

Lipoproteins and their subfractions in psoriatic arthritis: identification of an atherogenic profile with active joint disease

S M Jones, C P D Harris, J Lloyd, C A Stirling, J P D Reckless, N J McHugh

Abstract

Objectives—(a) To characterise the lipid profile in psoriatic arthritis and investigate whether there are similarities to the dyslipoproteinaemia reported in rheumatoid arthritis and other inflammatory forms of joint disease; (b) to investigate whether there is an atherogenic lipid profile in psoriatic arthritis, which may have a bearing on mortality.

Methods—Fasting lipids, lipoproteins, and their subfractions were measured in 50 patients with psoriatic arthritis and their age and sex matched controls.

Results—High density lipoprotein cholesterol (HDL cholesterol) and its third subfraction, HDL₃ cholesterol, were significantly reduced and the most dense subfraction of low density lipoprotein (LDL), LDL₃, was significantly increased in the patients with psoriatic arthritis. Twenty patients with active synovitis had significantly lower total cholesterol, LDL cholesterol, and HDL₃ cholesterol than their controls. 25% of the patients with psoriatic arthritis had raised Lp(a) lipoprotein levels (>300 mg/l) compared with 19% of controls, but this was not statistically significant.

Conclusion—Raised levels of LDL₃ and low levels of HDL cholesterol are associated with coronary artery disease. Such an atherogenic profile in a chronic inflammatory form of arthritis is reported, which may be associated with accelerated mortality.

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Patients with rheumatoid arthritis (RA) have an accelerated mortality compared with the general population, which may be attributed in part to an increased risk of cardiovascular disease.¹ Active RA is associated with an abnormal lipid profile (dyslipidaemia), though the relative contribution of this to the increased mortality is uncertain. Altered concentrations of serum^{2–6} and synovial lipids⁷ and lipoproteins may occur, including reduced serum cholesterol,² decreased serum triglycerides,^{3–6} and altered apoprotein concentrations.³ In addition, decreased cholesterol in low density lipoprotein (LDL), and cholesterol in high density lipoprotein (HDL) have been found, especially in association with active disease.⁴ The causes of mortality in patients with psoriatic arthritis are less well documented, though there is evidence that mortality may be increased.⁸ A pattern of dyslipoproteinaemia, similar to that

seen in RA, has previously been reported in psoriatic arthritis, which normalises with a reduction in disease activity.⁵

Routine plasma lipid measurement, which does not take account of lipoprotein composition, may not identify patients with risk factors for atherosclerosis. For instance, a reduction in HDL cholesterol contributes to a risk of atheroma, whereas a concomitant reduction in total LDL cholesterol may be protective. In population studies a low HDL cholesterol associated with a high LDL cholesterol has been associated with an increased risk of atherosclerosis.⁹ Increased knowledge of lipoprotein composition, and the identification of lipoprotein subfractions, have added to our understanding of the mechanisms of metabolic disturbance in lipid disorders.¹⁰ It is now well established that the smallest, most dense component of LDL (LDL₃ in our study), is the most important factor in contributing to atheroma.¹¹

Lp(a) lipoprotein has emerged as an important and independent contributing factor to the risk of atherosclerosis.^{12–14} It is a high density lipoprotein in which apoprotein B 100, the protein moiety of LDL, is linked to apoprotein(a) by one or two disulphide bridges. Increased levels of Lp(a) lipoprotein have been found in RA, but have not previously been measured in psoriatic arthritis.¹⁵ In this study we performed a detailed analysis of lipoprotein composition in psoriatic arthritis and found changes that may lead to increased atherosclerosis and shortened survival.

Patients and methods

PATIENTS AND CONTROLS

Fifty patients attending the psoriatic arthritis clinic at the Royal National Hospital for Rheumatic Diseases were studied. Twenty of these patients had active joint disease, and LDL and very low density lipoprotein (VLDL) subfraction data were obtained for 13 of these. All patients had psoriasis, an inflammatory arthropathy, and were seronegative for rheumatoid factor. Age and sex matched controls were obtained from a concurrent local population survey. Table 1 shows demographic details for both patients and controls. The exclusion criteria for patients and controls were diabetes, hypothyroidism, renal disease, excess alcohol intake, current treatment with a lipid lowering agent, admission to hospital with a severe illness within the previous three months, pregnancy, and breast feeding. Excess alcohol intake was defined as an intake of greater than the recommended upper limit for alcohol consumption for men and women (28 units for

Royal National Hospital for Rheumatic Diseases, Upper Borough Walls, Bath BA1 1RL, UK
S M Jones
N J McHugh

Bath Institute for Rheumatic Diseases, Trim Bridge, Bath BA1 1HD, UK
S M Jones
N J McHugh

Diabetes and Lipid Research Group, Wolfson Centre, Royal United Hospital, Bath, UK
C P D Harris
J Lloyd
C A Stirling
J P D Reckless

Correspondence to:
Dr S M Jones, Consultant Rheumatologist, University Hospital of Wales, Heath Park, Cardiff, Wales
Email: sharon.jones@uhw-tr.wales.nhs.uk

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Table 1 Clinical details of 50 patients and controls with specific reference to factors known to affect lipids

Factor	Patient	Control
Mean age (years, range)	44.8 (20–72)	44.8 (20–72)
Sex (M/F)	21/29	21/29
Mean body mass index (SD)	25.8 (5.6)	24.6 (4.7)
PASI* score (mean, range)	3.3 (0–8.7)	0
Subgroup of joint disease (number of patients)		
Oligoarthritis	21	0
Polyarthritits	27	0
Mutilans	1	0
Spondylitis	1	0
History of gout	0	4
Topical dovanex	1	0
NSAIDs*	48	0
Oral contraceptive	0	5
Hormone replacement therapy	0	7
Antihypertensive drugs		
β Blockers	1	1
Thiazides	1	1

No patient or control had concurrent infection, malignancy, ischaemic heart disease, liver disease or was taking corticosteroids or retinoids.

*PASI = psoriasis area and severity index; NSAIDs = non-steroidal anti-inflammatory drugs.

men and 21 units for women). Any other concurrent or previous illness known to affect the lipid profile (infection, malignancy, gout, ischaemic heart disease, or liver disease) was recorded. Four patients in the control group had a history of gout but were not hyperuricaemic at the time of the study.

Present and previous drugs were noted for all patients, particularly oral corticosteroids, retinoids, thiazides, β blockers, oral contraceptives, and hormone replacement therapy. Five of the control group were taking oral contraceptives and seven hormone replacement therapy. None of the controls for the 13 patients on whom LDL and VLDL subfractions were measured were taking hormone replacement therapy.

All patients and controls were eating a normal Western diet. Body mass indices (kg/m^2) were calculated for all patients. Blood samples were taken from all patients after a 14 hour fast, centrifuged within two hours of collection, and kept at -20°C until analysis. Samples for ultracentrifugation were analysed immediately.

ASSESSMENT OF DISEASE ACTIVITY

The inflammatory markers, plasma viscosity, erythrocyte sedimentation rate (ESR), and C reactive protein (CRP) were measured in all patients. Active disease was defined as at least one clinically inflamed joint in association with a raised ESR (>20 mm/1st h) and/or viscosity (>1.72 mPa), and/or CRP (>10 mg/l). The psoriasis area and severity index (PASI) were used to record the severity and activity of skin disease.¹⁶

MEASUREMENT OF LIPOPROTEINS

Automated measurements were performed using an Abbott VP supersystem autoanalyser (Abbott Diagnostic Division, Maidenhead, UK). Lipids and lipoproteins were measured by standard precipitation techniques. Briefly, VLDL, total HDL, and its third, most dense subfraction (HDL_3) were prepared by precipitation with sodium dodecyl sulphate, heparin-manganese chloride, and dextran sulphate respectively. Cholesterol and triglyceride were measured in these subfractions by cholesterol

oxidase *p*-amino-antipyrene and glycerol phosphate oxidase *p*-amino-antipyrene enzymatic calorimetric methods (Boehringer, Mannheim, Germany) (interassay coefficients of variation (CV) 4% and 5%, and intra-assay CV 3% and 2% respectively). HDL_2 (density 1.063–1.125 g/ml) was calculated by subtraction of HDL_3 (density 1.125–1.210 g/ml) from total HDL. LDL cholesterol and LDL triglyceride were calculated by subtraction of the directly measured HDL and VLDL fractions from total serum cholesterol and triglyceride.

Apolipoprotein A I and apolipoprotein B were measured by electroimmunodiffusion in agarose gel (Sebia, Issy-les-Moulineaux, France). Lp(a) lipoprotein was measured in 45 patients by enzyme linked immunosorbent assay (ELISA) (TintElize Lp(a) lipoprotein, Biopool, Sweden: Box 1454, S-901 24 Umea) (assay range 0–800 mg/l).

MEASUREMENT OF LIPOPROTEIN SUBFRACTIONS

In 13 patients (nine female, four male) with active psoriatic arthritis randomly selected from the total patient group and 13 age and sex matched healthy volunteers, blood samples were fractionated by cumulative flotation ultracentrifugation as described by Lindgren *et al.*⁹ Briefly, plasma was adjusted to a density of 1.118 g/ml by adding solid sodium chloride (NaCl). Density adjusted plasma (2 ml) was layered onto the surface of 0.5 ml of a NaCl/sodium bromide solution (density 1.182 g/ml) in an ultracentrifuge tube. Solutions with the following densities were layered onto the surface of the plasma: 1 ml of 1.0988 g/ml followed by 1 ml of 1.086 g/ml, 2 ml of 1.079 g/ml, 2 ml of 1.0722 g/ml, 1.5 ml of 1.0641 g/ml, and, finally, 1.5 ml of 1.0588 g/ml. Ultracentrifugation was carried out in an SW41 Ti rotor at 23°C . Seven consecutive runs were performed, calculated to float lipoproteins of the following flotation rates (Sf = Svedberg flotation units) to the top of the tube: chylomicrons (Sf >400), three subfractions of VLDL: VLDL_1 , Sf 100–400; VLDL_2 : Sf 60–100; VLDL_3 , Sf 20–60; and three subfractions of LDL: LDL_1 , Sf 12–20; LDL_2 , Sf 6–12; LDL_3 , Sf 3–6. After each run, chylomicrons, VLDL_1 , VLDL_2 , and VLDL_3 were aspirated from the top 0.5 ml of the tube and LDL_1 , LDL_2 , and LDL_3 were aspirated from the top 1.0 ml of the tube, and the tube refilled with the same amount of solution of density 1.0588 g/ml. The cholesterol and triglyceride components of these subfractions were measured by the enzymatic calorimetric methods described above and automated measurements were made using the Abbott VP supersystem autoanalyser.

DATA ANALYSIS

Data were entered onto an Apple Macintosh computer and analysis was performed using paired *t* tests for continuous variables following normality testing and the χ^2 test for comparing proportions. Before the analysis the non-normally distributed data, including all triglyceride fractions and ratios and the VLDL cholesterol:apolipoprotein B ratio, were loga-

Table 2 Lipid and lipoprotein concentrations in 50 patients with psoriatic arthritis and 20 patients with active disease and their age and sex matched controls. Results are expressed as means (SEM). Statistics: *t* test

Lipid/lipoprotein concentration (units)	Patients with psoriatic arthritis (n=50)	Controls	Patients with active disease (n=20)	Controls
Mean age (years, range)	44.8 (20–72)	44.8 (20–72)	42.5 (20–72)	42.5 (20–72)
Total cholesterol (mmol/l)	5.43 (0.2)	5.82 (0.13)	4.99 (0.24)***	6.08 (0.22)***
VLDL cholesterol (mmol/l)	0.51 (0.05)	0.49 (0.04)	0.44 (0.05)	0.51 (0.04)
LDL cholesterol (mmol/l)	3.67 (0.19)	4.0 (0.1)	3.3 (0.25)*	4.12 (0.25)*
HDL cholesterol (mmol/l)	1.12 (0.05)*	1.29 (0.1)*	1.09 (0.05)	1.33 (0.1)
HDL-3 cholesterol (mmol/l)	0.62 (0.04)***	0.75 (0.02)***	0.62 (0.1)*	0.77 (0.09)*
HDL-2 cholesterol (mmol/l)	0.52 (0.03)	0.57 (0.04)	0.49 (0.18)	0.56 (0.17)
Total cholesterol: HDL cholesterol	5.40 (0.34)	5.14 (0.47)	5.30 (0.65)	4.86 (0.33)
Total triglyceride (mmol/l)	1.15 (1.09)	1.13 (1.07)	0.99 (1.14)	1.35 (1.1)
VLDL triglyceride (mmol/l)	0.30 (1.15)	0.32 (1.13)	0.25 (1.22)	0.35 (1.27)
LDL triglyceride (mmol/l)	0.63 (1.1)	0.52 (1.1)	0.53 (1.16)	0.59 (1.13)
HDL triglyceride (mmol/l)	0.23 (1.04)	0.25 (1.15)	0.21 (1.06)	0.24 (1.11)
Total cholesterol: total triglyceride	4.57 (1.07)	5.00 (1.07)	4.95 (1.65)	4.44 (1.51)
VLDL cholesterol: VLDL triglyceride	1.35 (1.07)	1.36 (1.07)	1.36 (1.65)	1.23 (1.84)
LDL cholesterol: LDL triglyceride	5.47 (2.23)**	7.40 (1.07)**	5.75 (1.86)	6.69 (1.49)
HDL cholesterol: HDL triglyceride	4.76 (1.05)	4.95 (1.20)	4.71 (1.54)	5.26 (1.55)
Apolipoprotein A I (mg/l)	1370 (42.2)	1370 (48.8)	1340 (42.2)	1450 (48.8)
Apolipoprotein B (mg/l)	800 (36.8)	780 (58.6)	710 (36.8)	830 (58.6)
Apolipoprotein A I: HDL cholesterol	132 (6.8)	115 (6.2)	138 (16.7)	111 (4.16)
Apolipoprotein B: LDL cholesterol	24 (2.2)	19.9 (0.92)	25 (4.68)	21 (1.12)

Significant results for patients with psoriatic arthritis *v* controls: **p*<0.05; ***p*<0.01; ****p*<0.005. VLDL = very low density lipoprotein; LDL = low density lipoprotein; HDL = high density lipoprotein.

rhythmically transformed for data analysis, and are given in the text and tables as antilogs. Values are presented as means (SEM) for normally distributed data or as antilogs (means (SEM)) for non-normally distributed data. The Mann-Whitney U test was used for the non-parametric Lp(a) lipoprotein data. Pearson's coefficient of correlation was used for correlation analysis.

Results

CLINICAL CHARACTERISTICS

Fifty patients with psoriatic arthritis were recruited, 20 of whom met the criteria for clinically active peripheral joint disease. The patients spanned a spectrum of disease subgroups. All patients had mild skin disease only, at the time of the study, and no patient had a PASI score greater than 8.7 (table 1). There were no significant correlations between PASI scores and any lipid parameter.

The major differences in treatment between patients and controls were in the use of hormone replacement therapy (HRT) in seven of the controls, and non-steroidal anti-inflammatory drugs (NSAIDs) in all but two of the patients, which will be discussed. None of the nine female controls used in the ultracentrifuge study were taking HRT or oral contraceptives.

LIPID AND LIPOPROTEIN CONCENTRATIONS

Table 2 shows the lipid and lipoprotein results for 50 patients with psoriatic arthritis, including 20 patients with active joint disease, and their age and sex matched controls. HDL cholesterol was significantly reduced in the patients with psoriatic arthritis and the difference was related to cholesterol in HDL₃. There was no difference in the mean cholesterol in HDL₃ between the total group of 50 patients and those with active disease, so the significance of the difference between patients and controls was greater for the total group. Reduced total cholesterol levels were even more pronounced

in the 20 patients with active synovitis who were analysed separately. Patients with active arthritis had significantly lower total cholesterol and LDL cholesterol than their controls. The relative overall influence of LDL cholesterol and HDL cholesterol was expressed by calculating the ratio of serum total cholesterol concentration to that of HDL cholesterol (table 2). The ratio tended to be higher for patients than controls in both the total patient group and those with active disease, but did not reach statistical significance.

To assess any proportional changes in cholesterol and triglyceride in patients versus controls, the ratios of total cholesterol to triglyceride and their relative proportions in each lipoprotein were analysed (table 2). For the total group of 50 patients, the cholesterol:triglyceride ratio in LDL was significantly less than in the control subjects, indicating a relative depletion of cholesterol compared with triglyceride in this lipoprotein. There was a similar trend in patients with active arthritis, though the difference did not reach significance. The total cholesterol:total triglyceride ratio and proportions of cholesterol and triglyceride in HDL tended to be lower in the patient group, but the differences were not significant. The VLDL cholesterol:VLDL triglyceride ratio was similar for patients and controls.

APOLIPOPROTEINS

For the total group there were no significant differences in the apolipoproteins A I and B in the patients with psoriatic arthritis compared with controls (table 2). In the 20 patients with active disease, both apolipoproteins tended to slightly lower, but this was not significant. Apolipoprotein A I is the predominant protein in HDL and apolipoprotein B the predominant protein in LDL. Therefore the apolipoprotein A I:HDL cholesterol and apolipoprotein B:LDL cholesterol ratios were calculated and compared for patients and controls. Both ratios

Table 3 Concentration of cholesterol, triglyceride, phospholipid, and protein of each lipoprotein subfraction and their total mass for patients with psoriatic arthritis and controls (n=13). Results are expressed as means (SEM). Units mg/dl

	Total cholesterol		Triglyceride		Phospholipid		Protein		Total mass	
	Patient	Control	Patient	Control	Patient	Control	Patient	Control	Patient	Control
Chylomicrons	0.12 (0.03)	0.11 (0.02)	0.36 (0.13)	0.45 (0.14)	0.05 (0.01)*	0.37 (0.15)*	0.18 (0.03)	0.35 (0.18)	0.65 (0.16)	1.28 (0.29)
VLDL ₁	1.82 (0.59)	1.05 (0.27)	14.5 (4.44)	7.62 (1.48)	2.8 (0.9)	1.06 (0.2)	1.81 (0.59)	1.19 (0.32)	20.94 (6.49)	10.92 (1.99)
VLDL ₂	3.09 (1.05)	2.08 (0.41)	15.5 (4.48)	11.62 (2.09)	4.2 (1.3)	2.46 (0.33)	2.99 (0.89)	2.1 (0.34)	30.65 (18.35)	12.38 (3.03)
VLDL ₃	9.67 (2.66)	7.79 (1.43)	20.88 (4.83)	16.38 (1.94)	9.89 (2.37)	7.03 (1.05)	7.0 (1.88)	6.0 (0.85)	45.22 (12.04)	35.52 (3.96)
LDL ₁	13.95 (1.85)	15.24 (1.86)	9.49 (1.15)	7.68 (0.81)	9.99 (1.12)	9.12 (1.25)	9.56 (0.9)	9.03 (0.97)	42.99 (4.51)	41 (4.51)
LDL ₂	55.92 (2.99)	65.96 (4.92)	10.77 (1.33)	8.48 (1.03)	34.49 (3.17)	37.59 (2.95)	39.95 (1.96)	40.99 (2.66)	142.8 (9.46)	153.6 (9.97)
LDL ₃	25.59 (3.81)**	14.53 (0.79)**	4.02 (0.67)**	1.92 (0.23)**	13.98 (3.39)*	7.28 (0.72)*	20.74 (3.42)*	11.92 (0.91)*	61.9 (10.61)*	35.65 (2.18)*

Significant results for patients with psoriatic arthritis *v* controls: *p<0.05; **p<0.01.

tended to be greater for patients than controls, but in no case was this significant.

LIPOPROTEIN SUBFRACTION COMPOSITION

Thirteen patients with active joint disease, randomly selected from the group of 20 patients, were further studied to determine their lipoprotein subfraction composition. Their initial profiles were similar to the 20 patients with active disease (data not shown). Their mean age was 37 years (range 20–59). HDL cholesterol was again significantly reduced compared with controls (1.09 *v* 1.41 mmol/l; p<0.005).

On analysing LDL subfraction constituents (table 3) the major difference between patients with psoriatic arthritis and controls was an increase in all components of LDL₃. There were significantly greater concentrations of total cholesterol, in both its free and esterified forms, triglyceride, phospholipid, and protein in LDL₃. Thus the total mass of LDL (lipid + protein) and LDL₃:total LDL mass ratio was significantly greater in psoriatic arthritis than in controls (table 3). Thus there was a greater percentage of LDL₃ in the total LDL in patients with psoriatic arthritis (24.8%) than in controls (15.5%) (*t* test, p<0.001). The mean ratio of LDL₃:LDL₂, which further illustrates the value of small dense particles, was more than twice as great in the patients than in the controls (0.46 versus 0.22).

We next analysed the proportions of the various components making up the LDL lipoprotein subfractions. All components within LDL₃ were uniformly increased with no disproportion compared with controls, apart from an increase in phospholipids. However, there was significantly less cholesterol in LDL₁ and LDL₂ in patients than in controls and a concomitantly greater percentage of triglyceride in LDL₂.

There were no significant differences between patients and controls in the total mass of VLDL₁, VLDL₂, or VLDL₃ subfractions or in the concentration of their constituents, but there were some significant differences in the percentage composition of the various constituents. There was a trend for the triglyceride, cholesterol, and phospholipid concentrations in VLDL₁ and its total mass to be increased compared with controls (table 3). The mean

proportion of VLDL₁ in total VLDL was 22.3% versus 16.5% for controls. Also, the percentage of triglyceride in VLDL₃ was significantly reduced in the patients compared with controls, and there was a trend for an increase in the percentage of triglyceride in VLDL₁.

The chylomicron phospholipid concentration was significantly less in psoriatic arthritis than controls (table 3), which was reflected in a significant decrease in the percentage composition of phospholipid in chylomicrons.

LP(A) LIPOPROTEIN

There were no significant differences in Lp(a) lipoprotein levels in patients with psoriatic arthritis and controls (median 174 mg/l (range 10–800) *v* 157 mg/l (range 10–800)). When the patients with active synovitis were analysed separately, Lp(a) lipoprotein levels were found to be increased (median 187 mg/l *v* 88 mg/l), but this did not reach statistical significance (Mann-Whitney U test). Also, 25% of patients with psoriatic arthritis had Lp(a) lipoprotein levels greater than 300 mg/l compared with 19% of the controls, though the difference in the proportion was not significantly different. A power calculation indicates that 360 patients and controls would be required to gain a significant difference in the proportion of patients and controls with an Lp(a) lipoprotein of greater than 300 mg/l. There were weak positive correlations between Lp(a) lipoprotein levels and ESR (Pearson's *r*=0.27, p=0.098), plasma viscosity (*r*=0.27), and CRP (*r*=0.18).

Discussion

A pattern of dyslipidaemia similar to that found in RA has been reported in patients with psoriatic arthritis. Lazarevic *et al* studied 40 patients with psoriatic arthritis and found decreased concentrations of total lipids, total cholesterol, cholesterol in LDL, and cholesterol in HDL, which normalised with a reduction in disease activity.⁷ In our study we also found significantly reduced total cholesterol, LDL cholesterol, and HDL cholesterol, and a generalised suppression of total cholesterol, LDL and HDL cholesterol was most apparent in those patients with active joint disease. In addition, LDL₃ total mass and its cholesterol and triglyceride components were

significantly raised, and there was a tendency for Lp(a) lipoprotein to be increased. Neither of the lipid particles LDL₃ or Lp(a) lipoprotein have been previously studied in psoriatic arthritis.

Psoriasis alone may affect serum lipid levels, though usually only when severe, which was not the case in the current study.¹⁷ The effect of hormone replacement therapy, taken by seven of the controls, and NSAIDs, taken by 48 of the patients, requires discussion. Oestrogens tend to increase HDL cholesterol, reduce LDL cholesterol, especially small dense LDL (LDL₃ in this study) and may reduce Lp(a) lipoprotein¹⁸; progesterones tend to have the opposite effect. This might have had a small impact on the comparative data for the total group of 50 patients; however, we found a similar pattern with the controls for the 13 patients included in the ultracentrifuge study, in whom hormone replacement therapy was not a confounding factor. NSAIDs are not reported to affect lipid or lipoprotein levels but may have a minor effect on the acute phase response.

The decrease in total LDL cholesterol seen in our study group may imply protection from atherosclerosis. However, patients with active psoriatic arthritis had a significant shift in distribution towards the smallest, most dense particles of LDL (LDL₃), with normal or low levels of LDL₁ and LDL₂. LDL₃ constituted 24.8% of the total LDL for the patients compared with 15% for the controls. These findings are clinically relevant because high levels of LDL₃, in comparison with the levels of LDL₁ and LDL₂, are strongly associated with atherosclerosis in population studies.¹¹ A similar pattern has been reported in non-insulin dependent diabetes mellitus, in which LDL cholesterol may be normal or reduced in association with excess small dense LDL₃ and low HDL cholesterol.^{19,20} The shift in LDL composition is much more marked in diabetes mellitus, where the percentage of LDL₃ in total LDL may reach 40%. In diabetes the shift is associated with hypertriglyceridaemia and increased VLDL₁. High levels of VLDL₁ may be more slowly catabolised, particularly if there is reduced lipoprotein lipase activity. High levels of VLDL₁ encourage increased neutral lipid transfer of cholesterol ester from HDL and LDL to VLDL, in exchange for triglyceride, leading to small dense LDL (LDL₃). In the current study there were no significant differences in the total triglyceride levels or the concentration of VLDL subfractions compared with controls; however, there was a trend for a slightly greater proportion of VLDL₁ in relation to VLDL₂ and VLDL₃, which suggests that the postulated mechanism in diabetes may be operating to some extent in active psoriatic arthritis. Small dense LDL has also been linked to increased hepatic triglyceride lipase and it would be of value to measure this in a further study.²¹

The combination of a low HDL cholesterol and a high LDL₃, found in the current study, is strongly associated with an increased risk of atherosclerosis in population studies.²² Both subfractions of HDL were reduced compared with controls in this study, but only the depression of HDL₃ reached statistical significance.

HDL₃ is thought to be less "athero-protective" than HDL₂, so its increased suppression in relation to HDL₂ has less relevance to the cardiovascular risk.

There are a number of mechanisms whereby increased LDL₃ may cause atherosclerosis. LDL₃ becomes rapidly oxidised and has an enhanced ability to cross cell surfaces, where it may be directly toxic to endothelium. The clearance of LDL₃ from the circulation by the LDL receptor mechanism may also be impaired, making more LDL available for removal by the atherogenic scavenger pathway.²³ In the arterial wall, the resulting lipid-rich macrophages become foam cells that accumulate in early atheromatous lesions. An association between the susceptibility of LDL to oxidation *in vitro* and the extent of atherosclerosis of coronary vessels has been demonstrated.²⁴

Lp(a) lipoprotein is an independent risk factor for atherosclerosis and thrombosis, with values above 300 mg/l associated with a twofold increased risk of myocardial infarction¹² and an accelerated progression of coronary atheroma.¹³ Its mode of action is thought to be related to homology with plasminogen, resulting in inhibition of fibrinolytic activity and increasing the likelihood of thrombosis. Increased levels of Lp(a) lipoprotein have been reported in RA, where it may behave as an acute phase protein.¹⁴ NSAIDs may have a modest effect of reducing the Lp(a) lipoprotein by reducing the acute phase response. Our results show a similar pattern to that reported in RA, with a slight increase in Lp(a) lipoprotein levels and weak positive correlations with inflammatory markers. A power calculation indicates that 360 patients and controls would be needed to produce a significant proportional increase in Lp(a) lipoprotein in patients compared with controls.

Lipoproteins exist as packages containing predominantly cholesterol, triglyceride, and apolipoproteins. The synthesis and catabolism of each constituent can proceed independently of the other contents of the package, though a certain amount of covariance exists. LDL cholesterol and triglyceride may be high or low, without any change or with an opposing change in apolipoprotein concentration. Apolipoprotein A I is the predominant apolipoprotein in HDL, comprising 60% of the protein mass, and apolipoprotein B is the predominant apolipoprotein in LDL and VLDL, comprising 90% of the protein mass of LDL. LDL and VLDL have one apolipoprotein per lipoprotein package, so apolipoprotein concentration is an indication of the number of particles present. Lower apolipoprotein A I and high apolipoprotein B have been found in association with coronary artery disease. The apolipoproteins A I and B in the patients with psoriatic arthritis were not significantly different from those in controls, though they tended to be lower in the active group, perhaps partly reflecting the generalised reduction in cholesterol and cholesterol associated lipids. This notion is supported by the apolipoprotein A I:LDL cholesterol and apolipoprotein B:LDL cholesterol ratios, which tended to be greater in the patients than controls, reflecting a

greater relative suppression of HDL cholesterol than apolipoprotein A I and of LDL cholesterol than apolipoprotein B.

There are a number of reasons why dyslipidaemia may be associated with an active inflammatory arthritis. An increased production of acute phase proteins by the liver in inflammation may occur at the expense of lipoprotein production, thereby tending to reduce lipoprotein levels.² Enhanced reticuloendothelial system uptake of lipoproteins in chronic inflammation may occur, which is compatible with an accelerated atherosclerotic process at the vessel wall.⁶ Mediators of inflammation, such as the interferons (α , β , γ), CRP, and the proinflammatory cytokines, interleukin 1 and tumour necrosis factor α , produced by macrophages have been shown to suppress lipoprotein lipase activity and increase oxidative metabolism.²⁵⁻³¹ Reduced levels of the antioxidant selenium have also been found in psoriatic arthritis.³²

It is likely that a combination of factors related to the systemic inflammatory response may operate in psoriatic arthritis to produce the observed pattern of dyslipoproteinaemia.

A reported increase in occlusive vascular disease in psoriasis has led to various studies of lipids and lipoproteins, with conflicting results.¹⁷ Hypercholesterolaemia or hypertriglyceridaemia, or both, may occur, which contrasts with the findings in psoriatic arthropathy. Apolipoprotein B has been reported to be low, unchanged, or increased in different studies.¹⁷⁻³³ However, an increased prevalence of hypertension, diabetes mellitus, impaired glucose tolerance, and hyperuricaemia, all of which are known to be associated with dyslipoproteinaemia, is associated with psoriasis and may not have been adequately controlled in some studies. In addition the severity of psoriasis may affect the results.¹⁷ None of our patients had severe skin disease (defined as a PASI score of greater than 30) at the time of the study, making it unlikely that psoriasis itself contributed to our findings.

To conclude, this is the first report documenting high levels of LDL_s in relation to total LDL in an inflammatory form of arthritis. Lipoprotein subfractions and Lp(a) lipoprotein warrant further investigation in a larger group of patients with psoriatic arthritis, with the inclusion of hepatic triglyceride lipase measurement, and longitudinal data. Lipoprotein composition also warrants investigation in RA, where the increased mortality from atherosclerosis is more clearly established. In patients with a pattern of low HDL, high LDL_s, and high Lp(a) lipoprotein, long term follow up is needed to determine the predictive risk of macrovascular disease.

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