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REVIEW

The lipid paradox in rheumatoid arthritis: the dark horse of the augmented cardiovascular risk

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Abstract

Rheumatoid arthritis (RA) is an autoimmune disease characterized by chronic inflammation that, if left untreated, can cause joint destruction and physical impairments. The inflammatory process is systematic, and it is associated with increased morbidity and mortality. Over the last years, mortality presents a decreasing trend; still, there is a high burden of cardiovascular disease (CVD) in RA that seems to be related to coronary atherosclerosis. Chronic inflammation, physical inactivity, and drugs used to treat RA are some of the reasons. Thus, the management of CVD risk is essential and involves the patient's stratification using distinct parameters that include assessment of the blood lipid profile. However, 'dyslipidemia' in RA patients follows a different pattern under the impact of inflammatory processes, while therapies that target the underlying disease change the levels of specific lipid components. In this review, we explore the relationship between blood lipids and inflammation in the so-called ´lipid paradox´ in RA, and we present the existing knowledge over the influence of antirheumatic drugs on the lipid profile of RA patients.

Keywords Rheumatoid arthritis · Cardiovascular disease · Dyslipidemia · Inflammation · Lipid paradox · Lipoprotein metabolism

Abbreviations

ACPA	Anti-cyclic citrullinated protein antibodies
apo A-I	Apolipoprotein A-I
ABCA1	ATP-binding cassette transporter A1
ABCG1	ATP-binding cassette transporter G1 (ABCG1)
apo A-II	Apolipoprotein A-II
apo B-48	Apolipoprotein B-48
apo B	Apolipoprotein B-100
b	Biological
CETP	Cholesteryl ester transfer protein
CHD	Coronary heart disease
CHOL	Cholesterol
CRP	C-reactive protein
CVD	Cardiovascular disease
Cs	Conventional synthetic
DAS-28	Disease Activity Score-28 for Rheumatoid Arthritis
DMARDs	Disease-modifying antirheumatic drugs
ESR	Erythrocyte sedimentation rate
EULAR	European League Against Rheumatism
HDL	High-density lipoproteins
HDL-C	High-density lipoprotein cholesterol
HCQ	Hydroxychloroquine
IDL	Intermediate-density lipoproteins
IL-6	Interleukin-6
JAK inhibitors	Janus kinase inhibitors
LDL	Low-density lipoproteins
LDL-C	Low-density lipoprotein cholesterol
LDL-C	Low-density lipoprotein cholesterol
LDLR	LDL receptor
LCAT	Lecithin cholesterol acyltransferase
Lp(a)	Lipoprotein(a)
LPL	Lipoprotein lipase
FCR	Fractional catabolic rate
FFA	Free fatty acids
MTX	Methotrexate
Ox-LDL	Oxidized LDL
PON	Paraoxonase
RA	Rheumatoid arthritis

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RF	Rheumatoid factor
RChT	Reverse cholesterol transport
RTX	Rituximab
SR-B1	Class-B-scavenger receptor B1
TC	Total cholesterol
TGs	Triglycerides
TNF-a	Tumor necrosis factor-alpha
VLDL	Very low-density lipoproteins

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease that can cause the destruction of the synovial joints [1, 2]. The inflammatory process is systemic and may lead to several extra-articular manifestations. Among those, cardiovascular disease (CVD) is the most critical [2, 3]. Studies so far indicate that patients with RA have a 1.5-fold higher risk for heart attack, twofold risk for heart failure, and even higher for peripheral vascular disease compared to the general population [4–6]. Not surprisingly, the increased CVD risk among RA patients has led to an adjustment of the existing RA treatment guidelines. In 2017, the European League Against Rheumatism (EULAR) updated the recommendations for the screening and management of RA patients with CVD risk suggesting a cardiovascular assessment at least once every 5 years and further management of identified CVD risk factors [7]. According to these recommendations, total cholesterol (TC) and high-density lipoprotein cholesterol (HDL-C) should be used as part of the CVD risk assessment, while the TC/HDL-C ratio seems to be a better CVD risk predictor than the individual lipid components [7, 8]. In addition, these parameters should be measured when disease activity is stable or in remission, as current data show that in RA patients with active disease TC, low-density lipoprotein cholesterol (LDL-C), and HDL-C levels tend to be reduced [9]. The so-called lipid paradox is in contradiction to the conventional view that an atherogenic lipid profile is made up of increased TC, LDL-C, triglycerides (TGs), and decreased HDL-C. Interestingly, conventional synthetic(cs)and biological(b) disease-modifying antirheumatic drugs (DMARDs) increase lipid levels in RA patients and cause antiatherogenic changes in lipid composition and function [10].

Lipids and lipoproteins

Dyslipidemia is a term used when the plasma levels of lipids are altered. With increased cholesterol and TGsin plasma, atherogenicity occurs. The increased lipid levels are potentially related to increased lipid synthesis and/or decreased removal (clearance) or absorption. On the contrary, decreased lipid levels may be the result of decreased lipid synthesis and/or increased removal from the circulation (clearance).

An overview of current knowledge about the lipid metabolism is essential for understating the above processes: In general, lipids (cholesterol and TGs) are insoluble in water, and their transport via the blood circulation relies on their association with proteins. These proteins are called lipoproteins and are complex particles consisting of a central core that contains cholesterol esters and TGs. They are surrounded by a shell consisting of free cholesterol, phospholipids, and apolipoproteins, which facilitate lipoprotein formation and function (Fig. 1). Lipoproteins are classified according to their size, lipid composition, and apolipoproteins. There are several classes: chylomicrons and chylomicron remnants, very low-density lipoprotein (VLDL), intermediate-density lipoprotein (IDL), low-density lipoprotein (LDL), high-density lipoprotein (HDL)and lipoprotein-a (Lp-a). Chylomicron remnants, VLDL, IDL, LDL, and Lp-a, are all proatherogenic, while HDL is antiatherogenic.

The transport of dietary lipids in the blood is regulated by endogenous and exogenous pathways that act independently and achieve the lipid movement from the small intestine to the liver and peripheral tissues. A reverse transport mechanism exists, called reverse cholesterol transport (RChT), which removes excess cholesterol from peripheral tissues to the liver.

The exogenous lipoprotein pathway starts with the incorporation of dietary lipids into chylomicrons in the intestine. Chylomicrons are further metabolized in muscles and adipose tissue by the enzyme lipoprotein lipase (LPL), leading to the formation of free fatty acids (FFAs) and chylomicron remnants. These are then taken up by the liver (Fig. 2). The endogenous lipoprotein pathway starts in the liver with the formation of VLDL. The TGs carried in VLDL are metabolized in the peripheral tissues (muscles and adipose tissue) by LPL releasing FFAs, and IDL is formed. Then IDL is converted to LDL, which is taken up via the LDL receptor

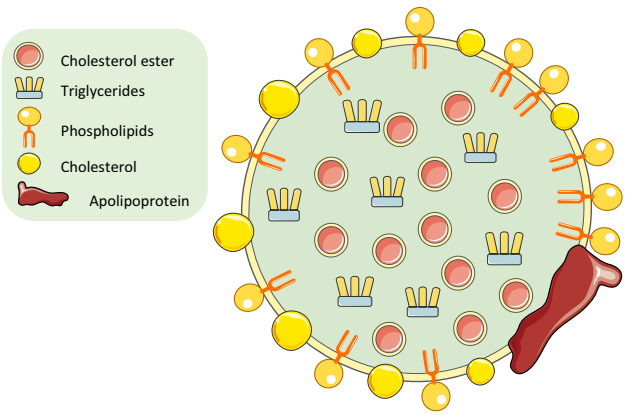

Fig. 1 Schematic representation of lipoprotein structure

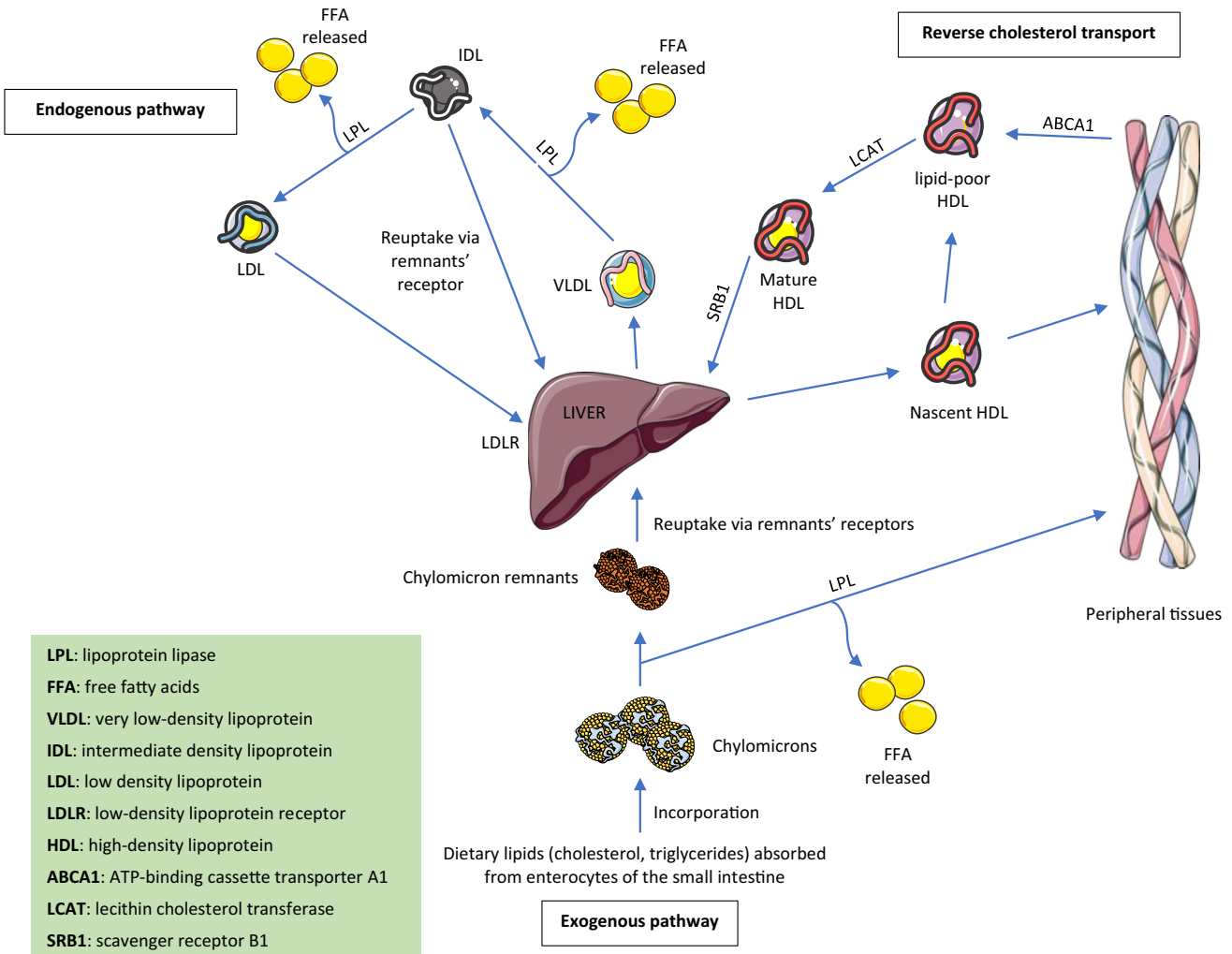

Fig. 2 Schematic representation of the endogenous and exogenous cholesterol pathways

(LDLR) in numerous tissues, especially by the liver, a primary site of LDL uptake (Fig. 2). RChT starts with the formation of nascent HDL by the liver and intestine (Figs. 2, 3). The enzyme ATP-binding cassette transporter A1 (ABCA1) mediates the transfer of cellular cholesterol and phospholipids from peripheral tissues to the nascent HDL (lipid-poor HDL), leading to the formation of mature HDL. The last process is mediated by lecithin cholesterol acyltransferase (LCAT) (Figs. 2, 3). Mature HDL can acquire additional cholesterol from cells via the enzyme ATP-binding cassette transporter G1 (ABCG1) and class-B-scavenger receptor B1 (SR-B1). Then HDL transports the cholesterol to the liver by interacting with the hepatic SR-B1, or by transferring the cholesterol to LDL, a process mediated by the cholesteryl ester transfer protein (CETP) [11–15]. Once delivered to the liver, it can leave the body via biliary excretion (Fig. 3).

LDL can be grouped based on its size: large low-density LDL particles are designated as pattern A, and small high-density LDL particles are designated as pattern B. Pattern B has been associated with CVD since smaller particles are more easily able to penetrate the endothelium of the target cells. Oxidized LDL (ox-LDL) is a general term for LDL particles with oxidative modified structural components. As a result, in combination with free radicals' attack, both lipids and protein parts of LDL can be oxidized in the vascular wall. Atherogenicity of ox-LDL has been explained by a lack of recognition of ox-LDL structures by the LDLR, preventing the normal metabolism of LDL particles and subsequently leading to atherosclerotic development [11–15].

In normal situations, HDL is responsible for the inhibition of ox-LDL and the cholesterol efflux from foam cells of the vessel wall [16]. There is no single explanation of the antiatherogenic and anti-inflammatory properties of HDL; however, it has become clear that the functional status of HDL depends on its protein component. In situations where there is an increased lipid production or decreased lipid

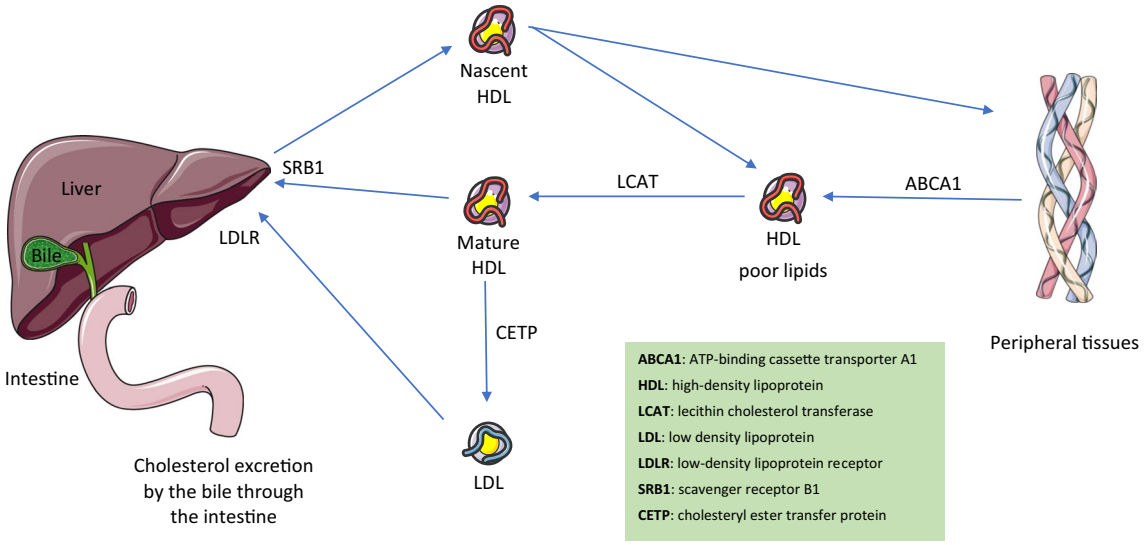

Fig. 3 Schematic representation of reverse cholesterol transport

clearance, a residual fraction of LDL is oxidized. Ox-LDL is incorporated or phagocytosed by macrophages and form the foam cells, which are further deposited on the arterial wall leading to atherosclerotic plaques. Thus, cholesterol movement or efflux through the RChT pathway is critical for maintaining cellular cholesterol homeostasis, not only in the context of the atherosclerotic lesion prevention but also for the restriction of "toxic" levels of cholesterol in every cell (Fig. 3).

Apolipoproteins are synthesized in the liver or intestine and are involved in lipid metabolism, as proteins that bind to lipids to form lipoproteins. They also act as ligands for lipoprotein receptors and co-factors of enzymes involved in lipoprotein metabolism. Particularly, apolipoprotein A-I (apo A-I), which is synthesized by the liver, is the major structural component of HDL, accounting for approximately 70% of the HDL protein structure while apolipoprotein A-II (apo A-II) accounts for 20%. Apolipoprotein B-48 (apo B-48) is synthesized exclusively by the intestine and is the major structural protein of chylomicrons and chylomicron remnants. Finally, apolipoprotein B-100 (apo B) is produced mainly in the liver and is the major structural protein component for VLDL, IDL, and LDL [11–15].

CVD risk factors in RA

Traditional CVD risk factors, including smoking, hypertension, dyslipidemia, insulin resistance, obesity, and physical inactivity, play an essential role, but alone do not fully explain the higher CVD risk in RA [17–20]. Non-traditional factors such as uncontrolled systemic inflammation, autoantibodies, and genetic factors are also essential pieces of this complex puzzle [21] (Fig. 4). Indeed, the elevation of the C-reactive protein (CRP) level has been shown to predict CVD in the general population [22], and also in RA patients where a significant association is observed between CRP and erythrocyte sedimentation rate (ESR) with atherosclerosis and higher risk for myocardial infarction and stroke [23–25]. Seropositivity, with either positive rheumatoid factor (RF) or anti-citrullinated protein antibodies (ACPA), is associated with increased coronary heart disease (CHD) and mortality from CHD, even in patients without articular symptoms [26]. This probably relates to the genetic contribution of the HLA-DRB1 shared epitope that is restricted to autoantibody-positive RA patients and is also associated with a higher cardiovascular mortality rate [27].

The lipid paradox in RA

'Dyslipidemia' plays a fundamental role in atherosclerosis, but in RA patients is paradoxical to the general population. To address this issue, we conducted a comprehensive search of the literature published up until January 2020 using the Medline and Embase electronic databases [keywords "rheumatoid arthritis (AND) lipid profile or lipoprotein metabolism"]. Our search was restricted to articles published in English, and the most relevant publications were included. [28, 29]. According to the existing literature, RA patients with active disease present low levels of TC, LDL-C, and HDL-C, which elevate with treatments that target the RA inflammatory pathways [9]. In this frequently so-called 'lipid paradox,' a qualitative U-shaped relationship is proposed between patients' lipid profile and CV risk, where patients with the lowest LDL-C levels have higher CV risk than those with moderate levels [30]. The HDL-C level reduction in RA patients results in a high atherogenic index of TC/HDLC

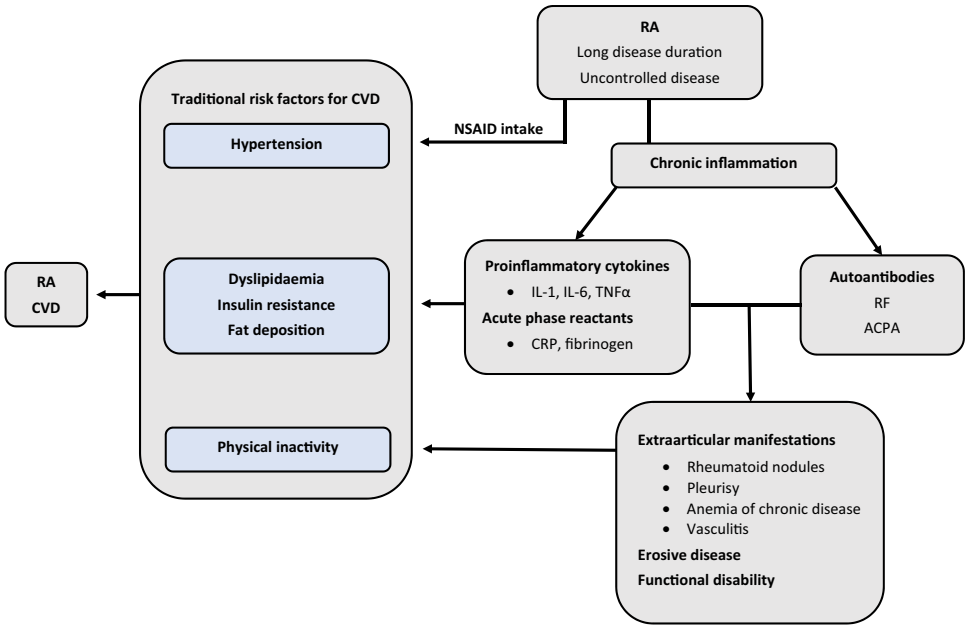

Fig. 4 Schematic representation of chronic inflammatory disease process in RA patients and the development of CVD. Data suggests a complex interplay between traditional CVD risk factors, such as dyslipidemia, insulin resistance, hypertension, limited physical activity, and obesity, and RA-related characteristics, including chronic high-grade inflammation and autoimmune activation

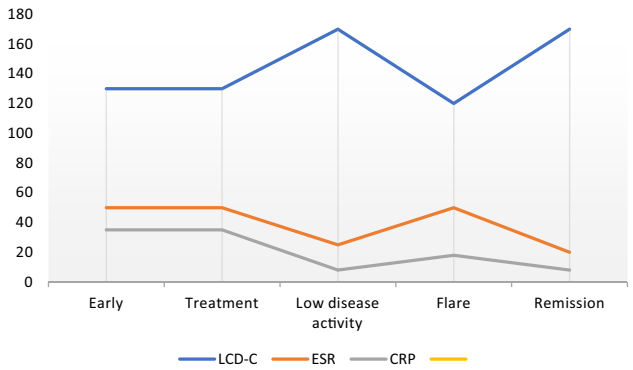

Fig. 5 Schematic representation of LDL-C levels during the RA disease course in relation to inflammatory markers. In early untreated disease with high levels of acute-phase reactants, the levels of LDL-C are low, while after treatment, when the disease is in remission with low acute phase reactants, the levels of LDL-C increase

ratio [30, 31]. This 'atherogenic' lipid profile is a feature of early RA and established disease [31, 32], while reports are showing a reduction in TC and LDL-C even 5 years before RA diagnosis, a pattern that needs further study [33]. An inverse correlation between lipid concentrations and inflammatory markers is observed in RA patients, mainly between LDL-C levels and CRP [34]. Still, HDL-C levels appear to remain relatively stable with changes in inflammation, although data over the impact of treatments on the HDL-C are conflicting [35–37]. Interestingly, changes in lipid levels are more closely associated with changes in CRP than the Disease Activity Score-28 for Rheumatoid Arthritis (DAS28), which includes clinical and laboratory data for the assessment of disease activity [38] (Fig. 5).

The exact underlying mechanism for the altered lipid profile in RA remains unknown. Studies indicate that this lipid paradox is driven by the inflammatory process and is associated mainly with the increased cholesterol catabolism. Proinflammatory cytokines such as tumor necrosis factor-alpha (TNF-a) and interleukin (IL)-6, up-regulate LDLR and SRB1 receptors on hepatocytes, resulting in an increased uptake of LDL by the liver and secretion of cholesterol into the bile [39, 40]. As a consequence, circulating LDL levels decrease. This process was demonstrated by studies that measured cholesterol metabolism by labeling lipids with stable isotopes, a method that is considered the gold standard for studying lipids and lipoprotein metabolism in humans [41]. Interestingly, Strang et al. showed a decrease of LDLR expression after treatment with anti-IL-6 inhibitor, tocilizumab [42]. To measure catabolic clearance, the fractional catabolic rate (FCR) was used in two studies: the first one, by Charles-Schoeman et al., demonstrated that the cholesterol ester FCR, at baseline, was higher in RA patients as compared to control groups suggesting higher catabolism of cholesterol esters leading to lower cholesterol levels in these patients. When tofacitinib, a JAK1 and JAK3 inhibitor, was used as a treatment option in these patients, the FCR for the cholesterol ester decreased, and cholesterol levels increased [43]. In a study by Robertson et al., the FCR of LDL at baseline was in hyper-catabolic range compared to that expected in the general population, suggestive of an active turnover. After treatment with tocilizumab, the FCR decreased, being approximately similar to that of the general population [44]. Another mechanism potentially leading to reduced circulating LDL levels is oxidation,

with studies showing that RA patients have higher levels of ox-LDL and antibodies against it [45, 46].

The level of inflammation correlates with the impact of LDL on CVD risk when ESR is more than 30 mm/h [47]. Also, high CRP in RA represents high inflammation, which correlates with the lipid paradox, and at the same time, it is associated with increased CVD risk [32, 48]. Indeed, studies have shown that markers of inflammation, such as the ESR and CRP, are associated with intima–media thickness [49, 50]. Interestingly, Ridker et al., while studying the effects of canakinumab, an interleukin-1 (IL-1) monoclonal antibody, in non-RA patients found that reduction of inflammation resulted in a decrease of CV events by 15% [51].

Moreover, the inflammation affects the antioxidant capacity of HDL. It has been demonstrated that the anti-inflammatory properties of HDL are impaired in animals [52, 53] and humans [54] during inflammation as it loses its ability to remove cholesterol from atherosclerotic plaques and becomes proatherogenic [29, 33]. This impaired HDL is proinflammatory and is characterized by a decrease of antioxidant factors [55] and gain of proinflammatory proteins [52]. It is also characterized by increased lipid hyperoxide content [54], leading to reduced potential efflux of cholesterol [56] and diminished ability to prevent ox-LDL [57]. As such, the levels of paraoxonase (PON), an antioxidant enzyme associated with HDL, are lower in RA than in controls [58], while in a study by Popa et al., changes in HDL antioxidant function were seen, expressed by an increased PON, after treatment with TNF-a inhibitor [59]. In addition, Watanabe et al. demonstrated that proinflammatory HDL in RA contains an altered proteome, including an increased amount of acute-phase proteins (such as fibrinogen, haptoglobin, and serum alpha-amyloid) and proteins of the complement system (C3, C4, and B-factor) [60]. Another study reported a reduction of the secretory phospholipase A2 and serum alpha-amyloid, during treatment with tocilizumab with modification of lipoprotein composition [61].

All the above indicate that the lipid paradox observed in RA and the high risk of CVD in these patients is mostly related to the qualitative aspects of lipids, especially the HDL, which loses its antiatherogenic function and finally becomes proatherogenic. Paradoxically, the treatment of RA patients reduces the inflammatory process but increases TC, LDL-C, and HDL-C, which is not associated with a rise in CV events [30].

The effect of antirheumatic drugs on lipid profile

The introduction of biological agents with the application of a treat to target therapy contributed to a better understanding of the underlying pathways related to CVD in RA. Studies provide considerable evidence on both csDMARDs and bDMARDs, but further work is needed to confirm and translate research findings into clinical practice.

DMARDs and corticosteroids

Corticosteroids are widely used in RA for symptomatic pain relief and reduction of the inflammatory process. They have many adverse effects, including an increase in CV risk factors such as carotid plaque formation and hypertension [62, 63]. Studies show that patients receiving high dose steroids (> 7.5 mg/day prednisone) have twice the risk of heart disease compared with those not taking steroids, while short-term, low-dose corticosteroids markedly affect plasma lipid levels mainly by elevating HDL-C levels [64].

The impact of csDMARDs on lipid profile has been studied extensively [29, 35, 65–69]. Hydroxychloroquine (HCQ), an antimalarial drug, is used to treat mild symptoms of RA and has been reported to increase HDL levels, either by reducing disease activity or by affecting lipid metabolism directly [65]. Methotrexate (MTX)is currently the first-line treatment for RA, and a recent meta-analysis showed that its use is related to 21% fewer CV events [66]. Evidence supports that MTX has an atheroprotective effect by promoting RChT and by limiting foam cell formation in THP-1 macrophages [67]. However, so far, in some human studies, MTX did not cause significant changes in lipid profile when administered alone or in combination with other cs or bDMARDs [68–71]. In contrast to the previous reports, other studies are indicating a significant increase in TC, LDL-C, and HDL-C cholesterol concentrations and cholesterol efflux capacity [35, 72, 73]. Nevertheless, the magnitude of the reported changes in the lipid fractions was smaller after 2 years of follow-up [74]. Interestingly, in patients with early RA, Georgiadis et al. [31, 32] showed, after 1 year of treatment with a steady dose of MTX in combination with prednisolone, elevations in TC, and HDL-C levels, although the TC/HDL-C ratio declined. A strong inverse relationship between CRP and HDL-C levels was observed, with no change in serum LDL-C levels.

Anti-tumor necrosis factor-alpha (anti-TNF-a) agents

Several short-term studies report a rapid increase in serum LDL-C or apoB levels after treatment with anti-TNF-a agents [75, 76]. In contrast, others indicate a neutral influence of infliximab treatment on lipid profile, since neither LDL-C levels nor TC/HDL-C and TGs/HDL-C ratios change significantly during therapy [77–79]. However, existing meta-analyses show a modest overall effect of TNF-a inhibitors on TC and HDL-C levels in RA patients with no significant effect on the atherogenic index [80–82]. Moreover, studies using a combination of anti-TNF-a agents, csDMARDs, and steroids show no significant interference with

RA patients' lipid profiles [83]. Thus, the overall favorable effect of infliximab treatment on cardiovascular comorbidity may relate to other factors such as arterial stiffness and insulin resistance improvement, but further investigation is needed to confirm this hypothesis [84, 85].

Anti-interleukin-6 (IL-6) agents

Tocilizumab, a humanized anti-IL-6-receptor monoclonal antibody that inhibits IL-6 signaling, presents a great therapeutic efficacy in RA patients. Current knowledge indicates that IL-6 affects lipid metabolism by stimulating lipid uptake via VLDLR induction, increasing hepatic and adipose tissue lipolysis, and decreasing hepatic lipid synthesis [86]. Several trials report that anti-IL6 therapy elevates serum TC, HDL-C, and TGs levels [87, 88]. Notably, the effect on the atherogenic index is inconsistent, but multiple studies show an increase in LDL-C levels by around 15–20% [88].

Janus kinase inhibitors (JAK inhibitors)

JAK inhibitors function by blocking the signaling JAK–STAT pathway, which results in the downregulation of immune response and RA remission. In phase III trials of tofacitinib, a dual JAK1–JAK3 inhibitor, LDL-C and HDL-C serum levels increased to approximately 21% and 14%, respectively, within 12 months of treatment [89]. Of note, these increases, in a head-to-head comparison between adalimumab and JAK inhibitors, were much higher than those seen after treatment with anti-TNF-a agents [90, 91]. A suggested mechanism for the increased cholesterol levels includes the reduction of cholesterol ester FCR that follows-JAK inhibitor treatment in RA patients [43].

Other agents

Rituximab (RTX), a chimerical monoclonal antibody to CD20 of B-lymphocytes, has been successfully used in the treatment of highly active RA. Some studies demonstrate that RTX improves lipid profile as well as the atherogenicity index [92, 93]. On the contrary, a study by Mathieu et al. [94], which included 33 patients with RA mostly non-responders to previous anti-TNF therapies, showed no improvement of arterial stiffness and even an increase of LDL-C and the atherogenicity index. Further prospective studies are needed to clarify the effects of RTX on cardiovascular risk factors in RA.

Statins are effective in improving the lipid profile and prevent CVD [95]. Similar to the general population, statins reduce CVD risk in RA patients as well [96, 97]. Regarding the lipid paradox in RA and the changes in lipid profile observed after RA treatment, statins should be used in accordance with CVD treatment guidelines for primary prevention in this population. So far, this approach is not regularly used in clinical practice [98].

Conclusions

In RA patients, the observed 'atherogenic' phenotype, which consists of reduced TC, HDL-C, and LDL-C levels, is linked to the increased CV risk. Emerging evidence indicates that chronic inflammation has a significant impact on patients' 'dyslipidemia' in both early and advanced disease. Moreover, suppressing inflammation through an antirheumatic treatment has a different influence on the degree and pattern of lipid profile change. Further understanding of the mechanisms underlying this paradox could maximize the effectiveness of used treatments and improve CV outcomes in such patients.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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