REVIEW ARTICLE

Statin Intolerance: Mechanisms, Risk Factors, Clinical Manifestations, And Management

ABSTRACT

The big cause of mortality across world is cardio vascular disease, and high levels of low-density lipoprotein-cholesterol is known to be a significant modifiable risk factor in occurrence of atherosclerotic cardiovascular disease. Main agent of lipid-lowering therapy is statins, which are 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, which have shown statistically significant reductions in cardiovascular morbidity and mortality. Besides reducing low-density lipoprotein-cholesterol, statins also have a number of pleiotropic effects such as endothelium promotion, reduction of vascular inflammation, as well as stabilization of atherosclerotic plaques. The established benefits and a positive safety profile of statins are usually disrupted by long-term adherence to statin therapy by intolerance, most often in form of Statin-associated muscle symptoms.

Statin intolerance is a multifactorial and complicated clinical entity that is dependent on pharmacological characteristics of statins, patient-specific risk factors, hereditary vulnerability, and possible drug-drug interactions. The mechanisms of intolerance implicated in mechanism are dysfunction in mitochondria caused by decreased production of coenzyme Q10, calcium homeostasis, immune mediated destruction of muscle, and genetic differences in drug transport and metabolism Increased susceptibility is the other risk factors, which involve advanced age, sex (female), less body mass index, comorbid metabolism disorders, and other concurrent medications.

This review summarizes the current literature regarding statin intolerance as to its pathophysiological processes, predisposing factors, manifestations, and the management of statin intolerance which is based on evidence. It also underscores the usefulness of organized diagnostic assessment such as evaluation of time of onset of symptoms, lab tests and dechallenge-rechallenge methods to determine actual intolerance and perceived negative effect. Individualised dosage, a change in combination of non-statin lipid-lowering or statin drugs to optimize statin therapy is important in order to sustain a proper cardiovascular risk reduction. Enhanced awareness and systematic testing of statin intolerance can be used to increase the rate of therapy compliance and guarantee that the patients remain enjoying the established cardioprotective impact of statin course.

Keywords: *Statin-associated muscle symptoms; Statin intolerance; HMG-CoA reductase inhibitors; Dyslipidemia; Cardiovascular disease; LDL cholesterol; Pharmacogenetics; Lipid-lowering therapy; Drugs safety; Cardiovascular risk manageme*

1. INTRODUCTION

1.1 Burden of Cardiovascular disease

This disease causes CVD, which is most common reason of death and morbidity in entire world as nearly a third of total number of deaths worldwide is due to disease [1]. According to Global Burden of Disease (GBD) 2023 study, CVD killed approximately 19.2 million people in the world where more than 620 million cases of the disease are prevalent, and this amount is quite high in comparison with the numbers in 1990 [1]. Ischemic stroke and heart disease are main causes of death and disability caused by CVDs in the world [1]. The leading contributors to the burden are population ageing, urbanization, and increased proportion of modifiable metabolic risk factors, such as high levels of LDL-C and high blood pressure, obesity and diabetes [1,2]. The fact that high LDL-C is viewed as the most important causal risk factors in the process of the atherosclerotic cardiovascular disease development are worth noting, which is why lipid-lowering instruments are vital in both primary and secondary prevention [2].

1.2 Role of Statins in Dyslipidemia

Dyslipidemia, especially, high levels of LDL-C, is amog the determinants of cardiovascular risk that can be modified. The most frequently used lipid lowering therapy is statins since it has a good evidence base and benefit profile across all the therapies. Statins act as competitive agents and inhibit hepatic production of cholesterol by inhibiting the rate-limiting enzyme in the process: the HMG-CoA reductase. This obstruction reduces cholesterol in cell and promotes the LDL receptor up-regulation into hepatocytes thus boosting clearance of the LDL-C in circulation [3].

Statins have other vascular protective effects in addition to the lipid reduction. Experimental and clinical research reveals that endothelial function, vascular inflammation, and atherosclerotic plaque stabilization have improved, which ultimately lead to lowering of the risk of thrombotic cardiovascular episode [4]. Meta-analyses and large-scale randomized trials all demonstrate a high degree of statin therapy in decreasing the occurrence of myocardial infarction, stroke, and cardiovascular mortality in primary and secondary prevention. Notably, extent of cardiovascular risk reduction is equal to the amount of LDL-C reduction, which provides evidence of recommendations in the guidelines on intensive statin therapy in persons who are high-risk and who are selected properly [5].

1.3 Clinical Importance of Statins

Statins a key in management of the cardiovascular system due to their consistent and reproducible effect in preventing adverse cardiovascular events in wide range of patients [6]. Significant evidence of statin therapy as an important intervention in myocardial infarction of the primary and secondary prevention, ischemic stroke, and cardiovascular mortality has been shown in huge randomized clinical trials and meta-analyses. Notably, extent of benefit is directly proportional to the complete change in LDL-C, and this reinforces the principle that larger the LDL-C lowering, the more reduction of cardiovascular risk will be [7].

In addition to the reduction of events, the statins also lead to plaque stabilization, endothelial functional improvement, and vascular inflammatory attenuation, which all decrease the risk of acute plaque rupture. These effects are especially detrimental in the high-risk group, such as people with pre-existing atherosclerotic cardiovascular disease, diabetes mellitus, or significantly increased LDL-C concentrations. The present international practice hence suggests use of statins as initial treatment in the process of managing lipids to patients who are at an intermediate to high cardiovascular risk [8].

Statins continue to be the common prescribed medications in the world due to their more quality of proof, good safety profile, as well as cost-effectiveness. Their clinical significance is in not just the lowering of lipids, but also the ability to significantly lower the long-term morbidity and mortality of the cardiovascular system in case of their proper and regular use.

1.4 Problem of Discontinuation Due to Intolerance

In spite of their good cardiovascular effects, long term compliance with statin therapy is still not optimal in clinical practice daily. Quite a significant percentage of patients either drop statins within a first year of intake, and in most cases, they report muscle-specific symptoms or perceived side effects as the main cause [9]. The evidence on the basis of observation shows that statin withdrawal or subpar adherence correlates with high risk of cardiovascular events and death, especially, in people under secondary prevention [10].

Statin-associated muscle syndrome is the major reported discontinuation cause. Nonetheless, controlled trials indicate that the actual rate of drugs-induced muscle toxicity is significantly lower than the actual cases resulting in routine practice, which is also because of expectation bias and the so-called nocebo effect [11]. False interpretation of nondiscriminate musculoskeletal symptoms to statin therapy tends to result in the untested and untrial discontinuation.

The clinical consequences of statin withdrawal are high. Discontinuation of treatment leads to re-increase of LDL levels, loss of accumulate-stabilizing action, and cardiovascular risk. Hence, distinguishing between actual statin intolerance and supposed intolerance is of paramount importance to guarantee continuity of therapeutic treatment, and to maximize cardiovascular events.

1.5 Need for Proper Evaluation

Stopping of statins in clinical practice can also be done without, though that should not be done, adequate evaluation; in most instances, this is done due to fear of adverse events and not due to intolerance. These decisions may inadvertently put high risk patients at risk of avoidable cardiovascular incidents. Thus, a close and well-organized evaluation is necessary prior to initiating treatment and when side effects are observed.

Premedical examinations (lipid profile, liver, and renal tests, blood glucose, thyroid tests etc.) should be recorded before the commencement. The use of secondary causes of dyslipidemia and attention to pre-existing muscle complaints prevents the misdiagnosis of subsequent symptoms of statins [12].

Clinicians must take a methodical approach when adverse effects are reported especially muscle symptoms. Not every symptom is really a statin related symptom. Specific laboratory testing (e.g., creatine kinase in case of clinical necessity), test of drug interaction, and a transient withdrawal and reintroduction to a reduced dose or other statin will help rule out the possibility of true intolerance [13,14]. There has been evidence that most of the patients who were initially intolerant may tolerate statins on reassessment.

Significantly, beneficence, nonmaleficence, and autonomy in risk-benefit analysis can support guided decision-making. The adverse effects of statins are manageable in high cardiovascular risk and therefore its protective effects overrule such effects. Adherence and long-term treatment success will be enhanced through the appropriate counseling and information.

2. OVERVIEW OF STATINS

2.1 Classification: Lipophilic and Hydrophilic Statins

Statins, HMG-CoA reductase inhibitors are a structurally varied group of inhibitors which vary mainly in terms of their lipophilicity. They are categorized as lipophilic and hydrophilic agents based on the solubility properties [15].

Atorvastatin, lovastatin, fluvastatin, simvastatin and pitavastatin are statins which are lipophilic that passively diffuse through cell membranes and show greater tissue distribution. Conversely, hydrophilic statins like rosuvastatin and pravastatin rely mostly on active transport systems to be taken up in the hepatocyte making them more selective in the hepatic tissue [15]. physicochemical differences may affect the tolerability profiles and have an impact on systemic exposure.

Pharmacokinetic analysis reveals that lipophilicity influences tissue penetration, metabolism and their ability to interact [16]. Comparative clinical studies also suggest that despite the both classes being effective in reducing the LDL cholesterol levels, patient specific characteristics tend to dictate the agent to be used [17].

2.2 Commonly Used Statins

the most frequent statins in use.

Atorvastatin

Rosuvastatin

Simvastatin

Pravastatin

Fluvastatin

Pitavastatin

The choice is based on Low density lipid-lowering potency, lipophilicity, metabolic pathway, comorbidities and possible drug-drug interactions [15–17].

2.3 Pleiotropic Effects of Statins

Along with the lipid lowering effect, statins have numerous vascular effects. There is experimental and clinical evidence of enhanced endothelial performance, reduction of oxidative stress, regulation of inflammatory mechanisms and stabilization of atherosclerotic plaques [18]

Partially due to decreased isoprenoid production and the following inhibition of intracellular signaling proteins, i.e., Rho and Rac, these pleiotropic effects can be ascribed [18]. Although LDL lowering is the most common biological protection of the cardiovascular system, these other biological effects can potentially increase the overall therapeutic effect.

2.4 Mechanism of Action: HMG-CoA Reductase Inhibition

The main lipid-lowering activity of all statins is the competitive inhibition of HMG-CoA reductase, the rate-limiting enzyme in the hepatic cholesterol biosynthesis. Based on the effects of the human medication, blocking of the HMG-CoA reductase lowers transformation of HMG-CoA to mevalonate, which results in lower intracellular cholesterol levels in hepatocytes [19]. This decrease causes the sterol regulatory element-binding proteins (SREBPs) to be activated; this leads to the expression of LDL receptor being increased. When LDL receptors are increased in density, it promotes receptor mediated clearance of LDL particles that are in circulation in the plasma [20,21].

This may also be related to cholesterol lowering, but also the blocking of the mevalonate pathway lowers production of isoprenoid intermediates, needed to prenylate small GTP-binding proteins [22]. The mechanism plays roles in some of the non-lipid biological (pleiotropic) effects of statin, such as endothelial and vascular inflammation.

2.5 LDL Reduction and Cardiovascular Impact

The prevention of LDL cholesterol is the primary treatment goal of statin-based treatment. A massive meta-analysis of personal information obtained in 27 randomized trials revealed that every 1 mmol/L decrease in LDL cholesterol is linked to a considerable proportional reduce in major vascular events in even the people whose risk is comparatively low at their baseline [23, 24].

Clinical efficacy is directly proportional to extent of LDL lowering, which supports significance of LDL receptor up-regulation and hepatic clearance increases in the above-described mechanisms [25].

3. DEFINITION AND CLASSIFICATION OF STATIN INTOLERANCE

The inability due to Statin intolerance to tolerate statin therapy at dosages needed to produce apposite lipid lowering because of the occurrence of adverse effects, which are temporary (related to the start of drug therapy), reversible on discontinuation, and repeatable with rechallenge [26,27]. The modern medical opinion defines total and partial intolerance: in the former, no dosage of statin could be tolerated, in the latter, patients can tolerate lower doses or use different statins but cannot meet the target of LDL-C [28].

Statin-associated muscle symptoms a spectrum between mild myalgia and severe rhabdomyolysis is the most reported manifestation [29]. Professional societies such as the National Lipid Association (NLA) and the European Atherosclerosis Society (EAS), point out so to diagnose true statin intolerance, the systematic assessment must be conducted, and, preferably, one should be exposed to minimum two different statins, one among them should be at minimum approved dose [30].

This should be a critical difference between the actual pharmacologic intolerance and the relative perceived intolerance. Quite a number of the symptoms reported can be affected by expectancy effects, which is sometimes termed as the nocebo effect, where expectation of negative effects leads to the occurrence of symptoms regardless of the drug being toxic or not [31,32]. This difference should be noted to avoid premature withdrawal of treatment and cardiovascular protection. The definition of intolerance gives the basis of studying the biological basis of the same.

4. PATHOPHYSIOLOGY OF STATIN INTOLERANCE

Statin intolerance is a multifactorial process whose mechanisms are not completely understood. It has been supported that the biochemical effects related to the muscles, genetic vulnerability, immune-mediated mechanisms, and pharmacokinetic interactions contribute to it.

4.1 Muscle-Related Mechanisms

Statins prevent the production of HMG-CoA reductase and thus cholesterol production along with intermediates of mevalonate pathway. A postulated model of muscle toxicity is the inhibition of coenzyme Q10 (ubiquinone) production, a vital part of the mitochondrial electron transport. Exhaustion can degrade oxidative phosphorylation and decrease generation of adenosine triphosphates, which predisposes myocytes to the effects of fatigue and damage.

It has been revealed that mitochondrial dysfunction has been implicated among susceptible people and indications have been made that the activity of respiratory sequence is impaired and that oxidative stress is usually elevated. Ca2+ homeostasis breakdown can also have a role since change of intracellular calcium levels can result in the release of proteolytic enzymes and facilitate myocyte damage [33].

In other settings, the apoptotic signalling pathways are triggered, and the cells undergo programmed cell death. Also, a decrease in prenylation of structural proteins and alteration of membrane stability can have an impact on myocyte integrity [34]. All these mechanisms together can offer a biologically plausible explanation of statin-associated muscle symptoms.

4.2 Genetic Susceptibility

A large part of the role of genetic variability in the pharmacokinetics and a toxicity risk of statin plays a role. ASLCO1B1 gene is an encoding gene that encodes the hepatic transporter OATP1B1 and may reduce uptake of certain statins by the liver leading to greater levels of the drug in the blood and exposures to the muscle [35]. The same effect may also be produced by cytochrome P450 enzyme variations and particularly the variations in the statins metabolism on the levels of drugs in the body and predisposition to adverse effects [36,37].

These results outline the reality that patient response heterogeneity exists even though genetic screening is not a regular procedure.

4.3 Immune-Mediated Mechanisms

Another rare but severe form of intolerance is immune-mediated necrotizing myopathy which is related to antibodies against HMG-CoA reductase. In contrast to usual SAMS, the symptoms might last even after statin withdrawal and usually involve the need of immunosuppressive treatment [38,39]. This entity is important to take note of because it is an autoimmune process instead of dose-dependent toxicity.

4.4 Mechanisms of Metabolism and Drug-Interaction

Drug-drug interactions have significant influence on the statin tolerability. Some statins increase the risk of muscle toxicity because their plasma concentrations can increase as a result of a CYP3A4 inhibition. Similarly, in case hepatic transporters are impaired, the distribution and excretion of drugs might be distorted [40]. The pharmacokinetic interactions allow one to comprehend the reason why intolerance may be experienced whenever there is an introduction of interacting drugs.

These processes indicate that statin intolerance is not an independent entity but rather a spectrum of biological heterogeneous processes.

5. RISK FACTORS FOR STATIN INTOLERANCE

Statin intolerance is a condition developed under patient-related and drug-related circumstances and that could predispose a particular individual to the adverse effects. The identification of the factors is significant both to determine patients who might be in more danger and to give reasonable therapeutic choices.

A number of patient attributes have been linked with increased risk of intolerance. Age is often cited as a significant risk factor potentially as a result of age-associated alterations in the pharmacokinetics of drugs, the occurrence of various comorbidities, polypharmacy, and decreased muscle mass or reserve [41]. It has also been indicated that female sex and reduced body mass index increases the risk of statin-associated muscle symptoms which could be attributed to dissimilarities in body composition and drug allocation within

the body [42]. Moreover, medical pathogenesis can also affect statin metabolism and clearance. Indicatively, renal or hepatic dysfunction can decrease statin clearance, leading to augmented blood exposure and an upsurge in events of adverse reactions. Some endocrine and metabolic diseases, hypothyroidism in particular, and nutritional deficiencies, including vitamin D deficiencies, can also predispose people to muscle-related symptomatic effects of statin therapy [43].

Statin intolerance is also due to drug regulations to a large extent. Adverse effects are more generally related to high-intensity statin regimens since they result in increased systemic exposure to drugs. Besides, lipophilic statins able to enter extrahepatic tissues more easily can contribute to the occurrence of muscle-related symptoms in vulnerable people. The risk may be further increased in the case of administering statins along with drugs with the effect of interfering with the metabolism or of blocking hepatic transport systems, causing an increase in the circulating drug levels. Along with these causes, the genetic variability can also provide the differences in the statin tolerance of individuals. Mutations in the SLCO1B1 gene, which transcodes hepatic transporter OATP1B1, have been implicated in diminished hepatic uptake of some statins as well as an increased propensity to statin-associated muscle toxicity [44].

On the whole, the close evaluation of these risk factors might assist clinicians to predict possible intolerance, introduce preventive measures, and maximize the lipid-lowering treatment and minimize its side effects.

6. CLINICAL MANIFESTATIONS

Statin intolerance is most often manifested by statin-associated muscle symptom, which are a spectrum of skeletal muscle events that may differ in the extent of occurrence in different individuals. The manifestations can also occur in the course of statin treatment and they are one of the most common adverse effects related to such drugs.

Myalgia, or muscle pain, soreness, or stiffness without a marked increase in serum creatine kinase (CK) is the most frequent manifestation. The proximal muscles involved which are normally the thighs, shoulders or the back, and may take weeks or months before the symptoms are realized. Despite the fact that myalgia is mild and reversible in most cases, it has the potential to influence patient compliance with treatment [45].

A severe variant is myopathy in which the symptoms of the muscles are observed along with high-level CK. The patient can develop muscle weakness or fatigue that can disrupt the activities of daily living. In some instances, myositis or inflammation of muscle tissue could also ensue and is usually accompanied with elevated muscle enzyme levels [46].

Rhabdomyolysis is a severe but uncommon complication and is specified by a great destruction of skeletal muscle fibres. It is a condition, which causes significantly high CK and myoglobin release into the circulation, which may cause acute kidney injury when not identified and treated in time [47].

There are rare cases where statins can be linked to immune-mediated necrotizing myopathy which is an autoimmune disease with progressive muscle weakness and significantly increased CK levels. This is an antibody-mediated disorder associated with antibodies against HMG-CoA reductase and may continue to persist despite the withdrawal of statin therapy, commonly necessitating immunosuppressive therapy [48,49].

Other than effects associated with muscle, other patients can have non-muscular adverse reactions such as a mild gastrointestinal adverse reaction or liver enzyme elevations. These effects tend to be rare and tend to disappear upon change in dose or withdrawal of the drug [50-52].

In general, the clinical symptoms of statin intolerance are mild muscle symptoms to uncommon but potentially severe complications. It is significant to detect these signs early so that the cardiovascular advantages of statin treatment are preserved and the signs are properly evaluated and treated.

7. DIAGNOSTIC EVALUATION

The initial phase in examination of suspected statin intolerance is a clinical examination. There is the need to establish the time association between onset of symptoms and initiation of statins or the escalation of dose or drugs interaction [53]. The fact that the symptoms vanish upon withdrawal of the drug and reappear upon trial is of more causality [54,55].

Laboratory assessment of CK should be performed in symptomatic patients. The levels that are significantly high are indicative of the need to explore further and termination, whilst low or normal levels do not exclude SAMS [56]. The appropriate test in the given cases can be liver enzyme test.

Even a combination of dechallenge-rechallenge approach is still a systematized method of diagnosis. Discontinuation of statin regime and reinstatement with lower dose or an alternative statin periodically would aid in identifying the true intolerance compared to incidental symptoms [57]. Meanwhile, the clinicians are expected to exclude the secondary causes of muscle symptoms which includes thyroid dysfunction, inflammatory myopathies and interacting medications [58].

To this end, this methodological procedure helps to avoid premature marking of intolerance and in its place, to further reduce cardiovascular risk, where feasible.

8. MANAGEMENT OF STATIN INTOLERANCE

The initial step in investigating the suspected statin intolerance includes a complete clinical examination. The time correlation between the development of the symptoms and the appointment of statins or dose or drug interaction increase must also be determined. That the symptoms are recovered when the drug is discontinued and re-appear when the challenge is encountered is more causal [59].

CK in symptomatic patients should be determined in the instances of laboratory test. High levels (significantly) confirm that there is need to research further and termination, but low levels (or normative) do not exclude SAMS. The current cases could be subject to liver enzyme test [60].

There is still an organized method of diagnosing using dechallenge-rechallenge strategy. Regular statin program suspension and a re-initiation of low dose statin or a new statin can aid in the determination of intolerance or incidental symptoms. Meanwhile, clinicians ought to rule out secondary pathogenesis of muscle symptoms that includes thyroid dysfunction, inflammatory myopathies and interacting medications [61].

The nature of the methodological process can prevent the too early labelling of intolerance and contribute to the further reduction of cardiovascular risk, where feasible.

9. CONCLUSION

The lipid-lowering therapy has been characterized by statins and it has persistently demonstrated resounding impacts of cardiovascular morbidities and mortalities in their respective customers. They also play a major role in stabilisation of atherosclerotic plaque and decrease in vascular inflammation and this is why they are introduced into the centre of the primary and secondary prevention measures.

Nevertheless, despite the recent trend to discuss the issue of statin intolerance in clinical practice, a more detailed examination of the problem will be predetermined with the fact that the phenomenon of the full-fledged intolerance is not so common. Majority of them are influenced by the changing factors, comorbid, or interaction or expectations of drugs or effects. The diagnosis system and assessment of time relationships, the special studies of the laboratory and the controlled discontinuations and rechallenge can contribute to manifesting the actual adverse reactions and avoid the unnecessary discontinuations.

It is important to note that the enormous proportion of patients who complain of the lack of tolerance can receive a modified dose in the future, switching to another statin or combination therapy. The further-reaching none-statin intervention therapies warrant a substitute of lipid repair and heart prophylaxis, which have already been known to be unbearable by the already known intolerant patients.

The concentration on the individual attention, risk-to-benefit ratio, and proper communication with the patient, in its turn, is the widest component of the guarantee of the greatest part of the resulting outcomes. It will in turn empower the clinicians to reinforce the earlier achieved positive effects of the statin treatment besides responding to the safety issues in the timely and evidence-based manner.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that they have no known competing financial interests OR non-financial interests OR personal relationships that could have appeared to influence the work reported in this paper.

Disclaimer (Artificial intelligence)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.) and text-to-image generators have been used during the writing or editing of this manuscript.

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ABBREVIATIONS

CVD – Cardiovascular disease; LDL-C – Low-density lipoprotein cholesterol; HMG-CoA – 3-hydroxy-3-methylglutaryl coenzyme A; SAMS – Statin-associated muscle symptoms; CK – Creatine kinase; NLA – National Lipid Association; EAS – European Atherosclerosis Society; BMI – Body mass index; CYP – Cytochrome P450; OATP1B1 – Organic anion transporting polypeptide 1B1; SLCO1B1 – Solute carrier

organic anion transporter family member 1B1; SREBPs – Sterol regulatory element-binding proteins; ATP – Adenosine triphosphate; CoQ10 – Coenzyme Q10.