Review

The Lipid Paradox as a Metabolic Checkpoint and Its Therapeutic Significance in Ameliorating the Associated Cardiovascular Risks in Rheumatoid Arthritis Patients

Tapan Behl 1,*, Ishnoor Kaur 1, Aayush Sehgal 1, Gokhan Zengin 2, Ciprian Brisc 3, Mihaela Cristina Brisc 3, Mihai Alexandru Munteanu 3, Delia Carmen Nistor-Cseppento 4 and Simona Bungau 5,*

1 Chitkara College of Pharmacy, Chitkara University, Punjab 140401, India; ishnoorkaur7@gmail.com (I.K.); aayushsehgal00@gmail.com (A.S.)
2 Department of Biology, Faculty of Science, Selcuk University Campus, 42130 Konya, Turkey; biyologzengin@gmail.com
3 Department of Medical Disciplines, Faculty of Medicine and Pharmacy, University of Oradea, 410073 Oradea, Romania; brisciprian@gmail.com (C.B.); briscristina@yahoo.com (M.C.B.); mihaimunteanual@yahoo.com (M.A.M.)
4 Department of Psycho-Neuroscience and Recovery, Faculty of Medicine and Pharmacy, University of Oradea, 410073 Oradea, Romania; delia_cseppento@yahoo.com
5 Department of Pharmacy, Faculty of Medicine and Pharmacy, University of Oradea, 410028 Oradea, Romania
* Correspondence: tapanbehl31@gmail.com (T.B.); sbungau@uoradea.ro (S.B.); Tel.: +40-726-776-588 (S.B.)

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Abstract: While the most common manifestations associated with rheumatoid arthritis (RA) are synovial damage and inflammation, the systemic effects of this autoimmune disorder are life-threatening, and are prevalent in 0.5–1% of the population, mainly associated with cardiovascular disorders (CVDs). Such effects have been instigated by an altered lipid profile in RA patients, which has been reported to correlate with CV risks. Altered lipid paradox is related to inflammatory burden in RA patients. The review highlights general lipid pathways (exogenous and endogenous), along with the changes in different forms of lipids and lipoproteins in RA conditions, which further contribute to elevated risks of CVDs like ischemic heart disease, atherosclerosis, myocardial infarction etc. The authors provide a deep insight on altered levels of low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) and triglycerides (TGs) in RA patients and their consequence on the cardiovascular health of the patient. This is followed by a detailed description of the impact of anti-rheumatoid therapy on the lipid profile in RA patients, comprising DMARDs, corticosteroids, anti-TNF agents, anti-IL-6 agents, JAK inhibitors and statins. Furthermore, this review elaborates on the prospects to be considered to optimize future investigation on management of RA and treatment therapies targeting altered lipid paradigms in patients.

Keywords: rheumatoid arthritis; cardiovascular disorders; lipid paradox; inflammatory burden; LDL-C; HDL-C; lipoproteins; atherosclerosis; DMARDs

1. Introduction

Rheumatoid arthritis (RA) is considered to be an autoimmune disorder which is prevalent in about 0.5–1% of the general population [1,2], with significant risks of comorbidities, disabilities and fatigue [3], along with cardiovascular disorders (CVDs), and long-term impact on socioeconomic and personal paradigms [4]. Even though no exact cause is known, the disease is considered to occur as
a result of a combination of epigenetic, genetic and environmental factors, and the progression of the disorder is considered to be initiated years before appearance of clinical signs and symptoms [5]. Therefore, several studies have established the importance of early diagnosis to provide treatment at early stages, which has proved to be beneficial, along with prognostic markers for remission [6,7].

A bioclinal and chemical aspect, comprising anti-citrullinated peptide antibodies (ACPA), has been incorporated by the 2010 American College of Rheumatology/European League of Rheumatism criteria for RA [8]. The identification of ACPA and rheumatoid factor (RF) autoantibodies, of different isotypes, in the circulation, are considered to be significant markers in early diagnosis of RA, prior to the clinical manifestation of the disorder [9]. RA patients exhibit metabolic alterations, which may elevate morbidity and mortality risks in the patients [10]. Such metabolic alterations are identified by evaluation of the basal metabolic rate (BMR) of RA patients, which is reported to elevate by 8%, unlike in the healthy individual [11].

Furthermore, significant alterations in the blood lipid are also reported in RA patients [12], which may depict increased cardiovascular (CV) risks in such patients. Furthermore, RA elevates the risk of CVDs by 50% (approximately) as compared to the general population [13,14], and CVDs are the leading cause of death in patients with RA [13,15–20]. The risk for myocardial infarction (MI) has been reported to be enhanced by 2-fold, compared to control groups, as observed in large retrospective RA investigations [15,21]. RA patients are more susceptible to ischemic heart disease, heart failure and CV mortalities, and also the pattern of CVDs in patients with RA is revealed to be different from that of general population [20].

Type 2 diabetes, hypertension and smoking are considered to be traditional risk factors of CVDs [22,23], which play a significant role in elevating the mortality rate in RA patients [24,25]. The elevation in CV risks is primarily driven by inflammatory responses related to RA [13,26]. Thus, enhanced inflammatory processes in RA patients are associated with atherosclerotic events, along with systemic inflammatory responses, which are responsible for adverse alterations in CV risk factors [26–30].

The RA-associated lipid paradox is related to an excessive inflammatory burden in RA patients, in which an inverse association is observed between cholesterol (a significant CV risk factor in general population) and CV risks in RA patients (untreated) [31,32]. On the other hand, inhibition of inflammatory events related to RA coincides with certain elevations in lipid concentration, along with amelioration in CV events [33]. The significance of minimizing CV risks in RA is considered to be fundamental as per the recommendations laid by the European League against Rheumatism (EULAR) for coronary heart diseases (CHDs) management associated with RA [33]. Evaluation of CV risks in RA patients is recommended on an annual basis [13].

Based on the metabolic alterations observed in RA patients and the role of these changes in inducing CV, the aim of this review is to provide a detailed overview of the lipid paradox, along with its role in developing CV risks in such subjects; we also focused on the impact of anti-rheumatoid therapies in the lipid scenario associated with RA. The authors highlight the relationship between elevated risks of CV, the inflammatory burden and altered lipid profiles in patients with RA. Significant information is also provided on the importance of lipid alterations associated with RA in serving as appropriate therapeutic targets. Over 350 references were searched and 221 of them were cited as supporting claims of the current study.

2. Metabolic Frontiers in Rheumatoid Arthritis and Their Therapeutic Significance

RA is an inflammatory disorder of the immune system, characterized by the production of self-antibodies such as ACPA, RF and anti-carbamylated protein antibodies (anti-CarP). [34]. This is accompanied by chronic inflammation of the synovial tissue and hyperplasia, damage to the bone and cartilage as well as systemic complexities, significantly related to the lungs, brain or CV system, which pose a fundamental threat to the socioeconomic balance and unmet needs [34,35]. RA is associated with progressive therapeutic advancement with conventional treatment therapies and disease modifying
anti-rheumatic drugs (DMARDS); however, these agents have been able to provide optimum response in only 60% of the RA patients [36].

Presently, the predictive biomarkers evaluating the prognostic approach, treatment efficacy and resistance to therapy, consisting of RF, C-reactive protein (CRP), ACPA and erythrocyte sedimentation rate (ESR), remain insufficient from a clinical perspective [5,37]. The immune system intolerance is marked as a primary event in RA pathogenesis, which is followed by inflammation of the joint [5,38], which is most likely to take place at the extracellular site [39]. The events (such as infiltration of leukocytes, production of new vasculature and elevated expression levels of chemokines and adhesion molecules) result in enhanced migration of leukocytes to the site of inflammation [34]. Furthermore, improper formation of lymphatic vessels restricts cell retreat, along with activation of fibroblasts, resulting in inflammation of the synovial tissue [40]. The joint resident and immune system cells compete for nutrients due to limited nutrient availability, at a rate exceeding that of their formation, thus elevating the metabolic requirement [41–45]. All these events significantly induce changes in the immune responses, resulting in immune intolerance, leading to inflammation and autoimmunity [34].

The investigation of metabolic intermediates and end products, relative to the functions of the immune cells, is a progressing area of research currently, which has been referred to as immunometabolism [46]. Certain molecules like acetyl-CoA, succinate, fumarate and lactate, function as signaling molecules, establishing significant associations between metabolic processes and inflammatory and immune responses (Figure 1) [34].

Figure 1. The inflammatory portfolio in RA (rheumatoid arthritis) synovium and impaired metabolic processes. Legend: IL-2,6,17,15, Interleukin-2,6,17,15; CD4, cluster of differentiation 4; Th1,7, T-helper cells; FLS, fibroblast-like synoviocytes; TNF-α, tumor necrosis factor alpha; ROS, reactive oxygen species; IL-1β, interleukin-1 beta; ATP, adenosine triphosphate; TCA, tricarboxylic acid cycle; α-KG, alpha-ketoglutaric acid; G6PD, glucose-6 phosphate dehydrogenase; PPP, pentose phosphate pathway; FAS, fatty acid synthase; CoA, coenzyme A.

Urine and serum sample metabolomics, based upon nuclear magnetic resonance (NMR) spectroscopy, has identified greater levels of lactate and 3-hydroxybutyrate among the metabolites in
a group of RA patients, unlike the control group, where the serum metabolic profile was evaluated using 1-dimensional (1) H-NMR spectroscopy [47]. Furthermore, mitochondrial DNA (mtDNA) mutations and production of reactive oxygen species (ROS) were reported to be present in greater amounts in patients with RA, as compared to osteoarthritis fibroblast-like synoviocytes (FLS), when 50 subjects with inflammatory arthritis went through arthroscopy and synovial tissue biopsies, where their synovial fluid was clinically evaluated [48]. Random mutation capture assay (RMCA) and specific cell fluorescent probes were employed for quantification of ROS, mitochondrial membrane potential (MMP), mass and mutagenesis. The elevated mitochondrial mutations are related to the inflammation of the synovial membrane, depicting a direct association between mutations and prime proinflammatory pathways [48]. Unlike T cells, RA FLS depict elevation in glycolytic metabolism under conditions of metabolic stress [49]. Similarly, lipid metabolism is also found to play an important role in regulation of the functions of the immune cells, according to the recent studies [50], which has brought the lipid mediators into light, as significant therapeutic targets in various allergic and autoimmune disorders [51]. Table 1 enlists various metabolic targets associated with RA.

| Cell Associated with RA | Abnormal Metabolic Process | Effective Therapeutic Targets |
|------------------------|---------------------------|-------------------------------|
| Fibroblasts             | Glycolysis; Lipid         | HK2; GLUT1; PFKFB3; Choline   |
| T cell                  | Lipid; PPP; Glycolysis    | FASN; PFKFB3; AMPK/mTOR; G6PD; Lactate |
| Dendritic cells         | Glycolysis                | iNOS; HK2; mTOR               |
| Macrophages/monocytes   | TCA; Glycolysis           | HIF; Lactate; PKM2; Succinate |

Legend: (TCA, tricarboxylic acid cycle; AMPK—5′ AMP-activated protein kinase; HK2, hexokinase-2; GLUT1, glucose transporter 1; PFKFB3, 6-phospho-fructo-2-kinase/fructose-2,6-bisphosphatase 3 enzyme; FASN, fatty acid synthase; mTOR, mammalian target of rapamycin; G6PD, glucose-6-phosphate dehydrogenase; iNOS, inducible nitric oxide synthase; HIF, hypoxia inducible factors; PKM2, pyruvate kinase M2.

Certain specific transcription factors function as metabolic sensors and regulate numerous anabolic and catabolic pathways, like 5′ AMP-activated protein kinase (5′ AMPK), i.e., a redox sensor [52], which regulates various metabolic activities, such as mitochondrial biogenesis, glucose uptake, cellular functions and lipid metabolism [34].

The experimental arthritis was found to be suppressed as a result of therapeutic activation of AMPK, like methotrexate-mediated AMPK-dependent pathway stimulation, which is depicted to exert protective effects against inflammation [53,54]. The activation of AMPK is dependent upon myristoylation, and the RA T cells exhibit a flaw in the function of N-myristoyl transferase (NMT), which disables the AMPK activation event and enables the activation of mammalian target of rapamycin (mTOR1) signaling, promoting differentiation of pro-inflammatory Th1 and Th17 [34]. The investigations regarding loss of function of NMT1 were found to induce in vivo and in vitro inflammatory responses, whereas, on the contrary, excessive expression levels of NMT1 were found to restore the activation of AMPK and inhibit inflammation of the synovial tissue [55].

Furthermore, an indirect activator of AMPK, metformin (anti-diabetic drug), has been reported to curb the disease progression in mouse arthritic models [56] by inhibiting the mTOR pathway, elevating autophagic flux and suppressing nuclear factor-kappa B (NF-Kb)- induced production of inflammatory cytokines [53]. The environmental signals, cellular functions and nutrient availability is regulated by both mTOR and AMPK [57,58]. However, activation of mTOR is marked with aging of the cells (senescence), therefore, rapamycin (inhibitor of mTOR complex 1) has been recognized as an agent in treating autoimmunity, degenerative and hyperproliferative disorders [59]. The potential of mTOR to synergize bioenergetics, nutrient supply and functions of T cells makes it a reliable therapeutic target in the suppression of abnormal differentiation of T cells during initial RA phases [59].
Similarly, several drugs affecting the metabolic signaling pathways are used to treat RA patients, such as glucocorticoids, which block the fructose 2, 6-biphosphate (glycolytic enzyme) in tycocytes in rats and modulate the rate of respiration in the peripheral blood mononuclear cells of rheumatic patients [60]. Regulation of purine and pyrimidine nucleotide metabolism is the prime mechanism of anti-inflammatory actions rendered by methotrexate [61].

Treatment with anti-tumor necrosis factor-α (anti-TNF-α) agents and janus kinase (JAK) inhibitors, like tofacitinib, mitigate glycolysis in the synovium of RA patients [62]. Tocilizumab (anti-IL-6 blocker) curbs the oxidative stress (OS) conditions in leukocytes of RA patients [63]. Therefore, numerous drugs have been identified in RA treatment by affecting the metabolic signaling pathways to mitigate inflammatory responses in both in vitro and in vivo models of RA [42,53,64,65]. Similarly, evaluating the role of lipid metabolism in RA can prove to be effective for the development of suitable therapeutic possibilities and associate lipid metabolism abnormalities to RA [34]. Figure 1 depicts the inflammatory processes in synovial tissue of RA patients, along with multiple metabolic alterations.

3. Cardiovascular Risk and Inflammatory Burden in RA

One of the major CV risk factors is inflammation, which is evident by data revealing lower CV risks in RA as a result of mitigated inflammatory responses [66–70]. Employment of traditional equations to assess CV risk factors, such as systemic coronary risk evaluation (SCORE) models and Framingham, are considered to underestimate this risk in RA patients, as they are not able to evaluate the role of systemic inflammation and its effect on lipid profiles in patients [24,71–73]. The occurrence and pathogenesis of CVDs and atherosclerosis in the general population are significantly affected by inflammation, according to evidence-based data [74–76].

Numerous pro-inflammatory molecular entities, like fibrinogen, CRP and cytokines, aid in the regulation of this process, as per the data obtained from epidemiological studies [77–79]. RA patients are marked with elevated levels of inflammatory molecules and cytokines which promote dysfunction of endothelial cells and structural vessel deformities, alongside induction of other CV risk factors, like insulin resistance, alterations in lipid levels and oxidative stress [80–82]. Furthermore, many investigational studies have established an important link between CVD risk and inflammatory processes in RA [32,83–90]. Inflammation plays a significant role in all the stages of atherosclerosis [16,82,91]. RA and atherosclerosis are associated with common inflammatory processes and the events resulting in the inflammation of synovial tissue are similar to those in the case of unstable atherosclerosis [78,82,91].

Inflammation is related to an inverse association between CV risks and lipid pattern in RA [32,66,92]. This kind of link has also been reported in the post-surgical time span, where an inverse relationship has been noted between cholesterol levels and IL-6 enhancement [93]. Numerous investigational studies have revealed elevation in the level of lipids, with a significant amelioration in RA progression after therapy with anti-inflammatory agents [94]. These outcomes reveal that the traditional elucidation of the lipid portfolio to carry out prediction of general CV risks may be expressed by prevalence of disease in RA patients [32,66].

The mechanisms concerned with the effect of inflammatory responses on lipid alterations are yet to be fully understood but might account for reticuloendothelial system (RES) suppression and abbreviated formation of low-density lipoprotein (LDL) [66]. There is a possibility of impairment of cholesterol trafficking in the liver due to overproduction of acute phase reactants (APR) under an elevated inflammatory burden [33]. Moreover, LDL and oxidized LDL (oxLDL) uptake is promoted by C-reactive protein (CRP), followed by LDL deposition and elevation in its uptake by liver cells [95,96]. Both quantitative and qualitative alterations in lipoproteins account for the inflammatory burden in RA [97]. High density lipoprotein (HDL) exhibits athero-protective and anti-inflammatory functions, facilitating reverse cholesterol transport (RChT) from the blood circulation to the liver and hampering oxidation of LDL [98].
CV risk-propagating pathological events might impair such protective actions [99-104]. Certain changes were found to exist in the composition of HDL, which was isolated from the patients with RA, according to the proteomic studies, along with the loss of reverse cholesterol transport and anti-inflammatory action [97,105,106]. Some studies depict anti-inflammatory HDL to be a more sensitive marker for CVDs, as compared to absolute HDL [33]. For instance, studies related to torcetrapib and dalcetrapib (cholesterol ester transfer protein inhibitors) report 30% to 70% elevation in the levels of circulating HDL, yet no cardioprotective action was revealed [107,108]. Dalcetrapib (600 mg/day) or placebo were administered to 15,871 patients with acute coronary syndrome, resulting in 4–11% elevation in HDL-C levels in the placebo group, as well as a 31–40% rise in the dalcetrapib group. There was a negligible effect observed on LDL-C levels by dalcetrapib administration. Unlike the placebo, there was no change in the risk of primary end point or total mortality. Moreover, the mean systolic blood pressure (BP) was reported to be 0.6 mm Hg greater and the level of median C-reactive protein was found to be 0.2 mg/L higher in the case of dalcetrapib administration, unlike the placebo [107]. Therefore, such studies depict the significance of both quantitative and qualitative alterations in the assessment of lipid profiles in RA patients [109–111].

4. An Overview of Lipids and Lipoproteins

Dyslipidemia refers to alterations in plasma lipid levels. Atherogenicity occurs as a result of elevated levels of cholesterol and triglycerides (TGs) in plasma. The elevated expression of lipids is significantly associated with the enhanced production of lipids and alleviated removal or absorption. On the other hand, abbreviated expression of lipids may occur as a result of reduced production of lipids and/or enhanced clearance [112]. The lipids, primarily TGs and cholesterol, are water insoluble forms, which are transported by blood, and depending upon their association with proteins are known as lipoproteins, which are complex entities comprised of cholesterol ester and TGs containing a central core [113]. These particles are surrounded by a shell comprised of phospholipids, apolipoproteins and free cholesterol, facilitating the functions and formation of lipids [112].

On the basis of composition of lipids, size and apolipoproteins, the lipoproteins are divided into the following categories: chylomicrons and chylomicron remnants. The very low-density lipoprotein (VLDL), high density lipoprotein (HDL), intermediate density lipoprotein (IDL), lipoprotein-a (Lp-a) and low-density lipoprotein (LDL) are all considered as chylomicron remnants by the authors; however, this is a basic biochemical misconception because of the different and type-specific apolipoproteins characterizing the different groups of lipoproteins, respectively ApoB-48 vs. ApoA-I and ApoA-II vs. ApoB-100. The VLDL, LDL, IDL and Lp-a are considered to be pro-atherogenic, whereas HDL is considered to be anti-atherogenic [112].

Two types of pathway, mainly the exogenous and endogenous pathway, act independently and promote the transportation of dietary lipids in the blood, promoting hepatic and peripheral movement of lipids from the small intestine (Figure 2).

The triglycerides and cholesterol esters in diet are emulsified by bile acids secreted by the liver, for hydrolysis by lipases in the intestine, followed by re-esterification of these fats to triglycerides and cholesterol esters, which are then packed into chylomicrons. Chylomicrons are large lipoproteins with density < water, which enter the blood and are rapidly cleared by lipoprotein lipase. This enzyme hydrolyzes triglycerides to free fatty acids which are utilized for production of energy, while the excess is stored as triglycerides in the adipose tissue. The remaining “chylomicron remnant” undergoes hepatic clearance. This part of metabolism of lipoproteins is named as the exogenous pathway [114].
The endogenous pathway comprises synthesis and secretion of very low-density lipoproteins (VLDL), which are degraded by lipoprotein lipase, resulting in production of intermediate density protein (IDL), followed by formation of low-density lipoprotein (LDL). In the presence of the LDL receptor, LDL gets stored in the liver and peripheral tissues, otherwise it undergoes oxidation and gets attached to the scavenger receptor on the macrophages [114]. LDL comprises the maximum amount of cholesterol that is in circulation. Furthermore, the high-density lipoproteins (HDL) play a significant role in reverse cholesterol transport from the peripheral tissues to the liver. HDL possesses anti-atherogenic, anti-thrombotic, antioxidant, anti-apoptotic and anti-inflammatory properties, and is abundant in cholesterol and phospholipids [115].

The excess of cholesterol is removed from the peripheral tissues to the liver by a reverse transport mechanism, referred to as reverse cholesterol transport (RChT) [112]. The exogenous lipoprotein pathway is initiated by administration of dietary lipids into intestinal chylomicron, which undergo further metabolism in the muscles and adipose tissue with the help of lipoprotein lipase enzyme, resulting in production of free fatty acids (FFSs) and chylomicron remnants, which then exhibit hepatic uptake. The endogenous pathway of lipoprotein is initiated in the liver, with the formation of VLDL, followed by metabolism of TGs (contained in VLDL) in the muscles and adipose tissue, with the help of lipoprotein lipase enzyme, resulting in the production of FFAs and IDL [112,116,117]. The IDL formed is transformed into LDL, which is taken up by the LDL receptor, mainly contained primarily in liver. The RChT is initiated by the formation of nascent HDL by the intestinal and hepatic tissue and ATP-binding cassette transporter A1 (ABCA1) facilitates the transportation of cholesterol and phospholipids in the cells from the peripheral tissue to nascent HDL, resulting in the production of mature HDL (by lecithin cholesterol acyltransferase, LCAT), which can further acquire more cellular cholesterol with the help of ABCG1 and class-B-scavenger receptor B1 (SR-B1). Cholesterol is transported to the liver, which is enabled by interaction between HDL and hepatic SR-B1, or by cholesterol transportation to LDL, with the help of cholesterol ester transfer protein (CETP) [115,118–120]. It can only exit the body by biliary excretion, once it enters the liver.
Depending upon the size, LDL can be grouped as large LDL, which is named pattern A, while small LDL is named as pattern B. The latter are related to CVDs, due to easy penetration ability of small particles into the target cell endothelium. Oxidized LDL (oxLDL) is a term used for LDL particles comprising oxidative modified structural components. Therefore, as a result of the attack by the free radicals, both protein components of LDL and lipids can undergo oxidation in the vascular wall [112]. The oxLDL particles are not recognized by the LDL receptor, which hinders the normal metabolism of LDL particles, resulting in atherosclerosis, which explains the atherogenicity of oxLDL [115,118–120].

Normally, HDL plays a significant role in oxLDL inhibition and efflux of cholesterol from the foam cells in the vessel wall [110]. There is no valid clarification of anti-inflammatory and atherogenic actions of HDL, but it has been reported that the functions exhibited by HDL are dependent upon its protein composition. Some amount of LDL is oxidized, in the case of elevated formation or reduced clearance of lipids, resulting in the formation of oxLDL, which is phagocytosed by macrophages, resulting in the formation of foam cells, followed by their deposition on the walls of the artery, facilitating atherosclerotic plaque formation. This establishes the significance of cholesterol efflux via RChT pathway, in order to maintain cholesterol homeostasis in the cells and promote prevention of atherosclerosis and reduction of toxic cholesterol expression in each cell [112].

Apolipoproteins are produced in the intestine and liver and contribute to metabolism of lipids, by functioning as lipoprotein receptor ligands and co-factors for lipid metabolism-associated enzymes. One of the primary components of the structure of HDL is apolipoprotein A-1 (Apo A-1), which is synthesized in the liver and accounts for 70% of the HDL structure, whereas, on the contrary, apolipoprotein A-2 (Apo A-2) accounts for 20% of the HDL structure. Other apolipoproteins, produced in the intestine, are referred to as apolipoprotein B-48 (Apo B-48), which is a significant structural component of chylomicrons and chylomicron remnants, and apolipoprotein B-100 (Apo B-100) which is primarily synthesized in the liver and forms an important structural component of VLDL, LDL and IDL [115,118–120]. Figure 2 illustrates endogenous and exogenous lipoprotein pathways, along with reverse cholesterol transport.

5. PUFAS and Phospholipids in RA Patients

The prime six types of lipids, as per the Lipid Maps, have been assessed in the plasma samples of healthy subjects where >500 species of lipids were recognized and samples were collected from 100 healthy subjects, representing common ethnicities in the USA, and stored post overnight fasting. Sterols like cholesterol was found to be present in heavy amounts in the samples, while prenols and diacylglycerols presented in limited amounts. The free fatty acids, triglycerides, sphingolipids and glycerophospholipids, were found in intermediate quantities in the sample. Polyunsaturated fatty acids (PUFAS) were also identified in the sample, with arachidonic acid and linoleic acid in abundance, along with anti-inflammatory fish oil derivatives, primarily, docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) [121,122]. The lipoxygenase (LOX) metabolites, like 5-HETE, and cyclooxygenase (COX) metabolites, like 15-deoxy-prostaglandin D2 (PGD2), were also detected, along with lipid mediator oxylipins [123]. PUFAS are dietary fatty acids, where n-3 PUFA EPA and DHA are anti-inflammatory while n-6 PUFA AA is considered to proinflammatory. The phospholipids comprise long chain fatty acids, like AA, EPA and DHA, which constitute the cell membrane [121]. Various investigations have been performed using n-3 supplements or fish oil derivatives, such as one where the authors observed significant variations in orally administered DHA and EPA (fish oil supplement) doses, after evaluating 23 studies. The time period of the investigations varied between 1–13 months and oils such as olive, paraffin and corn were used as placebo controls. The average sample size was found to be 20–30 patients per group. Various studies had methodological defects and no meta-analysis was carried out. The n-3 PUFAS administration was associated with swelling in joints, pain and morning stiffness, however, the overall effect was prudent [124]. Another study reported similar levels of free fatty acids in RA patients and healthy individuals [125], depicting no significant quantitative variation in the level of free fatty acids in the diseased state. In one
study, the serum samples of RA patients were found to exhibit lower ratios of phosphatidylcholine (PC)/lysophosphatidylcholine (LPC), unlike in healthy subjects [126], and portrayed greater activity of poly-lactic acid in patients with RA, which could enhance the level of free fatty acids that can further be metabolized into bioactive lipids. However, not only fatty acid precursors but also COX-generated lipid mediators (PGD2 and PGE2) were found to be present in serum samples of RA patients in significant amounts. [121,127]. The most abundant phospholipid found in the synovial fluid of RA patients was PC, followed by sphingomyelins and LPC, which were found in greater concentration in RA patients compared to controls [128]. The ratio of PC/LPC was greater in the synovial fluid of RA patients, unlike controls, which is the opposite to what was found in the serum [128]. The synovial fluid of RA patients was investigated for eicosanoids, where PGE2, PLA2 and COX were found to be greater in the synovium of RA patients [129,130]. Furthermore, more anti-inflammatory prostaglandins, like PGD2, and its metabolite 15-deoxy-PGJ2, along with leukotrienes, were also reported to be present in the RA patients [129]. Moreover, anti-inflammatory LOX products were also found to be present in the synovial fluid of RA patients, comprising anti-inflammatory and pro-resolving mediators lipoxin A4 (LXA4) as well as m-3 PUFA DHA derivatives, such as resolving D5 and maresin 1 [131]. This investigation was carried out on only five subjects and the role of pro-resolving lipids in RA was not investigated, however, they were recognized as suitable therapeutic agents for chronic inflammatory disorders due to their potential immune modulatory functions [132].

6. Lipid Metabolism in RA

RA patients show curbed LDL-C, HDL-C and TC levels, which are enhanced by therapies targeting inflammatory processes associated with RA [32]. A U-shaped association is proposed between CV risk and lipid pattern, in a so-called “RA lipid paradox”, where the patients with reduced LDL-C levels have greater risk of developing CVDs compared to those with moderate levels of LDL-C [92]. The abbreviated levels of HDL-C in patients with RA facilitates enhanced atherogenic index of TC/HDL-C ratio [92,133]. The early stages of RA are associated with an atherogenic lipid profile [133,134]. The concentration of lipids is inversely related to the inflammatory markers in RA patients [135]. Even though the data available regarding the influence of treatment on HDL-C are inconsistent, the levels of HDL-C are considered to be consistent relative to inflammatory alterations [106,136,137]. Furthermore, alteration in the level of lipids is more closely related to CRP changes than those of disease activity score 28 (DAS28) for RA, comprising clinical and laboratory data for evaluation of disease activity [138]. The definite cause for changes in the RA-associated lipid profile is yet to be fully understood, however, studies show that such a lipid paradox is due to inflammatory processes and elevated cholesterol catabolism [111,112]. The expression of LDL and SR-B1 receptors is enhanced by proinflammatory cytokines such as IL-6 and TNF-α, which lead to elevated liver uptake of LDL and biliary secretion of cholesterol [139,140], resulting in reduced levels of circulating LDL. This process was depicted by studies investigating metabolism of cholesterol by exhibiting lipid labeling with stable isotopes [141]. The fractional catabolic rate (FCR) was employed in two investigations to evaluate the catabolic clearance, where the first one reported greater levels of cholesterol ester FCR in patients with RA, as compared to those belonging to the control group, which demonstrated greater cholesterol ester catabolism, resulting in alleviated cholesterol levels in patients [112]. The FCR for cholesterol ester was abbreviated and the level of cholesterol was enhanced following treatment with tofacitinib [142]. Further, in one study the FCR of LDL was found to be in the hyper-catabolic range compared to the general population, which was decreased to the level similar to that of the general population after treatment with tocilizumab [143]. Moreover, oxidation is another mechanism which results in reduced levels of circulating LDL, where studies show that patients with RA exhibit a greater number of autoantibodies against mildly oxidized LDL, elaborating the alleviated action of lipoprotein-associated phospholipase A2 [144,145].

The extent of inflammation is related to the effect of LDL on CVD risk when the erythrocyte sedimentation rate exceeds 30 mm/h [89]. Greater inflammation in RA is represented by high CRP, which
is related to elevated CV risk [133,146]. Furthermore, investigations have depicted that inflammatory markers, like CRP and ESR, are related to the intima-media thickness [147,148]. In one study, the effects of canakinumab (IL-1 monoclonal antibody) were investigated and a 15% reduction in CV events was reported as a result of reduced inflammation [149]. Moreover, the antioxidant capacity of HDL is reported to be affected by inflammatory responses. The anti-inflammatory ability of HDL is disturbed in animals [103,104] and humans [111] as their ability to facilitate cholesterol clearance from atherosclerotic plaques is lost and it becomes pro-atherogenic [12,150]. The damaged pro-inflammatory HDL is marked by reduced antioxidant factors [101], along with elevation of pro-inflammatory proteins [104]. In addition, it comprises enhanced lipid hyperoxide levels [111], resulting in ameliorated cholesterol efflux [151] and reduced oxLDL preventive ability [152]. The levels of HDL-associated antioxidant enzyme, paraoxonase (PON), are abbreviated in RA patients as compared to controls [99], whereas an investigation revealed that alterations in the antioxidant function of HDL were observed, expressed by elevated PON, following therapy with TNF-α inhibitor [153]. Additionally, Watanabe et al. revealed the presence of an altered proteome in pro-inflammatory HDL in RA patients, comprising elevated levels of acute-phase proteins, like serum α amyloid, fibrinogen and haptoglobin, as well as proteins of the complement system [97]. The levels of secretory phospholipase A2 were found to be reduced along with serum α amyloid (SAA) during tocilizumab therapy with modifications of the composition of lipoproteins [154]. Therefore, all these investigations and events support the lipid paradox in RA, along with great C risks in patients with RA, mostly associated with lipid qualitative aspects (primarily the HDL) which become pro-atherogenic after losing the anti-atherogenic action. The inflammatory processes are reduced by therapeutic treatment of RA patients; however, the levels of LDL-C, HDL-C and TC are elevated, which is not related to increased CV events [92].

Short chain fatty acids (SCFAs) have been reported to carry out various functions of CD4+ cells by regulating the actions of histone deacetylases (HDAC) [155] and peroxisome proliferator-activated receptor (PPAR) signaling pathway [156]. Lipid metabolism is also crucial for T cell activation and proliferation, and elevation of sterol regulatory element binding protein (SREBP) levels [34]. The genetic inactivation promotes SREBP loss, which is harmful for the T cells, which exhibit post-activation clonal expansion [157]. Elevated fatty acid synthesis (FAS) has been revealed from T cells isolated from RA patients, resulting in enhanced tissue invasiveness [34]. Furthermore, 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 3 enzyme (PFKFB3) deficiency-mediated glycolytic flux propagates a shunt towards anabolic use of glucose (elevated PPP and FAS) and enhanced levels of podosome scaffold adapter protein TKS5 (SH3PXD2A), which contributes to the formation of protrusions in the cell membrane [64,158]. The cytoplasmic lipid droplets are accumulated as a result of increased FAS, which is fundamental for the functions of T cells, like growth and proliferation of cells, as well as transformation of naïve to memory T cell [34]. The locomotion of T cells can be regained as well as inflammation and tissue invasiveness can be minimized in diabetic severe combined immunodeficiency (SCID) mice, without obesity imbedded with synovial tissue of humans, by restoring pyruvate levels [34]. Additionally, tissue inflammation was curbed and the number of infiltrating T cells, receptor activation of nuclear factor kappa-B ligand (RANKL+) and interferon-gamma+ (INF-γ+) T cells was reduced [64]. The differentiation of Th17 cells was regulated by de novo production of fatty acids [159]. Sorafen A showed that in vitro inhibition of acetyl-CoA carboxylase (ACC) results in disrupted Th17 differentiation, which promotes Foxp3+ Treg cell differentiation instead of T-helper 17 (Th17) cells [159]. It has been also revealed the fact that when lactate is present in amounts as compared to those analyzed in the synovial tissue, the CD4+ T cells are found to elevate the de novo production of fatty acids, resulting in enhanced levels of IL-17 and curbed cell motility [160]. However, all such events were restored after treatment with FAS inhibitors which alleviated the NADPH levels induced by lactate [160]. Cholesterol metabolism regulates the CD4+ T cell-regulated anti-inflammatory response in humans, whereas de novo production of fatty acids plays a fundamental role in functions of effector CD4+ T cells [161]. A specific hindrance in the immune system resolution and a remarkable reduction in the levels of c-Maf/IL-10 has been shown by
25-hydroxycholesterol and atorvastatin-mediated inhibition of cholesterol biosynthesis during INF-γ+ to IL-10+ switching [161].

Lipid metabolism in RA and osteoarthritis FLS has been altered as per the metabolomics data. The synovial tissues in RA FLS were found to be greatly expressed with choline and choline-like transporter, CTL1 and CTL2, where the former exhibits high affinity and the latter exhibits low affinity [162,163]. Inhibition of their functions lead to the death of FLS cells [164]. These outcomes were aided by the results of positron emission tomography (PET) scanning with 11C-choline, depicting enhanced uptake in affected joints [164].

7. Effect of Anti-Rheumatic Therapies on Lipid Profile in RA

The administration of biological agents facilitates a treat-to-target approach contributing to greater understanding of CVD-associated risks in RA. Investigations provide a suitable amount of evidence related to the role of csDMARDs and bDMARDs, however, more clinical research is required in this regard [112]. Chen et al. depicted potential effects of biological therapy on insulin resistance and lipid profiles in RA patients, where they demonstrated an inverse relationship between LDL-C and disease progression, as well as a positive association between insulin resistance and DAS28 [165]. Similarly, insulin resistance exhibits a positive relationship with IL-6 and TNF levels [166].

The patients receiving biological therapeutic treatment were considered to exhibit lower insulin resistance as compared to those who were not [166]. The DMARDs and other biological therapies aid in the significant improvement of lipid profiles, along with curbed CV risk factors [67,167–169]; four out of ten RA patients fail to attain the desired targets for lipids, hypertension and diabetes diagnoses [170,171].

7.1. DMARDs and Corticosteroids

Corticosteroids provide symptomatic relief from pain in RA and also aid in amelioration of inflammatory events. However, they are associated with certain adverse effects, mainly elevation in CV risk factors such as hypertension and carotid plaque formation [172,173]. The risk of heart problems is twice more in the case of administration of high dose steroids, as compared to the cases without steroid administration, whereas the low dose, short-term corticosteroids alter the plasma lipid levels primarily by enhancing the levels of HDL-C [174].

Traditional DMARDs (like methotrexate, hydroxychloroquine etc.) exhibit protective actions against CV risks in RA, out of which methotrexate is considered to be the most significant drug [33]. Furthermore, csDMARDs have been considered to affect the lipid profile according to various studies conducted [136,150,168,175–178]. A drug used for malaria, hydroxychloroquine (HCQ), can be employed for the treatment of mild RA and has been considered to enhance the levels of HDL, either by ameliorating activity of the disease or by directly influencing the metabolism of lipids [168]. Methotrexate is presently employed as a first line drug in RA treatment and has been considered to reduce CV events by 21%, as per a meta-analysis report [175]. Additionally, methotrexate exhibits an athero-protective role by facilitating RChT and minimizing the formation of foam cells in THP-1 macrophages [176]. However, no alterations were reported in the lipid profile in some clinical studies after methotrexate administration, when the drug was administrated alone or combined with other bDMARDs [177–180].

Certain studies report a significant decline in the levels of LDL-C, TC and HDL-C as well as the capacity of cholesterol efflux [136,181,182]. Georgiadis et al. depicted enhanced TC and HDL-C expression, along with a reduced TC/HDL-C ratio, after a year-long treatment of RA patients with a methotrexate–prednisolone combination [133,134]. A strong inverse association between HDL-C and CRP levels was reported, without any alteration in serum LDL-C levels [112].
7.2. Anti TNF-α Agents

TNF is an important cytokine in chronic inflammation, which influences lipid metabolism, the function of the endothelial cells and insulin resistance [183,184]. Anti-TNF therapy has been reported to reduce inflammation and expression of levels of ESR and CRP [185,186]. Moreover, in combination with methotrexate or DMARDs, it also regulates the lipoprotein spectrum, and has been considered to ameliorate the CV risks in RA patients [68–70]. Certain studies have found that anti-TNF therapy has been associated with 54% reduction in CV risks [187]. This therapeutic approach has been found to regulate factors related to atherosclerotic CV risks in RA patients, such as mitigation of endothelial dysfunction [188–191], improved insulin sensitivity [184] and enhanced HDL anti-oxidative capacity [153]. Numerous investigations depict a significant elevation in the serum apoB and LDL-C levels following treatment with anti-TNF-α agents [185,192]. On the other hand, various other studies reveal a neutral impact of infliximab drug on lipid pattern, due to no alterations in LDL-C, TC/HDL-C or TGs/HDL-C levels during treatment [193–195]. TNF-α inhibitors are considered to affect the levels of TC and HDL-C, without exerting any effect on the atherogenic index in RA patients [94,196,197]. Furthermore, no significant relationship is reported between combined therapy of anti-TNF-α agents, steroids and csDMARDs with lipid profiles of RA patients [198]. Therefore, the resultant efficacy of infliximab on management of CV diseases may be associated with other factors, like improvement in insulin resistance and arterial stiffness; however, further studies are essential to support this hypothesis [199,200].

Published data have depicted elevated TG levels and an alleviated apolipoprotein B/A ratio as a result of long-term treatment with TNF inhibitors [94]. Moreover, the risk of acute coronary syndrome was lowered in RA patients receiving TNF inhibitors, unlike those who were biologically naïve, according to a national Swedish cohort study, which elaborated upon the future benefits of inhibiting this cytokine [201]. Mostly, older RA patients are associated with changes in lipid profiles and elevated CV risks, however, juvenile patients with idiopathic arthritic problems reported improvement in lipid profiles after treatment with etanercept (a TNF blocker) [202].

7.3. Anti-IL-6 Agents

An anti-IL-6 monoclonal antibody, tocilizumab, hinders the signaling process of IL-6 and shows potential therapeutic significance in RA. IL-6 is considered to influence metabolism of lipids by promoting uptake of lipids by VLDLR induction and elevating hepatic and adipose tissue lipolysis as well as abbreviating lipid production in the liver [203]. The serum TG, TC and HDL-C levels are reported to be enhanced by anti-IL-6 agents, as per numerous study outcomes [204,205]. It is noteworthy that the effect on atherogenic index is inconsistent, however, as various investigations demonstrate 15–20% elevation in LDL-C levels [205]. A MEASURE study (a randomized, parallel group, open-label, multicenter investigation to assess tocilizumab effects on vaccination in RA patients administered with methotrexate) also demonstrated the elevated LDL-C levels as a result of tocilizumab treatment, which also modified the HDL particles to anti-inflammatory composition [154]. Anti-atherogenic small and medium particles were reported to be enhanced with administration of tocilizumab. Moreover, the investigation also showed fundamental alterations in HDL-associated serum amyloid A (SAA) levels, paraoxonase 1 and secreted group 2A phospholipase A2 with tocilizumab treatment. The mono therapeutic response of tocilizumab and adalimumab (anti-TNF) was comparatively evaluated in methotrexate-intolerant RA patients in a double-blind adalimumab actemra (ADACTA) study (phase 4), where the results depicted elevated LDL, CRP, DAS28 (28-joint DAS) and ESR in 6 months in greater number of patients in the tocilizumab treatment group, as compared to the adalimumab treatment group [206]. Tocilizumab also exhibited greater abbreviation in Clinical Disease Activity Index (CDAI), which does not constitute an APR component [206]. Tocilizumab was also found to improve the insulin resistance in RA patients in a TOWARD (tocilizumab in combination with traditional DMARD therapy) meta-analysis investigation [207,208].
Moreover, the rates of myocardial infarction were numerically decreased with administration of tocilizumab as compared to the controls, in a double-blind phase of five core phase 3 tocilizumab trials, whereas evaluation of long-term safety of tocilizumab depicted a stable prevalence of CV events over time with tocilizumab treatment [209,210].

7.4. JAK Inhibitors

These agents hinder the JAK–STAT signaling pathway, resulting in reduced immune response and RA remission. A dual JAK1-JAK3 inhibitor, tofacitinib, upregulated the levels of HDL-C and LDL-C to about 14% and 21% within a year of treatment, in a phase 3, double-blind, placebo controlled, parallel group study of 611 subjects, who were assigned randomly in a ratio 4:4:1:1 to 5 mg of the drug two times a day, 10 mg drug two times a day, placebo for 3 months, followed by 10 mg of drug two times a day [211]. This elevation, in deadlocked comparison between JAK inhibitors and adalimumab, was greater than that observed post treatment with anti-TNF-α agents [165,212]. Ameliorated cholesterol water FCR might facilitate elevated cholesterol levels during JAK inhibitor therapy in patients with RA [142]. The US FDA has approved tofacitinib (JAK inhibitor) as a RA medication [112]. The levels of LDL and HDL were found to be significantly elevated with tofacitinib administration in a phase 3 study, as compared to adalimumab at 3 months [213]. The LDL and TCh levels were reported to be reduced to baseline levels by administration of combination of tofacitinib and atorvastatin in a phase 2 study [214].

7.5. Other Agents

A chimeral monoclonal antibody, rituximab, has been employed in RA treatment, where it has been considered to improve atherogenic index and lipid profile, as per certain studies [215,216]. Rituximab was administered to 55 women with RA and no CVDs, and the following parameters were assessed before and after 6 months of therapy: HDL-C, LDL-C, plasma total cholesterol (TC), serum C-reactive protein, RF IgM, triglycerides, AS (by digital volume pulse contour analysis), DAS 28-ESR and common cIMT (by high-resolution B-mode carotid ultrasound [215]. The patients were grouped under two categories based upon whether the results were good following 6 months of rituximab therapy or whether no response was observed. TC was elevated by 9%, HDL-C by 23%, AI was decreased by 14%, along with SI and RI by 57% and 24%, as a result of effective rituximab therapy [215]. In another study, intravenous administration of two infusions of 1000 mg rituximab was carried out in five women with RA, and branchial FMD and ccIMT was evaluated using high-resolution B-mode ultrasound, along with determination of HDL-C, TC and LDL-C levels. The results depicted elevated FMD, reduced TC (by 3–11%) and increased HDL-C levels (by 14–35%). Potential effects were exerted on endothelial dysfunction as well as plasma TC and HDL-C levels by two infusions of rituximab [216]. However, on the other hand, Mathieu et al. depicted no improvement in arterial stiffness, atherogenicity index or LDL-C in a study conducted on 33 non-responding RA patients to anti-TNF treatment therapies [217]. Therefore, further investigations are necessary to assess the definite effects of rituximab on CV risks in RA patients. Furthermore, the lipid profile can also be improved by statins, along with prevention of CV risks in general and RA patients [218–220]. These agents promoted small relative and absolute reduction in LDL-C levels in RA patients, as compared to those without RA [166]. However, these agents are not used much in clinical practice [221].

8. Future Directions and Conclusions

This review emphasizes the significance of the lipid paradox in RA and details the requirement for future research to deeply understand the lipid portfolio to facilitate a “treat-to-target” approach to reduce RA-associated CV risks. The RA metabolomics studies employ NMR and MS to extricate RA from other inflammatory conditions and controls [166]. Future prospects would more likely facilitate collaboration between metabolomic data of RA and human metabolic networks, like Recon 2 [166]. The metabolic pathways, enzymes, transcription factors and metabolites, which are altered
in patients with RA, are identified as significant therapeutic targets in RA management, as per the immune-metabolic studies. Many currently used drugs target the metabolic pathways in RA. However, there is a need to develop specific therapeutic approaches targeting RA-associated metabolic pathways. For instance, inflammatory responses have been found to be ameliorated in both in vitro and in vivo models of arthritis, as a result of specifically targeting metabolic processes in RA [64,6!]. Furthermore, metabolic intermediates like succinate and lactate are also becoming a potential possibility [34]. Animal models have proved to be quite effective in therapeutic screening during preclinical investigations; however, certain treatment therapies, which have exhibited safe and effective results in preclinical assessment, have failed to depict optimum results in clinical investigations in humans. Therefore, greater understanding of human immunology and identification of animal models similar to clinical models is required. Gender has been also found to exert a significant effect on RA immunometabolism, as RA prevalence is greater in women as compared to men [34]. This can be somewhat explained by the impact of sex hormones on regulation of the immune system, and their relationship with genetic and environmental aspects [34], but this still needs further investigation. Mass spectroscopy and NMR are considered to be significant tools for predicting the altered pathogenic pathways in RA [34].

In the future, the results might prove to be effective in identifying the risk of developing atherosclerosis in RA patients. Moreover, future studies should strive to differentiate RA conditions on the basis of the stage of the disorder, outcome and therapeutic response, by using specific metabolic signatures. Single cell RNA-seq and advanced RNS-seq techniques can be used as promising tools in cellular profiling in the future [34]. In addition, new biomarkers can be identified and novel therapeutic approaches, targeting impaired metabolic signaling pathways, can be developed, without hindering immune system homeostasis, with the help of single cell metabolomic analysis.

This review details the impact of an impaired lipid portfolio in RA and its relationship with occurrence of CV risks in patients. Numerous forms of metabolic checkpoints are highlighted in the text, out of which the review has emphasized the RA-associated lipid paradox. This is followed by an overview of CV risk and inflammatory burden associated with the lipid profile in RA patients. The authors provide a detailed overview of the pathways and processes comprising lipids and lipoproteins, along with the role of lipid metabolism in RA, which paves a way for understanding the impact of anti-rheumatoid therapeutic approaches on the lipid profile of RA patients.

Therefore, in the current review, the authors aim to provide a significant opportunity to the researchers to correlate RA-associated lipid profile with elevated CV risks, and to facilitate recognition of the impaired lipid paradox in RA as an appropriate therapeutic possibility, to reduce the RA-associated events along with related CVDs, thereby proposing an optimistic approach in the management of RA.

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