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ORIGINAL ARTICLE

Statins beyond Lipid Lowering: A Narrative Review of Their Pleiotropic Anti-inflammatory Mechanisms through Lipid Metabolism, Immune Modulation, and Cell Signaling

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KEYWORDS

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ABSTRACT: Statins, primarily known for their lipid-lowering properties, have emerged as significant agents in the field of anti-inflammatory and immunomodulatory therapies. This paper explores the pleiotropic effects of statins, which extend beyond cholesterol reduction, contributing to cardiovascular protection and potential therapeutic applications in various inflammatory and autoimmune diseases. The mechanisms by which statins exert these effects include the inhibition of isoprenoid-dependent signaling pathways, modulation of cytokine production, enhancement of endothelial function, and attenuation of immune cell activation. These actions are particularly relevant in conditions characterized by chronic inflammation, such as multiple sclerosis (MS) and neurodegenerative disorders. Research indicates that statins may mitigate the progression of MS, a disease marked by inflammation and myelin damage in the central nervous system, potentially offering protective benefits through their anti-inflammatory properties. Furthermore, studies have shown that statins can cross the blood-brain barrier, making them candidates for reducing neuroinflammation and delaying cognitive decline in diseases like Alzheimer's and Parkinson's. The findings suggest that statins could play a crucial role in managing not only cardiovascular diseases but also a range of inflammatory conditions, warranting further investigation into their full therapeutic potential beyond dyslipidemia. In conclusion, while statins are primarily prescribed for lowering cholesterol, their diverse mechanisms of action highlight their value in preventing and treating inflammatory conditions. This paper emphasizes the need for continued research to fully

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understand the implications of statins in various clinical settings, particularly in the context of chronic inflammatory diseases and neurodegenerative disorders'

INTRODUCTION

Statins are commonly used to manage high cholesterol and help prevent heart disease. They work by blocking an enzyme your body needs to make cholesterol, especially lowering the bad kind called LDL cholesterol[1]. There's solid evidence that statins can decrease the chances of heart events like heart attacks and strokes, mainly by reducing cholesterol levels. Statins demonstrate multifaceted anti-inflammatory effects by influencing immune responses, modifying the movement of leukocytes, and changing cellular signaling pathways. They affect lipid metabolism, boost nitric oxide synthesis, and control adhesion molecules, which leads to diminished inflammation and supports vascular integrity in different circumstances[2,3].

Although statins offer notable anti-inflammatory effects, some research indicates possible adverse effects, including myopathy and changes in inflammation status due to cholesterol reduction, highlighting the necessity for careful evaluation in clinical settings.

Studies have shown that statins might do more than just lower cholesterol. They appear to have anti-inflammatory properties, meaning they can help reduce inflammation. Research, including observational studies and clinical trials, indicates that statins can lower inflammation markers, stabilize plaque in arteries, and affect immune system responses, even when cholesterol levels don't change[4]. For example, the JUPITER trial found that people with high blood marker levels called hs-CRP but normal LDL cholesterol still benefited from statins, pointing to their potential anti-inflammatory effects. Some evidence suggests that statins may help with various inflammatory and autoimmune diseases like rheumatoid arthritis and multiple sclerosis[5, 6].

This article will examine how statins may help reduce inflammation, alter specific cellular processes, and their potential roles in diseases beyond cholesterol management.

Lipid metabolism

Lipid metabolism encompasses the creation and breakdown of primary lipid types, such as fatty acids, triacylglycerols, phospholipids, and isoprenoids regulated by acetyl-CoA[7]. It also involves cholesterol metabolism, an essential factor in cardiovascular disease, and the production of ketone bodies. In insects, lipid metabolism plays a vital role in development, reproduction, and other functions, mainly in the fat body. This process includes lipogenic and lipolytic enzymes, hormones, and transcription factors, making it a key focus for pest control methods. It is also a complex mechanism crucial for sustaining physiological functions. Disruptions in lipid metabolism can result in several diseases, including intervertebral disc degeneration (IDD), by facilitating the breakdown of the extracellular matrix, promoting cell death, and causing inflammation, ultimately contributing to IDD's development[8].

Lipid metabolism involves lipid biosynthesis and degradation, including fatty acid metabolism, triglyceride metabolism, and cholesterol metabolism. Key pathways include WNT-b-catenin and HIF12, regulating lipid synthesis, storage, and apoptosis, significantly impacting tumor growth and progression[9].

It involves multiple signaling pathways that generate bioactive lipid molecules, such as fatty acids and eicosanoids. These regulate cellular processes including growth, apoptosis, inflammation, and chemotherapy, ultimately influencing cancer therapy and drug resistance[10].

Functions of lipid metabolism

Energy Reserves: Lipids are efficient energy stores vital for cellular activities and survival [11]. Membrane Integrity: Lipids are essential elements of cell membranes, playing a key role in maintaining membrane fluidity and stability [11,12].

Signaling Agents: Different lipids are signaling agents, affecting inflammation and programmed cell death[11].

Lipid metabolism and cancer

Tumor Development: Changes in lipid metabolism are characteristic of cancer, facilitating tumor development and spread through increased fat uptake and storage [10].

Statins

Statins, or HMG-CoA reductase inhibitors, are primarily known for their cholesterol-lowering effects, significantly impacting cardiovascular disease management. They reduce total cholesterol and LDL levels and exhibit pleiotropic effects that contribute to cardiovascular protection beyond lipid regulation[14]. This multifaceted action includes improving endothelial function, reducing inflammation, and stabilizing atherosclerotic plaques, collectively lowering morbidity and mortality rates associated with atherosclerotic cardiovascular disease (ASCVD)[15]. Statins are cholesterol-lowering drugs that act as enzyme inhibitors, crucial in managing coronary heart disease. Notable examples include atorvastatin and simvastatin, which generated significant revenues in 2002, highlighting their dominance in the pharmaceutical market for cholesterol-lowering medications[16].

Statins work by inhibiting HMG-CoA reductase, which decreases cholesterol production and increases LDL receptor expression, reducing circulating LDL levels. They also influence the metabolism of isoprenoid intermediates, essential for activating signaling proteins like Ras and Rho, involved in multiple cellular functions. Statins display immunomodulatory properties by affecting the differentiation and functionality of immune cells, subsequently lowering inflammation. They reduce the levels of inflammatory cytokines and improve endothelial function, contributing to vascular health[17,18].

Statins interfere with the prenylation of small GTPases, impacting cell growth and inflammatory responses. They also boost nitric oxide synthase activity while inhibiting the expression of adhesion molecules, which enhances their anti-inflammatory properties[19].

Inhibition of isoprenoid synthesis and GTPase signaling

disorders. Gaining insights into these mechanisms could inform therapeutic approaches.hypochlorite solution for 10 minutes, washed three times with tap water and soaked in distilled water overnight. A planting substrate containing virgin soil(loamy)-sand (1:2 w/w) was used for planting pistachio seeds. Mineral sulfur (Table 1) treatments at three concentrations of 2%, 4% and 8% (w/w) were applied before and after inoculation with *V. dahliae*. Statins inhibit the HMG-CoA reductase enzyme, decreasing not only cholesterol synthesis but also the production of isoprenoid intermediates, such as farnesyl pyrophosphate (FPP) and geranylgeranyl pyrophosphate (GGPP). These molecules are necessary for the prenylation of small GTPases (e.g., Rho, Rac, Ras), which are involved in intracellular signaling cascades that regulate inflammation[20]. By disrupting GTPase function, statins suppress the NF-κB signaling pathway, a key regulator of inflammatory gene transcription. This leads to reduced expression of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6[15, 21].

Statins have various additional effects, including anti-inflammatory, antioxidative, antithrombotic, immunomodulatory, and vascular protective. These additional effects are primarily ascribed to inhibiting FPP and GPP prenylation, which disrupts small GTPases (Ras, Rho, Rac) and related signaling pathways that control inflammation, hypertrophy, and the production of reactive oxygen species (ROS)[19, 22]. Statins are currently being investigated for a range of therapeutic applications beyond treating dyslipidemia, such as in the management of autoimmune diseases, cancer, sepsis, preeclampsia, and heart failure. Notably, in cases of heart failure, whether ischaemic or non-ischaemic, statins may alleviate adverse cardiac remodeling by influencing the behavior of cardiomyocytes and fibroblasts, regardless of cholesterol levels[23, 24].

Though observational and experimental studies, such as those by Correale et al., indicate that lipophilic statins (like atorvastatin) can enhance ventricular function and lower the risk of cardiac death, randomized controlled trials (RCTs) involving hydrophilic statins (such as rosuvastatin in CORONA and GISSI-HF) did not

demonstrate significant improvements in outcomes. This inconsistency may be due to the limited tissue penetration of hydrophilic statins, which hinders their pleiotropic effects within the myocardium. Despite the encouraging findings, statins may also pose certain risks, including mitochondrial myopathy, depletion of selenoproteins, and pro-inflammatory reactions that can arise from excessive reductions in cholesterol. Therefore, additional randomized trials comparing the effects of lipophilic and hydrophilic statins are warranted[25].(Figure 1).

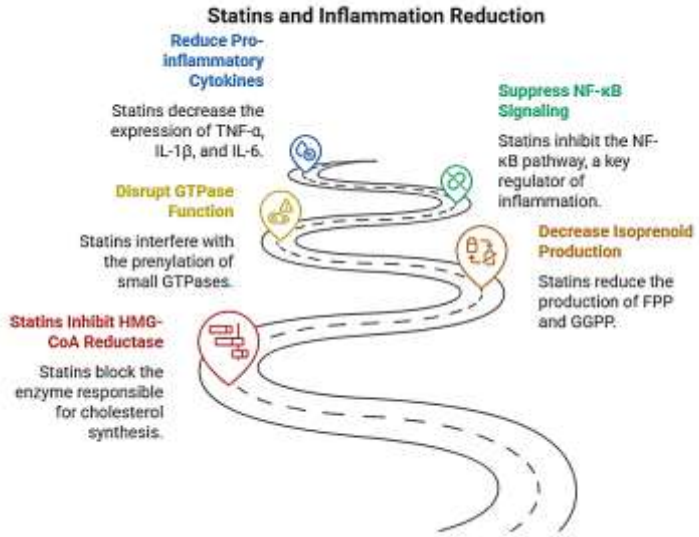

Figure 1. Schematic figure on statins and the reduction of inflammatory pathways.

Enhancement of endothelial function

A key mechanism through which statins exert anti-inflammatory effects is improving endothelial function, a critical factor in maintaining vascular homeostasis and preventing atherogenesis. Endothelial cells line the inner surface of blood vessels and regulate vascular tone, leukocyte adhesion, thrombosis, and barrier integrity. Endothelial dysfunction, characterized by reduced nitric oxide (NO) bioavailability and increased oxidative stress, is an early hallmark of cardiovascular disease and systemic inflammation[26,27].

Upregulation of eNOS and increased NO production

Statins promote the expression and activity of endothelial nitric oxide synthase (eNOS), the enzyme responsible for NO production in endothelial cells. They do this through multiple mechanisms[28]:

-Inhibition of RhoA and upregulation of eNOS mRNA: By inhibiting isoprenoid synthesis and preventing the activation of the small GTPase RhoA, statins promote eNOS expression.

-Activation of PI3K/Akt pathway: Statins enhance Akt-mediated phosphorylation of eNOS, increasing its enzymatic activity.

-Prevention of eNOS uncoupling: Statins help maintain eNOS in its functional dimeric form, preserving NO synthesis[29].

The resulting increase in NO production has several protective effects, such as vasodilation and improved blood flow, inhibition of platelet aggregation, suppression of vascular smooth muscle cell proliferation, and reduction of leukocyte adhesion and transmigration[23, 29].

Reduction of endothelial adhesion molecules

Inflammation induces the expression of adhesion molecules such as VCAM-1, ICAM-1, and E-selectin on endothelial cells, promoting leukocyte adhesion and migration into the vascular wall. Statins inhibit the expression of these molecules by suppressing NF-κB

signaling, thereby attenuating the initial steps of vascular inflammation[30].

Antioxidant effects on the endothelium

Oxidative stress impairs NO signaling by converting NO to peroxynitrite and promoting endothelial dysfunction. Statins reduce reactive oxygen species (ROS) production by inhibiting NADPH oxidase, increase antioxidant enzyme levels, such as superoxide dismutase (SOD) and preserve NO bioavailability by reducing oxidative degradation[31].

Inhibition of endothelial apoptosis

Statins have been shown to protect endothelial cells from apoptosis triggered by oxidized LDL, inflammatory cytokines, or disturbed flow. This cytoprotective effect supports vascular integrity and reduces endothelial activation[32].

Inhibition of cytokine production

Statins have been shown to significantly reduce the expression of several pro-inflammatory cytokines, including: Tumor necrosis factor-alpha (TNF-α), Interleukin-1 beta (IL-1β), Interleukin-6 (IL-6)[34].

These cytokines activate endothelial cells, recruit leukocytes, and amplify the inflammatory cascade. The suppression of cytokine expression by statins occurs through multiple mechanisms: Inhibition of NF-κB activation: Statins interfere with the NF-κB signaling pathway by preventing the prenylation of small GTP-binding proteins (e.g., Rho, Rac). NF-κB is a transcription factor central to the induction of cytokine genes[35]. (Figure 2)

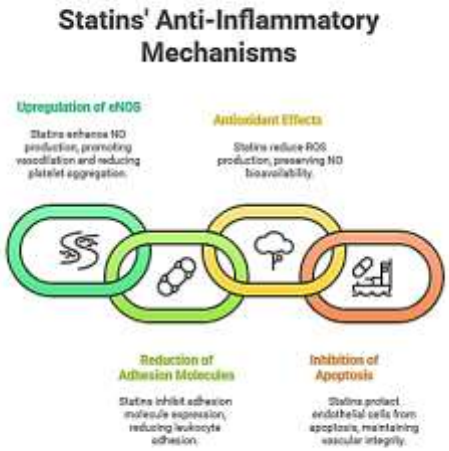

Figure 2. Statins' anti-inflammatory mechanism by upregulating NOS, antioxidant effect, reducing adhesion molecules, and reducing apoptosi

Reduced MAPK pathway signaling: Statins also blunt the mitogen-activated protein kinase (MAPK) pathway, contributing to cytokine gene transcription under inflammatory conditions[27]. These effects have been demonstrated in various cell types, including monocytes, macrophages, endothelial cells, and vascular smooth muscle cells.

Downregulation of chemokine production

Statins also suppress the synthesis of key chemokines, particularly: Monocyte chemoattractant protein-1 (MCP-1/CCL2), IL-8 (CXCL8), and RANTES (CCL5)[36].
These chemokines attract monocytes, neutrophils, and other leukocytes to sites of inflammation, such as atherosclerotic plaques or inflamed tissues. By decreasing chemokine expression, statins limit immune cell infiltration, stabilize plaque, and reduce tissue injury.

Effects in clinical and experimental models

Numerous in vitro studies, animal models, and clinical trials have validated the anti-cytokine effects of statins. In patients with coronary artery disease, statin therapy is associated with reduced serum levels of IL-6 and CRP, independent of lipid lowering. In murine models of arthritis and colitis, statins have shown efficacy in reducing cytokine-driven inflammation[26].

In sepsis and acute respiratory distress syndrome (ARDS) models, statins reduce TNF-α and IL-1β levels and improve outcomes, supporting their systemic immunomodulatory roles. Statins strongly inhibit pro-inflammatory cytokines and chemokines by modulating intracellular signaling pathways such as NF-κB and MAPKs. This suppression limits leukocyte activation and recruitment, reduces tissue inflammation, and contributes to statin therapy's broader anti-inflammatory and plaque-stabilizing effects[36, 37]. (Figure 3)

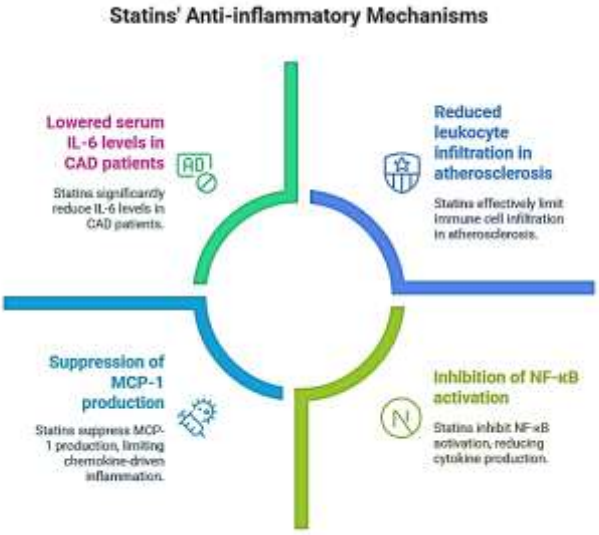

Figure 3. Anti-inflammatory effects of Statins by modulation the cytokines.

Immunomodulatory effects

Statins impact both innate and adaptive immunity. They reduce major histocompatibility complex class II (MHC-II) expression and co-stimulatory molecules (CD80/CD86) on antigen-presenting cells, thereby attenuating T-cell activation[38]. Furthermore, statins:

-Shift T-helper cell responses from Th1/Th17 toward a regulatory T cell (Treg) phenotype

-Inhibit dendritic cell maturation

-Suppress autoimmune reactivity

These immunomodulatory properties have implications for treating multiple sclerosis, rheumatoid arthritis, and systemic lupus erythematosus.

Multiple sclerosis is characterized by immune-mediated demyelination in the central nervous system. Statins can shift T-helper cell responses from a pro-inflammatory Th1 phenotype towards an anti-inflammatory Th2 phenotype, potentially reducing neuroinflammation. Some clinical trials have explored the use of statins as adjunct therapy in MS, with varying outcomes. For instance, a study evaluating rosuvastatin therapy observed changes in gene expression related to immune regulation, suggesting potential benefits[39].

Rheumatoid arthritis involves chronic inflammation of the joints, driven by autoimmune mechanisms. Statins have been shown to reduce levels of pro-inflammatory cytokines such as TNF-α and IL-6, which are central to RA pathogenesis. A meta-analysis indicated that statins are safe in RA patients and may reduce disease activity. Additionally, statin therapy has been associated with a

lower risk of major adverse cardiovascular events in this population[40].

SLE is a systemic autoimmune disease with diverse clinical manifestations. Statins can modulate immune responses by affecting antigen presentation and cytokine production. While some studies suggest that statins may reduce disease activity in SLE, the evidence remains inconclusive. A meta-analysis did not find definitive proof that statins effectively control SLE, highlighting the need for further research[41].

Antioxidant effects

Statins notably raised the levels of the antioxidant enzymes GPx and SOD in the bloodstream, but did not affect catalase levels, among patients with different cardiovascular risk factors. Statins limit oxidative stress by reducing reactive oxygen species (ROS) production and inhibiting NADPH oxidase. This contributes to their ability to stabilize atherosclerotic plaques and prevent endothelial dysfunction, further reinforcing their anti-inflammatory action. In 15 studies involving 17 treatment groups with a total of 773 participants (average age 53 years, 54% male), treatment with statins notably elevates the levels of antioxidant enzymes GPx and SOD in various biological samples, indicating the protective benefits of these medications against oxidative stress. Further intervention studies are needed to explore the antioxidant properties of statins as crucial factors in their beneficial roles for both primary and secondary cardiovascular prevention, to identify the ideal biological matrix for assessing GPx and SOD, and to pinpoint specific patient populations that may greatly benefit from the combined antioxidant and cholesterol-lowering effects of this drug class[42].

Clinical implications and emerging applications

While statins are prescribed primarily for dyslipidemia, a substantial portion of their cardiovascular benefits is now attributed to plaque stabilization, endothelial protection, and reduction of systemic inflammation. These effects reduce the incidence of acute coronary syndromes and stroke, even in patients with normal LDL-C but elevated high-sensitivity C-reactive protein (hs-CRP), as shown in the JUPITER trial[43].

Autoimmune and inflammatory disorders

As discussed in previous sections, statins have shown therapeutic potential as adjunct agents in diseases such as:

Rheumatoid arthritis (RA)

Individuals with rheumatoid arthritis (RA) face a 1.5 to 2.0 times higher risk of developing coronary artery disease (CAD) compared to the general population, a risk level comparable to that associated with diabetes mellitus. Furthermore, those with RA are twice as likely to experience heart failure. This heightened risk is even more significant in RA patients who test positive for rheumatoid factor than in those who are seronegative. Typically, patients with RA exhibit fewer classic signs and symptoms of heart failure, often receive less aggressive treatment, and experience poorer health outcomes. Additionally, RA patients tend to have decreased muscle mass and a low body mass index, which may result from ongoing inflammation, reduced physical activity, or a combination [44].

Low body weight in individuals with RA seems to correlate with a worse prognosis. In a study involving 430 patients with rheumatoid arthritis (181 exposed to statins and 249 not exposed), statins led to a 16% reduction in total cholesterol (TC) levels and were linked to a significant decrease in cardiovascular disease (CVD) risk (adjusted hazard ratio (HR) 0.45, 95% confidence interval) and all-cause mortality[45]. Similar findings were observed in a smaller cohort of 78 RA patients, where statin intervention resulted in a 15% reduction in TC levels for secondary prevention. Nevertheless, in this group, statins did not provide significant protection against CVD and all-cause mortality. The role of statins in enhancing clinical features of rheumatoid arthritis (RA) may be related to their ability to influence various stages of the disease's development. Persistent joint inflammation is caused by excessive production of various inflammatory substances, such as cytokines, growth factors, adhesion molecules, and T lymphocytes. Considering that TNF-α and interleukins play crucial roles in the chronic arthritis process, they are essential factors to consider[46].

Systemic lupus erythematosus (SLE)

SLE poses a comparable risk for cardiovascular disease as type 1 diabetes, making it an independent predictor of cardiovascular events (CVE). The prevalence of cardiovascular disease among SLE patients has been estimated to range from 6% to 16%, with one extensive population study revealing that 25.6% of hospitalized SLE patients had atherosclerotic CVD[47]. The rapid progression of atherosclerosis in SLE has been linked to the higher occurrence of conventional risk factors, such as hypertension and dyslipidemia, along with disease-specific risk factors and harmful effects from medications used in its treatment. Endothelial dysfunction is thought to be the initial step in the pathophysiological chain, as evidenced by the upregulated expression of adhesion molecules including ICAM-1 (intercellular adhesion molecule-1), VCAM (vascular adhesion molecule-1), VEGF (vascular endothelial growth factor), pentraxin-3, thrombomodulin, IP-10 (interferon-γ-induced protein 10), and MCP-1 (monocyte chemoattractant protein-1)[47,48].

A significant factor contributing to cardiovascular disease (CVD) in systemic lupus erythematosus (SLE) is early onset atherosclerosis. Several elements play a role in this issue. Firstly, inflammation promotes the development of atherosclerosis. Additionally, treatments designed to reduce inflammation, such as corticosteroids and disease-modifying antirheumatic drugs, may have adverse cardiovascular effects. Furthermore, SLE patients often experience higher rates of traditional cardiovascular risk factors, including smoking, hypertension, and obesity. There are multiple treatment approaches to mitigate CVD-related complications in SLE. The foundational strategy involves managing overall inflammation with anti-inflammatory medications, which can help alleviate the atherosclerosis driven by inflammation. Another crucial approach is addressing dyslipidemia with statins. In addition to lowering cholesterol production within cells, statins provide various benefits, such as preventing thrombosis and endothelial dysfunction, stabilizing plaques, and modulating the immune system[49].

Multiple sclerosis (MS)

Multiple sclerosis (MS) is a disease characterized by inflammation and damage to the myelin in the central nervous system (CNS), commonly leading to disability in younger individuals. Approximately 2.5 million people worldwide are affected, with a lifetime risk estimated at one in 400. The onset of this condition typically occurs between the ages of 20 and 50, and it is more prevalent in females than males. Research has shown that statins may help mitigate and even reverse the progression of experimental autoimmune encephalomyelitis (EAE), which serves as a mouse model for MS. Statins could provide protective benefits through various mechanisms relevant to MS[50].

Statins might exhibit anti-inflammatory effects by promoting the downregulation of pro-inflammatory Th1 cytokines from T cells, increasing the release of anti-inflammatory Th2 cytokines, encouraging the transition of Th1 cells to Th2 cells, and facilitating the differentiation of Th0 cells into Th2 cells[27].

Statins can reduce the activity of inducible nitric oxide synthase (iNOS), which produces nitric oxide (NO) that can have harmful effects in the CNS. Additionally, statins have neuroprotective properties and can enhance remyelination within the CNS. Integrating statins into treatment regimens for autoimmune diseases may improve outcomes when combined with immunosuppressants or biologics, especially in patients at elevated cardiovascular risk[51,52].

Infectious diseases and sepsis

Given their endothelial-protective and anti-inflammatory effects, statins have been studied in acute infections, including:

Sepsis and acute respiratory distress syndrome (ARDS)

Acute respiratory distress syndrome (ARDS) is a serious condition marked by widespread damage to the alveoli caused by inflammation, damage to the endothelium, and lung remodeling that follows an initial injury (1). In the United States, it is estimated that there are over 150,000 cases and more than 70,000 deaths from ARDS annually (2). Despite decades of research, there remains no effective pharmacologic treatment for ARDS (3). Statins

have anti-inflammatory effects in addition to their ability to lower lipid levels (5). Consequently, there is significant interest in using statins not only as a treatment for inflammatory diseases such as septic shock and ARDS but also to prevent inflammatory complications such as ARDS following an injury (6). Initial findings from animal studies of lung injury support these strategies (7–9), and observational studies have indicated better outcomes for patients who took statins before developing pneumonia, sepsis, and other inflammatory or infectious diseases (10–13). Nevertheless, evidence demonstrating improved outcomes in human lung injury cases is insufficient, and a recent study by Kor et al indicated no advantages in outcomes for patients with acute lung injury or ARDS who were administered statins before hospitalization.COVID-19: Retrospective data suggest that statin use may be associated with reduced mortality and improved outcomes in hospitalized patients, likely due to anti-inflammatory and endothelial-stabilizing effects.

Neurodegenerative disorders

Inflammation plays a critical role in the pathogenesis of Alzheimer's disease and other neurodegenerative conditions. Statins, which can cross the blood-brain barrier—especially the lipophilic ones—are being evaluated for their potential to reduce neuroinflammation and delay cognitive decline. However, the findings are not yet definitive. In a study involving 288,515 participants, 144,214 patients received statin therapies, while 144,301 did not undergo statin treatment. The average duration of follow-up was 5.1 years with a standard deviation of 2.3 years. The use of statins was associated with a decreased occurrence of Alzheimer's disease, dementia, multiple sclerosis, Parkinson's disease, and amyotrophic lateral sclerosis[53]. For all neurodegenerative diseases (NDD), the incidence was lower for all statins except fluvastatin, indicating variations based on individual risk profiles. Pathway analysis revealed distinct and shared profiles related to the effectiveness of risk reduction. In the discussion, it is emphasized that both the advantages and disadvantages of statins regarding neurological outcomes must be considered when prescribing them to populations at risk for NDD. The common pathways activated by statins underscore essential systems necessary for reducing risk, while the unique targets present opportunities for advancing a tailored medical approach to preventing neurodegenerative diseases[53].

So, statins can potentially influence microglial activation, reducing proinflammatory substances contributing to neurodegeneration. Scientists have discovered that they can decrease the production of amyloid-beta, a key component in the pathology of Alzheimer's disease. Statins also affect apolipoprotein E (ApoE) levels, which are crucial for synaptic function and may influence neurodegenerative processes[54].

Cancer

Emerging data suggest that statins may influence tumor microenvironments, reduce cancer cell proliferation, and modulate immune responses, particularly in inflammation-associated malignancies (e.g., colorectal, prostate, breast cancers). Clinical trials are ongoing to evaluate statins as adjuvant therapies in oncology.

The expanding knowledge of statins' anti-inflammatory and immunomodulatory mechanisms supports their repurposing in diverse clinical settings. While robust evidence supports their benefits in cardiovascular and autoimmune diseases, further randomized controlled trials are needed to establish their efficacy and safety in infectious diseases, neurodegenerative disorders, and oncology. Statins may thus represent a cost-effective adjunct strategy in managing complex, inflammation-driven diseases[55].

Table 1. Summary of key studies on anti-inflammatory and pleiotropic effects of statins [56–65].

Target Pathways / Mechanisms	Key Findings	Model/System	Statin(s)	Study Type	Year	Author(s)
Rho/ROCK, cytokine suppression	↓ Atherosclerosis, ↓ MMPs	ApoE-/- mice	Atorvastatin	In vivo	2000	Kwak et al.
MHC II modulation, T cell regulation	↓ Th1/Th17 response, ↑ Treg cells	EAE mouse model	Simvastatin	In vivo	2002	Youssef et al.
NF-κB, AP-1, STAT	Overview of immune effects	Multiple	Various	Review	2003	Blanco-Colio et al.
NF-κB inhibition	↓ IL-6, ↓ ICAM-1	HUVEC cells	Simvastatin	In vitro	2005	Jain et al.
eNOS upregulation, Rac inhibition	Endothelial protection, antioxidant effects	-	-	Review	2005	Liao & Laufs
Systemic inflammation	↓ hs-CRP independent of LDL-C	17,802 patients	Rosuvastatin	Clinical trial	2008	Ridker et al. (JUPITER)
TLR4/MyD88 pathway	↓ TNF-α, ↓ IL-1β	THP-1 macrophages	Lovastatin	In vitro	2011	Bu et al.
NF-κB, NLRP3, TLR pathways	↓ NLRP3, ↓ IL-1β, TLR2/4 suppression	Atherosclerosis/immune studies	Various	Review	2021	Sahebkar et al.
AMPK, mitochondrial regulation	Pleiotropic control over mitochondria and cellular metabolism	Muscle inflammation, metabolism	Various	Review	2021	Mollazadeh et al.
↓ TNF-α, IL-6, oxidative stress	Anti-inflammatory liver protection in NASH	NASH / human clinical	Multiple	Systematic review	2024	Zhang et al. (Molecules)

CONCLUSIONS

Anti-inflammatory and Immune Modulating Effects: Statins exhibit significant anti-inflammatory properties through various mechanisms. These mechanisms involve blocking isoprenoid-dependent signaling pathways, regulating cytokine production, enhancing endothelial function, and reducing immune cell activation. Such actions highlight the potential role of statins in managing inflammatory disorders. Therapeutic Potential in Inflammatory Conditions: The results suggest that statins might be advantageous for both preventing and treating a range of inflammatory conditions, including multiple sclerosis (MS) and rheumatoid arthritis (RA). For instance, in MS, statins may modify T-helper cell responses, potentially reducing neuroinflammation; meanwhile, in RA, they have been associated with a lower risk of cardiovascular disease and all-cause mortality. Effects on Neurodegenerative Diseases: Statins are currently being evaluated for their ability to cross the blood-brain barrier and reduce neuroinflammation, which is crucial in the development of neurodegenerative conditions like Alzheimer's and Parkinson's. Existing evidence indicates that statin users show a decreased incidence of these diseases, although the findings are not yet definitive. Need for Additional Research: Despite promising results, the paper emphasizes the need for further exploration into the full therapeutic potential of statins beyond their cholesterol-lowering effects. This will entail investigating their role in various inflammatory and autoimmune disorders, as well as understanding the advantages and disadvantages of their use in these contexts.

Conflict of interests

No conflict

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