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Atherogenic lipid profiles in rheumatoid arthritis

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Abstract

Aims Rheumatoid arthritis is associated with an excess mortality from cardiovascular disease, and this may be related to an atherogenic lipid profile. We set out to identify whether there was a correlation between disease activity and levels of different lipid fractions in a stable population of patients with rheumatoid arthritis on disease-modifying therapy.

Methods Patients with rheumatoid arthritis were selected from our database and requested to have inflammatory markers and a fasting lipid profile taken at their next visit for monitoring of their disease modifying therapy.

Results 204 patients were recruited for the study. A statistically significant relationship exists between reduced HDL and elevated CRP ($p=0.01$) and ESR ($p=0.041$). Elevated ESR, but not elevated CRP, was associated with raised LDL cholesterol ($p=0.014$). Fourteen patients (6.8%) were receiving statin therapy and 71 (34.8%) were taking prednisone. Use of prednisone, independent of dose, was associated with elevated triglyceride levels ($p=0.041$).

Conclusions This study supports previous work showing that rheumatoid arthritis is associated with an adverse lipid profile. While good disease control is clearly important, we should not neglect management of traditional cardiovascular risk factors.

Patients with rheumatoid arthritis have an increased mortality from cardiovascular disease, and untreated patients have an atherogenic lipid profile¹ which can be positively influenced by the use of disease-modifying antirheumatic drugs (DMARD) therapy.² There is, however, some doubt as to the significance of these changes—since it has been shown previously that the increased cardiovascular risk is not completely explained by traditional risk factors.³

Interestingly, use of glucocorticoids which are known to cause hypercholesterolaemia in this population, has also been shown to increase high-density lipoprotein (HDL) and reduce the total cholesterol/HDL ratio,⁴ thus suggesting a causative role for the inflammatory response in generating this lipid abnormality. Previous studies have been hampered by analysis of stored specimens for lipid analysis which can falsely reduce HDL levels.⁴

This study was designed to investigate whether—in our population of patients with stable rheumatoid arthritis on disease-modifying therapy—there was an association between inflammatory markers, glucocorticoid-use, and lipid levels using specimens analysed on the same day as collection.

Methods

Our database of patients currently taking disease-modifying therapy was searched; patients were invited to participate in the study if they had rheumatoid arthritis and had been on disease-modifying

therapy for at least 3 months. Fasting lipid profile, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) were performed with the next routine blood monitoring for their DMARD therapy. DMARD-use was recorded along with any concurrent use of prednisone and lipid-lowering therapy.

The data was analysed using Microsoft Excel software to assess the presence and strength of any association between disease activity and different lipid fractions.

Results

300 patients were invited to participate initially, and positive responses were received from 204 patients within the 3.5 month period allotted for data collection, thus giving a response rate of 68%. Forty-six (22%) were male with an average age of 58.63 years (range 34 to 87 years). 159 (78%) of the patients were female with an average age of 59.61 years (range 22 to 90 years).

Seventy-one (34.8%) of patients were taking prednisone in doses ranging from 2 mg to 40 mg, and 14 (6.8%) were receiving lipid-lowering therapy with an HMG-CoA reductase inhibitor and another two (0.98%) with a fibrate.

Mono-therapy with methotrexate was used in 92 (45%) of patients, with a further 43 (21%) using leflunomide. Combination therapy (methotrexate and leflunomide) was used in 23 patients (11%), whilst single therapy with sulphasalazine was found in 15 (7%) of patients. The remaining 31 patients were on various regimes (either alone or in combination) using hydroxychloroquine, gold, azathioprine, and penicillamine. Small sample sizes for many of these groups prevented statistical analysis.

Suggested optimal lipid levels from the latest New Zealand Guidelines Group publication on assessment of cardiovascular risk⁵ were used for this analysis; these levels are presented in Table 1 along with the numbers of patients who did not meet these suggested criteria.

Table 1. Optimal lipid levels suggested by the New Zealand Guideline Group,⁵ and numbers of patients not meeting this recommendation

Lipid fraction	Optimal value	Number of patients not meeting this recommendation
Total Cholesterol (TC)	<4.0 mmol/L	191 (93.6%)
LDL Cholesterol	<2.5 mmol/L	152 (74.5%)
HDL Cholesterol	>1.0 mmol/L	21 (10.3%)
TC:HDL ratio	<4.5	59 (28.9%)
Triglycerides	<1.7 mmol/L	78 (38.2%)

LDL=low-density lipoprotein; HDL=high-density lipoprotein.

Associations between inflammatory markers and different lipid fractions were assessed using the Chi-squared test, and the p values obtained are shown in Table 2. Insufficient patients were on lipid-lowering therapy to permit statistical analysis of statin therapy with regard to inflammatory markers.

A statistically significant relationship is demonstrated between elevated ESR and raised LDL (p=0.041). Reduced levels of HDL was associated with raised ESR (p=0.041) and CRP (p=0.01). In addition, being on prednisone (independent of dose)

was associated with a statistically significant increase in triglyceride concentrations (p=0.041).

Table 2. P values for Chi-squared tests between lipid fractions & inflammatory markers and prednisone

Lipid fractions & inflammatory markers	ESR>20	CRP>5	On prednisone
Cholesterol >4.0	0.264	0.306	0.375
LDL > 2.5	0.014	0.469	0.838
TC:HDL >4.5	0.076	0.155	0.075
HDL <1.0	0.041	0.010	0.283
Triglycerides >1.7	0.512	0.630	0.041
ESR>20	–	<0.00001	0.728
CRP >5	–	–	0.762

Significant associations are shown in **bold**; CRP=C-reactive protein; ESR=erythrocyte sedimentation rate; LDL=low-density lipoprotein; HDL=high-density lipoprotein; TC=total cholesterol.

Discussion

We have demonstrated a statistically significant association between raised ESR & CRP and reduced HDL cholesterol in this population as well as confirming the results of a previous study,⁴ which showed a relationship between use of prednisone and increased triglyceride levels.

Elevated ESR is associated with statistically significant alterations in HDL and LDL cholesterol levels, but this is not the case for elevated CRP where a relationship was only seen with reduced HDL levels. This most likely reflects the fact that ESR and CRP are independent variables. CRP has been shown to reflect the acute phase response more closely than ESR in patients with rheumatoid arthritis because elevations in the ESR can be created by high titres of rheumatoid factor and immunoglobulins which may not rise acutely.⁶

This study is limited by the fact that we did not control for patients' weight, menopausal status, and other comorbidities which are known to affect lipid profiles.⁷ In addition, no allowance was made for disease duration apart from the fact that patients had stable disease for at least 3 months. Unfortunately, small patient numbers prevented the analysis of any effect of lipid-lowering therapy on inflammatory markers as well as analysis of different DMARD sub-groups with regard to lipid levels and inflammatory markers.

Recent data has shown that better disease control (leading to improvement in quality of life and reduced radiographic progression of disease) can be achieved using intensive outpatient treatment at no additional cost.⁸ In addition, use of methotrexate has shown a reduced mortality mainly as a result of a reduction in cardiovascular deaths.⁹

Therefore, good control of disease should be the priority given that both quality of life and longer-term outcomes can be improved. Nevertheless, rheumatoid arthritis patients appear to have a high prevalence of abnormal blood lipid profiles—and given

that so few of our patients were receiving lipid-lowering therapy, it is clear that we are not managing traditional risk factors for cardiovascular disease as part of our routine care.

Data from the trial of atorvastatin in rheumatoid arthritis¹⁰ demonstrated that patients who received atorvastatin 40 mg had improvement in disease severity scores, swollen joint counts, and inflammatory markers with no increase in adverse events compared to placebo.

Whilst the routine use of statins as disease-modifying therapy for patients with rheumatoid arthritis is not yet routine practice, their use in selected patients with abnormal lipid profiles could also benefit their arthritis.

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