

Lipid Disorders and Rheumatic Diseases

K H Leong, *FAMS, M Med (Int Med), FRCP (Edin)

Abstract

Lipid abnormalities can exist in patients with rheumatic diseases. Many mechanisms give rise to these abnormalities and include treatment with corticosteroids and upregulation of certain cytokines in active rheumatic disease. Premature atherosclerosis can occur in these patients with significant morbidity and mortality. Greater awareness and earlier treatment of these lipid problems may lead to better outcomes.

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Introduction

The relationship between lipid disorders and arthritis is manifold. Hyperlipidaemia may manifest clinically in the musculoskeletal system. In 1968, Khachadurian¹ studied 14 families of whom 18 homozygotes of Type II hyperlipidaemia were identified. Ten of these patients experienced a migratory polyarthritis resembling rheumatic fever. Since then, numerous studies have been done but the results are conflicting as the association between familial hyperlipidaemia and rheumatic syndromes remains unclear.

Lipid microspherules have been found in the joints of patients with rheumatoid arthritis. Ananth et al² analysed levels of cholesterol, apolipoprotein A-I and apolipoprotein B in the synovial fluids of twelve untreated classic rheumatoid arthritis (RA) patients as well as eight patients with degenerative joint disease. The mean apo A-I, apo B and cholesterol levels were significantly higher in the synovial fluid of the RA patients. A likely explanation is the increased permeability for these lipoproteins constituents across RA synovial membranes. Lazarevic et al³ did not find concomitant systemic lipid abnormalities nor the presence of serum antilipoprotein antibodies in such patients. Whether these synovial lipoproteins are involved in the pathogenesis of RA is unclear.

Many rheumatic diseases carry a predisposition to premature atherosclerotic events, contributing significantly to late morbidity and mortality.

In addition, dyslipidaemia may be a consequence of rheumatic diseases. Active rheumatic disease can cause a picture resembling type IV hyperlipidaemia, possibly

mediated by the effect of cytokines on lipoprotein lipase or the effect of anti-lipoprotein antibodies. In lupus nephritis, the nephrotic syndrome often produces a type IIb picture.

Lastly, drugs such as steroids and hydroxychloroquine can affect blood lipid profiles.

Rheumatic Disorders and Their Patterns of Dyslipidaemia

Rheumatic diseases can contribute to dyslipidaemia in several ways. Active disease has been shown to be associated with low high density lipoprotein (HDL) levels. Ilowite et al⁴ identified this distinct pattern in a set of paediatric systemic lupus erythematosus (SLE) patients studied longitudinally. The mean HDL-cholesterol and apo-AI were markedly lower in untreated and clinically active SLE patients compared with controls. When the illness was treated and SLE became inactive, HDL-cholesterol and apo-AI rose. Svenson et al⁵ studied 48 patients with untreated rheumatoid arthritis and 21 with seronegative spondyloarthropathy. Compared to healthy controls, these patients with active disease had lower levels of very low density lipoprotein (VLDL)-cholesterol, VLDL-triglyceride, HDL-triglyceride and HDL-cholesterol. Possible mechanisms include the suppression of lipoprotein lipase activity by cytokines upregulated in active rheumatic disease, the effect of anti-lipoprotein antibodies and the role of acute phase reactants such as serum amyloid A protein in modifying HDL metabolism.

Corticosteroids usage contributes to a type IIb hyperlipidaemia as well as the presence of a nephrotic syndrome which is common in lupus nephritis. Ettinger et

* Consultant Rheumatologist, Gleneagles Medical Centre

Visiting Consultant, Tan Tock Seng Hospital and KK Women's and Children's Hospital

Address for Reprints: Dr Leong Keng Hong, 6 Napier Road, #04-18 Gleneagles Medical Centre, Singapore 258499.

al⁶ compared 46 SLE patients and 30 controls and found that SLE patients who were on corticosteroids had higher levels of total cholesterol, total triglyceride and low density lipoprotein (LDL)-cholesterol. Those who were not on steroids had levels similar to controls except for a lower HDL cholesterol level.

Lipid abnormalities have been described in various cohorts of SLE patients. In a predominantly Oriental population of 100 SLE patients, Leong et al⁷ found that 35 had a type IIb hyperlipidaemia with a raised mean total cholesterol level of 361 mg/dl, LDL of 236 mg/dl, HDL of 50.4 mg/dl and triglyceride level of 354 mg/dl. These levels are very grossly abnormal compared to the mean values of the Singaporean Chinese population. There was a significant association with renal involvement and the use of corticosteroid. Both factors were present in local patients. In contrast, in a cohort of SLE patients at Bath, United Kingdom, it was found that compared to age and gender matched controls, the patients had lower levels of total cholesterol, LDL, TG, apo A-I and apo-B.⁸ Interestingly, HDL2 was lower but not HDL3. This is consistent with suppression of lipoprotein lipase activity. However, in these patients, there were no significant differences in the lipoprotein lipase activity between patients with active and inactive SLE. Only 6% of the Bath patients had renal involvement and only 46% were on corticosteroids.

Lazarevic et al⁹ studied 60 patients with active rheumatoid arthritis, 40 patients with psoriatic arthritis, 21 with osteoarthritis and 65 healthy blood donors. Patients with severe rheumatoid activity had lower levels of LDL cholesterol and HDL cholesterol. When their illness became less active, the serum lipids normalised. This was also the case for psoriatic arthritis patients but not for osteoarthritis.

Besides the effect of upregulated cytokines on lipoprotein lipase activity, another mechanism could be mediated via the presence of anti-lipoprotein antibodies. Lazarevic et al¹⁰ found that anti-lipoprotein antibodies against VLDL and LDL were present in 26 of 39 (38%) patients with active rheumatoid arthritis but not in patients with osteoarthritis, psoriatic arthritis or healthy blood donors. Patients with these antibodies had lower cholesterol levels in all subfractions and elevated serum triglycerides.

Another mechanism could be mediated via acute phase reactants such as serum amyloid A protein. Kumon et al¹¹ showed that in patients with rheumatic disease, total HDL cholesterol, apoprotein A-I and apoprotein A-II were lower than in normal subjects and were inversely correlated with plasma concentrations of serum amyloid A protein (SAA). SAA displaces apo A-I and apo A-II which results in increased catabolism of HDL. Oxidised LDL may also be an important part of the pathogenesis of inflammation in rheumatoid arthritis.

Links Between Lipaemia, Rheumatic Disorders and Mortality

Rheumatoid arthritis is associated with increased mortality. Prior et al¹² studied 489 consecutive patients with classical rheumatoid arthritis followed up for a mean of 11.2 years and found a three-fold increase in overall mortality compared with age and sex-specific rates in the general population. Cardiovascular deaths were 2.5 times higher than expected values compared to age and sex matched population figures. Rasker and Cosh¹³ followed up a cohort of 100 RA patients for 18 years. Of the 43 who died, 16 were related to RA while 27 were unrelated. In the latter group, 14 were cardiac deaths and 8 were cerebrovascular events.

Urowitz et al¹⁴ recognised a bimodal pattern in the morbidity and mortality of SLE with early events due to active disease or infections and late events related to atherosclerotic complications. Petri et al¹⁵ studied prospectively the risk factors for coronary artery disease in 229 SLE patients. Nineteen patients (8.3%) had coronary artery disease and accounted for 3 out of 10 deaths in this cohort. The most significant factors using a best multiple logistic regression model were age at diagnosis, duration of prednisone use, requirement for anti-hypertensive treatment, maximum cholesterol level and obesity.

Many studies including some involving autopsies have shown premature coronary atherosclerosis and myocardial infarction in relatively young patients with SLE. Bulkley and Roberts¹⁶ compared necropsy findings of 36 SLE patients with findings in patients who were not on corticosteroids. Subepicardial and myocardial fat was increased in all 36 patients. In 42% of the 18 patients who received corticosteroids for more than one year, the lumen of at least one of the three major coronary arteries was narrowed by more than 50% by atherosclerotic plaques. In contrast, none of the 17 patients who received corticosteroids for less than one year had such findings.

Current data therefore suggest that there is a tendency for premature death in patients with rheumatic diseases. The presence of cardiovascular or cerebrovascular disease greatly influences mortality figures. Hence a heightened awareness of factors associated with premature atherosclerosis is critical in the therapy of rheumatic patients.

Management

Rationale for Treatment

Rheumatic diseases carry an increased risk of morbidity and mortality from premature atherosclerosis. In patients on long-term corticosteroid therapy, the main abnormalities are in the LDL subfraction. There have been many studies which clearly show the relationship between hypercholesterolaemia and the risk of

coronary artery disease. The Framingham Study¹⁷ showed that this risk is positively associated with levels of LDL cholesterol and inversely associated with HDL levels. This is particularly interesting, as active rheumatic diseases have been found to be associated with low HDL and in some instances, high triglyceride levels.

There is strong evidence that the treatment of lipid abnormalities results in improved outcomes. The US Lipid Research Clinics Coronary Primary Prevention Trial¹⁸ randomised 3806 men in a double blind study lasting 7 to 10 years. The treatment group received cholestyramine and showed a reduction in the total and LDL cholesterol levels. This was associated with a reduction in primary endpoints of deaths related to coronary artery disease and non-fatal myocardial infarctions. There was also a reduction in angina, positive exercise ECG and requirement for coronary bypass surgery. The Helsinki Heart Study¹⁹ showed that lowering of serum triglyceride and raising of HDL levels led to a reduction in fatal and non-fatal myocardial infarction.

There have also been studies which use angiographic evidence of regression of coronary atherosclerosis as endpoints. The Cholesterol-Lowering Atherosclerosis Study²⁰ showed that colestipol combined with niacin can lead to regression in coronary atherosclerosis as assessed by coronary angiography.

Besides causing clinical events related to vascular thrombosis, dyslipidaemia can accelerate the progression of renal disease. The obese Zucker rat was an animal model that illustrates this point.²¹ These animals developed hyperlipidaemia by the age of two weeks and renal injury by 16 to 18 weeks especially if they were fed a high-cholesterol diet. The use of lipid lowering therapy prevented this injury. The mechanism of injury is possibly through the presence of cholesterol or triglyceride rich VLDL particles. These particles bind to receptors on macrophages resulting in the formation of foam cells which are often found in atheromatous plaques and glomeruli. Lipoproteins in the mesangium undergo oxidative modification and are taken up by scavenger receptors on macrophages and mesangial cells.

Type IV and type IIb hyperlipidaemia are known to be associated with chronic renal disease and nephrotic syndrome. Although long-term studies are lacking in resolving whether treatment of persistent hyperlipidaemia in the nephrotic syndrome could lower the risk of atherosclerotic-clinical events, it appears logical that patients with renal disease should, as far as possible, be rendered normolipidaemic.

Treatment

Risk factors for hyperlipidaemia have to be assessed for the individual patient. Some of these factors are

amenable to modification. Smoking cessation is of major importance as is weight control.

Dietary modification plays a major role in the management of hyperlipidaemia. In mild cases, this may be the only intervention that is necessary to achieve the therapeutic target. The level of serum lipid to be attained would be based on studies in the indigenous population. An example is the US National Cholesterol Education Programme guidelines.²² Desirable levels of serum lipids were defined as total cholesterol of less than 5.2 mmol/l, LDL cholesterol less than 4 mmol/l, HDL cholesterol greater than 1 mmol/l and triglyceride less than 2 mmol/l. Abnormal values were defined as total cholesterol greater than 6.5 mmol/l, LDL cholesterol greater than 5 mmol/l, HDL cholesterol less than 0.9 mmol/l, triglyceride greater than 2.5 mmol/l. Anything in between these values was considered borderline. Special lipid lowering diets (step one and step two diets) were devised which should reduce serum cholesterol by 0.5 to 1.5 mmol/l.

In some patients, dietary measures alone are inadequate and pharmacological agents have to be used. These include statins, fibrates, niacin, cholestyramine and probucol. The choice of a specific agent depends on the pattern of dyslipidaemia. High levels of low density lipoprotein can be lowered with a statin whereas low HDL and high TG can be treated with a fibrate. Combinations should be used cautiously. Randomised controlled trials are needed to determine the best approach to treatment.

The Role Of Hydroxychloroquine

Hydroxychloroquine is often used in the treatment of mild SLE and RA. Besides its immune-modulating effects, it has a protective role with regards to hyperlipidaemia induced by corticosteroids. Although the exact mechanism of its action on lipids is unknown, several authors have noted a beneficial effect on lipid profiles. Hodos et al²³ performed a case-control study comparing patients with SLE who were on hydroxychloroquine versus those who were not. The treatment group had 35% to 45% lower levels of total triglyceride, VLDL-triglyceride, LDL-triglyceride, HDL-triglyceride, VLDL-cholesterol and apoprotein CIII. Wallace et al²⁴ studied 155 women with RA or SLE and divided them into four groups, namely hydroxychloroquine without steroids, steroids without hydroxychloroquine, both steroids and hydroxychloroquine and neither. They found that hydroxychloroquine was strongly associated with low serum levels of cholesterol, triglycerides and LDL-cholesterol regardless of concomitant steroid use. Petri et al²⁵ performed a cohort longitudinal study involving 264 patients with SLE. In a regression model for steroid use, a change in prednisone dose of 10 mg was associated with a change in cholesterol level of 7.5 ± 1.46 mg%

and a weight gain of 5.5 ± 1.23 pounds. On the other hand, hydroxychloroquine at 200 mg or 400 mg per day were both associated with lower serum cholesterol.

Conclusion

Lipid abnormalities exist in patients with rheumatic diseases. A clear understanding of the mechanisms leading to dyslipidaemia will lead to improved treatment strategies and better outcomes in morbidity and mortality.

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