Safe use of statins: focus on muscle toxicity

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\textbf{ABSTRACT}

Muscle toxicity can be classified as myopathy, myalgia, myositis or rhabdomyolysis (RM). RM can occur in patients with muscular dystrophy, alcoholic myopathy, peripheral artery disease and myocardial infarction as well as prolonged convulsions or immobility. Also, RM can occur, in otherwise healthy individuals, after viral illness, crush or high-voltage electrical injury, hyperthermia, severe exercise and taking certain drugs, particularly 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins). Muscle disorders provoked by statin use have been named “stain-associated myopathy (SAM)”. There is no commonly accepted definition of SAM, although recently a score system was introduced and the European Atherosclerosis Society (EAS) proposed a definition of SAM. There are several possible explanations for SAM; for example, genetic predisposition, decreased intracellular cholesterol levels, reduced production of coenzyme Q10 and related ubiquinones and decreased production of prenylated proteins. Due to the widespread use of statins, it is very important to diagnose SAM and particularly its severe presentation, RM. Early treatment will prevent serious complications. This review will focus on SAM.

\textbf{Introduction}

Muscular toxicity can be classified as myopathy (general term referring to any disease of muscles, can be acquired or inherited and can occur at birth or later in life), myalgia [muscle ache or weakness without creatine kinase (CK) elevation], myositis (muscle symptoms with CK elevation) and rhabdomyolysis (RM, muscle symptoms with marked serum CK elevation, typically $>10\times$ the upper limit of normal (ULN), creatinine elevation consistent with renal failure, and usually with dark-red coloured urine with myoglobinuria).\textsuperscript{[1]}

RM is a relatively rare condition of skeletal muscle defined as necrosis of muscle cells and leakage of substances, located inside the cell body, to the extracellular fluid and bloodstream (see below) causing systemic complications.\textsuperscript{[2–4]} This condition occasionally can be recurrent.\textsuperscript{[4]} RM can occur in patients with muscular dystrophy, alcoholic myopathy, peripheral artery disease, myocardial infarction or prolonged convulsions or immobility.\textsuperscript{[3,4]} RM can also occur in otherwise healthy individuals, after viral illness, crush or high-voltage electrical injury, hyperthermia, severe exercise such as marathon running (which emphasises physical fitness) or certain drugs, particularly 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor (statins). Muscle disorders provoked by statins use have been named “stain-associated myopathy (SAM)”\textsuperscript{[3,4]} Classically, RM presents with muscle pain, weakness, tenderness and swelling of the affected muscle, fever, dark-red-coloured urine, and/or a marked elevation of CK ($5–10\times$ ULN serum levels),\textsuperscript{[5]} oliguria (rarely anuria)\textsuperscript{[6]} and symptoms associated with electrolyte abnormalities (see below).\textsuperscript{[7]} In RM caused by statins, the CK level cut-off is considered as $10\times$ ULN.\textsuperscript{[8]}

This review will focus on SAM.

\textbf{Pathophysiology of muscular toxicity}

Irrespective of the cause of muscular toxicity and particularly RM, the consequences of muscle damage have a similar pathophysiology. Muscle cells undergo membrane destruction, which allows the leakage of substances from inside the cell to the extracellular fluid and bloodstream.\textsuperscript{[9]} Of note is that all RM causes (independently of aetiology) share the same pathophysiological pathway, which is mainly an increased concentration of intracellular calcium (see below). The main substrates presented inside the muscle cell are proteins, glycogen, CK and electrolytes such as calcium, potassium and phosphorus.
**Proteins**

Myoglobin (Mb) is a muscle protein with a molecular weight of 18,800 Daltons and one iron atom. Mb is responsible for temporary oxygen storing (in the presence of adequate supply of oxygen to the muscles, the cytochromes are involved).[10] Normally, the plasma concentration of Mb is 0–0.003 mg/dl and it is loosely bound to plasma globulins. During muscle anoxia, Mb reduces the need for glycolytic processes by releasing its contained oxygen and allowing a continuance of the much more efficient oxidative breakdown of lactate, pyruvate and similar metabolites. When >100 g of skeletal muscle are damaged, serum haptoglobin binding capacity becomes saturated[10,11] and circulating Mb becomes “free” and is filtered by the kidneys. There, Mb may cause distal renal tubular necrosis, by acting directly in the nephrons (see below).

**CK**

The enzyme CK is presented in all types of muscles. Following muscle damage, CK escapes into the bloodstream.[10] Thus, the increased level of serum CK is a marker of RM.[10] CK is involved in muscle energy metabolism.[12,13] There are three isoenzymes of CK: muscle-type (CK-MM), brain-type (CK-BB) and CK-MB. After muscle injury, CK is elevated in the first 12 h, peaks within the first 3 days, and returns to the baseline level at 3–5 days after the injury.[13] The half-life of CK is 1.5 days. Following damage of the striated muscle cells, the release of CK-MM is observed (may reach >100,000 IU/ml).[13] The blood concentration of CK is elevated much longer than of Mb (Mb is rapidly metabolised by the liver).[13] Therefore, tests for Mb in plasma or urine are not a sensitive diagnostic procedure.

**Calcium**

The calcium concentration in the extracellular space is 10,000 times higher compared with the intracellular space. Thus, even small changes of calcium penetrability into the cellular membrane may result in impaired cell function.[14] The excessive work of the muscle cells increases sarcoplasmic influx of sodium, chloride and water, leading to cell swelling and finally auto-destruction.[15] As a rescue process, calcium penetrates to the cell, in exchange for intracellular sodium.[16] Transmembrane proteins, most of which are energy-dependent, normally maintain muscle cells calcium homeostasis.[14] When muscle cells are damaged, the ATP escapes from the cells causing ATPase pump dysfunction. As a consequence of that, the increase in intracellular Na⁺ concentration activates the 2Na⁺/Ca²⁺ exchanger in order to correct ionic abnormalities.[17] This causes the increase in intracellular calcium, which activates phospholipase A2 (PLA2) and other proteases, which destroys both cellular and mitochondrial membranes.[18] Any interruption of membrane cell continuity, results in a considerable influx of extracellular calcium into the cytoplasm pushed by its chemical gradient. The injury of the sarcoplasmic reticulum and mitochondria (plays critical role in the generation of metabolic energy) leads to release of stored calcium ions into the cytoplasm.[18] As a consequence of all the above, the high calcium concentration within the cytoplasm, which triggers persistent contraction, ATP depletion, cellular exhaustion, will eventually result in cell death.

**Potassium**

Muscle contains a considerable amount of potassium and its escape from damaged cells can lead to hyperkalaemia and cardiac arrhythmias (e.g. ventricular fibrillation) and sudden death.[11,19]

**Phosphorus**

The large amount of intracellular phosphorus in muscle is presented mainly as ATP and CK and it is probable that during extended and acute RM, hyperphosphataemia occurs. Hyperphosphataemia causes deposition of calcium–phosphate complexes in tissues and suppression of 1α-hydroxylase (responsible for the production of the active vitamin D analogue calcitriol), contributes to the early hypocalcaemia and to kidney failure, in turn kidney failure can cause hyperphosphataemia.[10,17]

**RM consequences**

**Metabolic changes**

Necrosis of the muscle cells increases fluid volume in the affected limb(s) (can be >10 l/limb) causing dehydration, hypernatraemia, hypovolaemic shock and acute renal failure.[20] In the beginning, dehydration causes hyperalbuminaemia, which later shifts to hypoalbuminaemia caused by malnutrition, inflammation, capillary leak and fluid overload. The escape of lactic acid from dying muscle cells provokes acidosis,[21] which aggravates hyperkalaemia and enables intratubular precipitation of Mb and uric acid. In the presence of hyperkalaemia, a severe hypocalcaemia (due to hyperphosphataemia, deposition of calcium–phosphate complexes in tissues and suppression of 1α-hydroxylase) can develop, which may lead to cardiac arrhythmia, muscular contraction or seizures. At the later stages of SAM, hypercalcaemia occurs (released from the storage sites or supplemented by treatment at the hypocalcaemia stage).[22]
Renal failure

Several mechanisms have been proposed to explain the development of acute renal failure caused by RM (the severe form of SAM).[23] These include hypovolaemia, myoglobinuria, metabolic acidosis and release of uric acid. [24] During muscle damage, intracellular fluid escapes into extracellular spaces and the decrease intravascular volume activates the renin-angiotensin-aldosterone system causing a reduction in renal blood flow.[24] Furthermore, the release of cytotoxic intracellular components (see below) provokes capillary injury that leads to third spacing of fluids.[5] Oedema, ischaemia and cell necrosis cause additional metabolic acidosis and electrolyte abnormalities, continuing the vicious cycle of cell death.[25] On the other hand, when massive release of Mb into the bloodstream is observed after muscle damage, the binding capacity of the plasma globulins is exceeded and the kidney excretes Mb. Mb exerts a cytotoxic effect on the nephron both directly and through its breakdown compounds such as iron, which reacts with hydrogen peroxide compounds, creating reactive oxygen species (ROS), leading to renal tubular damage.[14] Another mechanism, which can lead to renal damage, concerns the iron from Mb, which oxides with lipid membrane components and cause lipid peroxidation (called redox cycling).[14] The presence of metabolic acidosis promotes cast formation and physical tubular obstruction, and pronounced Mb nephrotoxicity.5

Muscle damage also, provokes uric acid release, which forms crystals, further adding to tubular obstruction.[26]

Statins and myotoxicity

Statins [atorvastatin, cerivastatin (withdrawn in 2001, due to its side effects), fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, simvastatin] are effective lipid lowering drugs.[27] Statins lower total and low density lipoprotein cholesterol (LDL-C) levels by up to 60%. [28] Statins side effects concern muscles, gastrointestinal tract, reproductive system, skin, eyes, bones and joints and others. Also, hepatotoxicity and new onset of diabetes mellitus can occur.[27–30] The most frequent cause of drug-induced RM today is the use of statins. The withdrawal of these drugs is crucial in patients complaining of muscle pain or if CK rises >10× ULN (see below). The risk of drug-induced muscle disease is exaggerated by combination with drugs such as erythromycin, danazol, nicotinic acid, cyclosporine, fibrates (especially gemfibrozil) and other drugs.[29]

Oshima evaluated data of 8610 cases of drug-associated RM reported to the US Food and Drug Administration (FDA) from 2004 to 2009 and found that simvastatin, atorvastatin and rosuvastatin were responsible for 3945 (45%) of RM cases [30] and 927 (10.8%) fatal outcomes. Joy and Hegele, reported that RM secondary to statin use is particularly rare [31] and Guyton believes that the mortality risk correlated with RM is by far compensated by the reduction in all-cause mortality seen with statin use (0.3/100,000 person-years compared with reduction of all-cause mortality observed in statin trials by 360/100,000 person-years).[32] Chang et al. [33] examined the FDA’s database for RM in relation to statin monotherapy and combination statin/fibrate use and calculated the reporting rates for this event to be 1/100,000 prescriptions (except cerivastatin, which was 3–4/100,000 prescriptions). Furthermore, 56% of RM cases were associated with monotherapy and 44% were related to combination therapy. Hoffman et al. [34] analysed the FDA Adverse Event Reporting System (FAERS) database in order to evaluate SAM. They found that, rosuvastatin has the highest and lovastatin and pravastatin the lowest SAM risk.[34] Sakaeda et al. [35], Cham et al. [36] and Alsheikh-Ali et al. [37] supported these findings. According to patient-targeted statin use, Cham et al. reported that the highest potency statins (rosuvastatin and atorvastatin) showed higher SAM rates, simvastatin, with intermediate potency, showed intermediate SAM rates, and pravastatin and lovastatin, with lower potencies, showed the lowest SAM rates.[36] Surprisingly, fluvastatin although belonging to the statins with the lowest potencies did not have the lowest SAM rate. Likely reasons could be that fluvastatin, is usually prescribed for patients who do not tolerate other statins (disproportionate use in statin non-tolerators may produce higher apparent adverse effect rates) and for patients in which drug interactions or other factors heighten toxicity.38 Law and Rudnicka assessed the incidence of adverse effects in patients treated with statins from 20 randomised controlled trials. For statins other than cerivastatin, the incidence of RM was 3.4 (1.6–6.5)/100,000 person-years.[39] Case fatality was 10%. The FAERS reported rates of 1.07 cases of RM/1,000,000 statin prescriptions from 1998 to 2000, with an increase to 3.56 cases of RM/1,000,000 statin prescriptions from 1998 to 2000, with an increase to 3.56 cases of RM/1,000,000 statin prescriptions from 2002 to 2004.[40] The FAERS also documented that RM rates were lowest for pravastatin (1.63 cases) and highest for rosvuastatin (13.54 cases).[40] However, the results should be considered with caution since symptoms were self-reporting and elevated CK classification was different from classification of RM of the American College of Cardiology/American Heart Association/National Heart, Lung and Blood Institute ACC/AHA/NHLBI.[1] With regard to fatal outcome of RM, there were 1 case/5,200,000 lovastatin prescriptions, 1 case/8,300,000 simvastatin prescriptions, 1 case/23,400,000 atorvastatin prescriptions, and 1 case/27,100,000 pravastatin prescriptions.[40] Staffa et al. did not observe any fatal RM event in patients taking fluavastatin.[41] According to the US National Lipid Association Statin Safety Assessment Task Force [42],
a meta-analysis of 21 clinical trials providing 180,000 person-years of follow-up, and RM, defined by CK levels >10,000 IU/l or >10× ULN with an elevation in serum creatinine or requirement for hydration therapy, occurs in 1.6/100,000 person-years. [39]

All statins may cause muscle damage in a dose-dependent manner, although they vary in several characteristics. [36] Simvastatin, atorvastatin, and lovastatin are metabolised by CYP3A4 (the most common cytochrome P450 isozyme, which catabolises many other drugs) and due to competition with other drugs; plasma statin levels rise predisposing to toxicity. [43] Rosuvastatin and fluvastatin are metabolised by the CYP2A9 isozyme and consequently carry lower risk of drug interaction. [43] The 0.08–10% of patients being treated with statins alone or in combination with other hypolipidaemic drugs experiences some kind of muscle damage. [44–46] However, <1% have significant elevation of serum CK levels. [47] It is estimated that up to two thirds of all statin-related side effects involve muscle tissue. [48–50]

**SAM causation and prevalence**

As with numerous other medical conditions, it has been implied that appearance of SAM symptoms may have a causal genetic predisposition. These include genes involved in muscular dystrophy (DMD (codifies dystrophin), MYOT (codifies myotilin), LMNA (codifies lamin), CAV3 (codifies caveolin)), muscle tissue vascularisation ([AGTR 1 (angiotensin II type 1 receptor), NOS 3 (nitric oxide synthase 3)], rare disorders linked to muscle tissue energy metabolism (PYGM (codifies myophosphorylase), GAA (trinucleotide, codifies frataxin), CPT2 (carnitine palmitoyltransferase II), statin concentrations in the plasma (variants of SLC (solute carrier organic anion transporters, known also as OATP), ABC (ATP-binding cassette transporters), CYP), variability in coenzyme Q10 (COQ10A, COQ10B), and others. [51–53]

The variants of CYP gene (particularly CYP2D6, CYP3A4 polymorphisms) [54,55] and variants of CoQ10 gene [56] (have been shown to double the risk of SAM) [57] are frequently evaluated genes in SAM symptomatic patients. However, there is still no definite relationship between SAM and genetic predisposition, because studies evaluating this problem include small sample sizes and varied populations. Furthermore, there is usually no confirmatory work. However, there is a genome-wide association study (GWA), which reported that SLCO1B1 (rs4149056) is strongly associated with an increased risk of SAM in patients taking high doses of simvastatin. [58]

SAM symptoms present mainly weeks to months after introduction of therapy or increase in dose (90% of all cases appear in first 6 months, 75% in the first 12 weeks) and are more common in patients on high dose therapy and/or who are also taking other medication. [49,50] There is no commonly accepted definition for SAM. Many doctors have reported SAM when muscular symptoms occurred during statin use with/without CK elevation in the plasma. SAM may manifest as muscle tenderness, cramming as well as muscle pain and weakness. [51] The problem to diagnose SAM arise as symptoms are non-specific and can be present with other diseases such as infections, rheumatoid and orthopaedic diseases and endocrine disorders. Even more important is that the clinicians have to rely on patient description, which is not measurable. Vrablik et al. introduced a score system. [51] They gave to typical clinical picture of symmetrical muscle aches, to occurrence within 4 weeks from the initiation of therapy, to resolving with the interruption of therapy and to family history of SAM 1 point to each. They gave to elevations of CK >5× ULN and to positive re-challenge test 2 points to each and to confirmed RM 5 points and to histological confirmation of SAM also 5 points. Thus, a patient can be categorised as having possible SAM (1–2 points), probable SAM (3–4 points) or definite SAM (5 or more points). [51] This classification may be helpful in the differentiation of usual myalgias from those stimulated by statin use. The European Atherosclerosis Society (EAS) [59] also, proposed a definition of SAM. They classify muscle symptoms with normal CK (called also myalgia), muscle symptoms with minor elevation of CK (CK > ULN <4× ULN or CK > 4 < 10× ULN), muscle symptoms and CK >10× ULN (also called myositis or myopathy) and muscle symptoms and CK >40× ULN (also called RM).

The frequency of SAM was evaluated in the Prediction of Muscular Risk in Observational Conditions (PRIMO) study. The PRIMO observational study involved 7,924 hyperlipidaemic patients receiving high dose of statins. [60] SAM was reported in 10.5% of patients, with the highest in those receiving simvastatin (18.2%), followed by atorvastatin (14.9%), pravastatin (10.9%) and fluvastatin (5.1%).

There are several possible explanations for the manifestation of SAM. [61] SAM may be related to decreased intracellular cholesterol levels, reduced production of coenzyme Q10 and related ubiquinones [62,63] decreased production of prenylated proteins, increased uptake of cholesterol from the extracellular space, increased uptake of phytosterols, disruption of calcium metabolism, decreased renewal of damaged muscle cells via the ubiquitin pathway, inhibition of selenoprotein synthesis, genetic factors and unmasking of pre-existing muscular disorders. The depletion of coenzyme Q10 in myocyte mitochondria may cause muscle-related toxicities including RM. [64] Currently, the routine use of coenzyme Q10 in statin-treated patients is not recommended. [65] Other conditions (age, female gender, low BMI (body mass index), Asian descent, high level of physical activity,
vitamin D deficiency,[66] excess alcohol intake, surgery, trauma, polypharmacy, and presence of other diseases (particularly, diabetes mellitus, hypothyroidism, renal failure, organ transplant recipients)), may also add to the risk of developing SAM.

The International Lipid Expert Panel published in 2015 the position paper concerning SAM and defined SAM as inability to tolerate at least two different statins (one statin at the lowest starting average daily dose and the other statin at any dose), intolerance associated with confirmed, intolerable statin-related adverse effect(s) or significant biomarker abnormalities, symptoms or biomarker changes resolution or significant improvement upon dose decrease or discontinuation, symptoms or biomarker changes not attributable to established predispositions such as drug-drug interactions and recognised conditions increasing the risk of statin intolerance.[67,68]

**Treatment**

It is very important to diagnose SAM, and especially RM, early and treat it immediately, because this results in fewer systemic complications.[51] There are no particular guidelines for the SAM and even RM management, however, expert societies have published clinical recommendations for its identification and management.[1,42,43,48,50,59] Also, there are no randomised controlled trials of SAM treatment. Management of RM is presently based on observations from retrospective studies, case reports and case series, which describe various RM treatments, particularly for its renal complication.[7]

To prevent development of RM, if intolerable muscle symptoms develop, the hypolipidaemic drug should be discontinued regardless of CK levels and re-used only after the patient becomes asymptomatic. If muscle symptoms are tolerable and CK elevation is present, the hypolipidaemic drugs could also be discontinued. RM requires in-hospital treatment, which includes intensive intravenous hydration, urinary alkalisation and close monitoring to prevent acute kidney failure.[18]

Once in hospital, aggressive intravenous normal saline infusion should begin immediately to promote vigorous diuresis and to dilute the released toxic products. Potassium or lactate containing solutions should be avoided because of the risk of RM associated hyperkalaemia and lactic acidosis.[11]

Alkalisation of urine (by sodium bicarbonate) is encouraged for the purpose of decreasing cast formation, minimising the toxic effects of Mb on the renal tubules, inhibiting lipid peroxidation and decreasing the risk for hyperkalaemia.[11,24] However, in patients with RM and a good urinary response to fluid administration, alkalisation of the urine may not be necessary.[18]

In hyperkalaemia (may be a life-threatening complication of RM), treatment should be initiated with insulin, glucose therapy and intravenous calcium (ineffective in patient with hyperphosphataemia).[18] If hyperkalaemia persists, emergency dialysis will become an option.

Hypocalcaemia observed early in RM usually requires no treatment. Hypocalcaemia responds to saline diuresis and intravenous furosemide.[11,18] Hyperphosphataemia should be treated with oral phosphate binders when serum levels exceed 7 mg/dl. Similarly, the hypophosphataemia, which may occur late in RM, requires treatment only when the serum level is below 1 mg/dl.[20] In case of vitamin D deficiency, suplementations may be provided.[69–71]

Dialysis should be considered as a lifesaving procedure for patients with rising or elevated potassium level, persistent acidosis, or oliguric renal failure with fluid overload.[24]

The best treatment of SAM is to avoid (checking for hypothyroidism and renal function before initiating statins) or to treat it from the first clinical signs of SAM and not to allow further progression.[72] This can be achieved by discontinuing the statin, decreasing statin dosing (if needed combine the low dose of statin with other hypolipidaemic drugs), switching to a different statin or to a different hypolipidaemic drug such as ezetimibe, bile acid sequestrants and fibrates (alone or in combination; some caution is needed when combining fibrates with a statin; gemfibrozil should never be used in combination with a statin), treat with new hypolipidaemic drugs (e.g. proprotein convertase subtilisin/kexin 9 inhibitors).[73,74]

**Conclusions**

SAM will become more prevalent due to the increasing use of statins. The management of SAM is less complex if diagnosed early. Thus, it is very important to be familiar with the diagnosis of SAM, especially RM, because early treatment can improve the adverse effects and outcome.

**Disclosure statement**

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**References**

[1] Pasternak RC, Smith SC Jr, Bairey-Merz CN, et al. ACC/AHA/NHLBI clinical advisory on the use and safety of statins. Stroke. 2002;33:2337–2341.
[2] Huerta-Alardin AL, Varon J, Marik PE. Bench-to-bedside review: rhabdomyolysis an overview for clinicians. Crit. Care. 2005;9:158–169.

[3] Giannoglou GD, ChatzizisisYS, Misirli G. The syndrome of rhabdomyolysis: pathophysiology and diagnosis. Eur. J. Intern. Med. 2007;19:90–100.

[4] Chavez LO, Leon M, Einav S, et al. Beyond muscle destruction: a systematic review of rhabdomyolysis for clinical practice. Crit. Care. 2016;20:135. doi:10.1186/s13054-016-1314-5.

[5] Vanholder R, Sever MS, Erek E, et al. Rhabdomyolysis. J. Am. Soc. Nephrol. 2000;11:1553–1561.

[6] Khan FY. Rhabdomyolysis: a review of the literature. Neth. J. Med. 2009;67:272–283.

[7] Poels PJ, Gabréëls FJ. Rhabdomyolysis: a review of the literature. Clin. Neurol. Neurosurg. 1993;95:175–192.

[8] Brumbach BA, Feeback DL, Leech RW. Rhabdomyolysis in childhood: a primer on normal muscle function and selected metabolic myopathies characterized by disordered energy production. Pediatr. Clin. North Am. 1992;39:821–858.

[9] Knochel JP. Mechanisms of rhabdomyolysis. Curr. Opin. Rheumatol. 1993;5:725–731.

[10] Sauret JM, Marinides G, Wang GK. Rhabdomyolysis. Am. Fam. Physician. 2002;65:907–912.

[11] Buttner BM, Borecki IB. Rhabdomyolysis: the spectrum of metabolic myopathies. Int. J. Cardiol. 2012;159:169–176.

[12] Marei IA, El Hallaoui F, Adam M, et al. Statin-related rhabdomyolysis: a systematic review and meta-analysis. J. Lipid Res. 2011;52:278–292.

[13] Chang JT, Staffa JA, Parks M, et al. Rhabdomyolysis with HMG-CoA reductase inhibitors and gemfibrozil combination therapy. Pharmacoepidemiol. Drug Saf. 2004;13:417–426.

[14] Hoffman KB, Kraus C, Dimbil M, et al. A survey of the FDA's AERS database regarding muscle and tendon adverse events linked to the statin drug class. Plos One. 2012;7:e42866.

[15] Alsheikh-Ali AA, Kivin JT, et al. The safety of rosuvastatin as used in common clinical practice: a postmarketing analysis. Circulation. 2005;111:3051–3057.

[16] Rallidis LS, Fountoulaki K, Anastasiou-Nana M. Review managing the underestimated risk of statin-associated myopathy. Int. J. Cardiol. 2012;159:169–176.

[17] Law M, Rudnicka AR. Statin safety: a systematic review. Am. J. Cardiol. 2006;97:52C–60C.

[18] Davidson MH, Clark JA, Glass LM, et al. Statin safety: an appraisal from the adverse event reporting system. Am. J. Cardiol. 2006;97:32C–43C.

[19] Staffa JA, Chang J, Green L. Cerivastatin and reports of fatal rhabdomyolysis. N. Engl. J. Med. 2002;346:539–540.

[20] McKenney JM, Davidson MH, Jacobson TA, et al. National Lipid Association Statin Safety Assessment Task Force. Final conclusions and recommendations of the National Lipid Association Statin Safety Assessment Task Force. Am. J. Cardiol. 2006;97:89C–94C.

[21] Norata GD, Tibolla G, Catapano AL. Statins and skeletal muscles toxicity: from clinical trials to everyday practice. Pharmacol. Res. 2014;88:107–113.

[22] Iwere RB, Hewitt J. Myopathy in older people receiving statin therapy: a systematic review and meta-analysis. Br. J. Clin. Pharmacol. 2015;80:363–371.

[23] Antons KA, Williams CD, Baker SK, et al. Clinical perspectives of statin-induced rhabdomyolysis. Am. J. Med. 2006;119:400–409.
[46] Harper CR, Jacobson TA. The broad spectrum of statin myopathy: from myalgia to rhabdomyolysis. Curr. Opin. Lipidol. 2007;18:401–408.

[47] van Staa TP, Carr DF, O’Meara H, et al. Predictors and outcomes of increases in creatine phosphokinase concentrations or rhabdomyolysis risk during statin treatment. Br. J. Clin. Pharmacol. 2014;78:649–659.

[48] Raju SB, Varghese K, Madhu K. Management of statin intolerance. Indian J. Endocrinol. Metab. 2013;17:977–982.

[49] Jacobson TA. Toward “pain-free” statin prescribing: clinical algorithm for diagnosis and management of myalgia. Mayo Clin. Proc. 2008;83:687–700.

[50] Katsiki N, Athyros VG, Karagiannis A. Exploring the management of statin intolerant patients: 2016 and beyond. Curr. Vasc. Pharmacol. 2016 Feb 26 [Epub ahead of print].

[51] Vrablik M, Zlatohlavek L, Stulc T, et al. Statin-associated myopathy: from genetic predisposition to clinical management. Physiol. Res. 2014;63(Suppl 3):S327–S334.

[52] Ragia G, Kolovou V, Tavridou A, et al. Lack of association of the p450 oxidoreductase *28 single nucleotide polymorphism with the lipid-lowering effect of statins in hypercholesterolemic patients. Mol. Diagn. Ther. 2014;18:323–331.

[53] Kolovou G, Kolovou V, Ragia G, et al. CYP3A5 genotyping for assessing the efficacy of treatment with simvastatin and atorvastatin. Genet. Mol. Biol. 2015;38:129–137.

[54] Frudakis TN, Thomas MJ, Ginjupalli SN, et al. CYP2D6*4 polymorphism is associated with statin-induced muscle effects. Pharmacogenet. Genomics. 2007;17:695–707.

[55] Zuccaro P, Mombelli G, Calabresi L, et al. Tolerance of statins is not linked to CYP450 polymorphisms, but reduced CYP2D6 metabolism improves cholesterolaemic response to simvastatin and fluvastatin. Pharmacol. Res. 2007;55:310–317.

[56] Emmanuele V, López LC, Berardo A, et al. Heterogeneity of coenzyme Q10 deficiency: patient study and literature review. Arch Neurol. 2012;69:978–983.

[57] Oh J, Ban MR, Miskie BA, et al. Genetic determinants of statin intolerance. Lipids Health Dis. 2007;6:7. doi: 10.1186/1476-511X-6-7.

[58] SEARCH Collaborative Group, Link E, Parish S, et al. SLCO1B1 variants and statin-induced myopathy—a genomewide study. N. Engl. J. Med. 2008;359:789–799.

[59] Stroes ES, Thompson PD, Corsini A, et al. Statin-associated muscle symptoms: impact on statin therapy-European Atherosclerosis Society Consensus Panel Statement on assessment, aetiology and management. Eur. Heart J. 2015;36:1012–1022.

[60] Bruckert E, Hayem G, Dejager S, et al. Mild to moderate muscular symptoms with high-dosage statin therapy in hyperlipidemic patients —the PRIMO study. Cardiovasc. Drugs Ther. 2005;19:403–414.

[61] Ghatak A, Faheem O, Thompson PD. The genetics of statin-induced myopathy. Atherosclerosis. 2010;210:337–343.

[62] Banach M, Serban C, Uroniu S, et al. Statin therapy and plasma coenzyme Q10 concentrations—a systematic review and meta-analysis of placebo-controlled trials. Pharmacol. Res. 2015;99:329–336.

[63] Banach M, Serban C, Sahebkar A, et al. Effects of coenzyme Q10 on statin-induced myopathy: a meta-analysis of randomized controlled trials. Mayo Clin. Proc. 2015;90:24–34.

[64] Owczarek J, Jasińska M, Orszulak-Michalak D. Drug-induced myopathies. An overview of the possible mechanisms. Pharmacol. Rep. 2005;57:23–34.

[65] Mas E, Mori TA. Coenzyme Q(10) and statin myalgia: what is the evidence? Curr. Atheroscler. Rep. 2010;12:407–413.

[66] Khayznikov M, Hemachandra K, Pandit R, et al. Statin intolerance because of myalgia, myositis, myopathy, or myonecrosis can in most cases be safely resolved by vitamin D supplementation. N. Am. J. Med. Sci. 2015;7:86–93.

[67] Banach M, Rizzo M, Toth PP, et al. Statin intolerance - an attempt at a unified definition. Position paper from an International Lipid Expert Panel. Expert. Opin. Drug Saf. 2015;14:935–955.

[68] Banach M, Rizzo M, Toth PP, et al. Statin intolerance - an attempt at a unified definition. Position paper from an International Lipid Expert Panel. Arch. Med. Sci. 2015;11:1–23.

[69] Glueck CJ, Budhani SB, Masineni SS, et al. Vitamin D deficiency, myositis, myalgia, and reversible statin intolerance. Curr. Med. Res. Opin. 2011;27:1683–1690.

[70] Michalska-Kasiczak M, Sahebkar A, Mikhailidis DP, et al. Analysis of vitamin D levels in patients with and without statin-associated myalgia – a systematic review and meta-analysis of 7 studies with 2420 patients. Int. J. Cardiol. 2015;178:111–116.

[71] Katsiki N, Athyros VG, Karagiannis A, et al. Vitamin D deficiency, statin-related myopathy and other links with vascular risk. Curr. Med. Res. Opin. 2011;27:1691–1692.

[72] Phan K, Gomez YH, Elbaz L, et al. Statin dose in renal failure? Which statin to select? Statin treatment non-adherence and discontinuation: clinical implications and potential solutions. Curr. Pharm. Des. 2014;20:6314–6324.

[73] Agouridis A, Athyros VG, Mikhailidis DP. Strategies to overcome statin intolerance. Expert. Opin. Drug Metab. Toxicol. 2015;11:851–855.

[74] Tziomalos K, Athyros VG, Mikhailidis DP. Statin discontinuation: an underestimated risk? The downside of statin discontinuation in high risk patients. Curr. Med. Res. Opin. 2008;24:3059–3062.