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STATIN INDUCED MYOPATHY: MECHANISMS, CLINICAL CHALLENGES AND ROLE OF LIPOPROTEIN (A) IN CARDIOVASCULAR RISK

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ABSTRACT

Statins are the cornerstone of lipid-lowering therapy and play a crucial role in reducing cardiovascular morbidity and mortality. However, their use is frequently limited by statin-associated muscle symptoms **(SAMS)**, ranging from mild myalgia to severe conditions such as rhabdomyolysis and immune-mediated necrotizing myopathy. Although relatively uncommon, statin-induced myopathy significantly affects treatment adherence and may compromise cardiovascular risk reduction. The pathogenesis is multifactorial, involving disruption of the mevalonate pathway, mitochondrial dysfunction, oxidative stress, and genetic susceptibility. Management strategies include dose adjustment, switching statins, intermittent dosing, and the use of non-statin therapies. In addition, lipoprotein(a) [**Lp(a)**] has emerged as an independent contributor to residual cardiovascular risk, particularly in statin-intolerant patients, as its levels are minimally affected by statins. A personalized approach integrating clinical evaluation and alternative therapeutic options is essential for optimizing outcomes. Emerging therapies and advances in pharmacogenomics offer promising directions for improving the management of dyslipidemia.

KEYWORDS: Statin-induced myopathy, Statin-associated muscle symptoms (**SAMS**), Statin intolerance, Lipoprotein(a), Cardiovascular risk, Dyslipidemia, HMG-CoA reductase inhibitors, Mitochondrial dysfunction, Pharmacogenomics, (SLCO1B1) polymorphism.

1. INTRODUCTION

1.1) BURDEN OF ISCHEMIC HEART DISEASE

Ischemic heart disease (IHD) remains a leading cause of morbidity and mortality worldwide, accounting for a substantial proportion of cardiovascular-related deaths.[1] The rising prevalence of sedentary lifestyles, obesity, diabetes, and dyslipidemia has significantly contributed to the increasing burden of atherosclerotic cardiovascular disease. Among modifiable risk factors, elevated low-density lipoprotein cholesterol (LDL-C) plays a central role in the pathogenesis of atherosclerosis, making lipid-lowering strategies essential for both primary and secondary prevention of IHD.[2]

1.2) ROLE OF STATINS IN PREVENTION OF IHD

Statins, also known as HMG-CoA reductase inhibitors, are the cornerstone of lipid-lowering therapy due to their well-established efficacy in reducing LDL-C levels and improving cardiovascular outcomes. By inhibiting the rate-limiting step in cholesterol biosynthesis, statins decrease hepatic cholesterol production and upregulate LDL receptors, thereby enhancing clearance of circulating LDL-C.[3] Large-scale clinical trials and meta-analyses have consistently demonstrated that statin therapy reduces the risk of myocardial infarction, stroke, and cardiovascular mortality, establishing their role as first-line agents in the management of dyslipidemia.[2,4]

1.3) STATIN-INDUCED MYOPATHY: A CLINICAL CHALLENGE

Despite their proven benefits, statins are associated with adverse effects, among which statin-associated muscle symptoms (SAMS) are the most frequently reported. Statin-induced myopathy encompasses a spectrum of muscle-related manifestations ranging from mild myalgia to severe conditions such as rhabdomyolysis and immune-mediated necrotizing myopathy.[5] These adverse effects can significantly impact patient adherence, often leading to dose reduction or discontinuation of therapy, thereby compromising cardiovascular risk reduction.[6] Although true statin-induced myopathy is relatively uncommon, the perception and reporting of muscle symptoms are high, creating a major clinical challenge in routine practice.[7]

1.4) NEED FOR RISK STRATIFICATION AND EMERGING BIOMARKERS

In patients who are unable to tolerate statin therapy or fail to achieve optimal lipid control, residual cardiovascular risk remains a significant concern. In this context, emerging biomarkers such as Lipoprotein(a) have gained increasing attention. Lipoprotein(a) is an

independent and genetically determined risk factor for atherosclerotic cardiovascular disease, and elevated levels are associated with an increased risk of premature IHD.[7] Importantly, statins have minimal effect on Lp(a) concentrations, highlighting the need for its assessment, particularly in patients with statin intolerance or unexplained cardiovascular risk.[7,8]

1.5) AIM OF THE REVIEW

This review aims to provide a comprehensive overview of statin-induced myopathy, focusing on its molecular mechanisms, clinical manifestations, risk factors, diagnostic approaches, and management strategies. Additionally, the review explores the emerging role of Lipoprotein(a) in cardiovascular risk assessment, particularly in patients with statin intolerance, thereby emphasizing the need for a more personalized approach to lipid management.

2. METHODOLOGY

This narrative review was conducted using a comprehensive literature search of electronic database including PubMed, Scopus and Google Scholar. Relevant articles published between (2000 and 2026) were considered.

Search terms: Statin-induced myopathy, statin-associated muscle symptoms (SAMS), statin intolerance, SLCO1B1 polymorphism, immune-mediated necrotizing myopathy, and lipoprotein (a).

Inclusion criteria

- Peer-reviewed articles
- English language publications
- Clinical trials, observational studies, meta-analyses and review articles
- Studies addressing mechanisms, risk factors, diagnosis and management of statin-induced myopathy.
- Articles evaluated the role of lipoprotein(a) in cardiovascular risk

Exclusion criteria

- Non-peer-reviewed sources
- Non-English publications
- Case reports with limited clinical relevance.
- Studies lacking clear methodological or clinical significance.

3) STATINS: MECHANISM AND CLINICAL IMPORTANCE

3.1) MECHANISM OF ACTION OF STATINS

Statins are competitive inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, the rate-limiting enzyme in the mevalonate pathway responsible for cholesterol biosynthesis. Inhibition of this enzyme reduces hepatic cholesterol production, leading to upregulation of low-density lipoprotein (LDL) receptors on hepatocytes and enhanced clearance of circulating LDL cholesterol (LDL-C).[3] In addition to lipid-lowering effects, statins exhibit pleiotropic properties, including improvement of endothelial function, stabilization of atherosclerotic plaques, and reduction of oxidative stress and inflammation.[4]

3.2) CLASSIFICATION OF STATINS[13]

Statins can be broadly classified based on their physicochemical properties into lipophilic and hydrophilic agents, which influence their tissue distribution and potential adverse effects.

- **Lipophilic statins,** such as Simvastatin and Atorvastatin, can readily diffuse across cell membranes and have wider tissue distribution, including skeletal muscle.
- **Hydrophilic statins,** such as Rosuvastatin and Pravastatin, are more hepato-selective and rely on active transport mechanisms for cellular uptake, which may be associated with a lower risk of muscle-related adverse effects.

3.3) CLINICAL IMPORTANCE OF CARDIOVASCULAR DISEASE

Statins are the cornerstone of pharmacological therapy for the prevention and management of atherosclerotic cardiovascular disease. Extensive clinical trials and meta-analyses have demonstrated that statin therapy significantly reduces the risk of major cardiovascular events, including myocardial infarction, stroke, and cardiovascular mortality.[2,4] Their benefits extend to both primary and secondary prevention across diverse patient populations. Despite their well-established efficacy and safety profile, the occurrence of statin-associated muscle symptoms remains a major barrier to optimal adherence. Discontinuation or suboptimal dosing due to perceived or actual adverse effects may lead to inadequate lipid control and increased residual cardiovascular risk. Therefore, understanding both the therapeutic benefits and potential adverse effects of statins is essential for optimizing patient outcomes.

3.4) COMPARISON OF COMMONLY USED STATINS

PARAMETER	SIMVASTATIN	ATORVASTATIN	ROSUVASTATIN	PRAVASTATIN
Type	Lipophilic	Lipophilic	Hydrophilic	Hydrophilic
Potency	Moderate	High	Very High	Moderate

(LDL↓)				
Metabolism	CYP3A4	CYP3A4	Minimal CYP	Non-CYP
Half-life	Short (≃ 2 hrs)	Long (≃ 14 hrs)	Long (≃ 19 hrs)	Short (≃ 2 hrs)
Muscle Penetration	High	High	Low	Low
Myopathy Risk	Higher	Moderate-High	Lower	Lower
Drug Interactions	High	Moderate	Low	Minimal
Dose Range (mg/day)	10-40 (mg/day)	10-80 (mg/day)	5-40 (mg/day)	10-40 (mg/day)
Clinical Use	Moderate LDL reduction	High-intensity therapy	High-Intensity, potent	Safer option in intolerance

4) DEFINITION AND CLASSIFICATION OF STATIN-INDUCED MYOPATHY[14]

Statin-associated muscle symptoms (SAMS) represent a spectrum of muscle-related adverse effects associated with statin therapy. Statin-induced myopathy is a broad term encompassing various clinical presentations ranging from mild muscle discomfort to severe, life-threatening conditions. Although the overall incidence of true statin-induced myopathy is relatively low, muscle-related complaints are among the most commonly reported reasons for statin discontinuation.[5,6]

4.1) STATIN-ASSOCIATED MUSCLE SYMPTOMS (SAMS)

(SAMS) is a general term used to describe all muscle-related symptoms occurring during statin therapy, regardless of causality. These symptoms typically include muscle pain, tenderness, stiffness, or weakness, often affecting proximal muscle groups such as the thighs and shoulders. Importantly, many cases of (SAMS) may occur without objective biochemical abnormalities, and a proportion may be influenced by the nocebo effect.

4.2) MYALGIA

Myalgia is the most common presentation of statin-induced muscle toxicity and is characterized by muscle pain or discomfort without significant elevation of serum creatine kinase (CK) levels. Symptoms are usually symmetrical and may be exacerbated by physical activity. Although generally mild, myalgia can significantly affect quality of life and adherence to therapy.

4.3) MYOSITIS

Myositis refers to muscle symptoms associated with elevated CK levels, indicating underlying muscle inflammation or injury. Patients may present with muscle pain, weakness,

and biochemical evidence of muscle damage. This condition is less common than myalgia but warrants closer monitoring and possible modification of statin therapy.

4.4) RHABDOMYOLYSIS

Rhabdomyolysis is a rare but serious complication characterized by extensive muscle breakdown, marked elevation of CK levels (often >10 times the upper limit of normal), and release of myoglobin into the bloodstream. This can lead to acute kidney injury and may be life-threatening if not promptly recognized and managed. The risk is higher with high-dose statins and in the presence of drug interactions or comorbid conditions.

4.5) IMMUNE-MEDIATED NECROTIZING MYOPATHY

A rare but distinct form of statin-associated myopathy is Immune-mediated necrotizing myopathy, which is characterized by progressive muscle weakness, markedly elevated CK levels, and the presence of autoantibodies against HMG-CoA reductase (anti-HMGCR antibodies).[14] Unlike other forms of statin-induced myopathy, symptoms may persist or even progress after discontinuation of the statin, often requiring immunosuppressive therapy.

5) MOLECULAR MECHANISM OF STATIN-INDUCED MYOPATHY

The pathogenesis of Statin-induced myopathy is multifactorial and not completely understood. Several interrelated mechanisms have been proposed, primarily involving disruption of the mevalonate pathway, mitochondrial dysfunction, impaired cellular energy production, and genetic susceptibility.

5.1) INHIBITION OF THE MEVALONATE PATHWAY

Statins inhibit HMG-CoA reductase, the key enzyme in the mevalonate pathway responsible for cholesterol synthesis. This pathway also produces several important non-sterol isoprenoids, including farnesyl pyrophosphate and geranylgeranyl pyrophosphate, which are essential for cellular signaling and membrane integrity. Inhibition of these intermediates may impair protein prenylation and disrupt normal muscle cell function, contributing to myocyte injury.[3]

5.2) COENZYME Q10 DEPLETION

Coenzyme Q10 (ubiquinone) is synthesized via the mevalonate pathway and plays a crucial role in mitochondrial electron transport and ATP production. Statin therapy may reduce CoQ10 levels, leading to impaired oxidative phosphorylation and decreased energy

availability in muscle cells. However, clinical evidence regarding the benefit of CoQ10 supplementation in preventing or treating statin-induced myopathy remains inconsistent.[9]

5.3) MITOCHONDRIAL DYSFUNCTION AND OXIDATIVE STRESS

Mitochondrial dysfunction is considered a central mechanism in statin-induced muscle toxicity. Statins may impair mitochondrial respiratory chain activity, leading to reduced ATP generation and increased production of reactive oxygen species (ROS). The accumulation of oxidative stress can damage muscle cell membranes, proteins, and DNA, ultimately resulting in muscle fiber injury and apoptosis.[8,10]

5.4) DISTURBANCE OF CALCIUM HOMEOSTASIS

Statins have been shown to alter calcium signaling within skeletal muscle cells by affecting calcium release from the sarcoplasmic reticulum. Disruption of intracellular calcium homeostasis can activate proteolytic enzymes and promote muscle cell damage. This imbalance may also contribute to muscle weakness and fatigue observed in affected patients.[11]

5.5) GENETIC SUSCEPTIBILITY

Genetic factors play a significant role in determining individual susceptibility to statin-induced myopathy. Variants in genes encoding drug transporters and metabolizing enzymes can influence statin pharmacokinetics. In particular, polymorphisms in the SLCO1B1 gene, which encodes the hepatic uptake transporter OATP1B1, are strongly associated with increased statin plasma concentrations and a higher risk of myopathy.[12] Variations in cytochrome P450 (CYP450) enzymes may also contribute to altered drug metabolism and toxicity.[12]

5.6) IMMUNE-MEDIATED MECHANISMS

A rare but important mechanism involves immune-mediated muscle injury. In some patients, statins may trigger an autoimmune response characterized by the formation of antibodies against HMG-CoA reductase. This leads to Immune-mediated necrotizing myopathy, a condition marked by progressive muscle weakness and persistent elevation of creatine kinase levels, even after discontinuation of statin therapy. This form typically requires immunosuppressive treatment.[14]

6) RISK FACTORS

6.1) PATIENT-RELATED FACTORS

Advanced age, female sex, and low body mass index are associated with increased susceptibility to statin-induced myopathy. Comorbid conditions such as renal or hepatic impairment, hypothyroidism, and possibly vitamin D deficiency may further increase the risk.[5,6]

6.2) STATIN-RELATED FACTORS

Higher statin doses are consistently linked to a greater risk of muscle toxicity. Lipophilic statins, such as Simvastatin and Atorvastatin, have wider tissue distribution and may pose a higher risk, whereas hydrophilic statins like Rosuvastatin and Pravastatin are relatively safer.[13]

6.3) DRUG INTERACTIONS

Concomitant use of drugs such as fibrates, macrolide antibiotics, azole antifungals, and certain calcium channel blockers can increase statin levels by inhibiting metabolism, thereby elevating the risk of myopathy.[13]

6.4) GENETIC FACTORS

Genetic variation, particularly in the SLCO1B1 gene, can impair statin uptake and increase systemic exposure, predisposing individuals to muscle toxicity.[12]

7) CLINICAL PRESENTATION AND DIAGNOSIS

The clinical presentation varies widely, ranging from mild muscle discomfort to severe muscle injury. Early recognition is important to prevent complications and ensure appropriate management.

7.1) CLINICAL PRESENTATION

Patients commonly present with symmetrical muscle pain, tenderness, or weakness, particularly involving proximal muscle groups such as the thighs and shoulders. Symptoms may occur weeks to months after initiation of therapy and can be exacerbated by physical activity. In severe cases, patients may develop features of Rhabdomyolysis, including muscle weakness, dark-colored urine, and fatigue.[7]

7.2) LABORATORY EVALUATION

Measurement of serum creatine kinase (CK) is the primary laboratory test used to assess muscle injury. Mild cases may show normal CK levels, whereas significant elevations suggest myositis or rhabdomyolysis. Additional investigations, including liver and renal function tests, may be required to evaluate associated complications.[7]

7.3) ADVANCED DIAGNOSTIC METHOD

Detection of anti-HMG-CoA reductase antibodies can help identify Immune-mediated necrotizing myopathy. Electromyography and muscle biopsy may be considered in selected patients to confirm diagnosis and exclude other neuromuscular disorders.[14]

7.4) DIFFERENTIAL DIAGNOSIS

It is essential to exclude other causes of muscle symptoms, including hypothyroid myopathy, vitamin D deficiency, fibromyalgia, and inflammatory myopathies. Careful clinical assessment and appropriate investigations are required to differentiate these conditions from statin-induced muscle toxicity.

8) MANAGEMENT OF STATIN-INDUCED MYOPATHY

The management of Statin-induced myopathy focuses on relieving symptoms while maintaining adequate cardiovascular risk reduction. A stepwise and individualized approach is recommended.

8.1) STATIN DECONTINUATION AND RECHALLENGE

In patients presenting with significant muscle symptoms, temporary discontinuation of the statin is advised. Symptoms often resolve within days to weeks after withdrawal. Once symptoms improve, rechallenging with the same or a lower dose of statin can help confirm causality and re-establish therapy.[17]

8.2) DOSE ADJUSTMENT AND SWITCHING STATINS

Reducing the statin dose or switching to a different statin may improve tolerability. Hydrophilic statins such as Rosuvastatin and Pravastatin are often better tolerated compared to lipophilic agents.[13]

8.3) INTERMITTENT DOSING STRATEGIES

For patients unable to tolerate daily statin therapy, intermittent dosing (e.g., alternate-day or twice-weekly regimens) may be considered. This approach can provide partial lipid-lowering benefits with improved tolerability.

8.4) NON-STATIN THERAPIES[18]

- **Ezetimibe** reduces intestinal cholesterol absorption
- (PCSK9 inhibitors) such as **Evolocumab** significantly lower LDL-C levels
- **Bempedoic acid** offers an additional oral option for LDL reduction

These agents can be used alone or in combination to achieve lipid targets.

8.5) MANAGEMENT OF SEVERE CASES

In rhabdomyolysis, immediate discontinuation of statin therapy and supportive care, including hydration and renal monitoring, are essential. For Immune-mediated necrotizing myopathy, immunosuppressive therapy may be required.[19]

9) LIPOPROTEIN(a) AND RESIDUAL CARDIOVASCULAR RISK

Despite effective statin therapy, a significant proportion of patients continue to experience cardiovascular events, a phenomenon referred to as residual cardiovascular risk. In patients with Statin-induced myopathy, this risk may be further increased due to dose reduction or discontinuation of therapy. In this context, Lipoprotein(a) has emerged as an important and often underrecognized contributor to cardiovascular risk.[20]

9.1) OVERVIEW OF LIPOPROTEIN(a)

Lipoprotein(a) [**Lp(a)**] is a low-density lipoprotein-like particle consisting of an apolipoprotein B-100 moiety linked to **apolipoprotein(a)**. It is genetically determined and remains relatively stable throughout life. Elevated [Lp(a)] levels are associated with increased atherogenesis, inflammation, and thrombosis, contributing to the development of ischemic heart disease.[21]

9.2) ROLE IN ISCHEMIC HEART DISEASE

High [**Lp(a)]** levels are an independent risk factor for atherosclerotic cardiovascular disease, including myocardial infarction and stroke. Unlike LDL-C, [Lp(a)] levels are minimally influenced by lifestyle modifications and are not significantly reduced by statin therapy, which may even slightly increase its levels in some individuals.[22]

9.3) IMPORTANCE IN STATIN-INTOLERANT PATIENTS

In patients who are unable to tolerate adequate statin therapy, unrecognized elevated [Lp(a)] may explain persistent or unexplained cardiovascular risk. Identification of high [Lp(a)] levels in such individuals can help guide more aggressive risk management strategies, including the use of non-statin lipid-lowering therapies.

9.4) CLINICAL IMPLICATIONS AND TESTING

Current guidelines recommend measuring [Lp(a)] at least once in adulthood, particularly in individuals with a family history of premature cardiovascular disease or unexplained high risk. Elevated levels can support early and more intensive intervention, even when conventional lipid parameters appear controlled.[21]

10) CONTROVERSIES AND EVIDENCE GAPS

10.1) OVERDIAGNOSIS vs TRUE MYOPATHY

Although muscle symptoms are frequently reported in patients receiving statins, the actual incidence of true statin-induced myopathy is relatively low. Randomized controlled trials have shown similar rates of muscle-related symptoms in statin and placebo groups, suggesting that many reported cases may not be directly attributable to statin therapy.[5]

10.2) THE NOCEBO EFFECT

It is defined as, when a negative expectation of treatment lead to perceived adverse effects which has been proposed as a significant contributor to statin intolerance. Patients who are aware of potential side effects may be more likely to report muscle symptoms, even in the absence of a pharmacological cause. This highlights the importance of patient education and counseling.[5]

10.3) COENZYME Q10 SUPPLEMENTATION

Coenzyme Q10 has been implicated in the pathogenesis of statin-induced myopathy, clinical trials evaluating (CoQ10) supplementation have produced inconsistent results. While some studies suggest symptomatic improvement.[9]

10.4) GAPS IN EVIDENCE

There is still limited understanding of why only certain individuals develop statin-induced myopathy despite widespread use of these drugs. Variability in genetic susceptibility, drug interactions, and environmental factors requires further investigation.

11) FUTURE PERSPECTIVES

Statin-induced myopathy are paving the way for more personalized and effective approaches to lipid management. Future research is focused on improving risk prediction, developing targeted therapies, and optimizing treatment strategies for statin-intolerant patients.

11.1) PHARMACOGENOMICS AND PERSONALIZED THERAPY

Emerging evidence highlights the role of pharmacogenomics in predicting susceptibility to statin-induced myopathy. Genetic screening, particularly for variants in the (**SLCO1B1**) gene, may help identify individuals at higher risk and guide personalized statin selection and dosing. This approach has the potential to improve safety and adherence.[12]

11.2) NOVEL LIPID-LOWERING THERAPIES

The development of non-statin therapies offers promising alternatives for patients who are unable to tolerate statins. Agents such as (**Evolocumab)** and other (**PCSK9 inhibitors)** have demonstrated significant reductions in LDL-C levels and cardiovascular events. Newer agents, including **(inclisiran)** and (**bempedoic acid**), provide additional options for long-term lipid control.[12]

11.3) EMERGING THERAPIES TARGETING LIPOPROTEIN(a)

Targeted therapies aimed at reducing Lipoprotein(a) levels are currently under investigation. These include antisense (**oligonucleotides**) and **small interfering RNA** (siRNA) based treatments, which have shown promising results in lowering [Lp(a)] concentrations. Such therapies may play a crucial role in addressing residual cardiovascular risk, particularly in statin-intolerant patients.[20]

12) CONCLUSION

Statin-induced myopathy represents a clinically significant but relatively uncommon adverse effect of statin therapy. Although most muscle-related symptoms are mild and manageable, they remain a major cause of poor adherence and discontinuation, potentially compromising cardiovascular outcomes. A clear understanding of underlying mechanisms, risk factors, and clinical presentation is essential for early recognition and appropriate management.

Individualized treatment strategies, including dose adjustment, statin switching, and the use of non-statin therapies, can help maintain effective lipid control in affected patients. In addition, assessment of [**Lipoprotein(a)**] provides valuable insight into residual

cardiovascular risk, particularly in individuals with statin intolerance or unexplained disease progression.

Future advances in pharmacogenomics and the development of novel lipid-lowering agents, including therapies targeting lipoprotein (a), are expected to further improve the management of dyslipidemia. A personalized approach integrating clinical, biochemical, and genetic factors will be essential for optimizing cardiovascular risk reduction while minimizing adverse effects.

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