International Journal of Science and Research (IJSR)
ISSN: 2319-7064
SJIF (2020): 7.803

Statin Induced Myopathy: A Clinical Review

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Abstract: ***Statins are one of the most frequently used drug groups among patients with cardiovascular disease. Muscle pain isvery frequent among patients using statins[1]. Muscle weakness and elevated creatine kinase (CK) are frequent side effects of statins with an incidence of about 15%[2]. It is important to distinguish patients with benign muscle pain without significant biochemical correlates from patients with serious myopathies. Statin-associated myopathy is more common in people who receive multiple drugs, the elderly or women but the mechanism underlying it is still unclear. These symptoms generally improve after drug discontinuation. In this review we have discussed the four types of muscle disorders associated with the use of statins along with their features and management based on creatine kinase concentration.***

Keywords: Atorvastatin, myositis, myopathy, creatine kinase, Rhabdomyolysis

1. Introduction

Cholesterol is one of the final product of mevalonate pathway in which, HMG-CoA (B-hydroxy B-methylglutaryl-CoA) reductase located in the endoplasmic reticulum converts HMG-CoA to mevalonate and this constitutes to the rate limiting step[3].This enzyme is inhibited by group of drugs called statins which are redistributed in the liver and are structural analogue of HMG-CoA, thereby putting a stop to synthesis of mevalonate[4].Since their introduction for the treatment of hypercholesterolaemia in 1987, the use of statins has grown to over 100 million prescriptions per year[5].About 1.5-3% of statin users in randomised controlled trials and up to 10-13% of participants enrolled in prospective clinical studies develop myalgia[6,7].

Incidence of statin-induced myopathy

In one large, population based cohort study of patients from general practices in the United Kingdom between 1991 and 1997, the mean incidence of myopathy (defined in this trial as muscle weakness and raised concentrations of creatine kinase) in patients taking statins was 1.2per 10 000 person years (95% confidence interval 0.3 to 4.7)[8].In another large study that examined rhabdomyolysis in a hospital population, the average incidence per 10 000 person years for monotherapy with atorvastatin, pravastatin, or simvastatin was 0.44 (0.20 to 0.84) and for cerivastatin was5.34 (1.46 to 13.68)[9]. The gamut of statin induced myopathy varies from myalgia, myositis and rhabdomyolysis to high up CK levels whichmight remain asymptomatic, with mean duration of statintherapy prior to onset of symptoms ranges from 1-60 days.

Spectrum of statin induced myopathy

The clinical spectrum of statin induced myopathy includes myalgia, myositis, rhabdomyolysis, and an asymptomatic increase in the concentration of creatine kinase. Muscle related adverse events can be difficult todescribe because the terminology used is inconsistent, but the proposed definitions in the table provide a useful guide. The term myopathy is often used to include the entire spectrum of muscle related adverse events (as in this article), but other definitions are common, especially when the term is used in clinical trials.

Clinical features of statin induced myopathy

Symptoms of statin induced myopathy include fatigue, muscle pain, muscle tenderness, muscle weakness, nocturnal cramping, and tendon pain. The muscle symptoms tend to be proximal, generalised, and worse with exercise.

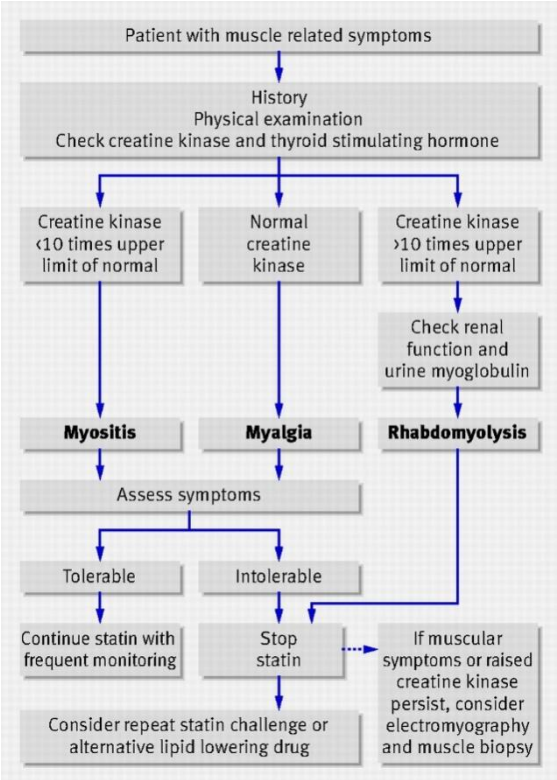


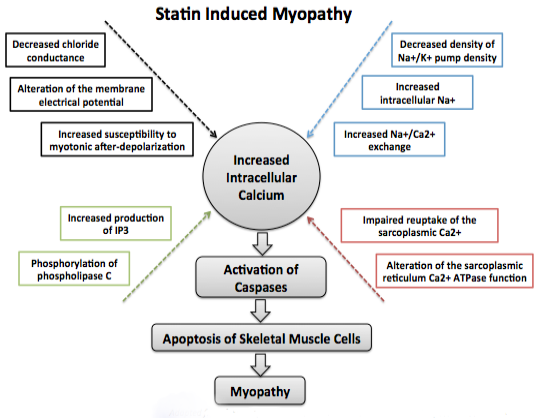
Figure 1: Approach to Statin Induced Myopathy

Clinical Entity	ACC/AHA/NHLBI (2)	NLA (4)	FDA (3)
Myopathy	General term referring to any disease of muscles	Symptoms of myalgia (muscle pain or soreness), weakness, or cramps, plus creatine kinase >10 × ULN	Creatine kinase ≥10 × ULN
Myalgia	Muscle ache or weakness without creatine kinase elevation	NA	NA
Myositis	Muscle symptoms with creatine kinase elevation	NA	NA
Rhabdomyolysis	Muscle symptoms with significant creatine kinase elevation (typically >10 × ULN), and creatinine elevation (usually with brown urine and urinary myoglobin)	Creatine kinase >10 000 IU/L or creatine kinase >10 × ULN plus an elevation in serum creatinine or medical intervention with intravenous hydration	Creatine kinase >50 × ULN and evidence of organ damage, such as renal compromise

ACC/AHA/NHLBI = American College of Cardiology/American Heart Association/National Heart, Lung, and Blood Institute; FDA = U.S. Food and Drug Administration; NA = not available; NLA = National Lipid Association; ULN = upper limit of normal.

Mechanism of Statin Induced Myopathy

The mechanism of statin induced myopathy is unknown. One proposal is that impaired synthesis of cholesterol leads to changes in the cholesterol in myocyte membranes and changes the behaviour of the membrane[10]. However, inherited disorders of the cholesterol synthesis pathway that reduce cholesterol concentrations are not associated with myopathy[11].Another proposed mechanism is impaired synthesis ofcompounds in the cholesterol pathway—in particular deficiency of coenzyme Q_{10}—which could lead to impaired enzyme activity in mitochondria[12]. Although low serum concentrations of coenzyme Q_{10} have been noted in patients taking statins, concentrations inmuscle have not consistently shown this pattern[13].A third proposed mechanism is depletion of isoprenoids—lipids that are a product of the hydroxymethyl glutaryl coenzyme A reductase pathway and that prevent myofiber apoptosis[14].



Risk Factors for Statin Induced Myopathy

Evidence from well-designed randomised controlled trials shows that myopathy correlates most closely with dose of statins and is independent of reductions in low density lipoprotein cholesterol[15].No clear data are available about the relative risks associated with individual factors, since the dose, and possibly the type, of statin affects the risk of precipitating myopathy. Risk factors such as advanced age, female sex, low body mass index, diminished hepatic and renal function, multiple comorbidities or medications, excess alcohol, intercurrent infections, surgery ortrauma, drug interactions, and dietary effects have been largely derived from clinical trials and through reporting of adverse events[16,17].Any factor that increases the serum concentration ofa statin has the potential to increase the risk ofmyopathy.Therefore, factors that affect the pharmacokinetics of statins, leading to increased concentrations of the drugs in blood or tissue, may predispose to myopathy. Although evidence shows a link between increasing serum statin concentrations and muscle complaints, no direct link has been shown between intramuscular statin concentrations and myopathy[15]. Pharmacodynamic factors, such as transporters affecting the bioavailability of statins, are probably important in determining toxicity, although no direct evidence has been found in humans. Drug responses can also be affected by predisposing genetic factors. For example, a cross sectional study of 136 patients withstatin induced myopathy showed a higher prevalence of underlyingmetabolic muscle disease (deficiencies in myophosphorylase, carnitine palmitoyl transferase II, and myoadenylate deaminase) than expected in the general population[18].No definite evidence has been found that statins are harmful in patients with pre-existing non-metabolic myopathy.In a small randomised controlled trial, concentrations of creatine kinase after treadmill exercise were significantly higher in patients assigned tolovastatin than in the placebo group. The authors of this study

Box 1- Factors that may increase the risk of statin induced myopathy

Advanced age (>80 years old)
Female sex
Low body mass index
Multisystem diseases (for example, diabetes mellitus)
Diseases affecting kidney or liver function
Hypothyroidism (untreated)
Drug interactions, especially with drugs that are inhibitors or substrates of the cytochrome P450 pathway (for example, fibrates, nicotinic acid, calcium channel blockers, ciclosporin, amiodarone, thiazolidinediones, macrolide antibiotics, azole antifungals, protease inhibitors, warfarin)
Vigorous exercise
Excess alcohol
Intercurrent infections
Major surgery or trauma
Diet (excessive grapefruit or cranberry juice)
Genetic factors (for example, polymorphisms of the cytochrome P450 isoenzymes or drug transporters, inherited defects of muscle metabolism, traits that affect oxidative metabolism of fatty acids)

Box 2- Drug-Induced or Treatment related risk factors

High-dose Statin Therapy
Interactions with concomitant drugs
Fibrates
Cyclosporine
Antifungals
Macrolide Antibiotics
HIV protease inhibitors
Nefazodone
Amiodarone
Ticagrelor
Verapamil

proposed that statins exacerbated exercise induced injury of skeletal muscles, but without tissue evidence from a muscle biopsy, this conclusion is debatable[19].

Is the risk of Myopathy same for all statins??

In vitro and in vivo experiments suggest that lipophilic statins (for example, simvastatin, atorvastatin, lovastatin) aremore likely toproducemuscular effects than arerelatively hydrophilic agents (such as pravastatin, rosuvastatin, and Fluvastatin)[20]. Lipophilic statins (for example; atorvastatin, lovastatin andsimvastatin) have aloft potential to penetrate into muscle tissue and may enhance the potential for myotoxic effects thanthe hydrophilic statins (for example; rosuvastatin,pravastatin and Fluvastatin) in patients with already existingmuscle disease.One small observational study showed that pravastatin was associated with a lower incidence of myopathy than the more lipophilic simvastatin in patients who underwent cardiactransplant[21].Therefore, it is prudent to use a more hydrophilic agent in patients with pre-existing muscle disease.

Name of statin	Metabolism	Drug interaction increasing risk of myopathy[1]
Lovastatin	Mainly CYP3A4	Potent inhibitor of CYP3A4[2]
Simvastatin	Mainly CYP3A4	Potent inhibitor of CYP3A4
Pravastatin	Sulphation, biliary, and urinary excretion	
Fluvastatin	CYP2C9 (some CYP2C8)	Inhibitors of CYP2C9
Atorvastatin	CYP3A4	Potent inhibitor of CYP3A4
Rosuvastatin	Minimal metabolism (via CYP2CP and some CYPC19)	
Pitavastatin	Minimal metabolism (via CYP2C8 and CYP2C9), lactonisation and biliary excretion	Unclear

[1]With all statins, the risk of myopathy also increases with concomitant use of ciclosporin and gemfibrozil, and possibly other fibrates; prescribing information provides further details and interaction, [2]Including itraconazole, ketoconazole, erythromycin, clarithromycin, telithromycin, nefazodone, HIV protease inhibitors, and regular ingestion of grapefruit juice,[30] HIV: Human immunodeficiency virus

Role of Creatine kinase

The statin advisory panel of the American Heart Association and National Heart, Lung and Blood Institute recommend measuring creatine kinase before starting statin therapy, but the National Lipid Association's muscle expert panel does not consider this measurement necessary[15,16].A reasonable compromise would be to measure baseline creatine kinase in high risk groups, but it is unclear what constitutes an acceptable rise in creatine kinase after statins are started.

To prevent unnecessary investigations, it is important to note that slightly raised concentrations of creatine kinase are common in the general population. In the Heart Protection Study, in which more than 20 000 people with cerebrovascular disease and other major vascular events were randomised to simvastatinor placebo, no significant difference in levelsof creatine kinase was noted between the two groups for participants in whom creatine kinase was persistently raised up to four times the upper limit of normal[27].Physical activity, especially when unaccustomed, and concurrent medical conditions, such as hypothyroidism, may also increase creatine kinase.Routine monitoring of creatine kinase inasymptomatic patients is not recommended by the American College of Cardiology/American Heart Association/National Heart, Lung and Blood Institute advisory committee and the National Lipid Association's muscle expertpanel[15,16].In patients with muscle weakness or pain, creatine kinase should be measured to assess severity of muscle damage and aid in deciding whether to continue treatment, although in these patients a normal creatine kinase concentration does not necessarily rule out ongoing muscle damage related to statins.[24]

Management of Statin Induced Myopathy

Figure 1 provides a guide to diagnosing and managing statin induced myopathy in clinical practice. When a patient on statins presents with muscle pain or weakness, a detailed history should be taken to assess predisposition to myopathy. Initial blood tests should include creatine kinase (to assess muscle damage) and thyroid stimulating hormone (because hypothyroidism is a common cause of hypercholesterolaemia and raised creatine kinase, and predisposes to statin inducedmyopathy). If the patient has brown urine or markedly raised creatine kinase, renal function and urine myoglobulin should be assessed because of the possibility of rhabdomyolysis. If a patient's history, physical examination, and creatine kinase measurements show features of statin induced myopathy, *first line management* is to *stop statins*, *observe symptoms*, and *monitor creatine kinase*. A repeat challenge with statins may be attempted to assess whether features of statin induced myopathy return; many patients with myalgia or myositis will tolerate reintroduction of the same statin, preferably at a lower dose, after symptomsresolve[15]. If muscular symptoms are tolerable and creatine kinase is not raised, or is less than 10 times the upper limit of normal, statins may be continued, with frequentmonitoring of symptoms and creatine kinase, as long as symptoms are not progressive. In patients with tolerable muscle related problems and creatine kinase concentration more than 10 times the upper limit of normal, or in those with rhabdomyolysis, statin therapy should bediscontinued and its risks and benefits should be assessed.The use of lower dose of same statin or replacing other statin in place of the prior one orusing other class of lipid lowering drugs such as bile acidbinding resins and ezetimibe is used for managing dyslipidaemia if the benefits seem to outweigh the risks.

Role of Electromyography

No prospective studies have assessed the usefulness of electromyography in statin induced myopathy or have provided detailed electromyography findings in various manifestations of the condition. However, as a general point of good practice, electromyography is often done in conjunction with muscle biopsy in atypical cases of statin induced myopathy. Electromyography findings are commonly reported to show myopathic changes, usually in the proximal muscles, in agreement with clinical findings.

Role of Muscle Biopsy

Although muscle biopsy is not routinely needed for statin induced myopathy, it may be helpful in atypical cases; advice from a specialist is desirable. Persistent muscular problems or raised creatine kinase after statins have been withdrawn; this should prompt investigation for other causes of myopathy (figure)[23]. Muscle pathology in statin induced myopathy is nonspecific, with necrosis, degeneration, and regeneration of fibres and phagocytic infiltration. In some

cases, lipid filled vacuoles, subsarcolemmal accumulations, cyclo-oxygenase negative fibres, and ragged red fibres are seen[24]. Ultrastructural skeletal myocyte damage includes the breakdown of the T-tubular membranes and subsarcolemmal fissuring (separating the myofilaments from the plasma membrane, but leaving the plasma membrane intact). These changes occur even in patients who do not have symptoms[25].

Role of Coenzyme Q_{10} Statin Induced Myopathy

Reports of myocellular concentrations of coenzyme Q10 in patients being treated with statins therapy have noted increased, decreased, and unchanged levels[25]. Therefore, the usefulness of this compound in statin induced myopathy is unclear. In one small randomised double-blind trial, 41 patients taking statins who had muscle pain received either coenzyme Q10 or vitamin E. After one month of treatment, 18 of 21 patients taking coenzyme Q10 reported improvement in muscle pain, compared with three of 20 taking vitamin E ($P<0.001$)[26]. More studies, though, are needed before coenzyme Q10 can be recommended for this condition[16].

ONGOING RESEARCH
Current research includes examining the role of genetic factors in statin induced myopathy, the effectiveness of treatments such as coenzyme Q_{10}, the effect of statins on muscle performance, and the mechanisms of statin induced myopathy.

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