effect on elevated blood pressure was also recorded. MTX users versus non-MTX users differed only by a larger decrease in CRP, while dietary intervention prevented increases in LDL cholesterol associated with DMARD use only. The protective effect of MTX against the occurrence of CV events in RA may therefore indeed relate to acute phase response suppression independently of other CV risk factors\textsuperscript{10,15}.

WHAT MORE DO WE NEED TO KNOW?

Markers of disease activity and severity have been consistently associated with CV disease in RA\textsuperscript{1,2,11,12}. Wallberg-Jonsson and colleagues also found subtle dyslipidemia to predict subclinical atherosclerosis in RA\textsuperscript{14}. However, disease activity was uncharacteristically low in their patients, i.e., the ESR was 22 mm/h. Since recent studies revealed that the acute phase response is associated with not only dyslipidemia but also with insulin resistance\textsuperscript{6,7,15,16}, the potential independent as well as interdependent roles of the respective risk factors for atherosclerosis in RA need further study. Also, the role of other potential risk factors including raised homocysteine concentrations, glucocorticoids, and type 2 diabetes mellitus need to be investigated\textsuperscript{13,7,11}. Once the contribution of these different risk factors to CV disease is determined, the potential benefits of targeted intervention need to be addressed prospectively.

COULD CV EVENTS BE PREVENTED IN RA AT THE PRESENT STAGE?

According to the National Cholesterol Education Program (NCEP)\textsuperscript{5}, the LDL target is 2.6 mmol/l in patients at high risk for CV events, which applies to RA\textsuperscript{1-4}. The NCEP further recommends addressing metabolic syndrome features in individual patients, particularly abdominal obesity, hypertension, low HDL cholesterol, and aberrant glucose metabolism\textsuperscript{7}. According to the World Health Organization, insulin resistance per se needs to be determined in confirming the presence of the metabolic syndrome in non-diabetic subjects\textsuperscript{18}. We believe that the interactions between the acute phase response, dyslipidemia, and insulin resistance need consideration in applying the NCEP recommendations in RA. The most important and initial intervention may be suppression of disease activity with DMARD in order to reduce the acute phase response and insulin resistance and to revert reductions in HDL cholesterol\textsuperscript{12,15}. MTX may be superior to other traditional DMARD in this context\textsuperscript{10,15}. Acute phase response suppression, on the other hand, can unmask elevated LDL cholesterol\textsuperscript{11,15}. This seems particularly important when the acute phase response (ultrasensitive CRP) remains incompletely suppressed, as CRP and lipids act synergistically in CV event occurrences\textsuperscript{8}. We further recommend dietary intervention, since it prevents the rise in LDL cholesterol associated with suppression of disease activity\textsuperscript{15}. Intake of n-3 fatty acids also attenuates disease activity in RA\textsuperscript{19}. Lifestyle changes are particularly important in the treatment of insulin resistance\textsuperscript{8}. Apart from dietary intervention, exercise was shown not to worsen disease activity in RA\textsuperscript{20}. In patients who remain at increased CV risk subsequent to the institution of the above-mentioned measures, statins are the preferred agents for patients with high LDL cholesterol, while fibrates and niacin are more effective at elevating low HDL cholesterol concentrations\textsuperscript{5}.

In conclusion, alarming frequencies of CV disease and events have been reported in RA. CV risk assessment may be indicated in all patients with RA. Disease activity and its effects on insulin sensitivity, lipid metabolism, and blood pressure may well constitute major CV risk factors in RA. Therefore adequate prevention of CV events in this condition may not only entail strict application of recommendations such as the NCEP guidelines. Indeed, vigorous control of systemic inflammation may be of primary importance. DMARD therapy in inflammatory arthritis is associated with beneficial effects on the acute phase response, insulin resistance, low HDL cholesterol, and elevated blood pressure, while its adverse effects on LDL cholesterol can be attenuated by dietary intervention.
REFERENCES