

## Statin induced myopathy

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Since their introduction for the treatment of hypercholesterolaemia in 1987, the use of statins has grown to over 100 million prescriptions per year.<sup>1</sup> 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.<sup>1-4</sup> As a conservative estimate, at least 1.5 million people per year will experience a muscle related adverse event while taking a statin. In this review we discuss statin induced myopathy and its management in the light of recent epidemiological studies, randomised controlled trials, and guidelines.

### How common is 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 1.2 per 10 000 person years (95% confidence interval 0.3 to 4.7).<sup>5</sup> 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 was 5.34 (1.46 to 13.68).<sup>6</sup>

### What is the clinical 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 to describe 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.

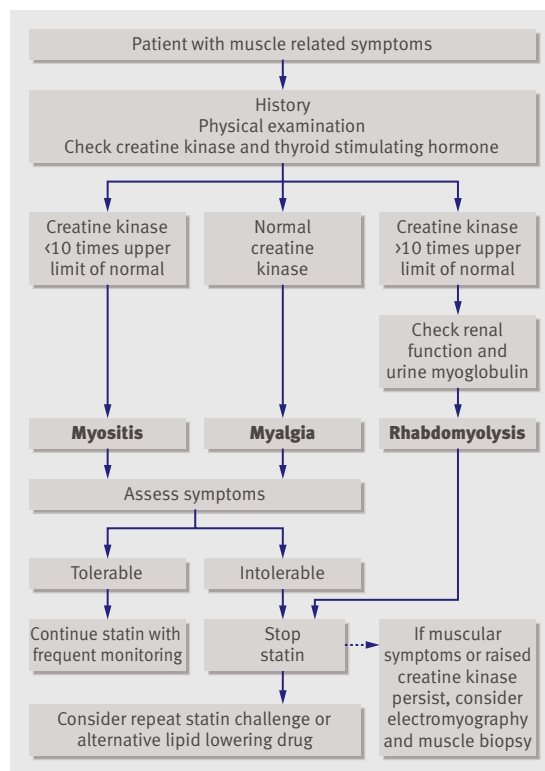
### What are the clinical features of statin induced myopathy?

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. In a small retrospective study of 45 patients, the mean duration of statin therapy before onset of symptoms was 6.3 (SD 9.3) months (range 1 week to 4 years). In this study, the mean duration of myalgia after stopping statin therapy was 2.3 (SD 3.0) months (range 1 week to 4 months).<sup>7</sup> Muscle symptoms that develop in a patient who has been taking statins for several years are unlikely to have been caused by these drugs.

### What are the proposed mechanisms 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.<sup>8</sup> However, inherited disorders of the cholesterol synthesis pathway that reduce cholesterol concentrations are not associated with myopathy.<sup>9</sup>



Diagnosis and management of statin induced myopathy

**Tips for non-specialists**

- Slightly increased creatine kinase is common in the general population
- Myopathy that develops after a patient has been taking statins for several years is unlikely to have been caused by these drugs
- Thyroid stimulating hormone should be checked in patients on statins who develop a myopathy because hypothyroidism is a common cause of hypercholesterolaemia and raised creatine kinase
- If muscle-related symptoms or raised creatine kinase concentrations persist after statin therapy is stopped, consider further investigations such as electromyography and muscle biopsy, in conjunction with a specialist

Another proposed mechanism is impaired synthesis of compounds in the cholesterol pathway—in particular deficiency of coenzyme Q<sub>10</sub>—which could lead to impaired enzyme activity in mitochondria.<sup>10</sup> Although low serum concentrations of coenzyme Q<sub>10</sub> have been noted in patients taking statins, concentrations in muscle have not consistently shown this pattern.<sup>11</sup> A third proposed mechanism is depletion of isoprenoids—lipids that are a product of the hydroxymethyl glutaryl coenzyme A reductase pathway and that prevent myofibre apoptosis.<sup>12</sup>

**What are the 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.<sup>13</sup> Several risk factors have been proposed, mainly by experts on the basis of published evidence (box 1).<sup>14,15</sup> 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 or trauma, drug interactions, and dietary effects have been largely derived from clinical trials and through reporting of adverse events.<sup>14,15</sup>

Any factor that increases the serum concentration of a statin has the potential to increase the risk of myopathy. 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.<sup>13</sup> 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 with statin induced myopathy showed a higher prevalence of underlying metabolic muscle disease (deficiencies in myophosphorylase, carnitine palmitoyltransferase II, and myoadenylate deaminase) than expected in the general population.<sup>16</sup> 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 to lovastatin than in the placebo group. The authors of this study proposed that statins exacerbated exercise induced injury of skeletal muscles, but without tissue evidence from a muscle biopsy, this conclusion is debatable.<sup>17</sup>

**Is the risk of myopathy equal for all statins?**

In vitro and in vivo experiments suggest that lipophilic statins (for example, simvastatin, atorvastatin, lovastatin) are more likely to produce muscular effects than are relatively hydrophilic agents (such as pravastatin, rosuvastatin, and fluvastatin).<sup>18</sup> Lipophilic compounds are more likely to penetrate into muscle tissue, enhancing the potential for myotoxic effects. One small observational study showed that pravastatin was associated with a lower incidence of myopathy than

**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)

**Clinical spectrum of statin induced myopathy**

Terminology	Definition
Myalgia	Muscle pain or weakness without raised creatine kinase
Myositis	Muscle symptoms with raised creatine kinase, typically less than 10 times upper limit of normal
Rhabdomyolysis	Muscle symptoms with markedly raised creatine kinase, typically more than 10 times the upper limit of normal
Asymptomatic raised creatine kinase	Raised creatine kinase without muscle symptoms

**Box 2 Differential diagnoses of muscle related symptoms**

Bursitis

Myofascial pain

Muscle strain

Osteoarthritis

Radiculopathy

Tendinitis

was the more lipophilic simvastatin in patients who underwent cardiac transplant.<sup>19</sup> Therefore, it is prudent to use a more hydrophilic agent in patients with pre-existing muscle disease.

**Is measuring baseline creatine kinase necessary before starting statin therapy?**

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.<sup>13,14</sup> 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.<sup>20</sup>

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 simvastatin or placebo, no significant difference in levels of 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.<sup>21</sup>

Creatine kinase concentrations differ between population subgroups. For example, creatine kinase concentrations have been found to be higher in black people than in white people.<sup>22</sup> "Idiopathic hyperCK-emia"—in which creatine kinase is raised in the absence of clinical or histological evidence of neuromuscular disease—is a genetically heterogeneous condition found in all ethnic groups and is more common in men than in women.<sup>23</sup> Physical activity, especially when unaccustomed, and concurrent medical conditions, such as hypothyroidism, may also increase creatine kinase.

**Does creatine kinase need to be monitored after statins are started?**

Routine monitoring of creatine kinase in asymptomatic patients is not recommended by the American College

**ONGOING RESEARCH**

Current research includes examining the role of genetic factors in statin induced myopathy, the effectiveness of treatments such as coenzyme Q<sub>10</sub>, the effect of statins on muscle performance, and the mechanisms of statin induced myopathy.

of Cardiology/American Heart Association/National Heart, Lung and Blood Institute advisory committee and the National Lipid Association's muscle expert panel.<sup>13,14</sup> 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.<sup>24</sup>

**How is statin induced myopathy managed?**

The figure provides a guide to diagnosing and managing statin induced myopathy in clinical practice. When a patient taking statins reports muscle pain or weakness, a detailed history should be taken to assess predisposition to myopathy, and a physical examination should be done to exclude other common conditions (box 2). 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 induced myopathy). If the patient has brown urine or markedly raised creatine kinase, renal function and urine myoglobin 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 symptoms resolve.<sup>13</sup>

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 frequent monitoring 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 be discontinued and its risks and benefits should be assessed. An alternative class of lipid lowering drug might need to be considered, or statin therapy could be resumed if the benefits seem to outweigh the risks.

**What is the role of electromyography?**

No prospective studies have assessed the usefulness of electromyography in statin induced myopathy or have

**Additional educational resources****Resources for healthcare professionals**

National Lipid Association ([www.lipid.org](http://www.lipid.org))—provides various guidelines on statin therapy

McKenney JM. Report of the National Lipid Association's Statin Safety Task Force. *Am J Cardiol* 2006;97(suppl): S1-98

Pasternak RC, Smith SC Jr, Bairey-Merz CN, Grundy SM, Cleeman JJ, Lenfant C, et al. ACC/AHA/NHLBI clinical advisory on the use and safety of statins. *Circulation* 2002;106:1024-8

**Resources for patients**

Statins ([www.patient.co.uk/showdoc/40024969](http://www.patient.co.uk/showdoc/40024969))—overview of statins from Patient UK website

**SOURCES AND SELECTION CRITERIA**

We searched PubMed using the term “statin” in conjunction with “myotoxicity”, “myopathy”, “myalgia”, “myositis” and “rhabdomyolysis”. Where necessary, we made additional searches relating to the themes highlighted by the original search.

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.

**When is muscle biopsy necessary?**

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).<sup>25</sup> Muscle pathology in statin induced myopathy is non-specific, 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.<sup>26</sup> 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.<sup>27</sup>

**Does coenzyme Q<sub>10</sub> have a role in treating statin induced myopathy?**

Reports of myocellular concentrations of coenzyme Q<sub>10</sub> in patients being treated with statins therapy have noted increased, decreased, and unchanged levels.<sup>28</sup> 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 Q<sub>10</sub> or vitamin E. After one month of treatment, 18 of 21 patients taking coenzyme Q<sub>10</sub> reported improvement in muscle pain, compared with three of 20 taking vitamin E (P<0.001).<sup>29</sup> More studies, though, are needed before coenzyme Q<sub>10</sub> can be recommended for this condition.<sup>14</sup>

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**SUMMARY POINTS**

Four types of muscle disorders are associated with statins: myalgia, myositis, rhabdomyolysis, and asymptotically increased creatine kinase  
 Although the rate of statin induced myopathy among statin users is low, the high volume of statin prescriptions means that the condition is commonly encountered in clinical practice  
 Statin-induced myopathy correlates most closely with the dose of statins, but any factor that increases the serum concentration of a statin potentially increases the risk of myopathy  
 If a patient presents with features suggesting statin induced myopathy, first line management is to stop statin therapy and observe any effect on symptoms and concentration of creatine kinase

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