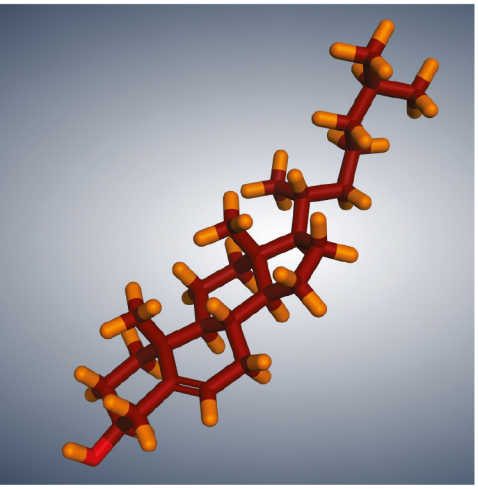
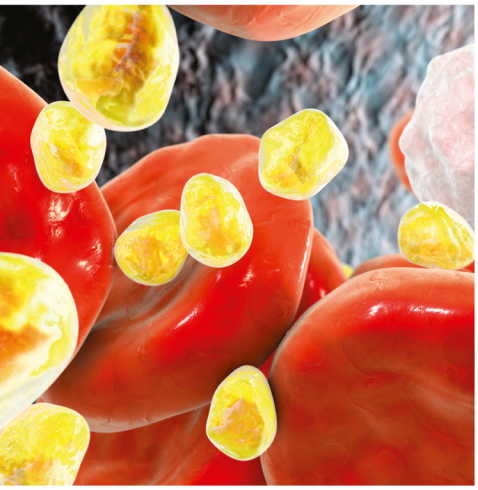
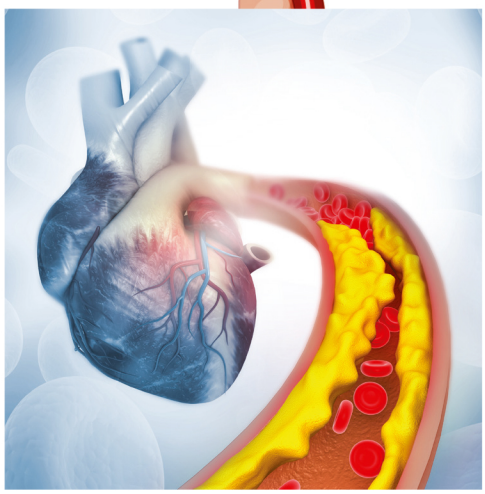
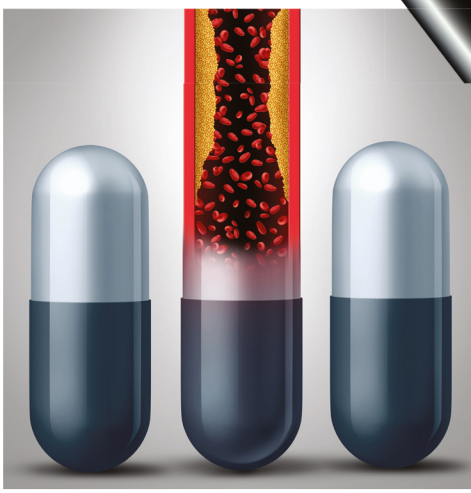
# CHOLESTEROL

## From Chemistry and Biophysics to the Clinic









Edited by
**Anna N. Bukiya, PhD**
**Alex M. Dopico, MD, PhD**

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## From Chemistry and Biophysics to the Clinic

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CHAPTER

# 35

# Hyperlipidemia and rheumatoid arthritis

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## Abbreviations

| | |
|---|---|
| **ACPA** | anticitrullinated protein antibodies |
| **ADA** | adalimumab |
| **Anti-TNF-a** | antitumor necrosis factor-alpha |
| **ASCVD** | atherosclerotic CVD |
| **bDMARDs** | biologic DMARDs |
| **CEC** | cholesterol efflux capacity |
| **CRP** | C-reactive protein |
| **csDMARDs** | conventional sDMARDs |
| **CVD** | cardiovascular disease |
| **CZP** | certolizumab pegol |
| **DAS** | disease activity score |
| **DMARD** | disease-modifying antirheumatic drug |
| **EAMs** | extra-articular manifestations |
| **ESR** | erythrocyte sedimentation rate |
| **ETN** | etanercept |
| **GLM** | golimumab |
| **HDL-C** | high-density lipoprotein cholesterol |
| **HLA** | human leukocyte antigen |
| **IFX** | infliximab |
| **IL** | interleukin |
| **IMT** | intima-media thickness |
| **INF-γ** | interferon-γ |
| **LDL** | low-density lipoprotein |
| **LDL-C** | low-density lipoprotein cholesterol |
| **LFN** | leflunomide |
| **Lp(a)** | lipoprotein(a) |


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| | |
|---|---|
| **MHC** | major histocompatibility complex |
| **MI** | myocardial infarction |
| **MMPs** | matrix metalloproteases |
| **MTX** | methotrexate |
| **NSAIDs** | nonsteroidal anti-inflammatory drugs |
| **ox-LDL** | oxidized low-density lipoprotein |
| **RA** | rheumatoid arthritis |
| **RANKL** | receptor activator of nuclear factor KB ligand |
| **RF** | rheumatoid factor |
| **ROS** | reactive oxygen species |
| **RTX** | rituximab |
| **sDMARDs** | synthetic DMARDs |
| **TC** | total cholesterol |
| **TCZ** | tocilizumab |
| **TG** | triglyceride |
| **Th** | T helper |
| **TNF** | tumor necrosis factor |
| **tsDMARDs** | targeted sDMARDs |
| **VEGF** | vascular endothelial growth factor |

## Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease that is generally considered one of the world's most common autoimmune diseases. Its prevalence is estimated at approximately 0.5%–1% in the adult population, and RA presents two to three times more commonly in women than in men (Alamanos, Voulgari, & Drosos, 2006; van der Woude & van der Helm-van Mil, 2018). The disease affects mainly the joints, and is characterized by persistent inflammation in the synovial tissues, which, if left untreated, can cause joint erosion and, subsequently, destruction of the underlying bone (Smolen et al., 2018). The progressing joint damage may lead patients to functional impairment and significant disability (Kapetanovic et al., 2015), with a high economic burden for both patients and community health services (Cooper, 2000; Hsieh et al., 2020).

Several autoantibodies can be detected in the serum of patients, among which are rheumatoid factor (RF), anticitrullinated protein antibodies (ACPA), and anticarbamylated protein antibodies. These autoantibodies may form immune complexes in the joint that contribute to the inflammatory process and lead to articular damage. RA patients can be subdivided as seropositive or seronegative, depending on the presence or absence of RF and ACPA (de Brito Rocha, Baldo, & Andrade, 2019).

The most common clinical feature of the disease is symmetrical polyarthritis that affects the small joints of hands and feet, early morning stiffness and, occasionally, constitutional symptoms. At present, no diagnostic criteria exist for RA, and disease diagnosis is based on a combination of clinical and laboratory features: joint involvement, serology (RA and anti-CCP), levels of acute-phase reactants, and the duration of the symptoms (Smolen et al., 2018; Sparks, 2019). The newest classification criteria for RA may also help physicians to reach an accurate diagnosis (Aletaha et al., 2010).

Still, RA is a highly heterogeneous disease, and some patients may present extra-articular manifestations (EAMs) in other organs, such as the skin, lung, and heart (Das & Padhan,

2017). Patients are also at increased risk of developing comorbidities, among which cardiovascular disease (CVD) is the most critical (Crowson et al., 2013). Interestingly, when compared to the general population, RA patients with active disease present reduced levels of total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C). Thus, "dyslipidemia," a traditional CVD risk factor and a critical player in RA patients' atherosclerosis, is paradoxical (Myasoedova et al., 2011). Moreover, some of the antirheumatic drugs used for RA alter patients "atherogenic lipid profile" and cause changes in lipid composition and function (Myasoedova, 2017).

Below, we review pathophysiologic mechanisms, clinical manifestations, and RA treatment options. These sections will be followed by extensive review of RA comorbidities with the focus on CVD complications and lipid profile of RA patients. We will review in details mechanisms that are thought to contribute into paradoxical relation between RA patients' lipid profile and CVD events. Finally, we will focus on the effects of pharmacological treatments, dietary, and other lifestyle interventions on blood lipid profile of RA.

## Pathophysiologic mechanisms in rheumatoid arthritis (RA)

The etiology of RA remains unknown, although recent evidence implicates epigenetic processes and environmental factors such as dust, tobacco, and the microbiome, which act in genetically predisposed individuals (Kronzer & Davis 3rd, 2021). The initial genetic susceptibility is mainly defined by human leukocyte antigen (HLA)-DR4 and -DR1, and hormonal factors (Alpizar-Rodriguez et al., 2017; Raychaudhuri et al., 2012). Emerging data also indicate the critical role of mucosal surface exposed to a high bacterial antigens load, such as the periodontium, gut, and lung. These extra-articular surfaces, and not the synovium, may represent the initial place of autoimmune generation (Brusca, Abramson, & Scher, 2014). Studies show that infectious agents like *Porphyromonas gingivalis*, *Aggregatibacter actinomycetemcomitans*, and Epstein-Barr virus can induce citrullination or deamination of peptides, a posttranslational modification mediated by peptidylarginine deiminases, and substantially lead to the production of ACPAs and RF (Arvikar et al., 2021; Konig et al., 2016; Masuoka et al., 2018; Sakkas, Daoussis, Liossis, & Bogdanos, 2017; Wegner et al., 2010). Citrullinated peptides activate major histocompatibility complex (MHC) class II-dependent T cells that help B cells to form more ACPA. The generation of antibodies causes immune-complexes formation, complement activation, and further migration of macrophages into the synovial joint, which is the disease's primary targeted tissue (Nevius, Cordeiro Gomes, & Pereira, 2016).

The hyperplastic synovium is the dominant RA feature due to the inflammation and the proliferation of fibroblast-like synoviocytes. The inflammatory infiltrate is composed of macrophages, T cells, B cells, fibroblasts, and dendritic cells, which initiate and maintain the inflammation in both the synovium and synovial fluid through the production of cytokines like tumor necrosis factor (TNF)-a, interleukin (IL)-1, IL-6, and IL-17A (Guo et al., 2018; Tran, Lundy, & Fox, 2005), and other mediators like the receptor activator of nuclear factor KB ligand (RANKL) (Ridgley, Anderson, & Pratt, 2018; van Beers et al., 2013). Finally, the inflammation and synovial proliferation cause migration of endothelial cells related to angiogenesis, the release of matrix metalloproteases (MMPs), reactive oxygen species (ROS), and the activation of osteoclasts by the RANK/RANKL pathway, leading to articular destruction

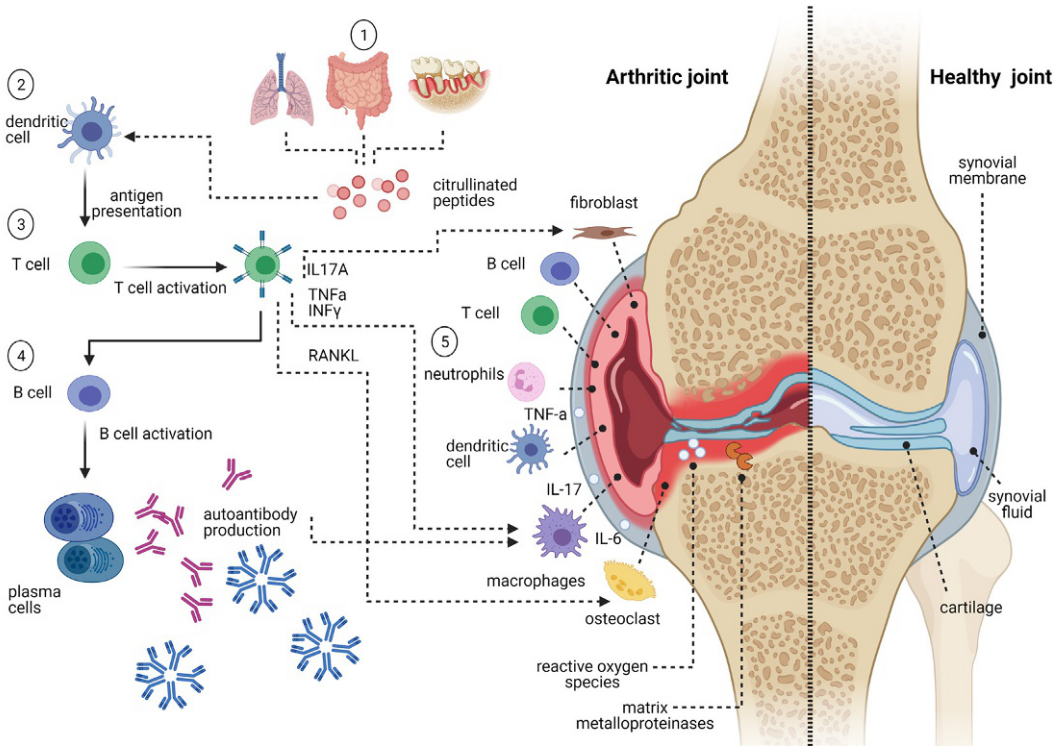


**FIG. 1** Differential contribution of cells from the innate and adaptive immune system into RA: Genetic and environmental factors may predispose to the production of citrullinated peptides (1). Activation of dendritic cells, with the production of pro-inflammatory cytokines (2). T-cell activation leads to further production of cytokines (3). Activation of B-cells and the production of autoantibodies (4). The inflammatory cells invade the synovium with further production of cytokines and metalloproteinases, leading to joint destruction (5). *IL-*, interleukin-; *INF-γ*, interferon-γ; *RANKL*, receptor activator of nuclear factor KB ligand; *TNFa*, tumor necrosis factor a.

(Burrage, Mix, & Brinckerhoff, 2006; Mirshafiey & Mohsenzadegan, 2008; Sato & Takayanagi, 2006) (Fig. 1). All the above interplay among cells of the innate and adaptive immune system is crucial, and leads to chronic inflammatory joint disease. Still, RA may have systemic effects as cytokines released in the inflamed joints can also target other organs and tissues.

## Articular and extra-articular manifestations of RA

RA can affect any joint, but usually targets the metacarpophalangeal, proximal interphalangeal, and metatarsophalangeal joints, as well as in the wrists and knees. Joint synovitis causes swelling, tenderness to palpation with morning stiffness, and may lead to motion impairment (Jeffery, 2014; Zhang et al., 2020).

However, RA is a multisystem disease, and patients with RA can present various extra-articular manifestations, either in the beginning or during the course of their disease (Conforti et al., 2021). Studies show that up to 40% of patients with established disease may present

extra-articular manifestations (Cimmino et al., 2000). Higher incidence of EAMs has been associated with high RF titers, anti-CCP, homozygous DRB1*04 subtype, and smoking (Nyhäll-Wåhlin et al., 2009; Turesson, Jacobsson, Bergström, Truedsson, & Sturfelt, 2000; Turesson, O'Fallon, Crowson, Gabriel, & Matteson, 2003; Voskuyl et al., 1996; Weyand, Xie, & Goronzy, 1992). Various manifestations have been observed in RA patients, including rheumatoid nodules, vasculitis and, moreover, pulmonary, neurologic, cardiac, hematological, and cutaneous complications (Cojocaru, Cojocaru, Silosi, Vrabie, & Tanasescu, 2010; Metafratzi et al., 2007).

## Rheumatoid arthritis treatment

Treatment for RA has evolved over the past 25 years, from providing only symptomatic relief to a target strategy with therapeutic drugs that impact disease activity and slow structural joint damage (Cardiel, 2013; Drosos, Pelechas, & Voulgari, 2019; Drosos, Pelechas, & Voulgari, 2020; Upchurch & Kay, 2012). Analgesics and nonsteroidal anti-inflammatory drugs (NSAIDs) are used as adjunctive therapy in RA treatment as they are fast-acting and ameliorate pain and stiffness symptoms. NSAIDs inhibit cyclooxygenase enzymes (COX-1 and COX-2) and restrain prostaglandins synthesis leading to reduced joint swelling and pain. Still, they do not retard joint destruction and therefore are not sufficient for the treatment of RA. Due to the reduction of prostaglandins production in the gastrointestinal mucosa, NSAIDs can cause gastrointestinal complications and compromise cardiovascular safety (Crofford, 2013; Grosser, Ricciotti, & FitzGerald, 2017).

Glucocorticoids (GCs) are useful for short periods during severe flares of disease activity or when the disease is not responding to NSAIDs. They prevent the release of phospholipids and decrease prostaglandins and cytokines' actions, provoking a decrease in inflammation. However, they have serious side effects, especially when given in high doses for long periods, such as weight gain, eye cataract, risk of infection, muscle wasting, osteoporosis, and metabolic syndrome (Caporali, Todoerti, Sakellariou, & Montecucco, 2013).

Disease-modifying antirheumatic drugs (DMARDs) are immunosuppressive and immunomodulatory agents used to treat autoimmune diseases such as RA. They are classified as either synthetic DMARDs (sDMARDs) or biologic DMARDs (bDMARDs). sDMARDs are further divided into conventional sDMARDs (csDMARDs) that evolved empirically without a fully understood mechanism and targeted sDMARDs (tsDMARDs), designed to target a specific molecular target. csDMARDs include methotrexate (MTX), leflunomide (LFN), hydroxychloroquine (HCQ), and sulfasalazine, while tsDMARDs are presented by tofacitinib and baricitinib that both are Janus kinase (JAK) inhibitors. bDMARDs, which were first introduced in the late 1990s, include anti-TNF-a agents, IL-6 inhibitors, B cell depletion agents, and inhibitors of T-cell costimulation (Fig. 2).

Currently, csDMARDs are widely used for the treatment of patients with RA (Kim, Yelin, Tonner, & Solomon, 2013; Sizova, 2008). MTX is the initial drug of choice of most rheumatologists (Padjen, Crnogaj, & Anić, 2020). Guidelines of the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) target early disease treatment and suggest the use of DMARDs as soon as the diagnosis is completed (Singh et al., 2016; Woodworth & den Broeder, 2015). Notably, the 2019 updated EULAR recommendations suggest using MTX combined with GCs for newly diagnosed patients. Upon insufficient

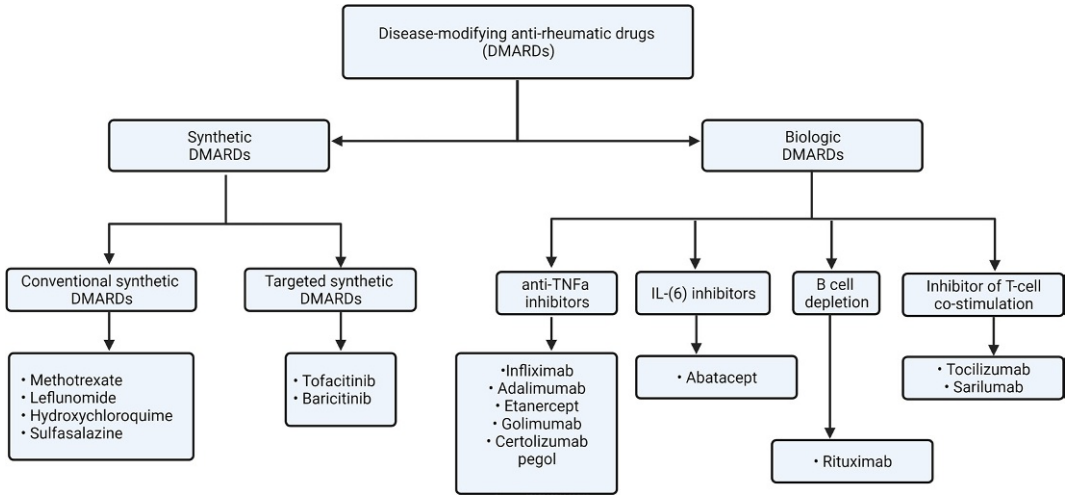


**FIG. 2** Overview of DMARDs approved for the treatment of RA. *DMARDs*, disease-modifying antirheumatic drugs.

response to this therapy within 3–6 months, further stratification is recommended according to risk factors. With poor prognostic factors (presence of autoantibodies, high disease activity, early erosions, or failure of two csDMARDs), any bDMARD or csDMARD could be added to the csDMARD. If this fails, any other bDMARD (from another or the same class) or tsDMARD is recommended. On sustained remission, DMARDs may be tapered but should not be stopped (Smolen et al., 2020).

## Comorbidities in RA

The prevalence of comorbidities in RA varies between 40% and 66%, and studies show that they may shorten these patients' life expectancy. Patients with RA present numerous comorbidities, mainly represented by pulmonary and CVD [myocardial infarction (MI), stroke], infections, cancer, osteoporosis, and depression (Luque Ramos et al., 2019). Still, comorbidities are associated with many factors including the use of GCs and prolonged DMARDs, the advanced age of patients, positive RF, and traditional risk factors, such as tobacco smoking (Dougados et al., 2014).

## CVD: A major comorbidity in RA

Overall, RA patients have a shorter life expectancy: 3–10 years less when compared to the general population (Dadoun et al., 2013; Løppenthin et al., 2019). Notable, over 40% of all RA patients' deaths are caused by CV events (ischemic heart disease, stroke) (Symmons & Gabriel, 2011). Studies also show a 1.5-fold higher risk for heart attack, a 2-fold risk for heart failure, and an even higher risk of peripheral vascular disease in RA patients compared to the general population (Aviña-Zubieta et al., 2008; Chuang et al., 2016; Stamatelopoulos et al., 2010).

Classical or traditional CVD risk factors for the general population are hypertension, age, cigarette smoking, dyslipidemia, family history, diabetes mellitus, obesity, and physical inactivity (de Goma, Knowles, Angeli, Budoff, & Rader, 2012). However, these factors cannot fully explain the higher CVD risk observed in RA patients. Interestingly, increased C-reactive protein (CRP) levels have been shown to predict CVD in the general population (Osman, L'Allier, Elgharib, & Tardif, 2006). At the same time, in RA patients, a significant association is observed between CRP and erythrocyte sedimentation rate (ESR) with atherosclerosis, and a higher risk for MI and stroke (Gonzalez-Gay, Gonzalez-Juanatey, & Martin, 2005; Goodson et al., 2005; Zhang et al., 2014). On the other hand, a higher prevalence of preclinical atherosclerosis is found in RA patients independently of traditional risk factors, reinforcing the possible link between inflammation and disease severity to this population's atherogenicity (Roman et al., 2006). Furthermore, increased coronary heart disease (CHD) and CHD mortality are observed in autoantibody-positive RA patients, even in those who do not present any joint symptoms. These relate to the HLA-DRB1 shared epitope that is associated with a higher cardiovascular mortality rate in advance. Thus, the puzzle of CVD in RA seems to be far more complex, including both traditional CVD risk factors, such as insulin resistance, hypertension, limited physical activity, and obesity, and nontraditional risk factors, that relate to RA such as uncontrolled systemic inflammation, autoantibodies, genetic factors, and altered lipid profile (Toms, Symmons, & Kitas, 2010) (Fig. 3).

## CVD risk assessment in RA

Current advances in understanding the high CVD burden in RA patients have driven a significant adjustment of RA treatment guidelines. Thus, rheumatologists currently monitor disease activity and manage all possible CVD risk factors. This necessity is displayed in the treatment guidelines published by the European Society of Cardiology and the European Atherosclerosis Society (Mach et al., 2020). In 2017, EULAR recommendations for the screening and management of CVD risk in RA patients proposed a cardiovascular risk assessment for all patients with RA at least once every 5 years and whenever major antirheumatic therapy changes occur. When applying prediction models for CVD risk, a 1.5 multiplication factor should be adapted for all patients with RA, while screening with carotid ultrasound for asymptomatic atherosclerotic plaques may be considered part of the CVD risk evaluation. In addition, TC and HDL-C should be used as part of the CVD risk assessment and ideally be measured when disease activity is stable or in remission. In turn, the TC/HDL-C ratio is considered a better CVD risk predictor than the individual lipid components (Agca et al., 2017).

## CVD and atherosclerosis in RA

Atherosclerotic cardiovascular events (ASCVE) are related to atherosclerotic plaque formation, where cumulative plaques narrow and block blood arteries. Atherosclerosis is an inflammatory process provoked by many mediators, which are also associated with inflammatory activity in RA (Cinoku, Mavragani, & Moutsopoulos, 2020; Gonzalez-Gay et al., 2005; Sattar, McCarey, Capell, & McInnes, 2003). A pro-inflammatory state, oxidative stress,

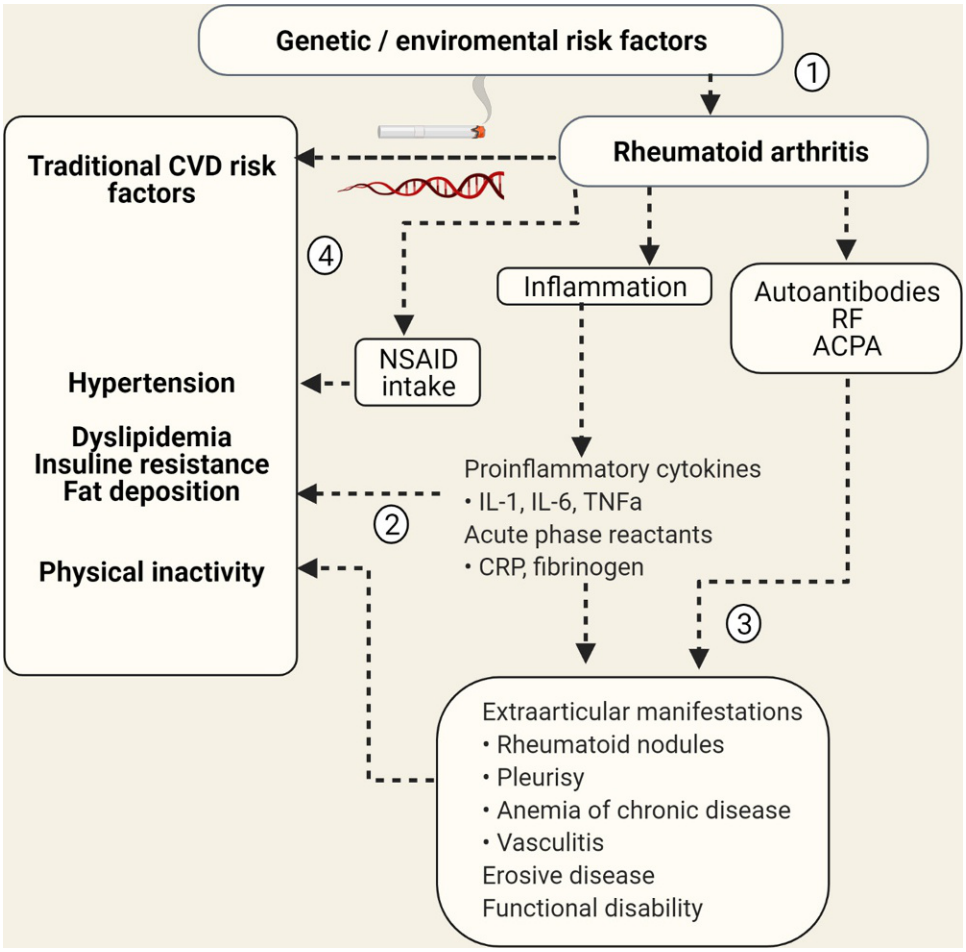


**FIG. 3** Puzzle of CVD risk in RA. Genetic and environmental factors predispose to RA development (1). In RA patients, inflammation and autoantibodies may lead to dyslipidemia, insulin resistance and fat deposition (2) and extra-articular manifestations and physical inactivity (3). The use of NSAIDs may cause hypertension along with other traditional CVD risk factors (4). All of the above dynamically interact with each other and form the cardiovascular risk in RA patients. *ACPA*, anticitrullinated protein antibodies; *CRP*, C-reactive protein; *CVD*, cardiovascular disease; *IL-*, interleukin-; *NSAID*, nonsteroidal anti-inflammatory drug; *RF*, rheumatoid factor; *TNFa*, tumor necrosis factor a.

hyperhomocysteinemia, and insulin resistance are commonly observed in RA and atherogenic conditions (Pelechas, Voulgari, & Drosos, 2021; Sattar & McInnes, 2005). A potential mechanism explaining the interplay of RA and atherosclerosis involves the production of pro-inflammatory cytokines, such as TNF-a, IL-1, and IL-6 by the synovium that are released into the systemic circulation. Through several pathways, these cytokines cause changes in specific organs like skeletal muscles, adipose tissues, liver, and vascular endothelium and lead to insulin resistance, dyslipidemia, prothrombotic procedures, and finally, endothelial dysfunction (Fig. 4).

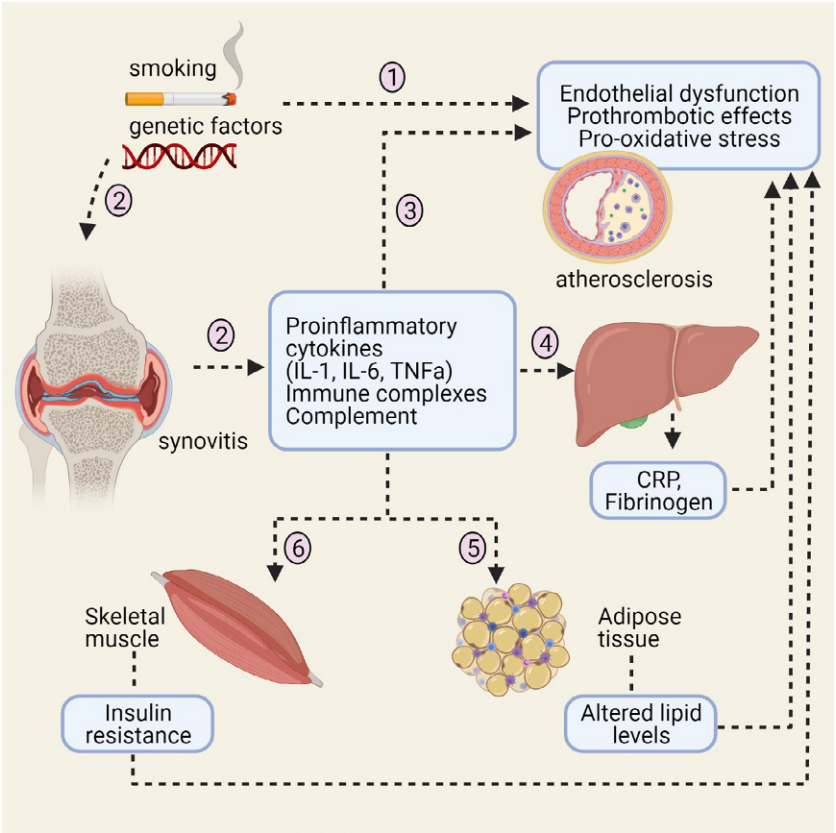


**FIG. 4** Pathways linking RA to atherosclerosis: Environmental and genetic factors contribute to endothelial dysfunction (1). In RA, genetic variants and environmental factors trigger pathological immune response and expression of pro-inflammatory cytokines in the synovium (2). These cytokines act directly over the endothelium (3) and provoke the release of further inflammatory mediators like CRP and fibrinogen from the liver (4). They further contribute to several changes observed in adipose tissues (5) and skeletal muscles (6) leading to altered lipid profiles and insulin resistance. The interaction of all these events causes an activation of the endothelium and the progression of atherosclerosis. *CRP*, C-reactive protein; *IL-*, interleukin-; *TNFa*, tumor necrosis factor a.

This process is dynamic, and during each step inflammatory cytokines facilitate the accumulation of lipids in the subendothelial space, making the atherosclerotic process a chronic inflammatory disease. Following endothelial cell injury, the observed accumulation and oxidation of LDL to oxidized LDL (ox-LDL) constitutes the first step of atherosclerosis that drives macrophages transformation into foam cells and ultimately leads to the production of a fibrous cap, which contains smooth muscle cells and stabilizes the plaque. The stable plaque is a barrier that prevents plaque rupture. In contrast, when the foam cell core is highly inflammatory, the plaque becomes vulnerable and may lead to exposure of lesion prothrombotic factors to blood, thrombus formation, and clinical events (Li et al., 2021).

High blood cholesterol eventually begins to accumulate in arteries and contribute to atherosclerotic plaque formation. Elevated levels of LDL-C and apolipoprotein B (apo B), the

main structural protein of LDL, are directly associated with the risk for ASCVE, where LDL-C levels and ASCVE present a log-linear relationship (Feingold et al., 2000; Ference et al., 2017). Thus, studies show that lower LDL-C levels are associated with a much lower risk of CVD and vice versa, while high HDL-C levels in the blood have been related to a lower risk for heart disease and stroke (Després, Lemieux, Dagenais, Cantin, & Lamarche, 2000; Parhofer, 2015). Still, raising only plasma HDL-C is unlikely to reduce the risk of Atherosclerotic CVD (ASCVD) events. Finally, increased risk of ASCVD has been associated with high triglycerides (TG) levels, especially in combination with HDL-C low levels (Peng, Luo, Ruan, Peng, & Li, 2017) and higher plasma Lp(a) lipoprotein concentrations. Studies have unveiled Lp(a) as an independent contributing factor to the risk of atherosclerosis (Rosengren, Wilhelmsen, Eriksson, Risberg, & Wedel, 1990). Still, if Lp(a) blood levels are extremely high, an underlying inherited lipid disorder cannot be excluded (Wu et al., 2019).

Regarding RA, the Apolipoprotein MOrtality RISk (AMORIS) study showed that even though TC and TG levels were significantly lower in patients with RA, these patients had a 1.6 times higher rate of acute MI and stroke than people without RA (Semb et al., 2010). Still, the predictive value of TC and TG in RA was not consistent. The relationship between dyslipidemia in RA and CVD events was reported a few years earlier by Myasoedova et al. (2011). This study revealed a higher risk of CVD events in RA patients with the lowest LDL-C (i.e., $<70$ mg/dL) than those with higher LDL-C levels. Thus, patients with the lowest LDL-C levels present a higher CVD risk than those with moderate LDL-C levels in a qualitative U-shaped relationship, which deviates from the typical link between high LDL-C levels and high CVD risk (Liao, Liu, Lu, Solomon, & Kim, 2015; Robertson, Peters, McInnes, & Sattar, 2013). Moreover, a reduction in HDL-C level in RA patients results in a high atherogenic TC/HDL-C ratio index.

## Lipid profile in RA patients

In the general population, an atherogenic lipid profile consists of high TC, high LDL-C, and low HDL-C. On the contrary, RA patients with active disease present low TC, LDL-C, and HDL-C levels. Thus, dyslipidemia in RA is considered paradoxical, and thus frequently described in the literature as a "lipid paradox" (Venetsanopoulou, Pelechas, Voulgari, & Drosos, 2020). The prevalence of dyslipidemia is notably higher in RA patients and in some studies reaches up to 65.3% of patients (Akiyama et al., 2015; Dormohammadi Toosi et al., 2018; Haye Salinas et al., 2013). Reduction in TC and LDL-C can be observed even 5 years before RA diagnosis. However, this altered lipid profile is characteristic not only in early RA but also in patients with established disease (Curtis, John, & Baser, 2012; Kavanaugh, 1994).

Accumulating evidence suggests that the pro- or antiatherogenic properties of LDL-C and HDL-C depend on their particle size and plasma concentration. Small-sized LDL and HDL particles play a role in the atheroma, and their analysis may contribute to CVD risk assessment. Data from RA patients show an alteration in the concentrations of specific lipid subfractions: small HDL, HDL-2, and HDL-3 particles are reported to have lower counts compared with control subjects (Arts et al., 2012; Hurt-Camejo et al., 2001).

Moreover, apo B, which is an essential component of the very low-density lipoprotein (VLDL), intermediate-density lipoprotein (IDL), and LDL, is found in higher amount and in

association to carotid plaque progression (Ajeganova et al., 2011). A higher ratio of apo B to apo A is a better predictor of future CVD events than standard lipid concentrations among RA patients (Öhman, Öhman, & Wållberg-Jonsson, 2014). Thus, although TC and LDL-C levels may be lower in RA patients, alteration in the concentrations of specific lipid subfractions, higher apolipoprotein levels, and lower HDL-C levels may drive pro-atherogenic dyslipidemia in RA.

## Mechanisms related to dyslipidemia in RA

The exact underlying mechanism for the altered lipid profile in RA remains unknown. Studies show that RA patients' lipoproteins, except for concentration differences, present dysfunctional properties associated with a high incidence of CVD events in RA. These primarily relate to qualitative aspects of lipids, especially to HDL, which loses its antiatherogenic function and finally becomes proatherogenic.

## Lipid concentration and inflammatory markers

Current knowledge indicates that lipid concentrations in RA highly relate to the patient's inflammatory status. Following this premise, the correlation between lipid levels and inflammatory markers in RA is found to be inversed (Ridker et al., 2009). Interestingly, changes in lipid levels are more closely associated with CRP changes than with the disease activity score for RA (DAS28), a composite measure of RA disease activity that includes objective and subjective criteria for the disease assessment. A decrease in CRP by at least 10 mg/L over 2 years is associated with a rise in LDL and an increase of HDL cholesterol efflux capacity (CEC) from lipid-laden plaques (Liao et al., 2015), even though it has been described that HDL-C levels remain relatively stable with changes in inflammation (Van Lenten, Reddy, Navab, & Fogelman, 2006). High inflammation correlates with high CRP in RA patients, which also relates to both lipid paradox and increased CVD risk (Sattar et al., 2003).

## Atherosclerosis and inflammation

It is widely accepted that inflammation plays a crucial role in all stages of atherosclerosis development in RA patients. Carotid ultrasound is an easily used imaging tool to assess atherosclerosis by measuring carotid intima-media thickness (IMT). Carotid IMT detects early atherosclerosis and predicts ASCVE in the general population (Tschiderer, Klingenschmid, Seekircher, & Willeit, 2020). Increased carotid IMT is present in RA patients, even from the early stages of the disease, and relates to accelerated atherosclerosis. A more severe inflammatory status (as expressed by high DAS28, CRP, and ESR) significantly impacts carotid IMT (Hannawi, Haluska, Marwick, & Thomas, 2007; Targońska-Stepniak, Drelich-Zbroja, & Majdan, 2011). Also, RA patients present a significant association between inflammatory markers with atherosclerosis and, as mentioned previously in the text between CRP and ESR, all leading to a higher risk for MI and stroke (Libby, 2021; Zhang et al., 2014).

## Lipid metabolism and inflammation

Lipid metabolism is a complex process highly influenced by chronic inflammatory conditions. In RA, pro-inflammatory cytokines from the synovial membrane leak into the systemic circulation, interact with mediators in distant organs, and finally lead to significant lipid metabolism effects. This interplay includes tissues such as adipose, liver, and vascular endothelium. Specific pro-inflammatory cytokines, such as IL-1 and IL-6, and TNF-a, are linked to increased cholesterol catabolism.

## The impact of cytokines on LDL

TNF-a and IL-6 reduce circulating LDL-C levels by increasing LDL-receptor and scavenger B1 receptor on hepatocytes and further promoting LDL-C uptake by the liver and cholesterol secretion into the bile (Hashizume & Mihara, 2012; Venetsanopoulou, Pelechas, et al., 2020). Metabolic clearance of radiolabeled lipids has been measured using the fractional catabolic rate (FCR) (Magkos & Mittendorfer, 2009). Two studies used this metric to examine the role of each of two different DMARDs, tofacitinib and tocilizumab (TCZ), in RA patients' lipid profile. In the tofacitinib study, RA patients had a higher cholesterol ester FCR at baseline than controls, which explains the lower TC levels in these patients. Following tofacitinib treatment at a dose of 5 mg twice daily for 6 weeks, the FCR for the cholesterol esters decreased, while cholesterol levels increased (Charles-Schoeman et al., 2015). In the TCZ study, the investigators measured the LDL-C FCR before and after 10 weeks of TCZ 8 mg/kg intravenous treatment. At baseline, RA patients with active disease had an LDL-C FCR in a hypercatabolic range that pointed out a markedly active turnover. After treatment with TCZ, FCR decreased, reaching levels similar to those observed in the general population (Robertson et al., 2017).

## Lipid peroxidation

Lipid peroxidation is another mechanism potentially leading to reduced LDL-C levels. When lipids oxidize due to oxidative stress, they become dysfunctional and may decompose, causing the formation of several unstable, small reactive molecules that can react with proteins and change their function (Desai, Manjunath, Kadi, Chetana, & Vanishree, 2010). Thus, levels of malondialdehyde (MDA), one of the final products of polyunsaturated fatty acids peroxidation in the cells, have been significantly higher in RA patients' blood, plasma, serum, synovial fluid, erythrocytes, and urine. MDA levels have also been positively correlated with disease activity and levels of ROS (Datta et al., 2014; Tsikas, 2017). Thus, cytokines that provoke superoxide secretion from monocytes and endothelial cells are also responsible for LDL oxidative modification. High levels of ox-LDL and autoantibodies against ox-LDL have been featured in patients with early RA, suggesting an essential role of these parameters in the pathophysiology of RA and the accelerated atherosclerosis observed in these patients (Kim et al., 2004; Lourida et al., 2007).

## Altered HDL function and structure

HDL is commonly known as the "good" cholesterol as its high levels are associated with reduced CVD levels. Studies have shown that HDL participates in reverse cholesterol transport, a process responsible for transferring excess cholesterol from peripheral sites to the liver (Venetsanopoulou, Pelechas, et al., 2020). Its ability to accept cholesterol from macrophages through the function of CEC is one of the most well-recognized pathways underlying HDL's antiatherogenic nature. CEC is inversely associated in population studies, independently of HDL-C levels, with carotid IMT and a higher incidence of CVD events (Hunjadi et al., 2020; Rohatgi et al., 2014). In RA patients, CEC is impaired (Ronda et al., 2014), but the epidemiological data are inconsistent, as not all the studies have shown that the CEC is significantly lower in RA patients than in healthy individuals (Ormseth et al., 2016). Either way, in RA patients, CEC is independently associated with subclinical carotid atherosclerosis (Tejera-Segura et al., 2017).

Furthermore, studies indicate that a higher proportion of RA patients have low HDL antioxidant capacity (Gómez Rosso et al., 2014; McMahon et al., 2006). HDL's antioxidant activity inhibits the oxidation of both LDL and HDL itself, a process that is directly involved in the initial phases of arteriosclerosis. Specific qualitative characteristics of the HDL particle influence HDL's antioxidant capacity (Ormseth & Stein, 2016). Thus, levels of paraoxonase-1 (PON-1), an antioxidant enzyme produced in the liver and circulating with HDL, are lower in RA than in controls (Tanimoto et al., 2003). A wide range of other structural changes lead to a dysfunctional HDL (Gómez Rosso et al., 2014), which thus becomes pro-inflammatory. HDL is characterized by a decrease in antioxidant factors and a gain of pro-inflammatory proteins. Acute-phase proteins identified in the HDL complexes are significantly increased in RA patients with pro-inflammatory HDL. These proteins include apolipoprotein J, fibrinogen, haptoglobin, serum amyloid A, and complement factors (B, C3, C9) (Watanabe et al., 2012).

## Effects of antirheumatic therapy on serum lipid levels

Early disease diagnosis and applying a target-focused treatment strategy may prevent joint damage and lead patients to better long-term results. Following the introduction of new biological agents, studies on their safety and efficacy led to the identification and better understanding of pathways that link RA to an increased CVD risk. Besides reducing the inflammatory process, RA treatment may also increase TC, LDL-C, and HDL-C levels (Fomicheva et al., 2021). The following sections describe the available evidence of the effect of currently used drugs on the lipid profile of RA patients.

## Glucocorticoids (GCs)

GCs present a wide range of biological activities, including anti-inflammatory and immunosuppressive effects (Hardy, Raza, & Cooper, 2020). One of their main actions includes their impact on the production of arachidonic acid metabolites. They also interfere with

macrophages and fibroblasts' function, inhibit the release of cytokines, and further influence lymphocytes' action and the proliferation and activation of T cells. However, they are related to many adverse effects, including hypertension and carotid plaque formation (Davis 3rd et al., 2007). A meta-analysis of 236,525 RA patients reported a 47% increased risk for all cardiovascular events and an elevated risk for MI, congestive heart failure, and stroke with prednisone use (Roubille et al., 2015).

Regarding lipid concentrations, low-dose corticosteroid therapy in RA patients is associated with an increase in HDL-C without increasing LDL-C or TGs (García-Gómez et al., 2008). In some patients, however, TC is found higher upon treatment with prednisolone (Hafström et al., 2007). A higher dose of GCs (prednisone $\geq$7.5 mg/day) has been associated with an increased HDL-C but no change in LDL-C or TC/HDL-C ratio (Schroeder, Tang, Wasko, & Bili, 2015). These results suggest that GC dose is not associated with an atherogenic lipid profile in RA. Although GC-induced elevations in HDL-C would appear to be protective, GC treatment adversely affects traditional CV risk factors, including glucose metabolism, blood pressure, and body weight. GC treatment also furthers endothelial dysfunction, which leads to atherosclerosis (Iuchi et al., 2003).

## DMARDs

Treatment with cDMARDs helps RA patients achieve clinical remission, less structural damage and better functional outcomes. The above results from a significant suppression of inflammation, which also reduces the development of atherosclerosis and subsequently CVD (van Halm, Nurmohamed, Twisk, Dijkmans, & Voskuyl, 2006). The effect of csDMARDs on RA lipid profile has been studied thoroughly as detailed below.

**HCQ**, which is a 4-aminoquinolone, is a drug initially used to treat malaria. It is widely used for treating rheumatic disorders, especially in immune-mediated cases such as systemic lupus erythematosus and RA. HCQ improves synovitis, pain, and physical disability in RA, although it has no protective result on radiographic progression (The HERA Study Group, 1995). The exact mechanism of action of HCQ is not fully understood. Still, HCQ has been shown to interfere with lysosomal activity and autophagy and to decrease T cells' stimulation and granulocyte migration, thus inhibiting cytokine production, and downregulating the whole autoimmune response (Nirk, Reggiori, & Mauthe, 2020). HCQ use has a potential benefit on the atherogenic lipid profile in patients with RA. A study by Morris et al. that analyzed a cohort of 706 patients with an RA median duration of 1.98-year found a decrease in LDL-C, TC, LDL-C/HDL-C, and TC/HDL-C with HCQ use (Morris et al., 2011). Changes in lipid profile have been reported very early after the initiation of HCQ (Rahman et al., 1999). An increase of 15% in HDL-C has been reported in a prospective randomized clinical trial of 12 months' duration in 100 RA patients compared to a 12% decrease in patients treated with gold ($p = 0.006$) (Munro et al., 1997). The mechanism underlying this effect is uncertain. Still, it is unlikely mediated by solely controlling inflammation. It seems that HCQ influences the metabolism of lipids. Chloroquine, an antimalarian agent structurally related to HCQ, acts on isolated hepatocytes inhibiting cholesterogenesis (Beynen, van der Molen, & Geelen, 1981).

**MTX** is a folate analog that inhibits dihydrofolate reductase and thus blocks the folate-dependent steps in de novo purine and pyrimidine biosynthesis. Its mechanism of action is

complex: it includes inhibition of purine and pyrimidine synthesis, suppression of transmethylation reactions, reduction of antigen-dependent T-cell proliferation, and promotion of adenosine release with adenosine-mediated suppression of inflammation (Cronstein, 1997). MTX currently is the anchor drug and the first-line treatment after RA diagnosis. In a meta-analysis that included 28 studies ofRA, a beneficial association between MTX and reduction in the risk of all CV events, including MI, was found when compared with other synthetic DMARDs (Roubille et al., 2015). The mechanism underlying the atheroprotective effect of MTX may relate to its capacity to activate adenosine A2A receptor and promote reverse cholesterol transport, while limiting foam cell formation in THP-1 macrophages (Reiss et al., 2008).

In early RA cases, 1 year of treatment with a steady dose of MTX in combination with prednisolone promotes elevations in TC, and HDL-C levels, although the TC/HDL-C ratio may decline (Georgiadis et al., 2006). The same researchers also observed a strong inverse relationship between CRP and HDL-C levels, with no change in serum LDL-C levels (Georgiadis et al., 2008). Navarro-Millàn et al., after 24-week MTX treatment in 226 patients with RA, observed an increase in TC (+30%), LDL-C (+28%), and HDL-C (+39%) concentrations. Similar changes were reported with a combination of MTX and etanercept ($n$ =155) or with triple therapy of MTX, sulfasalazine and HCQ ($n$ =78) (Navarro-Millán et al., 2013). Additionally, it was found, using MTX monotherapy, that such changes on lipid profile were smaller after a 2-year follow-up (Charles-Schoeman et al., 2016). In contrast to previous reports, other studies have not shown any significant modification of lipid concentrations with MTX use whether as monotherapy or in combination with other csDMARDs or bDMARDs (Ormseth, Yancey, Solus, et al., 2016; Rho, Oeser, Chung, Milne, & Stein, 2009).

**LFN** is an immunomodulatory drug that inhibits the mitochondrial enzyme dihydroorotate dehydrogenase and thus the pyrimidine nucleotide de novo biosynthesis. Its primary mechanism of action includes the regulation of lymphocyte proliferation (Breedveld & Dayer, 2000). Prolonged treatment with LFN appears to be associated with a reduced risk of CV disease (Naranjo et al., 2008). However, hypercholesterolemia has been described as adverse effect during LFN treatment (Laborde, Loeuille, & Chary-Valckenaere, 2004), and thus, lipid profile should be monitored during the follow-up.

## Antitumor necrosis factor-alpha (anti-TNF-a) agents

Several anti-TNF-a agents have been approved for the treatment of RA: infliximab (IFX), etanercept (ETN), adalimumab (ADA), golimumab (GOL), and certolizumab pegol (CZP). These drugs provide clinical improvement in the signs and symptoms of patients with RA and inhibit progressive joint damage (Ma & Xu, 2013). Kiortsis et al. have shown that IFX treatment may have beneficial effects on insulin sensitivity in the most insulin-resistant patients with RA (Kiortsis, Mavridis, Vasakos, Nikas, & Drosos, 2005). Short anti-TNF-a treatment has been associated with increased TC and HDL-C levels, which correlates with decreased disease activity but with no significant effect on the atherogenic index (Seriolo, Paolino, Sulli, Fasciolo, & Cutolo, 2006). An increase in serum LDL-C or apo B levels after treatment has also been described in patients treated with anti-TNF-a agents (Wijbrandts et al., 2009). Therapy with IFX has been shown to improve HDL antioxidative capacity, while stable increases of PON-1 activities were observed throughout the same period (Popa et al., 2009). In contrast,

other studies show a modest effect on TC and HDL-C levels in RA patients (Kiortsis et al., 2006) even when using a combination of anti-TNF-a, csDMARDs, and steroids (van Sijl et al., 2011). Results on qualitative lipid changes (structure and function) may be more relevant to their presumed vascular benefits, a theory that requires further study.

## Anti-interleukin-6 (IL-6) agents

TCZ is a humanized anti-IL-6-receptor monoclonal antibody that inhibits IL-6 signaling and presents a good efficacy and safety profile in RA treatment (Markatseli et al., 2019). Regarding its impact on lipid profile, a decrease of LDL-receptor expression after treatment with TCZ has been reported (Strang et al., 2013). Modification of lipoprotein composition has been observed due to reducing the secretory phospholipase A2 and serum alpha-amyloid levels (McInnes et al., 2015). Kawashiri et al. (2011) have shown an elevation in serum levels of TC, HDL-C, LDL-C, Apo A-1, and Apo A-2 after 3 months of treatment with TCZ, while the researchers didn't observe any significant change in Apo B, the atherogenic index, and TC/HDL-C by the TCZ treatment. Several other trials have reported the same results on serum TC, HDL-C, and TGs levels (Cacciapaglia et al., 2018). TCZ, when compared with placebo, has also induced elevations in LDL-C and alteration of HDL to an anti-inflammatory composition (Pierini et al., 2021). Still, these observations require further investigation.

## Janus kinase inhibitors (JAK inhibitors)

JAK inhibitors target the intracellular kinase JAK and block the JAK-STAT signaling pathway, which influences the response to many cytokines. Since their release, they quickly became a promising class of oral therapeutics that proved effective in treating RA. Regarding JAK inhibitors' effect on lipids, it is proposed that increased cholesterol levels relate to the reduction of cholesterol ester FCR after JAK inhibitor treatment in RA patients (Venetsanopoulou, Pelechas, et al., 2020). In a double-blind, placebo-controlled, parallel-group phase III trial of tofacitinib, which is a dual JAK1–JAK3 inhibitor, there was an increase in HDL-C and LDL-C levels of about 14% and 21%, respectively, within a year of treatment (Fleischmann et al., 2012). The LDL-C and HDL-C levels were also found to be significantly elevated with tofacitinib administration in a phase III trial, compared to ADA at 3 months. These increases were much higher than those seen after treatment with anti-TNF-a agents (van Vollenhoven et al., 2012).

## Other agents

**Rituximab** (RTX) is a chimeric, murine-human monoclonal antibody directed against the B-lymphocyte-specific antigen CD20 on the surface. It induces rapid and sustained depletion of peripheral B-cells (Edwards et al., 2004). Since 2006, RTX has been approved for use in patients with moderate-to-severe RA refractory to DMARDs or anti-TNF-a agents. After treatment with the standard approved dosage (two infusions 1 g given 2 weeks apart), most individuals achieve a significant improvement in RA disease activity (Cohen et al., 2006).

Some studies demonstrate a reduction in TC and an increase in HDL-C levels after RTX, by 11% and up to 35%, respectively. However, a study that included 33 RA patients, who previously did nonrespond to anti-TNF-a treatment, showed that treatment with RTX did not improve the arterial stiffness, atherogenicity index, or LDL-C (Mathieu, Pereira, Dubost, Lusson, & Soubrier, 2012). Future investigations may clarify the exact effects of RTX on CV risk factors in RA patients.

The overall effect of RA treatment on CVD risk is shown in Fig. 5.

**Statins** are commonly prescribed both for primary and secondary prevention of CHD. They induce a wide range of changes in lipid profile, including reduction of TC, LDL-C, and of TG (albeit, at a lesser degree) while increasing HDL-C levels. Statins reduce cholesterol biosynthesis by acting mainly in the liver where they exert modulation of lipid metabolism, derived from their effect of inhibition of 3-hydroxy-3-methylglutaryl-CoA reductase (Stancu & Sima, 2001). Statin treatment initiation is associated with a lower risk of mortality among RA patients, similar to the general population (Schoenfeld et al., 2016). Statins should be used for primary prevention in RA patients according to national recommendations and risk assessment tools (Kitas et al., 2019).

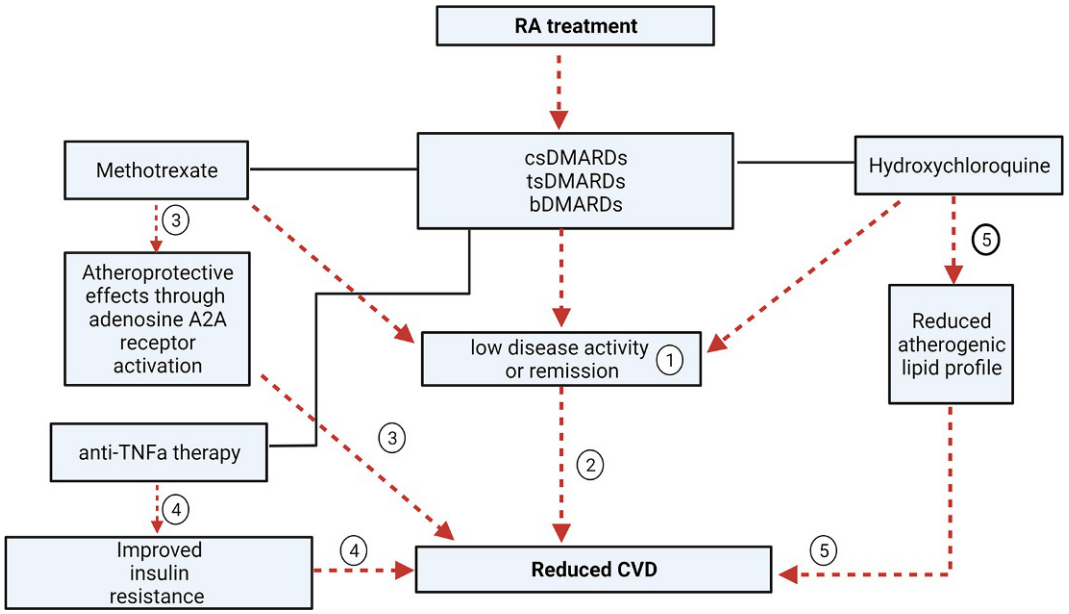


**FIG. 5** Schematic representation of RA treatment and its effect on CVD risk. The treat-to-target approach with GCs, cDMARDs, and bDMARDs leads to remission or low disease activity (1) and may reduce CVD (2). MTX use has a dual effect on CVD risk through its impact on disease activity (1,2) and its ability to promote reverse cholesterol transport (3). Anti-TNF-a therapy also improves insulin resistance with a further reduction of CVD risk (4). HCQ has a beneficial effect on atherogenic lipid profile (4) alongside improving synovitis (1). *Anti-TNF-a*, antitumor necrosis factor-alpha; *CVD*, cardiovascular disease; *DMARD*, disease-modifying antirheumatic drug; *csDMARDs*, conventional synthetic DMARDs; *MTX*, methotrexate; *RA*, rheumatoid arthritis; *tsDMARDs*, targeted synthetic DMARDs.

## Mediterranean diet and RA

Mediterranean diet is based on the eating habits of Greece, Italy, and Spain in the 1960s. It emphasizes consuming vegetables, fruits, grains, fish, and unsaturated fats such as olive oil, while it includes less dairy and meat when compared to a typical Western diet.

In RA, studies reveal a beneficial effect of the Mediterranean diet in reducing pain and increasing patients' physical function (Forsyth et al., 2018; Sköldstam, Hagfors, & Johansson, 2003; Vranou et al., 2020), while some researchers have related adherence to the Mediterranean diet with a possible reduction of the high risk of RA among ever-smoking women (Nguyen et al., 2021). Extra virgin olive oil significantly reduces the levels of pro-inflammatory cytokines and prostaglandin E2 in the joint of collagen-induced arthritis model mice in the joint, leading to a downregulation of the arthritic process (Rosillo et al., 2014). In humans, a recent study showed that high adherence to the Mediterranean diet related to lower disease activity and a healthier gut microbiota composition, with a significant decrease in *Lactobacillaceae* and an almost complete absence of *Prevotella copri* (Picchianti Diamanti et al., 2020).

Several studies have advanced the beneficial role of the Mediterranean diet in controlling the main risk factors for the development of arteriosclerosis through the downregulation of cellular and inflammatory biomarkers related to atherogenesis (Estruch, 2010). Olive oil consumption, which is a key component of the Mediterranean diet, has been shown to decrease the plasmatic levels of LDL-C and increases those of HDL-C (Alarcón de la Lastra, Barranco, Motilva, & Herrerías, 2001). Other diet patterns or even fasting mimicking diets may also suppress the inflammatory process (Venetsanopoulou, Voulgari, & Drosos, 2020), but their impact on CVD risk needs further investigation.

## The role of exercise in RA

Exercise and quality of life are closely linked together. Studies have shown that exercise optimizes physical and mental health in patients with long-term illnesses. Exercise directly increases strength, balance, and flexibility. Also, it has excellent physical benefits such as improving cardiovascular endurance, reducing high blood pressure, increasing HDL-C, maximizing bone density, and helping weight management. People who do not exercise may experience more fatigue and pain because a lack of movement leads to decreased joint motion, stiffness, and muscle weakness. Studies indicate that in RA patients, exercise is safe and improves their quality of life, functionality, pain, and number of swollen joints (Hernández-Hernández & Díaz-González, 2017). Individualized aerobic and resistance exercise for muscle strength is recommended as a routine practice. Moreover, in older RA patients (ages 65–75 years), it has been shown to improve physical fitness in terms of aerobic capacity, endurance, and strength (Hurkmans, van der Giesen, Vliet Vlieland, Schoones, & Van den Ende, 2009; Lange et al., 2019). This type of physical intervention can significantly improve low cardiorespiratory fitness, a significant predictor of CVD in RA (Stavropoulos-Kalinoglou et al., 2013). Studies also indicate that exercise in RA patients is associated with a more protective CV risk factor profile: lower waist-hip ratio, higher HDL particle concentration, lower vascular stiffness, and a lower prevalence of hypertension (Byram et al.,

2018). The impact of several different kinds of exercise has been studied: Tai chi, a noncompetitive, self-paced physical exercise and stretching, has shown to improve endothelial dysfunction and arterial stiffness in older women with RA (Shin et al., 2015). Thus, exercise should be an integral part of treating RA patients.

## Conclusions

The relationship between dyslipidemia in patients with RA, inflammatory pathways, and atherosclerosis is complex. The altered lipid profile in RA is paradoxical to the general population in patients with active disease and is characterized by low TC, LDL-C, and HDL-C levels. Studies have identified that inflammation is indeed the key player to many of RA's lipid changes. Thus, RA patients' treatment to decrease the risk of hyperlipidemia as a cardiovascular risk factor is still necessary disregarding their paradoxical lipid profile. Moreover, a treat to target approach with csDMARDs and or ts/bDMARDs leading to low disease activity or disease remission is mandatory. Still, future investigation is required and could lead to a better stratification of CVD risk in RA beyond the established risk factors.

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