

# Atherogenic lipid profiles and its management in patients with rheumatoid arthritis

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**Abstract:** Cardiovascular morbidity and mortality are enhanced in rheumatoid arthritis, which might be due to an increased prevalence of cardiovascular risk factors such as dyslipidemia. The dyslipidemia observed in RA appears to be dependent on disease activity, ie, a higher disease activity is associated with lower total cholesterol levels and even more depressed high density lipoprotein levels, leading to a higher (ie, unfavorable) atherogenic index. It appears that this dyslipidemia is already present long before the clinical onset of rheumatoid arthritis. Antirheumatic drug treatment with disease modifying antirheumatic drugs as well TNF-blocking agents has, in general, favorable, albeit moderate, effects on the lipid profile. Therefore, it is unlikely that the observed beneficial effects of antirheumatic drug treatment on cardiovascular morbidity and cardiovascular mortality in rheumatoid arthritis is mediated through effects on the lipid metabolism. Management of dyslipidemia in rheumatoid arthritis should be part of a general cardiovascular risk management. Hence, in addition to the assessment of the lipid profile, other cardiovascular risk factors should be determined and appropriate treatment installed when indicated. Lower treatment thresholds should be considered in view of the enhanced cardiovascular risk in rheumatoid arthritis and guidelines should be developed based on epidemiological data.

**Keywords:** cholesterol, dyslipidemia, rheumatoid arthritis, cardiovascular disease

## Introduction

Rheumatoid arthritis (RA), a chronic inflammatory joint disease of unknown etiology, affects approximately one percent of the general population (Lems and Dijkman 2000). Estimated standardized mortality ratio's associated with RA range from 1.3 to 3.0 (Van Doornum et al 2002; Goodson and Solomon 2006). This increased mortality is largely attributable to cardiovascular disease (CVD), particularly coronary atherosclerosis (Solomon et al 2003; Maradit-Kremers, Crowson et al 2005). The cardiovascular morbidity found in RA patients appears to be increased by twofold or more compared to the general population (age and sex matched).

This increased cardiovascular risk in RA patients could have several causes. Firstly, the prevalence of new or established cardiovascular risk factors, such as dyslipidemia, diabetes mellitus, hypertension, higher body mass index (BMI), higher waist to hip-ratio or impaired physical fitness, might be increased (Pincus and Callahan 1986; Dessein et al 2005; Goodson and Solomon 2006). Secondly, undertreatment of risk factors may play a role (Redelmeier et al 1998; Boers et al 2004). Finally, RA itself, particularly its chronic inflammatory component, could be an independent cardiovascular risk factor (Maradit-Kremers, Nicola et al 2005).

Recently, new data on dyslipidemia in RA have been published which changed our insights about the lipid profile in RA. In this article, the current literature about dyslipidemia in RA will be reviewed with a focus on the more recent papers as well as a brief overview of the management modalities for RA and the effects of antirheumatic

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drugs on the lipid profile. Finally, treatment directions for dyslipidemia in RA will be discussed. The relevant literature was retrieved from a PubMed literature search using “rheumatoid arthritis” as one term and cholesterol, dyslipidemia and lipid profile as the other terms. Moreover, citations from the retrieved articles for additional studies were scanned.

## The lipid profile in rheumatoid arthritis

It is known that increased levels of total cholesterol (TC), low-density-lipoprotein (LDL)-cholesterol (LDL-C) and a decreased level of high-density lipoprotein (HDL) cholesterol (HDL-C) are associated with an increased incidence of cardiovascular disease in the general population. The available literature on lipid profiles in patients with RA is contradictory. There have been studies reporting either increased, decreased or similar levels for TC, LDL-C and HDL-C in comparison to control subjects (Heldenberg et al 1983; Lorber et al 1985; Lakatos and Harsagyi 1988; Kavanaugh 1994; Asanuma et al 1999). The discrepancies in the lipid values observed in the various studies might be due to differences in studied populations as well as in disease activity. There have been a few reports on lipid levels and their association with disease activity. One cross-sectional study in 28 patients with RA, with a mean disease duration of 7 years, demonstrated an inverse relationship between disease activity and lipid levels (Svenson et al 1987a). These findings were recently confirmed by a larger cross-sectional study in 204 patients with RA, demonstrating an inverse association between elevated CRP and HDL-C-levels (White et al 2006).

An important metabolic feature of RA is the catabolic state leading to loss of body cell mass due to an accelerated loss of skeletal muscle (Walsmith et al 2004). This is known as rheumatoid cachexia and important mediators are TNF $\alpha$  and other proinflammatory enzymes. These mediators are also associated with lowered TC and HDL-C levels (Kotler 2000), and as a higher disease activity in RA is accompanied with a higher TNF level this might explain the relationship between disease activity and lipid levels.

During the last decade interest has focused on apolipoprotein A-1 (apo A-1), apolipoprotein B (apo B) and lipoprotein(a) (Lp(a)). Apo A-1 is the protein present on the HDL-C particles, whereas apo B is found on the LDL-C, very low density lipoprotein (VLDL) and chylomicrons particles. Hence, assessment of plasma apo A-1 and apo B allow an assessment of the total number of anti-atherogenic and atherogenic particles, respectively. Lp(a) is modified form of LDL in which apo A-1 is bound to apo B.

There is some evidence that apo B might be a better predictor for cardiovascular events than LDL-C and that the apo B/apo A-1 ratio is an accurate risk factor for cardiovascular disease (Rader et al 1994; Walldius and Jungner 2006). In other words: Apo A-1 might protect against cardiovascular disease whereas apo B might increase the cardiovascular risk (Stampfer et al 1991; Sharrett et al 2001; Walldius et al 2001).

One of the first controlled studies reporting on apolipoprotein levels in RA was performed in 42 untreated patients (mean disease duration 27 months) and 42 age- and sex-matched controls (Park et al 1999). The investigators found significantly lower levels of apolipoprotein A1 and HDL-C in patients than in controls (128.5 mg/dL vs 151.8 mg/dL, 41.2 mg/dL (1.07 mmol/L) vs 54.9 mg/dL (1.43 mmol/L), respectively) and significantly higher levels Lp(a) (27.1 vs 18.0 mg/dL, respectively). The ratios of apo B/apo A1, total cholesterol/HDL-cholesterol were significantly higher in patients than in controls (0.82 vs 0.67, 4.4 vs 3.4, respectively). CRP levels had an inverse correlation with apolipoprotein A1 and HDL-C indicating an adverse effect of disease activity on lipid profile.

Lp(a) appears to have predictive value for cardiovascular disease in patients with hypercholesterolemia (Cantin et al 1998). Several earlier studies showed significantly lower Lp(a) levels in RA patients and a significant association with acute phase response (Rantapaa-Dahlqvist et al 1999). However, a later study found no significant elevation of Lp(a) in RA patients, nor a significant relationship between Lp(a) and the acute phase response (Lee et al 2000). Altogether, Lp(a) determination in RA seems to be of limited value.

## When does the dyslipidemia in RA start?

Altogether, it appears that dyslipidemia is already present in early RA and the question raises whether or not this phenomenon starts in the preclinical phase of RA. Hence, we investigated the lipid profile over time and its relationship with inflammation and serological markers, in subjects who later developed RA (Van Halm, Nielen et al 2006).

The lipid profile was determined in 1078 serial blood bank samples, of 79 blood donors who later developed RA. These samples were compared with 1071 control samples of unselected blood donors, matched for age and sex.

The samples of future RA patients displayed, on average, 4% higher TC, 9% lower HDLc, 17% higher triglyceride and 6% higher apo B levels compared to matched controls ( $p \leq 0.05$ ), at least ten years before the onset of symptoms.

Although the differences in the various lipid values were small they have clinical relevance, in the light of results from other studies (Menotti and Lanti 2003; Sprecher et al 2003; Menotti et al 2004). For instance, in a placebo controlled study with fibrates, the differences of the lipid values between the active treatment and the placebo group were similar to the found differences in the present study and the individuals treated with fibrates had ultimately a more than 20% risk reduction for CVD (Rubins et al 1999).

As inflammation only explained a small part of the observed differences in lipids between the persons who later develop RA and the controls we hypothesized that a less favorable lipid profile might be related to the development of RA by a common or linked background. This could be a socio-economic (including dietary) or a genetic background. Alternatively, lipids might modulate the susceptibility to the development of inflammatory diseases such as RA.

## Subfractions and functional properties of lipid particles

Proton nuclear magnetic resonance spectroscopy (NMR) quantifies subclasses of lipoproteins, lipid content and average particle size. LDL is divided in to three classes (LDL-1–LDL-3), and HDL into five classes of increasing particle size.

Hurt-Camejo et al demonstrated in a small controlled study significantly higher levels of small dense (eg, more atherogenic) LDL (LDL-1) and significantly lower levels of small dense HDL (HDL-2) in 31 RA patients and 28 sex- and age matched control subjects (Hurt-Camejo et al 2001). Concomitant “normal” LDL levels were lower in the RA patients whereas HDL levels were similar between the two groups. The observed rise of small dense LDL is important, in view of its association with cardiovascular disease in the general population.

The observed rise of small dense LDL might be due to increased levels of secretory group IIa phospholipase A2, an acute phase protein and an independent cardiovascular risk factor.

Another group looked at the function of HDL. Atherosclerosis starts when LDL infiltrates the artery wall and is oxidized by reactive oxygen species to oxidized LDL (ox-LDL). Ox-LDL leads to phospholipid release, activating endothelial cells, thereby initiating an inflammatory process which leads to the formation of foam cells and subsequent fatty streaks. Normal HDL exerts its antiatherogenic role by protecting LDL from oxidation (Ansell et al 2004) in addition to the inhibition of the expression of adhesion molecules

and its role in the reverse cholesterol transport. This anti-inflammatory HDL can be distinguished from the so-called proinflammatory HDL which does have these properties and actually may promote inflammation (Navab et al 2001).

Recently, McMahon and colleagues showed that proinflammatory HDL was detected more often in RA patients ( $n = 48$ ) than in control subjects, ( $n = 72$ ), ie, 20% versus 4% respectively (McMahon et al 2006). As the rate in RA was approximately half of that was observed in patients with systemic lupus erythematosus proinflammatory HDL might be a novel biomarker for the increased atherosclerotic risk in RA.

## Management of rheumatoid arthritis

The management of RA consists of co-ordinated multidisciplinary care, eg, with physical and occupational therapy and drug treatment. Successful treatment to limit joint damage and functional loss requires early diagnosis and timely initiation of disease-modifying agents.

The pain in RA is caused by joint inflammation and therefore non-steroidal anti-inflammatory drugs (NSAIDs) are preferred over analgesics for pain management, in view of their anti-inflammatory effects (American College of Rheumatology Subcommittee on Rheumatoid Arthritis 2002). Analgesics may be added when NSAIDs alone are not enough for pain relief. However, these agents do not change the course of the disease, nor do they prevent joint damage. Therefore, patients with persisting disease activity require (early) treatment with disease modifying antirheumatic drugs (DMARDs). Evidence is accumulating that DMARDs can reduce or prevent joint destruction (Fries 2000). Active RA may cause irreversible joint destruction in the first months of the disease and therefore DMARDs should be initiated early in those patients with active disease, ie, persisting joint pain, morning stiffness or fatigue, active arthritis or persisting elevation of the CRP or ESR. In general, early application of DMARDs implies initiating treatment within several weeks after the first visit to the rheumatologist. Conventional DMARDs include methotrexate, leflunomide, sulphasalazine and hydroxychloroquine. Methotrexate is considered the drug of choice with a better long-term efficacy than the other conventional DMARDs (Rau 2000). Several investigations have demonstrated that combination DMARD therapy might be more effective than mono-DMARD therapy in patients with early disease (Boers 2001). The place of corticosteroids is a continuing matter of debate in view of their side effects, particularly with long-term use. There is no doubt that corticosteroids rapidly and effectively suppress inflammation in RA and their use might be justified for short-term therapy,

eg, for “bridging therapy” between the period between initiation and response to DMARD therapy (Kirwan 2001).

TNF $\alpha$  is a pivotal cytokine in the pathogenesis in RA and TNF $\alpha$  blockade was shown to be very effective and rapid in controlling disease activity. TNF $\alpha$  antagonists, frequently in combination with methotrexate, appear to be the most effective antirheumatic drugs and the safety data available so far do not indicate major safety problems.

Presently, three anti-TNF $\alpha$  blockers are available for clinical use. Infliximab is a chimeric mouse/human anti-TNF $\alpha$  monoclonal antibody and binds to soluble as well as membrane-bound TNF $\alpha$ . Infliximab is intravenously administered and after the initial infusion it is given at two, six and then every 8 weeks thereafter. Etanercept consists of two human TNF $\alpha$  receptors linked to each other and binds to circulating as well as cell-bound TNF $\alpha$  molecules. Etanercept is given subcutaneously once or twice weekly. Adalimumab is a human immunoglobulin (Ig) G1 antibody and administered subcutaneously once every two weeks.

## Antirheumatic treatment and lipid profile

### Disease modifying antirheumatic drugs

A 9 month follow-up study in 11 patients with RA demonstrated normalisation of the lipid levels during antirheumatic treatment after 9 months (Svenson et al 1987b). This was confirmed by a larger uncontrolled investigation in 42 patients (Park et al 2002). The majority of responding patients were treated with methotrexate, and approximately 50% received low-dose prednisolone. In the responders, HDL-C levels increased by 21%, apoA-I levels increased by 23% and the ratio TC/HDL-C decreased by 9%. Recently, another uncontrolled investigation showed similar findings (Georgiadis et al 2006).

Until recently, no randomized investigations studying the effect of antirheumatic treatment (including corticosteroids) on lipid profile have been reported in patients with early RA. Therefore, we studied the effects of combination treatment with prednisolone on total and high-density lipoprotein (HDL) cholesterol levels in patients with RA and the relationship between lipid levels and disease activity (Boers et al 2003). Total and HDL cholesterol levels were determined in stored samples from a previously conducted, 56-week multicenter trial among patients with early RA investigating the value of intensive combination therapy (COBRA); the combination of sulfasalazine, methotrexate (stopped at 40 weeks) and prednisolone (initially 60 mg/day,

tapered in 6 weekly steps to 7.5 mg/day and stopped after 28 weeks) was compared to sulfasalazine alone (Boers et al 1997). Contrary to expectations, both total and HDL cholesterol were decreased in these patients with active RA at baseline, and increased on antirheumatic therapy. We found that combination therapy with prednisolone rapidly improved the atherogenic index (total/HDL cholesterol), an important prognostic cardiovascular risk factor. Early antirheumatic and especially corticosteroid (combination) treatment may improve cardiovascular risk in RA, and it appears that the use of corticosteroids is not a risk factor for cardiovascular disease in patients with RA, which is also suggested by other investigators (Wallberg-Jonsson 1997; Banks et al 2000).

Also lipid profiles in patients with established RA were assessed and we found that in established RA total cholesterol levels were only slightly raised, irrespective of disease activity. However, HDL cholesterol was significantly higher in patients in remission than in patients with active disease.

As several studies suggested an association between hydroxychloroquine and lipid concentrations, Munro et al conducted a randomized one-year trial in patients with established RA where 100 patients were either treated with hydroxychloroquine (n = 51) or gold (n = 49) (Munro et al 1997). This trial revealed a significant rise of 15% and a decrease of 12% in HDL values in the patients treated with hydroxychloroquine and gold, respectively, whereas there was no significant change in TC levels.

Altogether, conventional DMARD (including corticosteroids) treatment has favorable effects on the lipid profile. As there is mounting evidence for favorable effects of DMARD treatment on the cardiovascular risk in RA (Van Halm, Nurmohamed et al 2006) this might be (partially) mediated by favorable effects on the lipid profile.

It is therefore of interest to investigate whether more powerful immunosuppressive agents, ie, biologicals have more profound effects on the lipid profile in RA.

### TNF-blocking agents

There is an increasing number of reports about the effects of treatment with tumor necrosis factor (TNF) blocking agents on the lipid profile in RA patients with active disease. One of the first reports, in a very limited number (n = 15) of patients with RA and psoriatic arthritis, showed that the lipid profile changed to a more atherogenic profile during treatment with infliximab (Cauza et al 2002). Therefore, we prospectively investigated the effects of infliximab, a drug with no known



direct effects on the lipid profile in a cohort of 69 patients with active, established RA during 6 weeks of infliximab treatment (Vis et al 2005). The Disease Activity Index score (DAS-28) was 5.9 at baseline and decreased to 4.6 after 2 weeks and further to 4.1 after 6 weeks. Total cholesterol level was 5.2 mmol/L (200.2 mg/dL) at baseline and increased to 5.7 mmol/L (219.5 mg/dL) ( $p < 0.001$ ) at 2 weeks, and was 5.6 mmol/L (215.6 mg/dL) ( $p < 0.001$  vs baseline) at Week 6. For HDL-cholesterol these values were 1.47 (56.60), 1.60 (61.60) ( $p < 0.001$ ), and 1.59 (61.22) mmol/L (mg/dL) ( $p < 0.001$  vs baseline), respectively. Changes in disease activity were significantly, inversely, associated with changes in total cholesterol and HDL-cholesterol levels. The atherogenic index, however, remained constant. Corticosteroid use at baseline was associated with significantly higher total cholesterol and HDL-cholesterol levels and a lower (more favorable) atherogenic index at baseline.

Seriolo et al (2006) determined lipid profiles after 24 weeks anti-tnf treatment (ie, infliximab or etanercept), in 34 patients with RA and also found enhanced TC and HDL-C levels whereas the atherogenic index remained constant. Another investigation, in 60 patients with inflammatory rheumatic diseases (ie, RA, ankylosing spondylitis or psoriatic arthritis) of which 24 had RA, demonstrated the persistence of modest increased HDL-C levels up to 6 months after infliximab treatment whereas the TC increase was transient (Spanakis et al 2006). In contrast, Kiortsis et al (2006) found no changes in lipid levels after one year infliximab treatment in 50 RA patients, whereas Dahlqvist et al (2006) reported worsening of the lipid profile after two years infliximab treatment in 51 RA patients.

In a 48 week study of 80 infliximab treated patients we found that lipid levels improved significantly during infliximab therapy (Peters et al 2007). However, at the end of the study period all lipid changes, except for Apo A-1 levels, returned to baseline values. Longitudinal analyses revealed a significant inverse association between lipid levels and disease activity and a significant association between lipid levels and prednisone doses. Improvement according to the DAS-28 score of 1 point was associated with an increase of 0.016 mmol/L (0.62 mg/dL) in total cholesterol and 0.045 mmol/L (1.74 mg/dL) in HDL cholesterol. In addition, 10 mg reduction of prednisone dose was associated with a decrease of 0.04 mmol/L (1.54 mg/dL) total- and 0.16 mmol/L (6.18 mg/dL) HDL cholesterol. Altogether this study indicates that the fact that no changes in serum lipid levels were observed after 48 weeks of infliximab treatment may be the result of opposing effects of changes in disease

activity and changing (ie, decreasing) in prednisone dose on the lipid profile.

In a two week placebo-controlled study with another TNF blocking agent, ie, adalimumab, the investigators observed, in the 33 adalimumab treated patients a 6% increase in TC levels (5.02 vs 4.70 at baseline) as well as a 15% increase in HDL-C levels (0.98 mmol/L (37.7 mg/dL) vs 0.86 mmol/L (33.1 mg/dL) at baseline) after two weeks treatment (Popa et al 2005). These significant changes of lipid levels were also accompanied by a significant decrease of the atherogenic index.

Altogether these investigations with TNF blocking agents reveal a transient increase of TC and HDL-C mostly accompanied with improvement of the atherogenic index, during the first few months of the TNF blocking agents. Thereafter the results become divergent between the studies. This might be due to differences in disease activity, (changes of) comedication, particularly prednisone, dietary intake and physical activity. Hence, future studies should appropriately address these potential confounders to reach valid conclusions.

Nevertheless, the lipid changes due to TNF-blocking agents appear to be moderate and the favorable effect of these agents on cardiovascular comorbidity are likely not be mediated to a great extent by effects on lipid metabolism, but long-term investigations are needed to investigate this topic.

## Treatment of the atherogenic lipid profile in RA

In view of the enhanced cardiovascular risk in RA, treatment of dyslipidemia should be part of cardiovascular risk management in these patients.

First of all one should consider, for every RA patient, yearly screening of cardiovascular risk factors, ie, smoking, blood pressure, lipid profile, plasma glucose, family history for cardiovascular disease, diet, alcohol intake, physical activity, body mass index, waist/hip ratio. Then, the 10 year risk cardiovascular disease can be assessed by using a risk function calculator, eg, the Framingham risk score, which is indicative for targeted risk factor reduction. For instance, several guidelines recommend a targeted risk factor approach for a 10 year CVD risk above 20% for patients without evidence for prior CVD.

For patients with a history of verified CVD guidelines for secondary prevention should be followed.

However, these risk function calculations (functions) are based on the general population and cardiovascular risk factor functions for RA are not available. In view of the enhanced CVD risk in RA one could consider lower thresholds for

targeted risk function reduction or multiply the 10 year risk by two.

Alternatively, as the risk in RA might be comparable to that of diabetes one could adopt similar treatment thresholds for risk factor reduction as in diabetes, eg, treatment with statins when LDL-C is above 2.5 mmol/L (96.3 mg/dL) and or treatment with antihypertensive agents with a systolic blood pressure above 140 mmHg. Particularly, statins are of interest in view of their anti-inflammatory properties in addition to their cholesterol lowering effects, and a recent trial showed a moderate disease reduction in patients with active RA (McCarey et al 2004). Finally, in view of the clear relationship between diseased activity and cardiovascular disease in RA a tight disease control is mandatory. This will also have some, albeit moderate, (favorable) effects on the lipid profile.

## Discussion and recommendations

Recent research has shown that systemic inflammation plays a pivotal role in the development of atherosclerosis. Hence, inflammation might explain the increased cardiovascular risk in RA patients (Sattar et al 2003). In addition, inflammation leads to pro-atherogenic changes of the lipoprotein metabolism and an increased disease activity is associated with lower TC levels and even more depressed HDL-C levels and lowered apo A1 levels.

Conventional DMARD treatment has beneficial effects on the lipid profile in RA and it is tempting to speculate that the favorable effect of DMARD treatment on the cardiovascular morbidity and cardiovascular mortality in RA might be partially mediated by this mechanism.

It was expected that the effects of TNF-blocking therapy on the lipid profile would be more pronounced than that of DMARD treatment but also TNF blocking therapy induces not more than moderate changes of the lipid profile. Moreover, some studies indicate that these favorable changes level off after the first few months of TNF blocking therapy, but favorable effects might be masked by changes in comedication, particularly corticosteroids. We found that lowering the prednisone dose results in a decreasing TC, predominantly due to a lower HDL-C resulting in a higher atherogenic index (as the effect on total cholesterol was less pronounced). Vice versa, increasing the prednisone dose might have favorable effects on the lipid profile. Nevertheless, it is not known whether or not this beneficial effect is ultimately offset by other cardiovascular side effects of long-term prednisone use, as insulin resistance and hypertension.

Even though the observed differences of DMARD treatment and TNF-blockers on the lipid profile are small they

might have clinical relevance, eg, The Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT) as well as the Framingham Study demonstrate that a 0.026 mmol/L (1 mg/dL) increment of baseline HDL cholesterol is associated with an approximately 3.5% risk reduction for coronary heart disease (The Framingham Study 1978; Gordon et al 1986). Another study performed by Rubins et al revealed that a 6% increase in HDL cholesterol is associated with an absolute risk reduction of 4.4% of death from coronary heart disease or non-fatal infarction (Rubins et al 1999).

Whether or not these moderate effects can explain the favorable effect of TNF-blocking therapy on cardiovascular morbidity and mortality observed in the literature, (Jacobsson et al 2005, 2006) remains to be established by long-term investigations.

Management of dyslipidemia should be considered as a part of cardiovascular risk management in RA patients. It is evident that tight disease control lowers the cardiovascular risk in RA and may have also some beneficial effects on the lipid profile. In addition, cardiovascular risk factor screening and appropriate treatment is necessary. In view of the enhanced cardiovascular risk in RA lower treatment thresholds should be considered but presently precise guidelines are lacking and need to come from currently conducted epidemiological investigations. Until these are available a pragmatic approach could be adopted, eg, by adjusting the, for the general population available, cardiovascular risk score functions.

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