BJCP British Journal of Clinical Pharmacology

DOI:10.1111/bcp.12360

Mechanisms and assessment of statin-related muscular adverse effects

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Keywords
adverse effects, efflux transporters, myopathy, organic anion transporters, rhabdomyolysis, statins

Received
5 November 2013

Accepted
14 February 2014

Accepted Article Published Online
20 February 2014

Statin-associated muscular adverse effects cover a wide range of symptoms, including asymptomatic increase of creatine kinase serum activity and life-threatening rhabdomyolysis. Different underlying pathomechanisms have been proposed. However, a unifying concept of the pathogenesis of statin-related muscular adverse effects has not emerged so far. In this review, we attempt to categorize these mechanisms along three levels. Firstly, among pharmacokinetic factors, it has been shown for some statins that inhibition of cytochrome P450-mediated hepatic biotransformation and hepatic uptake by transporter proteins contribute to an increase of systemic statin concentrations. Secondly, at the myocyte membrane level, cell membrane uptake transporters affect intracellular statin concentrations. Thirdly, at the intracellular level, inhibition of the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase results in decreased intracellular concentrations of downstream metabolites (e.g. selenoproteins, ubiquinone, cholesterol) and alteration of gene expression (e.g. ryanodine receptor 3, glycine amidinotransferase). We also review current recommendations for prescribers.

Introduction

Statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors) are the most important class of lipid-lowering drugs. The beneficial effects of statins in coronary artery disease have been shown in large randomized trials [1, 2] and statins have an acceptable safety record. However, rhabdomyolysis is a well-recognized severe, although rare, complication of statin therapy. Less severe muscular adverse effects occur more frequently. Statin use was shown to be an independent factor associated with muscular complaints in primary care patients [3].

While muscular adverse affects of lipid-lowering agents have been the subject of several review articles [4–9], our review focuses on insight into mechanisms of statin-related muscular adverse effects and recommendations to prevent complications of statin-related myopathy.

Methods

A literature search of MEDLINE was performed for articles published from 1966 through January 2014, using the following MeSH (Medical Subject Heading) terms: 'hydroxymethylglutaryl-CoA reductase inhibitor', 'antilipidaemic agents', 'anticholesterolaemic agents', 'hyperlipidaemias', 'lipids', 'cholesterol', 'drug therapy', 'statin' matched with 'muscular diseases', 'muscle cramps', 'pain', 'muscles'. From the references of relevant articles, we extracted additional literature relevant to the topic.

Types of statin-associated skeletal muscular adverse effects

Commonly, muscular adverse effects of statins are collectively termed as myopathy and present a broad range of clinical symptoms and signs. The term myopathy includes

Table 1

Definitions of muscular adverse effects of statin therapy (according to ACC/AHA/NHLBI and NLA and FDA* [11] [86])

Asymptomatic CK elevation	Elevation of CK serum activity without muscular complaints
Myopathy†	Every kind of muscular complaints
Myalgia‡	Muscle pain or weakness without CK elevation
Myositis‡	Muscular complaints with CK elevation
Rhabdomyolysis§	Muscular complaints with pronounced CK elevation (typically more than 10 times the ULN) with elevation of creatinine serum concentration, commonly with brown urine and myoglobinuria, histopathologic findings of myositis or myolysis and serum electrolyte abnormalities

CK, creatine kinase; ULN, upper limit of normal. *ACC/AHA/NHLBI, American College of Cardiology/American Heart Association/National Heart, Lung and Blood Institute; FDA, U.S. Food and Drug Administration; NLA, National Lipid Association. †NLA and FDA include a 10-fold ULN creatine kinase elevation for the definition of myopathy. ‡not defined by the NLA and the FDA. §FDA, CK >50 times ULN and evidence of organ damage such as renal compromise; NLA, CK >10 000 IU l^{-1} or >10 times ULN plus an elevation in serum creatinine or medical intervention with intravenous hydration.

muscular pain, tenderness, cramps, heaviness, stiffness or weakness [10], but no consensus on the definition exists [11] (Table 1).

Frequency of myopathy and rhabdomyolysis

Different frequencies of statin myopathy have been reported. Rhabdomyolysis is a rare event. On the other hand, less severe side effects occur more frequently. For example, myalgia is reported as frequently as 2 to 10.5%. These diverging rates are probably due to variable assessment stringency [12], which includes different definitions, assessment methods and reporting biases (e.g. drug reporting systems, awareness and publicity) (see Table 2). In addition, most statin clinical trials were not designed to assess specifically muscle-related complaints [12]. Only few clinical trials are of sufficient size and duration to detect rhabdomyolysis [13].

Risk factors

Several patient-related risk factors of statin-associated myopathy have been identified (Table 3). An increase of creatine kinase (CK) serum activity and muscle discomfort were reported with statin therapy after strong physical exertion [14]. Muscle pain can also be induced by physical exertion with statin therapy without an increase of CK serum activity [15].

Patients with inborn metabolic muscle diseases such as myophosphorylase deficiency (McArdle disease), carnitine palmitoyltransferase II deficiency or myoadenylate deaminase deficiency are more susceptible to the development of muscle symptoms on statin therapy. Genetic variants in these enzymes, either in a heterozygous or homozygous manner, have been found more frequently in symptomatic patients (10%) than in asymptomatic patients (3%) on statin therapy [16]. An association between carrying a specific allele of dystrophia myotonica-protein kinase (DMPK) and myalgia in statin users was found [17].

The concept of a dose-dependent increased risk of statin-related muscular adverse effects is supported by the results of a meta-analysis. Overall, the observed excess of rhabdomyolysis was 4 per 10 000 patients with more intensive *vs*. less intensive statin therapy compared with 1 per 10 000 patients on standard statin regimens *vs*. control (at least 2 years follow-up). All of the excess with more intensive therapy occurred in trials of 80 mg *vs*. 20 mg simvastatin daily [18]. Again, in the SEARCH study with more than 12 000 survivors of myocardial infarction, myopathy was observed in two (0.03%) cases among patients taking 20 mg simvastatin daily and in 53 (0.9%) cases in the 80 mg group (6 years mean follow-up) [19]. As a result of these data, the Food and Drug Administration issued safety-labelling changes for simvastatin [20] (see below, Recommendation for myopathy prevention in lipid-lowering drug therapy).

In addition to high doses of statins specific concomitant medications (Table 4) appear to increase the risk of statin-associated myopathy. Among 601 cases of statin-associated rhabdomyolysis, 99 patients concomitantly used mibefradil, 80 fibrates, 51 ciclosporin, 42 macrolide antibiotics, 33 warfarin, 26 digoxin, 12 azole antifungals [21]. Some of these drugs have the potential to inhibit the metabolism of most statins leading to an increase of statin concentrations. Grapefruit juice contains inhibitors, furanocoumarin derivatives, of statin metabolism [22]. There are case reports of CK increases with or without myalgia after adding ezetimibe to a well-tolerated statin therapy [23].

In a recently published population-based cohort study, coprescription of a statin with clarithromycin or erythromycin, within 30 days of the antibiotic prescription, was significantly associated with a higher risk for hospitalization with rhabdomyolysis (absolute risk increase, 0.02%; relative risk, 2.17) [24].

Suggested underlying pathomechanisms

As of now, the exact pathomechanism of statin-associated myopathy is unclear. A number of factors have been discussed. Since high dosage of statins predisposes to

Table 2

Examples of frequencies of muscular adverse effects associated with lipid-lowering drug therapy

Rhabdomyolysis	3339 cases of rhabdomyolysis, MedWatch system of the American Food and Drug Administration, observation from 1990 to 2002 [4]. Death rate of 1.5 cases of rhabdomyolysis per 10 million statin prescriptions from 1987 to 1997. 10–50 times higher risk of fatal rhabdomyolysis on cerivastatin, positive dose-related tendency, positive association with gemfibrozil [92]. Incidence of hospitalized rhabdomyolysis [per 10,000 person-years] [30]: 0.44 (atorvastatin, pravastatin or simvastatin), 5.34 (cerivastatin), 2.82 (fibrate), 5.98 (fibrate + atorvastatin, pravastatin or simvastatin), 1,035 (cerivastatin + fibrate)
Myalgia	1.5% in both groups (n = 521) with hypercholesterolaemia developed myalgia during a 6 month study period (randomized double-blind simvastatin 40 *vs.* 80 mg day^{-1}), no controls [93]. 2% of patients treated with statins (n = 3500) had myalgia (meta-analysis of patients receiving different doses and substances), no controls [94]. 6%, not differing from placebo groups (randomized, simvastatin 40 mg day^{-1}, 20,000 patients with coronary heart disease, 5 years of follow-up) [95]. 7% of patients treated with statins (cross-sectional study), no controls [96]. 2.7% (pravastatin, mostly 40 mg day^{-1}) and 3.3% (atorvastatin, mostly 80 mg day^{-1}) of patients after acute coronary syndromes (n = 4100) during 2 years of follow-up (no controls) [97]. 2.2% (atorvastatin, 80 mg day^{-1}) and 1.1% (simvastatin, 20 mg day^{-1}) of patients with previous myocardial infarction (n = 8888), no controls [98].
Myositis	No cases in the atorvastatin (80 mg day^{-1}) or placebo group (randomized) of patients after acute coronary syndrome (n = 3000), 4 months of follow-up [99].
Unspecified	Muscular symptoms in 10.5% of patients on high dose statin therapy (n = 7900), cross-sectional, no controls [100]. 2 to 3 myopathy cases per year and 10,000 hyperlipidaemic patients taking statins, population-based follow-up, significantly differing from controls (n = 0 cases) [101].

Table 3

Patient-related risk factors of statin-associated myopathy (according to [86] [102] [103])

Female gender
Hypothyroidism
Viral infections
Advanced age (>80 years of age in particular)
Small body frame and frailty
Multisystem disease (e.g. chronic renal insufficiency, especially due to diabetes mellitus)
Hepatic disorders
Peri-operative periods
Injuries
Alcohol abuse
Polypharmacotherapy
Specific concomitant medications (see Table 4)
Physical exertion

adverse muscular effects, pharmacokinetic factors are of interest when considering total body burden of xenobiotics. At the level of the injured organ, i.e. muscle, transport of statins across myocyte cell membranes is of additional interest. Also, mechanisms acting at the intracellular level may be distinguished

Pharmacokinetic factors

Drug metabolism In long term statin treatment, clearance by hepatic metabolism is the principal determinant of concentration (Figure 1). Most statins undergo CYP3A4-mediated biotransformation. Atorvastatin, a substrate of CYP3A4, is converted *in vivo* to its lactone. In a comparative study, patients with atorvastatin-related myopathy had higher plasma concentrations of atorvastatin lactone and CYP3A4-generated metabolites, *o*- and *p*-hydroxyatorvastatin, than healthy volunteers, but not significantly different plasma concentrations of the parent compound [25]. Interestingly, high atorvastatin lactone, but low hydroxylated metabolite concentrations were found in patients receiving concomitant treatment with a CYP3A4 inhibitor [26]. Concomitant treatment with an inhibitor of CYP3A4 has frequently been reported in patients developing statin-associated myopathy and rhabdomyolysis [21, 27]. In persons taking simvastatin, lovastatin or atorvastatin, 60% of cases of rhabdomyolysis involved drugs known to inhibit CYP3A4, such as erythromycin and azole antifungals [1, 28].

CYP3A4 inhibition, however, does not account for all cases of statin-related myopathy. Some cases were also reported with non-substrates of CYP3A4, e.g. fluvastatin (a substrate of CYP2C9) and pravastatin (no relevant CYP-dependent metabolism) [21]. Gemfibrozil and its glucuronide metabolite do not inhibit CYP3A4 [29]. They do however inhibit CYP2C8 which is important in the metabolism of cerivastatin. Cerivastatin was withdrawn from the market in 2001. It was more frequently associated with fatal rhabdomyolysis than other statins. Interestingly, the combination of cerivastatin and gemfibrozil was associated with a particularly high risk [30]. Gemfibrozil decreases considerably the area under the concentration–time curve (AUC) of the metabolite of cerivastatin formed

Table 4

Drug-related risk factors of statin-associated myopathy [20, 86]

	FDA recommendations for patients on simvastatin.
High dose of statin	See text
Gemfibrozil	Contraindicated with simvastatin
Ezetimibe (?)	–
Nicotinic acid	–
Ciclosporin	Contraindicated with simvastatin
Azole antifungal agents (itraconazole, ketoconazole, posaconazole)	Contraindicated with simvastatin
Macrolide (erythromycin, clarithromycin) and ketolide antibiotics (telithromycin)	Contraindicated with simvastatin
HIV protease inhibitors	Contraindicated with simvastatin
Danazole	Contraindicated with simvastatin
Verapamil, diltiazem	Do not exceed 10 mg day^{-1} of simvastatin
Amiodarone	Do not exceed 10 mg day^{-1} of simvastatin
Ranolazine	Do not exceed 20 mg day^{-1} of simvastatin
Amlodipine	Do not exceed 20 mg day^{-1} of simvastatin
Grapefruit juice	Avoid large quantities (>1 qt day^{-1})* of grapefruit juice

*1 qt is approximately 1 litre. FDA, U.S. Food and Drug Administration.

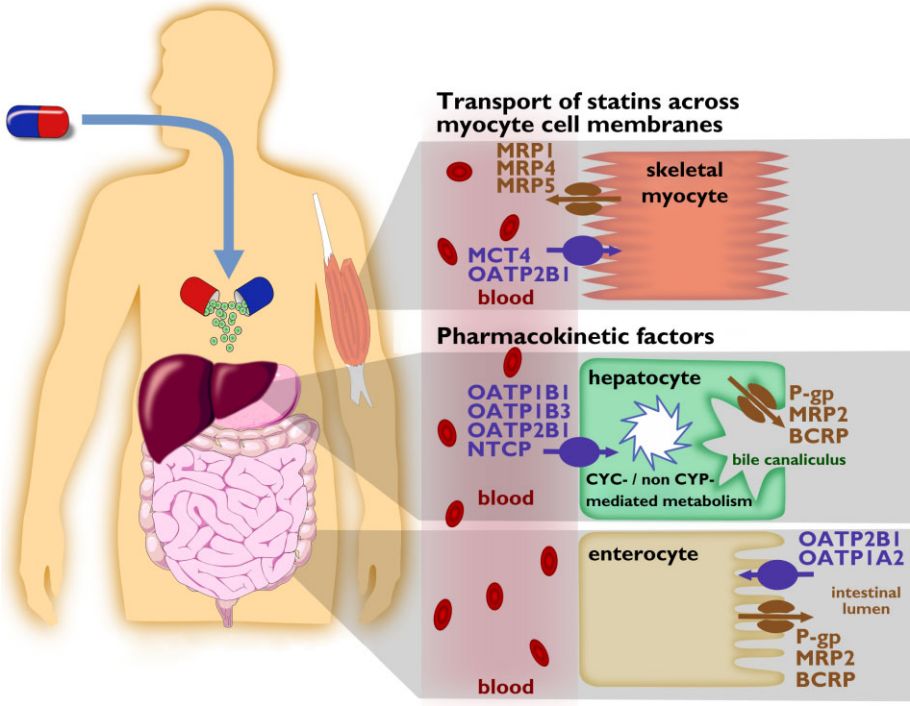

Figure 1

Drug targets potentially involved in statin myopathy. 1) Pharmacokinetic factors, affecting total body burden of statins (lower part). Pharmacokinetic factors include (A) uptake into hepatocytes by membrane transporters, i.e. OATP1B1, OATP1B3, OATP2B1 and NTCP, (B) hepatic biotransformation (CYP-mediated, non-CYP-mediated) to metabolites (e.g. acids, lactones) and (C) efflux transport into the bile canaliculi via P-gp, MRP2 and BCRP. Uptake of statins into enterocytes from the luminal site is mediated by OATP2B1 and OATP1A2. Efflux transporters involved in the secretion of statins from enterocytes into the intestinal lumen are P-gp, MRP2 and BCRP. 2) Factors related to the transport of statins across muscle cell membranes (upper part). In sarcolemmal membrane of human skeletal muscle MCT4 is expressed. Moreover intracellular concentrations of statins are affected by the uptake transporter proteins OATP2B1 and the efflux transporters MRP1, MRP4, and MRP5. →, uptake transporter; →, efflux transporter

by CYP2C8 and increases considerably the AUC of cerivastatin and its lactone, as well as the metabolite formed by CYP3A4 [31]. In the mechanism of interaction with gemfibrozil coadministration, glucuronidation has also been postulated as a potential factor. Gemfibrozil was shown to inhibit atorvastatin glucuronidation *in vitro* to a minor degree [32].

In a case series ($n = 82$), insufficient and low serum vitamin D concentrations have been associated with statin-treated patients with myalgia. Thirty-eight of the 82 myalgic vitamin D deficient patients were given vitamin D while continuing statins. Interestingly, in 35 of these 38 patients, myalgia disappeared [33, 34]. According to these findings, vitamin D deficiency was suggested to potentiate statin-induced myalgia and/or that statins cause vitamin D deficiency. Other studies found increased serum vitamin D concentrations following treatment with atorvastatin (or rosuvastatin) [35, 36]. 1,25-dihydroxycholecalciferol, the active metabolite of vitamin D, binds to the vitamin D receptor, activating CYP3A4 that metabolizes atorvastatin [37], so it has been suggested that low serum vitamin D might reduce CYP3A4 activity, increasing atorvastatin concentrations [38] and therefore statin toxicity. Indeed, supplementation of vitamin D in a small group of atorvastatin-treated patients ($n = 16$) lowered serum atorvastatin and its active metabolites [39]. However, there is not enough evidence to recommend vitamin D supplementation as treatment for statin-associated muscle complaints in the absence of low vitamin D concentrations [40].

Drug transport Transport processes play an important role in drug absorption, distribution and excretion (Figure 1). Statins have been found to be substrates of several organic anion transporting polypeptide (OATPs) transport proteins [41]. Accordingly, polymorphisms of *SLCO1B1* (solute carrier organic anion transporter family, member 1B1), encoding OATP1B1, an uptake transporter expressed on the sinusoidal membrane of human hepatocytes [42], were shown to affect markedly the pharmacokinetics of simvastatin but also to a lesser degree other statins [43]. The *SLCO1B1* c.521T>C single nucleotide polymorphism (SNP) is common (15–20% in Caucasians) and has been associated with reduced activity of OATP1B1 *in vitro*. In healthy volunteers carrying the *SLCO1B1* c.521CC genotype, the AUC of simvastatin acid is significantly higher as compared with the c.521TC and c.521TT genotypes [44, 45].

The SEARCH Collaborative Group (Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine) identified a strong association between simvastatin-related myopathy and the *SLCO1B1* c.521T>C (rs4363657) genetic variant ($P < 1.6 \times 10^{-7}$). In this genome-wide association study, 300 000 genetic markers were screened in 85 subjects with definite and incipient myopathy and in matched controls. All of them were taking 80 mg simvastatin day^{-1} and were participants of a large clinical trial involving approximately 12.000 participants. The prevalence of the c.521C allele was 46% in cases of myopathy and 13% in controls. The odds ratio for myopathy was 4.5 (95% confidence interval [CI], 2.6, 7.7) in heterozygotes, and 16.9 (95% CI, 4.7, 61.1) in homozygous variant patients for c.521C allele as compared with the references sequence [46]. In data from the SEARCH study, the clinical sensitivity was 70%, specificity 74%, positive predictive value 4.1% and negative predictive value 99% of a test for the C allele to predict definite or incipient myopathy during 5 years of 80 mg day^{-1} simvastatin use [47].

This SNP also alters the pharmacokinetics of pravastatin, a hydrophilic substrate of OATP1B1. Higher pravastatin concentrations with single dosing were found in carriers of the *SLCO1B1* c.521CC genotype [48, 49]. Also, with multiple dosing, higher plasma concentrations of pravastatin were found in carriers of a *SLCO1B1* variant haplotype group [50]. Haplotypes have been found to be more informative in predicting the *SLCO1B1* phenotype than single SNPs [49]. The frequency of the *SLCO1B1*15* haplotype, in which the c.521T>C SNP exists, is significantly higher in Japanese patients who experienced myopathy after receiving pravastatin or atorvastatin than in patients without myopathy [51]. In the STRENGTH (Statin Response Examined by Genetic Haplotype Markers) study, the *SLCO1B1*5* haplotype was found in 37% of patients ($n = 99$) with a composite adverse event (discontinuation for any side effect, myalgia or CK >three times the ULN). In those without adverse events ($n = 410$) this haplotype was found in 25% [52]. A recent analysis of data from the JUPITER (Justification for Use of Statins in Prevention) placebo-controlled trial showed no increased risk of myalgia among users of rosuvastatin who carry the rs4363657C or the rs4149056C allele in *SLCO1B1* [53].

In addition to metabolism, transporter proteins are also be involved in drug–drug interactions. The gemfibrozil–cerivastatin interaction may also have a basis on the transport level since gemfibrozil and its glucuronide have been shown to inhibit the OATP1B1-mediated hepatic uptake of statin acids [31].

Moreover other membrane transporters are involved in hepatic statin transport. The transporters OATP1B3, OATP2B1 and the Na^+-taurocholate cotransporting polypeptide (NTCP) [42, 54, 55] are expressed at the sinusoidal membrane, thereby involved in the uptake of statins. The ATP dependent transporters P-glycoprotein (P-gp, ABCB1), multidrug resistance-associated protein 2 (MRP2) and breast cancer resistance protein [BCRP, ABCG2]) [54, 56] are efflux transporters and are expressed at the canalicular membrane with consequences for statins. Although genetic variation of some of these uptake and efflux transporter proteins have been reported to affect pharmacokinetics of statins (e.g. pravastatin) [43], so far it is unclear on whether genetic but also epigenetic and/or non-genetic factors (e.g. drug–drug interaction) may

significantly increase a patient's susceptibility for statin-related myopathy.

Intestinal secretion is also important for the pharmacokinetics of statins. Efflux transporters are involved in the secretion from intestinal cells into the intestinal lumen. Among those, P-gp, MRP2 and BCRP are suggested to be important [43, 57, 58]. Ciclosporin, a potent inhibitor of several membrane transporters (e.g. P-gp), increases the AUC and the peak plasma concentration of pravastatin (a statin not depending on metabolism by CYP). This interaction profile may be due to an increased bioavailability of statins by inhibition of intestinal efflux transporters by ciclosporin [31]. In addition the membrane proteins OATP2B1 and OATP1A2 [59, 60] contribute to statin uptake from the luminal site of enterocytes. However, the clinical impact of intestinal transporter proteins on statin-related myopathy and particularly the contribution of genetic variation is unclear and needs further investigation.

Transport of statins across the myocyte cell membrane

To get into myocytes, xenobiotics may undergo passive diffusion and/or active transport. Proteins involved in the transport of drugs across cell membranes may be assumed to modulate drug concentration within myocytes by mediating influx and efflux of statins. Thus, transport protein function at the cellular level of myocytes could be involved in the development of myopathy. Statins are considered to be substrates of monocarboxylate transporter-4 (MCT4) mediating the uptake of drugs. MCT4 is expressed in skeletal muscle. Inhibition of MCT4 abolished simvastatin-induced alteration in calcium homeostasis [61] and statin-related inhibition of L-lactic acid transport is mediated by MCT4 potentially leading to alteration of muscle homeostasis [62]. However, whether MCT4 and/or other transporters of statins across membranes of myocytes play a role in myopathy is unclear. More recently, the uptake transporter OATP2B1 (SLCO2B1) and the efflux transporters multidrug resistance-associated proteins 1 (MRP1, ABCC1), 4 (MRP4 ABCC4) and 5 (MRP5, ABCC5) have been shown to be expressed on the sarcolemmal membrane of human skeletal muscle fibres proposing a role for OATP2B1 in sensitizing skeletal muscle cells to statin toxicity and for the statin efflux transporters MRP1, MRP4 and MRP5 in protection for muscle from toxicity [63].

Mechanisms acting at the intracellular level

Statins inhibit HMG-CoA reductase, mediating the conversion of 3-hydroxy-3-methyl-glutaryl-CoA to mevalonate and subsequently to isopentenyl pyrophosphate (IPP). Concentrations of metabolites downstream to this HMG-CoA reductase-mediated reaction may be assumed to be decreased by statins (Figure 2). Among those are selenoproteins (a), ubiquinone (coenzyme Q10, CoQ10) (b) and prenylated proteins (c). In addition, depletion of cholesterol itself (d) may be involved as a key process. Also, impairment of mitochondrial function (e), atrogin-1 as a critical mediator (f), MHC-I (major histocompatibility complex I) expression (g) and the up-regulation of the expression of ryanodine receptor 3, a protein located in the T-tubule membrane involved in calcium release (h), have been implicated.

(a) Impairment of the enzymatic isopentenylation of selenocystein-tRNA (Sec-tRNA) results in a decrease of available selenoproteins. This concept was generated because selenium deficiency shares common features with statin myopathy. Prominent examples of human selenoproteins are key regulators of cellular redox state. However, selenium substitution as a general co-treatment to statins is not recommended [64, 65].

(b) CoQ10 is involved in mitochondrial energy production and consequently total cell integrity [66]. Polymorphisms of the *CoQ2* gene, which encodes the second enzyme in the CoQ10 biosynthetic pathway, have been associated with increased odds of statin myopathy [67]. An association between carrying a specific allele of CoQ2 (rs4693570) and myalgia in statin users was described [17]. However, in the Clinical Practice Research Datalink study, no such association was found [68]. As of now, evidence that CoQ10 has an aetiologic role in statin-associated myopathy is insufficient, and the routine use of CoQ10 in statin-treated patients is not recommended [69, 70].

(c) Farnesyl pyrophosphate and geranyl-geranyl pyrophosphate, metabolites downstream of IPP, are used for the prenylation of various proteins which are essential for cytoskeleton and cell membrane integrity [64, 71].

(d) The depletion of cholesterol itself has been proposed to be the key to the understanding of statin myotoxicity. Statin therapy is associated with ultrastructural damage in skeletal muscle with characteristic disruption of the T-tubular system. These findings are recapitulated by extraction of membrane cholesterol *in vitro* [72]. It is consistent with this hypothesis that all lipid-lowering agents (i.e. statins, fibrates, nicotinic acid or others) increase the vulnerability of skeletal muscle cells by reducing the cholesterol content of cell membranes [4]. However, not all findings support this hypothesis. Squalene is the direct precursor of cholesterol, and the inhibition of squalene synthase does not cause myotoxicity in *in vitro* systems [73, 74].

Using a novel *in vitro* cell-based screening method for gene-by-treatment effects on transcriptional expression, glycine amidinotransferase (*GATM*) was recently identified as a genetic locus associated with statin-induced myopathy. It is proposed that simvastatin reduced GATM expression in carriers of the rs9806699 SNP, reducing creatine availability and creatine phosphate storage [75]. Possibly, reduced creatine phosphate storage modifies skeletal muscle cellular energy

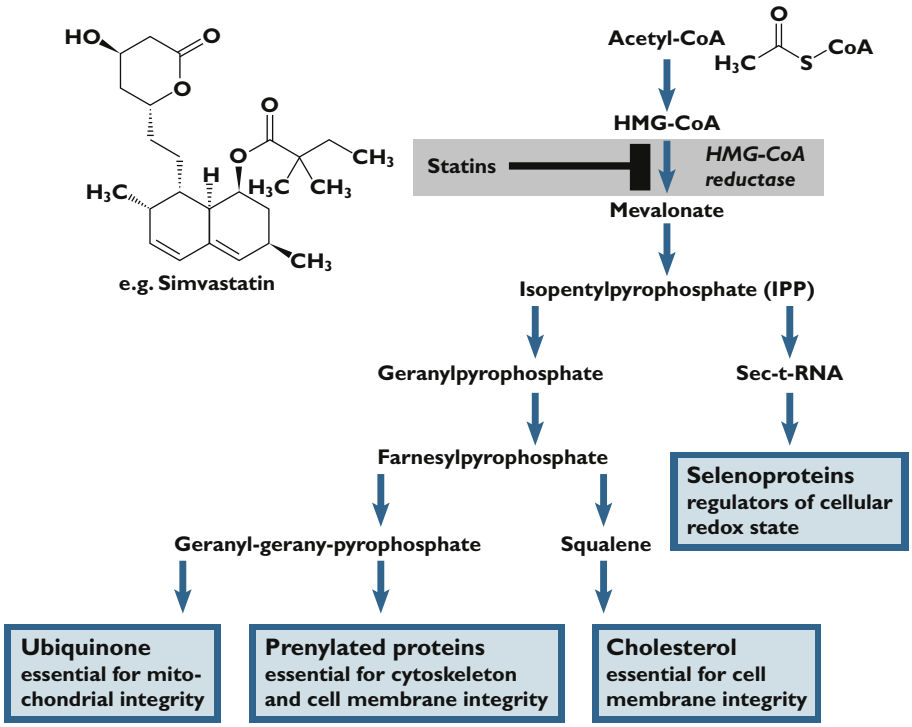

Figure 2

Biochemical pathways in cholesterol biosynthesis possibly related to statin-associated myopathy [adapted from [65]. Reprinted from *Trends in Cardiovascular Medicine*, Vol. 14, Moosmann and Behl, 'Selenoproteins, Cholesterol-Lowering Drugs, and the Consequences Revisiting of the Mevalonate Pathway', Pages 273–281, Copyright 2004, with permission from Elsevier.]. Statins inhibit HMG-CoA reductase, mediating the conversion of 3-hydroxy-3-methyl-glutaryl-CoA to mevalonate and subsequently to isopentenyl pyrophosphate (IPP). Statins may decrease concentrations of metabolites downstream of IPP like selenoproteins, ubiquinone (coenzyme Q10, CoQ10) and prenylated proteins. The depletion of cholesterol itself may be involved as a key process

pathways leading to reduced susceptibility to statin myopathy [76].

(e) As an additional mechanism acting at the cellular level, simvastatin has been shown to impair mitochondrial function by interfering with the respiratory chain. Subsequently, mitochondrial membrane depolarization and Ca^{2+} efflux to the cytoplasm by permeability transient pore or Na^{+}/Ca^{2+} exchanger may occur. This might be an important step triggering muscle fibre death [61, 77]. The mitochondrion plays a central role in regulating apoptosis. It has been shown that statins can induce apoptosis in a variety of cell types, including skeletal myocytes.

Simvastatin impaired ADP-stimulated mitochondrial respiration supported by complex I substrates in differentiated primary human skeletal muscle cells. Simvastatin also induced mitochondrial oxidative stress, demonstrated by increased levels of reactive oxygen species in concert with the up-regulation of the mitochondrial-mediated apoptotic mechanisms in primary human skeletal myotubes, suggesting that simvastatin induces cell death through oxidative stress [78].

(f) Furthermore, experiments suggest that the muscle atrophy-linked protein, atrogin-1, may be a critical mediator of muscle damage induced by statins. The background is that the ubiquitin-proteasome pathway (UPP) is the main intracellular system for protein degradation in atrophying muscle and atrogin-1 is among the UPP components. Peroxisome proliferator-activated receptor-gamma (PPAR-γ) cofactor-1 alpha (PGC-1α) is a mitochondrial biogenesis regulator. The beneficial effect of PGC-1α expression in reducing statin-associated muscle injury suggests that increased number and/or improved function of mitochondria may be central to maintain muscle integrity. Forced overexpression of PGC-1α suppresses statin-induced atrogin-1 expression and protects from statin-induced muscle damage. Statins induce marked expression of atrogin-1 in human skeletal muscle, cultured muscle cells and in animal models of statin myopathy in zebrafish. Moreover, in the absence of atrogin-1, cells and animals are less vulnerable to the toxic effects of statins [79]. Statin-induced muscle damage and atrogin-1 induction is the result of a geranylgeranylation defect [80].

(g) In patients with statin-induced necrotizing myopathy, diffuse or multifocal up-regulation of MHC-I expression (major histocompatibility complex) was also found in non-necrotic muscle fibres. This up-regulation may be

due to an endoplasmatic reticulum stress response [81].

(h) A significant muscle injury was observed among 44 myopathic patients who were receiving statins or who were discontinuing statin use (median 12 weeks ago) compared with a control group ($n = 39$) without muscular symptoms with or without statin use (19 and 20 patients, respectively). A typical histo-pathological appearance of statin-associated myopathy, characterized by vacuolization of the T-tubular system, was identified. Significant damage was defined as 2% or more damaged fibres per biopsy sample and was associated with a significant expression of ryanodine receptor 3 mRNA. Increased expression of ryanodine receptor 3, a protein located in the T-tubule membrane, could represent a potential defect in calcium homeostasis which could result in myofibre damage in statin users [82].

Recommendations to prevent myopathy complications in statin therapy

Drug-associated myopathy should be considered if a patient presents with unspecific muscular symptoms. While case numbers of rhabdomyolyis have been counted, only scanty information of the frequency of lower grades of muscular symptoms or asymptomatic CK elevation is available and the clinical relevance of these adverse effects is unclear. Specifically, the risk of asymptomatic CK elevation or of myopathy without CK elevation to proceed to rhabdomyolysis is unknown. A summary of the key recommendations is given in Table 5.

Recommendations before starting statin therapy

Patients should be informed about the risks and symptoms of myopathy [83] and the concomitant administration of drugs known to inhibit the metabolism of statins, e.g. protease inhibitors, ciclosporin, amiodarone, or some fibrates (Table 4). Although the National Lipid Association's (NLA) Muscle Expert Panel does not consider obtaining a baseline CK level in all patients absolutely necessary [84], it may be reasonable in patients who are at high risk (Tables 3 and 4) of muscle injury by statins [85]. Statin manufacturers recommend measuring the CK activity prior to starting lipid-lowering drug therapy if at least one of the following risk factors is present: impaired renal function, hypothyroidism, genetic myopathy in history or family history, history of statin- or fibrate-associated myopathy, history of hepatic disease and/or significant alcohol abuse and elderly patients (>70 years) with additional risk factors (Table 3). If pretreatment CK levels are elevated >five times the ULN, CK measurement should be repeated within 5 to 7 days (drug information). Manufacturers recommend not to start therapy if CK activity exceeds five-fold ULN in these patients. The NLA Muscle Safety Expert Panel strongly advocates CK values for patients on medications that might affect statin metabolism [84, 85] (Table 4). A clinical advisory panel recommends the evaluation of muscle symptoms before starting therapy and 6 to 12 weeks after initiating and to obtain a CK measurement if persons have muscular soreness, tenderness or pain [86]. Reference values of CK pair measurements (before and after initiating therapy), however, do not exist for patients. When interpreting those CK pairs, a high background variability, as shown in healthy blood donors without statin treatment, needs to be taken into account [87]. The Clinical Pharmacogenomics Implementation Consortium (CPIC) guideline does not argue that *SLCO1B1* genotyping is absolutely necessary. However, when genotyping is available, the consortium recommends restricting the use of 80 mg dose of simvastatin to patients who have been taking it for a long time (e.g. 12 months or more) without signs or symptoms of clinically significant toxic effects on muscle and are carriers of the rs4149056 TT genotype (i.e. normal myopathy risk). In carriers of the TC (intermediate myopathy risk) or CC (high myopathy risk) genotype, the FDA recommends against 80 mg of simvastatin, prescribing a lower dose, or considering an alternative statin. In CC carriers, the FDA also recommends considering routine CK surveillance [45].

Recommendations during statin therapy

In asymptomatic patients receiving statin therapy without risk factors for myopathy, it is not necessary to monitor CK serum activity [85]. No specific CK monitoring recommendations are given for asymptomatic patients who have one or several risk factors for myopathy but a normal CK level before start of statin treatment.

Therapy should be discontinued if muscular symptoms with CK elevation exceeding five-fold ULN (e.g. drug information Sortis®, Zocor®), or severe muscular symptoms occur (with or without CK elevation five-fold ULN), or CK elevation is 10-fold ULN (with or without muscular symptoms), or signs of rhabdomyolysis are present. CK measurement should be obtained in symptomatic patients [85].

Manufacturers recommend to discontinue statin therapy if CK activity is five times ULN or if CK elevation is less than five times ULN and significant muscular symptoms exist (e.g. simvastatin or atorvastatin). If CK activity is found to be elevated less than five-fold ULN, repeating the test within 1 week is recommended [88]. The NLA Muscle Expert Panel recommends, if the patient has intolerable muscle symptoms, to discontinue the statin, regardless of CK level, until the patient is asymptomatic. Once the patient is asymptomatic, the same statin can then be restarted at the same dose to test the reproducibility of symptoms, at a lower dose with or without other lipid-lowering medications or a different statin can be used instead [11, 84]. In a randomized, double-blind, trial, 199

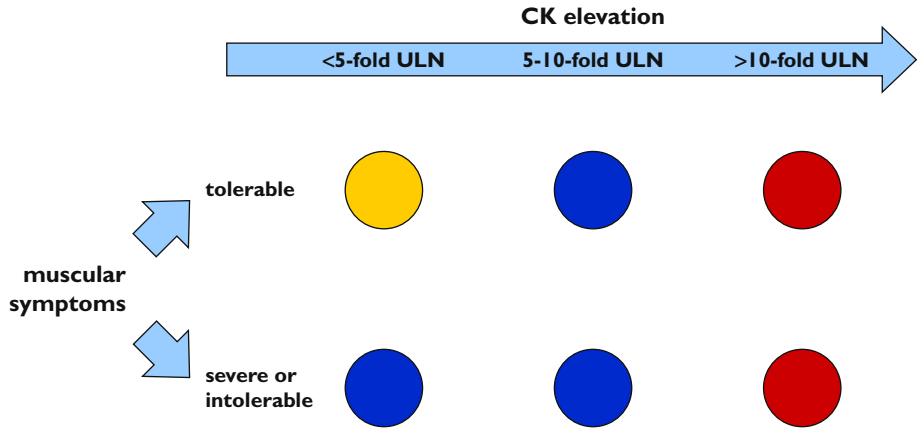

Figure 3

Recommendations to prevent myopathy complications during statin therapy (summary of recommendations according to NLA [84], ACC/AHA/NHLBI [86], Ballantyne [88] and manufacturers). Yellow ● – statin therapy can be continued at the same or reduced doses with symptoms used as the clinical guide to stop or continue therapy. Repeat CK within 1 week. Blue ● – discontinue the statin until the patient is asymptomatic. Once the patient is asymptomatic, the same statin can then be restarted at the same dose to test the reproducibility of symptoms, at a lower dose with or without other lipid-lowering medications, or a different statin can be used instead. Red ● – stop statin therapy. ACC, American College of Cardiology; AHA, American Heart Association; CK, creatine kinase; NHLBI, National Heart, Lung and Blood Institute; NLA, National Lipid Association; ULN, upper limit of normal

Table 5

Recommendations to prevent myopathy complications (summary of recommendations according to NLA [84], ACC/AHA/NHLBI [86], Ballantyne [88] and manufacturers)

Before treatment
• Inform the patient about the risks and symptoms of myopathy and of interacting drugs
• Evaluate muscle symptoms before starting therapy and measure CK if the patient reports muscular symptoms
• Obtain CK baseline in patients at high risk of muscle injury by statins and/or on medications that might affect statin metabolism (see Tables 3 and 4). If pretreatment CK is elevated >five times the ULN, repeat CK measurement within 5 to 7 days. If CK is >five-fold ULN in patients with risk factors, do not start statin therapy
• No recommendation is currently given (by CPIC) on whether or not SLCO1B1 genotyping should be performed in any patient prior to receiving simvastatin
During treatment
• Obtain CK in patients who develop muscular symptoms
• See Figure 3
• If genotyping is available, restrict the use of 80 mg dose of simvastatin to patients under long term therapy (12 months or more) without muscular symptoms who are carriers of the rs4149056 TT genotype [45]

ACC, American College of Cardiology; AHA, American Heart Association; CK, creatine kinase; CPIC, Clinical Pharmacogenomics Implementation Consortium; NHLBI, National Heart, Lung and Blood Institute; NLA, National Lipid Association; SLCO1B1, solute carrier organic anion transporter 1B1; ULN, upper limit of normal.

patients with previous symptomatic myopathy after receiving a statin (other than fluvastatin) received either fluvastatin 80 mg day^{-1} or ezetimibe 10 mg day^{-1} or both and were followed for 12 weeks. In the fluvastatin group ($n = 69$), 4% discontinued therapy due to recurrent myopathic symptoms. 8% and 3% of the patients discontinued therapy due to recurrent symptoms in the ezetimibe group ($n = 66$) and in the group receiving both fluvastatin and ezetimibe ($n = 64$), respectively [89]. Alternative therapeutic strategies, however lacking prospective evaluation, may include altered dosing regimens (e.g. non-daily dosing) or once a week rosuvastatin [90] or the addition of a non-statin such as ezetimibe or bile acid-binding resin [11, 91].

In patients with tolerable muscle symptoms and no or mild CK elevation (CK<10 times the ULN), the Muscle Expert Panel recommends that statin therapy can be continued at the same or reduced doses with symptoms used as the clinical guide to stop or continue therapy. If the patient has tolerable muscle complaints but moderate (CK levels ≥10-fold ULN, but <50-fold ULN) or severe (CK levels ≥50-fold ULN) CK elevations or clinically important rhabdomyolysis, statin therapy should be stopped [84].

Competing Interests

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years and no other relationships or activities that could appear to have influenced the submitted work.

The skilful technical assistance of Mr Bernd Borstel is gratefully acknowledged. The work has been supported by the Robert Bosch Stiftung, Stuttgart, Germany, the Federal Ministry for Education and Research (BMBF, Berlin, Germany)

grant 03 IS 2061C and 0315755 and the Deutsche Forschungsgemeinschaft KFO 274 (grant SCHW858/1-1).

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