Introduction

Rheumatoid arthritis (RA) patients are at increased risk for cardiovascular disease (CVD) [1,2]. Comprehensive cardiovascular risk assessment comprises both determination of lipoprotein profiles in the individual patient and identification of other components of the metabolic syndrome [3].

In RA and other inflammatory arthritides, the acute phase response is associated with low low-density lipoprotein (LDL)-cholesterol and high-density lipoprotein (HDL)-cholesterol, as well as insulin resistance [4–8]. Subtle dyslipidemia predicts atherosclerosis in RA [9]. The acute phase response, body mass index (BMI), insulin resistance, HDL-cholesterol, triglycerides, and blood pressure interlink in this condition in the same manner as they do in the metabolic syndrome [6,7]. Also, C-reactive protein (CRP) may directly contribute to atherosclerosis [10]. Disease-modifying antirheumatic drugs (DMARDs) may have an attenuating effect on CVD risk and death in RA [11]. In a more recent report [12], the use of methotrexate in RA was associated with a 70% (95% confidence interval 30–80) reduction in risk for cardiovascular death [12]. Those investigators postulated that this finding was related to the profound effects of methotrexate on inflammation.

In the present study, we identified inflammatory arthritis (IA) patients with active disease who were insulin resistant BMI = body mass index; CVD = cardiovascular disease; CRP = C-reactive protein; DMARD = disease modifying agents; HDL = high-density lipoprotein; HOMA = Homeostatis Model Assessment for Insulin Resistance; IA = inflammatory arthritis; LDL = low-density lipoprotein; QUICKI = Quantitative Insulin Sensitivity Check Index; RA = rheumatoid arthritis.
[6,7] or dyslipidemic [3], or both; who had not taken DMARDs over the previous 3 months; and who were not following any dietary recommendations. We re-evaluated these patients during the third month after DMARDs and dietary intervention (aimed at improving insulin resistance and dyslipidemia) were initiated. We tested the following hypotheses: that DMARDs and dietary intervention attenuate cardiovascular risk; and that those who comply with the diet and those who use methotrexate experience more favorable changes in cardiovascular risk than those who do not comply with the diet and those not on methotrexate.

Materials and method
Patients and investigations
Twenty-two patients, 15 of whom met the American College of Rheumatology criteria for RA [13] and seven of whom met the criteria of the European Spondyloarthritis Study Group for spondyloarthropathy [14], were identified in our outpatient clinic. Their baseline characteristics are presented in Table 1.

Patients on lipid-lowering agents or insulin were excluded. None of the patients had taken DMARDs during the previous 3 months and none were following any dietary advice. All had clinically active disease and a raised CRP. Hypertension was defined as a blood pressure greater than 140/90 mmHg (measured on three occasions) or prescription of antihypertensive drugs. None of the patients changed their degree of physical activity or smoking habits during the study period. Seventeen patients were on nonsteroidal anti-inflammatory agents. The remaining five were either intolerant of (n = 2) or reported that they did not benefit from nonsteroidal anti-inflammatory agents (n = 3). Two patients were taking prednisone (20 mg/day and 5 mg/day). Over the 2 months following enrolment, those doses were decreased to 15 mg/day and 2 mg/day.

At enrolment and during the third month after initiation of antirheumatic agents and dietary intervention, fasting blood samples (between 0800 h and 1000 h) were taken. These were used to determine ultrasensitive CRP (Tina’ quant C-reactive protein latex particle enhanced immunoturbidimetric assay on Hitachi 917, Roche Diagnostics, Rotkreuz, Switzerland); total cholesterol, HDL-cholesterol, and triglycerides (Olympus Diagnostics, County Clare, Ireland); LDL-cholesterol (Randox Laboratories Ltd, Crumlin, UK); and plasma glucose and serum insulin (Abbott, Chicago, Illinois). Laboratory testing was done using autoanalyzers, enzymatic methods (for lipids), and microparticle enzyme immunoassay on the Axsym system (for insulin; Abbott Laboratories, Diagnostic Division, Abbott Park, IL, USA). The intra-assay and interassay coefficients of variance for CRP were 0.43% and 1.34%, respectively; those for insulin were 1.9% and 1.2%, respectively.

Insulin resistance was estimated using the Homeostasis Model Assessment for Insulin Resistance (HOMA), using the following formula: insulin (µU/ml) × glucose (mmol/l)/22.5. Insulin sensitivity was estimated using the Quantitative Insulin Sensitivity Check Index (QUICKI), using the following formula: 1/(log insulin [µU/ml] × log glucose (mg/dl). In accordance with our findings in a recent study on healthy volunteers investigated in our laboratory [6], we used a threshold HOMA value of 2.29 (µU. mmol/ml . l) for identification of insulin resistance and a threshold QUICKI value of 0.337 for identification of decreased insulin sensitivity.

Disease-modifying antirheumatic drug treatment
At enrolment, we used pulsed methylprednisolone as bridge therapy as an alternative to oral glucocorticoids (Table 2) and in view of its reported favorable efficacy and side-effect profile [4,15–17]. In keeping with previous reports, methylprednisolone was administered intra-articularly (n = 20) and/or intramuscularly (n = 3) or intravenously (n = 4) over 1–3 days. The dose and route of administration were guided by the number of joints involved and the perceived level of disease activity [15–18]. Except for the two patients who were taking oral glucocorticoids at enrolment, no further patients received glucocorticoids subsequent to the initial pulsed methylprednisolone therapy. The same parameters and previous patient exposure to and experience with DMARDs were taken into consideration when electing to institute DMARD therapy (Table 2). Eight patients did not receive methotrexate (Table 2).

Dietary intervention
Dietary recommendation consisted of calorie restriction to 1500 cal/day, carbohydrate restriction to 40% of total calorie intake, and replacement of saturated by monounsaturated and n-3 polyunsaturated fats. The latter constituted 30% of the calorie intake, and patients were advised to use canola oil and canola oil margarine, olive oil and olive oil margarine, avocados, macadamia nuts, almonds, and peanuts and peanut butter as sources of monounsaturated fats, whereas n-3 polyunsaturated fats were recommended in the form of fish at least four times a week. We reported these dietary measures previously in gout [19], and they were shown to attenuate insulin resistance and have a corrective effect on dyslipidemia. At the second evaluation, compliance was assessed by questioning patients about their food intake over the previous week and confirmed further by body weight measurements. All compliant patients had lost weight. The seven noncompliant patients (Tables 1 and 2) had not lost or gained weight (n = 2). Reasons for noncompliance included lack of motivation (n = 5) and not seeing the need for the intervention (n = 2).
Statistical analyses

Comparisons of medians were made using the Mann–Whitney U test. Associations were analyzed using simple linear regression. Analysis of covariance was used to compare changes in total and LDL-cholesterol between those who were compliant and noncompliant with the diet, while controlling for differences in disease duration. Results are expressed as median (interquartile range). \( P < 0.05 \) was considered statistically significant.

Results

Changes in cardiovascular disease risk in all 22 patients

The baseline clinical and biochemical features, and use of DMARDs and changes in cardiovascular risk factors in all 22 patients are presented in the second columns of Tables 1 and 2, respectively. At enrolment, the median BMI was in the overweight range. The median weight loss was 4.3% (0–8.4%). The CRP decreased in all except one patient (increased from 4 to 6 mg/l). Three patients were known to be diabetic and were on oral hypoglycemic agents. Another two were found to have fasting hyperglycemia (i.e. 7.3 and 7.9 mmol/l) at enrolment. The glucose level was normal at the second assessment in each patient, namely 5.5 mmol/l in a patient who was noncompliant with the diet and 5.1 mmol/l in a patient who was compliant. Twenty (89%) patients were insulin resistant at enrolment. There was a 36% (26–61%) decrease in insulin resistance, and only 10 (47%) patients were still
insulin resistant at the second assessment. The LDL-cholesterol remained essentially unchanged. The HDL-cholesterol increased by 13% (0–25%) and triglycerides decreased by 26% (11–41%). These changes did not reach statistical significance. In 11 (50%) patients the LDL-cholesterol was greater than 3.4 mmol/l, and in seven (32%) the HDL-cholesterol was below 0.1 mmol/l at enrolment. In three of the patients with a blood pressure greater than 140/90 mmHg (one of whom was on treatment) at enrolment, blood pressure had normalized at the second assessment without changing antihypertensive therapy (one was noncompliant and two were compliant with the diet).

Weight loss was associated with an improvement in insulin sensitivity ($r^2 = 0.144; P = 0.04$), and decreases in LDL-cholesterol ($r^2 = 0.162; P = 0.04$) and total cholesterol ($r^2 = 0.242; P = 0.01$). The decrease in CRP was associated with a reduction in triglycerides ($r^2 = 0.152; P = 0.04$).

### Changes in cardiovascular risk in diet compliant versus diet noncompliant patients

In the third and fourth columns of Tables 1 and 2, we subdivided patients into diet compliant and diet noncompliant patients. The disease duration was longer ($P < 0.006$) in nondieters. Although not significant, there were numerically more smokers, the baseline median CRP was higher, and the baseline median BMI was lower in nondieters as compared with dieters. Changes in CRP and glucose metabolism were similar in dieters and nondieters. However, although total cholesterol and LDL-cholesterol

### Table 2

| Treatment used   | All patients ($n = 22$) | Dieters ($n = 15$) | Nondieters ($n = 7$) | Methotrexate ($n = 14$) | No methotrexate ($n = 8$) |
|------------------|-------------------------|-------------------|----------------------|-------------------------|---------------------------|
| Treatment used   |                         |                   |                      |                         |                           |
| Pulsed methylprednisolone ($mg$) | 200 (160 to 360) | 200 (160 to 230) | 200 (140 to 730) | 200 (160 to 360) | 200 (120 to 730) |
| Chloroquine ($n [%]$) | 15 (68) | 12 (80) | 3 (43) | 10 (71) | 5 (63) |
| Methotrexate ($n [%]$) | 14 (64) | 10 (67) | 4 (67) | 14 (100) | 0 (0) |
| Minocyclin ($n [%]$) | 9 (41) | 7 (47) | 2 (29) | 7 (50) | 2 (25) |
| Azathioprine ($n [%]$) | 2 (9) | 0 (0) | 2 (29) | 0 (0) | 2 (25) |
| Nonmethotrexate | 1 (1 to 2) | 1 (1 to 2) | 1 (1 to 1) | 2 (1 to 2) | 1 (1 to 2) |
| DMARD per patient ($n$†) |                  |                   |                      |                         |                           |
| Changes in cardiovascular risk |                         |                   |                      |                         |                           |
| Weight† ($kg$) | –4 (–6.5 to +0) | –4.6 (–8.6 to –4) | 0 (0 to 0.8) | –3.4 (0 to 8.6) | –4 (–6.2 to 0) |
| C-reactive protein† ($mg/l$) | –14 (–36 to –6)* | –12 (–36 to –5) | –19 (–35 to –13) | –27 (–83 to –6) | –10 (–13 to –3)**
| Insulin† ($µU/ml$) | –4.5 (–8.8 to –2.5)* | –3.4 (–7.9 to –1.5) | –6.4 (–11.7 to –2.6) | –4.5 (–10.2 to –2.9) | –4.5 (–6.4 to –1.5)
| Glucose† ($mmol/l$) | –0.5 (–0.8 to –0.3) | –0.5 (–0.9 to –0.3) | –0.4 (–0.8 to –0.1) | –0.5 (–1.8 to –0.3) | –0.5 (–0.8 to +0.1)
| HOMA† ($µU . mmol/ml . l$) | –0.95 (–1.49 to –0.50)* | –0.89 (–2.20 to –0.76) | –1.45 (–2.92 to +0.82) | –1.08 (–2.99 to –0.85) | –0.87 (–0.20 to –0.49)
| QUICKI† | 0.023 (0.014 to 0.049)* | 0.021 (0.009 to 0.042) | 0.035 (0.023 to 0.046) | 0.026 (0.042 to 0.015) | 0.022 (0.045 to 0.007)
| Total cholesterol† ($mmol/l$) | –0.05 (–0.9 to +0.5) | –0.6 (–1.2 to 0.0) | 0.8 (0.2 to 0.9)* | 0.0 (–0.5 to +0.7) | –0.35 (–1.7 to +0.9)
| LDL-cholesterol† ($mmol/l$) | –0.15 (–0.6 to +0.3) | –0.3 (–0.8 to +0.2) | 0.3 (0.0 to 0.9)** | –0.15 (–0.4 to –0.2) | –0.05 (–1.5 to –0.8)
| HDL-cholesterol† ($mmol/l$) | 0.15 (0.0 to 0.20) | 0.20 (0.02 to 0.21) | 0.10 (0.00 to 0.51) | 0.20 (0.11 to 0.21) | 0.06 (–0.11 to +0.50)
| Triglycerides† ($mmol/l$) | –0.35 (–1.1 to –0.1) | –0.51 (–0.4 to –0.2) | –0.21 (–0.4 to +0.2) | –0.47 (–1.0 to –0.1) | –0.22 (–0.3 to +0.1)
| Time between assessments† (months) | 3 (2.5 to 3) | 3 (2.5 to 3) | 3 (2 to 3) | 3 (2.5 to 3) | 3 (2 to 3)

†Results expressed as median (interquartile range). In the second column, the significance for changes in cardiovascular risk was analyzed. Nondieters were compared with dieters, and nonusers of methotrexate with users in the other columns. *$P < 0.006$, **$P = 0.015$, ***$P = 0.04$. DMARD, disease-modifying antirheumatic drugs; HDL, high-density lipoprotein; HOMA, Homeostatis Model Assessment for Insulin Resistance; LDL, low-density lipoprotein; QUICKI, Quantitative Insulin Sensitivity Check Index.
increased by 8% (2–9%) and 3% (0–9%) in nondieters, the respective lipid values decreased by 10% (0–20%) and 9% (6–20%) in those who complied with the diet. These differences remained significant after controlling for differences in disease duration ($P < 0.02$).

**Changes in cardiovascular risk in methotrexate users versus nonusers of methotrexate**

In the fifth and sixth columns of Tables 1 and 2, we subdivided patients into users and nonusers of methotrexate. Baseline characteristics and the use of antirheumatics other than methotrexate were also similar in both groups. No difference in changes in glucose or lipid metabolism between the groups was seen. However, patients on methotrexate experienced a 76% (71–94%) decrease in CRP, as compared with a 61% (28–77%) reduction in CRP in patients not on methotrexate ($P < 0.04$).

**Changes in cardiovascular risk in users versus nonusers of chloroquine**

Chloroquine users ($n = 15$) and nonusers ($n = 7$) did not differ in baseline characteristics, used treatment (apart from chloroquine), and changes in lipid and glucose metabolism and CRP (results not shown).

**Discussion**

In the present study we found that, in IA patients with insulin resistance and/or dyslipidemia, the use of DMARD in combination with dietary intervention was associated with a marked improvement in insulin resistance and sensitivity, whereas changes in lipid values were not significant. The latter may be related to the small number of cases in our cohort and the relatively short follow-up period. Thus, a median increase of 0.15 mmol/l in HDL-cholesterol, as we found, is associated with a reduction by 10–15% in risk for CVD events, which is independent of LDL-cholesterol concentrations and therefore may still be clinically relevant [20]. An increase in HDL-cholesterol and decrease in insulin resistance on DMARDs has been reported in IA [4,5].

When we compared those who were compliant with those who were noncompliant with the diet, the latter experienced similar improvements in insulin resistance. Calorie and carbohydrate limitation and the use of unsaturated fats were previously both found to improve insulin sensitivity [19]. Our results therefore suggest that the acute phase response is more important than food composition and excess weight in the development of insulin resistance in IA. A high prevalence of diabetes (a long-term complication of insulin resistance) has been reported in RA [7,21]. We recently documented a prevalence rate of 41% of insulin resistance in RA [7], and this was attributable to the acute phase response. Those who were noncompliant with the diet did, however, experience an increase in total and LDL-cholesterol – a major CVD risk factor [3,20]. Because a raised acute phase response is associated with low LDL-cholesterol and HDL-cholesterol, its suppression is expected to increase the respective lipoprotein concentrations [4]. Changes in LDL-cholesterol of 0.3 mmol/l and HDL-cholesterol of 0.10 mmol/l, as we recorded in noncompliant patients, are predictive of an 8–12% increase and a 6–9% decrease in CVD risk, respectively [20]. By contrast, compliance with dietary recommendations resulted in a decrease in total and LDL-cholesterol – an effect expected from the use of unsaturated fats [3].

Nonsignificant but numerically different baseline features between dieters and nondieters included a higher number of smokers, a lower median BMI, and a higher median CRP in the latter. None of the patients changed their smoking habits during the study period, and replacement of saturated by unsaturated fats was found equally effective at lowering LDL-cholesterol in a study on normal weight persons [22], as applied to the nondieting patients in the present study (the median BMI was 22.2 kg/m²). We cannot exclude that differences in baseline CRP between dieters and nondieters did not contribute to our findings with regard to changes in total and LDL-cholesterol. However, weight loss was associated with decreases in total and LDL-cholesterol, whereas changes in CRP did not statistically predict increases in the respective lipoproteins. This suggests a predominant effect of dietary intervention on total and LDL-cholesterol.

The role of dietary intervention in preventing cardiovascular events in IA deserves further study. Replacing carbohydrates by monounsaturated fats as a source of calories raises HDL-cholesterol without affecting LDL-cholesterol. This intervention may also improve insulin sensitivity [23]. Mediterranean populations experience a very low mortality rate from coronary heart disease, and this was attributed to the use of olive oil [23]. N-3 fatty acids (present in fish) and n-6 fatty acids (present in vegetable oils such as sunflower oil) have strong cholesterol-lowering effects [24]. In addition, n-3 derived eicosanoids exhibit antithrombotic and anti-inflammatory effects, whereas n-6 derived eicosanoids have proinflammatory and prothrombotic effects [24]. A high ratio of n-6 to n-3 fatty acid intake is associated with CVD and type 2 diabetes [24]. A recent study showed that the use of n-3 polyunsaturated fats had a protective effect against sudden cardiac death [25]. This was presumably due to a reduction in malignant arrhythmias via a cardiomyocyte-stabilizing effect [25]. Fish-eating populations experience low rates of coronary artery disease [24]. Finally, the use of n-3 fatty acids, with or without avoidance of their competitors n-6 fatty acids, was shown to attenuate disease activity in 13 randomized controlled trials in RA [25].
Because methotrexate use in RA was recently reported to be protective against death from CVD [12], we compared methotrexate users with patients not on methotrexate. Although there were no differences in changes in glucose and lipid metabolism between both groups, the patients on methotrexate experienced a greater reduction in CRP concentrations. The reported reduction in CVD event rate with methotrexate may therefore relate to reduced CRP concentrations, independent of altered lipid and glucose metabolism. This confirms the mechanism suggested by Choi et al. [12]. CRP may indeed be involved more directly in atherosclerosis. CRP activates complement, and it is generally present together with activated complement in atherosclerotic plaques [10]. CRP binds to LDL and particularly partly degraded LDL [10]. It also increases macrophage production of tissue factor—a major procoagulant that is also present in atherosclerotic plaques [10]. Human CRP, via its capacity to activate complement, greatly increases infarct size after experimental coronary artery ligation [10]. The acute phase response is further associated with raised fibrinogen and Von Willebrand Factor concentrations, which are implicated in RA-related CVD [21].

Limitations of the present study include the small number of patients studied and short duration of follow up. Patients were selected on the basis of the presence of excess cardiovascular risk. The changes observed, particularly with regard to improvements in insulin resistance and sensitivity, were marked. In view of the above-mentioned limitations, results of our statistical analyses may underestimate the implications of our findings. For example, changes not only in weight but also in HDL-cholesterol and triglycerides in all patients, and particularly in diet compliant and methotrexate using patients, were marked but did not reach significance. Also, we used calculated insulin resistance rather than the euglycaemic clamp technique. However, both the HOMA and QUICKI have been validated and found to be reliable surrogate markers of insulin resistance [7].

Conclusion

IA patients with increased CVD risk experience a marked improvement in insulin resistance and divergent effects (increased LDL-cholesterol and HDL-cholesterol) on dyslipidemia upon acute phase response suppression with DMARDs. Methotrexate may protect against CVD through acute phase response reduction, independent from more conventional CVD risk factors such as dyslipidemia and insulin resistance. Dietary intervention prevents increases in total and LDL-cholesterol on acute phase response suppression with DMARDs in IA. The benefits of DMARDs and polyunsaturated fats may extend beyond their effects on disease activity, and may indeed be beneficial with regard to the excess CVD risk event rate in IA [12,26].

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