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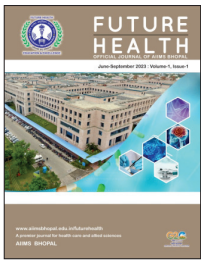

*Review Article*

# Understanding statin intolerance: Challenges, mechanisms, and management strategies

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## ABSTRACT

Statins are among the most commonly prescribed drugs for the treatment and prevention of cardiovascular diseases (CVD), such as coronary artery disease and stroke. They function by blocking HMG-CoA reductase that produces cholesterol, which lowers the levels of low-density lipoprotein (LDL) cholesterol. But despite its demonstrated ability to lower cardiovascular risk, a sizable portion of individuals develop adverse effects that result in statin intolerance. Statin intolerance is a frequent cause of statin cessation or noncompliance. It is linked to fewer clinical benefits and less-than-ideal cardiovascular risk management. This review article explores the concept of statin intolerance, including its occurrence, causes, symptoms, diagnosis, and treatment options.

**Keywords:** Statin, Cardiovascular diseases, Low-density lipoprotein

## INTRODUCTION

Statins, or HMG-CoA reductase inhibitors, are among the most widely prescribed medications for the prevention and management of cardiovascular diseases (CVD), including hyperlipidemia, coronary artery disease, and stroke. They work by inhibiting the enzyme responsible for cholesterol synthesis in the liver, thereby lowering low-density lipoprotein (LDL) cholesterol levels. However, despite their proven efficacy in reducing cardiovascular risk, a significant number of patients experience side effects that lead to what is known as statin intolerance.

Statin intolerance is a common reason for discontinuation or non-adherence to statin therapy. It is associated with reduced clinical benefits and suboptimal management of cardiovascular risk. This review article examines the concept of statin intolerance, including its prevalence, mechanisms, clinical manifestations, diagnosis, and strategies for management.

### Prevalence and impact of statin intolerance

Statin intolerance is a poorly defined condition characterized by the inability to tolerate statin therapy due to its side effects. The reported prevalence of statin intolerance varies widely, ranging from 5% to 25% of patients, depending on the study population and definitions used.[1] While some individuals experience mild, transient side effects, others face more debilitating symptoms that can lead to permanent discontinuation of therapy.

The burden of statin intolerance is significant, as it can prevent patients from achieving optimal lipid-lowering goals and reduce the benefits of statin therapy in terms of reducing cardiovascular

morbidity and mortality. Non-adherence to statin therapy due to intolerance is associated with increased healthcare costs, hospitalizations, and a higher incidence of adverse cardiovascular outcomes.

### Mechanisms of statin intolerance

The exact mechanisms underlying statin intolerance remain incompletely understood, but several theories have been proposed. Broadly, these mechanisms can be categorized into pharmacokinetic, pharmacodynamic, and genetic factors, as well as the influence of statins on comorbid conditions.

### Muscle-related side effects

The most commonly reported form of statin intolerance is muscle-related symptoms, which affect approximately 10–15% of patients on statin therapy. These symptoms include myalgia (muscle pain), myopathy (muscle weakness), and, in rare cases, rhabdomyolysis (severe muscle breakdown). Muscle-related side effects are thought to result from the depletion of coenzyme Q10 (CoQ10) and other bioactive molecules involved in mitochondrial function, which are downstream products of the mevalonate pathway, the same pathway inhibited by statins.[2]

### Genetic factors

Genetic predisposition plays a significant role in statin intolerance. Certain genetic variants, including polymorphisms in the SLCO1B1 gene, have been associated with an increased risk of muscle-related adverse effects. This gene codes for a transporter involved in the hepatic uptake of statins. Patients with specific SLCO1B1 variants have an increased risk of statin-induced muscle toxicity, particularly with certain statins like simvastatin.[3]

Other genetic factors related to mitochondrial dysfunction, inflammatory responses, and drug metabolism may also contribute to statin intolerance.

### Pharmacokinetic interactions

Statins are metabolized by liver enzymes, particularly cytochrome P450 enzymes. Patients who are on medications that interfere with these enzymes may experience increased statin levels, leading to an increased risk of adverse effects. Additionally, impaired renal function can lead to higher statin concentrations, particularly for hydrophilic statins like rosuvastatin and pravastatin.

### Other factors

Other factors that may increase the risk of statin intolerance include older age, female sex, obesity, and comorbidities such as diabetes mellitus and hypothyroidism. These conditions may alter statin metabolism or exacerbate muscle-related side effects, contributing to intolerance.

### Clinical manifestations of statin intolerance

The symptoms of statin intolerance can range from mild discomfort to severe, disabling conditions. The most common manifestations include:

- Myalgia: Generalized muscle pain or discomfort without elevation of creatine kinase (CK) levels.
- Myopathy: Muscle weakness accompanied by elevated CK levels, indicating muscle injury.
- Rhabdomyolysis: A rare but serious complication characterized by severe muscle damage, elevated CK levels, and the release of muscle proteins like myoglobin into the bloodstream, which can lead to kidney damage.

In addition to these , some patients report non-muscle-related side effects, including:

- Gastrointestinal symptoms: Nausea, constipation, and abdominal pain.
- Cognitive effects: Memory loss, confusion, or “brain fog,” although these symptoms are less frequently reported.
- Liver enzyme elevation: A small percentage of patients may experience liver enzyme abnormalities, though these are typically reversible upon discontinuation of the drug.

### Diagnosis of statin intolerance

The diagnosis of statin intolerance is primarily clinical, based on the patient’s history and reported symptoms. The following steps are typically involved:

1. History and Symptom Assessment: Detailed evaluation of the patient's symptoms, including onset, duration, and severity, as well as any prior history of statin use.
2. Exclusion of Other Causes: Differential diagnosis should rule out other potential causes of muscle pain, such as thyroid disorders, autoimmune diseases, and electrolyte imbalances.
3. Discontinuation Challenge: In cases of suspected statin intolerance, discontinuing the statin may help confirm the diagnosis if symptoms resolve and reappear upon rechallenge with the same or a different statin.

Laboratory tests, including muscle enzyme levels (e.g., CK) and liver function tests, may also be useful in assessing the extent of muscle or liver injury. However, they are not always diagnostic of statin intolerance.

### Management of statin intolerance

Managing statin intolerance involves a multifaceted approach aimed at minimizing the side effects while maintaining adequate cardiovascular risk reduction. The following strategies have been suggested.

### Statin dose adjustment or switch

For many patients, reducing the statin dose or switching to a different statin may improve tolerance. Hydrophilic statins, such as pravastatin or rosuvastatin, are less likely to cause muscle-related side effects compared to lipophilic statins like simvastatin and atorvastatin. Additionally, lower doses of statins may be better tolerated without compromising their lipid-lowering efficacy.

### Coenzyme Q10 supplementation

There is some evidence to suggest that CoQ10 supplementation may alleviate muscle-related side effects, although data is not conclusive. CoQ10 is involved in mitochondrial energy production, and statin-induced depletion of CoQ10 may contribute to muscle discomfort. However, further clinical studies are needed to confirm its benefit.

### Alternative lipid-lowering therapies

If statin intolerance persists despite dose adjustments, alternative lipid-lowering agents may be considered. These include:

- Ezetimibe: A cholesterol absorption inhibitor that can lower LDL cholesterol by inhibiting cholesterol absorption in the small intestine.
- PCSK9 Inhibitors: Monoclonal antibodies such as evolocumab and alirocumab can significantly lower LDL cholesterol by inhibiting the PCSK9 protein, a regulator of LDL receptor degradation.
- Bempedoic Acid: A newer agent that inhibits ATP-citrate lyase, an enzyme upstream of HMG-CoA reductase in the cholesterol biosynthesis pathway, and may be an option for patients who cannot tolerate statins.

### Non-pharmacological approaches

Lifestyle interventions, such as dietary modifications (e.g., low saturated fat, increased fiber), weight management, and regular physical activity, should always be a part of the strategy to manage dyslipidemia, especially for those unable to tolerate statins.

## CONCLUSION

Statin intolerance remains a significant challenge in the management of cardiovascular risk, but with careful attention to diagnosis and individualized treatment strategies, many patients can still achieve effective lipid-lowering and cardiovascular protection. Understanding the underlying mechanisms of statin intolerance, coupled with newer therapeutic options, provides hope for those who are unable to tolerate traditional statin therapy. Tailored management, including dose adjustments, alternative medications, and supportive interventions, can help mitigate the adverse effects of statins while ensuring optimal outcomes for patients at risk of cardiovascular disease.

### Author contributions

SB and AS: Contributed to the design, literature search and writing of the manuscript.

### Ethical approval

Institutional Review Board approval is not required.

### Declaration of patient consent

Patient's consent not required as there are no patients in this study.

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### Conflicts of interest

There are no conflicts of interest.

### Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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