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HDL Function in Rheumatoid Arthritis

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Abstract

Purpose of review—Patients with rheumatoid arthritis (RA) have accelerated atherosclerosis despite the appearance of having a less atherogenic lipid profile; however, lipoprotein function rather than concentration may be a better indicator of atherosclerotic risk. The purpose of this review is to summarize recent findings concerning HDL function in patients with RA.

Recent findings—Two major activities of HDL, its antioxidant and cholesterol efflux functions have been examined in RA. HDL antioxidant capacity is inversely associated with inflammation and RA disease activity; however, there is no clear consensus if antioxidant capacity is altered significantly in RA compared to control subjects. Moreover, despite numerous studies there is no consensus whether HDL cholesterol efflux capacity is significantly altered in RA compared to control subjects or influenced by inflammation or disease activity.

Summary—Additional studies will be valuable to consolidate existing data and find consensus. Moreover, studies evaluating the impact of various HDL functions on cardiovascular disease in RA are needed.

Keywords

Rheumatoid arthritis; HDL; cholesterol efflux; atherosclerosis

Introduction

There is great interest in HDL function in patients with rheumatoid arthritis (RA), a chronic inflammatory autoimmune disease affecting an estimated 1.5 million adults in the United States. Despite 2-fold higher cardiovascular (CV) risk in patients with RA, their LDL cholesterol concentrations tend to be lower and HDL cholesterol (HDL-C) concentrations similar to those of matched control subjects(1, 2). Several studies in patients with RA made paradoxical observations: 1) in the setting of high oxidative stress, high HDL-C concentrations, rather than being protective, were associated with increased coronary atherosclerosis, measured by coronary artery calcium score(3); 2) in the setting of high inflammation, a lower total cholesterol-to-HDL-C ratio, rather than being protective, was associated with increased CV events(4). Such findings suggested that HDL function may be

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altered in RA, reducing its usual protective effects or even rendering it harmful, and that HDL-C is not a good measure of HDL function. Initial studies that examined HDL function in RA focused on its antioxidant effects by measuring the ability of HDL (prepared as HDL enriched serum(5) or purified HDL(6)) to prevent LDL oxidation determined by a fluorescent probe, dihydrodichlorofluorescein (DCF). One study found that a higher proportion of RA patients had poor HDL antioxidant capacity, termed “proinflammatory HDL”, compared to control subjects (20% vs 4%)(Table)(5). In this study proinflammatory HDL, when added to control LDL, created a greater fluorescent signal than LDL alone. This suggested that HDL did not prevent or reverse LDL oxidation, but rather increased it. In another study, proinflammatory HDL was significantly correlated with RA disease activity measured by DAS28 score, which is a composite score including tender and swollen joint counts, a patient-reported visual analog score of health, and an inflammatory marker, (rho=0.54, P>0.0001) in 132 patients (Table)(6). These findings were key to generating interest in HDL function in RA. This review focuses on major contributions to knowledge about HDL function in RA over the past 2 years.

HDL antioxidant capacity in RA

Methods to determine the antioxidant capacity of HDL have been technically challenging due to several factors. First, fluorochromes are unstable and assays are sensitive to hemolysis(15). Second, as with other measures of HDL function such as cholesterol efflux or anti-inflammatory capacity, there is no gold standard for its measurement. A recent study used a method different from the work summarized above to measure the ability of HDL to prevent oxidation of LDL(7). HDL was purified and then HDL subfractions were isolated by ultracentrifugation. Individual or combined HDL subfractions were added to LDL and a water-soluble azo-initiator (2-amidinopropane or AAPH) and the oxidation rate was measured by absorbance over time, indicating production of conjugated dienes(8).

Using this technique Gomez Rosso et al studied 12 patients with active RA (mean DAS28 = 4.0 units) and 10 healthy age-matched control subjects(7). All subjects were normolipidemic, postmenopausal females. Unlike the previous studyl(5), oxidation of LDL rates were not significantly different overall with the addition of RA or control total or small dense HDL, although statistical power was limited by small sample size. Moreover, activities of serum PON1 and Lp-PLA2, lipoprotein-associated enzymes thought to inactivate oxidized lipids, were not significantly different between RA and control subjects(7). However, oxidation rates with the addition of HDL from RA patients with high inflammation (high sensitivity C-reactive protein (hsCRP) > 10mg/l, N=4) compared to low inflammation (hsCRP<10mg/l, N=8) were 56% higher for total HDL, and 41% higher for HDL3c (Table). To obtain mechanistic insights, investigators evaluated the lipidome of HDL3c among RA and control subjects. While lipid composition was similar among RA patients with high and with low inflammation, overall RA HDL3c had more phosphatidic acid and this resulted in impaired antioxidant activity. Thus, this study suggests that 1) the antioxidant capacity of HDL in patients with RA overall may not be significantly different from controls, and 2) similarly to previous findings(6) high inflammation or disease activity may be associated with poor antioxidant capacity in RA.

HDL cholesterol efflux capacity in RA

Initial studies of HDL function in RA focused on its anti-oxidant capacity, but an early study also examined the cholesterol efflux capacity (CEC) of HDL in RA. In a cross-sectional study including 40 patients with RA (median DAS28 = 4.65 units) and 40 control subjects matched for age and sex, the CEC of standard concentrations of HDL purified by dextran sulfate precipitation and subsequent HDL bead isolation was measured using radiolabelled cholesterol in murine RAW264.7 cells(8). There was no significant difference in CEC between RA and control subjects; however, there was approximately a 26% reduction in CEC for patients with high (DAS28 > 5.1, N=18) compared to low DAS28 scores (DAS28 < 2.6, N=7, P=0.01)(Table)(8). Furthermore, CEC and antioxidant capacity of HDL measured using methods discussed in the introduction were weakly but significantly correlated with each other (rho=−0.34, P=0.03) and with plasma myeloperoxidase (MPO) activity (rho= −0.35, P=0.03). Thus, these findings suggested that MPO may damage HDL through oxidative modifications, altering its function.

Vivekanandan-Giri et al tested the hypothesis that MPO-associated oxidative modifications alter CEC(9). RA patients (N=38) with primarily well-controlled disease (median DAS28 = 1.9 units), of whom 18 had known cardiovascular disease (CVD), were compared to 20 healthy control subjects. The CEC of apolipoprotein B (apoB)-depleted serum prepared by polyethylene glycol precipitation was measured using radiolabelled cholesterol loaded J774 murine cells. There was approximately a 21% reduction (P<0.001) in CEC among RA compared to control subjects but no difference among patients with and without known CVD (Table)(9). No adjustment was made for HDL-C concentration, though CEC was significantly positively associated with HDL-C concentration. There was no correlation between CEC and CRP, ESR or DAS28 score in patients with RA(9), unlike findings by others(8). Among patients with RA, MPO-specific oxidative HDL modifications: 3-chlorotyrosine and 3-nitrotyrosine were increased in RA compared to control subjects, and the greater the abundance of HDL 3-chlorotyrosine modifications, the lower the CEC(9). Contrary to expectations, the lower the DAS28 score, the greater the oxidative modification of HDL by 3-chlorotyrosine, and there was no significant correlation between oxidative modification and markers of inflammation including ESR and CRP(9). These findings may indicate that oxidative modifications that could contribute to impaired CEC in some patients with RA may be RA-specific and not related to inflammation or disease activity. This is in contrast to the previous study(8) and others described below.

Liao et al examined whether HDL CEC was affected by changes in inflammation (CRP) among patients with RA by measuring CEC in 90 patients with RA before and after a substantial reduction in inflammation (≥10mg/l reduction in CRP over one year)(10). The CEC of apoB-depleted serum was measured using radiolabelled cholesterol loaded J774 murine cells. With a median reduction in CRP of 23.5mg/l, there was a modest 5.7% increase in CEC (P=0.002)(Table)(10). The unadjusted correlation between change in CRP and CEC was significant (rho=0.24, P=0.03), but not after adjusting for changes in HDL-C or apolipoprotein-A1 (apoA1) concentrations. There was also no significant correlation between change in DAS28 and CEC despite the increase in CEC with CRP reduction.

In a study reported in abstract we examined whether CEC is altered and associated with coronary atherosclerosis in RA in a cross-sectional study(16). In 134 patients with RA and 76 control subjects, frequency-matched for age, race and sex, CEC was measured using acetylated LDL-loaded, differentiated THP-1 human monocytes. After treatment with apoB-depleted serum in a standard cholesterol concentration, remaining cellular cholesterol was measured by gas liquid chromatography, yielding the net CEC accounting for potential bidirectional transfer of lipid by HDL. We found that CEC was similar among RA and control subjects (P=0.73), and that while there was a trend that lower CEC was associated with increased atherosclerosis measured by coronary calcium score, it was not statistically significant. Moreover, there was no association between CEC and DAS28, ESR, or CRP(16).

Two additional studies examined CEC in RA by different transporter pathways. In the first study CEC mediated by SR-B1, ABCG1, ABCA1, and aqueous diffusion using apoB-depleted serum was measured by radiolabelled cholesterol in a variety of cell lines in 30 patients with RA with active disease (mean DAS = 4.36 units) and 30 age and sex matched control subjects(11). Only CEC by ABCG1 was decreased in patients with RA compared to control subjects, and CEC by this pathway was inversely associated with DAS28 scores in patients with RA; however, there was no correlation between CEC by any pathway and CRP or ESR.

In a second study by the same group, the CEC of serum (without HDL enrichment or purification) by different transporter pathways was compared before and after two RA treatments: methotrexate (MTX) alone or MTX plus adalimumab (ADA)(12). The study included 56 patients with RA, of whom 34 were starting MTX and 22 were starting MTX + ADA. Investigators measured serum CEC by SR-B1, ABCG1, ABCA1, and aqueous diffusion by radiolabelled cholesterol in a variety of cell lines as discussed above. MTX alone modestly increased serum CEC by approximately 6% via SR-B1 and by approximately 7% via ABCG1 at month 6 (estimated from figures) (Table). However, there was no sustained impact on CEC by any pathway in MTX + ADA users. There was a cross sectional association serum CEC and HDL-C concentration (positive) and DAS28 (negative) at month 6 only in MTX+ADA users. Serum CEC was not associated with markers of inflammation at any time point. CEC measurements were not adjusted for HDL concentrations, thus increases in HDL after drug treatment could have affected the results.

Summary of recent HDL cholesterol efflux capacity studies in RA

The first four studies measuring CEC in RA described above(8–10, 16), had different findings regarding the impact of inflammation or disease activity on CEC and whether CEC is altered significantly in RA. Different study designs may have contributed to these findings. One study used purified HDL by standard protein concentration(8) and a second added apoB-depleted serum based on standard cholesterol concentration(16), both giving intrinsic control for HDL concentration within the study design. The other two added a standard volume of apoB-depleted serum(9, 10). Thus, in the latter two studies(9, 10), unadjusted analyses may be due to differences in HDL concentration rather than a change in function of individual HDL particles. In fact, in adjusted analyses the association between

reduction in CRP and CEC was no longer significant after adjustment for HDL-C or apoA1 concentration(10). It could be argued; however, that small sample size did not provide the ability to detect an independent relationship.

Regarding selection of controls, the three studies(8, 9, 16) which compared CEC of RA and control subjects had very different criteria for selection of control subjects. In the study which found significant differences between RA and controls(9), the control subjects were extremely healthy having no hypertension, diabetes or tobacco use, and though not statistically significantly younger, trended 5 years younger than patients with RA. The other studies(8, 16) used non-RA controls from the general population some of whom had hypertension, tobacco use, and family history of premature CVD and found no difference between RA and control subjects.

The two studies by Ronda et al(11, 12), which analyzed different CEC pathways, suggested that CEC by the ABCG1 pathway is altered in RA and modifiable by MTX but not MTX +ADA, and that inflammation is not associated with CEC. These studies did not adjust for HDL concentration(11, 12) and in the study comparing RA and control subjects, the investigators indicate that “really healthy” controls were chosen with no CVD, dyslipidemia, hypertension, diabetes, chronic drug use, smoking or renal disease(11). Thus, it is difficult to conclude from the studies to date whether CEC is impaired in RA compared to the general population and if it is influenced by inflammation.

Lipid metabolism in RA

While CEC typically refers to HDL’s ability to remove cholesterol from foam cells, HDL additionally exchanges lipid with LDL. Impaired transfer of unesterified cholesterol from LDL to HDL is associated with the presence of coronary artery disease in several populations, and this ability of HDL to accept lipid from LDL was evaluated in patients with RA. An LDL-like nanoemulsion containing radiolabelled cholesteryl esters, unesterified cholesterol, triglycerides and phospholipids was incubated with subject plasma from 30 patients with RA, of whom 16 were in remission (DAS28<2.6) and 14 had high disease activity (DAS28>5.1), and 30 control subjects matched for age, sex and body mass index(13). Contrary to expectations, only cholesteryl ester transfer to HDL was reduced in RA compared to controls (approximately 25%), but there was no significant difference in removal of unesterified cholesterol, which is associated with CAD, or differences comparing those with high and low disease activity(13). The authors suggested that the difference in cholesteryl ester transfer is likely not meaningful.

Another study compared *in vivo* cholesterol and lipoprotein kinetics between patients with RA (N=36) before and 6 weeks after starting tofacitinib and control subjects (N=33) matched for age, race, sex, and menopausal status(14). The investigators measured changes in plasma cholesterol and lipoprotein pools after infusions of radiolabelled free cholesterol and leucine. They found no difference in cholesterol efflux rate across the three groups, though this method is different from CEC discussed above and also accounts for HDL’s bidirectional transfer of cholesterol to and from cholesterol to peripheral tissues. Also, patients with RA had increased (~12%) cholesterol ester catabolism compared to controls,

and tofacitinib treatment decreased cholesterol ester catabolism (~8%). Decreasing cholesterol ester catabolism was associated with increasing HDL-C and HDL particle number, yet there was no change in HDL or LDL catabolic rates, suggesting increased SR-B1 mediated uptake of cholesterol esters in active RA(14). Although the clinical significance of this finding is unclear, it appears that this would have a beneficial effect for patients with RA resulting in increased removal and disposal of cholesterol esters via the liver, or increased delivery to steroidogenic organs in times of stress, and that this is reversed by tofacitinib.

Thus both studies suggested that lipid metabolism either is not altered in RA, or may be modified to possibly beneficial ends. Further studies will be necessary to determine the impact of these changes on CV events in RA.

Conclusion

Although several interesting studies examining HDL function in RA have been published recently, consistent findings are lacking. This is likely due to differences in methodology and study populations. Regarding HDL antioxidant capacity, there is no current consensus whether HDL antioxidant capacity is impaired significantly in patients with RA compared to control subjects, but it appears that inflammation or disease activity has a detrimental effect on this HDL function. Regarding HDL CEC, there is also little consensus whether CEC is significantly impaired in RA or altered by inflammation or disease activity. Additional studies, including larger sample sizes and consensus on methodology likely will help unify findings. Important knowledge gaps to date are whether impaired CEC or antioxidant capacity increase CV risk in RA in prospective studies. Given that traditional risk factors fall short in explaining increased CV risk in RA, the impact of these HDL functions on CV risk must be defined.

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Key points

- There is no current consensus whether HDL antioxidant capacity is impaired significantly in patients with RA compared to control subjects, but it appears that inflammation or disease activity may detrimentally affect this HDL function.
- There is no consensus whether HDL CEC is impaired significantly in patients with RA compared to control subjects or if it is influenced by disease activity or inflammation.
- There is no information available to determine if impaired CEC or antioxidant capacity increases CV risk in patients with RA.

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Table

Summary of historical and recently published studies (**bold**) of HDL function in RA

Article	Design	N	HDL parameter	Purpose	Method	Results
Antioxidant capacity						
McMahon et al(5)	Cross sectional	48 RA, 72 controls	Antioxidant capacity of apoB-depleted serum	Antioxidant capacity RA vs controls	DCF based cell free assay: control LDL with patient HDL and DCF. Fluorescence with HDL > with LDL= pro-oxidant. ApoB-depleted serum added based on cholesterol concentration.	More RA with pro-oxidant HDL (20.1%) vs controls (4.1%) Pro-oxidant HDL correlated with ESR (SLE and RA combined analysis) Inherent control for HDL-C within assay design
Charles-Schoeman et al(6)	Cross-sectional	132 RA	Antioxidant capacity of purified HDL	Antioxidant capacity RA relative to protein cargo	DCF based cell free assay: control LDL with patient HDL and DCF. Fluorescence with HDL > with LDL= pro-oxidant. HDL by dextran sulfate precipitation then magnetic HDL bead isolation.	Pro-oxidant HDL associated with ↑ESR and hsCRP and ↑DAS28 Altered HDL associated proteins in pro-oxidant HDL Inherent control for HDL within assay design
Gomez Rosso et al.(7)	Cross-sectional	12 active RA (N=4 with CRP>10, N=8 with CRP <10), 10 controls	Antioxidant capacity of purified HDL	Antioxidant capacity of total and small dense HDL RA vs controls	Azo-initiator based cell-free assay: control LDL with patient HDL and azo-initiator. Rate of conjugated dienes formed indicate oxidation.	Oxidation rate of small, dense and total HDL similar in RA and controls RA patients with CRP >10 had ↑ oxidation rates in total HDL (56% ↑) and HDL3c (41% ↑) Antioxidant capacity related to phosphatidic acid composition Inherent control for HDL within assay design
Cholesterol efflux capacity						
Charles-Schoeman et al(8)	Cross-sectional	40 RA (N=18 with high DAS, N=7 with low DAS) 40 controls	CEC of purified HDL	CEC difference RA vs Controls	Radiolabelled cholesterol, RAW264.7, dextran + bead isolated HDL.	No difference in CEC in RA vs controls ~ 26% ↓ CEC in RA high vs low DAS28* Inverse association with ESR Inherent control for HDL within assay design

Article	Design	N	HDL parameter	Purpose	Method	Results
Vivekanandan-Giri et al(9)	Cross-sectional	38 RA (N=20 without and N=18 with known CVD) and 20 healthy controls	CEC of apoB-depleted serum	CEC difference RA vs control, correlation with MPO-specific HDL changes	Radiolabelled cholesterol, J774 macrophages.	~21% ↓CEC in RA vs controls No difference in CEC in RA with vs without CVD RA HDL had greater 3-chlorotyrosine content, which was inversely associated with CEC No adjustment for HDL
Liao et al(10)	Prospective (baseline and after ≥10mg/l reduction in CRP)	90 RA	CEC of apoB-depleted serum	Effect of inflammation on CEC	Radiolabelled cholesterol, J774 macrophages.	↑ CEC by 5.7% after absolute ↓ in CRP by 23.5mg/l NS results after adjusting for change in HDL-C or apoA1 concentrations NS correlation between change in DAS28 and CEC
Ronda et al(11)	Cross-sectional	30 RA, 30 controls	CEC of apoB-depleted serum	Efflux difference of various pathways in RA vs controls	Radiolabelled cholesterol, J774 (ABCA1/aqueous diffusion), Rat hepatoma Fu5AU (SR-B1), Chinese hamster ovary cells (ABCG1).	~15% decreased ABCG1 mediated CEC in RA compared to control subjects* No difference in ABCA1, SRB1 or aqueous diffusion mediated CEC in RA ABCG1 mediated CEC inversely correlated with DAS28, but not with CRP or ESR No adjustment for HDL
Ronda et al(12)	Prospective baseline and 6 weeks/6 months after MTX or ADA+MTX	56 RA (34 MTX, 22 ADA+MTX)	CEC of whole serum	Effect of treatment on CEC by different pathways	Radiolabelled cholesterol, J774 (ABCA1/aqueous diffusion) Rat hepatoma Fu5AU (SR-B1) Chinese hamster ovary cells (ABCG1).	MTX ↑ CEC by ~ 6% via SR-B1 and ~ 7% by ABCG1* ADA+MTX without sustained effect on CEC by any transporter In ADA+MTX users, ABCG1 CEC positive correlation with HDL-C, inverse correlation with DAS28 at month 6, NS correlation with CRP or ESR No adjustment for HDL
Lipid metabolism						
Pozzi et al(13)	Cross-sectional	30 RA (N=16 remission, N=15 high DAS), 30 controls	Lipid transfer from LDL to dextran sulfate-$MgCl_2$ precipitated plasma	Ability of HDL to accept lipid from LDL in RA	Radiolabelled nanoemulsion incubated with subject plasma then radioactivity of dextran sulfate-$MgCl_2$ precipitated plasma is measured.	~25% reduction in cholesterol ester transfer in RA compared to controls No difference in any lipid transfer comparing high to low disease activity No adjustment for HDL

Article	Design	N	HDL parameter	Purpose	Method	Results
Charles-Schoeman et al(14)	Cross-sectional, prospective (before and 6 weeks after tofacitinib)	36 RA and 33 controls	In vivo cholesterol and lipoprotein kinetics	Cholesterol kinetics in RA and change by tofacitinib	22 hour radiolabeled free cholesterol infusion, and 20 hour radiolabelled leucine infusions with frequent plasma measurements.	~12% ↑ in cholesterol ester catabolism in RA vs controls ~8% ↓ in cholesterol ester catabolism in RA after tx No difference in cholesterol efflux rate in RA vs controls or after tx No difference in other cholesterol or lipoprotein kinetics in RA vs controls or after tx

Bold designates recent study.

*Estimated relative change based on graph. Percent changes are relative, not absolute changes, unless otherwise specified. RA= rheumatoid arthritis, apoB= apolipoprotein B, DCF= dihydrodichlorofluorescein, LDL= low density lipoprotein, HDL= high density lipoprotein, CRP= C-reactive protein, CEC= cholesterol efflux capacity, DAS28= disease activity based on 28 joint count, apoB= apolipoprotein B, apoA1= apolipoprotein A1, ABCG1= ATP-binding cassette sub-family G member 1, ABCA1= ATP-binding cassette sub-family A member 1, SRB1= scavenger receptor class B1.