REVIEW ARTICLE

A Neuromuscular Approach to Statin-Related Myotoxicity

Steven K. Baker, Imtiaz A. Samjoo

ABSTRACT: Approximately 95% of statin-treated patients tolerate this form of cholesterol management without any adverse effects. However, given their efficacy in reducing low density lipoproteins and cardiovascular events large numbers of patients are selected for statin therapy. Therefore muscle complications are, in fact, quite common. Limited understanding of the underlying pathophysiology has hampered physicians' ability to identify patients at risk for developing statin myotoxicity. A growing number of published case reports/series have implicated statins in the exacerbation of both acquired and genetic myopathies. A clinical management algorithm is presented which outlines a variety of co-morbidities which can potentiate the adverse effects of statins on muscle. In addition, a rational approach to the selection of those patients most likely to benefit from skeletal muscle biopsy is discussed. Ongoing work will define the extent to which statin-intolerant patients represent carriers of recessive metabolic myopathies or pre-symptomatic acquired myopathies. The expanding importance of pharmacogenomics will undoubtedly be realized in the field of statin myopathy research within the next few years. Such critical information is needed to establish more definitive management and diagnostic strategies.

RÉSUMÉ: Approche neuromusculaire de la myotoxicité due aux statines. Près de 95% des patients qui reçoivent une statine tolèrent bien ce traitement hypocholestérolémiant, sans réactions indésirables. Cependant, les complications musculaires sont relativement fréquentes parce qu'un grand nombre de patients reçoivent ce traitement à cause de son efficacité pour abaisser le taux de lipoprotéines de faible densité et pour diminuer l'incidence d'événements cardiovasculaires. Comme on connaît mal leur pathophysiologie, il est difficile d'identifier les patients à risque de développer une myotoxicité sous statine. Il y a de plus en plus de cas ou de séries de cas rapportés qui impliquent les statines dans l'exacerbation de myopathies tant acquises que génétiques. Nous présentons un algorithme concernant la conduite à tenir le cas échéant, qui énumère différentes co-morbidités pouvant potentialiser les effets indésirables des statines sur le muscle. De plus, nous discutons d'une démarche rationnelle pour identifier les patients qui sont les plus susceptibles de bénéficier d'une biopsie musculaire. Les travaux en cours permettront de définir dans quelle mesure les patients qui sont intolérants aux statines sont porteurs de myopathies métaboliques récessives ou de myopathies acquises pré-symptomatiques. L'importance croissante de la pharmacogénomique jouera sans doute un rôle dans le domaine de la recherche sur la myopathie due aux statines dans les prochaines années. Cette information est d'une grande importance pour établir des stratégies de diagnostic et de traitement.

Can. J. Neurol. Sci. 2008; 35: 8-21

The statins, as a class, are one of the most widely prescribed medications. An estimated 25 million patients worldwide (13 million Americans) are treated with statins of the 200 million patients worldwide (36 million patients in the United States) being eligible for hypolipemic therapy.[1,2] Numerous randomized controlled trials have demonstrated both their general tolerability and efficacy in reducing cardiovascular end-points.[3-6] In fact myogenic complaints rarely differed between placebo and statin groups. However, continuing post-market surveillance suggests that treatment-limiting myalgias or myopathies occur in approximately 5-7% of patients. Thus 1.75 million (i.e., 0.07 x $25x10^6$) hypercholesterolemic patients may be withdrawn from a form of therapy which significantly reduces cardiovascular end-points. This has potentially significant health economic implications as statins reduce cardiovascular end-points by approximately 30%. Therefore, 525,000 (i.e., 0.30 x 1.75 x 10^6) patients may experience earlier cardiovascular events secondary to the withdrawal of statins. If the average cost of a non-fatal stroke or myocardial infarction is estimated at $10,000 CAD, then statin withdrawal secondary to myalgias alone may cost the global healthcare system $5.25 billion. With the ever increasing profile of statins, spurred by positive landmark trials[6-8] and the growing trend to make them available over-the-counter,[9] the global use of statins will increase, resulting in a proportionate rise in the incidence of clinical statin myotoxicity. Furthermore,

From the Department of Medicine, Neuromuscular Disease Clinic, McMaster University, Hamilton, Ontario, Canada .

Received December 15, 2006. Final Revisions Submitted October 23, 2007.
Reprint requests to: S. K. Baker, Department of Medicine, Neuromuscular Disease Clinic, HSC 2H22, McMaster University, Hamilton, Ontario, L8N 3Z5, Canada.

up to 30% of patients who develop hyperCKemia or symptom-limiting side-effects from the statins do not readily recover after drug discontinuation,[10] making the task of finding preemptive management strategies and effective treatments more germane.

Introduction to Statin Pharmacology

At the pharmocodynamic level (i.e., their site of action) all statins function similarly by selectively binding to the active site of hydroxymethylglutaryl co-enzyme A (HMG-CoA) reductase thus inhibiting the enzyme competitively.[11] However, at the pharmocokinetic level (i.e., their absorption, distribution, metabolism, and excretion), they have metabolic differences related to their physiochemical properties, which in turn may translate into differences in their myotoxic potential.

The clinical benefits of statins are thought to arise primarily from their ability to lower serum total cholesterol and low-density lipoprotein cholesterol (LDLc) levels (Table 1). There are currently six statins approved for prescription in North America: lovastatin (Mevacor), simvastatin (Zocor), pravastatin (Pravachol), fluvastatin (Lescol), atorvastatin (Lipitor), and rosuvastatin (Crestor). The portion of the statin structure attributed to enzyme inhibition is an HMG mimic. First-generation statin drugs, which include lovastatin, simvastatin, and pravastatin, are fungal natural products or semi-synthetic with similar chemical structures containing a substituted decalin ring structure.[12,13] Second-generation statin drugs, which include fluvastatin, atorvastatin, cerivastatin (Baycol), and rosuvastatin, are synthetic and structurally dissimilar compounds containing fluorophenyl groups linked to the HMG-like moiety.[13] Due to these structural differences, statins vary in half-life, systemic exposure, maximum plasma concentration, bioavailability, protein binding, lipophilicity, metabolism, and excretion routes (Table 1).[13] For example, statins with low systemic bioavailability (i.e., lovastatin and simvastatin) exhibit greater increases in serum levels when the activity of cytochrome P450 is slowed or inhibited compared to statins with higher bioavailabilities (i.e., fluvastatin). Pravastatin is not metabolized by the P450 system but rather undergoes cytosolic sulfation.[14] Cytochromes 2C9 and 2C19 contribute minimally to the breakdown of rosuvastatin.[15]

Transmembrane pumps that transport statins represent additional levels of potential pharmacokinetic interactions. Examples of these include the P-glycoprotein system, which

Table 1: Pharmacokinetic Parameters of HMG-CoA Reductase Inhibitors

	Lovastatin	Simvastatin	Pravastatin	Fluvastatin	Atorvastatin	Rosuvastatin	Cerivastatin
Efficacy							
LDLc (% decrease)	21-40	14-47	22-34	17-35	26-60	45-63	28
TG (% decrease)	16	18	24	10	29	10-35	13
HDLc (% increase)	9	12	12	8	6	8-14	10
Absorption							
Dose range (mg/d)	10-80	10-80	10-40	10-80	10-80	5-40	0.3
Fraction absorbed (%)	30	60-80	34	98	30	-	98
T_{max} (h)	2-4	1.3-2.4	0.9-1.6	0.5-1	2-3	3	2.5
C_{max} (ng/mL)	10-20	10-34	45-55	448	27-66	37	2
Bioavailability (%)	5	5	18	19-29	12	20	60
Effect of food	increased	no effect	decreased	decreased	decreased	minimal	no effect
Distribution							
Fraction bound (%)	>95	94-98	43-55	>99	80-90	88	>99
Lipophilicity*	lipophilic	lipophilic	hydrophilic	lipophilic	lipophilic	hydrophilic	lipophilic
Metabolism							
Hepatic extraction (%)	>70	78-87	46-66	>68	>70	-	-
Cytochrome(s) involved (CYP)	3A4	3A4	NS	2C9	3A4	2C9,2C19	3A4,2C8
Effect on P-glycoprotein[165]	inhibitor	inhibitor	no significant inhibition	no significant inhibition	inhibitor	no significant interaction	-
Excretion							
$t_{1/2}$ (h)	2.9	2-3	1.3-2.8	0.5-2.3	15-30	20	2.1-3.1
Urinary excretion (% of dose)	10	13	20	6	2	10	30
Fecal excretion (% of dose)	83	58	71	90	70	90	70

T_{max}, time to peak concentration; C_{max}, maximum concentration; $T_{1/2}$, elimination half-life; LDLc, low-density lipoprotein-cholesterol; TG, triglyceride; HDLc, high-density lipoprotein-cholesterol; - , unknown; NS, not significant. Modified from Corsini et al,[13] Sabia et al,[12] and Bellosta et al[166]
*Lipophilicity: simvastatin=cervistatin>lovastatin=fluvastatin=atorvastatin>pravastatin=rosuvastatin. Potency: rosuvasatin>atorvastatin>cerivastatin>simvastatin>fluvastatin>pravastatin.

https://doi.org/10.1017/S0317167100007514 Published online by Cambridge University Press

serves as an efflux pump for toxic compounds (Table 1), and the human organic anion transporter polypeptides (OATPs), which deliver the statins across the hepatic and sarcolemmal membranes. Cyclosporine inhibits P-glycoprotein,[16] as well as cytochrome 3A4[17] and the hepatic statin transporter, OAPT2,[18] thereby decreasing transport. Various other mechanisms, however may also explain the interaction between cyclosporine and statins. For example, the hydrophilic statins, pravastatin and rosuvastatin, likely interact with cyclosporine via hepatic uptake as they are not substrates or inhibitors of P-glycoprotein or cytochrome 3A4 although they are transported by OATP2.[19,20] Despite growing evidence of numerous potential modes of drug-drug interactions, the exact mechanisms that determine statin myotoxity remain enigmatic. However, since the risk of myopathy appears dose-dependent,[21]understanding the factors governing intramuscular statin concentration are of prime importance.

Clinical Management of Statin Related Myotoxicity

The statins have attracted widespread notoriety with respect to potential musculoskeletal side-effects. While the pathophysiology of statin myopathy is unknown, there are accepted muscle-related side-effects which include myalgia, cramps, myopathy, myositis, and rhabdomyolysis. A lack of general consensus regarding these definitions has complicated clinical management. For example, myalgia, defined as simply muscle aches or flu-like symptoms, may or may not occur in the context of an underlying myopathy. The latter diagnosis implies pathology and should be supported by findings on a muscle biopsy. Myositis and rhabdomyolysis are arbitrarily defined as serum creatine kinase (CK) levels of less than or greater than ten times the upper limit of normal, respectively. Low-grade hyperCKemia can be caused by disorders that are not primarily myogenic which renders a diagnosis of statin-myositis based only on a CK levels challenging. The diverse pathophysiology of statin-related muscle side-effects poses further challenges. For example, a patient with myalgia may have biopsy-proven myopathy, myositis, or neither whereas another patient may have asymptomatic rhabdomyolysis. Thus there is a clear need for a rational clinical algorithm to assist in the management of these patients.

Given the high degree of public awareness regarding the possible muscle effects of statins, patients may inappropriately ascribe myalgias to the statin. Therefore, a complete neuromusculoskeletal exam should be performed to exclude common conditions such as muscle strain, bursitis, tendonitis, osteoarthritis, radiculopathy, and myofascial pain. Physical findings will dictate the need for subsequent investigations such as x-ray, ultrasound, computerized tomography, magnetic resonance imaging (MRI), or electromyography (EMG). In cases where statins appear culpable in the production of muscle side-effects, with or without CK elevation, there are five immediate issues that require consideration (Figure).

(1) Drug-Drug Interactions

Myalgias may be attributed to drug-drug interactions. Lipid-soluble statins (i.e., atorvastatin, lovastatin, simvastatin) have been detected at elevated levels in serum when co-administered with other cytochrome P450 3A4-dependent drugs.[22] For example, we recently reported a case of colchicine (3A4-dependent) triggered fulminant rhabdomyolysis in a long-term simvastatin-exposed patient.[23] By contrast, there is limited risk for drug-drug interactions with the hydrophilics (i.e., rosuvastatin and pravastatin). Simple pharmacokinetics, however, cannot explain the entirety of statin myotoxicity. Indeed, a recent correlational study did not find any relationship between CYP450 polymorphisms and the expression of muscular side effects in 100 statin-treated patients–half of whom were asymptomatic.[24] Additionally, the highest incidence of drug interaction associated statin rhabdomyolysis occurs when other lipid lowering agents, particularly fibrates, are added to statin therapy.[25,26]

A final issue regarding drug interactions is that of co-administered drugs with independent myotoxic potential. While gemfibrozil raises statin activity,[27,28] fenofibrate does not.[28,29] Yet fenofibrate carries a risk for drug interaction-induced statin rhabdomyolysis.[30-32] This argues for an effect of combined therapy independent of statin levels (i.e., pharmacodynamic interaction). Melli et al,[33] found that the antipsychotics, as a class, were responsible for more cases of rhabdomyolysis than were the statins in a review of hospitalized toxic myopathy patients. Therefore, systematically excluding multiple myotoxic medications represents a logical approach to discerning the responsible drug.

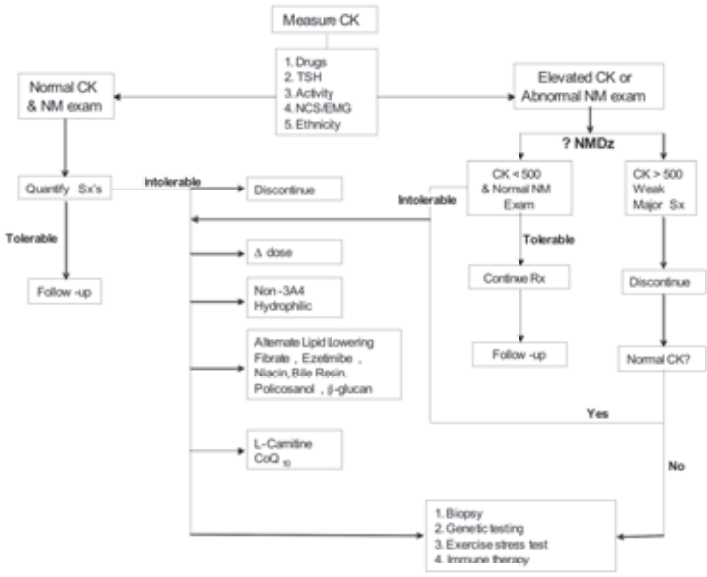

Figure: *Management algorithm for statin-induced muscle disease. CK, creatine kinase; CoQ_{10}, co-enzyme Q_{10};NCS, nerve conduction studies; NM, neuromuscular; NMDz, neuromuscular disease; Rx, therapy; Sx, symptoms.*

(2) Hypothyroidism

Hypothyroidism is a cause of secondary hypercholesterolemia and is known to increase the risk for statin myopathy.[34,35] Thyroid hormone regulates HMG-CoA reductase messenger

https://doi.org/10.1017/S0317167100007514 Published online by Cambridge University Press

RNA.[36] Thus a combination of statin treatment and pre-existing hypothyroidism may compound the reduction in enzyme activity. Both overt and sub-clinical hypothyroid myopathy may also be independently associated with CK elevations[37] and further predispose a patient to statin myotoxicity. Conversely, simvastatin has been associated with thyroid stimulating hormone (TSH) elevations in L-thyroxine-treated patients, possibly via accelerated T4 metabolism through CYP450 3A4.[38]

Statins have been implicated in carnitine dyshomeostasis. Sinclair et al,[39] documented a significant inverse correlation between serum TSH and muscle carnitine levels. Gamma-butyrobetaine hydroxylase is the terminal rate-limiting enzyme in carnitine synthesis and its reduced activity in hypothyroidism[40] may explain reductions in tissue carnitine levels. This therefore suggests another level of interaction in hypothyroid patients. Treating sub-clinical hypothyroidism or increasing L-thyroxine levels in patients with existing hypothyroidism may mitigate symptoms; however, evidence to justify such an approach is required.

Table 2: Non-iatrogenic causes of asymptomatic hyperCKemia

Disorder	Reference
Inflammatory Myopathy	
Polymyositis	53
Macrophagic myositis	53
Inclusion body myositis	53
Non-specific myositis	53
Muscular Dystrophy	
Dystrophinopathy (including carrier status)	53,136,167
α-glucosidase deficiency	53
Sarcoglycanopathy	167
FKRP deficiency	53
Caveolinopathy	53,168
Calpainopathy	53
Dysferlinopathy	53
Distal myopathy (pre-symptomatic)	169
Myofibrillar myopathy	53
Myotonic Dystrophy type 2	170
Metabolic Myopathy	
McArdle disease	53,167
Mitochondriopathy	53,54
Alcoholism	54,171
Malignant hyperthermia	172-174
Central core disease	167
Myoadenylate deaminase deficiency	56,175
Partial phosphorylase B kinase deficiency	56
Partial carnitine palmitoyl transferase deficiency	56
Endocrine/Nutritional Myopathy	
Hypothryoidism	171
Hypoparathyroidism	176
Alcoholism	177
Non-specific Myopathy	
Desminopathy	178
Myopathy with tubular aggregates	167

FKRP - Fukutin-related protein

(3) Physical Activity

Identifying activity patterns prior to CK measurement is exceedingly important, particularly because statins are associated with exaggerated exercise-induced CK elevations. For example, Thompson et al,[41] found that five weeks of lovastatin treatment (40 mg/d) increased CK elevations 24 hours after 45 minutes of downhill (−15% grade) walking by a mean of 191 U/L compared to 103 U/L for placebo ($P<0.05$). Similarly, elite athletes with familial hyperlipidemia are generally intolerant to statin therapy as a result of their rigorous training.[42] Eccentric (i.e., muscle lengthening) contractions are particularly damaging to myofibers. Eccentric upper extremity activity (2 sets of 25 reverse biceps curls) raised CK to a mean of > 7000 U/L in 203 healthy subjects by day four post-exercise (range: 55 – 80550 U/L). In 51 subjects the CK was > 10000 U/L on day four.[43] This highlights the extreme inter-individual variability that must be considered when interpreting CK values. Another factor influencing post-exercise CK is the patient's (task-specific) fitness. Unaccustomed muscular work causes far greater elevations in CK compared to work for which an individual is trained.[44,45] However, even in highly trained endurance athletes prolonged submaximal running can produce extreme exertional hyperCKemia. For example, the mean CK of 39 ultramarathoners (mean age 41) upon completion of a 246 km continuous race averaged 43,763 ± 6,764 U/L.[46] By contrast, a single day 230 km mountainous road cycling race produced trivial excursions in CK in 38 males (mean age 35) from a pre-race value of 63 U/L to a 24-hr post-race value of only 234 U/L.[47]

These divergent CK responses to exercise support the well-known observation that myocellular damage can be induced by eccentric activity[48] and highlight the importance of clarifying any muscular activity that occurred prior to CK measurement. To obtain an unbiased measurement, patients should abstain from exercise for ≥ 72 hours prior to the blood draw. Even with this precaution physicians must recognize that CK levels can remain elevated for over a week after eccentric exercise.[49]

(4) Radiculopathic and Neuropathic HyperCKemia

Clues to presence of lumbosacral radiculopathy or motor neuropathy should be sought. Indeed, denervation is known to cause mild creatine kinase elevations.[50,51] Whether statins potentiate denervation-related CK elevation is not known. Equally unclear is whether statin-treated patients with motor neuropathy or radiculopathy experience higher resting CK levels or greater post-exercise CK elevations compared to individuals without these conditions. In this context the value of thorough neuromuscular and electrodiagnostic examinations cannot be overstated.

(5) Ethnicity & Idiopathic HyperCKemia

Asian populations may be particularly susceptible to statin related muscle adverse effects possibly due to higher serum drug concentrations.[52] A recent attempt to ascribe such ethnic idiosyncrasy to polymorphisms in the human organic anion transporting polypeptide 1B1 (which contributes to hepatic uptake of the statins) failed to correlate genotypes with pharmacokinetic parameters.[52] Therefore, it appears that other

factors may underlie the observed ethnic variability in serum statin levels.

African-Americans may have elevated baseline CK levels with certain healthy individuals harboring values persistently exceeding four times the upper limit of normal (i.e., 800-1000 U/L). The cryptogenic factors which give rise to this benign hyperCKemia may also contribute to the modest CK elevations evident in these individuals when treated with statins. Idiopathic hyperCKemia (IH) is found across all ethnic groups and is more common amongst men than women. A normal clinical and family history, neuromuscular exam, and electrodiagnostic study tends to exclude the need to perform comprehensive investigations although extensive work-up may disclose pathology in up to 55% of cases. [53-56] In 46% of cases IH may occur in a familial form.[57] Idiopathic hyperCKemia is genetically heterogeneous exhibiting autosomal dominance in 60% of kindreds, with increased penetrance in males.[57] These patients manifest persisting hyperCKemia despite statin withdrawal. Muscle biopsies appear normal or display minor nonspecific changes (i.e., variability in fiber-type proportion or size).[57] Statin therapy for asymptomatic patients whose CK level does not normalize after withdrawal should be reinstated for cardiovascular protection. Judicious clinical follow-up and intermittent CK monitoring should be performed to ensure patient tolerance.

Normal vs. Elevated Creatine Kinase

After the above five determinants of statin-intolerance have been considered, it is necessary to assess the CK levels. An important caveat is that a subclinical myopathy may exist even when the CK is normal.[58,59] The histological changes may include mild lipidosis, cytochrome oxidase-negative fibers, and ragged red fibers. Creatine kinase levels cannot be used as an absolute biomarker of muscle damage. However, a normal level tends to exclude myositis.

Various myopathic reactions to statins are documented (Table 3). While skeletal muscle may undergo pathologic alterations in response to statins, muscle experts agree that a biopsy need not be performed in every symptomatic patient.[60]

Baseline CK levels are clinically useful. Individuals with pre-statin elevations warrant serial CK monitoring. Currently, there is a lack of consensus on the definition of an acceptable rise in CK after statin introduction. For example, a 30% rise in creatinine within the first two months of angiotensin-converting enzyme inhibitor therapy is considered acceptable.[61] Similar information should be available to physicians prescribing statins. However, the variability of serum CK values and their fluctuations in response to physical activity make such a numbers-driven approach less tenable. This emphasizes the importance of clinical acumen in the management of statin-treated patients.

Normal CK Levels

If the CK is normal (i.e., left-side of algorithm), it is important to confirm that the pain stems from the muscle. Tendinopathies,[62] arthropathies,[63,64] lupus-like syndromes,[64,65-67] and neuropathies[68-70] have been attributed to statins. Chance association might account for these observations which require additional support in the literature. Muscle-derived symptoms, if tolerable, should be closely followed and the statin continued. If the symptoms are intolerable the statin must either be discontinued or replaced with another lipid-lowering drug. Alternatively, if cholesterol targets are achieved, a down-titration may be considered although the latest Canadian cholesterol management guidelines make this option less likely for patients receiving secondary prevention therapy (i.e., 2006: LDL ≤ 2.0 mmol/L[71] vs. 2003: LDL ≤ 2.5 mmol/L[72]). When a drug-drug interaction is thought to be responsible for the emergence of symptoms, converting to a non-cytochrome P450-dependent or hydrophilic statin (i.e., pravastatin or rosuvastatin) may be considered. Golomb et al[73,74] reported that statin-intolerant patients have a 55% chance of symptom recurrence if a subsequent lower potency statin is prescribed compared to 95% chance if an equipotent statin dose is used, independent of lipophilicity.

Table 3: Clinical spectrum of myotoxic reactions to statin drugs

1. Myalgias ± cramping ± stiffness
2. Myopathy[§] ± weakness
   a. with elevated serum CK
      i. CK ≤ 500 U/L
      ii. CK ≥ 500 U/L
   b. without elevated CK (muscle biopsy required)
3. Rhabdomyolysis
   - with renal failure
   - without renal failure
4. Asymptomatic hyperCKemia

§ The definition of clinical myopathy implies the presence of weakness; however, histological changes can occur without weakness or CK elevation. Therefore, clinical and histologic myopathy should be differentiated when possible.

Alternate Lipid-lowering Therapies

Alternatively, agents such as ezetimibe, fibrates, or niacin can be prescribed. Ezetimibe is a novel lipid-lowering agent that binds to the Niemann-Pick C1 Like 1 transporter,[75] which critically regulates intestinal cholesterol absorption at the brush-border surface[76] and whole-body cholesterol homeostasis.[77] Ezetimibe has not been systematically evaluated in statin-myopathy patients and numerous reports implicate it in muscle adverse effects.[78-80] Phillips et al,[80] reported that the majority of statin-intolerant patients also exhibit intolerance to ezetimibe secondary to recurrent myotoxicity. Ezetimibe may also exhibit pharmacogenomic myotoxicity, given the report of rhabdomyolysis being triggered in a patient with McArdle's disease.[81] A recent retrospective review[82] of administrative claims data reported similar relative risk estimates for myopathy requiring hospitalization for gemfibrozil (0.84), ezetimibe (0.98), atorvastatin (1.0), simvastatin (1.24), pravastatin (1.25), and rosuvastatin (1.36). Niacin, fenofibrate, cerivastatin, and

https://doi.org/10.1017/S0317167100007514 Published online by Cambridge University Press

concomitant use of CYP3A4 inhibitors were associated with 2.5, 4.3-, 6.7- and 6.0-fold higher reporting rates for myopathy compared to atorvastatin, respectively. Close monitoring for muscle side-effects is required in any statin-intolerant patient testing alternative lipid lowering therapies.

Bile acid resin monotherapy has not been associated with rhabdomyolysis. In four patients, pre-existing myopathy lead to exaggerated myopathic symptoms upon exposure to statins, fibrates, or niacin. By contrast, cholestyramine was well tolerated.[83] This finding was recently extended by Phillips and colleagues,[84] who reported on the clinical efficacy and safety of colsevelam in statin myopathy patients. Finally, policosanols, a mixture of long-chain primary aliphatic saturated alcohols derived from the waxes of such plants as sugar cane (*Saccharum officinarium*) and yams (*Dioscorea opposita*), as well as β-glucan, a soluble fiber derived from oatmeal and oat bran, have been used as nutraceutical options to lower LDL. While preliminary small trials[20,21,85-88] provided promising results for policosanols, two recent randomized controlled trials[89,90] failed to establish a cholesterol-lowering effect. Dietary oat bran (56 g/day) supplementation for six weeks produced a 16% reduction in LDL.[91] A meta-analysis concluded that 3.0 g soluble fiber from oats (3 servings of oatmeal, 28 g each) can decrease total and LDL cholesterol by approximately 0.13 mmol/L.[92] There are no reports on the LDL-lowering effects of combining cholestyramine with policosanols or β-glucan. For patients with multi-agent lipid-lowering myopathy, these nutraceutical options require increased consideration.

Myoprotective Supplements

The clinical utility of co-enzyme Q_{10} is unproven. Numerous studies suggest that blood levels of co-enzyme Q_{10} are reduced by statin treatment.[93-110] This effect is most likely a function of lipoprotein reduction as these proteins serve as carriers for co-enzyme Q_{10}.[100,105] There are conflicting data regarding the effect of statins on myocellular levels of co-enzyme Q_{10}. Several studies have reported an increase by 9.0 to 46.6% after one to six months of simvastatin therapy (20 mg/day).[93,100] Päivä et al [111] documented a 33.5% reduction after eight weeks of simvastatin (80 mg/day) but not atorvastatin (40 mg/day) treatment. Additionally, the mitochondrial volume marker, citrate synthase, was reduced to 55% of baseline activity suggesting that statins may impair mitochondrial biogenesis. Vladutiu et al[10] found reduced skeletal muscle co-enzyme Q_{10} levels in 47% of 41 biopsy specimens from statin-intolerant patients with varying CK levels. By contrast, Lamperti et al found similar mean muscle co-enzyme Q_{10} levels between controls and statin myositis patients.[107] Three of 18 patients with statin myositis had muscle levels greater than two standard deviations below the control mean. However, no mitochondrial abnormalities or TUNEL (terminal deoxynucleotidyl transferase-mediated deoxyuridine triphosphate nick-end labeling) positive nuclei were noted in these patients.

Conflicting reports of muscle co-enzyme Q_{10} levels underscore the uncertain utility of this compound in the treatment of statin myopathy. Preliminary evidence from a randomized blinded trial demonstrated improved myalgias in 18 of 21 patients who received 100 mg/d of co-enzyme Q_{10} for four weeks as opposed to 3 of 20 who received 400 IU of vitamin E ($P < 0.001$).[112] Additional randomized-controlled double-blinded trial evidence is needed to address this issue in order to establish more definitive evidence-informed management guidelines.

Elevated CK Levels

In cases where CK levels are elevated (i.e., right-side of algorithm), whether symptomatic or not, a complete neuromuscular exam should be performed to assess for evidence of muscle weakness. In oligo-/asymptomatic patients, if the neurological examination is normal and CK levels are not above 500 U/L, the statin can be continued in agreeable patients. Patients requesting statin discontinuation should be prescribed alternate lipid lowering therapies. Patients should be advised about the potential for vigorous or unaccustomed exercise to cause hyperCKemia and the theoretical potential of rhabdomyolysis particularly with dehydration.[113,114] In certain individuals it may still be informative to discontinue the statin for approximately one month in order to document a decline in serum CK. Some patients with modest CK excursions (i.e., 250–400 U/L) may be found to harbour muscle pathology, however there is a need to establish minimum biopsy criteria in order to select patients with abnormal histopathology. Patients manifesting muscle weakness or CK values above 500 U/L warrant statin discontinuation and serial CK monitoring to determine if the values normalize. If the CK returns to pre-statin levels then the "normal CK" arm of the algorithm can be worked through.

In the context of either a persistently elevated CK or an abnormal neurologic exam consideration should be given to a growing list of neuromuscular disorders attributed to statin therapy.[58,94,115-129] Included in this list are the idiopathic inflammatory myopathies [i.e., overlap myositis (personal observation), polymyositis,[125] dermatomyositis,[123,126-128] and inclusion body myositis[124]], myasthenia gravis,[117,118] mitochondrial myopathy,[58,94,130] McArdle disease,[121,122,130] acid maltase deficiency,[129] carnitine-palmitoyl transferase deficiency,[120] rippling muscle disease (RMD),[115] malignant hyperthermia (MH),[116,119] myotonic dystrophy type 1 (DM1),[130] Kennedy disease,[130] and amyotrophic lateral sclerosis.[131] For genetically-based muscle disorders statins are believed to trigger myogenic symptoms more readily than in normal muscle. It seems likely that the diverse neuromuscular phenotypes associated with statin use reflect multiple mechanisms acting either singly or synergistically.

Patients with significant stereotypic hyperCKemia in response to multiple statins, a single exuberant episode of hyperCKemia (including rhabdomyolysis), weakness, or treatment-limiting myopathic symptoms should be biopsied to determine if the pathology is more typical of a known neuromuscular disorder or statin-induced damage as has been previously reported in rodent and human statin myopathy (Tables 4 & 5). Enzymology (i.e., mitochondrial respiratory chain, CPT, myophosphorylase), muscle co-enzyme Q_{10} and L-carnitine quantification, and genetic analyses of the three commonest triggerable metabolic myopathies (i.e., *AMPD1*, MIM 102770; *PYGM*, MIM 232600; and *CPT2*, MIM 255110) are additional considerations. Recently, statin myopathy patients were found to be 20-fold and 13-fold more likely to be carriers of McArdle disease and CPT2 deficiency, respectively, compared to the

https://doi.org/10.1017/S0317167100007514 Published online by Cambridge University Press

Table 4: Histomorphologic changes in skeletal muscle after pharmacologic doses of lovastatin (1 mg/g body weight for 30 days)

Microscopy	Pathologic Observations
Light	Increased variability in fiber diameter Myofiber splitting Increased nuclear internalization Perimysial fibrosis Coarsening of intermyofibrillar membranous network Clumping of intermyofibrillar membranous material Diffuse decrease in NADH dehydrogenase staining in non-necrotic myofibers Myofiber necrosis with macrophage invasion Hypercontacted fibers Relative sparing of slow-twitch oxidative fibers with earlier involvement of fast-twitch glycolytic fibers
Electron	Two types of mitochondrial alterations: (1) fragmented inner mitochondrial membrane (IMM) or absent or effaced cristae; replacement of cristae with fine granular material; outer MM (OMM) intact (2) spared IMM and matrix; redundant and thickened OMM ± circular loops formed by OMM material Dilated cisterns of the sarcoplasmic reticulum Normal T-tubules Myeloid figures in degenerating mitochondrial membranes Vacuolization Intermyofibrillar and subsarcolemmal accumulations of abnormal mitochondria Z-band streaming

Adapted from Waclawik, A.J., Lindal, S., Engel A.G. Experimental lovastatin myopathy. J Neuropathology and Experimental Neurology 1993, 52: 542-9 (with permission). Biopsies were taken from Lewis rat superficial (white/glycolytic) and deep (red/oxidative) regions of the gastrocnemius and soleus (red/oxidative) muscles on days 5, 10, 12, 14, and 30. Therefore, selected features from the above list were not observed in each animal. Longer treatment was associated with worsening myopathologic changes.

Table 5: Pathological abnormalities reported from patients manifesting statin-related adverse muscle effects

Cytochrome oxidase negative fibers
Electron-dense membranous debris
Fiber atrophy
Glycogen storage
Increased oxidative enzyme staining
Inflammatory infiltrate
Lipid-filled vacuoles
Necrosis
Paracyrstalline inclusions (mitochondrial)
Ragged-blue fibers (Succinate dehydrogenase stain)
Ragged-red fibers (Gomori trichrome stain)
Vacuolization

general population.[10] This preliminary data offers compelling evidence that latent partial deficiencies of metabolic pathways when further "stressed" by pharmacologic toxicity will produce symptomatic muscle disease. Conceptually, this is similar to a statin accelerating symptom onset in patients with a sub-clinical inflammatory myopathy. Indeed, when such pathology is found treatment with routine agents is warranted (i.e., prednisone, azathioprine, methotrexate, cyclosporine, cyclophosphamide, intravenous immunoglobulin, mycophenolate mofetil, plasma exchange, or rituximab; for excellent reviews see references).[132-135]

Statins and Neuromuscular Diseases: Pathophysiologic Considerations

Idiopathic Inflammatory Myopathies and Myasthenia Gravis

There are a variety of mechanisms that may account for triggering or aggravating muscular disorders upon statin treatment. For example, given the autoimmune pathogenesis of idiopathic inflammatory myopathies and myasthenia gravis, it is possible that statin use could induce a dysimmune process.[118,123] With inflammatory myopathies this may well occur as a result of low grade myotoxicity exposing muscle antigens thereby facilitating loss of tolerance in susceptible individuals.[136] Alternatively, statins are immunomodulatory insofar as they increase production of Th2 cytokines (i.e., IL-4, 5, & 10).[137] The documentation of patients requiring long-term immunosuppression for an acquired inflammatory myopathy that developed shortly (i.e., one - three months) after statin treatment supports the triggering potential of these drugs in chronic myopathy. It is, however, possible that these patients were destined to develop the myopathy and the statin served as an accelerant. However, chance associations cannot be dismissed and thus further observation is warranted.

Presynaptic statin-induced coenzyme Q_{10} depletion/ mitochondrial dysfunction may also contribute to inefficient neuromuscular transmission in myasthenia gravis. Interestingly, the mitochondrial disorder, chronic progressive external ophthalmoparesis, is associated with jitter on single-fiber electromyography.[138] This supports the importance of mitochondrial function in neuromuscular transmission. Another hypothesis for the triggering effect of statins in myasthenia gravis is the dependency of nicotinic acetylcholine receptor clustering on the actin[139] and microtubule[140] cytoskeleton, both of which may be vulnerable to the effects of HMG-CoA reductase inhibition.[141]

Metabolic Myopathies

The metabolic disorders (i.e., mitochondrial myopathy, McArdle disease, and carnitine palmitoyl transferase deficiency) may be precipitated by statin-triggered metabolic dysregulation. For example, inhibition of HMG CoA-reductase depletes cellular farnesyl levels which are required for the synthesis of the ten isoprene unit tail of ubiquinone. Farnesylation of the redox active quinoid nucleus functionalizes co-enzyme Q_{10} by conferring lipophilicity and thus mobility within the inner mitochondrial membrane. Co-enzyme Q_{10} shuttles reducing equivalents from complexes I and II to complex III in the electron transport chain. Reductions in muscle co-enzyme Q_{10} levels are variable amongst statin-intolerant patients with hyperCKemia.[107] Only a minority of patients manifest levels below control values which argues against the primary pathogenicity of co-enzyme Q_{10} depletion in statin myopathy. However, in patients with mitochondrial disorders any subtle deterioration of electron transport chain function must be

https://doi.org/10.1017/S0317167100007514 Published online by Cambridge University Press

avoided even if speculative. The triggering of a MELAS syndrome in two patients treated with statins supports the contention that mitochondrial fidelity may be sensitive to HMG-CoA reductase inhibitors.[94,142] Indeed the Michaelis-Menton constant (K_m) of NADH cytochrome c reductase for co-enzyme Q_{10} (2.4 ± 1.7 nmol/mg protein) is within the physiologic range for intra-mitochondrial co-enzyme Q_{10} (1-4 nmol/mg protein).[143] Statin-induced decrements in co-enzyme Q_{10} may therefore impair complex I-III activity and unmask myopathic symptoms in patients harboring mutations in mitochondrial genes encoded by either nuclear or mitochondrial DNA. Regarding the latter, subthreshold myopathy may exist due to replicative tissue segregation (i.e., heteroplasmy). Drug-induced triggering of genetic defects is referred to as pharmacogenomic synergism.

A role for genetics as a potential determinant was recently demonstrated in subjects who developed myopathy on statin monotherapy.[144] Single nucleotide polymorphisms (SNP) in the CoQ2 gene encoding para-hydroxybenzoate-polyprenyl transferase–the second enzyme in the CoQ_{10} biosynthetic pathway–was significantly associated with inter-individual variation in statin tolerability (odds ratios: SNP1, 2.42; SNP2, 2.33; 2-SNP haplotype, 2.58).[144] These preliminary pharmacogenetic results suggest that statin-induced muscle intolerability is associated with genomic variation in CoQ2 and thus perhaps with the CoQ_{10} biosynthetic pathway.

Preliminary evidence in animal models suggests that statins may impair fatty acid oxidation by reducing tissue carnitine levels[145] or enzymes of β-oxidation.[146] For example, serum acylcarnitines increased while tissue carnitine levels decreased in rabbits fed lovastatin (30 mg/d x 16 weeks). *In vitro*, the lipohilic statins exhibited mitochondrial toxicity through various mechanisms involving electron transport and β-oxidation. This was associated with dissipation of membrane potential, cytochrome c release, and apoptosis.[146] These results suggest that individuals with partial metabolic deficiencies upstream of or involving oxidative phosphorylation may be more susceptible to statin-induced downregulation of critical enzymes or substrates necessary for intermediary metabolism.

Malignant Hyperthermia (MH) and Rippling Muscle Disease (RMD)

Simvastatin has been shown to produce mitochondrial Ca^{2+} efflux *in vitro* through both the permeability transition pore and the Na^{+}-Ca^{2+} exchanger prior to larger secondary sarcoplasmic reticulum-mediated Ca^{2+} release.[147] These perturbations may be particularly relevant to the deranged calcium release in MH. *In vitro* contracture tests were positive in seven of nine patients with statin-associated hyperCKemia.[148] Two exhibited both halothane- and caffeine-induced contracture confirming MH susceptibility whereas five were positive for a single test. The authors did not specify whether patients were taking the statin at the time of the biopsy.

Another disorder with presumed calcium dysregulation is RMD. The unusual manifestations of muscle hyperexcitability (i.e., percussion-induced rapid contractions, myoedema, and rippling) in this condition may be due to calcium transients that ostensibly arise from silent action potentials within the T-tubular system.[149] We recently reported a case of immune-mediated RMD which was unmasked by simvastatin exposure.[115] After publication this patient was treated with ezetimibe which also produced clinical worsening of his rippling. Interestingly, hereditary RMD is due to caveolin-3 mutations[150] and caveolin trafficking from the Golgi to the plasma membrane is exquisitely dependent on the cholesterol microenvironment of the cell.[151] Therefore, despite the fact that statins deplete membrane expression of caveolins,[152] it may be alterations in cellular cholesterol that determines symptomatic aggravation in RMD patients treated with lipid lowering therapy.

In these and other scenarios, a single disruption of two pathways or a double disruption of one pathway appears necessary to manifest disease in a subset of patients. Statins may thus unmask muscle pain, weakness, or serum CK elevations in an asymptomatic carrier (recessive condition) or pre-/oligosymptomatic patient (dominant or acquired condition). Further support of this can be found in the report of combined partial deficiencies of carnitine palmitoyl transferase II and mitochondrial complex I presenting with hyperCKemia.[153] Similarly, the combination of a heterozygous R50X nonsense mutation in the myophosphorylase gene and 7444 G>A transition in cytochrome oxidase subunit I gene produced proximal myopathy, high CK and lactate, and exercise intolerance.[154] The multiple pathway synergy model is an attractive explanation for the numerous potential neuromuscular manifestations of statin therapy and may account for a wide range of clinical maifestations (i.e., drug-drug, drug-gene, and gene-gene).[155]

Conclusions

A Pubmed search, limited to the last ten years and review articles, using the key words “statin myopathy” revealed 166 items. The literature is indeed replete with numerous views and opinions on statin safety. A clear management algorithm for statin myotoxicity, which addresses the growing list of associated neuromuscular disorders, has thus far been lacking. Many patients with moderate to severe myotoxic reactions to statins will be referred for specialist evaluation. The current algorithm offers a logical approach to triage and manage these patients in primary and tertiary care settings. Additionally, awareness of the growing spectrum of neuromuscular disorders attributed to statin treatment will enable the specialist to provide optimal management strategies for patients intolerate to statins. Determining the clinical utility of myoprotective supplementation strategies is another important area of research given that the number of statin “myopathy” patients rivals other diagnostic categories in neuromuscular disease.

The fact that some individuals can tolerate statins while others cannot, attests to an underlying cryptogenic predisposition. Indeed, supratherapeutic doses of any statin will cause myopathy, although the toxic dose will vary between individuals. Similar idiosyncratic tolerances or thresholds are an accepted phenomenon in the epilepsy literature and are largely attributed to genetic variability in ion channels.[156] Subclinical metabolic defects in potentially numerous proteins may expose vulnerable muscle to statin toxicity. Ongoing work, employing metabolomics and gene arrays, into the permissive genetic defects associated with statin myotoxicity will hopefully provide a deeper understanding into the pleotropy of this class of drugs in susceptible individuals.

https://doi.org/10.1017/S0317167100007514 Published online by Cambridge University Press

Appendix: Application of Management Algorithm

Case 1

A 52-year-old Caucasian female, with a history of non Q-wave myocardial infarction, hypercholesterolemia, and 30-pack-years of smoking, was found to have hyperCKemia (570 U/L) upon routine surveillance approximately one year after starting atorvastatin. She reported mild weakness, cramping, and myalgias in her upper arms and legs. Ezetimibe monotherapy perpetuated her myalgias and was discontinued. The CK remained elevated. Neurological examination revealed grade 4 MRC (medical research council) strength proximally in the arms and legs.

Nerve conduction studies were normal. Electromyography demonstrated spontaneous activity (i.e., positive sharp waves or fibrillations) in the right deltoid and vastus medialis.

Chest plain films were unremarkable. Cervical spine MRI demonstrated moderate diffuse disc bulging at C5-C6 and C6-C7 with mild flattening of the spinal cord. Scattered inflammatory infiltrates around both vessels and myofibers, macrophage invasion, variable fiber morphology, and type II atrophy were noted on muscle biopsy. Allele specific amplification using polymerase chain reaction failed to detect mutations in *PYGM* (R49X, G204S), *CPT2* (P50H, S113L, Q413fs, G549D), and *AMPD1* (Q12X, P48L) genes.

Bloodwork revealed an elevated anti-phospholipid antibody titre at 39 GPL Unit (normal < 15) and a non-specific inhibitor. These tests remained positive six months later.

Prednisone (20 mg daily) normalized her strength and CK level. Methotrexate (20 mg weekly) was added and the prednisone was tapered slowly (1 mg q 2 weeks). Low dose rosuvastatin (5 mg daily) was initiated without symptom aggravation.

This case highlights the importance of underlying muscle disorders which can masquerade as statin-myopathy. Anti-phospholipid antibody syndrome with myositis has been previously reported.[157] It is impossible to determine if the statin was an accelerant or a trigger for the myositis. It is important to note that pre-existing myopathies likely renders muscle more vulnerable to the myotoxic effects of statins. For example, when the above patient was treated for her myositis she tolerated statin re-introduction.

Case 2

A 38-year-old Caucasian male heavy machine operator reported stiffness, proximal weakness, myalgias, and fatigue within approximately six months of starting atorvastatin. Both simvastatin and rosuvastatin caused bilateral calf tightness particularly in the morning. His CK was elevated (956 U/L) but dropped by approximately 50% after statin discontinuation.

Neuromuscular examination revealed temporalis wasting, subtle bilateral ptosis, and oral tenting. Cataracts were not observed on indirect ophthalmoscopy. Motor examination demonstrated reduced distal bulk. Strength testing revealed both proximal and distal weakness. Forceful eyelid and hand closure produced mild slowness of reopening. Thenar percussion brought the thumb into abduction/opposition for a few seconds prior to relaxation. Muscle stretch reflexes were present but diffusely hypoactive. Sensory testing was normal.

Sensory and motor nerve conduction studies were normal. Needle EMG demonstrated 1+ to 2+ myotonia proximally and distally in the arms and legs.

Genetic testing of the *DMPK* gene revealed a pathologic allele possessing 150 CTG repeats. A diagnosis of myotonic dystrophy type 1 (E0 = 50-200 repeats) was confirmed. An electrocardiogram revealed a normal PR interval of 182 ms. His hemoglobin A1C was 5.5% and testosterone levels were normal.

Cholesterol's role in membrane chloride conductance was first evidenced in patients treated with clofibrate who presented with acute muscular syndromes characterized by muscle cramping, weakness, stiffness, and myopathic changes. Statins produce electrophysiologic myotonia by impairing membrane chloride conductance.[158] In experiments employing both rats[159,160] and rabbits[158,161] pravastatin exerted little to no effect on electromyographic activity and membrane chloride conductance whereas simvastatin caused dose-dependent reductions in the latter. Despite pravastatin's reduced potential to cause myotonia in experimental models, a 37-year-old man with sarcoidosis experienced severe myotonia after receiving pravastatin.[162] Patients with myotonic disorders may be at risk for symptomatic aggravation in response to statins and their use should be guarded. The absence of reported myotonic side-effects from ezetimibe, niacin, and bile acid resins suggests that these agents are preferable to manage hyperlipidemia in this unique patient group.

Case 3

A 62-year-old male with hypertension, hypercholesterolemia, bilateral calcified pleural plaques from asbestos exposure, and biclonal gammopathy of undetermined significance developed shoulder girdle pain and weakness two months after starting Lipitor (20 mg/day). His CK was elevated at 855 U/L. After discontinuation the myalgias subsided but the hyperCKemia persisted (range: 523 to 725 U/L). He reported ongoing weakness in overhead activities that had not been present prior to the statin exposure.

He had neck flexion, scapulohumeral, and hip flexion weakness. Muscle stretch reflexes and sensory testing were normal.

Electrophysiologic studies revealed normal sensory and motor amplitudes and conduction velocities. Fibrillations and positive sharp waves were noted in the right deltoid (2+), biceps (2+), and bracioradialis (1+) on needle EMG. The motor unit action potentials displayed an admixture of normal and early, brief, polyphasic morphologies.

Bloodwork revealed a mildly positive antinuclear antibody titer at 1:80 in a speckled pattern. Pulmonary single positron emission computerized tomography (SPECT) revealed no increased uptake of fluoro-2-deoxy-D-glucose tracer in the lung fields nor elsewhere.

Skeletal muscle biopsy revealed multifocal inflammatory infiltrate consisting of lymphocytes and histiocytes. Immunohistochemistry for UCHL1 was highly reactive confirming a T-cell predominance. The B-cell marker L26 was immunonegative. Passive T-cell invasion of non-necrotic muscle cells was noted.

The patient was started on prednisone (20 mg/day), bisphosphonate, and vitamin D. His strength normalized to 5/5 in

the upper extremities and his CK dropped from 465 to 159 U/L over two months.

This case represents a statin-triggered polymyositis. Asbestosis has been associated with myositis, however the negative SPECT tends to rule this diagnosis out. Similar cases have been reported previously (see above). A chance occurrence of symptom onset after statin initiation cannot be excluded. Similarly it is unknown whether statins act as an accelerant for existing sub-clinical acquired muscle disease or whether they truly cause the inflammation. Campbell has recently hypothesized that statins may favour a pro-inflammatory state through reduction of endogenous steroid synthesis or possibly through enhanced apoptosis thereby inciting immune cells against apoptotic remnants.[163] Indeed statins do cause increased apoptosis in numerous cell types[164] although such findings are not universal.

References

1. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). JAMA. 2001; 285: 2486-97.
2. Mitka M. Expanding statin use to help more at-risk patients is causing financial heartburn. JAMA. 2003; 290:2243-5.
3. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet. 1994; 344:1383-9.
4. Sacks FM, Pfeffer MA, Moye LA, Rouleau JL, Rutherford JD, Cole TG, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and recurrent events trial investigators. N Engl J Med. 1996; 335:1001-9.
5. Shepherd J, Cobbe SM, Ford I, Isles CG, Lorimer AR, MacFarlane PW, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. N Engl J Med. 1995; 333:1301-7.
6. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. Lancet. 2002; 360:7-22.
7. Nissen SE, Nicholls SJ, Sipahi I, Libby P, Raichlen JS, Ballantyne CM, et al. Effect of very high-intensity statin therapy on regression of coronary atherosclerosis: the ASTEROID trial. JAMA. 2006; 295:1556-65.
8. Amarenco P, Bogousslavsky J, Callahan A, 3rd, Goldstein LB, Hennerici M, Rudolph AE, et al. High-dose atorvastatin after stroke or transient ischemic attack. N Engl J Med. 2006; 355:549-59.
9. Rashid S. Should cholesterol-lowering medications be available in Canada without a prescription? Can J Cardiol. 2007; 23:189-93.
10. Vladutiu GD, Simmons Z, Isackson PJ, Tarnopolsky M, Peltier WL, Barboi AC, et al. Genetic risk factors associated with lipid-lowering drug-induced myopathies. Muscle Nerve. 2006; 34:153-62.
11. Corsini A, Maggi FM, Catapano AL. Pharmacology of competitive inhibitors of HMG-CoA reductase. Pharmacol Res. 1995; 31: 9-27.
12. Sabia H, Prasad P, Smith HT, Stoltz RR, Rothenberg P. Safety, tolerability, and pharmacokinetics of an extended-release formulation of fluvastatin administered once daily to patients with primary hypercholesterolemia. J Cardiovasc Pharmacol. 2001; 37:502-11.
13. Corsini A, Bellosta S, Baetta R, Fumagalli R, Paoletti R, Bernini F. New insights into the pharmacodynamic and pharmacokinetic properties of statins. Pharmacol Ther. 1999; 84:413-28.
14. Kitazawa E, Tamura N, Iwabuchi H, Uchiyama M, Muramatsu S, Takahagi H, et al. Biotransformation of pravastatin sodium (I). Mechanisms of enzymic transformation and epimerization of an allylic hydroxy group of pravastatin sodium. Biochem Biophys Res Commun. 1993; 192:597-602.
15. White CM. A review of the pharmacologic and pharmacokinetic aspects of rosuvastatin. J Clin Pharmacol. 2002; 42:963-70.
16. Ejendal KF, Hrycyna CA. Differential sensitivities of the human ATP-binding cassette transporters ABCG2 and P-glycoprotein to cyclosporin A. Mol Pharmacol. 2005; 67:902-11.
17. Kajosaari LI, Niemi M, Neuvonen M, Laitila J, Neuvonen PJ, Backman JT. Cyclosporine markedly raises the plasma concentrations of repaglinide. Clin Pharmacol Ther. 2005; 78:388-99.
18. Shitara Y, Itoh T, Sato H, Li AP, Sugiyama Y. Inhibition of transporter-mediated hepatic uptake as a mechanism for drug-drug interaction between cerivastatin and cyclosporin A. J Pharmacol Exp Ther. 2003; 304:610-6.
19. Hsiang B, Zhu Y, Wang Z, Wu Y, Sasseville V, Yang WP, et al. A novel human hepatic organic anion transporting polypeptide (OATP2). Identification of a liver-specific human organic anion transporting polypeptide and identification of rat and human hydroxymethylglutaryl-CoA reductase inhibitor transporters. J Biol Chem. 1999; 274:37161-8.
20. Brown CD, Windass AS, Bleasby K, Lauffart B. Rosuvastatin is a high affinity substrate of hepatic organic anion transporter OATP-C [abstr]. Atheroscler Suppl. 2001; 2:90.
21. Pasternak RC, Smith SC, Jr., Bairey-Merz CN, Grundy SM, Cleeman JI, Lenfant C. ACC/AHA/NHLBI Clinical advisory on the use and safety of statins. Stroke. 2002; 33:2337-41.
22. Jacobson TA. Comparative pharmacokinetic interaction profiles of pravastatin, simvastatin, and atorvastatin when coadministered with cytochrome P450 inhibitors. Am J Cardiol. 2004; 94: 1140-6.
23. Baker SK, Goodwin S, Sur M, Tarnopolsky MA. Cytoskeletal myotoxicity from simvastatin and colchicine. Muscle Nerve. 2004; 30:799-802.
24. Zuccaro P, Mombelli G, Calabresi L, Baldassarre D, Palmi I, Sirtori CR. Tolerability of statins is not linked to CYP450 polymorphisms, but reduced CYP2D6 metabolism improves cholesteraemic response to simvastatin and fluvastatin. Pharmacol Res. 2007.
25. Staffa JA, Chang J, Green L. Cerivastatin and reports of fatal rhabdomyolysis. N Engl J Med. 2002; 346:539-40.
26. Chang JT, Staffa JA, Parks M, Green L. Rhabdomyolysis with HMG-CoA reductase inhibitors and gemfibrozil combination therapy. Pharmacoepidemiol Drug Saf. 2004; 13:417-26.
27. Backman JT, Kyrklund C, Kivisto KT, Wang JS, Neuvonen PJ. Plasma concentrations of active simvastatin acid are increased by gemfibrozil. Clin Pharmacol Ther. 2000; 68:122-9.
28. Bergman AJ, Murphy G, Burke J, Zhao JJ, Valesky R, Liu L, et al. Simvastatin does not have a clinically significant pharmacokinetic interaction with fenofibrate in humans. J Clin Pharmacol. 2004; 44:1054-62.
29. Martin PD, Dane AL, Schneck DW, Warwick MJ. An open-label, randomized, three-way crossover trial of the effects of coadministration of rosuvastatin and fenofibrate on the pharmacokinetic properties of rosuvastatin and fenofibric acid in healthy male volunteers. Clin Ther. 2003; 25:459-71.
30. Graham DJ, Staffa JA, Shatin D, Andrade SE, Schech SD, La Grenade L, et al. Incidence of hospitalized rhabdomyolysis in patients treated with lipid-lowering drugs. JAMA. 2004; 292: 2585-90.
31. Jacob SS, Jacob S, Williams C, Deeg MA. Simvastatin, fenofibrate, and rhabdomyolysis. Diabetes Care. 2005; 28:1258.
32. Jones PH, Davidson MH. Reporting rate of rhabdomyolysis with fenofibrate + statin versus gemfibrozil + any statin. Am J Cardiol. 2005; 95:120-2.
33. Melli G, Chaudhry V, Cornblath DR. Rhabdomyolysis: an evaluation of 475 hospitalized patients. Medicine (Baltimore). 2005; 84:377-85.
34. Tokinaga K, Oeda T, Suzuki Y, Matsushima Y. HMG-CoA reductase inhibitors (statins) might cause high elevations of creatine phosphokinase (CK) in patients with unnoticed hypothyroidism. Endocr J. 2006; 53:401-5.

35. Shek A, Ferrill MJ. Statin-fibrate combination therapy. Ann Pharmacother. 2001; 35:908-17.
36. Choi JW, Choi HS. The regulatory effects of thyroid hormone on the activity of 3-hydroxy-3-methylglutaryl coenzyme A reductase. Endocr Res. 2000; 26:1-21.
37. Hekimsoy Z, Oktem IK. Serum creatine kinase levels in overt and subclinical hypothyroidism. Endocr Res. 2005; 31:171-5.
38. Kisch E, Segall HS. Interaction between simvastatin and L-thyroxine. Ann Intern Med. 2005; 143:547.
39. Sinclair C, Gilchrist JM, Hennessey JV, Kandula M. Muscle carnitine in hypo- and hyperthyroidism. Muscle Nerve. 2005; 32:357-9.
40. Galland S, Georges B, Le Borgne F, Conductier G, Dias JV, Demarquoy J. Thyroid hormone controls carnitine status through modifications of gamma-butyrobetaine hydroxylase activity and gene expression. Cell Mol Life Sci. 2002; 59:540-5.
41. Thompson PD, Zmuda JM, Domalik LJ, Zimet RJ, Staggers J, Guyton JR. Lovastatin increases exercise-induced skeletal muscle injury. Metabolism. 1997; 46:1206-10.
42. Sinzinger H, O'Grady J. Professional athletes suffering from familial hypercholesterolaemia rarely tolerate statin treatment because of muscular problems. Br J Clin Pharmacol. 2004; 57:525-8.
43. Clarkson PM, Kearns AK, Rouzier P, Rubin R, Thompson PD. Serum creatine kinase levels and renal function measures in exertional muscle damage. Med Sci Sports Exerc. 2006; 38: 623-7.
44. Graves JE, Clarkson PM, Litchfield P, Kirwan JP, Norton JP. Serum creatine kinase activity following repeated bouts of isometric exercise with different muscle groups. Eur J Appl Physiol Occup Physiol. 1987; 56:657-61.
45. Clarkson PM, Byrnes WC, Gillisson E, Harper E. Adaptation to exercise-induced muscle damage. Clin Sci (Lond). 1987; 73:383-6.
46. Skenderi KP, Kavouras SA, Anastasiou CA, Yiannakouris N, Matalas AL. Exertional Rhabdomyolysis during a 246-km continuous running race. Med Sci Sports Exerc. 2006; 38: 1054-7.
47. Neumayr G, Pfister R, Hoertnagl H, Mitterbauer G, Getzner W, Ulmer H, et al. The effect of marathon cycling on renal function. Int J Sports Med. 2003; 24:131-7.
48. Armstrong RB. Muscle damage and endurance events. Sports Med. 1986; 3:370-81.
49. Schwane JA, Buckley RT, Dipaolo DP, Atkinson MA, Shepherd JR. Plasma creatine kinase responses of 18- to 30-yr-old African-American men to eccentric exercise. Med Sci Sports Exerc. 2000; 32:370-8.
50. Streichenberger N, Meyronet D, Fiere V, Pellissier JF, Petiot P. Focal myositis associated with S-1 radiculopathy: report of two cases. Muscle Nerve. 2004; 29:443-6.
51. Lima AF, Evangelista T, de Carvalho M. Increased creatine kinase and spontaneous activity on electromyography, in amyotrophic lateral sclerosis. Electromyogr Clin Neurophysiol. 2003; 43: 189-92.
52. Lee E, Ryan S, Birmingham B, Zalikowski J, March R, Ambrose H, et al. Rosuvastatin pharmacokinetics and pharmacogenetics in white and Asian subjects residing in the same environment. Clin Pharmacol Ther. 2005; 78:330-41.
53. Fernandez C, de Paula AM, Figarella-Branger D, Krahn M, Giorgi R, Chabrol B, et al. Diagnostic evaluation of clinically normal subjects with chronic hyperCKemia. Neurology. 2006; 66: 1585-7.
54. Finsterer J, Neuhuber W, Mittendorfer B. Reconsidering idiopathic CK-elevation. Int J Neurosci. 2004; 114:1333-42.
55. Prelle A, Tancredi L, Sciacco M, Chiveri L, Comi GP, Battistel A, et al. Retrospective study of a large population of patients with asymptomatic or minimally symptomatic raised serum creatine kinase levels. J Neurol. 2002; 249:305-11.
56. Simmons Z, Peterlin BL, Boyer PJ, Towfighi J. Muscle biopsy in the evaluation of patients with modestly elevated creatine kinase levels. Muscle Nerve. 2003; 27:242-4.
57. Capasso M, De Angelis MV, Di Muzio A, Scarciolla O, Pace M, Stuppia L, et al. Familial idiopathic hyper-CK-emia: an underrecognized condition. Muscle Nerve. 2006; 33:760-5.
58. Phillips PS, Haas RH, Bannykh S, Hathaway S, Gray NL, Kimura BJ, et al. Statin-associated myopathy with normal creatine kinase levels. Ann Intern Med. 2002; 137:581-5.
59. Troseid M, Henriksen OA, Lindal S. Statin-associated myopathy with normal creatine kinase levels. Case report from a Norwegian family. APMIS. 2005; 113:635-7.
60. Thompson PD, Clarkson PM, Rosenson RS. An assessment of statin safety by muscle experts. Am J Cardiol. 2006; 97: 69C-76C.
61. Bakris GL, Weir MR. Angiotensin-converting enzyme inhibitor-associated elevations in serum creatinine: is this a cause for concern? Arch Intern Med. 2000; 160:685-93.
62. Chazerain P, Hayem G, Hamza S, Best C, Ziza JM. Four cases of tendinopathy in patients on statin therapy. Joint Bone Spine. 2001; 68:430-3.
63. Beattie MS, Lane NE, Hung YY, Nevitt MC. Association of statin use and development and progression of hip osteoarthritis in elderly women. J Rheumatol. 2005; 32:106-10.
64. Harada K, Tsuruoka S, Fujimura A. Shoulder stiffness: a common adverse effect of HMG-CoA reductase inhibitors in women? Intern Med. 2001; 40:817-8.
65. Noel B, Panizzon RG. Lupus-like syndrome associated with statin therapy. Dermatology. 2004; 208:276-7.
66. Graziadei IW, Obermoser GE, Sepp NT, Erhart KH, Vogel W. Drug-induced lupus-like syndrome associated with severe autoimmune hepatitis. Lupus. 2003; 12:409-12.
67. Hanson J, Bossingham D. Lupus-like syndrome associated with simvastatin. Lancet. 1998; 352:1070.
68. Chong PH, Boskovich A, Stevkovic N, Bartt RE. Statin-associated peripheral neuropathy: review of the literature. Pharmacotherapy. 2004; 24:1194-203.
69. Lo YL, Leoh TH, Loh LM, Tan CE. Statin therapy and small fibre neuropathy: a serial electrophysiological study. J Neurol Sci. 2003; 208:105-8.
70. Vaughan TB, Bell DS. Statin neuropathy masquerading as diabetic autoimmune polyneuropathy. Diabetes Care. 2005; 28:2082.
71. McPherson R, Frohlich J, Fodor G, Genest J. Canadian Cardiovascular Society position statement--recommendations for the diagnosis and treatment of dyslipidemia and prevention of cardiovascular disease. Can J Cardiol. 2006; 22:913-27.
72. Genest J, Frohlich J, Fodor G, McPherson R. Recommendations for the management of dyslipidemia and the prevention of cardiovascular disease: summary of the 2003 update. CMAJ. 2003; 169:921-4.
73. Golomb BA. Implications of statin adverse effects in the elderly. Expert Opin Drug Saf. 2005; 4:389-97.
74. Golomb G, Yang E, Denenberg J, Criqui M. Statin-associated adverse effects. Circulation. 2003; 107:e7028-9.
75. Garcia-Calvo M, Lisnock J, Bull HG, Hawes BE, Burnett DA, Braun MP, et al. The target of ezetimibe is Niemann-Pick C1-Like 1 (NPC1L1). Proc Natl Acad Sci USA. 2005; 102:8132-7.
76. Altmann SW, Davis HR, Jr., Zhu LJ, Yao X, Hoos LM, Tetzloff G, et al. Niemann-Pick C1 Like 1 protein is critical for intestinal cholesterol absorption. Science. 2004; 303:1201-4.
77. Davis HR, Jr., Zhu LJ, Hoos LM, Tetzloff G, Maguire M, Liu J, et al. Niemann-Pick C1 Like 1 (NPC1L1) is the intestinal phytosterol and cholesterol transporter and a key modulator of whole-body cholesterol homeostasis. J Biol Chem. 2004; 279:33586-92.
78. Davidson MH, Maccubbin D, Stepanavage M, Strony J, Musliner T. Striated muscle safety of ezetimibe/simvastatin (Vytorin). Am J Cardiol. 2006; 97:223-8.
79. Fux R, Morike K, Gundel UF, Hartmann R, Gleiter CH. Ezetimibe and statin-associated myopathy. Ann Intern Med. 2004; 140: 671-2.
80. Phillips PS. Ezetimibe and statin-associated myopathy. Ann Intern Med. 2004; 141:649.
81. Perez-Calvo J, Civeira-Murillo F, Cabello A. Worsening myopathy associated with ezetimibe in a patient with McArdle disease. Q J Med. 2005; 98:461-2.

82. Cziraky MJ, Willey VJ, McKenney JM, Kamat SA, Fisher MD, Guyton JR, et al. Statin safety: an assessment using an administrative claims database. Am J Cardiol. 2006; 97: 61C-68C.
83. Franc S, Bruckert E, Giral P, Turpin G. [Rhabdomyolysis in patients with preexisting myopathy, treated with antilipemic agents]. Presse Med. 1997; 26:1855-8.
84. Phillips P, Gray N, McDonald F, Blaszcak M, Wolfson T, Sullivan M. Colesevelam HCL is safe and effective in patients with statin myotoxicity. Atheroscler Thromb Vasc Biol Online Journal. 2005; 25:e97.
85. Castano G, Fernandez L, Mas R, Illnait J, Gamez R, Mendoza S, et al. Effects of addition of policosanol to omega-3 fatty acid therapy on the lipid profile of patients with type II hypercholesterolaemia. Drugs R D. 2005; 6:207-19.
86. Mas R, Castano G, Fernandez J, Gamez R, Illnait J, Fernandez L, et al. Long-term effects of policosanol on obese patients with Type II Hypercholesterolemia. Asia Pac J Clin Nutr. 2004; 13: S102.
87. Castano G, Mas R, Fernandez JC, Fernandez L, Illnait J, Lopez E. Effects of policosanol on older patients with hypertension and type II hypercholesterolaemia. Drugs R D. 2002; 3:159-72.
88. Castano G, Menendez R, Mas R, Amor A, Fernandez JL, Gonzalez RL, et al. Effects of policosanol and lovastatin on lipid profile and lipid peroxidation in patients with dyslipidemia associated with type 2 diabetes mellitus. Int J Clin Pharmacol Res. 2002; 22:89-99.
89. Berthold HK, Unverdorben S, Degenhardt R, Bulitta M, Gouni-Berthold I. Effect of policosanol on lipid levels among patients with hypercholesterolemia or combined hyperlipidemia: a randomized controlled trial. JAMA. 2006; 295:2262-9.
90. Greyling A, De Witt C, Oosthuizen W, Jerling JC. Effects of a policosanol supplement on serum lipid concentrations in hypercholesterolaemic and heterozygous familial hypercholesterolaemic subjects. Br J Nutr. 2006; 95:968-75.
91. Davidson MH, Dugan LD, Burns JH, Bova J, Story K, Drennan KB. The hypocholesterolemic effects of beta-glucan in oatmeal and oat bran. A dose-controlled study. JAMA. 1991; 265:1833-9.
92. Brown L, Rosner B, Willett WW, Sacks FM. Cholesterol-lowering effects of dietary fiber: a meta-analysis. Am J Clin Nutr. 1999; 69:30-42.
93. Laaksonen R, Jokelainen K, Laakso J, Sahi T, Harkonen M, Tikkanen MJ, et al. The effect of simvastatin treatment on natural antioxidants in low-density lipoproteins and high-energy phosphates and ubiquinone in skeletal muscle. Am J Cardiol. 1996; 77:851-4.
94. Chariot P, Abadia R, Agnus D, Danan C, Charpentier C, Gherardi RK. Simvastatin-induced rhabdomyolysis followed by a MELAS syndrome. Am J Med. 1993; 94:109-10.
95. De Pinieux G, Chariot P, Ammi-Said M, Louarn F, Lejonc JL, Astier A, et al. Lipid-lowering drugs and mitochondrial function: effects of HMG-CoA reductase inhibitors on serum ubiquinone and blood lactate/pyruvate ratio. Br J Clin Pharmacol. 1996; 42:333-7.
96. Elmberger PG, Kalen A, Lund E, Reihner E, Eriksson M, Berglund L, et al. Effects of pravastatin and cholestyramine on products of the mevalonate pathway in familial hypercholesterolemia. J Lipid Res. 1991; 32:935-40.
97. Folkers K, Langsjoen P, Willis R, Richardson P, Xia LJ, Ye CQ, et al. Lovastatin decreases coenzyme Q levels in humans. Proc Natl Acad Sci USA. 1990; 87:8931-4.
98. Willis RA, Folkers K, Tucker JL, Ye CQ, Xia LJ, Tamagawa H. Lovastatin decreases coenzyme Q levels in rats. Proc Natl Acad Sci USA. 1990; 87:8928-30.
99. Ghirlanda G, Oradei A, Manto A, Lippa S, Uccioli L, Caputo S, et al. Evidence of plasma CoQ10-lowering effect by HMG-CoA reductase inhibitors: a double-blind, placebo-controlled study. J Clin Pharmacol. 1993; 33:226-9.
100. Laaksonen R, Jokelainen K, Sahi T, Tikkanen MJ, Himberg JJ. Decreases in serum ubiquinone concentrations do not result in reduced levels in muscle tissue during short-term simvastatin treatment in humans. Clin Pharmacol Ther. 1995; 57:62-6.
101. Schaefer WH, Lawrence JW, Loughlin AF, Stoffregen DA, Mixson LA, Dean DC, et al. Evaluation of ubiquinone concentration and mitochondrial function relative to cerivastatin-induced skeletal myopathy in rats. Toxicol Appl Pharmacol. 2004; 194:10-23.
102. Walravens PA, Greene C, Frerman FE. Lovastatin, isoprenes, and myopathy. Lancet. 1989; 2:1097-8.
103. Strey CH, Young JM, Molyneux SL, George PM, Florkowski CM, Scott RS, et al. Endothelium-ameliorating effects of statin therapy and coenzyme Q10 reductions in chronic heart failure. Atherosclerosis. 2005; 179:201-6.
104. Stocker R, Pollicino C, Gay CA, Nestel P, Colquhoun D, Whiting M, et al. Neither plasma coenzyme Q10 concentration, nor its decline during pravastatin therapy, is linked to recurrent cardiovascular disease events: a prospective case-control study from the LIPID study. Atherosclerosis. 2006; 187:198-204.
105. Berthold HK, Naini A, Di Mauro S, Hallikainen M, Gylling H, Krone W, et al. Effect of ezetimibe and/or simvastatin on coenzyme Q10 levels in plasma : a randomised trial. Drug Saf. 2006; 29:703-12.
106. Mabuchi H, Higashikata T, Kawashiri M, Katsuda S, Mizuno M, Nohara A, et al. Reduction of serum ubiquinol-10 and ubiquinone-10 levels by atorvastatin in hypercholesterolemic patients. J Atheroscler Thromb. 2005; 12:111-9.
107. Lamperti C, Naini AB, Lucchini V, Prelle A, Bresolin N, Moggio M, et al. Muscle coenzyme Q10 level in statin-related myopathy. Arch Neurol. 2005; 62:1709-12.
108. Colquhoun DM, Jackson R, Walters M, Hicks BJ, Goldsmith J, Young P, et al. Effects of simvastatin on blood lipids, vitamin E, coenzyme Q10 levels and left ventricular function in humans. Eur J Clin Invest. 2005; 35:251-8.
109. Mabuchi H, Haba T, Tatami R, Miyamoto S, Sakai Y, Wakasugi T, et al. Effects of an inhibitor of 3-hydroxy-3-methylglutaryl coenzyme a reductase on serum lipoproteins and ubiquinone-10 levels in patients with familial hypercholesterolemia. 1981. Atheroscler Suppl. 2004; 5:51-5.
110. Rundek T, Naini A, Sacco R, Coates K, DiMauro S. Atorvastatin decreases the coenzyme Q10 level in the blood of patients at risk for cardiovascular disease and stroke. Arch Neurol. 2004; 61:889-92.
111. Päivä H, Thelen KM, Van Coster R, Smet J, De Paepe B, Mattila KM, et al. High-dose statins and skeletal muscle metabolism in humans: a randomized, controlled trial. Clin Pharmacol Ther. 2005; 78:60-8.
112. Kelly P, Vaso S, Gelato M, McNurlan M, Lawson W. Coenzyme Q10 improves myopathic pain in statin treated patients [abstract]. J Am Coll Cardiol. 2005; 45 (3 Suppl A):3A.
113. Inui D, Fukuta Y, Oto J, Miki T, Suzue A, Kawahito S, et al. [Six cases of rhabdomyolysis induced by dehydration]. Masui. 2005; 54:1024-6.
114. Kodama K, Ikeda K, Kawamura S, Oyama T, Fujita S, Kobayashi Y. A case of severe dehydration with marked rhabdomyolysis. Jpn J Med. 1985; 24:150-4.
115. Baker SK, Tarnopolsky MA. Sporadic Rippling muscle disease unmasked by simvastatin. Muscle Nerve. 2006. Oct;34(4): 387-90.
116. Krivosic-Horber R, Depret T, Wagner JM, Maurage CA. Malignant hyperthermia susceptibility revealed by increased serum creatine kinase concentrations during statin treatment. Eur J Anaesthesiol. 2004; 21:572-4.
117. Parmar B, Francis PJ, Ragge NK. Statins, fibrates, and ocular myasthenia. Lancet. 2002; 360:717.
118. Cartwright MS, Jeffery DR, Nuss GR, Donofrio PD. Statin-associated exacerbation of myasthenia gravis. Neurology. 2004; 63:2188.
119. Guis S, Bendahan D, Kozak-Ribbens G, Figarella-Branger D, Mattei JP, Pellissier JF, et al. Rhabdomyolysis and myalgia associated with anticholesterolemic treatment as potential signs of malignant hyperthermia susceptibility. Arthritis Rheum. 2003; 49:237-8.
120. Delgado-Lopez F, Bautista-Lorite J, Villamil-Fernandez F. [Worsening for using statin in carnitine palmityol transferase deficiency myopathy]. Rev Neurol. 2004; 38:1095.

121. Livingstone C, Al Riyami S, Wilkins P, Ferns GA. McArdle's disease diagnosed following statin-induced myositis. Ann Clin Biochem. 2004; 41:338-40.
122. Baker SK, Vladutiu GD, Tarnopolsky MA. McArdle disease unmasked by statin exposure. Muscle Nerve. 2003; S73-4.
123. Vasconcelos OM, Campbell WW. Dermatomyositis-like syndrome and HMG-CoA reductase inhibitor (statin) intake. Muscle Nerve. 2004; 30:803-7.
124. Huynh T, Cordato D, Yang F, Choy T, Johnstone K, Bagnall F, et al. HMG CoA reductase-inhibitor-related myopathy and the influence of drug interactions. Intern Med J. 2002; 32:486-90.
125. Giordano N, Senesi M, Mattii G, Battisti E, Villanova M, Gennari C. Polymyositis associated with simvastatin. Lancet. 1997; 349:1600-1.
126. Hill C, Zeitz C, Kirkham B. Dermatomyositis with lung involvement in a patient treated with simvastatin. Aust N Z J Med. 1995; 25:745-6.
127. Khattak FH, Morris IM, Branford WA. Simvastatin-associated dermatomyositis. Br J Rheumatol. 1994; 33:199.
128. Rodriguez-Garcia JL, Serrano Commino M. Lovastatin-associated dermatomyositis. Postgrad Med J. 1996; 72:694.
129. Voermans NC, Lammens M, Wevers RA, Hermus AR, van Engelen BG. Statin-disclosed acid maltase deficiency. J Intern Med. 2005; 258:196-7.
130. Tsivgoulis G, Spengos K, Karandreas N, Panas M, Kladi A, Manta P. Presymptomatic neuromuscular disorders disclosed following statin treatment. Arch Intern Med. 2006; 166:1519-24.
131. Edwards IR, Star K, Kiuru A. Statins, neuromuscular degenerative disease and an amyotrophic lateral sclerosis-like syndrome: an analysis of individual case safety reports from vigibase. Drug Saf. 2007: 515-25.
132. Dalakas MC. Therapeutic approaches in patients with inflammatory myopathies. Semin Neurol. 2003; 23:199-206.
133. Dalakas MC. Molecular pathogenesis of inflammatory myopathies and future therapeutic strategies. Suppl Clin Neurophysiol. 2004; 57:288-303.
134. Dalakas MC. Inflammatory disorders of muscle: progress in polymyositis, dermatomyositis and inclusion body myositis. Curr Opin Neurol. 2004; 17:561-7.
135. Dalakas MC. Update on the molecular pathogenesis of inflammatory myopathies. Autoimmun Rev. 2004; 3 Suppl 1:S37-9.
136. Griggs RC, Mendell JR, Brooke MH, Fenichel GM, Miller JP, Province M, et al. Clinical investigation in Duchenne dystrophy: V. Use of creatine kinase and pyruvate kinase in carrier detection. Muscle Nerve. 1985; 8:60-7.
137. Youssef S, Stuve O, Patarroyo JC, Ruiz PJ, Radosevich JL, Hur EM, et al. The HMG-CoA reductase inhibitor, atorvastatin, promotes a Th2 bias and reverses paralysis in central nervous system autoimmune disease. Nature. 2002; 420:78-84.
138. Krendel DA, Sanders DB, Massey JM. Single fiber electromyography in chronic progressive external ophthalmoplegia. Muscle Nerve. 1987; 10:299-302.
139. Dai Z, Luo X, Xie H, Peng HB. The actin-driven movement and formation of acetylcholine receptor clusters. J Cell Biol. 2000; 150:1321-34.
140. Bloch RJ. Acetylcholine receptor clustering in rat myotubes: requirement for CA2+ and effects of drugs which depolymerize microtubules. J Neurosci. 1983; 3:2670-80.
141. Bifulco M, Laezza C, Aloj SM, Garbi C. Mevalonate controls cytoskeleton organization and cell morphology in thyroid epithelial cells. J Cell Physiol. 1993; 155:340-8.
142. Thomas JE, Lee N, Thompson PD. Statins Provoking MELAS Syndrome. A Case Report. Eur Neurol. 2007; 57:232-5.
143. Estornell E, Fato R, Castelluccio C, Cavazzoni M, Parenti Castelli G, Lenaz G. Saturation kinetics of coenzyme Q in NADH and succinate oxidation in beef heart mitochondria. FEBS Lett. 1992; 311:107-9.
144. Oh J, Ban MR, Miskie BA, Pollex RL, Hegele RA. Genetic determinants of statin intolerance. Lipids Health Dis. 2007; 6:7.
145. Bhuiyan J, Seccombe DW. The effects of 3-hydroxy-3-methylglutaryl-CoA reductase inhibition on tissue levels of carnitine and carnitine acyltransferase activity in the rabbit. Lipids. 1996; 31:867-70.
146. Kaufmann P, Torok M, Zahno A, Waldhauser KM, Brecht K, Krahenbuhl S. Toxicity of statins on rat skeletal muscle mitochondria. Cell Mol Life Sci. 2006; 63:2415-25.
147. Sirvent P, Mercier J, Vassort G, Lacampagne A. Simvastatin triggers mitochondria-induced Ca2+ signaling alteration in skeletal muscle. Biochem Biophys Res Commun. 2005; 329:1067-75.
148. Guis S, Figarella-Branger D, Mattei JP, Nicoli F, Le Fur Y, Kozak-Ribbens G, et al. In vivo and in vitro characterization of skeletal muscle metabolism in patients with statin-induced adverse effects. Arthritis Rheum. 2006; 55:551-7.
149. Lamb GD. Rippling muscle disease may be caused by "silent" action potentials in the tubular system of skeletal muscle fibers. Muscle Nerve. 2005; 31:652-8.
150. Minetti C, Sotgia F, Bruno C, Scartezzini P, Broda P, Bado M, et al. Mutations in the caveolin-3 gene cause autosomal dominant limb-girdle muscular dystrophy. Nat Genet. 1998; 18:365-8.
151. Pol A, Martin S, Fernandez MA, Ingelmo-Torres M, Ferguson C, Enrich C, et al. Cholesterol and fatty acids regulate dynamic caveolin trafficking through the Golgi complex and between the cell surface and lipid bodies. Mol Biol Cell. 2005; 16:2091-105.
152. Weis M, Heeschen C, Glassford AJ, Cooke JP. Statins have biphasic effects on angiogenesis. Circulation. 2002; 105:739-45.
153. Tsao CY, Mendell JR. Combined partial deficiencies of carnitine palmitoyltransferase II and mitochondrial complex I presenting as increased serum creatine kinase level. J Child Neurol. 2002; 17:304-6.
154. Aguilera I, Garcia-Lozano JR, Munoz A, Arenas J, Campos Y, Chinchon I, et al. Mitochondrial DNA point mutation in the COI gene in a patient with McArdle's disease. J Neurol Sci. 2001; 192:81-4.
155. Baker SK, Tarnopolsky MA. Statin myopathies: pathophysiologic and clinical perspectives. Clin Invest Med. 2001; 24:258-72.
156. Mazzuca M, Lesage F, Lazdunski M. Ion channels and epilepsy. Epileptic Disord. 2006; 8 Suppl 1:1-16.
157. Sherer Y, Livneh A, Levy Y, Shoenfeld Y, Langevitz P. Dermatomyositis and polymyositis associated with the antiphospholipid syndrome-a novel overlap syndrome. Lupus. 2000; 9:42-6.
158. Sonoda Y, Gotow T, Kuriyama M, Nakahara K, Arimura K, Osame M. Electrical myotonia of rabbit skeletal muscles by HMG-CoA reductase inhibitors. Muscle Nerve. 1994; 17:891-7.
159. Pierno S, De Luca A, Tricarico D, Ferrannini E, Conte T, D'Alo G, et al. Experimental evaluation of the effects of pravastatin on electrophysiological parameters of rat skeletal muscle. Pharmacol Toxicol. 1992; 71:325-9.
160. Pierno S, De Luca A, Tricarico D, Roselli A, Natuzzi F, Ferrannini E, et al. Potential risk of myopathy by HMG-CoA reductase inhibitors: a comparison of pravastatin and simvastatin effects on membrane electrical properties of rat skeletal muscle fibers. J Pharmacol Exp Ther. 1995; 275:1490-6.
161. Nakahara K, Kuriyama M, Sonoda Y, Yoshidome H, Nakagawa H, Fujiyama J, et al. Myopathy induced by HMG-CoA reductase inhibitors in rabbits: a pathological, electrophysiological, and biochemical study. Toxicol Appl Pharmacol. 1998; 152:99-106.
162. Riggs JE, Schochet SS, Jr. Myotonia associated with sarcoidosis: marked exacerbation with pravastatin. Clin Neuropharmacol. 1999; 22:180-1.
163. Campbell WW. Statin myopathy: the iceberg or its tip? Muscle Nerve. 2006; 34:387-90.
164. Dirks AJ, Jones KM. Statin-induced apoptosis and skeletal myopathy. Am J Physiol Cell Physiol. 2006; 291: C1208-12.
165. Holtzman CW, Wiggins BS, Spinler SA. Role of P-glycoprotein in statin drug interactions. Pharmacotherapy. 2006; 26:1601-7.
166. Bellosta S, Paoletti R, Corsini A. Safety of statins: focus on clinical pharmacokinetics and drug interactions. Circulation. 2004; 109:III50-7.
167. Reijneveld JC, Notermans NC, Linssen WH, Bar PR, Wokke JH. Hyper-CK-aemia revisited. Neuromuscul Disord. 2001; 11: 163-4.
168. Fee DB, So YT, Barraza C, Figueroa KP, Pulst SM. Phenotypic variability associated with Arg26Gln mutation in caveolin3. Muscle Nerve. 2004; 30:375-8.

169. Galassi G, Rowland LP, Hays AP, Hopkins LC, DiMauro S. High serum levels of creatine kinase: asymptomatic prelude to distal myopathy. Muscle Nerve. 1987; 10:346-50.
170. Merlini L, Sabatelli P, Columbaro M, Bonifazi E, Pisani V, Massa R, et al. Hyper-CK-emia as the sole manifestation of myotonic dystrophy type 2. Muscle Nerve. 2005; 31:764-7.
171. Nevins MA, Saran M, Bright M, Lyon LJ. Pitfalls in interpreting serum creatine phosphokinase activity. JAMA. 1973; 224:1382-7.
172. Monsieurs KG, Van Broeckhoven C, Martin JJ, Van Hoof VO, Heytens L. Gly341Arg mutation indicating malignant hyperthermia susceptibility: specific cause of chronically elevated serum creatine kinase activity. J Neurol Sci. 1998; 154:62-5.
173. Sunohara N, Takagi A, Nonaka I, Sugita H, Satoyoshi E. Idiopathic hyperCKemia. Neurology. 1984; 34:544-7.
174. Weglinski MR, Wedel DJ, Engel AG. Malignant hyperthermia testing in patients with persistently increased serum creatine kinase levels. Anesth Analg. 1997; 84:1038-41.
175. Brewster LM, de Visser M. Persistent hyperCKemia: fourteen patients studied in retrospect. Acta Neurol Scand. 1988; 77:60-3.
176. Shane E, McClane KA, Olarte MR, Bilezikian JP. Hypoparathyroidism and elevated muscle enzymes. Neurology. 1980; 30:192-5.
177. Osborn LA, Rossum A, Standefer J, Jackson J, Skipper B, Beeson C, et al. Evaluation of CK and CK-MB in alcohol abuse subjects with recent heavy consumption. Cardiology. 1995; 86:130-4.
178. Prelle A, Rigoletto C, Moggio M, Sciacco M, Comi GP, Ciscato P, et al. Asymptomatic familial hyperCKemia associated with desmin accumulation in skeletal muscle. J Neurol Sci. 1996; 140:132-6.

https://doi.org/10.1017/S0317167100007514 Published online by Cambridge University Press