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Review

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Mechanisms by Which Lipid-Lowering Agents Modulate the Lipid-Inflammation Circuit and Their Stratified Clinical Use in Rheumatic Immune-Mediated Diseases

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Abstract: Rheumatic immune-mediated diseases, including rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and spondyloarthritis, combine persistent inflammation with increased cardiovascular risk. Inflammation alters lipoprotein production, remodeling, function, and clearance, explaining why low or apparently normal cholesterol concentrations may coexist with accelerated atherosclerosis. Modified lipids can influence nuclear factor-kappa B (NF-κB), the NLR family pyrin domain-containing 3 (NLRP3) inflammasome, and immune-cell signaling, creating a reciprocal lipid-inflammation circuit. This review examines established and emerging lipid-lowering agents, their molecular targets, and the clinical evidence across rheumatic diseases. Particular attention is given to dynamic cholesterol- and sphingolipid-enriched membrane nanodomains, cholesterol homeostasis, and the distinction between experimental immunomodulation and clinical outcomes. Statins have the most developed rheumatic-disease evidence; findings for other agents remain limited or are extrapolated from cardiovascular populations. Clinical use should be stratified by overall cardiovascular risk, low-density lipoprotein cholesterol goals, comorbidities, drug interactions, and tolerability, alongside assessment of rheumatic disease activity. Future studies should distinguish lipid-mediated vascular benefit from drug-specific immune effects using matched lipid-lowering comparators, validated rheumatic outcomes, and cardiovascular endpoints.

Keywords: rheumatic immune-mediated diseases; lipid-inflammation circuit; lipid-lowering agents; immunomodulation; cardiovascular comorbidity management

1. Introduction

Loss of immune tolerance and persistent inflammation define many rheumatic immune-mediated diseases, but the resulting burden is not confined to the joints, skin, or internal organs. As disease-modifying antirheumatic drugs and targeted biologic therapies have improved survival, cardiovascular and metabolic complications have become increasingly prominent determinants of long-term outcome. Patients with RA, SLE, or spondyloarthritis experience atherosclerosis and cardiovascular events more often than the general population, and conventional factors such as age, smoking, and hypertension account for only part of this excess risk [1–4]. Persistent

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inflammation also changes the quantity and quality of circulating lipoproteins; vascular risk may therefore remain high even when total cholesterol or low-density lipoprotein cholesterol is not overtly elevated.

Cholesterol, fatty acids, and lipid-derived mediators are not passive structural components or metabolic fuels. They organize receptor-rich membrane domains, shape inflammasome activity and lymphocyte differentiation, and participate in both the initiation and resolution of inflammation. The relationship is reciprocal: inflammation disturbs lipid transport and utilization, whereas oxidized and otherwise modified lipids amplify innate and adaptive immune responses [5–8]. This biology raises a clinically important question: can drugs prescribed for lipid lowering also modify rheumatic inflammation? Experimental findings support the possibility, although translation into a clinically meaningful anti-inflammatory effect cannot be assumed.

The literature has often considered statins, individual rheumatic diseases, or cardiovascular risk in isolation. Such an approach can blur the substantial differences between mechanistic experiments, observational associations, and randomized clinical evidence, particularly for newer agents studied mainly in non-rheumatic cardiovascular populations. Here, established and emerging lipid-lowering strategies are examined within a common framework, with experimental plausibility, surrogate outcomes, and demonstrated patient benefit kept analytically distinct. The review centers on how lipid management can be integrated with rheumatologic care and which proposed immune effects have clinical support.

2. Bidirectional Interactions between Inflammation and Lipid Metabolism

2.1. Characteristic Disturbances of Lipid Metabolism in Rheumatic Immune-Mediated Diseases

RA, SLE, and spondyloarthritis share increased cardiovascular risk but differ in their lipid disturbances. In active RA, inflammation can suppress total cholesterol and low-density lipoprotein cholesterol (LDL-C), whereas SLE may also feature elevated triglycerides, impaired HDL function, and metabolic effects of nephritis or glucocorticoids. In spondyloarthritis and psoriatic arthritis, obesity and insulin resistance frequently coexist with inflammation. These patterns make a single cholesterol measurement an incomplete description of vascular risk and support disease-aware interpretation of the lipid profile [2,4,8–11].

2.2. Mechanisms Underlying the Clinical Lipid Paradox

The lipid paradox is especially well described in RA: lower total cholesterol and LDL-C during active inflammation may coexist with greater cardiovascular risk. This apparently paradoxical pattern reflects inflammation-induced changes in lipoprotein production, remodeling, function, and clearance rather than protection from atherosclerosis. Cytokine-driven changes in hepatic metabolism and peripheral lipid handling can reduce circulating concentrations while increasing the exposure of tissues to modified lipids. HDL may become enriched in acute-phase proteins and lose antioxidant and cholesterol-efflux capacity, whereas LDL becomes more susceptible to oxidative modification. Similar functional disturbances occur in SLE, although its lipid profile is heterogeneous and should not be assumed to reproduce the RA pattern [2,4,8,9]. The conversion of protective HDL to dysfunctional HDL and the associated amplification of NF-κB signaling are illustrated in Figure 1 [12].

Original epidemiological evidence supports this association. In a population-based cohort of 651 patients with incident RA, Myasoedova et al. found a nonlinear relationship between total cholesterol and cardiovascular disease: total cholesterol below 4 mmol/L was associated with a 3.3-fold higher risk (95% CI 1.5–7.2). This observational result links low cholesterol to the inflammatory disease context; it does not imply that lowering LDL-C therapeutically increases cardiovascular risk [13].

Treatment-associated lipid increases are particularly evident with IL-6 receptor blockade and JAK inhibition. In the randomized MEASURE trial (132 patients with RA), median total cholesterol and LDL-C increased by 12.6% and 28.1%, respectively, with tocilizumab at week 12, compared with 1.7% and 2.2% with placebo. Changes in HDL-associated proteins and other vascular biomarkers occurred alongside these concentration changes, illustrating why cholesterol concentrations alone provide an incomplete assessment of treatment effects [14].

JAK inhibition also produces measurable lipid changes. In the ORAL Solo trial, mean LDL-C increased over months 0–3 by 13.6% with tofacitinib 5 mg twice daily and 19.1% with 10 mg twice daily, compared with 3.5% with placebo; these were trial regimens rather than a dosing recommendation [15]. Such increases can reflect changes in inflammation and lipid handling together with agent-specific effects. They warrant repeat lipid assessment and cardiovascular risk management, while cardiovascular safety should be judged from outcome evidence for the individual treatment rather than inferred from the lipid rise alone [14–16].

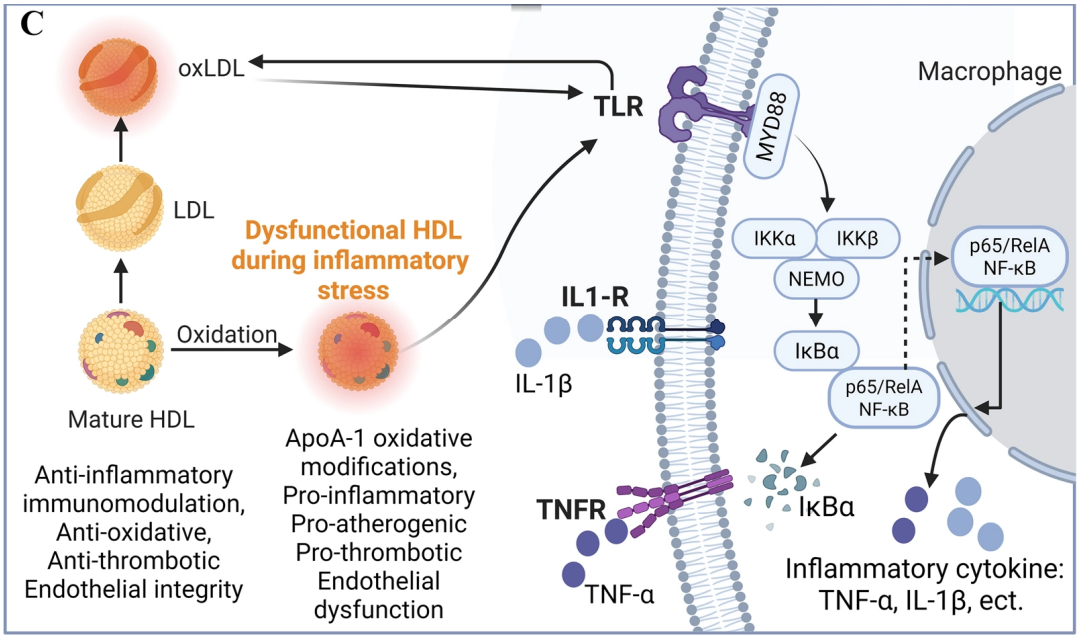


Figure 1. Inflammation-induced HDL dysfunction and amplification of NF-κB signaling. Adapted from Fang et al. [12] (CC BY 4.0).

2.3. Therapeutic Relevance of the Lipid-Inflammation Axis

The therapeutic relevance of the lipid-inflammation axis extends beyond circulating cholesterol concentrations. Lipid availability influences membrane organization and cellular energetics, while the mevalonate pathway supplies isoprenoid intermediates required for small-GTPase signaling. Interventions that alter these processes can affect immune-cell behavior as well as hepatic lipid handling [5,8,17]. The clinically relevant issue is not whether an effect can be demonstrated in vitro, but whether it occurs at achievable exposure and improves outcomes that matter to patients.

Immune-cell activation changes lipid requirements, but these requirements vary with cell type, nutrient availability, and tissue context. Effector T-cell expansion often involves increased lipid synthesis, whereas regulatory T-cell metabolism is more heterogeneous than a simple fatty-acid-oxidation classification implies. In macrophages, altered cholesterol synthesis, trafficking, and efflux can influence lipid accumulation and inflammasome activity. Synovial fibroblast metabolism provides another potential link between inflammation and tissue injury. These observations identify candidate mechanisms, not a uniform metabolic program across all rheumatic diseases [5,6,8,18,19].

3. Pleiotropic Anti-Inflammatory Potential of Lipid-Lowering Agents

3.1. Statins

Statins inhibit HMG-CoA reductase, reducing cholesterol synthesis and mevalonate-derived isoprenoid availability. Beyond hepatic LDL-C lowering, experimental studies describe changes in immune-cell activation, antigen presentation, adhesion, and cytokine signaling. These effects depend on the agent, concentration, and experimental system. Reduced prenylation of small GTPases and changes in membrane cholesterol provide distinct candidate mechanisms. Mevalonate or isoprenoid rescue, exposure measurements, and lipid-matched comparators are needed to separate these mechanisms from nonspecific cellular effects [17,20–22].

In RA, selected randomized trials and pooled analyses report improvement in DAS28 and inflammatory markers with statin treatment, although trial sizes, regimens, and effect estimates vary. TARA provided evidence of an adjunctive disease-activity benefit, whereas TRACE RA primarily addressed cardiovascular prevention and was limited by early termination and a lower-than-expected event rate. These outcomes should be interpreted separately: improvement in a rheumatic activity measure does not establish cardiovascular event reduction, and observational vascular associations do not establish an anti-inflammatory indication [7,23–25].

3.2. Cholesterol Absorption Inhibitors and ATP Citrate Lyase Inhibitors

Ezetimibe inhibits Niemann-Pick C1-like protein 1 (NPC1L1)-dependent intestinal cholesterol absorption. Experimental identification of NPC1L1 supports this target, while clinical use as additional LDL-C-lowering

therapy is grounded in cardiovascular prevention guidance. Ezetimibe does not directly inhibit the mevalonate pathway, making comparisons that achieve similar LDL-C reduction informative for testing whether statin-associated immune effects are pathway-specific [26–28].

Bempedoic acid inhibits ATP citrate lyase and reduces hepatic cholesterol synthesis upstream of HMG-CoA reductase. Its tissue-selective activation limits activation in skeletal muscle. Cardiovascular trials in statin-intolerant populations report LDL-C and hs-CRP reductions and cardiovascular benefit in selected settings; these findings do not establish improvement in rheumatic synovitis. Fixed-dose combination studies provide evidence for bempedoic acid plus ezetimibe [29–35].

3.3. Fibrates and Omega-3 Polyunsaturated Fatty Acids

Fibrates activate peroxisome proliferator-activated receptor-alpha (PPARα) and remain principally indicated for hypertriglyceridemia. Although experimental studies suggest suppression of NF-κB-dependent transcription [36–39], evidence for clinically relevant anti-inflammatory activity in rheumatic disease is limited. The risk of muscle toxicity increases with statin-fibrate combinations, advanced age, and renal impairment; renal function and concomitant treatment should therefore guide agent and dose selection [40–42].

Eicosapentaenoic acid and docosahexaenoic acid remodel membrane fatty-acid composition, reduce arachidonic-acid availability for proinflammatory mediator synthesis, and serve as substrates for specialized pro-resolving mediators [8,43–47]. Effects on macrophage inflammatory programs have also been described, although binary M1/M2 classifications do not capture the diversity of macrophage states in human tissue. In RA, pooled data suggest a modest reduction in tender-joint counts, whereas effects on CRP and DAS28 are inconsistent. Omega-3 fatty acids are therefore best considered a possible adjunct for selected symptoms, with formulation and outcome-specific evidence [48–51]. The biosynthetic pathways linking arachidonic acid, EPA, and DHA to specialized pro-resolving mediators are summarized in Figure 2 [52].

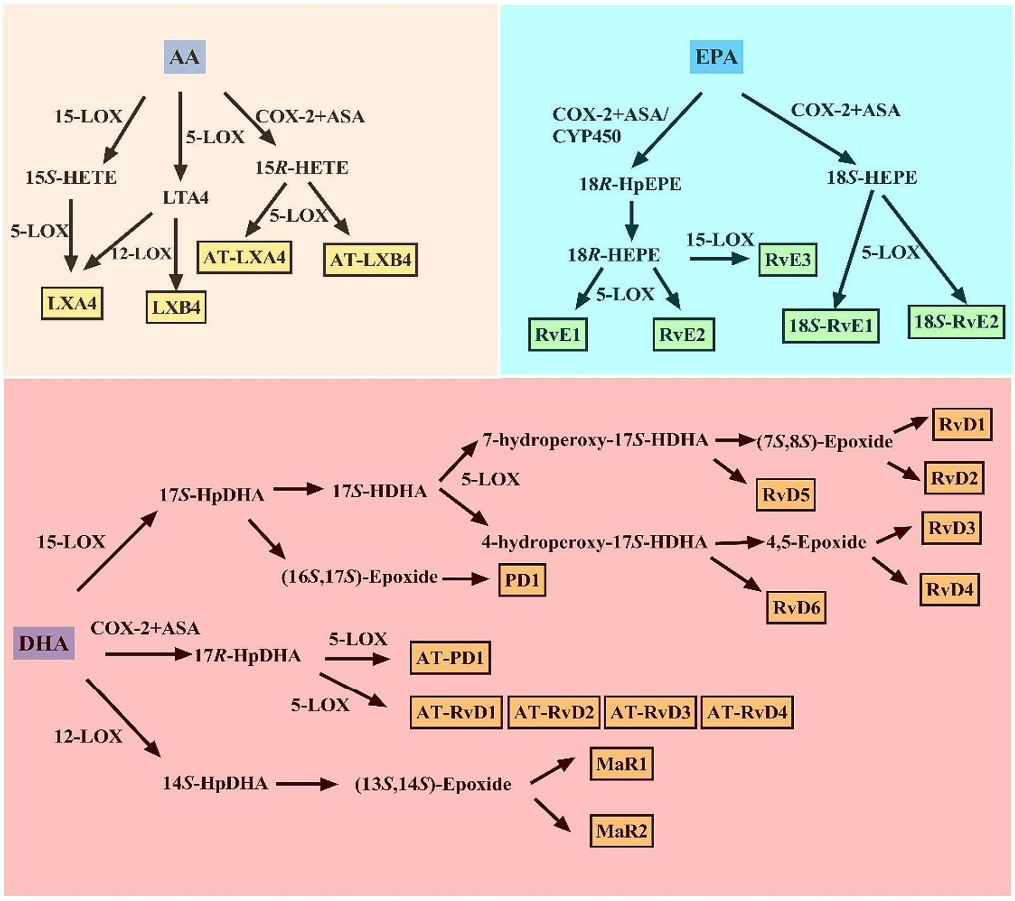


Figure 2. Biosynthesis of specialized pro-resolving mediators from omega-3 and omega-6 polyunsaturated fatty acids. Reproduced from Liu et al. [52] (CC BY 4.0). AA, arachidonic acid; ASA, acetylsalicylic acid; COX, cyclooxygenase; CYP450, cytochrome P450; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; LOX, lipoxygenase; LX, lipoxin; MaR, maresin; PD1, protectin D1; Rv, resolvin; SPM, specialized pro-resolving mediator.

3.4. New Targeted Lipid-Lowering Therapies

PCSK9 monoclonal antibodies and small interfering RNA agents such as inclisiran increase hepatic LDLR availability and lower LDL-C. They act at different steps: antibodies inhibit extracellular PCSK9, whereas inclisiran reduces hepatic PCSK9 synthesis. Experimental studies implicate PCSK9 in inflammatory pathways beyond LDLR, including Syk-PKCδ-NF-κB signaling in atherosclerosis models. A multicenter prospective cohort study involving 89 patients with RA and 50 healthy controls associated circulating PCSK9 with disease activity and the Th17/Treg ratio; reductions during csDMARD treatment were associated with better treatment outcomes. These observational findings do not establish the therapeutic efficacy of PCSK9 inhibition or its effects on synovial pyroptosis. A FOURIER subgroup analysis informs cardiovascular outcomes in participants with autoimmune or inflammatory conditions; it does not establish control of rheumatic disease activity. The RA-rat atrial-remodeling study is retained as preclinical evidence [53–59]. The canonical effect of PCSK9 on LDLR recycling is illustrated in Figure 3 [54].

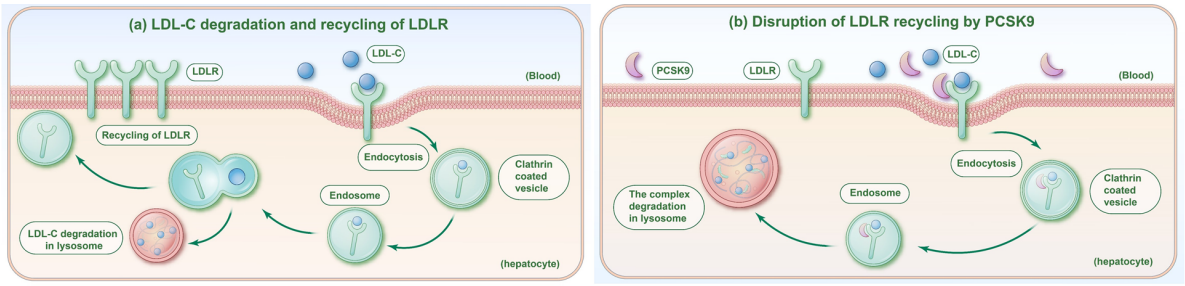


Figure 3. LDLR recycling in the absence of PCSK9 and disruption of LDLR recycling by PCSK9. Adapted from Bao et al. [54] (CC BY 4.0).

Lipoprotein(a)-directed RNA therapies and ANGPTL3-directed therapies address distinct targets. The phase 2 olpasiran study demonstrated substantial lipoprotein(a) lowering in patients with cardiovascular disease; dedicated rheumatic-disease efficacy remains unestablished [60]. Evinacumab targets ANGPTL3 and lowers LDL-C through an LDLR-independent pathway in homozygous familial hypercholesterolemia, whereas zodasiran is an RNA interference therapy targeting ANGPTL3 studied in mixed hyperlipidemia. The evinacumab studies inform ANGPTL3-directed treatment [61–65].

Representative clinical studies are summarized in Table 1.

Table 1. Representative clinical studies of lipid-lowering and lipid-modifying interventions in rheumatic immune-mediated diseases.

Study	Population	Intervention and Follow-Up	Clinical Focus	Main Finding and Limitation
Trial of Atorvastatin in Rheumatoid Arthritis (TARA) [24]	RA; n = 116	Atorvastatin 40 mg vs. placebo; 6 months	Disease activity and inflammation	Modest improvement in DAS28, CRP and ESR; small, short trial.
Trial of Atorvastatin for the Primary Prevention of Cardiovascular Events in Patients with Rheumatoid Arthritis (TRACE RA) [25]	RA; n = 3002	Atorvastatin 40 mg vs. placebo; median 2.5 years	Major cardiovascular events	LDL-C reduction and acceptable safety; event reduction was not statistically significant after early termination and a low event rate.
Lupus Atherosclerosis Prevention Study (LAPS) [66]	Adult SLE; n = 200	Atorvastatin 40 mg vs. placebo; 2 years	CAC, CIMT, plaque and disease activity	No significant effect on subclinical atherosclerosis or SLE activity.
Atherosclerosis Prevention in Pediatric Lupus Erythematosus (APPLE) [67]	Pediatric SLE; n = 221	Atorvastatin vs. placebo; 36 months	CIMT progression	Primary CIMT endpoint was negative; LDL-C and hs-CRP decreased, and treatment was well tolerated.
Rajaei et al. [68]	Active RA receiving DMARDs; n = 60	Omega-3 fatty acids vs. placebo; 12 weeks	Disease activity, joint symptoms and analgesic use	Several clinical measures improved; interpretation is limited by the small, short, single-center design.

Abbreviations: APPLE, Atherosclerosis Prevention in Pediatric Lupus Erythematosus; CAC, coronary artery calcium; CIMT, carotid intima-media thickness; CRP, C-reactive protein; DAS28, Disease Activity Score in 28 joints; DMARDs, disease-modifying antirheumatic drugs; ESR, erythrocyte sedimentation rate; hs-CRP, high-sensitivity C-reactive protein; LAPS, Lupus Atherosclerosis Prevention Study; LDL-C, low-density lipoprotein cholesterol; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; TARA, Trial of Atorvastatin in Rheumatoid Arthritis; TRACE RA, Trial of Atorvastatin for the Primary Prevention of Cardiovascular Events in Patients with Rheumatoid Arthritis.

4. Core Molecular and Cellular Mechanisms Linking Lipid Metabolism to Inflammation in Rheumatic Immune-Mediated Diseases

4.1. Remodeling of Lipoprotein Structure and Transport by Chronic Inflammation

Inflammation changes hepatic lipoprotein production, acute-phase remodeling, and peripheral cholesterol transport. The direction and magnitude depend on the cytokine milieu, cell type, and disease stage; IL-6 and type I interferon should not be assigned a single universal effect on HMG-CoA reductase or ATP-binding cassette transporter A1 (ABCA1). Renal disease and glucocorticoid exposure add further metabolic pressure. Experimental studies illustrate this context dependence: SCAP-SREBP2 signaling integrates cholesterol biosynthesis with NLRP3 activation in macrophages, whereas oxysterol-mediated restraint of cholesterol synthesis can limit AIM2 inflammasome activation [6,8,69].

Lipoprotein function may be as relevant as concentration. Native HDL participates in cholesterol efflux and antioxidant defense, whereas inflammation-associated remodeling may impair these functions. Modified LDL can be internalized through scavenger receptors, promoting lipid accumulation and inflammatory responses in vascular macrophages. These observations help explain the lipid paradox, but the relative contributions of these mechanisms to synovial injury require disease- and tissue-specific evidence [4,5,8,70].

4.2. Dynamic Membrane Nanodomains and Lipid-Dependent Immune Signaling

Membrane cholesterol influences receptor organization as well as cellular lipid stores. Lipid rafts are dynamic, heterogeneous cholesterol- and sphingolipid-enriched membrane nanodomains, not fixed structures with stable boundaries. Their assembly and remodeling depend on lipid composition, protein interactions, and the cytoskeleton. They can regulate the proximity of receptors, kinases, and adaptor proteins, thereby altering signaling thresholds and the duration of immune responses. Experimental reconstitution and T-cell studies show that cholesterol and sphingomyelin support T-cell receptor (TCR) nanoclustering; altered raft composition and aggregation have also been observed in T cells from patients with SLE [71,72].

Membrane cholesterol provides one pharmacological link between lipid lowering and immune signaling. By inhibiting cholesterol synthesis, statins can alter the cholesterol available to membrane domains, affecting receptor organization and signaling-protein recruitment in experimental systems. In T cells obtained from patients with SLE, atorvastatin altered the raft-associated distribution of Lck and CD45, reduced active Lck, and inhibited Lck recruitment to the immunological synapse while restoring ERK phosphorylation after stimulation. This ex vivo study connects a specific drug to abnormal raft-associated signaling in a rheumatic disease, although its findings do not establish clinical suppression of lupus activity [73].

Isoprenoid depletion constitutes a separate mechanism. Inhibition of the mevalonate pathway reduces the availability of farnesyl pyrophosphate and geranylgeranyl pyrophosphate, substrates required for the prenylation of small GTPases such as Ras, Rho, and Rac. Altered membrane localization and function of these signaling proteins can affect immune-cell activation and migration independently of changes in raft cholesterol. Cholesterol-dependent membrane effects and prenylation-dependent signaling should therefore be evaluated in separate rescue experiments, using cholesterol replenishment and appropriate isoprenoid intermediates alongside viability and exposure controls [17,20,22].

EPA and DHA provide another drug- and nutrient-related route to membrane remodeling. In Jurkat T cells, EPA treatment enriched polyunsaturated fatty acids in isolated raft lipids and displaced Lck and the linker for activation of T cells (LAT), supporting a role for altered lipid composition in protein partitioning [74]. In EL4 cells, DHA reduced raft clustering and increased domain size, whereas EPA did not reproduce these particular changes, demonstrating that the two fatty acids need not have identical effects [75]. In CD4+ T cells from n-3-PUFA-enriched fat-1 mice, increased membrane order at the immunological synapse coexisted with reduced recruitment of PKCθ, PLCγ1, and F-actin and reduced proliferation [76]. These findings favor remodeling of domain composition, organization, and signaling over a uniform model of raft depletion.

The membrane effects of statins and EPA/DHA are thus mechanistically distinct and depend on cell type, lipid composition, exposure, and the experimental readout. Detergent-resistant fractions provide biochemical evidence but should be interpreted with imaging of intact membranes, functional signaling assays, and viability controls. Establishing clinical relevance in RA or SLE requires evidence that these changes occur at achievable exposure and accompany validated disease outcomes [73–76].

4.3. A Feed-Forward Lipid-Inflammation Loop Links Joint and Vascular Injury

A reciprocal circuit emerges when inflammation perturbs lipid handling and the resulting lipid signals reinforce immune activation. Macrophage cholesterol homeostasis can influence NLRP3 signaling, while modified lipoprotein uptake and defective efflux contribute to vascular foam-cell formation. These mechanisms are relevant to the joint-vascular connection, but evidence from atherosclerosis models should be distinguished from direct demonstrations in rheumatic synovium. Lowering atherogenic particle exposure and changing immune-cell signaling are related but experimentally separable effects (Figure 4) [5,6,8,12,70].

Adaptive immunity and stromal activation extend this circuit beyond macrophages. T helper 17 (Th17) cells produce IL-17A, whereas regulatory T (Treg) cells contribute to immune restraint; their relative abundance and function vary with disease and treatment. In a small RA study, atorvastatin treatment was associated with increased Treg numbers and suppressive function, providing a clinical-mechanistic signal rather than proof of a general drug-class effect on Th17/Treg balance [77].

Th17 cells also interact directly with synovial fibroblasts. Coculture of primary Th17 cells from patients with early RA with RA synovial fibroblasts increased IL-6, IL-8, MMP-1, and MMP-3 production, while experiments in human RA tissue showed that IL-17A, particularly in combination with other inflammatory cytokines, promotes matrix turnover and cartilage degradation [78,79]. These interactions provide the tissue-level rationale for including Th17/Treg cells, synovial fibroblasts, and matrix metalloproteinases (MMPs) in Figure 4. The figure distinguishes this inflammatory network from established hepatic LDL-C lowering and from experimental membrane effects.

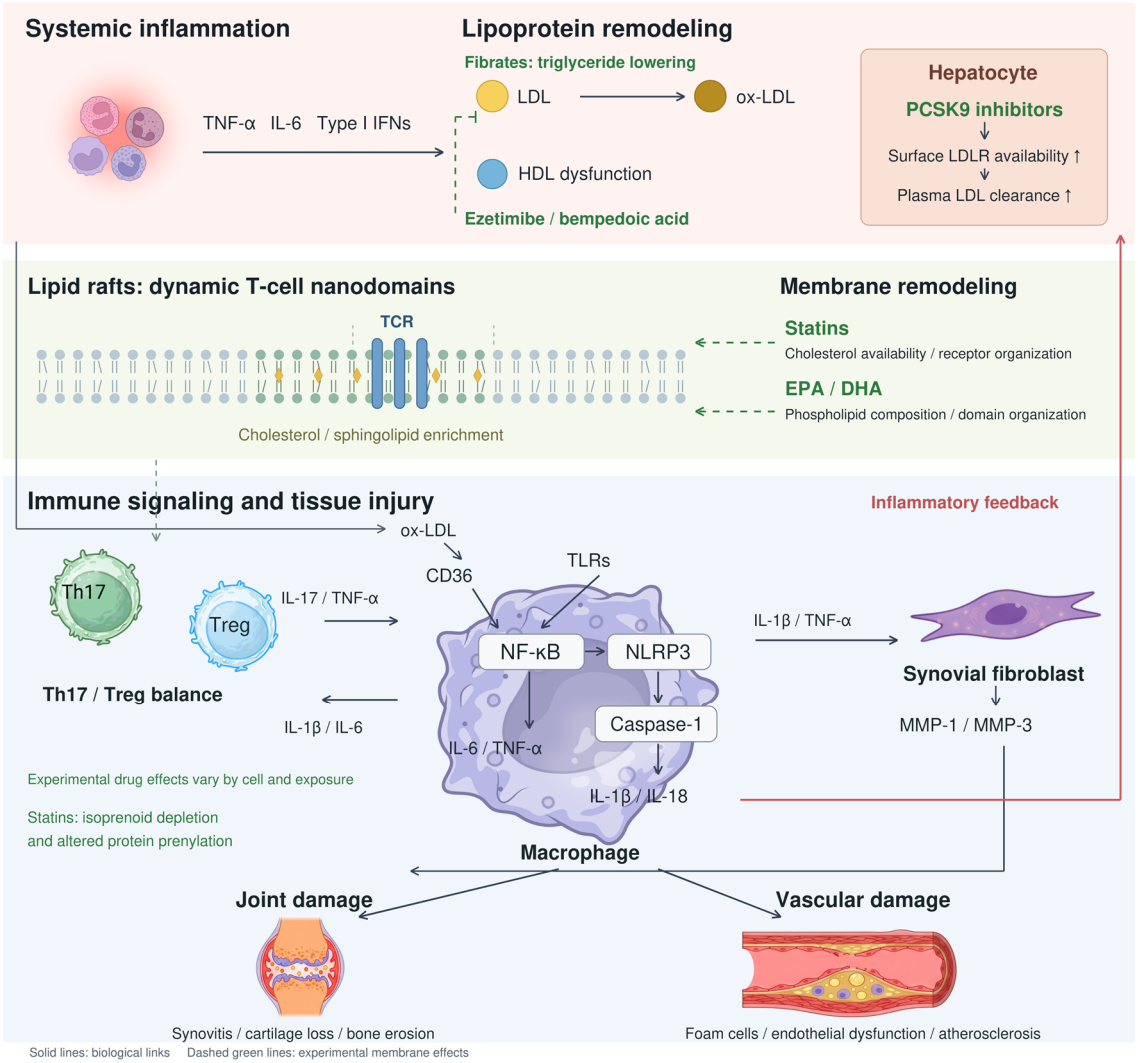


Figure 4. The lipid-inflammation circuit and sites of action of lipid-lowering agents. Original figure created by the authors.

Systemic cytokines promote lipoprotein remodeling and HDL dysfunction. Modified lipids and inflammatory signals engage macrophage CD36-associated lipid uptake, Toll-like receptor signaling, and the NF-κB-NLRP3-

caspase-1 axis. Interactions among macrophages, Th17/Treg cells, and synovial fibroblasts link inflammation and MMP production to joint injury; disturbed lipid handling also contributes to vascular injury. The membrane inset depicts a continuous bilayer with dynamic cholesterol- and sphingolipid-enriched nanodomains and associated T-cell receptors. Statins and EPA/DHA can alter domain organization through distinct experimental mechanisms; statin-associated isoprenoid depletion affects protein prenylation separately. The hepatic branch shows increased surface LDLR availability and plasma LDL clearance with PCSK9 inhibition. Red denotes inflammatory feedback; green denotes drug-related effects, with dashed green arrows identifying experimental membrane effects. Relationships are schematic, not to scale, and do not indicate equivalent clinical anti-inflammatory efficacy across agents.

Abbreviations: CD36, cluster of differentiation 36; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; HDL, high-density lipoprotein; IFNs, interferons; IL, interleukin; LDL, low-density lipoprotein; LDLR, low-density lipoprotein receptor; MMPs, matrix metalloproteinases; NF-κB, nuclear factor-kappa B; NLRP3, NLR family pyrin domain-containing 3; ox-LDL, oxidized LDL; PCSK9, proprotein convertase subtilisin/kexin type 9; TCR, T-cell receptor; Th17, T helper 17; TLRs, Toll-like receptors; TNF-α, tumor necrosis factor-alpha; Treg, regulatory T.

5. Stratified Clinical Evidence for Lipid-Lowering Therapy across Rheumatic Immune-Mediated Diseases

5.1. Rheumatoid Arthritis

RA provides the broadest rheumatic-disease evidence for statins, including TARA, TRACE RA, and pooled analyses. The disease-activity signal from short studies differs from the cardiovascular question examined in longer trials. Observational associations with lower cardiovascular events and mortality are encouraging but remain susceptible to confounding. Lipid treatment selection should therefore integrate established atherosclerotic cardiovascular disease (ASCVD), conventional risk factors, persistent inflammatory burden, and the LDL-C response to tolerated therapy. PCSK9-directed agents are considered according to lipid and cardiovascular indications; a rheumatic disease-modifying indication has not been established [7,16,23–25,57].

5.2. Systemic Lupus Erythematosus

In SLE, cardiovascular prevention should account for nephritis, renal function, glucocorticoid exposure, and conventional risk factors. LAPS and APPLE did not meet their primary vascular surrogate endpoints, and pooled studies did not show a consistent SLE disease-activity benefit, despite lipid reductions. This favors individualized risk-based treatment rather than statin initiation solely for lupus activity [1,66,67,80,81]. Drug-target Mendelian randomization associated genetically proxied PCSK9 inhibition with lower SLE risk in a European dataset but not an East Asian dataset. Ancestry, instrument validity, and the difference between lifelong genetic exposure and drug treatment limit therapeutic interpretation [82].

5.3. Spondyloarthritis and Psoriatic Arthritis

Spondyloarthritis and psoriatic arthritis frequently coexist with obesity, insulin resistance, hypertension, and dyslipidemia, creating a cardiovascular burden that cannot be attributed to inflammation alone [10,11,83–86]. Studies of statins and other lipid-modifying interventions are largely observational, include heterogeneous populations, and rarely incorporate imaging or validated musculoskeletal outcomes. A small fall in CRP should not be taken as evidence of improvement in enthesitis, axial inflammation, or structural progression.

In spondyloarthritis and psoriatic arthritis, management combines control of inflammation with assessment of obesity, hypertension, insulin resistance, and dyslipidemia. Lipid-lowering treatment is selected according to cardiovascular risk and response; CRP changes should be considered separately from enthesitis, axial inflammation, function, or structural progression. Disease-specific treatment effects of statins or omega-3 supplementation remain insufficiently characterized [10,11,16,87,88].

5.4. Systemic Vasculitis and Sjögren's Syndrome

For systemic vasculitis and Sjögren's syndrome, intervention evidence is particularly sparse and derives mainly from single-center cohorts and retrospective analyses [89–92]. Immune-mediated inflammation of the vessel wall is mechanistically distinct from lipid-driven atherosclerosis, although the two may coexist. Cardiovascular and metabolic comorbidity are increasingly recognized in Sjögren's syndrome [93–97], but this recognition has not yet translated into robust trials of lipid-lowering therapy.

Statins remain appropriate when dyslipidemia or cardiovascular risk warrants treatment, but available data do not show suppression of primary vasculitic inflammation or Sjögren's disease activity. Lipid management should follow general prevention principles, while disease-specific immunosuppression is selected independently [1,89,90,93–95,98].

5.5. Evidence Base and Clinical Framework for Lipid-Lowering Interventions in Rheumatic Immune-Mediated Diseases

5.5.1. Interpreting the Evidence across Diseases

Evidence varies markedly by drug class, disease, and outcome. Statins in RA have been examined in randomized trials, observational cohorts, and meta-analyses; SLE trials have focused largely on lipid levels, disease activity, and surrogate vascular measures, with several neutral results. For spondyloarthritis, vasculitis, and Sjögren's syndrome, most inferences remain observational or are extrapolated from cardiovascular populations [1,7,16,23–25,66,67,81,89]. A mechanistic experiment, a short biomarker trial, and a cardiovascular outcome study answer different questions and should not carry equal evidential weight.

Cell and animal models are valuable for dissecting lipid-immune pathways, but the concentrations used in vitro may not be clinically attainable. Mevalonate-rescue experiments and parallel comparators can strengthen causal inference and help separate vascular from synovial mechanisms [5,6,8,17,19]. Genetic approaches such as drug-target Mendelian randomization provide another layer of evidence, but their validity depends on instrument specificity, ancestry, colocalization, and the assumption that lifelong genetic exposure approximates pharmacological treatment [82].

Clinical studies differ in size, duration, comparator, and outcome selection. Future trials should specify whether the primary objective is LDL-C control, rheumatic disease activity, or cardiovascular events. Trials testing immune effects should include validated disease-activity measures and, when appropriate, joint imaging, tissue markers, or functional lipoprotein assays. Comparators achieving similar LDL-C reduction through different targets would help separate drug-specific effects from lipid-mediated benefit. Longer follow-up and reporting of neutral outcomes are needed; the cardiovascular findings of FOURIER should not be used as evidence of rheumatic efficacy [24,25,57,66,67].

Representative pooled analyses are summarized in Table 2; standardized and raw mean differences should not be compared as equivalent scales.

Table 2. Representative systematic reviews and meta-analyses of lipid-modifying interventions in rheumatic immune-mediated diseases.

Review	Evidence Base	Intervention	Key Pooled Result	Main Limitation
Li et al. [7]	RA; 15 RCTs	Statins, predominantly atorvastatin	DAS28: SMD −2.001 (95% CI −3.191 to −0.811); CRP: SMD −3.033 (−4.460 to −1.606); ESR: SMD −2.097 (−3.408 to −0.786). SMDs are unitless, not DAS28 points or laboratory units.	Variation in regimens and trial characteristics; large standardized effects require cautious interpretation and are not directly comparable with raw changes in TARA.
Rahmadi et al. [23]	RA; 6 studies; n = 40,307	Statin exposure	Lower MACE: OR 0.67 (95% CI 0.51–0.89); lower mortality: OR 0.73 (95% CI 0.62–0.88). These are the pooled estimates reported by the review.	Only one RCT; pooled estimates were driven mainly by observational studies.
Artola et al. [81]	SLE; 8 studies; n = 814	Statins	TC: MD −23.48 mg/dL (95% CI −34.57 to −12.39); LDL-C: MD −20.70 mg/dL (−30.51 to −10.89); hs-CRP: MD −0.40 mg/dL (−0.64 to −0.16). No SLEDAI benefit.	Mixed designs and follow-up ranging from 1 month to 7 years.
Wang et al. [49]	RA; 18 RCTs; n = 1018	Omega-3 supplementation	TG: SMD −0.47 (95% CI −0.78 to −0.16); tender-joint count: SMD −0.59 (−0.79 to −0.39). DAS28, CRP, and ESR were not significantly reduced.	Dose, formulation and treatment duration varied across trials.
Sigaux et al. [51]	Inflammatory rheumatic diseases; 30 RCTs; n = 1420	Oral n-3 or n-6 PUFA supplementation	Pain, joint counts, DAS28, HAQ and ESR improved; CRP did not. Most evidence came from RA.	Substantial clinical diversity; few trials in diseases other than RA.

Abbreviations: CI, confidence interval; CRP, C-reactive protein; DAS28, Disease Activity Score in 28 joints; ESR, erythrocyte sedimentation rate; HAQ, Health Assessment Questionnaire; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; MACE, major adverse cardiovascular events; MD, mean difference; n-3, omega-3; n-6, omega-6; OR, odds ratio; PUFA, polyunsaturated fatty acid; RA, rheumatoid arthritis; RCT, randomized controlled trial; SLE, systemic lupus erythematosus; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index; SMD, standardized mean difference; TC, total cholesterol; TG, triglycerides.

5.5.2. Safety and Boundaries of Clinical Use

Muscle symptoms require a structured differential diagnosis because rheumatic disease, statin-associated muscle symptoms (SAMS), glucocorticoid myopathy, thyroid disease, strenuous exercise, and drug interactions can overlap. Assessment should establish the timing relative to statin initiation or dose escalation, the distribution of pain, objective proximal weakness, creatine kinase (CK), renal function, and features of rheumatic disease activity. SAMS commonly involve symmetrical proximal muscle discomfort and can occur with normal CK. Synovitis, enthesitis, disease-specific organ activity, or a compatible inflammatory myopathy phenotype favor alternative or concurrent explanations; CRP or ESR alone is not diagnostic [42,99].

When clinically appropriate, a supervised statin interruption and subsequent rechallenge can clarify temporal causality. Severe weakness, marked CK elevation, or renal injury warrants prompt assessment rather than routine rechallenge. Persistent proximal weakness and CK elevation after statin withdrawal raise concern for immune-mediated necrotizing myopathy; anti-HMGCR testing and specialist assessment, including imaging or biopsy when indicated, can help distinguish this condition from self-limited toxicity. Confirmed intolerance can be managed with a tolerated statin regimen and additional non-statin therapy according to cardiovascular risk [27,28,99,100].

Cardiovascular risk and the required LDL-C reduction guide treatment intensity. Patients with ASCVD generally require intensive therapy, while primary prevention incorporates age, renal disease, conventional risk factors, and inflammatory burden. The disease-specific framework in Table 3 uses ESC/EAS risk-based LDL-C goals; these are not separate targets validated specifically for RA, SLE, or spondyloarthritis. Statin intensity, non-statin additions, and follow-up should reflect response, tolerability, renal or hepatic function, and interactions. Fibrates primarily address hypertriglyceridemia, and prescription omega-3 indications should be distinguished from supplements studied for joint symptoms. Pregnancy and lactation require agent-specific specialist assessment [1,16,27,28,101,102].

Table 3. Risk-based clinical framework for lipid-lowering therapy in rheumatic immune-mediated diseases.

Disease Context	When to Initiate or Intensify	LDL-C Goal	Selection and Adjustment
Rheumatoid arthritis	Assess at diagnosis and reassess with changes in disease activity or treatment. Start promptly for established ASCVD; in primary prevention, use overall cardiovascular risk and persistent inflammation.	Use the common risk-based goals below; RA alone does not define a separate LDL-C target.	Use an appropriate tolerated statin intensity. Add ezetimibe and consider PCSK9-directed therapy if the goal remains unmet in an eligible high-risk patient. Review muscle symptoms and interactions.
Systemic lupus erythematosus	Assess cardiovascular risk with nephritis, renal impairment, blood pressure, glucocorticoid exposure, and conventional factors. Initiate for cardiovascular indications, not lupus activity alone.	Use the common risk-based goals below; renal disease may change risk classification.	Adjust agent or dose for renal/hepatic function and interactions. Discuss reproductive plans. Escalate non-statin treatment according to LDL-C response and eligibility.
Spondyloarthritis and psoriatic arthritis	Assess cardiovascular risk together with obesity, hypertension, diabetes, smoking, and disease activity. Initiate or intensify according to cardiovascular indication.	Use the common risk-based goals below; no validated disease-specific target.	Select statin intensity by required LDL-C reduction and tolerance. Add non-statin therapy if needed; assess musculoskeletal activity separately from lipid response.

Framework adapted from EULAR recommendations and ESC/EAS guidance [1,16,27,28]. Common ESC/EAS goals: very high risk, LDL-C <1.4 mmol/L (<55 mg/dL) and ≥50% reduction from baseline; high risk, <1.8 mmol/L (<70 mg/dL) and ≥50% reduction; moderate risk, <2.6 mmol/L (<100 mg/dL); low risk, <3.0 mmol/L (<116 mg/dL). These are cardiovascular risk-category goals, not treatment thresholds or disease-specific trial targets. Reassess lipids after initiation or dose change, generally within 8 ± 4 weeks, and individualize thereafter. Intensity and product-specific dosing should follow local labeling, organ function, interactions, and tolerability. ASCVD, atherosclerotic cardiovascular disease; LDL-C, low-density lipoprotein cholesterol.

6. Conclusions and Perspectives

The lipid paradox highlights why lipid concentrations must be interpreted in the context of inflammation, lipoprotein function, and overall cardiovascular risk. Lipid-lowering agents address different nodes in a reciprocal lipid-inflammation circuit, but their established vascular actions and candidate immune effects have different evidential foundations. Statins provide the most developed rheumatic-disease evidence, with variable findings across RA and SLE; newer agents offer effective lipid lowering but have limited direct evidence for rheumatic outcomes [4,7,8,24,57,66,67,81].

The practical implication is integrated care: assess cardiovascular risk alongside rheumatic disease activity, select a tolerated lipid-lowering regimen to achieve the relevant LDL-C goal, and monitor outcomes appropriate to each treatment objective. Research should prioritize whether molecular effects occur at clinically achievable

exposures and translate into meaningful tissue or patient benefit. Lipid-matched comparative trials, disease-specific stratification, functional lipoprotein measurements, and paired rheumatic and cardiovascular endpoints would help distinguish these effects. Multicenter studies of PCSK9-directed and other emerging therapies, with attention to ancestry, renal disease, and background treatment, are needed to identify reproducible benefits and the patients most likely to obtain them [1,16,27,28,59,82].

Lipid-lowering agents should serve as adjunctive therapies within comprehensive rheumatic-disease care, prescribed according to lipid and cardiovascular indications, and must never replace anti-inflammatory or disease-modifying antirheumatic treatment.

Author Contributions

L.W.: conceptualization, investigation, writing—original draft preparation; Y.W.: investigation, data curation, visualization, writing—original draft preparation; B.Z.: investigation, writing—review and editing; M.W.: conceptualization, supervision, writing—review and editing; F.L.: conceptualization, supervision, writing—review and editing. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest

The authors declare no conflict of interest.

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During the preparation of this work, the authors used ChatGPT (OpenAI) to assist with language editing and manuscript preparation. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

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