

Dyslipidaemia and rheumatoid arthritis

In this issue of the *Annals of the Rheumatic Diseases*, Munro and colleagues¹ report a comparative study of intramuscular gold and hydroxychloroquine in rheumatoid arthritis (RA). They demonstrate a beneficial effect of hydroxychloroquine on lipid profiles compared with gold and suggest that hydroxychloroquine might be considered for RA patients at adverse cardiovascular risk.

Should rheumatologists be interested in their patients' cardiovascular and lipid status? The answer to this question is an unqualified 'yes'. Several studies suggest that cardiovascular diseases account for about half of all deaths in RA.² Cardiovascular deaths are more pronounced in the younger age group (<55 years), and may contribute to the substantial reduction in life expectancy, with estimates of standardised mortality ratios ranging from 1.1 to 3.³

We previously suggested that cardiovascular disease in RA may result from accelerated atherosclerosis caused by clinical or subclinical vasculitis.⁴ The main determinants of cardiovascular risk in the general population, however, are the concentrations of serum low density lipoprotein (LDL) and high density lipoprotein (HDL) cholesterol. In men who are middle aged or over, a ratio of total to HDL cholesterol over 5 associates with increased risk of a first myocardial infarction.⁵ Oxidative modification of LDL may also be important and it is of interest that oxidised LDL has been noted in RA synovial biopsy specimens.⁶ Products of LDL oxidation may be recognised by the scavenger receptor leading to increased uptake of the modified lipoprotein particle by macrophages; they may be directly cytotoxic to endothelial cells, chemotactic for inflammatory cells, and cause functional changes in smooth muscle.⁷ The inflammatory environment and disturbed antioxidant mechanisms in RA⁸ may promote LDL oxidation, thereby facilitating atherogenesis at lower ambient lipid concentrations and placing RA patients at higher cardiovascular risk. Though attractive, this hypothesis remains to be tested.

Lipid metabolism in RA has received only modest attention. With the exception of a single study,⁹ most investigators agree that total, LDL and HDL cholesterol and triglycerides are reduced in active RA compared with inactive disease, non-inflammatory arthritis or normal controls¹⁰⁻¹³ (table 1), with inverse correlation between lipid values and the acute phase response.

With the exception of low HDL, which is an adverse prognostic factor, the remaining lipid profile in active RA may appear advantageous. It is however difficult to predict the overall impact of individual lipid changes on RA patients, during the course of the disease though for the general population the risk for a first myocardial infarction depends on the total to HDL cholesterol ratio rather than their absolute values.⁵ This has not been resolved in previous studies of RA, but Munro¹ found that the median values were promisingly under 5 for both treatment groups. Lipoprotein (a), an important independent factor in atherogenesis and thrombogenesis¹⁴ is increased in RA, correlating positively with the acute phase response.¹²⁻¹⁵

The apparent reduction of total cholesterol may result from reduced synthesis, increased clearance via the scavenger receptor pathway or increased oxidation¹⁰ triggered by the inflammatory process. Alternatively the presence of circulating autoantibodies to VLDL and LDL in active RA¹⁶ may be responsible. These may also have pre-atherogenic effects on the vascular wall by forming immune complexes.

Effects of anti-rheumatic treatment should also be taken into account. Non-steroidal anti-inflammatory drugs do not seem to have any effect on lipids in RA¹¹ and a study from 1976 suggested that long term anti-inflammatory aspirin use did not convey cardiovascular protection.¹⁷ The lipid raising effects of corticosteroids are well reported¹⁸ though their use in RA may not be associated with an increased risk for a cardiovascular event.¹⁹⁻²⁰ No large prospective studies have assessed the effect of slow acting anti-rheumatic drugs (SAARDs) on lipids. Control of disease activity by certain SAARDs may lead to 'normalisation' of the lipid profile (increase of total, LDL and HDL cholesterol)¹¹—this is supported by Munro's data¹ for intramuscular gold, which is not thought to have a direct effect on lipid metabolism. Cyclosporin may have an enhanced effect as some reports suggest that it contributes to accelerated atherosclerosis in subjects who have undergone renal transplantation.²¹

In contrast, the antimalarial agents seem to hold an exceptional position with regard to their effects on lipids. Wallace *et al* have previously reported a 15-20% decrease in serum triglyceride, cholesterol, and LDL concentrations and a reversal of the lipid raising effects of corticosteroids in 150 patients with lupus and RA,²² while in Svenson's study¹¹ in RA chloroquine was found to differ from other agents by reducing the values of cholesterol and triglycerides. It has been suggested that chloroquine may lower cholesterol by inhibiting the proteolysis of internalised cholesterol esters leading to increased LDL receptor values.²³ Munro¹ now reports substantial changes in HDL cholesterol and % HDL cholesterol (HDL cholesterol expressed as a percentage of total cholesterol), reaching significance between groups at six months (median HDL: +15% for hydroxychloroquine, -12% for gold; median % HDL: +9% for hydroxychloroquine, -15% for gold). Triglycerides rose by 0.5 mmol/l in the gold group (31%), a finding that may also have adverse cardiovascular impact.²⁴

To place such results in context, lipid lowering diets reduce serum total cholesterol concentrations by 2% to 13%,²⁵ while statins generally cause a 20 to 30% fall of cholesterol and 15% rise of HDL. A 10% fall in serum total cholesterol concentration reduces the risk of death from coronary heart disease by 10% (95% confidence intervals (CI) 3%, 16%) and of non-fatal myocardial infarction by 21% (95% CI 15%, 27%).²⁶⁻²⁷ Pravastatin reduced total cholesterol by 20% and LDL cholesterol by 26% in the WOSCOPS study of hypercholesterolaemic

Table 1 Fasting serum cholesterol and triglycerides in active and inactive RA

Lipid	Active RA*		Inactive RA*		ranked ANOVA	
	n	median (IQR)	n	median (IQR)	z	p Value
Cholesterol	57	4.83 (4-5.75)	35	5.47 (5.08-6.57)	3.6	0.0004
Triglyceride	51	1.47 (1.19-1.65)	30	1.5 (1.02-1.87)	0.6	0.54

*Active RA defined as those requiring initiation or change in SAARD, inactive RA as those with minimal joint inflammation and low ESR and CRP. Unpublished data from Mulherin *et al*.³¹

subjects, equating to a 31% reduction in risk of non-fatal myocardial infarction or death by five years.²⁸

It seems therefore that the advantageous effects of anti-malarial drugs on lipid profile compare well with those achieved by using specific lipid lowering treatment. In this respect, hydroxychloroquine may offer advantages over other SAARDs in the treatment of RA patients at increased cardiovascular risk. With the shift to aggressive early treatment of RA, however, it is more likely to be used in combination therapy rather than alone.²⁹

What are the implications for clinical practice? Modifiable cardiovascular risk factors should be considered including smoking, diabetes, hypertension, and hormone replacement therapy in post-menopausal women (oestrogen and progesterone can reduce the risk of a first myocardial infarction by 50%).³⁰ Attention must be paid to lipids for those with a previous history of a cardiovascular event. Hydroxychloroquine should be considered in combination therapy regimens for patients with severe RA and adverse cardiovascular risk. Further research examining the relation between cardiovascular mortality in RA, dyslipidaemia, and the effects of chronic inflammation on vascular biology, lipids, and atherosclerosis might prove fruitful both to rheumatologists and cardiologists.

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