



Managing myopathy in the statin-intolerant patient

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Patients on statin therapy may develop musculoskeletal side effects. Careful monitoring is required and alternative therapies may be needed in these patients.

Key points

- **Musculoskeletal side effects are the most common adverse effects of statin therapy, usually occurring with higher doses and within the first few months of dose initiation or uptitration.**
- **Risk factors for statin myopathy include increasing age, small muscle mass, hypothyroidism, low levels of vitamin D, concomitant therapy with cytochrome P4503A4 inhibitors and a history of muscle symptoms.**
- **Statin myopathy may occur without elevated creatine kinase levels; no specific therapy is available other than dose reduction or withdrawal.**

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Statin intolerance may be complete (intolerance to any dose of any statin) or partial (tolerance only to low doses of some statins). Almost any system in the body can be affected by this intolerance (Table 1).

As musculoskeletal complaints are the most common side effects of statin intolerance, this article will focus on statin-associated myopathy, the term generally used for musculoskeletal adverse reactions to statins. These adverse reactions can vary widely from day to day in intensity and location, and can be difficult to distinguish from degenerative symptoms, especially in older patients. The diagnosis is suspected mainly from the clinical scenario.

Statin-associated myopathy is most reliably defined by a recurrence of musculoskeletal symptoms and/or elevated levels of creatine kinase, a marker for muscle damage, after statin withdrawal and re-challenge at the same dose.^{2,3} Many patients with muscle symptoms, however, have no significant change in their creatine kinase levels.

Mild forms of statin-associated myopathy occur in 5 to 10% of patients taking statins, especially in those taking higher doses of statins, which are being used more frequently as LDL-cholesterol targets become lower, as in current guidelines from the National Vascular Disease Prevention Alliance.⁴

The various types of statin-associated myopathy are described in Table 2 and examples are shown in Figures 1 and 2.



Table 1. Sites affected by statin intolerance

Major site affected	Symptoms	Prevalence (clinical practice)	Prevalence (randomised trials)
Musculoskeletal system	Aches and pains, cramps, stiffness, tenderness, weakness, fatigue and muscle atrophy (rare)	2 to 5% at low doses; 5 to 10.5% at high doses	1 to 2%
Central nervous system	Headache, visual disturbance and memory loss	Uncommon (<1%)	<1%
Gastrointestinal tract	Dyspepsia, bowel disturbance, bloating, abdominal discomfort and jaundice (rare)	<1%	<1%
Skin	Rash	Rare	Rare
Hair and nails	Alopecia	Rare	Rare
Autoimmune	Vasculitis	Very rare	Very rare
Genitourinary	Erectile dysfunction	Rare	Rare
Endocrine	New-onset diabetes	Unknown	6% increase (meta-analysis of statin trials) ¹

Table 2. Classification of the types of statin-associated myopathy

Type	Symptoms	Incidence
Myalgia	Muscle symptoms with creatine kinase levels less than three times the upper limit of normal	5 to 10% in clinical practice
Myositis	Muscle symptoms with creatine kinase levels three to 10 times the upper limit of normal	1 to 2% in practice, <1% in randomised controlled trials
Myopathy (Figure 1)	Muscle symptoms with creatine kinase levels more than 10 times the upper limit of normal	<1% in practice, <0.01% in randomised controlled trials
Rhabdomyolysis (Figure 2)	Severe symptoms with creatine kinase levels excessively more than 10 times (often more than 40 times) the upper limit of normal, accompanied by myoglobinaemia, myoglobinuria, urinary pigmented casts, acute renal failure, increased creatinine or need for IV hydration	Very rare (one per million statin prescriptions), but more frequent with underlying metabolic myopathies

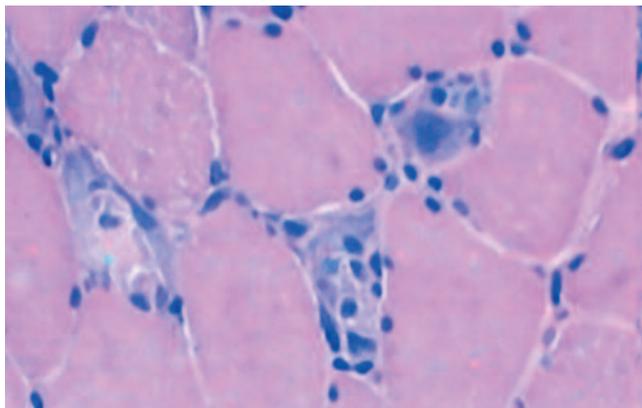


Figure 1. Necrotising myopathy in a patient on atorvastatin. Haematoxylin and eosin-stained necrotic fibres (blue staining) undergoing myophagia and regeneration.

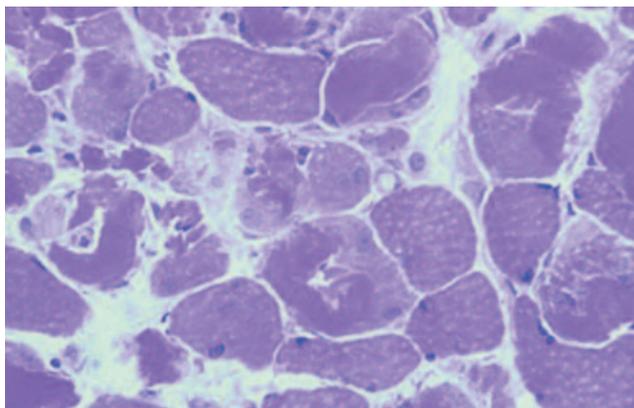


Figure 2. Severe rhabdomyolysis. Haematoxylin and eosin-stained section showing phagocytic breakdown of muscle fibres and associated regenerative changes.

The PRIMO study

The *Prédiction du Risque Musculaire en Observationnel* (Prediction of Muscular Risk in Observational conditions; PRIMO) study provided a wealth of information on the symptoms of statin-associated myopathy and its predisposing factors. This study involved 7924 patients treated with high-dose statins by 2752 GPs in France. Statin-associated myopathy occurred in 10.5% of patients, with several predisposing factors shown on multivariate analysis (Table 3).⁵

The PRIMO study showed an association with family history, which suggests a genetic predisposition for statin-associated myopathy. This was indeed demonstrated by the Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) investigators using a genome-wide association study in patients treated with high-dose simvastatin.⁶ As a result of this higher incidence of statin-associated myopathy, the Food and Drug Administration recently advised against initiating statin therapy with simvastatin 80 mg, and more closely monitoring those continuing to take simvastatin 80 mg.⁷

Before starting statins, 13% of patients in the PRIMO study had muscular symptoms similar to statin-associated myopathy, suggesting a 'myalgia propensity'. Such a propensity is made symptomatic by triggering factors, which occurred in 40% of cases, and included unusual physical exertion (53%), taking new medications (30%), resting or lying down (13%) and exposure to cold (9%). The new medications included hepatic cytochrome P450 (CYP) 3A4 inhibitors, which reduce the metabolism of either simvastatin or atorvastatin, leading to increased statin blood levels and increased incidence of statin-associated myopathy (see the box on this page).^{8,9} Other drugs increasing the risk of statin-associated myopathy include cyclosporin and gemfibrozil.

In the PRIMO study, most episodes of statin-associated myopathy occurred within one month of starting or uptitrating statin therapy or with the addition of an interacting drug.

Table 3. The PRIMO study: factors predicting statin-associated myopathy on multivariate analysis in 832 patients⁵

Factor	Odds ratio
Unexplained muscle pain with other lipid therapy	10.1*
Unexplained cramps	4.1*
History of elevated creatine kinase levels	2.0*
Family history of muscle symptoms	1.9†
Family history of muscle symptoms with lipid therapy	1.9†
Hypothyroidism	1.7†
More than three months of statin therapy	0.28*
Antidepressant therapy	0.51†

* = p<0.0001; † = p<0.01; ‡ = p<0.05

Hepatic cytochrome P4503A4 inhibitors or competitors increasing the incidence of statin myotoxicity^{8,9}

- Antifungal 'conazoles'
- Anti-HIV protease inhibitors
- Amiodarone
- Chloramphenicol
- Cimetidine
- Clarithromycin
- Diltiazem
- Erythromycin
- Fluoroquinolones
- Fluoxetine
- Grapefruit juice (large quantities)
- Isoniazid
- Tacrolimus
- Verapamil
- Warfarin

Factors increasing the risk of statin-associated myopathy

- Age (>80 years; especially in women)
- Small muscle mass
- Multisystem diseases (especially diabetic chronic kidney disease)
- Multiple medications
- Acute illness, surgery or trauma
- Alcohol misuse
- Grapefruit juice consumption – more than 1 litre/day (with simvastatin or atorvastatin use)
- Exercise
- Trauma
- Falls
- Accidents
- Seizures
- Shaking chills
- Infections
- Carbon monoxide poisoning
- Polymyositis
- Dermatomyositis
- Illicit drug use (cocaine, amphetamines, heroin, phencyclidine hydrochloride)
- Vitamin D deficiency
- Genetic myopathies
- Hypothyroidism
- Asian ethnicity



Managing statin-associated myopathy

Patients experiencing statin-associated myopathy should be asked about possible triggering factors and warned to avoid them as far as possible. Statins can also be withheld temporarily in the presence of severe infection, hypotension, major surgery or trauma, uncontrolled epilepsy and severe endocrine, metabolic or electrolyte disorders.¹⁰

The box on page 17 lists other factors that may increase a patient's risk of developing myopathy.¹¹

The case scenario in the box on this page describes the typical management of statin-associated myopathy in a patient with myositis in whom statin therapy was usually withdrawn and re-introduced after resolution of symptoms.

In asymptomatic patients, or those tolerating statin-associated myopathy with creatine kinase levels less than 10 times the upper limit of normal, the guidelines are to continue statin therapy at the same or a reduced dose, using the presence of symptoms to guide therapy.¹⁰ In clinical trials, creatine kinase levels less than 10 times the upper limit of normal are not regarded as significant because they can normally vary within this range as a result of exercise or minor trauma.¹⁰ A more conservative approach is to cease statin therapy in patients with creatine kinase levels between three and 10 times the upper limit of normal, and wait for a return to normal creatine kinase levels before re-commencing statin therapy.

If muscle symptoms recur with statin re-challenge, other statins

Case scenario

Mr JW, a 59-year-old accountant with hypertension that was well controlled by an angiotensin receptor blocker, came to see you for a cholesterol check. His blood pressure was 140/75 mmHg, body mass index was 27 kg/m² and lipid profile was a total cholesterol of 5.8 mmol/L, triglycerides of 2.2 mmol/L, HDL-cholesterol of 0.8 mmol/L and LDL-cholesterol of 4.0 mmol/L.

Mr JW was a nonsmoker, was not diabetic and drank less than two standard drinks daily. He walked his dog around the block most days and occasionally experienced cramps in his calves at night. He had no family history of cardiovascular disease. His calculated five-year cardiovascular disease risk was 10 to 15% (moderate or intermediate risk).

After six weeks of dietary intervention, his lipid profile was unchanged and he met PBS criteria for reimbursement of drug therapy in patients with hypertension (total cholesterol >5.5 mmol/L and HDL-cholesterol <0.9 mmol/L). He had normal results for thyroid, hepatic and renal function tests. His levels of creatine kinase, glucose and vitamin D were also normal.

You decided to start him on statin therapy with a goal LDL-cholesterol level of less than 2.0 mmol/L.⁴ You started him on simvastatin 40 mg/day, in view of the results of the Heart Protection Study, and expected to lower his LDL-cholesterol level by about 40% and achieve an LDL-cholesterol level of about 2.4 mmol/L.¹²

Four weeks later, Mr JW came back to see you because he had been experiencing frequent cramping of his calves and generalised muscle aching, more pronounced in his calves and thighs, which was aggravated by walking. He thought his limbs felt 'heavy', and he also noticed muscle fatigue on walking. He had taken aspirin and paracetamol without relief. There were no obvious aggravating factors such as unaccustomed exercise or infection, and Mr JW had not taken any new medications or increased his dose of statin.

On examination, there were no abnormal physical signs other than borderline bilateral quadriceps weakness. His creatine kinase level

was more than four times the upper limit of normal at 650 mmol/L (upper limit of normal, 160 mmol/L).

You explained to Mr JW that he was having an adverse reaction to his statin that had affected his muscles. You advised him to stop his statin treatment and wait for his symptoms to resolve, which should occur within a week. He could then use a lower dose of simvastatin or change to a different statin, possibly with the addition of ezetimibe as this should not aggravate his myalgia and helps lower LDL-cholesterol levels.

Mr JW preferred to try a different statin. You started him on rosuvastatin 5 mg every other day in combination with ezetimibe 10 mg/day. This combination was predicted to lower his LDL-cholesterol level by more than 50%, and to achieve his target LDL-cholesterol level.

After checking his creatine kinase level, lipid profile and liver function as recommended in recent guidelines, you advised Mr JW to stop taking his statin therapy immediately if his muscle symptoms recurred and otherwise to come back eight weeks later for review.⁸

Eight weeks later, his lipid profile showed a total cholesterol level of 3.6 mmol/L, triglycerides level of 1.1 mmol/L, HDL-cholesterol level of 1.2 mmol/L and LDL-cholesterol level of 1.9 mmol/L. His liver function and creatine kinase levels were normal.

You asked Mr JW to continue his present therapy and come back for review in four months (when he was due for a repeat prescription), and to have a repeat lipid profile one week before that appointment.

You explained it would not be necessary to repeat the measurement of his creatine kinase level and liver function tests in the absence of symptoms and because recent results were normal.⁸

Most importantly, you explained he would need to stay on his lipid therapy indefinitely to reap the rewards of continued cholesterol control with continued protection from cardiovascular disease events. You reminded him that a cholesterol level that is 1% lower results in a 1% decrease in cardiovascular disease events over five years, and even greater benefit with longer treatment. This was the best investment he was likely to make.

can be tried at low doses, gradually increasing the dose as tolerated. It may be necessary to consider nonstatin LDL-cholesterol-lowering medications, including ezetimibe, plant sterols, bile acid sequestrants and nicotinic acid. Fibrates may also aggravate statin-associated myopathy, especially in those patients previously intolerant of statins.

Preventing statin-associated myopathy

As statin-associated myopathy is dose-related, the lowest statin dose to achieve target LDL-cholesterol levels should be used, if necessary with ezetimibe as a 'statin-sparing' agent in patients with risk factors for statin-associated myopathy. Certain statins have less propensity to cause statin-associated myopathy. Rosuvastatin may be used in doses of 2.5 to 5.0 mg three times weekly.¹³ Extended-release fluvastatin daily or every other day may also be used.¹³

Statin withdrawal should be considered in patients with acute illness, those having surgery or patients experiencing trauma. Hepatic CYP3A4 inhibitors should be used with caution in patients taking atorvastatin or simvastatin. Cyclosporin may aggravate statin-associated myopathy with all statins. Submaximal doses of renally excreted statins (rosuvastatin and pravastatin) should be used in patients with renal impairment.

Gemfibrozil should be used with caution in patients taking simvastatin, fluvastatin or atorvastatin, whereas fenofibrate is generally safe with statin therapy, as shown in the recent ACCORD trial.

The role of coenzyme Q10

Coenzyme Q10 is an essential component of the electron transport chain, which is responsible for generating ATP within mitochondria and contributing to the energy required for muscle contraction. Plasma levels of coenzyme Q10 are reduced with statin therapy, largely because it is transported within LDL-cholesterol and partly because statins may reduce hepatic synthesis of coenzyme Q10 by inhibiting hepatic HMGCoA reductase activity.

Most, but not all, studies have shown mitochondrial levels of coenzyme Q10 to be normal with statin therapy,¹⁴ and data are conflicting with regard to the efficacy of coenzyme Q10 supplements in preventing statin-associated myopathy. This may be because individual studies used different potencies, doses or purity of coenzyme Q10 preparations, or different patient populations. Uncommonly, patients may require coenzyme Q10 supplements to tolerate statin therapy, but it must be kept in mind that a placebo effect may be substantial for any pain-preventing medication, and few well-controlled randomised studies of the efficacy of coenzyme Q10 supplements are available. Coenzyme Q10 supplements are generally ineffective in treating patients with statin-associated myopathy.

Other strategies

Statin-associated myopathy may improve with thyroid or vitamin D replacement therapy in patients with hypothyroidism or vitamin D deficiency. There is no role for carnitine or selenium supplementation other than in rare individuals with proven deficiency in these substances or carnitine-related genetic myopathies.

Mechanisms of statin-associated myopathy

The exact mechanisms of statin-associated myopathy in individual cases are unknown. Several mechanisms have been postulated and some are related to prenylation of signalling proteins involved in muscle function. It is known that statin-associated myopathy occurs with high levels of statins in the blood and high systemic exposure to statins, which relate to high doses, impaired excretion, impaired first-pass extraction by the liver or altered tissue distribution of statins.

There are families in whom a genetic predisposition to statin-associated myopathy is evident.¹⁵

Laboratory tests are not available currently to determine which mechanism is responsible for individual cases of statin-associated myopathy. Blood statin levels (a logical way to monitor propensity to statin-associated myopathy) are only available in research settings.

Summary

Patients with muscle aches and pains are seen frequently in general practice, whether they are on statin therapy or not. If there is any doubt as to the aetiology, it is reasonable to withdraw the statin for a short period, monitor symptoms and re-challenge the patient using the same dose of the same statin to confirm the diagnosis. Suitable alternatives are then to add ezetimibe (which is usually well tolerated) and consider using low doses of a potent statin, given every other day. It is important to check thyroid function and vitamin D levels, because these may need to be corrected. **CT**

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COMPETING INTERESTS: Professor Hamilton-Craig is a member of the lipid advisory boards of Abbott, AstraZeneca, Amgen and Merck, Sharp and Dohme (Australia).