Gene Expression **2024** vol. 000(000) | 000–000 Epub
DOI: 10.14218/GE.2024.00036

Review Article

Proatherogenic Disorders of Blood Lipid and Lipoprotein Metabolism in Patients with Rheumatoid Arthritis

Elena V. Gerasimova[1*], Tatiana V. Popkova[1], Maria V. Shalygina[1] and Daria A. Gerasimova[2]

[1]*V.A. Nasonova Research Institute of Rheumatology, Moscow, Russia;* [2]*I.M. Sechenov First Moscow State Medical University (Sechenov University), Moscow, Russia*

Received: March 26, 2024 | **Revised:** May 02, 2024 | **Accepted:** June 11, 2024 | **Published online:** July 23, 2024

Abstract

Disorders of blood lipids and lipoproteins are a global problem and a high-risk factor for atherosclerosis in patients with rheumatoid arthritis (RA). This article presents data on the influence of inflammation on proatherogenic disorders of lipid and lipoprotein metabolism, with an emphasis on proinflammatory cytokines. It analyzes the blood lipid profile in RA patients and identifies the need to study subfractions of high-density lipoproteins and their function in reverse cholesterol transport in RA patients as a more promising direction for clarifying cardiovascular risk. Depending on their type and metabolites, lipids may either promote disease progression or protect against RA. Supported by the close connection between altered lipid metabolism and chronic autoimmune inflammation, specific lipid profiles are emerging as unique disease biomarkers with diagnostic, predictive, and prognostic potential. Studying the influence of the immunoinflammatory process on lipids and lipoproteins in the blood of patients with RA will not only deepen knowledge about the pathogenesis of chronic inflammation but also expand understanding of the pathogenetic and prognostic significance of lipids, allowing for early diagnosis of dyslipidemia in RA at a qualitatively new level.

Introduction

In chronic inflammation, lipid abnormalities are important components of atherogenesis that determine the progression and clinical manifestations of atherosclerosis.[1,2]

During the acute phase of inflammation associated with trauma or infection, there are marked changes in the composition and concentration of plasma lipids and lipoproteins.[3] Early studies have shown that experimental modeling of systemic inflammatory processes leads to changes in lipid metabolism, characterized by hypertriglyceridemia, increased levels of free fatty acids (FA), and decreased levels of low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C).[4] Hypertriglyceridemia associated with acute-phase inflammatory proteins develops due to increased formation and decreased clearance of very-low-density lipoproteins.[5] Reduction in lipoprotein lipase (LPL) and hepatic lipase activity also contributes to hypertriglyceridemia and suppresses the formation of a specific HDL subclass associated with cholesterol efflux capacity (CEC).[6] Furthermore, significant changes occur in the protein and lipid composition of lipoproteins, which may not only redefine their function but also increase their atherogenic and inflammatory properties.[7]

Dyslipidemia often occurs in autoimmune diseases such as rheumatoid arthritis (RA), type 1 diabetes, psoriasis, inflammatory bowel disease, and other diseases. An imbalance in lipid metabolism accelerates inflammatory reactions and contributes to the development of atherosclerosis. While there have been numerous studies on the relationship between abnormal lipid metabolism and RA, and evidence suggests that lipid abnormalities occur in the preclinical stages of RA, it remains unclear whether dyslipidemia plays a unique role in the onset and progression of RA.

The purpose of this review is to present the latest data on the effect of inflammation on proatherogenic disorders of lipid and lipoprotein metabolism, with an emphasis on proinflammatory cytokines. It aimed to analyze lipid and lipidomic blood profiles based on disease phase, inflammation activity, and research methods. The review identifies the necessity to study high-density lipoprotein subfractions and their role in reverse cholesterol transport in RA patients as a promising direction for clarifying cardiovascular risk.

Effects of proinflammatory cytokines on lipid and lipoprotein metabolism

Numerous studies have shown that inflammation and inflamma-

Keywords: Lipid; Lipoprotein; Cholesterol; Cholesterol efflux capacity; Proinflammatory cytokines; Rheumatoid arthritis.

***Correspondence to:** Elena V. Gerasimova, V.A. Nasonova Research Institute of Rheumatology, Moscow 115522, Russia. ORCID: https://orcid.org/0000-0001-5815-561X. Tel: +7-495-1092910, Fax: +7-495-1092910, E-mail: gerasimovaev7@gmail.com

How to cite this article: Gerasimova EV, Popkova TV, Shalygina MV, Gerasimova DA. Proatherogenic Disorders of Blood Lipid and Lipoprotein Metabolism in Patients with Rheumatoid Arthritis. *Gene Expr* 2024;000(000):000–000. doi: 10.14218/GE.2024.00036.

tory cytokines are closely related to lipid metabolism. Pro-inflammatory cytokines are involved in the regulation of adipocyte proliferation and apoptosis by stimulating lipolysis, inhibiting lipid synthesis, and reducing blood lipid concentration. Under the influence of pro-inflammatory cytokines during the inflammatory process, structural modifications and a decrease in HDL-C concentration occur, which are associated with the reduction of CEC proteins.[8,9]

Key cytokines affecting lipid metabolism include tumor necrosis factor alpha (TNF-α), interleukin 6 (IL-6), and IL-1β. The most important source of pro-inflammatory cytokines is adipose tissue, consisting mainly of adipocytes, macrophages, and endothelial cells.[10] Increased TNF-α levels in adipose tissue are associated with increased lipolysis, disruption of insulin action on glucose transport, decreased LPL expression, inhibition of fat cell recruitment, and induction of apoptosis in fat cells.[4]

Several studies have demonstrated a negative effect of TNF-α on lipid metabolism.[11,12] TNF-α affects LPL reduction and triglyceride (TG) hydrolysis and enhances lipid mobilization from fat depots, which probably causes proatherogenic changes in the blood lipid profile.[13] In parallel, TNF-α stimulates the production of LDL in the liver, leading to the development of hypertriglyceridemia, which modulates the movement of cholesterol esters from HDL to LDL in exchange for TG mediated by cholesteryl ester transfer protein (CETP). Researchers found that lipolysis is mediated by TNF-α through the regulation of lipid droplet-associated perilipin protein expression, hormone-sensitive adipose tissue lipase, and triglyceride lipase.[14,15] It has been suggested that the main physiological goal of increased TNF-α expression may be to limit adipose tissue overgrowth and subsequently induce insulin resistance and further disorders of glucose and lipid metabolism.[16]

The central inflammatory mediator IL-6 has a similar effect. IL-6 is known to be produced by visceral adipose tissue cells, including adipocytes and resident immune cells, primarily macrophages.[17,18] In obesity, the number of macrophages significantly increases, and adipocyte hypertrophy is accompanied by increased IL-6 production.[19]

Administration of recombinant human IL-6 to rhesus macaques resulted in changes in lipid metabolism, including a reduction in apolipoprotein (apo) A1, apoA2, and apoB levels, a decrease in HDL-C and LDL-C concentrations, and an increase in TG.[20] Under the influence of IL-6, the ratio of proatherogenic and antiatherogenic lipids, lipoproteins, and their protein components (apoB/apoA1) is disturbed, which obviously increases cardiovascular risk.[21]

It is important to note that overexpression of IL-6 and its receptors is found in areas of the vascular bed that are more exposed to atherosclerotic lesions (coronary, brachiocephalic, and peripheral arteries).[22,23] Cytokine involvement and the protective function of IL-6 receptor inhibitors have been demonstrated in ischemia-reperfusion injury of human cardiac myocytes.[24]

There was a marked increase in plasma concentrations of IL-1, IL-6, IL-8, IL-10, and TNF-α receptor antagonists in men after marathon running.[25] The increase in plasma concentrations of free FA, IL-6, and TNF-α during marathon running may be related to the release of angiopoietin-related protein 4. This mechanism is considered compensatory against lipotoxicity and oxidative stress.[26] IL-6 and TNF-α can stimulate adipose tissue lipolysis during prolonged exercise independently of catecholamines and other factors.

The effects of pro-inflammatory cytokines on lipid metabolism may be mediated through increased formation of acute-phase proteins.[27] Inflammation primarily increases the production of C-reactive protein (CRP), synthesized under the influence of IL-6, IL-1β, and TNF-α in liver and adipose tissue cells.[28]

The native circulating form of CRP is the pentameric form, which is released into the bloodstream after exposure to inflammatory stimuli.[29] Native CRP is able to bind specifically to LDL when the pentameric structure of CRP changes to a monomeric structure or when LDL is modified/oxidized.[30,31] Several *in vitro* studies have convincingly demonstrated CRP-mediated opsonization of LDL with phagocytic cells through interaction with the immunoglobulin receptors, Fc gamma receptors I and II.[32–34]

In earlier studies, native CRP was shown to induce the release of proinflammatory cytokines from endothelial cells (vascular cellular adhesion molecule-1 (VCAM-1), intercellular adhesion molecule 1 (ICAM-1), and E-selectin) and monocytes (Monocyte chemoattractant protein-1), endothelial dysfunction, and monocyte adhesion to the endothelium.[35] The negative effect of CRP on the vascular wall has been confirmed by studies of its interaction with angiotensin II and its effects on the integrity of the endothelial glycocalyx,[36,37] as well as on increased expression of the lectin-like oxidized low-density lipoprotein receptor-1 involved in the damaging effect of oxidized low-density lipoproteins (ox-LDL).[38] Moreover, LDL-associated CRP deposits have been detected in foci of atherosclerotic lesions and myocardial damage induced by ischemia/reperfusion in experimental animals and humans.[39] These observations served as a basis to consider CRP as an active participant in atherosclerosis. Further study of the structural and functional relations of CRP *in vitro* and *in vivo*, and clearer diagnostics with separation of pentameric and monomeric forms of CRP, led to an understanding of the atheroprotective role of CRP.[33,40]

On the surface of activated platelets, apoptotic cells, and circulating cell-derived microparticles, upon ligand binding or under conditions of high oxidative potential of the extracellular environment, pentameric CRP irreversibly dissociates into insoluble monomers that have different pathophysiological functions from pentameric CRP.[41,42]

Monomeric CRP is thought to be involved in innate immunity processes through activation of the complement cascade,[43] angiogenesis, and atherothrombosis.[44] Pentameric CRP is not involved in thrombogenesis, whereas monomeric CRP induces platelet activation and thrombus growth. Additionally, pentameric and monomeric CRP have different pathways for stimulating endothelial cells and neutrophils, and different ways of binding to ligands, including LDL and C1q.[33,40]

The atheroprotective role of monomeric CRP is evidenced by its ability to retard foam cell formation by suppressing the aggressive response of macrophages to ox-LDL and to remove native LDL from the extracellular space, reducing the risk of modifications.[45,46] Moreover, monomeric CRP reduces the proatherogenic effects of macrophages in binding to lysophosphatidylcholine in ox-LDL and inhibits the association of ox-LDL with macrophages. These effects may partially slow the progression of atherosclerosis.[47]

Thus, CRP has conflicting proangiogenic and antiangiogenic effects that establish tissue remodeling in an atherosclerotic plaque (ASP) and in infarct-affected tissues.[33]

Myeloperoxidase (MPO) is considered a key element in oxidative damage to lipoproteins. MPO is a lysosomal enzyme that catalyzes the oxidation of various substrates, with hydrogen peroxide as a co-substrate. The specific oxidation products produced by MPO are found in ASP in large quantities.[48]

Table 1. Comparative characteristics of normal and pro-inflammatory HDL

Effects	Anti-inflammatory (normal) HDL	Pro-inflammatory HDL
Inflammatory	Apo AI reflects the antiatherogenic activity of lipoproteins and suppresses the atherogenic activity of ox-LDL; TNF-α regulation in macrophages; Prevention of EC IL-8, MCP-1 expression	Promote the oxidation of LDL; The synthesis of enzymes decreases under the influence of inflammation; Serum amyloid A, ceruloplasmin replace the usual components of HDL
Anti-oxidant properties	PON1 prevents the formation of oxidation products; Endothelial protection; Upregulation of EC and NO production; EC express receptors for apoA-I and HDL	The connection between PON1 and altered apoA1 is disrupted; PAPC interacts with the oxidation products of arachidonic acid to form biologically active oxidation products
Reverse cholesterol transport	ApoA1 and apoJ in HDL transport cholesterol from arterial vascular cells and macrophages to other lipids and liver cells for processing and disposal	The functions of apoA1 and apoJ are impaired by oxidative stress; Lipoprotein synthesis is reduced under the influence of inflammation
Platelet responses	Binding of mildly and native ox-LDL to apoER2′ and SR-BI on the platelet membrane induces signaling pathways that suppress platelet activation	Platelet activation through binding via CD36 to heavily oxidized HDL

AI, atherogenic index (TC/HDL-C); apo, apolipoprotein; apoER2, apoE receptor 2; EC, endothelial cells; HDL, high-density lipoprotein; IL-8, interleukin 8; MCP-1, monocyte chemoattractant protein 1; NO, nitric oxide; ox-LDL, oxidized low-density lipoproteins; PAPC, Paraxial protocadherin; PON-1, paraoxonase 1; SR-BI, scavenger receptors class B type I; TNF-α, tumor necrosis factor alpha.

The products of MPO-catalyzed reactions are strong oxidants that initiate lipid peroxidation and cause protein modification.[49] The enzyme increases the expression of P-selectin on the platelet surface and significantly raises the formation of oxygen radicals by platelets.[50]

MPO is thought to be a potent producer of oxidized LDL *in vivo*. Oxidized LDL accumulates in macrophages via class A1 scavenger receptors (SR) and SR-B1.[51] Another target of MPO is apoA1 HDL; by oxidizing this lipoprotein, MPO reduces its atheroprotective functions.[52] Modified HDLs are less effective in stimulating cholesterol efflux and are rapidly degraded by macrophages. Macrophages continue to engulf modified lipoproteins, and large amounts of lipids accumulate intracellularly, resulting in foam cell formation. Foam cells, in turn, have a pro-inflammatory effect by producing cytokines, chemokines, and growth factors, and by stimulating the secretion of adhesive molecules.[53]

Thus, systemic inflammation plays an important role in the development of disorders related to the blood cholesterol transport system. Data from numerous studies indicate the influence of cytokines (TNF-α, IL-6) on the proatherogenic potential of blood lipids and lipoproteins, supporting the concept of the contribution of chronic inflammation to the development of atherosclerosis.

Immunomodulatory effects of HDL

In recent years, there has been increasing evidence for the immunomodulatory properties of HDL. The determination of pro- or anti-inflammatory properties of HDL depends on the lipoprotein composition, the cholesterol content in macrophages, and the leading signaling pathways.[54,55]

HDLs undergo continuous remodeling processes in circulation, characterized by a wide variety of subtypes differing in size, density, shape, charge, and composition. This allows researchers to distinguish dysfunctional or even "proatherogenic" particles from "antiatherogenic" HDL.[56] The inflammatory process helps to reduce HDL levels and eliminate cholesterol from cells, leading to the production of proinflammatory HDL.[57,58] Proteins and enzymes responsible for the proinflammatory activity of HDL have been identified. The content of acute-phase proteins (such as serum amyloid A, fibrinogen, haptoglobin, apoJ, and complement factors B, C3, and C9) is elevated in proinflammatory HDL complexes compared to normal HDL.[59] In chronic inflammation, elevated concentrations of amyloid A, apoJ, and pancreatic phospholipase A2 are found in serum and can displace the usual HDL components (apoA1, HDL, etc.). Moreover, changes in the acetylhydrolase activity of HDL enzymes were observed: a decrease in paraoxonase 1 (PON1) and an increase in platelet-activating factor acetylhydrolase.[56] Together, these changes contribute to the proatherogenic potential of HDL.

On the other hand, HDLs inhibit the production of pro-inflammatory cytokines and chemokines, which may ultimately prevent immune cell activation and reduce inflammation.[60] The ability of HDL to inhibit the expression of ICAM-1, VCAM-1, and E-selectin has been demonstrated in endothelial cells.[61,62]

HDL and apoA1 can suppress inflammation by binding directly to lipopolysaccharide or lipoteichoic acid, thereby neutralizing them.[63,64] Several studies have clarified the immunomodulatory activity of HDL occurring without neutralization of lipopolysaccharide. HDL can block the ability of serum amyloid A to induce the production of reactive oxygen species and activate the NOD-like receptor protein 3 inflammasome involved in the formation of the active forms of IL-1β and IL-18.[65] Pretreatment of human endothelial cells with HDL reduced TNF-α-induced expression of ICAM-1, VCAM-1, and E-selectin.[66,67] Taborda *et al*.[67] studied the ability of HDL to mediate immune-inhibitory effects on innate immunostimulatory compounds via Toll-like receptors and inflammasomes without affecting the expression of pattern recognition receptors. These results suggest that HDL may modulate the immune response induced by various stimuli, thereby influencing the inflammatory response.[68]

The comparative characterization of normal and proinflammatory HDL is presented in Table 1.

In recent years, understanding of the mechanism of cholesterol transfer from biomembranes to HDL has greatly advanced through studies of plasma factors and cellular proteins in mouse models.[69] In 2022, researchers identified previously unknown membrane proteins associated with the regulation of lipoprotein metabolism and the cell's ability to release membrane cholesterol, thereby clarifying mechanisms of reverse cholesterol transport.[68,70] HDL

Table 2. Blood lipid spectrum in patients with early RA and in control (REMARCA trial), Me [25th; 75th percentile]

Blood lipids	RA (n = 154)	Control (n = 104)	*p*
Total cholesterol, mmol/L	5.22 [4.63; 5.98]	5.88 [5.45; 6.63]	0.036
LDL-C, mmol/L	3.41 [2.84; 4.14]	3.78 [3.53; 4.26]	0.01
HDL-C, mmol/L	1.32 [1.03; 1.62]	1.73 [1.43; 1.97]	0.023
TG, mmol/L	1.13 [0.86; 1.63]	1.03 [0.85; 1.39]	0.12
AIP (TG/HDL-C)	1.1 (0.6; 1.9)	0.6 (0.4; 1.5)	<0.001

AIP, atherogenic index of plasma; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; RA, rheumatoid arthritis; REMARCA, Russian invEstigation of MethotrexAte and biologicals in eaRly aCtive inflammatory Arthritis; TG, triglyceride.

directly transports cholesterol to SR-B1 receptors expressed in the liver. Alternatively, cholesterol from HDL transfers to LDL and very-low-density lipoproteins via CETP, then returns to the liver through LDL receptors, where it is metabolized into bile acids and excreted into the intestinal tract. Cholesterol exported from cells is transferred to large spherical HDL by the ATP-binding cholesterol transporter (ABC) G1. A related transporter, ABCA1, delivers cellular cholesterol to apoA1 and small dense HDL.[68]

The importance of the reverse cholesterol transport system has become evident from large cohort studies in humans, which consistently show an inverse association between the ability of apoB-containing lipoprotein-depleted plasma to uptake macrophage-derived cholesterol and cardiovascular disease (CVD) risk.[71,72] In healthy subjects with varying HDL-C and apoA1 levels, the ability of HDL to CEC from macrophages *in vitro* correlates inversely with measures of carotid intima-media thickness, independent of HDL-C and apoA1 concentrations.[73]

However, even with efficient acceptors, there may be factors limiting cholesterol efflux from membranes, potentially contributing to various proatherogenic abnormalities.[74–76]

The ability of serum to induce ABCA1-mediated CEC was reduced in patients with type 2 diabetes mellitus with microalbuminemia and proteinuria. The authors attributed this impaired CEC to low levels of preβ-1 HDL.[77] Additionally, depletion of preβ-1 HDL induced by chymase (a mast cell-secreted proteinase) therapy impaired ABCA1-mediated but not SR-B1-mediated, cholesterol efflux from J774 macrophages.[78] Specific genomic variants of lipoprotein receptors, apoB-100, Proprotein Convertase Subtilisin/Kexin type 9, and other loci may contribute to lipid metabolism abnormalities complicating vascular disorders in type 2 diabetes mellitus.[79,80]

Disorders of blood lipid and lipoprotein metabolism in patients with rheumatoid arthritis

RA is an autoimmune disease of unknown etiology characterized by chronic erosive arthritis with a progressive course, leading to serious complications and severe comorbidity. RA is associated with early disability and reduced life expectancy among patients.[81] CVDs play a significant role in the development of adverse outcomes in RA.[82] Numerous studies have shown that the relative risk of cardiovascular events in RA patients ranges from 1.4 to 3.7.[83] In a recent large cohort study, mortality rates remained high among RA patients (n = 16,047) observed from 2005 to 2018: the relative risk for death from all causes was 1.22 (95% confidence interval (CI) 1.15–1.30), from CVD - 1.63 (95% CI 1.51–1.75), from myocardial infarction - 2.00 (95% CI 1.78–2.26), and from stroke - 1.39 (95% CI 1.22–1.58). The risk of CVD in RA patients increases from the early years after diagnosis and does not decrease over time.[84]

The main mechanism leading to the development of CVD in RA is atherosclerotic vascular damage.[85] The multifactorial pathogenesis of atherosclerosis involves vascular, metabolic, and inflammatory components.[86] Disorders of blood lipid and lipoprotein metabolism are implicated in all three components and play a direct role in the formation of atherosclerotic vascular lesions in RA.[87,88] According to meta-analyses, patients with RA and hypercholesterolemia have a 73% higher incidence of CVD compared to patients without it.[87]

Blood lipid profile of RA patients

Inflammation in RA occurs with increased catabolism of lipoproteins, often leading to decreased serum levels of HDL and LDL. Despite this so-called "lipid paradox," patients remain at high risk of CVD.[89,90] Many researchers have observed lower concentrations of total cholesterol, LDL-C, and HDL-C in patients with active, untreated RA compared to healthy controls and patients with osteoarthritis.[91–96] In a prospective study, VanEvery *et al*.[97] have found an association between low LDL-C concentrations and RA risk. Other authors suggest that early-stage RA is associated with normal or reduced serum TG and total cholesterol levels, which, combined with a more pronounced reduction in HDL-C, may increase atherogenic potential.[98] Additionally, smaller, more atherogenic lipoprotein phenotypes have been detected in early RA patients compared to controls.[94] The formation of small dense LDL particles has been attributed to the acute phase reaction.[99]

In recent years, the atherogenic index of plasma (AIP), the logarithm of the ratio of TG/HDL-C, has been well-established as a predictor of coronary heart disease in the general population and in type 2 diabetes mellitus.[100–103] Hammam *et al*.[104] found associations between AIP and 10-year CVD risk as determined by the Framingham scale in patients with RA and systemic lupus erythematosus (SLE). The potential role of AIP in predicting and managing CVD risk in autoimmune rheumatic diseases has been investigated in several other studies.[105–108]

Similar data were obtained when analyzing the blood lipid spectrum in patients with untreated early RA included in the REMARCA (Russian invEstigation of MethotrexAte and biologicals in eaRly aCtive inflammatory Arthritis) trial. Decreased total cholesterol and HDL-C levels, along with increased AIP, were found in RA patients compared to healthy controls (Table 2).

In contrast, other studies have found higher levels of total cholesterol, LDL-C, TG, and, to a lesser extent, low HDL-C, resulting in significantly higher AIP in patients with early RA compared to healthy individuals.[109,110] It is important to note that total cholesterol and TG levels increase even before the clinical manifestations

of RA, and the subsequent development of chronic inflammation can explain the decrease in these indicators.[98]

Lipidomics has shown that serum lipid profiles in patients with active RA are similar to those of patients with preclinical RA, confirming alterations in lipid metabolism before disease onset.[111,112] In a prospective cohort study of anti-citrullinated protein antibody (ACPA) positive individuals, higher levels of monohydroxyeicosatetraenoic acids (5-HETE, an important precursor to leukotrienes) appeared to be associated with the subsequent development of inflammatory arthritis.[111] Other predictors of RA development in ACPA-positive individuals were decreased levels of apoA1 and ω-3 FA.[113,114] A body of research suggests a role for polyunsaturated FA metabolites in preclinical RA. However, the mechanism of their action is still poorly understood.[115,116]

A recent study by Koh *et al*.[117] demonstrated a marked shift in the lipidome profile in the synovial fluid of RA patients, correlating with disease activity and the degree of synovitis on ultrasound. In particular, lipid subclasses were decreased in lysophosphatidylcholine (LPC) and increased in phosphatidylcholine, its ester, triacylglycerol, and sphingomyelin. Similar changes, although less pronounced, were found in the serum lipidome profile. It is believed that the immunomodulatory effect of LPC depends on its biochemical structure: saturated and monounsaturated LPC species have a pro-inflammatory effect, whereas polyunsaturated species have an anti-inflammatory effect.[118]

Additionally, depletion of short-chain acylcarnitine was detected in the serum of women predisposed to RA.[119] The blood lipid spectrum in patients with active RA and high laboratory activity (CRP and erythrocyte sedimentation rate (ESR) levels) was similar to the lipid profile in patients with preclinical RA and normal CRP/ESR levels. This confirms the occurrence of dyslipidemia at the preclinical stage of RA.[119]

The relationship of lipid abnormalities with RA activity and acute-phase blood indices is also indicated in several other studies. Boers *et al*.[120] found the lowest levels of LDL-C and HDL-C in high RA activity. An association was found between levels of total cholesterol, CRP, and DAS28 activity index.[121] Park *et al*.,[122] in their study of lipid disorders in untreated RA patients, revealed a negative association of HDL-C and apoA1 concentrations with CRP. In the work of White *et al*.,[123] they confirmed the relationship between low HDL-C and high CRP/ESR levels. According to other data, lower serum HDL-C and apoA1 levels were observed in RA patients not only with high CRP levels but also with RF positivity and hand synovitis.[124,125]

During inflammation, lipoprotein (a) (Lp(a)) synthesis and expression increase, similar to acute-phase proteins.[126] Lp(a) is a cholesterol-rich plasma lipoprotein subclass consisting of LDL particles attached to apoA. In RA patients, blood Lp(a) concentration and apoB/apoA1 ratio were significantly higher than in the control group.[122,124] Higher levels of Lp(a), proinflammatory, and proatherogenic modified LDL associated with RA are independent risk factors for CVD.[127]

The comparative characterization of serum blood lipids in RA patients and healthy controls is presented in Table 3.[91-93,96,99,109,110,112,122-125,128-139]

In a study by Memon *et al*.,[140] it was observed that experimentally induced infection increases the level of oxidized lipids in serum, which may induce LDL oxidation *in vivo* and be a mechanism leading to increased CVD in patients with chronic infections and inflammatory diseases. The results of several subsequent studies confirmed higher blood levels of ox-LDL in RA patients compared to healthy controls.[141,142] LPC is known to be a major component of ox-LDL.[143] Recently published research in RA patients demonstrated a possible atherogenic effect of IgG anti-ox-LDL antibodies.[144,145] Specifically, it was shown that anti-ox-LDL titers (p = 0.020) may predict the presence of coronary ASP (noncalcified, partially calcified, and high-risk plaque) in RA patients with lower LDL-C levels (<1.8 mmol/L).[144]

The influence of pro-inflammatory cytokines on lipid metabolism and the pro-atherogenic potential of immune cells in RA is presented in Figure 1.

The most negatively charged LDL subcomponent associated with atherosclerosis is L5.[146] In RA, L5 may contribute to atherosclerosis by enhancing foam cell formation by macrophages and increasing the expression of M1 macrophage-associated markers (TNF-α, IL-6, and IL-8).[147]

Heterogeneity and functions of HDL

The first study on the determination of HDL subfractions in RA patients was carried out by Hurt-Camejo *et al*. in 2001.[99] The authors found a decrease in HDL2 in RA patients compared to healthy individuals, while the levels of total cholesterol, LDL-C, HDL-C, TG, apoB, and apoA1 did not differ.[99] In another study, lower levels of HDL2 and HDL3 were found in 45 patients with RA (especially women) compared to healthy controls.[148] The study demonstrated a moderate effect of RA activity on HDL2 levels. HDL2 concentration was reduced by 0.06 mmol/L with increasing DAS28 adjusted for sex, age, RA duration, and glucocorticoid use.

The inflammatory process in RA may attenuate the potential anti-atherogenic effect of HDL, causing a decrease in HDL-C levels and a reduction in antioxidant capacity. This reduction in antioxidant capacity may reduce the ability to eliminate cholesterol from cells, potentially leading to proinflammatory properties of lipoproteins.[57,58] Proinflammatory HDL has been detected in the blood of patients with CVD,[149] RA, and SLE.[150] Charles-Schoeman *et al*.[151] showed that proinflammatory HDLs were more frequently found in RA patients than in healthy individuals (20% and 4%, respectively, $p < 0.006$). Age, disease activity, erosive process, smoking, and non-Caucasoid race were correlated with proinflammatory HDL.

Further examination of the composition of proinflammatory HDL in RA patients revealed elevated levels of acute-phase proteins and complement factors compared to normal HDL.[59] Moreover, changes in the acetylhydrolase activity of HDL enzymes were observed: a decrease in PON1 and an increase in platelet-activating factor acetylhydrolase.

MPO may contribute to the atheroprotective effect of HDL in RA. MPO is an enzyme found in macrophages and neutrophils, acting as a mediator of inflammation and oxidative stress.[152,153] Several studies have found increased MPO concentration and activity in RA patients compared to healthy controls and patients with other rheumatic diseases (osteoarthritis, ankylosing spondylitis, SLE, and Sjögren's syndrome).[154–157] The high inflammatory status of RA and markers of acute-phase response (CRP, ESR) were associated with increased MPO activity.[154,156,158] MPO content in synovial fluid was higher in untreated RA patients compared to treated patients; moreover, in untreated patients, MPO concentration and activity correlated with IL-8 and IL-18 content.[157]

In a recent study by Alisik *et al.*,[138] MPO levels were higher in RA patients with concomitant CVD compared to RA patients without CVD. According to receiver operating characteristic analysis, the ratio of MPO to PON1, which characterizes HDL dysfunction, appeared to be more associated with CVD in RA.

Table 3. Lipid spectrum of the blood of rheumatoid arthritis (RA) patients, healthy controls (HC)

Researchers	Year	Number of RA patients/HC	Results
Lazarevic *et al*.[128]	1992	69/65	↓ LDL-C, TC, HDL-C, more pronounced in patients with high RA activity
Park *et al*.[122]	1999	42/42	↓ HDL-C и apoA1, ↑ Lp(a) and AI; correlations between HDL-C and CRP (r = −0.35), apoA1 and CRP (r = −0.44)
Hurt-Camejo *et al*.[99]	2001	31/28	TC, LDL-C, TG, HDL-C, apoB, apoA1 did not change. ↑ subfractions LDL_1, ↓ HDL
Kim *et al*.[91]	2004	54/50	↓ TC, LDL-C
Choi *et al*.[125]	2005	104/NHANES (>60 лет)	↓ HDL-C and apoA1; inverse correlations HDL-C levels with CRP, RF, and synovitis of the hands
White *et al*.[123]	2006	204/75	↑ LDL-C; ↓ HDL-C; ↑ AI; negative correlations HDL-C and CRP, HDL-C and ESR and positive – LDL-C and ESR
Georgiadis *et al*.[109]	2006	58/63	↑ TC, LDL-C, TG; ↓ HDL-C; ↑ AI
Popkova *et al*.[129]	2007	84/15	↑ TG, apoA1; ↓ LDL-C; TC and HDL-C did not differ
Gonzalez *et al*.[130]	2008	603/603	TC, HDL-C, LDL-C, TG, apo did not change
Myasoedova *et al*.[92]	2010	577/540	↓ TC, LDL-C: 5 years before the development of RA
Boyer *et al*.[131]	2011	2,956/3,713	↓ HDL-C
Liao *et al*.[93]	2013	2,005/NHANES	↓ TC and LDL-C
Pozzi *et al*.[132]	2015	30/30	TC, LDL-C, TG, apoA1 did not differ, ↑ HDL-C, apoE, ↓ apoB
Chavan *et al*.[110]	2015	50/50	↑ TC, LDL-C; ↓ HDL-C
Govindan *et al*.[124]	2015	30/30	↓ HDL-C and apoA1, ↑ AI
Kim *et al*.[133]	2016	33/13	↓ HDL-C, ↑TG, CETP, AGEs, apoA1
Ormseth *et al*.[134]	2016	169/92	↓ LDL-C; CEC did not differ
Rodríguez-Carrio *et al*.[135]	2017	113/113	↑ HDL-C, TG, ↓PON1; $TG^{high}HDL^{low}$ profile did not differ and was associated with increased TNF-α, MCP-1, leptin, and INF- γ-inducible protein-10 ($p < 0.05$ in all cases)
Tejera-Segura *et al*.[96]	2017	178/223	↓ HDL-C, LDL-C, apoA; ↑ Lp(a). In patients with RA activity, a decrease in CEC was detected, in contrast to patients with remission.
Burggraaf *et al*.[136]	2018	312/57	No differences were detected in the lipid profile; ↑ apoAI, apoB48. ApoB48 correlated with TG (r = 0.645, $p < 0.001$)
Dessie *et al*.[137]	2020	73/40	↑ TC, TG; ↑TC/HDL and LDL/HDL ratios; ↓ HDL-C; LDL-C did not differ. HDL-C negative correlation with CRP, and TC/HDL-C and LDL/HDL-C had a direct association with CRP ($p < 0.05$).
Alisik *et al*.[138]	2021	130/67	No differences were detected in the lipid profile; ↑ MPO/PON1 ratios in RA patients, especially high with CVD history. MPO/PON1 ratios were significant positive correlated with DAS28 scores (r = 0.357, $p < 0.001$)
Rodríguez-Carrio *et al*.[112]	2021	60/28	In RA patients, 2 oxylipin clusters (cluster I and cluster II) were identified in contrast to the control group ($p = 0.003$).
Chang *et al*.[139]	2023	80/15	↑ particle number, cholesterol ester, free cholesterol, and phospholipids in large/very large-sized HDL; small-sized HDL negative correlation with CRP; ACPA-positivity was associated with HDL- metabolites.

ACPA, anti-citrullinated protein antibody; AGEs, advanced glycation end products; AI, atherogenic index (TC/HDL-C); apo, apolipoprotein; CEC, cholesterol efflux capacity; CETP, cholesteryl ester transfer protein; CRP, C-reactive protein; CVD, cardiovascular disease; ESR, erythrocyte sedimentation rate; HC, healthy controls; HDL-C, high-density lipoproteins cholesterol; INF-γ, interferon-gamma; LDL-C, low-density lipoproteins cholesterol; Lp(a), lipoprotein (a); MCP-1, monocyte chemotactic protein; MPO, myeloperoxidase; NHANES, National Health and Nutrition Examination Surveys; PON1, paraoxonase-1; RA, rheumatoid arthritis; RF, rheumatoid factor; TC, total cholesterol; TG, triglycerides; TNF-α, tumor necrosis factor alpha.

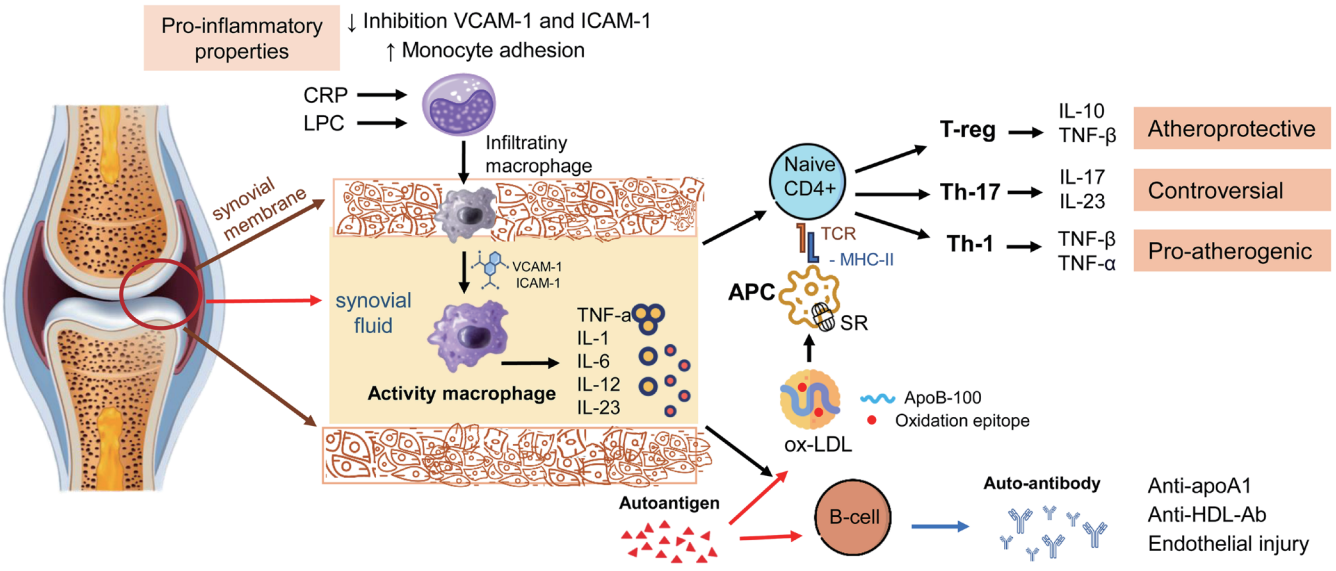

Fig. 1. The influence of pro-inflammatory cytokines on lipid metabolism and the pro-atherogenic potential of immune cells in RA. Pro-inflammatory cytokines (TNF-α, IL-6, and IL-1β) are produced in large quantities locally in the joints and subsequently enter the bloodstream. TNF-α and IL-6 may promote LDL metabolism by increasing the expression of LDLR and SR-B1 on the surface of liver cells. Moreover, TNF-α and IL-1β can reduce the formation of pro-ApoA1 particles in the liver by suppressing HDL production. Presentation of antigenic peptides from ApoB by antigen-presenting cells (APCs) promotes the formation of effector T cells from naïve ($CD4^+$) T helper cells. APCs oxidize LDL-C particles, process, and present peptides from ApoB on major histocompatibility complex molecules. The specific T cell receptor is responsible for recognizing antigen fragments in the form of peptides bound to major histocompatibility complex molecules. Under the influence of co-stimulatory signals and cytokines secreted by APCs, T cells express transcription factors that promote differentiation into distinct Th types, which produce specific cytokines that can act both atheroprotectively and proatherogenic. anti-apoA1, antibodies against apolipoprotein A1; anti-HDL-Ab, anti-HDL antibodies; APCs, antigen-presenting cells; CRP, C-reactive protein; HDL, high-density lipoproteins; ICAM-1, intercellular adhesion molecule 1; IL, interleukin; LDL-C, low-density lipoprotein cholesterol; LDLR, low density lipoprotein receptor; LPC, lysophosphatidylcholine; MHC, major histocompatibility complex; ox-LDL, oxidized low-density lipoproteins; RA, rheumatoid arthritis; SR, scavenger receptor; TCR, T-cell receptor; Th, T helper; TNF, tumor necrosis factor; VCAM-1, vascular cellular adhesion molecule-1.

The best-studied effects of MPO on CVD include the formation of dysfunctional atherogenic lipoproteins, decreased nitric oxide availability, and endothelial dysfunction leading to vasoreactivity and ASP instability.[159] These effects strongly suggest that MPO is directly involved in the pathophysiology of CVD in RA.[160,161]

Thus, inflammation and high RA activity may reduce antioxidant properties and contribute to the proatherogenic potential of HDL. However, there is no clear consensus on whether this mechanism affects CVD risk in RA.[161]

HDL becomes proatherogenic against the backdrop of inflammation due to decreased CEC from macrophages, which is an independent risk factor for CVD.[96,162]

The efficacy of CEC is known to correlate directly with the properties of plasma lipid transport proteins. Decreases in CETP mass and activity were found in RA patients compared to healthy subjects,[96] with the lowest rates observed in RA patients on glucocorticoids.[163]

Studies have shown no difference or a decrease in CEC in RA patients compared with healthy donors.[96,155,161,164,165] A meta-analysis confirmed no differences in HDL-C efflux capacity and concentration between patients with RA and controls.[166]

In a recent study including 195 SLE patients and 265 RA patients, more severe CEC impairment was noted in SLE patients compared to RA patients.[167] Although both diseases share common features of inflammatory dyslipidemia, RA patients had lower HDL-C levels and higher apoB levels than SLE patients.

Importantly, patients with high RA activity (DAS28 > 5.1) had lower CEC than patients in remission.[96,164] The association of high RA activity with suppression of CEC may be indicated by inverse correlations of cholesterol efflux with DAS28 ($r = -0.39$, $p = 0.01$) and ESR ($r = -0.41$, $p < 0.001$).[164] Multivariate analysis revealed that smoking, diabetes, ESR, and glucocorticoid use were correlated with CEC. However, according to Ormseth *et al*.,[161] cholesterol efflux was not associated with RA activity, the systemic inflammation index CRP, oxidative stress (urinary F2-isoprostanes), or insulin resistance measured by the HOMA index. The authors concluded that net cholesterol efflux capacity by HDL-enriched serum is not altered in patients with well-controlled RA.

Liao *et al*.[165] studied the blood lipid spectrum and CEC in RA patients with CRP concentration ≥10 mg/L. After one year of therapy and a 23.5 mg/L decrease in CRP, patients showed a 7.2% increase in HDL-C ($p = 0.02$) and a 5.7% increase in CEC ($p = 0.002$). The decrease in CRP concentration was accompanied by an increase in apoA1 ($r = 0.27$, $p = 0.01$) and CEC ($r = 0.24$, $p = 0.002$).

When CEC mediated by SR-B1, ABCG1, and ABCA1 were studied using apoB-depleted serum, Ronda *et al*.[168] found that only ABCG1-mediated CEC was lower in active RA patients compared with controls. The same authors later conducted a comparative study of CEC before and after 6 months of methotrexate as monotherapy and in combination with the TNF-α inhibitor adalimumab.[169] Methotrexate monotherapy moderately increased SR-B1- and ABCG1-mediated CEC by 6% and 7%, respectively. Multidirectional associations of ABCG1-mediated CEC with serum HDL-C concentration ($r = 0.18$, $p = 0.047$) and DAS28 ($r = -0.247$, $p = 0.018$) were observed in RA patients after 6 months of combination therapy with methotrexate and a TNF-α inhibitor. The study found no correlation between CEC and inflammatory

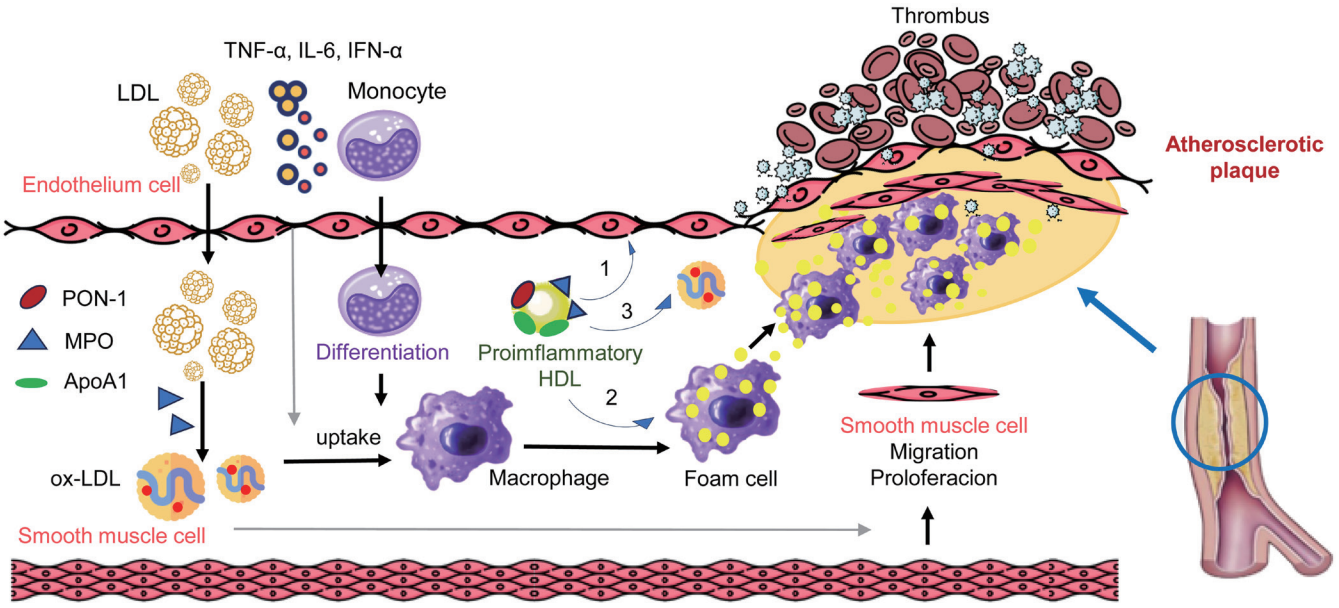

Fig. 2. LDL passes through the endothelium. Under the influence of MPO, LDL is oxidized. Under the influence of macrophages, ox-LDL is taken up and turns into foam cells. Proinflammatory HDL shows marked changes in proteins (↑ SAA and MPO and ↓ apoA1 and PON1). This circumstance leads to the inability of HDL to block the expression of ICAM/VCAM on endothelial cells (1), remove cholesterol from foam cells (2), and exhibit its antioxidant ability (3). Ox-LDL triggers the proliferation and migration of smooth muscle cells. A conglomerate of foam cells and smooth muscle cells forms an atherosclerotic plaque. Apo, apolipoprotein; HDL, high-density lipoproteins; ICAM-1, intercellular adhesion molecule 1; IFN-α, interferon-alpha; IL, interleukin; LDL, low-density lipoproteins; MPO, myeloperoxidase; ox-LDL, oxidized low-density lipoproteins; PON1, paraoxonase-1; SAA, serum amyloid A; TNF-α, tumor necrosis factor alpha; VCAM-1, vascular cellular adhesion molecule-1.

markers.

As noted by Ormseth & Stein in their review, there is no uniform data on the significance of impaired CEC in RA patients and the influence of disease activity or inflammation on it.[161] A meta-analysis of HDL cholesterol efflux capacity and concentration in RA showed improvement in CEC with early administration of antirheumatic therapy and control of inflammation.[166] However, the authors noted that the results should be interpreted with caution due to the heterogeneity of groups and methodologies in those studies.

CEC is considered a sensitive predictor of cardiovascular risk in the general population.[170,171] Nevertheless, the association of CEC with CVD risk in RA appears to be ambiguous.

In a study by Vivekanandan-Giri *et al*.,[155] no differences were found between RA patients with and without CVD. According to Ormseth *et al*.,[134] an increase in net CEC by HDL-enriched serum was not significantly associated with a decrease in coronary calcium score (odds ratio (OR) = 0.78 [95% CI 0.51–1.19], $p = 0.24$), adjusting for age, sex, race, the Framingham cardiovascular risk scale, and the presence of diabetes. Another study demonstrated the association of high CEC with a low risk of carotid ASP development in RA patients (OR = 0.94 [95% CI 0.89–0.98], $p = 0.015$).[96]

Convincing data on the impact of rheumatoid inflammation on CEC and its contribution to the development of atherosclerosis and associated CVD were reported in 2023. Karpouzas *et al*.[172] confirmed the inverse association of systemic inflammation measured by CRP and disease activity measured by DAS28-CRP with ABCA1-mediated CEC. ABCA1-mediated CEC was associated with less progression and fewer coronary ASPs in patients with low baseline and cumulative CRP levels, in patients not receiving glucocorticoids, and in patients on disease-modifying antirheumatic drug therapy. In contrast, ABCA1-mediated CEC was associated with accelerated development of coronary atherosclerosis in patients with baseline high CRP levels and in those receiving glucocorticoids but not methotrexate or biologic disease-modifying antirheumatic drugs.[173]

In another study by these authors,[172] ABCG1-mediated CEC was inversely correlated with a large number (≥5) of carotid ASPs (adjusted OR 0.50 [95% CI 0.28–0.88]), numbers of partially calcified (rate ratio 0.71 [0.53–0.94]), and low-attenuation plaques (rate ratio 0.63 [0.43–0.91] per standard deviation increment). Low-attenuation plaques on coronary computed tomography angiography are known to be associated with ASP progression and instability.

The general form of atherothrombosis in RA is shown schematically in Figure 2.

Thus, in well-treated RA with controlled disease activity, ABCA1-CEC may exhibit atheroprotective actions. Conversely, in uncontrolled RA, inflammation promotes the development of proatherogenic properties of ABCA1-CEC.[166,173]

Conclusions

Interest in the study of lipids and lipoproteins in RA remains high. New data on the development of lipid abnormalities have been obtained in the preclinical phase of RA research. Studies have demonstrated differences in lipid and lipidome profiles depending on disease phase, inflammation activity, and study methods. Lipids may contribute to progression or exert a protective effect in RA depending on their type and metabolites. Inflammation or disease activity appears to have a deleterious effect on HDL-mediated reverse cholesterol transport activity. Effective treatment of inflammation by adequate control of RA activity

can offset proatherogenic abnormalities in lipid and lipoprotein metabolism.

Acknowledgments

None.

Funding

This work was supported by the Russian Science Foundation (Grant # 22-15-00199).

Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Author contributions

Study concept and design (EG, TP), acquisition of data (EG, MS), analysis and interpretation of data (EG, TP, DG), drafting of the manuscript (EG, MS, DG), critical revision of the manuscript for important intellectual content (TP, DG), administrative, technical, or material support (TP), and study supervision (TP). All authors have made significant contributions to this study and have approved the final manuscript.

References

[1] Wolf D, Ley K. Immunity and Inflammation in Atherosclerosis. Circ Res 2019;124(2):315–327. doi:10.1161/CIRCRESAHA.118.313591, PMID:30653442.

[2] Getz GS, Reardon CA. Atherosclerosis: cell biology and lipoproteins. Curr Opin Lipidol 2020;31(5):286–290. doi:10.1097/MOL.0000000000000704, PMID:32773467.

[3] Carpentier YA, Scruel O. Changes in the concentration and composition of plasma lipoproteins during the acute phase response. Curr Opin Clin Nutr Metab Care 2002;5(2):153–158. doi:10.1097/00075197-200203000-00006, PMID:11844981.

[4] Read TE, Grunfeld C, Kumwenda ZL, Calhoun MC, Kane JP, Feingold KR, *et al*. Triglyceride-rich lipoproteins prevent septic death in rats. J Exp Med 1995;182(1):267–272. doi:10.1084/jem.182.1.267, PMID:7790821.

[5] Hardardóttir I, Grünfeld C, Feingold KR. Effects of endotoxin and cytokines on lipid metabolism. Curr Opin Lipidol 1994;5(3):207–215. doi:10.1097/00041433-199405030-00008, PMID:7952915.

[6] Li Y, Xu Y, Jadhav K, Zhu Y, Yin L, Zhang Y. Hepatic Forkhead Box Protein A3 Regulates ApoA-I (Apolipoprotein A-I) Expression, Cholesterol Efflux, and Atherogenesis. Arterioscler Thromb Vasc Biol 2019;39(8):1574–1587. doi:10.1161/ATVBAHA.119.312610, PMID:31291759.

[7] Niisuke K, Kuklenyik Z, Horvath KV, Gardner MS, Toth CA, Asztalos BF. Composition-function analysis of HDL subpopulations: influence of lipid composition on particle functionality. J Lipid Res 2020;61(3):306–315. doi:10.1194/jlr.RA119000258, PMID:31953305.

[8] Tahir A, Martinez PJ, Ahmad F, Fisher-Hoch SP, McCormick J, Gay JL, *et al*. An evaluation of lipid profile and pro-inflammatory cytokines as determinants of cardiovascular disease in those with diabetes: a study on a Mexican American cohort. Sci Rep 2021;11(1):2435. doi:10.1038/s41598-021-81730-6, PMID:33510184.

[9] McGillicuddy FC, de la Llera Moya M, Hinkle CC, Joshi MR, Chiquoine EH, Billheimer JT, *et al*. Inflammation impairs reverse cholesterol transport in vivo. Circulation 2009;119(8):1135–1145. doi:10.1161/CIRCULATIONAHA.108.810721, PMID:19221221.

[10] Ren Y, Zhao H, Yin C, Lan X, Wu L, Du X, *et al*. Adipokines, Hepatokines and Myokines: Focus on Their Role and Molecular Mechanisms in Adipose Tissue Inflammation. Front Endocrinol (Lausanne) 2022;13:873699. doi:10.3389/fendo.2022.873699, PMID:35909571.

[11] Hotamisligil GS, Shargill NS, Spiegelman BM. Adipose expression of tumor necrosis factor-alpha: direct role in obesity-linked insulin resistance. Science 1993;259(5091):87–91. doi:10.1126/science.7678183, PMID:7678183.

[12] Kapłon-Cieślicka A, Postuła M, Rosiak M, Peller M, Kondracka A, Serafin A, *et al*. Association of adipokines and inflammatory markers with lipid control in type 2 diabetes. Pol Arch Med Wewn 2015;125(6):414–423. doi:10.20452/pamw.2880, PMID:25978118.

[13] Park S, Zhang T, Yue Y, Wu X. Effects of Bile Acid Modulation by Dietary Fat, Cholecystectomy, and Bile Acid Sequestrant on Energy, Glucose, and Lipid Metabolism and Gut Microbiota in Mice. Int J Mol Sci 2022;23(11):5935. doi:10.3390/ijms23115935, PMID:35682613.

[14] Souza SC, de Vargas LM, Yamamoto MT, Lien P, Franciosa MD, Moss LG, *et al*. Overexpression of perilipin A and B blocks the ability of tumor necrosis factor alpha to increase lipolysis in 3T3-L1 adipocytes. J Biol Chem 1998;273(38):24665–24669. doi:10.1074/jbc.273.38.24665, PMID:9733764.

[15] Kralisch S, Klein J, Lossner U, Bluher M, Paschke R, Stumvoll M, *et al*. Isoproterenol, TNFalpha, and insulin downregulate adipose triglyceride lipase in 3T3-L1 adipocytes. Mol Cell Endocrinol 2005;240(1-2):43–49. doi:10.1016/j.mce.2005.06.002, PMID:16009485.

[16] Hauner H. Secretory factors from human adipose tissue and their functional role. Proc Nutr Soc 2005;64(2):163–169. doi:10.1079/pns2005428, PMID:15960861.

[17] Päth G, Bornstein SR, Gurniak M, Chrousos GP, Scherbaum WA, Hauner H. Human breast adipocytes express interleukin-6 (IL-6) and its receptor system: increased IL-6 production by beta-adrenergic activation and effects of IL-6 on adipocyte function. J Clin Endocrinol Metab 2001;86(5):2281–2288. doi:10.1210/jcem.86.5.7494, PMID:11344240.

[18] Tanaka T, Narazaki M, Kishimoto T. Interleukin (IL-6) Immunotherapy. Cold Spring Harb Perspect Biol 2018;10(8):a028456. doi:10.1101/cshperspect.a028456, PMID:28778870.

[19] Hoene M, Weigert C. The role of interleukin-6 in insulin resistance, body fat distribution and energy balance. Obes Rev 2008;9(1):20–29. doi:10.1111/j.1467-789X.2007.00410.x, PMID:17956545.

[20] Ettinger WH Jr, Sun WH, Binkley N, Kouba E, Ershler W. Interleukin-6 causes hypocholesterolemia in middle-aged and old rhesus monkeys. J Gerontol A Biol Sci Med Sci 1995;50(3):M137–M140. doi:10.1093/gerona/50a.3.m137, PMID:7743398.

[21] Khovidhunkit W, Kim MS, Memon RA, Shigenaga JK, Moser AH, Feingold KR, *et al*. Effects of infection and inflammation on lipid and lipoprotein metabolism: mechanisms and consequences to the host. J Lipid Res 2004;45(7):1169–1196. doi:10.1194/jlr.R300019-JLR200, PMID:15102878.

[22] Gotsman I, Stabholz A, Planer D, Pugatsch T, Lapidus L, Novikov Y, *et al*. Serum cytokine tumor necrosis factor-alpha and interleukin-6 associated with the severity of coronary artery disease: indicators of an active inflammatory burden? Isr Med Assoc J 2008;10(7):494–498. PMID:18751625.

[23] Ridker PM, Lüscher TF. Anti-inflammatory therapies for cardiovascular disease. Eur Heart J 2014;35(27):1782–1791. doi:10.1093/eurheartj/ehu203, PMID:24864079.

[24] Cheng HF, Feng Y, Jiang DM, Tao KY, Kong MJ. Protective function of tocilizumab in human cardiac myocytes ischemia reperfusion injury. Asian Pac J Trop Med 2015;8(1):48–52. doi:10.1016/S1995-7645(14)60186-3, PMID:25901924.

[25] Bernecker C, Scherr J, Schinner S, Braun S, Scherbaum WA, Halle M. Evidence for an exercise induced increase of TNF-α and IL-6 in marathon runners. Scand J Med Sci Sports 2013;23(2):207–214. doi:10.1111/j.1600-0838.2011.01372.x, PMID:22092703.

[26] Górecka M, Krzemiński K, Mikulski T, Ziemba AW. ANGPTL4, IL-6 and TNF-α as regulators of lipid metabolism during a marathon run. Sci Rep 2022;12(1):19940. doi:10.1038/s41598-022-17439-x, PMID:36402848.

[27] Zimmermann O, Li K, Zaczkiewicz M, Graf M, Liu Z, Torzewski J. C-reactive protein in human atherogenesis: facts and fiction. Mediators Inflamm 2014;2014:561428. doi:10.1155/2014/561428, PMID:24799767.

[28] Calabro P, Chang DW, Willerson JT, Yeh ET. Release of C-reactive protein in response to inflammatory cytokines by human adipocytes: linking obesity to vascular inflammation. J Am Coll Cardiol 2005;46(6):1112–1113. doi:10.1016/j.jacc.2005.06.017, PMID:16168299.
[29] Pepys MB, Hirschfield GM. C-reactive protein: a critical update. J Clin Invest 2003;111(12):1805–1812. doi:10.1172/JCI18921, PMID: 12813013.
[30] Wang MS, Black JC, Knowles MK, Reed SM. C-reactive protein (CRP) aptamer binds to monomeric but not pentameric form of CRP. Anal Bioanal Chem 2011;401(4):1309–1318. doi:10.1007/s00216-011-5174-1, PMID:21725632.
[31] Fu T, Borensztajn J. Macrophage uptake of low-density lipoprotein bound to aggregated C-reactive protein: possible mechanism of foam-cell formation in atherosclerotic lesions. Biochem J 2002;366(Pt 1):195–201. doi:10.1042/BJ20020045, PMID:12033985.
[32] Lu J, Marnell LL, Marjon KD, Mold C, Du Clos TW, Sun PD. Structural recognition and functional activation of FcgammaR by innate pentraxins. Nature 2008;456(7224):989–992. doi:10.1038/nature07468, PMID:19011614.
[33] Boncler M, Wu Y, Watala C. The Multiple Faces of C-Reactive Protein-Physiological and Pathophysiological Implications in Cardiovascular Disease. Molecules 2019;24(11):2062. doi:10.3390/molecules24112062, PMID:31151201.
[34] Lu J, Mold C, Du Clos TW, Sun PD. Pentraxins and Fc Receptor-Mediated Immune Responses. Front Immunol 2018;9:2607. doi:10.3389/fimmu.2018.02607, PMID:30483265.
[35] Pathak A, Agrawal A. Evolution of C-Reactive Protein. Front Immunol 2019;10:943. doi:10.3389/fimmu.2019.00943, PMID:31114584.
[36] Wang CH, Li SH, Weisel RD, Fedak PW, Dumont AS, Szmitko P, *et al*. C-reactive protein upregulates angiotensin type 1 receptors in vascular smooth muscle. Circulation 2003;107(13):1783–1790. doi:10.1161/01.CIR.0000061916.95736.E5, PMID:12665485.
[37] Devaraj S, Yun JM, Adamson G, Galvez J, Jialal I. C-reactive protein impairs the endothelial glycocalyx resulting in endothelial dysfunction. Cardiovasc Res 2009;84(3):479–484. doi:10.1093/cvr/cvp249, PMID:19620133.
[38] Li L, Roumeliotis N, Sawamura T, Renier G. C-reactive protein enhances LOX-1 expression in human aortic endothelial cells: relevance of LOX-1 to C-reactive protein-induced endothelial dysfunction. Circ Res 2004;95(9):877–883. doi:10.1161/01.RES.0000147309.54227.42, PMID:15472120.
[39] Pegues MA, McCrory MA, Zarjou A, Szalai AJ. C-reactive protein exacerbates renal ischemia-reperfusion injury. Am J Physiol Renal Physiol 2013;304(11):F1358–F1365. doi:10.1152/ajprenal.00476.2012, PMID:23535585.
[40] Singh SK, Agrawal A. Functionality of C-Reactive Protein for Atheroprotection. Front Immunol 2019;10:1655. doi:10.3389/fimmu.2019.01655, PMID:31379851.
[41] Thiele JR, Habersberger J, Braig D, Schmidt Y, Goerendt K, Maurer V, *et al*. Dissociation of pentameric to monomeric C-reactive protein localizes and aggravates inflammation: in vivo proof of a powerful proinflammatory mechanism and a new anti-inflammatory strategy. Circulation 2014;130(1):35–50. doi:10.1161/CIRCULATIONAHA.113.007124, PMID:24982116.
[42] Strang F, Schunkert H. C-reactive protein and coronary heart disease: all said—is not it? Mediators Inflamm 2014;2014:757123. doi:10.1155/2014/757123, PMID:24808639.
[43] Hakobyan S, Harris CL, van den Berg CW, Fernandez-Alonso MC, de Jorge EG, de Cordoba SR, *et al*. Complement factor H binds to denatured rather than to native pentameric C-reactive protein. J Biol Chem 2008;283(45):30451–30460. doi:10.1074/jbc.M803648200, PMID:18786923.
[44] Badimon L, Peña E, Arderiu G, Padró T, Slevin M, Vilahur G, *et al*. C-Reactive Protein in Atherothrombosis and Angiogenesis. Front Immunol 2018;9:430. doi:10.3389/fimmu.2018.00430, PMID:29552019.
[45] Ji SR, Wu Y, Potempa LA, Qiu Q, Zhao J. Interactions of C-reactive protein with low-density lipoproteins: implications for an active role of modified C-reactive protein in atherosclerosis. Int J Biochem Cell Biol 2006;38(4):648–661. doi:10.1016/j.biocel.2005.11.004, PMID:16376133.
[46] Krayem I, Bazzi S, Karam M. The combination of CRP isoforms with oxLDL decreases TNF-α and IL-6 release by U937-derived macrophages. Biomed Rep 2017;7(3):272–276. doi:10.3892/br.2017.949, PMID:28808571.
[47] Melnikov I, Kozlov S, Saburova O, Avtaeva Y, Guria K, Gabbasov Z. Monomeric C-Reactive Protein in Atherosclerotic Cardiovascular Disease: Advances and Perspectives. Int J Mol Sci 2023;24(3):2079. doi:10.3390/ijms24032079, PMID:36768404.
[48] Podrez EA, Abu-Soud HM, Hazen SL. Myeloperoxidase-generated oxidants and atherosclerosis. Free Radic Biol Med 2000;28(12):1717–1725. doi:10.1016/s0891-5849(00)00229-x, PMID:10946213.
[49] Kamal FZ, Lefter R, Jaber H, Balmus IM, Ciobica A, Iordache AC. The Role of Potential Oxidative Biomarkers in the Prognosis of Acute Ischemic Stroke and the Exploration of Antioxidants as Possible Preventive and Treatment Options. Int J Mol Sci 2023;24(7):6389. doi:10.3390/ijms24076389, PMID:37047362.
[50] O'Flynn J, Dixon KO, Faber Krol MC, Daha MR, van Kooten C. Myeloperoxidase directs properdin-mediated complement activation. J Innate Immun 2014;6(4):417–425. doi:10.1159/000356980, PMID:24355864.
[51] Delporte C, Van Antwerpen P, Vanhamme L, Roumeguère T, Zouaoui Boudjeltia K. Low-density lipoprotein modified by myeloperoxidase in inflammatory pathways and clinical studies. Mediators Inflamm 2013;2013:971579. doi:10.1155/2013/971579, PMID:23983406.
[52] Getz GS, Reardon CA. Myeloperoxidase-mediated dysfunctional high-density lipoprotein. Arterioscler Thromb Vasc Biol 2014;34(4):695–696. doi:10.1161/ATVBAHA.114.303282, PMID:24665120.
[53] Ross EA, Devitt A, Johnson JR. Macrophages: The Good, the Bad, and the Gluttony. Front Immunol 2021;12:708186. doi:10.3389/fimmu.2021.708186, PMID:34456917.
[54] van der Vorst EPC, Theodorou K, Wu Y, Hoeksema MA, Goossens P, Bursill CA, *et al*. High-Density Lipoproteins Exert Pro-inflammatory Effects on Macrophages via Passive Cholesterol Depletion and PKC-NF-κB/STAT1-IRF1 Signaling. Cell Metab 2017;25(1):197–207. doi:10.1016/j.cmet.2016.10.013, PMID:27866837.
[55] Fotakis P, Kothari V, Thomas DG, Westerterp M, Molusky MM, Altin E, *et al*. Anti-Inflammatory Effects of HDL (High-Density Lipoprotein) in Macrophages Predominate Over Proinflammatory Effects in Atherosclerotic Plaques. Arterioscler Thromb Vasc Biol 2019;39(12):e253–e272. doi:10.1161/ATVBAHA.119.313253, PMID:31578081.
[56] Pirillo A, Catapano AL, Norata GD. Biological Consequences of Dysfunctional HDL. Curr Med Chem 2019;26(9):1644–1664. doi:10.2174/0929867325666180530110543, PMID:29848265.
[57] Van Lenten BJ, Hama SY, de Beer FC, Stafforini DM, McIntyre TM, Prescott SM, *et al*. Anti-inflammatory HDL becomes pro-inflammatory during the acute phase response. Loss of protective effect of HDL against LDL oxidation in aortic wall cell cocultures. J Clin Invest 1995;96(6):2758–2767. doi:10.1172/JCI118345, PMID:8675645.
[58] Van Lenten BJ, Navab M, Shih D, Fogelman AM, Lusis AJ. The role of high-density lipoproteins in oxidation and inflammation. Trends Cardiovasc Med 2001;11(3-4):155–161. doi:10.1016/s1050-1738(01)00095-0, PMID:11686006.
[59] Watanabe J, Charles-Schoeman C, Miao Y, Elashoff D, Lee YY, Katselis G, *et al*. Proteomic profiling following immunoaffinity capture of high-density lipoprotein: association of acute-phase proteins and complement factors with proinflammatory high-density lipoprotein in rheumatoid arthritis. Arthritis Rheum 2012;64(6):1828–1837. doi:10.1002/art.34363, PMID:22231638.
[60] Spirig R, Schaub A, Kropf A, Miescher S, Spycher MO, Rieben R. Reconstituted high-density lipoprotein modulates activation of human leukocytes. PLoS One 2013;8(8):e71235. doi:10.1371/journal.pone.0071235, PMID:23967171.
[61] Wadham C, Albanese N, Roberts J, Wang L, Bagley CJ, Gamble JR, *et al*. High-density lipoproteins neutralize C-reactive protein proinflammatory activity. Circulation 2004;109(17):2116–2122. doi:10.1161/01.CIR.0000127419.45975.26, PMID:15078800.
[62] Holzwirth E, Fischer-Schaepmann T, Obradovic D, von Lucadou M, Schwedhelm E, Daum G, *et al*. Anti-inflammatory HDL effects are impaired in atrial fibrillation. Heart Vessels 2022;37(1):161–171. doi:10.1007/s00380-021-01908-w, PMID:34459957.
[63] Morin EE, Guo L, Schwendeman A, Li XA. HDL in sepsis - risk factor and therapeutic approach. Front Pharmacol 2015;6:244. doi:10.3389/

fphar.2015.00244, PMID:26557091.
[64] De Geest B, Mishra M. Impact of High-Density Lipoproteins on Sepsis. Int J Mol Sci 2022;23(21):12965. doi:10.3390/ijms232112965, PMID:36361756.
[65] Shridas P, De Beer MC, Webb NR. High-density lipoprotein inhibits serum amyloid A-mediated reactive oxygen species generation and NLRP3 inflammasome activation. J Biol Chem 2018;293(34):13257–13269. doi:10.1074/jbc.RA118.002428, PMID:29976759.
[66] Cockerill GW, Rye KA, Gamble JR, Vadas MA, Barter PJ. High-density lipoproteins inhibit cytokine-induced expression of endothelial cell adhesion molecules. Arterioscler Thromb Vasc Biol 1995;15(11):1987–1994. doi:10.1161/01.atv.15.11.1987, PMID:7583580.
[67] Taborda NA, Blanquiceth Y, Urcuqui-Inchima S, Latz E, Hernandez JC. High-Density Lipoproteins Decrease Proinflammatory Activity and Modulate the Innate Immune Response. J Interferon Cytokine Res 2019;39(12):760–770. doi:10.1089/jir.2019.0029, PMID:31335262.
[68] Ogura M. HDL, cholesterol efflux, and ABCA1: Free from good and evil dualism. J Pharmacol Sci 2022;150(2):81–89. doi:10.1016/j.jphs.2022.07.004, PMID:36055755.
[69] Rothblat GH, Phillips MC. High-density lipoprotein heterogeneity and function in reverse cholesterol transport. Curr Opin Lipidol 2010;21(3):229–238. doi:10.1097/mol.0b013e328338472d, PMID:20480549.
[70] von Eckardstein A, Nordestgaard BG, Remaley AT, Catapano AL. High-density lipoprotein revisited: biological functions and clinical relevance. Eur Heart J 2023;44(16):1394–1407. doi:10.1093/eurheartj/ehac605, PMID:36337032.
[71] Anastasius M, Luquain-Costaz C, Kockx M, Jessup W, Kritharides L. A critical appraisal of the measurement of serum 'cholesterol efflux capacity' and its use as surrogate marker of risk of cardiovascular disease. Biochim Biophys Acta Mol Cell Biol Lipids 2018;1863(10):1257–1273. doi:10.1016/j.bbalip.2018.08.002, PMID:30305243.
[72] Nordestgaard LT, Christoffersen M, Lauridsen BK, Afzal S, Nordestgaard BG, Frikke-Schmidt R, *et al*. Long-term Benefits and Harms Associated With Genetic Cholesteryl Ester Transfer Protein Deficiency in the General Population. JAMA Cardiol 2022;7(1):55–64. doi:10.1001/jamacardio.2021.3728, PMID:34613338.
[73] Cuchel M, Rader DJ. Macrophage reverse cholesterol transport: key to the regression of atherosclerosis? Circulation 2006;113(21):2548–2555. doi:10.1161/CIRCULATIONAHA.104.475715, PMID:16735689.
[74] Attie AD, Kastelein JP, Hayden MR. Pivotal role of ABCA1 in reverse cholesterol transport influencing HDL levels and susceptibility to atherosclerosis. J Lipid Res 2001;42(11):1717–1726. doi:10.1016/s0022-2275(20)31498-x, PMID:11714841.
[75] Ogasawara F, Kodan A, Ueda K. ABC proteins in evolution. FEBS Lett 2020;594(23):3876–3881. doi:10.1002/1873-3468.13945, PMID:33002191.
[76] Liu SL, Sheng R, Jung JH, Wang L, Stec E, O'Connor MJ, *et al*. Orthogonal lipid sensors identify transbilayer asymmetry of plasma membrane cholesterol. Nat Chem Biol 2017;13(3):268–274. doi:10.1038/nchembio.2268, PMID:28024150.
[77] Zhou H, Tan KC, Shiu SW, Wong Y. Cellular cholesterol efflux to serum is impaired in diabetic nephropathy. Diabetes Metab Res Rev 2008;24(8):617–623. doi:10.1002/dmrr.895, PMID:18802933.
[78] Favari E, Lee M, Calabresi L, Franceschini G, Zimetti F, Bernini F, *et al*. Depletion of pre-beta-high density lipoprotein by human chymase impairs ATP-binding cassette transporter A1- but not scavenger receptor class B type I-mediated lipid efflux to high density lipoprotein. J Biol Chem 2004;279(11):9930–9936. doi:10.1074/jbc.M312476200, PMID:14701812.
[79] Kane JP, Pullinger CR, Goldfine ID, Malloy MJ. Dyslipidemia and diabetes mellitus: Role of lipoprotein species and interrelated pathways of lipid metabolism in diabetes mellitus. Curr Opin Pharmacol 2021;61:21–27. doi:10.1016/j.coph.2021.08.013, PMID:34562838.
[80] Brunetti A, Chiefari E, Foti D. Recent advances in the molecular genetics of type 2 diabetes mellitus. World J Diabetes 2014;5(2):128–140. doi:10.4239/wjd.v5.i2.128, PMID:24748926.
[81] McInnes IB, Schett G. The pathogenesis of rheumatoid arthritis. N Engl J Med 2011;365(23):2205–2219. doi:10.1056/NEJMra1004965, PMID:22150039.
[82] Figus FA, Piga M, Azzolin I, McConnell R, Iagnocco A. Rheumatoid arthritis: Extra-articular manifestations and comorbidities. Autoimmun Rev 2021;20(4):102776. doi:10.1016/j.autrev.2021.102776, PMID:33609792.
[83] Avina-Zubieta JA, Thomas J, Sadatsafavi M, Lehman AJ, Lacaille D. Risk of incident cardiovascular events in patients with rheumatoid arthritis: a meta-analysis of observational studies. Ann Rheum Dis 2012;71(9):1524–1529. doi:10.1136/annrheumdis-2011-200726, PMID:22425941.
[84] Baviera M, Cioffi G, Colacioppo P, Tettamanti M, Fortino I, Roncaglioni MC. Temporal trends from 2005 to 2018 in deaths and cardiovascular events in subjects with newly diagnosed rheumatoid arthritis. Intern Emerg Med 2021;16(6):1467–1475. doi:10.1007/s11739-020-02581-z, PMID:33386606.
[85] Dijkshoorn B, Raadsen R, Nurmohamed MT. Cardiovascular Disease Risk in Rheumatoid Arthritis Anno 2022. J Clin Med 2022;11(10):2704. doi:10.3390/jcm11102704, PMID:35628831.
[86] Gusev E, Sarapultsev A. Atherosclerosis and Inflammation: Insights from the Theory of General Pathological Processes. Int J Mol Sci 2023;24(9):7910. doi:10.3390/ijms24097910, PMID:37175617.
[87] Baghdadi LR, Woodman RJ, Shanahan EM, Mangoni AA. The impact of traditional cardiovascular risk factors on cardiovascular outcomes in patients with rheumatoid arthritis: a systematic review and meta-analysis. PLoS One 2015;10(2):e0117952. doi:10.1371/journal.pone.0117952, PMID:25689371.
[88] Yan J, Yang S, Han L, Ba X, Shen P, Lin W, *et al*. Dyslipidemia in rheumatoid arthritis: the possible mechanisms. Front Immunol 2023;14:1254753. doi:10.3389/fimmu.2023.1254753, PMID:37954591.
[89] Myasoedova E, Crowson CS, Kremers HM, Roger VL, Fitz-Gibbon PD, Therneau TM, *et al*. Lipid paradox in rheumatoid arthritis: the impact of serum lipid measures and systemic inflammation on the risk of cardiovascular disease. Ann Rheum Dis 2011;70(3):482–487. doi:10.1136/ard.2010.135871, PMID:21216812.
[90] Venetsanopoulou AI, Pelechas E, Voulgari PV, Drosos AA. The lipid paradox in rheumatoid arthritis: the dark horse of the augmented cardiovascular risk. Rheumatol Int 2020;40(8):1181–1191. doi:10.1007/s00296-020-04616-2, PMID:32524301.
[91] Kim SH, Lee CK, Lee EY, Park SY, Cho YS, Yoo B, *et al*. Serum oxidized low-density lipoproteins in rheumatoid arthritis. Rheumatol Int 2004;24(4):230–233. doi:10.1007/s00296-003-0358-4, PMID:14628150.
[92] Myasoedova E, Crowson CS, Kremers HM, Fitz-Gibbon PD, Therneau TM, Gabriel SE. Total cholesterol and LDL levels decrease before rheumatoid arthritis. Ann Rheum Dis 2010;69(7):1310–1314. doi:10.1136/ard.2009.122374, PMID:19854708.
[93] Liao KP, Cai T, Gainer VS, Cagan A, Murphy SN, Liu C, *et al*. Lipid and lipoprotein levels and trend in rheumatoid arthritis compared to the general population. Arthritis Care Res (Hoboken) 2013;65(12):2046–2050. doi:10.1002/acr.22091, PMID:23925980.
[94] Rizzo M, Spinas GA, Cesur M, Ozbalkan Z, Rini GB, Berneis K. Atherogenic lipoprotein phenotype and LDL size and subclasses in drug-naïve patients with early rheumatoid arthritis. Atherosclerosis 2009;207(2):502–506. doi:10.1016/j.atherosclerosis.2009.07.015, PMID:19643412.
[95] Mathieu S, Lambert C, Fayet F, Couderc M, Beauger M, Malochet S, *et al*. Comparison of the cardiovascular risk profile of rheumatoid arthritis versus hand osteoarthritis patients. Rheumatol Int 2023;43(11):2065–2072. doi:10.1007/s00296-023-05405-3, PMID:37566254.
[96] Tejera-Segura B, Macía-Díaz M, Machado JD, de Vera-González A, García-Dopico JA, Olmos JM, *et al*. HDL cholesterol efflux capacity in rheumatoid arthritis patients: contributing factors and relationship with subclinical atherosclerosis. Arthritis Res Ther 2017;19(1):113. doi:10.1186/s13075-017-1311-3, PMID:28569219.
[97] VanEvery H, Yang W, Su J, Olsen N, Bao L, Lu B, *et al*. Low-Density Lipoprotein Cholesterol and the Risk of Rheumatoid Arthritis: A Prospective Study in a Chinese Cohort. Nutrients 2022;14(6):1240. doi:10.3390/nu14061240, PMID:35334896.
[98] Choy E, Sattar N. Interpreting lipid levels in the context of high-grade inflammatory states with a focus on rheumatoid arthritis: a challenge to conventional cardiovascular risk actions. Ann Rheum Dis 2009;68(4):460–469. doi:10.1136/ard.2008.101964, PMID:19286905.

[99] Hurt-Camejo E, Paredes S, Masana L, Camejo G, Sartipy P, Rosengren B, *et al*. Elevated levels of small, low-density lipoprotein with high affinity for arterial matrix components in patients with rheumatoid arthritis: possible contribution of phospholipase A2 to this atherogenic profile. Arthritis Rheum 2001;44(12):2761–2767. doi:10.1002/1529-0131(200112)44:12<2761::aid-art463>3.0.co;2-5, PMID:11762936.

[100] Wu J, Zhou Q, Wei Z, Wei J, Cui M. Atherogenic Index of Plasma and Coronary Artery Disease in the Adult Population: A Meta-Analysis. Front Cardiovasc Med 2021;8:817441. doi:10.3389/fcvm.2021.817441, PMID:34977202.

[101] Zhou K, Qin Z, Tian J, Cui K, Yan Y, Lyu S. The Atherogenic Index of Plasma: A Powerful and Reliable Predictor for Coronary Artery Disease in Patients With Type 2 Diabetes. Angiology 2021;72(10):934–941. doi:10.1177/00033197211012129, PMID:33949211.

[102] Si Y, Fan W, Han C, Liu J, Sun L. Atherogenic Index of Plasma, Triglyceride-Glucose Index and Monocyte-to-Lymphocyte Ratio for Predicting Subclinical Coronary Artery Disease. Am J Med Sci 2021;362(3):285–290. doi:10.1016/j.amjms.2021.05.001, PMID:33989563.

[103] Kosmas CE, Rodriguez Polanco S, Bousvarou MD, Papakonstantinou EJ, Peña Genao E, Guzman E, *et al*. The Triglyceride/High-Density Lipoprotein Cholesterol (TG/HDL-C) Ratio as a Risk Marker for Metabolic Syndrome and Cardiovascular Disease. Diagnostics (Basel) 2023;13(5):929. doi:10.3390/diagnostics13050929, PMID:36900073.

[104] Hammam N, Abdel-Wahab N, Gheita TA. Atherogenic Index of Plasma in Women with Rheumatoid Arthritis and Systemic Lupus Erythematosus: A 10-Year Potential Predictor of Cardiovascular Disease. Curr Rheumatol Rev 2021;17(1):122–130. doi:10.2174/1573397116666201007123403, PMID:33030132.

[105] Uslu AU, Kucuk A, Icli A, Cure E, Sakiz D, Arslan S, *et al*. Plasma Atherogenic Index is an Independent Indicator of Subclinical Atherosclerosis in Systemic Lupus Erythematosus. Eurasian J Med 2017;49(3):193–197. doi:10.5152/eurasianjmed.2017.17143, PMID:29123443.

[106] Min HK, Kim HR, Lee SH, Shin K, Kim HA, Park SH, *et al*. Four-year follow-up of atherogenicity in rheumatoid arthritis patients: from the nationwide Korean College of Rheumatology Biologics Registry. Clin Rheumatol 2021;40(8):3105–3113. doi:10.1007/s10067-021-05613-x, PMID:33576925.

[107] Dessie G. Association of atherogenic indices with C-reactive protein and risk factors to assess cardiovascular risk in rheumatoid arthritis patient at Tikur Anbessa Specialized Hospital, Addis Ababa. PLoS One 2022;17(6):e0269431. doi:10.1371/journal.pone.0269431, PMID:35657933.

[108] Ye L, Zhang X, Wu H, Chen Y, Zhou H, Wang Q, *et al*. Insulin resistance and adverse lipid profile in untreated very early rheumatoid arthritis patients: A single-center, cross-sectional study in China. Arch Rheumatol 2022;37(4):593–602. doi:10.46497/ArchRheumatol.2022.9117, PMID:36879573.

[109] Georgiadis AN, Papavasiliou EC, Lourida ES, Alamanos Y, Kostara C, Tselepis AD, *et al*. Atherogenic lipid profile is a feature characteristic of patients with early rheumatoid arthritis: effect of early treatment—a prospective, controlled study. Arthritis Res Ther 2006;8(3):R82. doi:10.1186/ar1952, PMID:16646989.

[110] Chavan VU, Ramavataram D, Patel PA, Rupani MP. Evaluation of serum magnesium, lipid profile and various biochemical parameters as risk factors of cardiovascular diseases in patients with rheumatoid arthritis. J Clin Diagn Res 2015;9(4):BC01–BC05. doi:10.7860/JCDR/2015/12206.5740, PMID:26023546.

[111] Polinski KJ, Bemis EA, Yang F, Crume T, Demoruelle MK, Feser M, *et al*. Association of Lipid Mediators With Development of Future Incident Inflammatory Arthritis in an Anti-Citrullinated Protein Antibody-Positive Population. Arthritis Rheumatol 2021;73(6):955–962. doi:10.1002/art.41631, PMID:33381911.

[112] Rodríguez-Carrio J, Coras R, Alperi-López M, López P, Ulloa C, Ballina-García FJ, *et al*. Profiling of Serum Oxylipins During the Earliest Stages of Rheumatoid Arthritis. Arthritis Rheumatol 2021;73(3):401–413. doi:10.1002/art.41537, PMID:33001576.

[113] van de Stadt LA, van Sijl AM, van Schaardenburg D, Nurmohamed MT. Dyslipidaemia in patients with seropositive arthralgia predicts the development of arthritis. Ann Rheum Dis 2012;71(11):1915–1916. doi:10.1136/annrheumdis-2012-201709, PMID:22586158.

[114] Gan RW, Young KA, Zerbe GO, Demoruelle MK, Weisman MH, Buckner JH, *et al*. Lower omega-3 fatty acids are associated with the presence of anti-cyclic citrullinated peptide autoantibodies in a population at risk for future rheumatoid arthritis: a nested case-control study. Rheumatology (Oxford) 2016;55(2):367–376. doi:10.1093/rheumatology/kev266, PMID:26370400.

[115] de Pablo P, Romaguera D, Fisk HL, Calder PC, Quirke AM, Cartwright AJ, *et al*. High erythrocyte levels of the n-6 polyunsaturated fatty acid linoleic acid are associated with lower risk of subsequent rheumatoid arthritis in a southern European nested case-control study. Ann Rheum Dis 2018;77(7):981–987. doi:10.1136/annrheumdis-2017-212274, PMID:29436473.

[116] Gan RW, Bemis EA, Demoruelle MK, Striebich CC, Brake S, Feser ML, *et al*. The association between omega-3 fatty acid biomarkers and inflammatory arthritis in an anti-citrullinated protein antibody positive population. Rheumatology (Oxford) 2017;56(12):2229–2236. doi:10.1093/rheumatology/kex360, PMID:29029330.

[117] Koh JH, Yoon SJ, Kim M, Cho S, Lim J, Park Y, *et al*. Lipidome profile predictive of disease evolution and activity in rheumatoid arthritis. Exp Mol Med 2022;54(2):143–155. doi:10.1038/s12276-022-00725-z, PMID:35169224.

[118] Law SH, Chan ML, Marathe GK, Parveen F, Chen CH, Ke LY. An Updated Review of Lysophosphatidylcholine Metabolism in Human Diseases. Int J Mol Sci 2019;20(5):1149. doi:10.3390/ijms20051149, PMID:30845751.

[119] Chu SH, Cui J, Sparks JA, Lu B, Tedeschi SK, Speyer CB, *et al*. Circulating plasma metabolites and risk of rheumatoid arthritis in the Nurses' Health Study. Rheumatology (Oxford) 2020;59(11):3369–3379. doi:10.1093/rheumatology/keaa125, PMID:32310291.

[120] Boers M, Nurmohamed MT, Doelman CJ, Lard LR, Verhoeven AC, Voskuyl AE, *et al*. Influence of glucocorticoids and disease activity on total and high density lipoprotein cholesterol in patients with rheumatoid arthritis. Ann Rheum Dis 2003;62(9):842–845. doi:10.1136/ard.62.9.842, PMID:12922956.

[121] Attar SM. Hyperlipidemia in rheumatoid arthritis patients in Saudi Arabia. Correlation with C-reactive protein levels and disease activity. Saudi Med J 2015;36(6):685–691. doi:10.15537/smj.2015.6.10557, PMID:25987110.

[122] Park YB, Lee SK, Lee WK, Suh CH, Lee CW, Lee CH, *et al*. Lipid profiles in untreated patients with rheumatoid arthritis. J Rheumatol 1999;26(8):1701–1704. PMID:10451065.

[123] White D, Fayez S, Doube A. Atherogenic lipid profiles in rheumatoid arthritis. N Z Med J 2006;119(1240):U2125. PMID:16924276.

[124] Govindan KP, Basha S, Ramesh V, Kumar CN, Swathi S. A comparative study on serum lipoprotein (a) and lipid profile between rheumatoid arthritis patients and normal subjects. J Pharm Bioallied Sci 2015;7(Suppl 1):S22–S25. doi:10.4103/0975-7406.155767, PMID:26015716.

[125] Choi HK, Seeger JD. Lipid profiles among US elderly with untreated rheumatoid arthritis—the Third National Health and Nutrition Examination Survey. J Rheumatol 2005;32(12):2311–2316. PMID:16331755.

[126] Ramharack R, Barkalow D, Spahr MA. Dominant negative effect of TGF-beta1 and TNF-alpha on basal and IL-6-induced lipoprotein(a) and apolipoprotein(a) mRNA expression in primary monkey hepatocyte cultures. Arterioscler Thromb Vasc Biol 1998;18(6):984–990. doi:10.1161/01.atv.18.6.984, PMID:9633941.

[127] Orsó E, Schmitz G. Lipoprotein(a) and its role in inflammation, atherosclerosis and malignancies. Clin Res Cardiol Suppl 2017;12(Suppl 1):31–37. doi:10.1007/s11789-017-0084-1, PMID:28188431.

[128] Lazarevic MB, Vitic J, Mladenovic V, Myones BL, Skosey JL, Swedler WI. Dyslipoproteinemia in the course of active rheumatoid arthritis. Semin Arthritis Rheum 1992;22(3):172–178. doi:10.1016/0049-0172(92)90017-8, PMID:1295090.

[129] Popkova TV, Novikova DS, Novikov AA, Alexandrova EN, Mach ES, Gawa TN, *et al*. Role of blood cholesterol transport system disturbances in atherosclerosis development in rheumatoid arthritis. Rheumatology Science and Practice 2007;45(5):4–10. doi:10.14412/1995-4484-2007-14.

[130] Gonzalez A, Maradit Kremers H, Crowson CS, Ballman KV, Roger VL, Jacobsen SJ, *et al*. Do cardiovascular risk factors confer the same risk for cardiovascular outcomes in rheumatoid arthritis patients as in

non-rheumatoid arthritis patients? Ann Rheum Dis 2008;67(1):64–69. doi:10.1136/ard.2006.059980, PMID:17517756.
[131] Boyer JF, Gourraud PA, Cantagrel A, Davignon JL, Constantin A. Traditional cardiovascular risk factors in rheumatoid arthritis: a meta-analysis. Joint Bone Spine 2011;78(2):179–183. doi:10.1016/j.jbspin.2010.07.016, PMID:20851020.
[132] Pozzi FS, Maranhão RC, Guedes LK, Borba EF, Laurindo IM, Bonfa E, *et al*. Plasma kinetics of an LDL-like non-protein nanoemulsion and transfer of lipids to high-density lipoprotein (HDL) in patients with rheumatoid arthritis. J Clin Lipidol 2015;9(1):72–80. doi:10.1016/j.jacl.2014.10.004, PMID:25670363.
[133] Kim JY, Lee EY, Park JK, Song YW, Kim JR, Cho KH. Patients with Rheumatoid Arthritis Show Altered Lipoprotein Profiles with Dysfunctional High-Density Lipoproteins that Can Exacerbate Inflammatory and Atherogenic Process. PLoS One 2016;11(10):e0164564. doi:10.1371/journal.pone.0164564, PMID:27736980.
[134] Ormseth MJ, Yancey PG, Yamamoto S, Oeser AM, Gebretsadik T, Shintani A, *et al*. Net cholesterol efflux capacity of HDL enriched serum and coronary atherosclerosis in rheumatoid arthritis. IJC Metab Endocr 2016;13:6–11. doi:10.1016/j.ijcme.2016.08.002, PMID:28243578.
[135] Rodríguez-Carrio J, Alperi-López M, López P, López-Mejías R, Alonso-Castro S, Abal F, *et al*. High triglycerides and low high-density lipoprotein cholesterol lipid profile in rheumatoid arthritis: A potential link among inflammation, oxidative status, and dysfunctional high-density lipoprotein. J Clin Lipidol 2017;11(4):1043–1054.e2. doi:10.1016/j.jacl.2017.05.009, PMID:28662934.
[136] Burggraaf B, van Breukelen-van der Stoep DF, van Zeben J, van der Meulen N, van de Geijn GM, Liem A, *et al*. Evidence for increased chylomicron remnants in rheumatoid arthritis. Eur J Clin Invest 2018;48(2):e12873. doi:10.1111/eci.12873, PMID:29231984.
[137] Dessie G, Tadesse Y, Demelash B, Genet S. Assessment of Serum Lipid Profiles and High-sensitivity C-reactive Protein Among Patients Suffering from Rheumatoid Arthritis at Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia: A Cross-Sectional Study. Open Access Rheumatol 2020;12:223–232. doi:10.2147/OARRR.S264466, PMID:33061690.
[138] Alisik T, Alisik M, Nacir B, Ayhan FF, Genc H, Erel O. Evaluation of dysfunctional high-density lipoprotein levels with myeloperoxidase/paraoxonase-1 ratio in rheumatoid arthritis. Int J Clin Pract 2021;75(7):e14172. doi:10.1111/ijcp.14172.
[139] Chang CK, Chiang EI, Chang KH, Tang KT, Chen PK, Yip HT, *et al*. The Sizes and Composition of HDL-Cholesterol Are Significantly Associated with Inflammation in Rheumatoid Arthritis Patients. Int J Mol Sci 2023;24(13):10645. doi:10.3390/ijms241310645, PMID:37445823.
[140] Memon RA, Staprans I, Noor M, Holleran WM, Uchida Y, Moser AH, *et al*. Infection and inflammation induce LDL oxidation in vivo. Arterioscler Thromb Vasc Biol 2000;20(6):1536–1542. doi:10.1161/01.atv.20.6.1536, PMID:10845869.
[141] Cvetkovic JT, Wållberg-Jonsson S, Ahmed E, Rantapää-Dahlqvist S, Lefvert AK. Increased levels of autoantibodies against copper-oxidized low density lipoprotein, malondialdehyde-modified low density lipoprotein and cardiolipin in patients with rheumatoid arthritis. Rheumatology (Oxford) 2002;41(9):988–995. doi:10.1093/rheumatology/41.9.988, PMID:12209031.
[142] Paimela L, Helve T, Leirisalo-Repo M, Vaarala O, Alfthan G, Palosuo T, *et al*. Clinical significance of antibodies against oxidised low density lipoprotein in early RA. Ann Rheum Dis 1996;55(8):558–559. doi:10.1136/ard.55.8.558, PMID:8774186.
[143] Huang LS, Hung ND, Sok DE, Kim MR. Lysophosphatidylcholine containing docosahexaenoic acid at the sn-1 position is anti-inflammatory. Lipids 2010;45(3):225–236. doi:10.1007/s11745-010-3392-5, PMID:20165929.
[144] Karpouzas GA, Ormseth SR, Ronda N, Hernandez E, Budoff MJ. Lipoprotein oxidation may underlie the paradoxical association of low cholesterol with coronary atherosclerotic risk in rheumatoid arthritis. J Autoimmun 2022;129:102815. doi:10.1016/j.jaut.2022.102815, PMID:35366608.
[145] Papamichail GV, Georgiadis AN, Tellis CC, Rapti I, Markatseli TE, Xydis VG, *et al*. Antibodies against oxidized LDL and atherosclerosis in rheumatoid arthritis patients treated with biological agents: a prospective controlled study. Clin Rheumatol 2024;43(1):481–488. doi:10.1007/s10067-023-06744-z, PMID:37642764.
[146] Chu CS, Chan HC, Tsai MH, Stancel N, Lee HC, Cheng KH, *et al*. Range of L5 LDL levels in healthy adults and L5's predictive power in patients with hyperlipidemia or coronary artery disease. Sci Rep 2018;8(1):11866. doi:10.1038/s41598-018-30243-w, PMID:30089847.
[147] García-Gómez C, Bianchi M, de la Fuente D, Badimon L, Padró T, Corbella E, *et al*. Inflammation, lipid metabolism and cardiovascular risk in rheumatoid arthritis: A qualitative relationship? World J Orthop 2014;5(3):304–311. doi:10.5312/wjo.v5.i3.304, PMID:25035833.
[148] Arts E, Fransen J, Lemmers H, Stalenhoef A, Joosten L, van Riel P, *et al*. High-density lipoprotein cholesterol subfractions HDL2 and HDL3 are reduced in women with rheumatoid arthritis and may augment the cardiovascular risk of women with RA: a cross-sectional study. Arthritis Res Ther 2012;14(3):R116. doi:10.1186/ar3842, PMID:22584154.
[149] Ansell BJ, Fonarow GC, Fogelman AM. The paradox of dysfunctional high-density lipoprotein. Curr Opin Lipidol 2007;18(4):427–434. doi:10.1097/MOL.0b013e3282364a17, PMID:17620860.
[150] McMahon M, Grossman J, FitzGerald J, Dahlin-Lee E, Wallace DJ, Thong BY, *et al*. Proinflammatory high-density lipoprotein as a biomarker for atherosclerosis in patients with systemic lupus erythematosus and rheumatoid arthritis. Arthritis Rheum 2006;54(8):2541–2549. doi:10.1002/art.21976, PMID:16868975.
[151] Charles-Schoeman C, Watanabe J, Lee YY, Furst DE, Amjadi S, Elashoff D, *et al*. Abnormal function of high-density lipoprotein is associated with poor disease control and an altered protein cargo in rheumatoid arthritis. Arthritis Rheum 2009;60(10):2870–2879. doi:10.1002/art.24802, PMID:19790070.
[152] Undurti A, Huang Y, Lupica JA, Smith JD, DiDonato JA, Hazen SL. Modification of high density lipoprotein by myeloperoxidase generates a pro-inflammatory particle. J Biol Chem 2009;284(45):30825–30835. doi:10.1074/jbc.M109.047605, PMID:19726691.
[153] Ndrepepa G. Myeloperoxidase - A bridge linking inflammation and oxidative stress with cardiovascular disease. Clin Chim Acta 2019;493:36–51. doi:10.1016/j.cca.2019.02.022, PMID:30797769.
[154] Feijóo M, Túnez I, Ruiz A, Tasset I, Muñoz E, Collantes E. [Oxidative stress biomarkers as indicator of chronic inflammatory joint diseases stage]. Reumatol Clin 2010;6(2):91–94. doi:10.1016/j.reuma.2008.12.016, PMID:21794688.
[155] Vivekanandan-Giri A, Slocum JL, Byun J, Tang C, Sands RL, Gillespie BW, *et al*. High density lipoprotein is targeted for oxidation by myeloperoxidase in rheumatoid arthritis. Ann Rheum Dis 2013;72(10):1725–1731. doi:10.1136/annrheumdis-2012-202033, PMID:23313808.
[156] Wang W, Jian Z, Guo J, Ning X. Increased levels of serum myeloperoxidase in patients with active rheumatoid arthritis. Life Sci 2014;117(1):19–23. doi:10.1016/j.lfs.2014.09.012, PMID:25261597.
[157] Nzeusseu Toukap A, Delporte C, Noyon C, Franck T, Rousseau A, Serteyn D, *et al*. Myeloperoxidase and its products in synovial fluid of patients with treated or untreated rheumatoid arthritis. Free Radic Res 2014;48(4):461–465. doi:10.3109/10715762.2014.886327, PMID:24460011.
[158] Feijóo M, Túnez I, Tasset I, Montilla P, Pérez-Guijo V, Muñoz-Gomariz E, *et al*. Infliximab reduces myeloperoxidase concentration in chronic inflammatory joint diseases. Pharmacology 2009;83(4):211–216. doi:10.1159/000200022, PMID:19204412.
[159] Maiocchi SL, Ku J, Thai T, Chan E, Rees MD, Thomas SR. Myeloperoxidase: A versatile mediator of endothelial dysfunction and therapeutic target during cardiovascular disease. Pharmacol Ther 2021;221:107711. doi:10.1016/j.pharmthera.2020.107711, PMID:33137376.
[160] Montes EG, Mansani FP, de Oliveira Toledo Júnior A, Schafranski MD, Zardo BQ, Dos Santos FA, *et al*. Myeloperoxidase as an important predictor of cardiovascular risk in individuals with rheumatoid arthritis. Inflammopharmacology 2021;29(6):1819–1827. doi:10.1007/s10787-021-00892-x, PMID:34825303.
[161] Ormseth MJ, Stein CM. High-density lipoprotein function in rheumatoid arthritis. Curr Opin Lipidol 2016;27(1):67–75. doi:10.1097/MOL.0000000000000256, PMID:26709471.
[162] Ronsein GE, Vaisar T. Inflammation, remodeling, and other factors affecting HDL cholesterol efflux. Curr Opin Lipidol 2017;28(1):52–59. doi:10.1097/MOL.0000000000000382, PMID:27906712.
[163] Ferraz-Amaro I, González-Gay MA, García-Dopico JA, Díaz-González

F. Cholesteryl ester transfer protein in patients with rheumatoid arthritis. J Rheumatol 2013;40(7):1040–1047. doi:10.3899/jrheum.121507, PMID:23678159.

[164] Charles-Schoeman C, Lee YY, Grijalva V, Amjadi S, FitzGerald J, Ranganath VK, *et al*. Cholesterol efflux by high density lipoproteins is impaired in patients with active rheumatoid arthritis. Ann Rheum Dis 2012;71(7):1157–1162. doi:10.1136/annrheumdis-2011-200493, PMID:22267330.

[165] Liao KP, Playford MP, Frits M, Coblyn JS, Iannaccone C, Weinblatt ME, *et al*. The association between reduction in inflammation and changes in lipoprotein levels and HDL cholesterol efflux capacity in rheumatoid arthritis. J Am Heart Assoc 2015;4(2):e001588. doi:10.1161/JAHA.114.001588, PMID:25637346.

[166] Xie B, He J, Liu Y, Liu T, Liu C. A meta-analysis of HDL cholesterol efflux capacity and concentration in patients with rheumatoid arthritis. Lipids Health Dis 2021;20(1):18. doi:10.1186/s12944-021-01444-6, PMID:33612101.

[167] Quevedo-Abeledo JC, Sánchez-Pérez H, Tejera-Segura B, de Armas-Rillo L, Armas-González E, Machado JD, *et al*. Differences in Capacity of High-Density Lipoprotein Cholesterol Efflux Between Patients With Systemic Lupus Erythematosus and Rheumatoid Arthritis. Arthritis Care Res (Hoboken) 2021;73(11):1590–1596. doi:10.1002/acr.24407, PMID:32770725.

[168] Ronda N, Favari E, Borghi MO, Ingegnoli F, Gerosa M, Chighizola C, *et al*. Impaired serum cholesterol efflux capacity in rheumatoid arthritis and systemic lupus erythematosus. Ann Rheum Dis 2014;73(3):609–615. doi:10.1136/annrheumdis-2012-202914, PMID:23562986.

[169] Ronda N, Greco D, Adorni MP, Zimetti F, Favari E, Hjeltnes G, *et al*. Newly identified antiatherosclerotic activity of methotrexate and adalimumab: complementary effects on lipoprotein function and macrophage cholesterol metabolism. Arthritis Rheumatol 2015;67(5):1155–1164. doi:10.1002/art.39039, PMID:25605003.

[170] Anastasius M, Kockx M, Jessup W, Sullivan D, Rye KA, Kritharides L. Cholesterol efflux capacity: An introduction for clinicians. Am Heart J 2016;180:54–63. doi:10.1016/j.ahj.2016.07.005, PMID:27659883.

[171] Mortensen MB, Afzal S, Nordestgaard BG, Falk E. The high-density lipoprotein-adjusted SCORE model worsens SCORE-based risk classification in a contemporary population of 30,824 Europeans: the Copenhagen General Population Study. Eur Heart J 2015;36(36):2446–2453. doi:10.1093/eurheartj/ehv251, PMID:26082084.

[172] Karpouzas GA, Papotti B, Ormseth SR, Palumbo M, Hernandez E, Adorni MP, *et al*. ATP-binding cassette G1 membrane transporter-mediated cholesterol efflux capacity influences coronary atherosclerosis and cardiovascular risk in Rheumatoid Arthritis. J Autoimmun 2023;136:103029. doi:10.1016/j.jaut.2023.103029, PMID:36996698.

[173] Karpouzas GA, Papotti B, Ormseth SR, Palumbo M, Hernandez E, Adorni MP, *et al*. Inflammation and immunomodulatory therapies influence the relationship between ATP-binding cassette A1 membrane transporter-mediated cholesterol efflux capacity and coronary atherosclerosis in rheumatoid arthritis. J Transl Autoimmun 2023;7:100209. doi:10.1016/j.jtauto.2023.100209, PMID:37520890.