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Statin therapy for NAFLD: Molecular underpinnings of myopathic consequences and treatment strategies

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ABSTRACT

Non-alcoholic fatty liver disease (NAFLD) encompasses a range of hepatic disorders characterized by excessive lipid accumulation in hepatocytes and is closely linked to metabolic syndrome. Statins, which are potent lipid-lowering agents, have emerged as potential therapeutic options for managing NAFLD. Recent meta-analyses have demonstrated the efficacy of statins in reducing liver enzymes, improving histological features, and attenuating disease progression in patients with NAFLD. Mechanistically, statins exert their beneficial effects by inhibiting cholesterol synthesis, modulating lipid metabolism, and exhibiting anti-inflammatory and antifibrotic properties. They target key pathogenic pathways in NAFLD, including the inhibition of sterol regulatory element-binding proteins (SREBPs), activation of peroxisome proliferator-activated receptor-alpha (PPAR-α), and enhancement of fatty acid β-oxidation. Additionally, statins mitigate hepatic inflammation by reducing pro-inflammatory cytokines and oxidative stress, while promoting fibrosis regression through the inhibition of RhoA/Rho kinase signaling and transforming growth factor-beta (TGF-β) pathways. However, statin-associated muscle symptoms (SAMS) remain a significant concern, often leading to treatment non-adherence or discontinuation. The molecular mechanisms underlying statin-induced myopathy involve the inhibition of the mevalonate pathway, coenzyme Q10 depletion, mitochondrial dysfunction, and disruption of the ubiquitin-proteasome system. Strategies to prevent and manage SAMS include alternative dosing regimens, statin switching, and the use of complementary therapies such as coenzyme Q10 and vitamin D supplementation. Novel approaches, including PCSK9 inhibitors and nutraceuticals, have also shown promise in mitigating statin-related muscle adverse effects. In conclusion, statins offer a promising therapeutic avenue for NAFLD management, particularly in patients with elevated cardiovascular risk. This review updated the statins' therapeutic potential in NAFLD, their molecular mechanisms, statin-induced myopathy, extra-hepatic effects, and preventive strategies for future research.

1. Introduction

Non-alcoholic fatty Liver Disease (NAFLD) is a group of hepatic disorders characterized by macrovesicular steatosis involving more than 5 % hepatocytes as a result of disruption of lipid metabolism and diurnal rhythmicity (Chalasani et al., 2018; Friedman et al., 2018). NAFLD has a global prevalence of 25.24 % with these variations regarding the region of the world (Younossi and Henry, 2021). NAFLD encompasses a spectrum of liver disorders characterized by the excessive accumulation of lipids, particularly triglycerides and free cholesterol, in hepatocytes (Friedman et al., 2018). This condition is closely related to metabolic syndrome, which includes a group of metabolic derangements, such as increased visceral fat, type 2 diabetes mellitus (T2DM), high blood pressure, and elevated triglyceride levels (Januário et al., 2024). NAFLD, in its progression, can further cause other severe hepatic disorders like Non-alcoholic steatohepatitis (NASH), fibrosis, and cirrhosis (Huang et al., 2021).

Pathologically, NAFLD is defined as the accumulation of lipids in hepatocytes, particularly triglycerides and cholesterol droplets. Presently, enhanced hydroxymethylglutaryl-CoA (HMG-CoA) reductase is associated with increased cholesterol synthesis, which worsens lipid

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Abbreviations:

NAFLD	Non-alcoholic fatty Liver Disease
NASH	Non-alcoholic steatohepatitis
HMG-CoA	β-Hydroxy β-methylglutaryl-CoA
SREBPs	Sterol Regulatory Element-Binding Proteins
SAMS	statin-associated muscle symptoms
HCC	Hepatocellular carcinoma
HSCs	hepatic stellate cells
IL-6	interleukin 6
UPS:	The ubiquitin-proteasome pathway
LDL:	Low-Density Lipoprotein
PPARα	Peroxisome Proliferator-Activated Receptor Alpha
TNFα	Tumor Necrosis Factor Alpha
RhoA/RhoA kinase	Rho-associated protein kinase
KLF2	Kruppel-Like Factor 2
TGF-β1	(Transforming Growth Factor Beta 1)

accumulation (Malhotra et al., 2020;Finelli, 2023). Excessive free cholesterol within hepatocytes is toxic and induces mitochondrial dysfunction, causing further inflammation and oxidative stress. This inflammation stimulates both hepatic Kupffer and stellate cells to aggravate liver injury and fibrosis. It disrupts normal hepatic function by promoting inflammation, oxidative stress, and mitochondrial dysfunction, thereby contributing to the progression toward non-alcoholic steatohepatitis (NASH), fibrosis, and ultimately, cirrhosis (LeFort et al., 2024; Huang et al., 2021). The resulting low-grade inflammation and dyslipidemia further increase the risk of cardiovascular disease and mortality in patients with NAFLD (Gantzel et al., 2021).

Over the past few decades, statins have emerged as cornerstones in the management of cardiovascular diseases owing to their effective lipid-lowering properties. These agents selectively inhibit 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, a rate-limiting enzyme in the cholesterol biosynthesis pathway. This inhibition not only curbs the synthesis of cholesterol within hepatocytes but also triggers a compensatory upregulation of LDL receptors, leading to enhanced clearance of circulating LDL cholesterol (Iqbal et al., 2018).

The current literature also provides preliminary and growing evidence that statins should be considered active therapeutic agents for various forms of liver diseases, including cirrhosis, NAFLD, and cholestatic liver disorders. Patients with NAFLD have elevated cardiovascular risk and multiple risk factors, making statins a critical choice for the treatment of NAFLD. The American Association of Clinical Endocrinology (AACE) Clinical Practice Guidelines for the Diagnosis and Management of NAFLD endorses moderate to high-intensity statins, namely atorvastatin and rosuvastatin, to treat atherogenic dyslipidemia in NAFLD patients (Chalasani et al., 2018). In addition to their strong antioxidant properties, statins possess many other activities and anti-inflammatory effects. The clinical importance of these actions extends beyond cardiovascular health. An imbalance in cholesterol homeostasis is pivotal in the pathogenesis of NAFLD. By targeting the central defect in cholesterol metabolism, statins provide a unique therapeutic bridge between liver and vascular health, offering hope for improved outcomes in patients burdened by intertwined epidemics of metabolic syndrome and NAFLD (Zhang et al., 2024).

Despite the extensive beneficial effects of statins in NAFLD and its associated complications, one of the potential side effects associated with statin use is statin-associated muscle symptoms (SAMS), which include myalgias, myopathy, myositis, and muscle injury. The side effects caused by statins are often associated with non-compliance and treatment abandonment, which is an issue in cardiovascular disease (CVD) prevention and management (Pereira et al., 2025). Statin-related myopathies include endogenous risk factors, such as age, sex, reduced body mass index, vitamin D deficiency, or carnitine palmitoyltransferase deficiency, and external factors such as ethnicity. Other external triggers that may modulate the risk of statin-induced myopathy include surgery, alcohol consumption, vigorous exercise, and/or drug interaction, particularly with food and drink.

However, the restricted biodistribution of statins into extra-hepatic tissues led to an increase in the synthesis of cholesterol and other mevalonate pathway intermediates, including isoprenoids. These derivatives can disable, enable, or modulate a range of cell signaling pathways that may change biological processes such as apoptosis, cell growth, and cell proliferation, and (Al-Shalchi and Mohammad, 2024) it is argued that denying statin access to extra-hepatic tissues might help lessen myotoxicity. Knowledge of these mechanisms may provide a direction for enhanced clinical investigations that can help in risk identification, diagnosis, and prevention, contributing to a smaller chance for SAMS to occur in the future.

This review aims to provide extensive mechanistic insight, recent clinical trial data, and the therapeutic benefits of statins in NAFLD management. Moreover, the review also highlighted statin-associated muscle disorders by emphasizing the associated molecular mechanisms and strategies to counteract the SAMS.

2. Statins in non-alcoholic fatty liver disease

Recent meta-analytical evidence has increasingly underscored the beneficial role of statins in managing NAFLD. Statins function by inhibiting HMG-CoA reductase, which is pivotal in cholesterol synthesis, resulting in a reduction in intrahepatic lipid accumulation and improvement in the serum lipid profile. A comprehensive meta-analysis by Boutari et al. (2022) demonstrated significant reductions in liver biochemical markers, particularly alanine aminotransferase (ALT) and aspartate aminotransferase (AST), following statin administration in NAFLD patients. Notably, the pooled data revealed a 17 % higher overall efficacy rate among patients receiving statins, suggesting marked improvement in liver health (Estruch et al., 2023). In a parallel evaluation, Dai et al. (2022) conducted a meta-analysis of four RCTs with a total of 169 participants. Their findings confirmed that statin therapy significantly lowered the serum levels of ALT, AST, triglycerides, and total cholesterol compared with controls. These outcomes highlight the biochemical and lipid-lowering effects of statins in NAFLD, especially in patients with concurrent hyperlipidemia (Dai et al., 2022).

Further supporting the safe profile of statin use, a meta-analysis study reviewed data from 22 placebo-controlled RCTs involving 2345 patients. This investigation confirmed that while statins improve key lipid parameters, they do not induce elevations in liver enzymes, such as ALT, AST, bilirubin, or alkaline phosphatase, a critical observation underscoring their safety in NAFLD treatment (Pastori et al., 2022). Collectively, these analyses demonstrate that statins not only mitigate hepatic inflammation and injury by lowering key transaminase levels but also enhance the overall lipid profile. This dual action supports their therapeutic potential in NAFLD management, particularly in patients predisposed to metabolic derangements and cardiovascular disease.

Recent studies have shown that statins, beyond their well-known lipid-lowering effects via HMG-CoA reductase inhibition, can modulate several key pathogenic pathways in non-alcoholic fatty liver disease (NAFLD). In addition to reducing hepatic cholesterol synthesis, statins exert anti-inflammatory, antifibrotic, and chemopreventive effects that may ultimately reduce the progression to cirrhosis and hepatocellular carcinoma (HCC) (Goh and Sinn, 2022).

Lange et al. discussed how the integration of lifestyle interventions with chemopreventive approaches to statin therapy, in particular, can alter the carcinogenic hepatic microenvironment in NAFLD. Notably, statins reduce chronic inflammation and fibrosis, thereby diminishing signals that promote malignant transformation (Lange et al., 2021). Metabolic dysfunction in fatty liver disease is driven by the dysregulation of lipid metabolism and systemic inflammation. Statins help to

lower LDL cholesterol and curb the inflammatory cascade primarily through inhibition of the mevalonate pathway, thereby reducing both cardiovascular and hepatic risks (Badmus et al., 2023). Another study emphasized that statins improve hepatic endothelial function by boosting NO bioavailability and mitigating hepatic stellate cell activation. This leads to reduced fibrosis and portal hypertension, which are critical factors for both cirrhosis progression and HCC risk (Sharpton and Loomba, 2023). Using transcriptomic analyses, Fujiwara et al. identified pro-oncogenic and inflammatory gene expression patterns that predict HCC risk. Statins may help modulate these transcriptional profiles by interfering with pathways that drive inflammation and carcinogenesis, thus lowering the risk of long-term HCC (Fujiwara et al., 2022). In the clinical setting in which effects of statins on the long-term risk of all-cause mortality, liver-related clinical events (LREs), and liver stiffness progression in patients with metabolic-associated steatotic liver disease were studied and reported lower risk of statins in these patients. Zhou et al., 2024). Chronic metabolic derangements, including persistent inflammation, insulin resistance, and oxidative stress, create a milieu conducive to HCC development. Statins mitigate these processes by reducing circulating lipid levels and inflammatory mediator levels, thereby exerting a protective effect against HCC (Kim and Kang, 2019). Table 1 summarizes the therapeutic effects of various statins in the treatment of NAFLD. These findings emphasize the potential of statins as available therapeutic strategies for the management of NAFLD.

3. Molecular mechanism of statins in NAFLD treatment

Based on their favorable effects on various molecular targets, statins can be used for NAFLD-related diseases such as steatosis, HCC, and NASH, with subsequent better liver histology (Gerges et al., 2021). This diagram illustrates the potential mechanisms through which statins can treat NAFLD. Statins may reduce steatosis by lowering LDL-cholesterol levels, influencing SREBPs, increasing PPARα activity, and enhancing fatty acid β-oxidation. In NASH, statins reduce pro-inflammatory cytokines, such as TNFα and IL-6, inhibit GTPase prenylation, and decrease oxidative and nitrosative stress. They may also contribute to fibrosis regression by inhibiting RhoA/RhoA kinase pathways, promoting KLF2 in sinusoidal endothelial cells, and reducing TGF-β1/Smad3 activity. Additionally, statins may prevent hepatocarcinoma through the IL-6-STAT3 signaling pathway, which is involved in cell cycle arrest and apoptosis, inhibition of cell proliferation and adhesion, and reduction of angiogenesis (Fig. 1).

Statins directly decreased IL-6-induced protein geranylation of proteins. Thus, the molecular mechanism of statin action fully inhibits CRP in Hepatocytes; CRP is linked to HCC biomarkers (Zeng et al., 2024). Simvastatin also selectively triggers apoptosis in HCC cells; however, its effects on normal cells make it suitable for use in managing HCC (Pan et al., 2020). Moreover, statins were found to suppress the synthesis of several prenylated proteins and affect the G-proteins Ras and Rho, which are involved in tumor formation.

This finding is supported by prior research revealing that statin therapy improves NASH and metabolic syndrome in the context of NAFLD. Moreover, statins affect some factors that are involved in NASH; LDL cholesterol levels and oxidized LDL cholesterol levels are both lowered by the use of statins (Cariou et al., 2021). Furthermore, it exert an effect on Sterol Regulatory Element Binding Proteins (SREBP), PPAR-α, and β-oxidation and decrease liver steatosis (Morsy et al., 2021). Statins possess anti-inflammatory effects owing to the stimulation of PPAR-α and inhibition of inflammatory mediators, whereas other effects result from the suppression of small GTPase prenylation and decreased signaling (Gorabi et al., 2021).

The use of statins appears to have additional advantages, including the ability to decrease fibrosis. Experimental investigations of their ability to inhibit the RhoA/Rho-kinase pathway in hepatic stellate cells (HSCs) and to improve sinusoidal endothelial function through the activation of KLF2 indicate a potential therapeutic pathway for fibrosis (Trebicka and Schierwagen, 2015).

Therefore, statins are endowed with exciting possibilities involving the manipulation of NAFLD components such as steatosis, HCC, NASH, and fibrosis. Consequently, owing to their multiple molecular interactions, they justified their potential as feasible therapeutic targets for NAFLD-related diseases, which requires additional stringent investigation to enhance the effectiveness of their use in clinical practice (Pham and Benhammou, 2024).

The drugs that belong to statins include atorvastatin, rosuvastatin, simvastatin, pitavastatin, pravastatin, and fluvastatin, have shown great

Table 1
Brief Summary of the therapeutic effects of various statins in NAFLD treatment.

Drug Name	Research Investigation	Research Type	Duration of Therapy	Key Findings & Elaboration	Reference
Atorvastatin	The Effect of Atorvastatin in the Treatment of Non-alcoholic Fatty Liver Disease Patients	Randomized Controlled Trial (RCT)	12 months	Atorvastatin significantly lowered hepatic fat content as assessed by imaging techniques. Improvements in serum liver enzymes (ALT, AST) were observed, indicating reduced hepatocellular injury, and decreases in inflammatory markers suggest a positive modulation of the hepatic inflammatory environment.	Eslami et al. (2024)
Simvastatin	Effect of Statin Use on Liver Enzymes and Lipid Profile in Patients with NAFLD	Randomized Controlled Trial (RCT)	12 months	Simvastatin administration led to significant reductions in liver enzymes, indicating decreased hepatocellular damage. Improvements in liver histology, along with better lipid profile parameters, highlight its potential to slow NAFLD progression by reducing inflammation. and lipid deposition processes.	Ho et al. (2024)
Rosuvastatin	Efficacy of Ezetimibe Plus Rosuvastatin Versus Rosuvastatin Monotherapy to Reduce Liver Fat in NAFLD	Randomized Controlled, Open-Label Trial	24 weeks	Combining ezetimibe with rosuvastatin produced a significantly greater reduction in liver fat content compared to rosuvastatin monotherapy, as assessed by MRI-PDFF and CAP measures. However, the improvement in liver fibrosis, as determined by MRE, was not statistically significant. This suggests the combination therapy is more effective at reducing steatosis rather than reversing existing fibrosis in the short term.	Cho et al. (2022)
Pitavastatin	Effect of Pitavastatin on NAFLD/NASH in Military Personnel: A Randomized Controlled Trial	Randomized Controlled Trial (RCT)	12 months	Pitavastatin treatment led to marked improvements in liver function tests and significant reductions in hepatic fat accumulation. The study demonstrated notable decreases in both the NAFLD Activity Score (NAS) and FIB-4 index, indicating robust anti-inflammatory and antifibrotic effects, thereby suggesting its potential in reversing histologic features of NAFLD/NASH.	Sfikas et al. (2021)

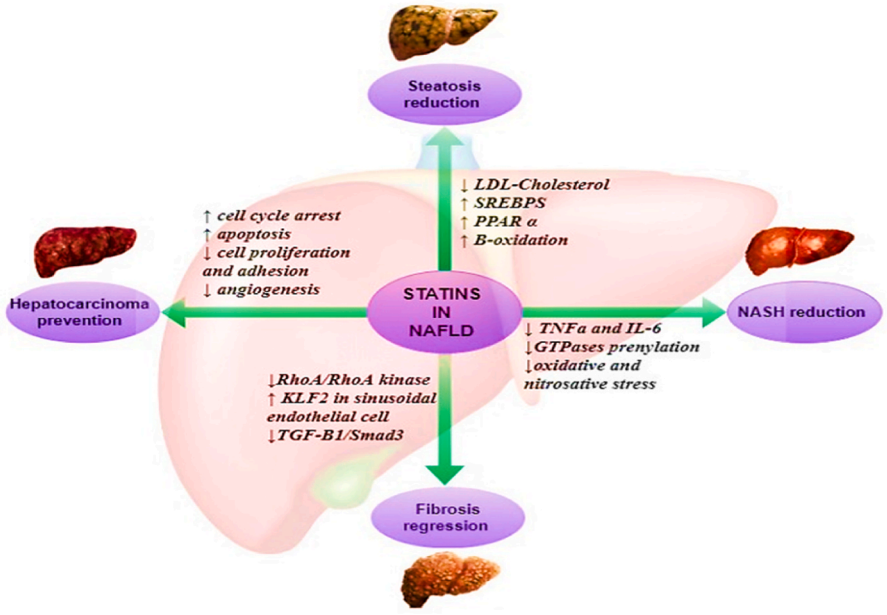

Fig. 1. Multifaceted effects of statins in non-alcoholic fatty liver disease (NAFLD)
This schematic diagram illustrates the multifaceted effects of statins in NAFLD: Statins reduce steatosis by lowering LDL-cholesterol and inhibiting SREBP activity, which enhances PPARα expression and β-oxidation to diminish hepatic fat deposition; they mitigate NASH through anti-inflammatory actions by downregulating TNF-α and IL-6, reducing GTPase prenylation, and decreasing oxidative and nitrosative stress; they promote fibrosis regression by inhibiting the RhoA/Rho kinase pathway while upregulating KLF2 in sinusoidal endothelial cells and suppressing the TGF-β1/Smad3 signaling cascade; and they contribute to hepatocarcinoma prevention by inducing cell cycle arrest and apoptosis, and reducing cellular proliferation, adhesion, and angiogenesis.

potential in managing different complications associated with NAFLD and NASH. Furthermore, they modulate several molecular targets and have therapeutic benefits for patients with NAFLD and other associated diseases.

Atorvastatin treatment did not have any negative effects on NAFLD/NASH patients but enhanced the positive effects. It not only reduced the cholesterol level but also offered a substantial clinical cardiovascular advantage over patients who received no treatment as well as those who received similar doses but were suffering from liver disorders; Atorvastatin improves the AMPK signaling pathway and overcomes the unfavorable effects of NAFLD;, combined therapy with vitamins E and C may reduce disease progression; (Athyros et al., 2018). Pre-clinical studies have demonstrated that rosuvastatin might hinder the development of HCC associated with NAFLD (Yeo et al., 2025). It also normalizes liver function and causes astounding changes in liver pathology in most patients with NASH (Eslam et al., 2022). It also has a high efficacy rating and is considered safe in patients with NAFLD and NASH. A prospective randomized open-label clinical trial demonstrated that ezetimibe/simvastatin and simvastatin monotherapy significantly decreased ALT levels in NAFLD patients. The effect of pitavastatin on NASH with dyslipidemia has been investigated and shows a trend in early-stage liver carcinoma associated with obesity. A 3-year follow-up showed that long-term pravastatin exposure was not accompanied by an increase in non-cardiovascular side effects. It has been used in the management of dyslipidemia in patients with NAFLD, and a meta-analysis was performed. Fluvastatin showed an ability to maintain cholesterol hemostasis, prevents lipid accumulation in hepatocytes, and reduces hepatic steatosis and fibrosis in NASH (Dehnavi et al., 2021).

Together, statins possess multi-targeting effects on different molecular signaling pathways, suggesting their potential for the treatment of NAFLD and NASH. However, patient-to-patient variability in pharmacokinetics and doses should not be ignored to achieve a full therapeutic benefit. Further research is required before statins can be used to treat NAFLD and its associated comorbidities.

4. Statin-associated myopathy and diverse effects on extra-hepatic tissues

Statins are essential for addressing NAFLD and NASH, as they reduce cholesterol synthesis in the liver and enhance liver enzymes. However, like any other drug, statins have side effects, most notably, myopathy, which has resulted in several controversies among clinicians and patients (Lonardo et al., 2022).

Statin-induced myopathy is mainly influenced by genetics, indicator number two. The pathogenesis of statin-induced myopathy is multifactorial and still under investigation; it probably has a genetic basis (Morsy et al., 2021). However, studies have established that there is a difference in the occurrence of SAM, where women complain more than men do. Furthermore, it has been found that while the risk of myopathy varies with the dose of statin used in men, this dose-response relationship does not apply to women, which is an important implication of sex-specific routes. More studies have shown the effect of genetic factors involved in statin-induced myopathy and have attempted to understand whether there exists a composite genetic pattern that increases the risk of suffering from this side effect (Ward et al., 2019).

Besides hereditary factors, side effects and drug interactions are postulated to be related to statin-induced myopathy. These data revealed that patients with myopathy often have more complex concurrent statin-related muscular diseases, thus underlining the need to critically consider broader perspectives regarding statin safety in clinical practice and therapy allocation. Nevertheless, as with any drug intervention therapy for NAFLD/NASH, patients should not be deprived of the therapeutic value of statins in reducing cardiovascular disease (CVD) (Finney et al., 2023). Separate data have proven that statin therapy effectively reduces CVD risk in NAFLD, further highlighting the importance of the systematic assessment of the benefit/risk ratio in clinical practice (Byrne and Targher, 2022).

Thus, age may also play a role in the propensity to develop statin-induced myopathy. Sometimes, elderly people, particularly women, are said to be more prone to muscular problems or issues that have been

linked with the use of statins (Balestrino and Adriano, 2019). However, there is a lack of evidence to substantiate this, showing that age is directly proportional to the risk of myopathy in statin users.

It has also been established that different statins may have different rates of myopathy. For example, atorvastatin has been shown to cause myopathy more often than other statins do (Manoj et al., 2017). There is mixed information regarding the frequency of statin side effects, especially simvastatin-induced myopathy. However, these risk factors can vary across different statins, and there is still much to be learned about these differences in detail.

Although statins are believed to effectively manage dyslipidemia and CVD, their impact on extrahepatic tissues, especially the muscles, is significant. The active transport of statins into skeletal muscles involves carrier proteins, such as OATP2B, and any variations in the genetic function of these proteins or their interactions with other medications will cause statin pharmacokinetic changes that enhance the systemic availability of statins, potentially increasing the risk of toxicity (Turner and Pirmohamed, 2019). Understanding how statins work to cause myopathy will help the scientific community design prevention and treatment interventions that address the needs of individual patients. Present clinical and pre-clinical studies have provided partial information about cellular changes, oxidative stress, and mitochondrial derangement as possible causes of muscle damage. Nevertheless, further studies are needed to clarify the processes and pathways by which statins can cause myopathy (Fairman et al., 2022).

Nonetheless, statin-induced myopathy remains an important clinical concern in NAFLD/NASH therapy. An evaluation of the hereditary, sex, age, and drug effects affecting myopathy is critical in obtaining the high, low-density lipoprotein cholesterol reduction offered by statin therapy with few adverse outcomes.

5. Molecular pathways associated with statin-induced skeletal muscle symptoms

The possible etiologies of statin-related side-effect manifestations in skeletal muscle are particularly relevant, although statins are effective in the management of chronic liver diseases such as NAFLD/NASH. A milder form of SAMS, myalgia is one of the less common adverse effects of statins and occurs in 6 %–14 % of patients and affects 5 %–7 % of patients receiving statins. Myopathy has been estimated to occur in 0.1 % of fatal patient complications on statin monotherapy (Gheorghe et al., 2020). Cerivastatin use has been associated with rhabdomyolysis, leading to its global withdrawal (Maghsoodi and Wierzbicki, 2016). SAMS has a vague and imprecise cause, which most likely involves genetic factors. Statin-induced mitochondrial damage is thought to be one of these mechanisms; however, the mechanism of action is not well understood and requires further research. The literature on some of the potential mechanisms that have been postulated to be involved in the development of skeletal muscle-related side effects is discussed in detail in the following sections (Bonifacio et al., 2017; Elam et al., 2017). Statin-induced skeletal muscle myopathy involves several interconnected molecular pathways that contribute to its pathogenesis (Fig. 2). The primary mechanism involves the inhibition of HMG-CoA reductase, the key enzyme in cholesterol biosynthesis. This inhibition decreases cholesterol synthesis, a vital component of cell membranes, potentially impairing muscle cell integrity. Mitochondrial dysfunction is another critical factor, as statins influence mitochondrial processes such as ATP production, oxidative stress (Reactive oxygen species (ROS) generation), and apoptosis. Disruption of mitochondrial function can trigger the mitochondrial permeability transition pore (MTP), leading to Cytochrome C (CytC)release and activation of caspases, which promote apoptosis. Statins also interfere with the protein synthesis and degradation pathways by modulating the mammalian target of rapamycin 1

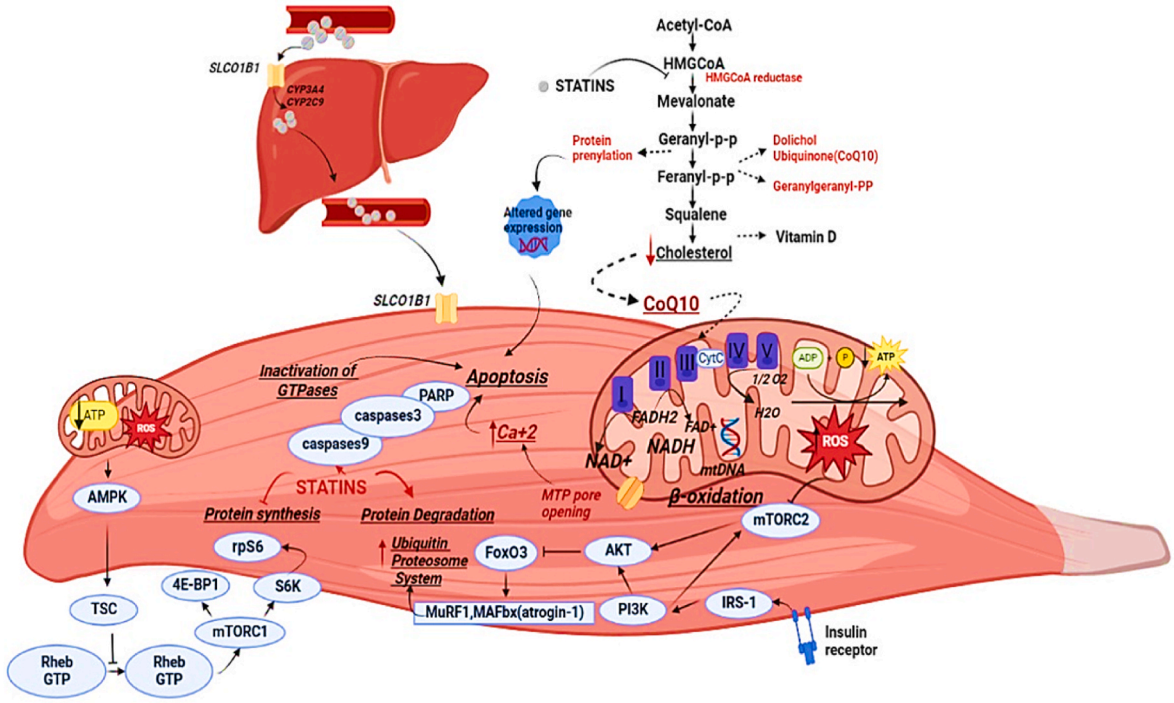

Fig. 2. Molecular pathways associated with statin-induced skeletal muscle myopathy. This figure illustrates the complex molecular pathways underlying statin-induced skeletal muscle myopathy. Statins primarily inhibit HMG-CoA Reductase (the enzyme responsible for converting HMG-CoA to mevalonate), which leads to reduced endogenous cholesterol synthesis and diminished production of vital isoprenoids and Coenzyme Q10 (CoQ10). The decline in CoQ10 compromises mitochondrial electron transport, resulting in decreased ATP production and enhanced generation of Reactive Oxygen Species (ROS). Elevated ROS levels, together with alterations in the NAD^+/NADH ratio, activate AMPK (AMP-activated protein kinase) and PARP (Poly [ADP-ribose] polymerase), exacerbating cellular energy deficits and oxidative stress.

and 2 (mTORC1 and mTORC2) activity. This imbalance affects downstream targets, such as Forkhead box O3 (FoxO3) and Muscle RING Finger 1 (MuRF1), contributing to muscle protein degradation and atrophy. Additionally, statins affect insulin signaling pathways, involving key molecules such as Phosphoinositide 3-kinase (PI3K), protein kinase B also called as AKT, and insulin receptor substrate 1 (IRS-1), which regulate glucose metabolism and energy homeostasis. Impairment of these pathways may exacerbate metabolic stress in the skeletal muscles. Collectively, these mechanisms cholesterol biosynthesis inhibition, mitochondrial dysfunction, disrupted protein homeostasis, and altered insulin signaling, interact in complex ways, leading to muscle weakness and pain, and, in severe cases, rhabdomyolysis. Understanding these pathways offers insights into the molecular basis of statin-induced myopathy and highlights potential targets for therapeutic intervention to mitigate the adverse effects while preserving the cardiovascular benefits of statins.

Disruption of mitochondrial function also facilitates the release of CytC through the opening of the Mitochondrial Permeability Transition Pore (MTP), which in turn activates apoptotic cascades via Caspase3/9. Concurrently, statins impair insulin signaling by interfering with IRS-1 (Insulin Receptor Substrate 1) and the PI3K/AKT pathway, leading to the reduced activation of mTOR complexes (mTORC1/mTORC2). This suppression hampers protein synthesis by modulating downstream targets such as 4E-BP1 and S6K (Ribosomal Protein S6 Kinase).

Furthermore, the attenuation of trophic signals contributes to the activation of the transcription factor FoxO3, which stimulates muscle atrophy by increasing the transcription of muscle-specific E3 ubiquitin ligases, MuRF1 andAFAtrogin-1, thereby promoting protein degradation. Additionally, the role of the SLC01B1 highlights its importance in statin uptake and distribution within the skeletal muscle. Collectively, these interconnected pathways illustrate how reduced cholesterol synthesis, mitochondrial dysfunction, enhanced oxidative stress, impaired insulin signaling, and activated proteolytic pathways converge to induce skeletal muscle damage and myopathy.

5.1. Inhibition of the mevalonate pathway by statins

Statins inhibit HMG-CoA reductase, thereby reducing cholesterol synthesis and the production of isoprenoids (e.g., farnesyl pyrophosphate and geranylgeranyl pyrophosphate) necessary for protein prenylation. Disruption in prenylation affects key cellular proteins, such as nuclear laminins and small GTP-binding proteins (Ras, Rab, and Rho families), which are vital for cell signaling, skeletal muscle integrity, and maintenance of the cellular skeleton. This interference with post-translational protein modification is thought to underlie adverse skeletal muscle effects, including statin-associated muscle symptoms (SAMS), such as myopathy and, in severe cases, necrotizing autoimmune myopathy and rhabdomyolysis (Szalmasi and Lehot, 2022).

5.2. Coenzyme Q10 and its interaction with statins

The cholesterol synthesis pathway also produces Coenzyme Q10 (CoQ10), an essential component of the mitochondrial electron transport chain, and a potent antioxidant. Statin-induced inhibition of this pathway leads to reduced CoQ10 levels, compromising mitochondrial ATP production, and enhancing oxidative stress. Therefore, diminished CoQ10 may contribute to muscle cell dysfunction and damage, which may exacerbate myopathic symptoms. While some studies suggested that CoQ10 supplementation might counteract these effects, further research is needed (Shimizu-Motohashi et al., 2018).

5.3. The ubiquitin-proteasome pathway (UPS) in statin-induced myopathy

Statins also affect the ubiquitin-proteasome system by disrupting isoprenylation, leading to alterations in muscle cell proliferation and survival. Increased activity of muscle-specific E3 ubiquitin ligases, such as Atrogin-1 and MuRF-1, triggers protein degradation and muscle atrophy. Immune-mediated responses and genetic polymorphisms further contribute to this process, highlighting the role of UPS in the development of statin-induced myotoxicity (Vinci et al., 2021).

5.4. Mitochondrial dysfunction as a contributing factor

Long-term statin use has been associated with mitochondrial dysfunction manifested by reduced mitochondrial density and impaired biogenesis (involving PGC-1 family proteins). This dysfunction leads to decreased ATP production, increased reactive oxygen species (ROS) generation, and initiation of apoptotic cascades, thereby contributing to muscle cell injury. Oxidative muscle fibers are particularly susceptible to these effects (Panajatovic et al., 2020).

5.5. Impact on the IGF-1/PI3K/Akt/mTOR pathway

Statin-induced inhibition of the insulin-like growth factor 1 (IGF-1) receptor/PI3K/Akt/mTOR signaling pathway interferes with muscle protein synthesis and cell survival. Reduced phosphorylation of Akt (notably at serine 473) leads to decreased mTORC activity, activation of FoxO transcription factors, and subsequent upregulation of muscle atrophy markers such as Atrogin-1 and MuRF1. This disruption not only contributes to myofiber atrophy and apoptosis but also links statin use to insulin resistance in skeletal muscle. Differences in the effects of lipophilic and hydrophilic statins have been observed, with simvastatin showing more pronounced effects than pravastatin (Wang et al., 2024; Nikolic et al., 2020).

6. Treatment approaches and prevention of statin-induced myopathy

Statin-induced myopathy often leads to non-adherence, switching, or discontinuation of medication, which can adversely affect the course of NAFLD. Therefore, it is essential to regulate SAMS to achieve a maximum-tolerated statin dose and other therapeutic goals for the successful treatment of patients with NAFLD. Therapeutic approaches include alternate-day dosing, switching statins, low-dose statins, and the use of additional medications, such as bile acid-binding resins, ezetimibe, nicotinic acid, and PCSK9 inhibitors (Zeng et al., 2024) (Fig. 3).

6.1. Role of complementary therapies

Recent research has highlighted the potential benefits of L-carnitine, produced by L-lysine and S-adenosylmethionine, as an endogenous fatty acid transporter in the mitochondrial matrix. L-carnitine supplementation may partially alleviate the detrimental effects of the ubiquitin-proteasome pathway (UPS). However, it is worth noting that L-carnitine supplementation in preclinical models has been shown to reduce UPS gene activity in skeletal muscles, potentially inhibiting the degradation of myofibrillar proteins. In contrast, coenzyme Q10, a crucial component of the oxidative phosphorylation process and mitochondrial electron transportation chain, is affected by statin therapy. Statin inhibit HMG-CoA reductase, leading to reduced CoQ10 production, which may be responsible for the adverse effects on muscles. Despite encouraging anecdotal evidence and small trials, recent well-designed RCTs, including a run-in phase to validate statin myalgia, have not found that coenzyme Q10 supplementation is beneficial (Virmani and Cirulli, 2022). Additionally, the relationship between vitamin D insufficiency and SAMS remains debatable. Some studies have suggested that statin users with myalgia have lower plasma vitamin D levels than those without SAMS. Vitamin D supplementation has shown potential benefits in reducing statin-related myotoxicity in certain cases, especially in individuals with previous statin resistance who receive challenge therapy (Kaur et al., 2020).

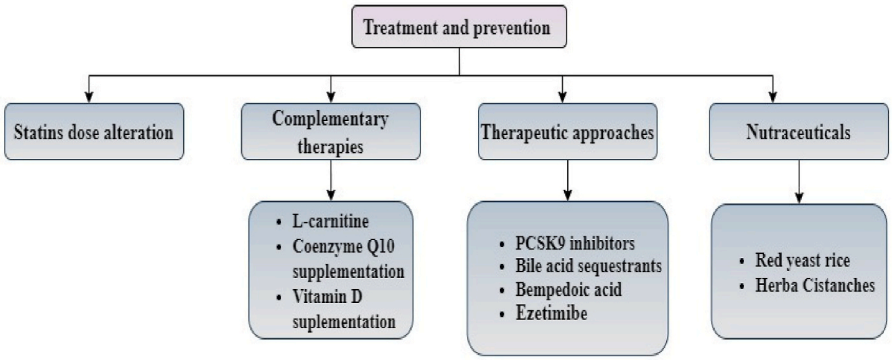

Fig. 3. Treatment approaches and prevention of statin-induced skeletal muscle myopathy.

6.2. Role of therapeutic approaches

PCSK9 inhibitors, such as alirocumab and evolocumab, have emerged as effective options for reducing circulating LDL-C levels by 50–70 % in individuals with or without background statin therapy. These monoclonal antibodies inactivated PCSK9, leading to decreased LDL receptor degradation and enhanced receptor recirculation to the hepatocyte surface. PCSK9 inhibitors are recommended as adjuncts to diet and are the most tolerable statin dose for individuals with clinically atherosclerotic CVD, heterozygous hereditary hypercholesterolemia, homozygous familial hypercholesterolemia (evolocumab), or other conditions requiring additional LDL-C lowering (Liu et al., 2022) Another approach involves the use of bile acid-sequestering resins, such as colestipol and cholestyramine, which can lower LDL-C by approximately 15–26 %. However, these resins are poorly tolerated and adhere to them, mainly due to adverse gastrointestinal effects. Bempedoic acid is a novel, orally administered medication with a once-daily dosing regimen that is being studied as a potential treatment for statin-associated muscle adverse effects. In contrast to statins, bempedoic acid is activated in hepatocytes rather than in skeletal muscle. Phase 2 studies demonstrated a 20–30 % reduction in LDL-C, and when administered with ezetimibe, reductions reached 40–50 %. However, it is essential to consider the occurrence of adverse outcomes linked to the muscles in statin-intolerant trial participants, although this difference is marginal. Some participants in the ongoing phase 3 trials discontinued their medication owing to these symptoms (Yarrarapu et al., 2024).

6.3. Role of nutraceuticals

Studies reported the effectiveness of several nutraceutical agents as a natural alternative in statin-intolerent patients (Banach et al., 2018). Some examples such as red yeast rice (RYR) have been explored for the treatment of statin intolerance. RYR, has been shown to lower triglyceride and LDL-C levels. However, it is associated with certain side effects, such as myalgia, vertigo, and stomach distress. HC extract has been shown to decrease muscle destruction and improve ATP production in rats after exercise(Becker et al., 2009).

6.4. Statin dose alteration

Given the high prevalence of statin intolerance and SAMS, it is essential to evaluate the benefits of prescribing secondary and subsequent statins in a specific order. Evidence suggests that lipophilic statins such as simvastatin, atorvastatin, and lovastatin, which have a higher risk of rhabdomyolysis, may pose the greatest risk of SAMS. However, hydrophilic statins, such as pravastatin and fluvastatin, which penetrate muscles less, are believed to have a lower risk of myopathy. Re-challenge with a lower dose of the same or different statin is more likely to achieve sustained LDL-C reduction. For example, slow-release fluvastatin XL 80 mg twice daily reduced LDL-C by 32.8 % in 97 % of patients with prior muscle-related statin intolerance. A retrospective study also found that switching to non-daily rosuvastatin, known for fewer muscle side effects, reduced LDL-C by 21 % in individuals unable to tolerate daily statins (Vinci et al., 2021).

Simvastatin is strongly correlated with LDL and triglyceride-rich lipoproteins. Enhanced cellular uptake of simvastatin by C2C12 myotubes, facilitated through a lipoprotein lipase-mediated mechanism and potentiated by a low-pH environment and hyperlipidemia, may contribute to increased muscle toxicity. Hence, healthcare providers must consider hyperlipidemia and acidosis when prescribing statins to minimize the risk of statin-associated muscle damage (Ballard-Hernandez and Irwin, 2024).

7. Summary and conclusion

Statins have demonstrated efficacy in modulating liver enzyme levels and improving histological features of non-alcoholic fatty liver disease (NAFLD). While the evidence base remains limited, it is more substantial than prior systematic reviews, supporting the potential role of statins in attenuating disease progression. Clinicians are encouraged to initiate statin therapy in patients with NALFD. particularly those with elevated cardiovascular risk, as observational studies have indicated potential benefits in non-alcoholic steatohepatitis (NASH). However, the absence of randomized controlled trials (RCTs) underscores the need for further investigation to delineate the specific effects of statins on NASH and their impact on cardiovascular outcomes in this cohort. Current clinical guidelines affirm the safety profile of statins in the NAFLD and NASH populations.

Mechanistically, statin-associated myopathy has been linked to several pathways, including mitochondrial dysfunction, oxidative stress, apoptosis, disrupted insulin signaling via the Akt/mTOR axis, and impaired protein prenylation. Despite these adverse effects, statins remain indispensable for hyperlipidemia management, offering substantial benefits in both primary and secondary cardiovascular prevention, as well as NAFLD/NASH management. Advancing our understanding of the molecular mechanism of statin-induced myopathy is critical for developing targeted strategies for prevention and mitigation, thereby enhancing the therapeutic utility of this drug class.

CRediT authorship contribution statement

Pratiksha Nanepag: Writing – original draft. **Shubhada Mangrulkar:** Writing – review & editing, Visualization, Conceptualization. **Aarti Shriwas:** Writing – review & editing, Writing – original draft, Data curation. **Mayur Kale:** Visualization, Validation, Data curation. **Sapana Kushwaha:** Supervision, Conceptualization. **Nitu Wankhede:** Writing – review & editing, Writing – original draft. **Brijesh Taksande:** Validation, Supervision. **Milind Umekar:** Validation, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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