Statin Myopathy

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8.1 Epidemiological Impact of Statins in Cardiovascular Disease

Statins inhibit 3-OH-3-methyl-glutaryl-CoA (HMG-CoA) and are the most potent drugs currently available to treat hypercholesterolaemia [1]. These agents form a mainstay of primary and secondary prevention of coronary artery disease and atherosclerosis and effectively reduce cardiovascular mortality [2]. It is estimated that the incidence of heart attacks and strokes is reduced by 20 % for each reduction of 1 mM in LDL cholesterol levels [3]. The average cholesterol-lowering effect of the highest approved statin doses is 33 % for fluvastatin (80 mg) and up to 55 % for atorvastatin (80 mg) [4, 5]. Besides simply reducing plasma cholesterol levels, statins also have pleiotropic (cholesterol-independent) effects, mainly anti-inflammatory and pro-apoptotic, which contribute to the beneficial actions of statins, but also to their side effects [6].

Shortly after their introduction in 1987, the first cases of statin-associated rhabdomyolysis were published in 1988 [7]. Despite this serious adverse event, the risk-benefit ratio remains very much in favour of statin therapy, and indeed statins are now amongst the most widely prescribed drugs worldwide. So far, only one statin, cerivastatin, had to be removed from the market due to an excess of rhabdomyolysis – 50 times greater than other statins [8]. Most deaths, however, had occurred with concomitant administration of other drugs, in particular fibrates and gemfibrozil.

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Table 8.1 Definitions of statin-associated muscle symptoms

Myalgia	Muscle discomfort (soreness, stiffness, tenderness, heaviness, cramps), with normal CK levels. Apparent weakness may occur secondary to pain
Myopathy	Weakness and/or myalgia with elevation of serum CK
Rhabdomyolysis	Myopathy with serum CK >10x ULN plus evidence of associated renal failure or serum CK >10,000 U/l (50-fold elevation)
Asymptomatic myo-pathy	CK elevation without clinical symptoms – this was not defined by the Task Force

8.2 Definition of Statin Myotoxicity

Amongst all side effects of statins, their muscular side effects remain most important and are the crucial factor for patient adherence to statin treatment. In one study [5], the muscle-related side effects were the reason for discontinuation of statin treatment in 65 % of cases.

There is still currently no consensus on the definition of statin myopathy which confuses the interpretation of observational studies of statin-associated muscle symptoms. Moreover, most studies on statin myotoxicity have been performed by non-neuromuscular experts.

In the literature, the most widely accepted definitions are those of the National Lipid Association (NLA) Statin Muscle Safety Task Force [9] – these will therefore be used throughout this chapter (Table 8.1).

Further confusion is added by the fact that many observational trials rely on patient self-reporting of statin side effects without objective proof of the muscular origin of these symptoms. Non-neuromuscular side effects, such as tendinopathies or arthropathies, with associated pain are fairly common and have been reported by up to 24 % of patients in the PRIMO study, an observational investigation [10].

8.3 Epidemiology of Statin-Related Myotoxicity

Information on statin-associated muscle symptoms (SAMS) has been derived from both controlled clinical trials and observational studies of statins in everyday clinical use. Whilst the latter indicates that 7–29 % of patients complain of SAMS [5, 10–12], the randomized controlled trials yield very different results: in RCTs, adverse event rates are similar in statin and placebo groups [1, 13, 14]. A large meta-analysis of 42 randomized trials covering almost 60,000 patients [15] found that 12.7 % reported muscle problems in the statin groups vs. 12.4 % in the placebo groups, a non-significant difference. In two studies, CARDS and SPARCL, the placebo groups even had a higher rate of myalgia than the verum group [15]. Only two trials [16, 17], however, had questioned participants systematically about muscle symptoms and reported an incidence for myalgia of 3 % [16] and 9.4 % [17], respectively.

The frequency of myopathy, as defined above, was much lower at less than 0.5 % [1, 18] with standard doses of statins, but extended up to 2 % at high-dose treatment

Table 8.2 Frequency of statin-associated muscle problems

	Verum groups	Placebo groups	Significant
Any muscle symptom			
(Meta-analyses)	12.7 %	12.4 %	No
(Observational trials)	7–29 %	–	–
Myopathy (CK >3x ULN)	0.5 %	0.3 %	Yes
Myopathy (CK >10x ULN)	0.2 %	0.16 %	No
Rhabdomyolysis	0.03 %	0.02 %	No

Adapted from Kjekshus et al. [16]

Table 8.3 Risk factors for statin myopathy

Patient features	Drug features
Age> 80 years	Statin dose
Comorbidity (renal, hepatic, hypothyroidism, diabetes, trauma, neuromuscular disease)	Type of statin (lipophilicity) *Higher risk*: simvastatin, lovastatin, atorvastatin *Lower risk*: pravastatin, fluvastatin, rosuvastatin
Diet (grapefruit juice)	Interacting drugs:
Pre-existing hyperCKemia	CYP3A4 inhibitors (macrolides, azoles, HIV-drugs, amlodipine, amiodarone, cyclosporine, tetracyclines)
Vitamin D deficiency	Fibrates, gemfibrozil, niacin
Previous statin intolerance	Steroids
Alcohol abuse	
Genetic predisposition (SLCO1B1, CYP3A4 polymorphisms)	

(atorvastatin 80 mg) [19, 20]. Thus, the overall frequency of myopathy is low, but increases at higher statin doses and with concomitant use of interacting medication (Table 8.2). Moreover, in the above meta-analysis [15], no myopathy was reported with fluvastatin, which was also associated with the least number of muscle symptoms in the PRIMO study [10].

Rhabdomyolysis, as defined above, was even rarer with an incidence of 0.03 % in two meta-analyses [15, 21] and its frequency was not different from the placebo groups (0.02 %) (Table 8.2). In all trials, rhabdomyolysis was not seen in patients who did not have additional risk factors (Table 8.3).

Why do the outcomes of clinical trials not reflect clinical practice, where SAMS are reported much more frequently (Table 8.2)?

First, clinical trials usually exclude patients with a history of muscle problems and other risk factors for myopathy. Second, most statin trials were not primarily designed to assess muscle complaints. Third, the lack of a placebo group in many observational studies often precludes verification of a causal relationship between statins and muscle symptoms, which are therefore overestimated. This particularly applies to patients with anxiety or depressive disorders who frequently complain of muscle soreness. Fourth, physical activity, an important trigger of "statin myopathy", has not been taken into account in most studies.

Considering the results from both randomized and observational studies, one may conclude that myalgias are not uncommon (2–10 %), but clinically significant myopathy with CK elevations and weakness is much rarer (~0.5 %) and rhabdomyolysis is even less frequent (<0.05 %) and almost always associated with concomitant medication.

8.4 Pathogenesis of Statin-Induced Myopathy

Several mechanisms have been proposed for the myotoxic effects of statins. Inhibition of the mevalonate pathway, the central step in cholesterol biosynthesis, by statins also interacts downstream with other important pathways (Fig. 8.1):

- Impaired production of coenzyme Q10, which forms an essential part of the respiratory chain, may lead to mitochondrial dysfunction. Although statin therapy has been shown to decrease CoQ10 plasma levels [22], the results of muscle CoQ10 analyses have been inconclusive [23, 24]. Some, but not all, patients show mitochondrial pathology in muscle biopsies, such as COX-negative and ragged-red fibres [24, 25], and depletion of mtDNA [26].
- Secondary mitochondrial changes, such as altered membrane fluidity, or changes in calcium homeostasis probably play a minor role.
- Prenylation of proteins is implicated in cell differentiation, signalling and proliferation and is also involved in immune responses. Impaired prenylation will therefore ultimately increase apoptosis. Since inhibition of cholesterol biosynthesis downstream of HMG-CoA reductase at the level of squalene synthase does not cause myotoxicity, impaired protein prenylation is regarded by many as being one of the most important pathogenic mechanisms [27].
- A subgroup of statin-associated myopathy may be triggered by an autoimmune process targeted against HMG-CoA reductase, clinically manifesting as a necrotizing myopathy [28]. However, in a large cohort of patients with HMGCR-antibodies, only 2/3 were ever exposed to statins [29]; interestingly, the latter responded better to immunosuppressive therapy than the statin-naïve patients [30]. The antibody was never found in asymptomatic statin users.
- Genetic predisposition to statin myotoxicity may be caused by pathogenic heterozygous variants in muscle disease-related genes [31]. These include CPT2-deficiency, Pompe disease, McArdle disease, Lipin1-deficiency and malignant hyperthermia. The most significant associations of statin myopathy with genetic polymorphisms have been reported for a hepatic transporter, encoded by SLCO1B1 [32], and for genetic variants in the detoxifying cytochrome P450 system [33]. A particular SLCO1B1 polymorphism is associated with an 18 % risk of developing a statin myopathy in homozygotes, a 3 % risk in heterozygotes and a 0.6 % risk in wild-type carriers [32]. A further association was verified for polymorphisms in the CoQ2-gene, which is involved in CoQ10 biosynthesis [34].

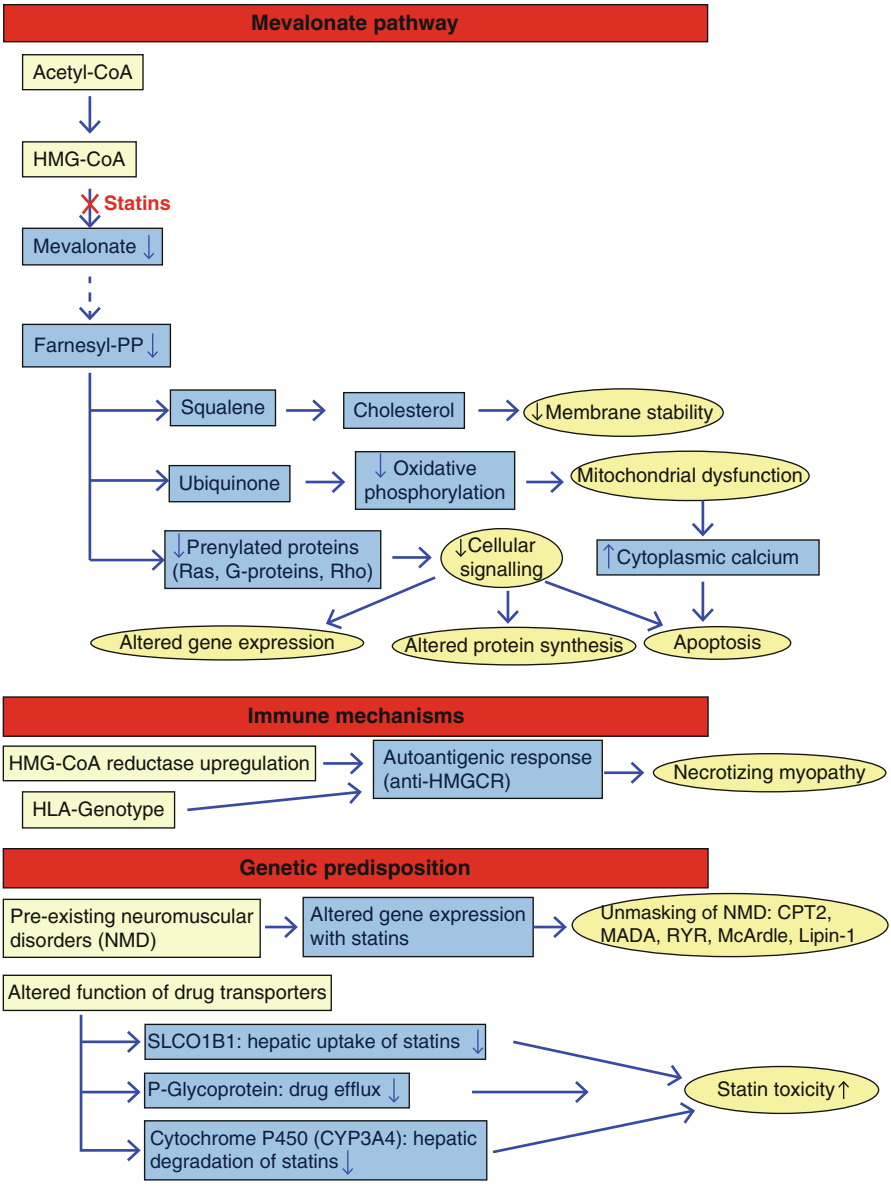

Fig. 8.1 Pathogenic mechanisms of statin myotoxicity

It should, however, be kept in mind that the benefit of reduced cardiovascular mortality far outweighs the risk of statin-related myopathy, even in those with the highest genetic risk known so far, i.e. the SLCO1B1 variants. Therefore, routine genotyping cannot be recommended.

8.5 Clinical Evaluation of Suspected Statin Myopathy

8.5.1 Clinical Features

Statin-induced myalgia and myopathy typically present as proximal, symmetric muscle pain and/or weakness, especially in the legs; nocturnal cramping is also common [17, 35]. The mean duration of statin therapy before symptom onset was 6 months; in 1/3 of patients, symptoms started within 1 month [35]. The mean interval to recovery after cessation of treatment was 2 months; 57 % of patients reported resolution of symptoms after 1 month and 93 % after 6 months [35]. The symptoms appear more frequently in exercising individuals and are often triggered by physical activity [10].

If symptoms persist for more than 6 months after discontinuation of the statin, alternative causes should then be investigated, i.e. underlying necrotizing or metabolic myopathies or heterozygous genetic variants thereof (→ 8.4).

A proportion of statin users shows an asymptomatic elevation of CK, usually <4x ULN, which resolves quickly after withdrawal of the drug. Some of these patients have mild morphological changes in a muscle biopsy [36].

Rhabdomyolysis, the most severe form of statin intolerance, is very rare (<0.1 %) and usually occurs with short delay after initiation of statins. It is characterized by severe muscle pain, weakness, very high CK and may lead to renal failure.

8.5.2 Diagnosis and Monitoring

The diagnosis of statin myotoxicity is usually straightforward and is based upon the temporal correlations of clinical symptoms and CK levels with initiation and termination of statin therapy (→ 8.5.1); sometimes a rechallenge of statin exposure may be necessary to firmly establish statin intolerance.

Current European guidelines [2] recommend to obtain a baseline CK in case symptoms develop, but there is no need for routine monitoring of CK, unless problems arise. In this case, CK should be measured to evaluate the severity of muscle damage and to decide whether treatment should be discontinued.

Electromyography, nerve conduction studies and MR imaging may be normal or show non-specific abnormalities; their main purpose is exclusion of other differential diagnoses.

Muscle biopsy is not routinely performed [2], except in those with persisting symptoms or hyperCKemia despite cessation of statin medication. It is then necessary to investigate for autoimmune necrotizing myopathy, because this specific complication requires immunosuppressive therapy [30].

8.5.3 Risk Factors for Statin Myopathy

The risk factors predisposing to statin-induced myopathy or myalgia can be classified into patient-related and drug-related factors (Table 8.3):

Amongst the patient characteristics, increased physical activity is probably the most important aspect to consider when statin patients complain of acute muscle symptoms [10, 37]. Other important risk factors are comorbidities, genetic polymorphisms and ethnicity (Asian descent carries a 3–4x increased risk).

In ALS, high cholesterol levels are associated with prolonged survival [38], and it seems prudent to stop statins in patients who develop ALS. Statins are also known to trigger muscle symptoms in cases of pre-existing muscle disease (→ 8.4), including myasthenia gravis, but at least in the latter case statin treatment is still regarded as safe, if required.

Amongst the drug characteristics, the statin dose is probably the most important predictor of side effects. Data from the SEARCH trial [19], comparing 80 mg of simvastatin with 20 mg of simvastatin, showed a minor decrease in efficiency with the lower dose but a 40 times higher frequency of myopathy with the higher dose. On the basis of this data, the FDA recommended not to use the higher dose any longer. The risk of myopathy appears to be lower with hydrophilic statins (fluvastatin, pravastatin, rosuvastatin) compared to lipophilic statins (simvastatin, lovastatin), because penetration into muscle tissue is related to lipophilicity. In the PRIMO study [10], fluvastatin appears to carry the lowest risk for myopathy.

In common with half of all the drugs which we take, most statins are metabolized by the cytochrome P450 (CYP3A4) system. Concurrent medication which inhibits CYP3A4 (Table 8.3) will therefore reduce clearance of CYP3A4-dependent statins (simvastatin, lovastatin, atorvastatin), thus increasing toxicity. Fluvastatin, pravastatin and rosuvastatin are metabolized via CYP2C9 and demonstrate less interactions with other drugs.

Increased susceptibility to myopathy is also seen in combination with fibrates [39], in particular gemfibrozil, niacin and drugs which are independently myotoxic (steroids, cyclosporine, zidovudine).

8.6 Management of Statin-Induced Myopathies

Following a recent consensus statement of the European Atherosclerosis Society [39], the first step should always be to reassess the indication for statin use and to evaluate whether the risk factors can be minimized (Table 8.3). Thereafter, the following scenarios are possible:

8.6.1 Creatine Kinase <4x ULN

(a) Tolerable symptoms:
The statin may be continued; symptoms and CK should be monitored regularly and used as guideline for possible discontinuation of treatment.

(b) Intolerable symptoms:
The statin should be discontinued regardless of CK levels, because compliance for taking the drug will be low.

If symptoms persist after a 4-week washout phase and the risk-benefit ratio warrants further treatment, the following options exist:

- Restart with lower dose of statin [19]
- Restart with less myotoxic statin (pravastatin, fluvastatin, rosuvastatin) [10]
- Try alternate-day dosing with long half-life statin (atorvastatin)
- Vitamin D deficiency should be corrected: some evidence supports vitamin D supplementation [40].
- CoQ10 administration (600 mg/d): a recent large meta-analysis [41] failed to show any benefit of CoQ10 supplementation.

If symptoms improve after discontinuation of the statin, treatment can be recommenced with either the same statin dose or according to the above protocol.

8.6.2 Creatine Kinase >4x ULN and <10x ULN

The statin should always be stopped and the need for treatment be reassessed. If considered necessary the statin may be restarted following the above options, once CK and symptoms have normalized. CK levels should then be continuously monitored and that particular treatment regimen be stopped if the levels exceed 10x ULN. An alternative regimen may be tried again or a non-statin-based therapy may be employed.

If CK persists to be high, the possibility of an underlying neuromuscular disease, in particular a necrotizing myopathy (→ 8.5.2), should be considered.

8.6.3 Creatine Kinase >10x ULN

Statin treatment should be stopped and renal function and risk factors be checked. If the CK level returns to normal, a second attempt with a lower dose of a different statin may be undertaken with careful monitoring of CK.

In case of rhabdomyolysis (affecting renal function), no further statins should be tried, and a non-statin-based lipid-lowering therapy be considered.

Following this algorithm (8.6.1–8.6.3), 43 % of patients with statin intolerance were eventually able to continue statin treatment with another lower-dose statin [35].

8.6.4 Complete Statin Intolerance

Even though rare (<0.2 % of statin users), alternative non-statin-based lipid-lowering therapies may become necessary in case of complete statin intolerance.

Ezetimibe, an intestinal cholesterol uptake inhibitor, is the first choice for these patients and may sometimes permit the use of statins concomitantly at low enough doses to limit muscle damage.

Other less efficient alternatives are bile acid sequestrants (cholestyramine), fenofibrate or niacin, which should be used in combination with ezetimibe.

Very recently, PCSK9 inhibitors (alirocumab) which target LDL receptors for degradation, were approved by the FDA and EMA. Studies have consistently shown large LDL reductions with a very low rate of muscle symptoms [42] which makes these drugs a good alternative for statins.

Finally, LDL apheresis may pose an option for statin-intolerant patients with very high LDL cholesterol levels, but this is reserved for the most severe cases.

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