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Lipids in RA: What do they mean?

Jorge Plutzky, MD¹ and Katherine P. Liao, MD, MPH²

¹Division of Cardiology, Brigham and Women's Hospital

²Division of Rheumatology, Immunology, and Allergy, Brigham and Women's Hospital

Abstract

In rheumatoid arthritis (RA), lipid levels are dynamic and can fluctuate along with changes in inflammation. A reduction in inflammation, most commonly as a result of disease modifying anti-rheumatic drug (DMARD) therapy, is associated with increases in total cholesterol (TC) and low density lipoprotein cholesterol (LDL-C). A similar pattern of increased lipids is observed across biologic and non-biologic disease modifying anti-rheumatic drugs (DMARDs), suggesting that the main driver of changes in lipids is inflammation rather than individual treatments. In this review, we discuss new evidence shedding light on the potential mechanism underlying changes in lipid levels observed with changes in inflammation. Measured lipid levels in the blood are a result of a balance between synthesis and catabolism or absorption. Recent human studies in active RA show that the catabolic rates of lipids are higher than expected compared to expected rates in the general population. DMARD therapy appears to allow a return to baseline lower catabolic rates, resulting in an apparent increase in lipids. Additionally, we discuss findings from the recently published randomized controlled clinical trial, Canakinumab Anti-inflammatory Thrombosis Outcome Study (CANTOS). Findings from CANTOS provide further evidence for tighter control of inflammation to reduce cardiovascular risk in RA.

Keywords

Rheumatoid arthritis; Lipids; Cardiovascular disease; Lipid metabolism

Rheumatoid arthritis (RA) patients can experience >30% increase in low density lipoprotein cholesterol (LDL-C) after treatment with a disease modifying anti-rheumatic drug (bDMARD)[1]. The increases in LDL-C are worrisome since RA patients already have a 1.5x higher risk of cardiovascular disease (CVD) than the general population[2, 3]. However, recent studies suggest that the increases in LDL-C may not necessarily correlate with higher CV risk. This review will focus on lipid values available in clinical practice, discuss new updates highlighting the mechanisms behind changes in lipid levels, and the potential clinical implication of these changes for CV management in RA.

A typical routine lipid panel consists of total cholesterol (TC), low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C) and triglyceride levels.

The Framingham Heart Study (FHS) as well as other population based cohorts, established a clear paradigm that higher cholesterol is associated with higher CV risk[4, 5]. However, when investigators examined this relationship in RA, a different relationship was observed. In a large population-based RA cohort study, lower TC was associated with higher CV risk compared to higher TC levels[6]. Subsequent studies found that low LDL-C was not necessarily associated with reduced CV risk when compared to subjects with higher LDL-C levels[7, 8]. This phenomenon was termed the “lipid paradox” in RA[6].

Subsequent studies have found that levels of inflammation in RA may explain this apparent paradoxical relationship. As a first step, if we presume inflammation is associated with lower LDL-C, we would anticipate LDL-C levels fall before RA diagnosis, that RA patients have lower LDL-C levels compared to the general population, and for levels to rise with treatment or control of RA (Figure 1). In fact, this pattern has indeed been observed across several studies.

TC and LDL-C has been shown to decrease in the five years prior to RA diagnosis[9]. Patients with established RA had on average 7% lower TC levels, and 11% lower LDL-C levels than the general population[10]. No significant difference in HDL-C levels was observed in this same cohort. This same general pattern was also observed in subsequent studies measuring lipid levels in RA compared to non-RA patients for the purposes of a clinical trial[11]. Finally, the expected rise in TC and LDL-C that would have been predicted with control of inflammation was observed in clinical trials in response to multiple different RA therapies[1, 12–14]. Increases in HDL-C were also documented, however, this was less consistent across all studies.

Two recent studies shed light on the mechanisms behind the observed fluctuations in lipid levels in the setting of RA and RA treatment. As a brief background, the concentration of cholesterol and lipids observed in a blood sample is determined by several inputs and outputs. Increasing lipid levels could be due to increased synthesis and/or decreased removal (clearance) or absorption of that particular lipid parameter from the circulation. Decreasing lipid levels could result from decreased synthesis and/or increased removal from the circulation. Identifying mechanisms underlying lipid/cholesterol changes can be performed by labeling lipids with stable isotopes, administering these molecules to subjects and tracing their subsequent uptake and metabolism. This stable isotope turnover approach is considered the gold-standard for studying lipid and lipoprotein metabolism in humans[15]. Two studies have reported the results of stable isotope testing in RA, one examining tofacitinib (TOFA) [14] and the other tocilizumab (TOCI)[16]. Both used the fractional catabolic rate (FCR) as the metric for metabolic clearance, or removal from circulation, of the radiolabeled lipid. The tofacitinib study followed 36 patients with active RA and 33 healthy volunteers. At baseline, the cholesterol ester FCR was higher in RA compared to controls, suggesting higher catabolism of cholesterol esters, potentially explaining the lower TC levels in these RA patients. Following TOFA treatment (10mg twice daily, 6 weeks), the FCR for the cholesterol esters decreased, and as expected, cholesterol levels increased.

The tocilizumab study focused on measuring the FCR of LDL before and after 10 weeks of TOCI 8mg/kg treatment. In this study of 11 RA patients with active disease, the FCR of

LDL at baseline was in the hypercatabolic range when compared to the expected FCR in the general population, suggestive of markedly active turnover. After treatment with TOCI, the FCR decreased, approximating that of the general population[16]. Interestingly, in the tofacitinib study, no difference in the FCR of mean-LDL-associated Apolipoprotein B (ApoB) was observed between RA and the healthy volunteers[14]. ApoB is a specific protein found on very low density lipoprotein (VLDL), which undergoes metabolism to form first intermediate density lipoprotein (IDL) and then LDL itself. Each individual particle VLDL, IDL and LDL have one ApoB molecule associated with them. The difference in findings for LDL with TOCI versus cholesterol with TOFA discussed above may be due to various factors, including relatively small sample sizes, differences among these cohorts or the different mechanism of action of TOFA vs. TOCI. Regardless, both studies demonstrated that during active disease, there is increased catabolism of cholesterol and LDL-C, providing a mechanistic link to explain why levels increase or decrease with treatment and control of inflammation (Figure 2).

While it has become clear that a reduction in inflammation is associated with increased TC and/or LDL-C, these increases may not necessarily portend increased CV risk. One challenge to studying the overall clinical impact on CV risk is due to the feasibility of recruiting sufficient RA patients to study incident CV events as the outcome. Thus, studies have focused on examining other factors associated with CV risk, particularly in regards to HDL function. In several studies, the increase in TC and LDL-C associated with a reduction in inflammation was also associated with increases in HDL-C, which is considered protective against CV disease[1, 14, 17, 18]. Additionally, there is evidence that the anti-atherogenic properties of HDL are improved when inflammation is decreased[19–21].

The major function of HDL is its ability to efflux cholesterol from lipid laden macrophages, including those located in atherogenic plaques – so called reverse cholesterol transport – an appealing mechanism for HDL's anti-atherogenic properties. This reverse cholesterol function, taking cholesterol from the periphery and bring it back to the liver, where excess cholesterol can be excreted in bile or the feces, is measured using measures of HDL cholesterol efflux capacity, again using radiolabeled materials. Impaired HDL cholesterol efflux capacity is independently associated with a higher rate of incident cardiovascular events, even adjusting for HDL-C level and other CV risk factors[22]. In RA, a reduction in inflammation is associated with improvement in cholesterol efflux capacity[19, 21].

Furthermore, while there appears to be a general association between a reduction in inflammation and improvements in HDL function, there is also evidence to suggest that some RA treatments may be associated with greater improvements in cholesterol efflux capacity compared to others[21, 23]. A study of 34 subjects treated with methotrexate (MTX), and 22 subjects treated with adalimumab (ADA), found that cholesterol efflux capacity improved only with MTX treatment and not ADA treatment[23]. In a study comparing MTX, ADA and TOCI, no improvement was observed in any treatment arm, with the exception of subjects with an impaired cholesterol efflux at baseline prior to starting TOCI[21]. More work is needed to confirm these findings due to the modest sample size of these studies. It is worth noting that thus far, in the general population, increasing the mass of HDL has not been shown to decrease CV events, which may be explained by the need to

have increased HDL mass also reflect increased HDL function, as could be especially relevant in RA.

Given that inflammation has long been proposed as contributing to atherosclerosis and known to predict CV events, the prospect that modulating inflammation might decrease myocardial infarctions has been pursued in the general population. The fact that some therapies, like statins, which are known to decrease CV risk, also lower measures of inflammation, such as high sensitivity C-reactive protein (CRP), has further fueled such speculation; however, statin studies cannot prove this hypothesis because they significantly lower LDL-C and only modestly reduce inflammation[24]. The recently published results of the Canakinumab Anti-inflammatory Thrombosis Outcome Study (CANTOS) have provided new evidence supporting reduction of inflammation can directly reduce CV risk[25]. This randomized, double-blind, placebo-controlled trial, recruited patient post-myocardial infarction who had an hs-CRP 2mg/L and who were already on aggressive measures to prevent recurrent CV events, randomizing patients to injection of either placebo or canakinumab, an antibody to interleukin 1 beta (IL1b). Patients with inflammatory diseases were excluded. Overall, a statistically significant 15% reduction in incident CV events in subjects receiving canakinumab (150mg every 3 months) was seen as compared to those receiving placebo. No significant changes in TC, LDL-C, HDL-C and tri were observed. CANTOS was the first study to offer direct proof of the hypothesis that reducing inflammation reduces CV risk independent of lipid changes. These findings with canakinumab is completely in line with the observational data in RA, where inflammation is associated with higher CV risk[26–28].

The lack of lipid changes in response to decreased inflammation with IL1b antibody in CANTOS may have been due to the relatively low level of inflammation in this population, who had a median hsCRP of 4.25mg/L, or other factors, including aggressive statin treatment. Previous studies in RA have shown a linear relationship between the magnitude of reduction in LDL-C with a reduction in CRP[19] as a result of improved control of their arthritis, however those RA patients had a median baseline CRP of 28.6 mg/L. Thus, even though inflammation was decreased in the CANTOS trial, the magnitude of the reduction in inflammation or the lower levels of inflammation at baseline may have limited detection of any changes.

Taken together, the data accumulated thus far from several sources argues that RA is not only associated with an increased risk of CV disease but that this risk derives from a defining component of RA, namely inflammation itself. In RA, inflammation is associated with increased metabolic clearance for TC and LDL-C, resulting in lower levels of these parameters, which may be misleading in terms of the CV risk such patients face. When RA patients are treated and control of inflammation is improved, the metabolic clearance of lipids is reduced, and thus TC and LDL-C levels increase, which may not necessarily portend worst outcomes. In some cases, this decrease in inflammation and increase in TC and LDL-C is also linked to increases in HDL-C and improvements in the anti-atherogenic, functional properties of HDL. The impact of these changes on overall CV risk remains to be seen and studies are underway to address this question[29, 30]; the results from CANTOS provide hope that decreased inflammation will be associated with a reduction in CV risk.

Lastly, one must keep in mind that LDL-C is a casual factor for CVD. While recent studies in RA observed an elevated CV risk among subjects with low LDL-C[6, 8, 31], subjects with high LDL-C are at an even higher level of CV risk. It remains possible that decreases in CV events anticipated in response to anti-inflammatory measures in RA may be offset to some extent by increases in TC and LDL-C. From the studies above, we now understand that the optimal window to assess CV risk in RA is when there is good control of RA disease activity, a time when the RA patient may be more likely to have their lipids and lipoproteins in a steady state. Statins remain first line therapy for RA subjects with elevated LDL-C levels; based on a recent large randomized controlled trial, statins are well tolerated and effective at reducing LDL-C levels in RA[32]. The prospect that RA treatments that decrease inflammation may also reduce CV risk remains but will require further study, including consideration of unique drivers of CV risk in RA, how to assess such CV risk and detailed consideration of shifts in levels of lipids as well as their metabolism.

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Figure 1. Schematic of low density lipoprotein cholesterol (LDL-C) levels from pre-RA through RA diagnosis and treatments based on data from lipid studies to date.

Figure 2.

The measured LDL-C level in the blood is a balance of synthesis and absorption/clearance from the blood stream. In the non-inflammatory state (A), there is typically a steady balance between synthesis and clearance, whereas in the setting of inflammation (B), there is evidence of increased clearance, resulting in lower LDL-C.