

Effects of statins on mitochondrial pathways

Hamid Mollazadeh^{1,2} , Erfan Tavana³, Giovanni Fanni⁴, Simona Bo⁵, Maciej Banach^{6,7} , Matteo Pirro⁸, Stephan von Haehling^{9,10}, Tannaz Jamialahmadi^{11,12} & Amirhossein Sahebkar^{13,14,15*} 

¹Department of Physiology and Pharmacology, Faculty of Medicine, North Khorasan University of Medical Sciences, Bojnurd, Iran, ²Natural Products and Medicinal Plants Research Center, North Khorasan University of Medical Sciences, Bojnurd, Iran, ³Student Research Committee, School of Medicine, North Khorasan University of Medical Sciences, Bojnurd, Iran, ⁴Department of Medical Sciences, University of Turin, Turin, Italy, ⁵Department of Medical Sciences, AOU Città della Salute e della Scienza di Torino, University of Turin, Turin, Italy, ⁶Department of Hypertension, WAM University Hospital in Lodz, Medical University of Lodz, Lodz/Poland, ⁷Polish Mother's Memorial Hospital Research Institute (PMMHRI), Lodz, Poland, ⁸Unit of Internal Medicine, Angiology and Arteriosclerosis Diseases, Department of Medicine, University of Perugia, Perugia, Italy, ⁹Department of Cardiology and Pneumology, University Medical Center Göttingen, Göttingen, Germany, ¹⁰German Center for Cardiovascular Research (DZHK), partner site Göttingen, Göttingen, Germany, ¹¹Department of Food Science and Technology, Islamic Azad University, Quchan, Quchan, Iran, ¹²Department of Nutrition, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran, ¹³Biotechnology Research Center, Pharmaceutical Technology Institute, Mashhad University of Medical Sciences, Mashhad, Iran, ¹⁴Neurogenic Inflammation Research Center, Mashhad University of Medical Sciences, Mashhad, Iran, ¹⁵Halal Research Center of IRI, FDA, Tehran, Iran

Abstract

Statins are a family of drugs that are used for treating hyperlipidaemia with a recognized capacity to prevent cardiovascular disease events. They inhibit β -hydroxy β -methylglutaryl-coenzyme A reductase, i.e. the rate-limiting enzyme in mevalonate pathway, reduce endogenous cholesterol synthesis, and increase low-density lipoprotein clearance by promoting low-density lipoprotein receptor expression mainly in the hepatocytes. Statins have pleiotropic effects including stabilization of atherosclerotic plaques, immunomodulation, anti-inflammatory properties, improvement of endothelial function, antioxidant, and anti-thrombotic action. Despite all beneficial effects, statins may elicit adverse reactions such as myopathy. Studies have shown that mitochondria play an important role in statin-induced myopathies. In this review, we aim to report the mechanisms of action of statins on mitochondrial function. Results have shown that statins have several effects on mitochondria including reduction of coenzyme Q10 level, inhibition of respiratory chain complexes, induction of mitochondrial apoptosis, dysregulation of Ca^{2+} metabolism, and carnitine palmitoyltransferase-2 expression. The use of statins has been associated with the onset of additional pathological conditions like diabetes and dementia as a result of interference with mitochondrial pathways by various mechanisms, such as reduction in mitochondrial oxidative phosphorylation, increase in oxidative stress, decrease in uncoupling protein 3 concentration, and interference in amyloid- β metabolism.

Overall, data reported in this review suggest that statins may have major effects on mitochondrial function, and some of their adverse effects might be mediated through mitochondrial pathways.

Keywords Statin; Myopathy; SAMS; Mitochondria; Apoptosis; Coenzyme Q10; Respiratory chain; Diabetes; Cognitive impairment

Received: 1 July 2020; Revised: 9 September 2020; Accepted: 20 October 2020

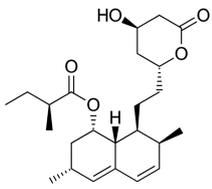
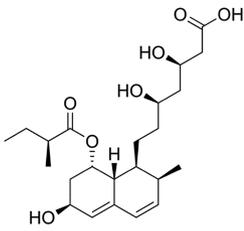
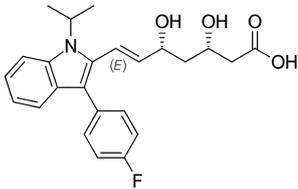
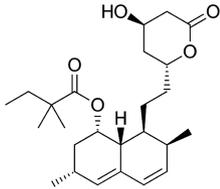
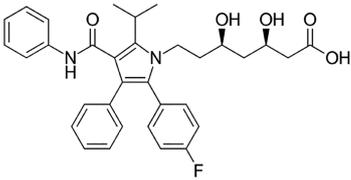
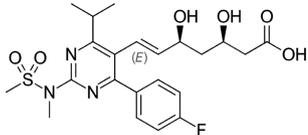
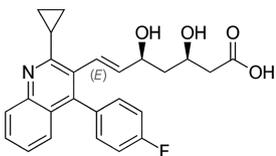
*Correspondence to: Amirhossein Sahebkar, Department of Medical Biotechnology, School of Medicine, Mashhad University of Medical Sciences, PO Box: 91779-48564, Mashhad, Iran. Phone: 985138002288, Fax: 985138002287, Email: amir_saheb2000@yahoo.com; sahebkar@mums.ac.ir

Introduction

Cardiovascular diseases (CVDs), such as myocardial infarction, angina, heart failure, and cerebrovascular accidents, contribute significantly to global mortality. World Health Organization estimated 17.9 million deaths in 2017 due to CVDs,

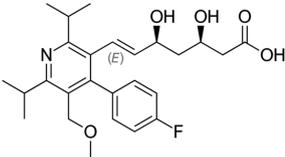
representing 31% of the whole global mortality.¹ The systematic analysis for the Global Burden of Disease Study estimates that CVD-associated mortality will raise to 23 million deaths per year by 2030.² Among the major risk factors, CVDs are associated with high plasma total cholesterol, low-density lipoprotein (LDL) cholesterol, and reduced high-density

Table 1 Statins and their structures and classification

Statin	Generation	Structure	Hydrophilicity/lipophilicity
Lovastatin	I		Hydrophilic
Pravastatin	I		Lipophilic
Fluvastatin	I		Hydrophilic
Simvastatin	II		Hydrophilic
Atorvastatin	II		Hydrophilic
Rosuvastatin	III		Lipophilic
Pitavastatin	III		Hydrophilic

(Continues)

Table 1 (continued)

Statin	Generation	Structure	Hydrophilicity/lipophilicity
Cerivastatin	Withdrawn		Lipophilic

lipoprotein cholesterol. CVD risk is reduced by ~22% per each 1 mmol/L LDL cholesterol decrease.³ There is overwhelming evidence showing an increasing clinical benefit when greater and earlier LDL cholesterol reductions are achieved.⁴ Apo B-containing lipoproteins (like LDLs), which are the key sources of cholesterol, are responsible for initiation and progression of atherogenesis.⁵ Therefore, one of the main goals of CVD prevention is LDL cholesterol level reduction.

β -Hydroxy β -methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, better known as statins, are among the most effective lipid-lowering agents.⁶ Besides lifestyle approaches like diet and exercise interventions,⁷ additional cholesterol-lowering therapies include nutraceuticals,^{8–10} ezetimibe, proprotein convertase subtilisin/kexin type 9 inhibitors, lomitapide, and mipomersen.^{11,12}

In 1976, Akira Endo isolated from *Penicillium citrinum*, a molecule (mevastatin) able to inhibit HMG-CoA reductase, a crucial enzyme in endogenous cholesterol biosynthesis.¹³ Statins are reversible and competitive HMG-CoA reductase inhibitors and determine a reduction in serum and tissue levels of total cholesterol, LDL cholesterol, apo B, and triglycerides. Statins are prescribed in order to reduce plasma cholesterol levels both in primary and secondary prevention of CVD.

Because HMG-CoA is a key enzyme in the mevalonate pathway, its inhibition results in a reduced bioavailability of farnesyl pyrophosphate, geranylgeranyl pyrophosphate, heme A, coenzyme Q10 (CoQ10; also known as ubiquinone), and other metabolites that play essential roles in cellular physiology.^{14,15} Moreover, cholesterol is not only a final product of this biochemical pathway but also itself an intermediate for many other compounds, such as corticosteroids, bile acids, and vitamin D.¹⁵ This explains why statins pharmacodynamically exert pleiotropic effects,^{16–21} which are responsible for both beneficial and adverse consequences during treatment. Apart from their cholesterol-lowering effect, statins are known to contribute to stabilization of atherosclerotic plaques,²² improvement of endothelial dysfunction,²³ and immunomodulation and show anti-inflammatory,²⁴ antioxidant, and anti-thrombotic effects.²⁵ Lipid-dependent and lipid-independent effects of statins may vary according to the potency,⁶ lipophilicity (Table 1), and pharmacokinetic properties^{14,26–28} of different agents.

Statins have been proved to be safe drugs. However, they may elicit adverse reactions (muscle, metabolic, liver, and neurological side effects), being muscle adverse effects the most frequently reported.²⁹ These adverse reactions are commonly named as statin-associated symptoms (SAS).²⁹ It is important to underline that the causative relationship between statins and SAS is not always clearly demonstrable: some patients complaining of SAS can tolerate a low statin dose, and some non-specific side effects have been reported by patients treated with placebo.²⁹ Most of SAS appear to be dose dependent; half of the patients on high statin dosages stop the drug within 1 year because of SAS.^{30–32} The risk of drug–drug interaction increases alongside with age and number of administered drugs.³³ Other risk factors for statin intolerance are frailty, surgery, infection, female sex, exertion, hypothyroidism, chronic kidney disease, and genetic predisposition.^{15,34}

Statins may interfere with mitochondrial activity both via direct mechanisms, i.e. impairment of electron transport chain (ETC) complexes, and via indirect ones, i.e. as a consequence of mevalonate pathway metabolites depletion, e.g. CoQ10 and isoprenoids. Growing evidence is being provided showing that SAS are mostly due not to their direct cholesterol-lowering effect but rather to the induced impairment on mitochondrial function, as supported by histopathological, laboratory, and molecular findings in cell lines, rat models, and humans.^{34,35} A better understanding of the pathogenic background of SAS will be fundamental for quickly identifying patients who are at major risk and acquire best results of treatment, so learning about their mechanisms, progression, and treatment is essential for better counteracting adverse reactions of statins responsible for therapy discontinuation.

Aims and methods

The aim of this review was to provide an overview of achieved knowledge about mechanisms that underlie SAS, focusing on muscle effects, statin-induced diabetes, and cognitive impairment. In particular, we focused on statin-driven

molecular mechanisms interfering both directly and indirectly with mitochondrial function.

This review is based on evidence gathered performing a PubMed query by using 'statin AND mitochondria AND adverse reaction' as search terms. The search strategy was implemented by hand searching the references reported by the most relevant studies on this topic.

Statin-associated muscle symptoms

Among all SAS, muscle side effects are the most frequently reported.^{29,36,37} About 7–29% of patients complain of statin-associated muscle symptoms (SAMS).³⁸ Symptoms usually occur after 4–6 weeks of treatment initiation but sometimes after many years.³⁹ Weakness, pain, and muscle fatigue are responsible for 30–62% statin treatment discontinuation.⁴⁰ SAMS present as a wide range of clinical manifestations, such as myalgia, weakness, tendon pain, night muscle cramping, and rhabdomyolysis in most severe cases.^{41,42} Weakness and pain usually involve large back muscles and proximal muscle groups symmetrically.⁴³ Underlying these manifestations is a statin-induced myopathy (SIM), whose pathophysiology has not been fully understood yet.⁴⁴ Further, the lack of reliable laboratory biomarkers for diagnosing myopathy complicates its clinical identification. The most used laboratory test is creatine kinase (CK) blood concentration, which however suffers from low sensibility and specificity.⁴⁵

Up to now, there is no universally established terminology used to describe SIM. The National Lipid Association describes myopathy as muscle pain, soreness, weakness, and cramps together with an at least 10-fold increase in CK levels above the upper limit of normal (ULN).⁴⁶ European Atherosclerosis Society (EAS) defines myopathy as the presence of muscle symptoms accompanied by CK over 10-fold the ULN.³⁸ According to the American College of Cardiology/American Heart Association/National Heart, Lung, and Blood Institute, myopathy can be identified by either myalgia (without CK elevation), myositis (CK elevation within 10-fold the ULN), or blunt rhabdomyolysis (CK elevation over 10-fold the ULN, increase in creatinemia, and reddish or brown urine).⁴⁷ On the contrary, rhabdomyolysis is defined by the Food and Drug Administration (FDA) as a condition characterized by an increase in CK blood concentration over 50-fold the ULN associated with myoglobin-induced acute renal injury.⁴⁸ Conversely, according to EAS, CK over 40-fold the ULN associated with renal impairment and/or myoglobinuria configures the presence of rhabdomyolysis.³⁸ Importantly, albeit rhabdomyolysis is the most severe statin-associated side effect, it is a rare complication occurring in about 0.01% of treated patients.⁴⁹ Myoglobinuria, deriving from muscle necrosis and the release of myoglobin in the blood circulation,

can cause mechanical obstruction and acute necrosis of the renal tubules and subsequently acute renal failure, a potentially life-threatening complication.⁵⁰

Statin-associated muscle symptom definition refers to any muscle symptom related to statin treatment. In this frame, the EAS Consensus suggested three criteria for the diagnosis of SAMS: correspondence between CK levels increase and onset of statin treatment; decline of symptoms at treatment withdrawal; and symptoms recurrence at statin treatment rechallenging.³⁸ However, it must be underlined that SAMS might occur in patients who do not show increased CK blood concentrations.²⁹

Mitochondria

Mitochondria are organelles often referred to as the power station of eukaryotic cells, because several phases of cellular respiration take place there, such as the Krebs cycle, the oxidative phosphorylation, and fatty acid β -oxidation.⁵¹ Oxidative phosphorylation is a key biochemical pathway in cellular respiration and is carried out by several protein complexes and molecules that are located at the inner mitochondrial membrane (IMM). It consists of two subsequent steps, the ETC and ATP synthesis. ATP synthesis consists of phosphorylation of ADP to ATP catalysed by ATP synthase, thanks to the proton motive force following the electrochemical gradient across the IMM. This electrochemical gradient is sustained by the proton translocation from mitochondrial matrix to intermembrane space (IMS) mediated by complexes I, III, and IV of the ETC.⁵²

Complex I (NADH : ubiquinone oxidoreductase) is responsible for reduction of NADH yielded during glycolysis and Krebs cycle. While transferring electrons from NADH, thereby reducing ubiquinone to ubiquinol, it mediates transport of four protons (H^+) from mitochondrial matrix to the IMS. Complex II (succinate : ubiquinone oxidoreductase) is part of the Krebs cycle. It catalyses succinate oxidation to fumarate while reducing ubiquinone to ubiquinol. Different to other complexes, complex II does not transport protons across the membrane. Complex III (cytochrome bc_1) catalyses reoxidation of ubiquinol (moving freely along the IMM and yielded by complex I and II enzymatic activities) to ubiquinone, transferring electrons to the membrane-attached cytochrome c and four protons from matrix to IMS. Eventually, cytochrome c is again oxidized by complex IV (cytochrome c oxidase) that yields H_2O from transferring electrons to O_2 and transfers four protons against gradient across the IMS.⁵² The electron transport system (ETS) is thought to be an important source of reactive oxygen species (ROS). As a consequence of many redox reactions, mitochondria yield an important amount of ROS, which can act either as cell signalling molecules or as oxidative stress factors^{52–54} (Figure 1).

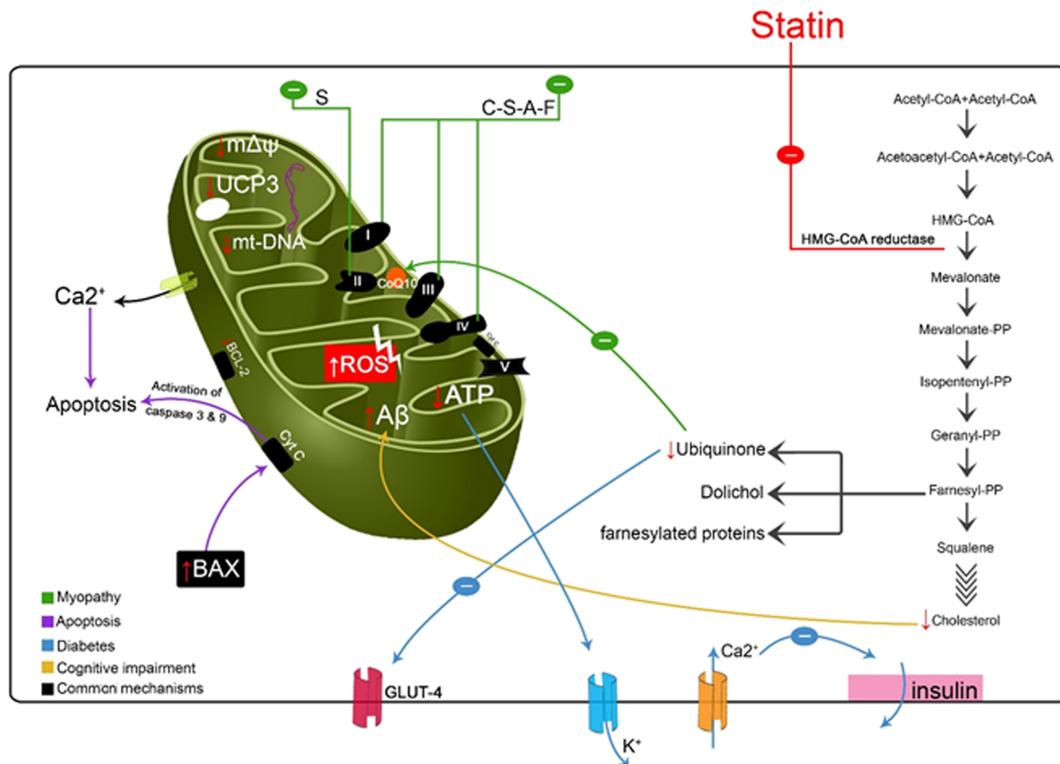


Figure 1 Effects of statins on mitochondrial function: (i) reduction in mitochondrial membrane potential; (ii) reduction in coenzyme Q10 (CoQ10) and GLUT-4 expression; (iii) increased reactive oxygen species (ROS) level and induction of intrinsic apoptosis; (iv) deregulation of Ca^{2+} metabolism; (v) mitochondrial depletion; (vi) decrease in uncoupling protein 3 (UCP3) expression and reduction in β -oxidation efficiency; (vii) increase in amyloid- β ($A\beta$) concentration in mitochondria; (viii) direct inhibition in respiratory chain. A, atorvastatin; C, cerivastatin; F, fluvastatin; HMG-CoA, β -hydroxy β -methylglutaryl-coenzyme A; mtDNA, mitochondrial DNA; PP, pyrophosphate; S, simvastatin.

Statin-associated muscle symptoms and mitochondrial dysfunction

Mitochondrial dysfunction is believed to play a pivotal role in the pathogenesis of SAMS, because skeletal muscles are avid energy consumers and closely depend on mitochondrial activity.⁵⁵ This is supported by histopathological findings, evidencing how SIM is characterized by lipid aggregation in mitochondria and ragged red fibres accumulating in subsarcolemmal region visible with Gömöri staining.^{56,57} Abnormal high blood lactate/pyruvate ratio⁵⁸ and increased mean metabolic recovery time as assessed by ³¹P magnetic resonance spectroscopy⁵⁹ in statin-treated patients when compared with untreated hypercholesterolaemic and healthy controls add evidence to this hypothesis. However, neither the LIFESTAT study nor 8 week treatment with simvastatin 80 mg/day on healthy subjects proved any difference in mitochondrial function after statin treatment.^{61,62} According to the LIFESTAT study, 20 healthy middle-aged men were treated with 80 mg/day simvastatin ($n = 10$) or 40 mg/day pravastatin ($n = 10$). After 14 days, 50% of participants presented a different range of side effects from soreness, myalgia, to stomach ache, but no changes in mitochondrial

function with respect to respiratory chain capacity, mitochondrial density, or Q10 content, except a reduction in complex IV activity in both groups.⁶¹ Hou et al. found the presence of mitochondrial dysfunction and abnormal respiratory chain enzyme activity in 24% and 10%, respectively, among 279 biopsies from patients with SIM. Hence, whether mitochondrial dysfunction may be considered a frequent pathogenic hallmark of SAMS is still debated.⁶³

In the following sections, the proposed pathogenetic mechanisms of SAMS involving mitochondrial dysfunction are described (Table 2).

Depletion of coenzyme Q10

Coenzyme Q10 (alias ubiquinone) is a hexameric quinone ring containing a 10-isoprenyl unit side chain; it is structurally similar to vitamin K and can be found in the hydrophobic layer of all cell membranes in mammals. Ubiquinone is an end product of the mevalonate pathway but can be supplied by diet being mostly present in some meats like beef, pork, and chicken^{64,65} and by dietary supplements/nutraceuticals.⁶⁶ Because of its chemical structure, CoQ10 presents a high antioxidant activity. The highest tissue

Table 2 Overview on statin mechanisms of mitochondrial toxicity

Type of statin	Mechanism	Adverse effect	Reference
Atorvastatin	Inhibition of complexes I, III, and IV	Myopathy	Salviati et al. ⁶⁸
	Dysregulation of calcium homeostasis	Myopathy	Liantonio et al. ⁶⁰
	Reduction in CoQ10 concentration	Myopathy	Saha and Whyne ⁶⁹
	mtDNA depletion	Myopathy	Saha and Whyne ⁶⁹
	PGC-1/Akt pathway disruption	Myopathy	Mullen et al. ⁸³
	ROS accumulation and oxidative stress	Induced apoptosis	Dirks and Jones ¹⁰⁴
	Akt pathway disruption	Induced apoptosis	Mikus et al. ⁸¹
Unknown	Impaired insulin secretion	Diabetes	Shepherd et al., Sattar et al., and Sadighara et al. ^{130,132,133}
	Unknown	Cognitive impairment	Ott et al. and Swiger et al. ^{153,154}
Fluvastatin	Inhibition of complexes I, III, and IV	Myopathy	Salviati et al. ⁶⁸
Lovastatin	Dysregulation of calcium homeostasis	Myopathy	Liantonio ⁶⁰
	CPT-2 inhibition	Myopathy	Ghatak et al. ¹²³
Pravastatin	Reduced activity of complex IV	Myopathy	Sirvent et al. ⁹¹
	Impaired insulin secretion	Diabetes	Shepherd et al. ¹³⁰
Rosuvastatin	Inhibition of complex IV	Myopathy	Phillips et al. ⁵⁷
Simvastatin	Akt pathway disruption	Induced apoptosis	Mikus et al. ⁸¹
	Impaired ETC function	Myopathy	Salviati et al., Saha and Whyne, Vaughan et al., Kwak et al., and Sirvent et al. ^{68,69,83,85,88,91}
Cerivastatin	Reduction in CoQ10 muscle concentration	Myopathy	Saha and Whyne and Sirvent et al. ^{69,91}
	mtDNA depletion or reduced citrate synthase activity	Myopathy	Saha and Whyne, Lamperti et al., Banach et al., Qu et al., and Schick et al. ^{69,76–79}
	PGC-1/Akt pathway disruption	Myopathy	Åberg et al., Stringer et al., and Singla et al. ^{67,80,82}
	Dysregulation of calcium homeostasis	Myopathy	De Pinieux et al., Murlasists and Radák, and Herminghaus et al. ^{58,95,96}
	Inhibition of complex IV	Myopathy	Phillips et al. ⁵⁷
	Calpain activation	Induced apoptosis	Hermann et al. ¹⁰³
	ROS accumulation and oxidative stress	Induced apoptosis	Vaughan et al. ⁸⁵
	Isoprenoid depletion	Induced apoptosis	Novelli and D'Apice and Guijarro et al. ^{109,110}
	Akt pathway disruption	Induced apoptosis	Stringer et al. and Mikus et al. ^{80,81}
	Peripheral insulin resistance	Diabetes	Sadighara et al. and Moro et al. ^{136,140}
Unknown	Cognitive impairment	Ott et al. ¹⁵³	
Cerivastatin	Inhibition of complexes I, III, and IV	Myopathy	Salviati et al. ⁶⁸
	Reduced activity of complex IV	Myopathy	Brookes ⁵³
	Isoprenoid depletion	Induced apoptosis	Hosseinzadeh et al. ¹⁰⁸

CoQ10, coenzyme Q10; CPT-2, carnitine palmitoyltransferase-2; ETC, electron transport chain; mtDNA, mitochondrial DNA; PGC-1, peroxisome proliferator-activated receptor gamma coactivator 1; ROS, reactive oxygen species.

concentrations of CoQ10 can be found in the kidney, liver, and heart.⁶⁷ As previously described, CoQ10 is an essential component of the ETC and therefore plays a pivotal role in cellular energy yield. Primary CoQ10 deficiency has been detected in several diseases comprising heart failure, nephrotic syndrome, and muscular and neurological disorders.^{68,69} In addition, secondary CoQ10 deficiency may occur. In this regard, the inhibitory effect of statins on the mevalonate pathway (Figure 1) may reduce CoQ10 levels by 16–54%⁶⁴ and cause mitochondrial dysfunction, revealed by inhibition of mitochondrial ETC complexes,^{70,71} disruption of mitochondrial membrane potential, decrease in mitochondrial DNA (mtDNA) copy number, interference with oxidative phosphorylation, mitochondrial swelling, and release of cytochrome *c*.^{71,72} However, decrease in plasma CoQ10 level is mostly due to the reduction of circulating lipoproteins, because around 74% of CoQ10 is carried in the blood by apo B-containing lipoproteins.⁶⁴ Accordingly, no significant

difference in CoQ10 to total cholesterol ratio was found before and after statin treatment.

Scarce and contradictory data are available about the impact of statin treatment on skeletal muscle CoQ10 concentration.⁷³ In a randomized controlled trial, 8 weeks of treatment with simvastatin 80 mg/day but not the treatment with atorvastatin 40 mg/day or placebo was associated with a significant decrease in muscle ubiquinone concentration.⁷² Analyses from a subgroup of patients showed that those with markedly reduced muscle CoQ10 had concurrent reduction in respiratory chain enzyme and citrate synthase activities.⁷² However, conflicting data showing either increase or no change in muscle ubiquinone concentrations after both short-term and long-term statin treatments have been provided.^{74–76}

Recent meta-analyses on the topic have led to controversial results about the effectiveness of CoQ10 supplementation in statin-treated patients in improving SIM and SAMS.^{77,78}

Mitochondrial depletion and oxidative stress

A significant reduction in mtDNA/nuclear DNA ratio was observed after 8 weeks of 80 mg/day simvastatin but not after 8 weeks of 40 mg/day atorvastatin.⁷⁹ The findings of this randomized controlled trial suggested a major impact of simvastatin on mitochondrial depletion due to its lipophilicity. Notably, changes in mtDNA/nuclear DNA ratio were irrespective of muscle symptoms but strongly associated with muscle CoQ10 concentration.⁷⁹ These results were replicated in a small cohort of patients experiencing SIM.⁸⁰

Exercise training can enhance mitochondrial function by increasing oxygen uptake by ~10% and citrate synthase activity, a marker of skeletal muscle mitochondrial content, by 13% in overweight or obese patients after 12 week exercise training.⁸¹ The addition of 40 mg/day simvastatin led to a lower increment of oxygen uptake during exercise training (1.5%) and a 4.5% reduction in citrate synthase activity.⁸¹ Similar results (3.6% reduction in citrate synthase activity and cardiorespiratory fitness impairment) have been reported in a cohort of patients with type 2 diabetes mellitus (T2DM) treated with 40 mg/day simvastatin for 12 weeks.⁸² Intriguingly, vitamin D supplementation resulted effective in preventing statin-related decrease in mitochondrial content and impairment in cardiorespiratory fitness.⁸²

Statin-induced toxicity could be due to the reduced phosphorylation of protein kinase B (Akt) and subsequent disruption of its pathway, which plays an important role in the mitochondrial health.^{83,84} The Akt pathway disruption is probably caused by decreased transcription and translation rates of peroxisome proliferator-activated receptor gamma coactivator (PGC)-1 α and PGC-1 β . In fact, these transcriptional co-factors act as activators of the Akt pathway and are considered master inductors of mitochondrial biogenesis.⁸⁵ Different cell lines both *in vitro* and *in vivo* have shown to be differentially susceptible to the disruption of the Akt pathway. Primary mouse skeletal muscle myocytes, C2C12 myotubes,⁸³ human rhabdomyosarcoma cells,⁸⁵ and skeletal muscle cells from deltoid biopsies⁷⁰ were susceptible to statin treatment in terms of mitochondrial dysfunction, as assessed by several parameters, including PGC-1 α mRNA transcription and mitochondrial oxidative capacity. Interestingly, mitochondrial dysfunction could be rescued either by administration of ubiquinol,⁸⁵ exogenous antioxidant agents, or by PGC-1 α overexpression.⁷⁰ In similar studies done on various models such as murine liver HepG2 cells,⁸³ oxidative muscle fibres,⁸⁶ and human cardiac muscle fibres,⁷⁰ statins showed mitochondrial dysfunctions. The production of ROS and oxidative stress could be crucial hallmarks of statin-induced toxicity and have a role in regulating mitochondrial biogenesis.^{87,88} In cells with high-efficient antioxidant systems, as cardiac myofibres, statin-induced ROS accumulation is limited and stimulates PGC-1 α activity, thus

promoting mitochondrial biogenesis and improving mitochondrial function. On the other hand, in cells with lower antioxidant capacity, such as fast glycolytic muscle fibres, a greater ROS increase could be responsible for the Akt pathway disruption.^{70,86} The differential response in terms of mitochondrial biogenesis according to ROS production is known as mitochondrial hormesis and can explain why some tissues and cells, in particular fast muscle fibres, are more susceptible to statin toxicity.⁷⁰ It is notable that PGC-1 β knockout mice showed mitochondrial dysfunction, increased ROS production, and induced apoptosis after oral administration of 5 mg/kg/day atorvastatin per 2 weeks both in glycolytic and oxidative muscle fibres.⁸⁶

Inhibition of electron transport chain complexes

Direct inhibition of ETC complexes has been proposed as a responsible mechanism for SIM.^{63,88–90} *In vitro*, functional impairment of complexes I, III, and IV occurred in L6 rat skeletal muscle cells after a 24 hour exposure to 100 μ mol/L cerivastatin, simvastatin, fluvastatin, or atorvastatin. On the contrary, no functional impairment was reported after exposure up to 1 mmol/l pravastatin.⁷¹ These findings were confirmed in human myocytes, onto which simvastatin acts mostly as an inhibitor of complex I.⁹¹ However, assays on fresh and frozen muscle samples from rats treated with different statin regimens failed to identify abnormalities in ETC complexes activity.^{92,93} A randomized controlled trial showed significant reduction in all ETC complexes activity in patients treated with simvastatin 80 mg/day for 8 weeks but not in those treated with atorvastatin 40 mg/day or placebo.⁷² However, a systematic review of several studies on cell cultures, animal models, and humans showed highly contradicting results on this topic.³⁴

In two patients affected by statin-induced rhabdomyolysis, skeletal muscle biopsies showed reductions in ubiquinone concentration and in complex IV activity.⁹⁴ A significant reduction by 60% of complex IV activity was identified in a patient presenting myoglobinuria after treatment with cerivastatin and gemfibrozil.⁵⁶

Statins are known to interfere with beneficial exercise training adaptations, which mostly rely on improvements of the mitochondrial function,^{81,82,95} and could be due to ETC complexes activity impairment.⁸¹ Finally, it has been suggested that impaired ETC function could be found out in other tissues as well, though data on these aspects are still very scarce.⁹⁶

Dysregulation of Ca²⁺ metabolism

As a consequence of mitochondrial dysfunction, studies on both animal and human models have identified an increased

Ca²⁺ efflux from the sarcoplasmic reticulum, leading to abnormalities in excitation–contraction coupling in skeletal muscle cells.⁹⁷ Sirvent *et al.* hypothesized that ETC disruption (and, above all, complex I inhibition) due to statin treatment could be responsible both *in vitro* and *in vivo* for calcium metabolism deregulation.⁹⁸ Alterations in spontaneous Ca²⁺ sparks (e.g. frequency and amplitude) in muscle cells indicate impaired Ca²⁺ homeostasis.⁹⁹ Decreased frequency of spontaneous Ca²⁺ sparks was found in patients treated with statin and complaining muscle symptoms but not in asymptomatic statin-treated patients when compared with healthy controls.⁹⁸ Increased Ca²⁺ spark amplitude was found in all statin-treated patients when compared with controls⁹⁸ and in individuals treated with 80 mg/day simvastatin for 8 weeks displaying increased serum CK concentrations.⁶² Statins have been demonstrated both *in vivo* and *in vitro* in animal and human models to raise cytosolic and sarcoplasmic Ca²⁺ concentration: this increase does not seem to be attributable to abnormal sarcolemma permeability but rather to a primary Ca²⁺ efflux from mitochondria mediated by mitochondrial permeability transition pore and Na⁺–Ca²⁺ exchanger.⁹⁹ The latter secondarily leads to Ca²⁺ release from the sarcoplasmic reticulum mediated by ryanodine receptors.^{60,70,96} The abnormal opening of mitochondrial permeability transition pore and Na⁺–Ca²⁺ exchanger may be caused by the decrease of mitochondrial membrane potential and depolarization of the IMM as a consequence of disrupted ETC activity.⁹⁹

Lactone toxicity

Statins are available in two different forms: hydroxy acid (active molecule) and the lactone (inactive prodrug). Interconversion through these two forms occurs spontaneously according to environmental pH or can be catalysed by enzymes, such as glucuronosyltransferases.¹⁰⁰ Lactone forms are more lipophilic and therefore more capable of crossing cell membranes and exerting their pharmacological activity.¹⁰⁰ Lactone forms have been described as more myotoxic both in rat and human cells *in vitro*.^{101,102} Individuals affected by SIM showed higher circulating levels of lactone metabolites than controls.¹⁰³ Acute administration of lactone forms of atorvastatin, cerivastatin, and pitavastatin in C2C12 myoblasts elicited a fast decrease of oxygen consumption rate, indicating a net inhibitory effect on mitochondrial respiratory function.⁹⁰ In particular, lactone forms showed a higher capacity to impair ETC complex III activity.⁹⁰ Therefore, the conditions altering the hydroxy acid/lactone forms ratio, such as pH disturbances and pharmacokinetic interactions, might play a role in amplifying the muscle damage of statin treatment.

Apoptosis

Statin-induced mitochondrial dysfunction has been correlated *in vitro* with an abnormal activation of the intrinsic apoptosis pathway, as a consequence of a decrease in the Bcl-2/Bax ratio. The statin-induced apoptosis occurs in different tissues and might be responsible for both beneficial pleiotropic and detrimental side effects of statin treatment.^{88,104}

Several mechanisms have been proposed to explain the abnormal apoptosis in cells exposed to statins. *In vitro* studies on human primary skeletal muscle cells identified calpain, a calcium-dependent protease implicated in a variety of cellular processes such as signal transduction, cell proliferation, cell cycle progression, differentiation, and apoptosis,¹⁰⁵ as a plausible upstream effector for the statin-induced initiation of the intrinsic apoptotic pathway, which is only partially dependent on mevalonate depletion.¹⁰⁶ In fact, statin-induced calpain activation could be subsequent to increased Ca²⁺ sarcoplasmic concentration, as discussed previously, and is responsible for Bax translocation to the outer mitochondrial membrane (OMM), leading to cytochrome *c* release into the cytosol and eventually to apoptosome assembly and activation of the caspases cascade.¹⁰⁶

Accumulation of ROS as a consequence of ETC impairment could contribute to inducing mitochondria-mediated apoptosis.^{88,107} Treatment with 10 mg/kg/day atorvastatin for 2 weeks suggests that statin-induced muscle cell apoptosis could be strictly dependent on the muscle fibre's metabolic phenotype. However, administration of quercetin, an antioxidant agent, resulted in apoptosis inhibition in fast glycolytic skeletal muscle fibres.¹⁰⁷ On the other hand, pretreatment with atorvastatin was able to protect human chondrocytes from high-glucose oxidative stress, by inducing expression of antioxidant enzymes, reducing ROS levels, and down-regulating the Bax/Bcl-2 ratio and caspase-3 activation.¹⁰⁸ Altogether, these findings imply that the differential cellular response to oxidative stress is an important determinant of tissue susceptibility to statins not only in terms of mitochondrial function but also in terms of apoptosis induction, according with the aforementioned concept of mitochondrial hormesis.⁷⁰

Impairment of mitochondrial energy production affects isoprenoid biosynthesis. Statin treatment leads to depletion of isoprenoids compounds, such as farnesyl pyrophosphate and geranylgeranyl pyrophosphate, as a consequence of the blockade on the mevalonate pathway.¹⁴ Protein farnesylation and geranylgeranylation are essential reactions for maintaining cellular homeostasis.¹⁰⁹ Depletion of isoprenoids may have a role in statin-related apoptosis induction, because HMG-CoA—but not squalene synthase inhibition—resulted in myotoxicity.^{104,110,111} Isoprenoid depletion is likely to cause abnormal activation of γ -phospholipase C and PI3K signalling pathways,^{89,112,113} thus leading to alteration in

calcium metabolism with the related detrimental consequences.¹⁰⁴ Finally, statins might alter the phosphorylation state of Akt by interfering with pathways involved in cell survival.^{83,84} Despite a large amount of *in vitro* experiments, very few *in vivo* studies are currently available about the apoptotic effects of statins.

Genetic background influences susceptibility to statin-associated symptoms

Polymorphisms on genes encoding for proteins involved in mitochondrial processes can modify the cell susceptibility to statin mitochondrial adverse effects. In fact, subclinical genetic mutations or polymorphisms have been associated with higher risk of SAS and SAMS.¹¹⁴ Polymorphisms on gene *COQ2*, encoding for an enzyme involved in endogenous ubiquinone biosynthesis, have been associated to SAS and SAMS.¹¹⁵ Similar findings have been reported for *ATP2B1*, encoding for a calcium transporting ATPase, and *DMPK*, encoding for a protein kinase with pathogenic implications in myotonic dystrophy.¹¹⁶

GATM gene

The *GATM* gene encodes for the mitochondrial enzyme glycine amidinotransferase, which is the rate-limiting enzyme in creatine biosynthesis.¹¹⁷ In a study carried out on lymphoblastoid cells of 480 statin-treated individuals, acute *in vitro* administration of simvastatin was associated with reduced gene expression levels and with reduced creatine synthesis in carriers of the rs9806699 single nucleotide polymorphism.¹¹⁸ Moreover, the minor *GATM* allele, which is responsible for a reduced creatine yield, was associated with lower SIM rates but not with CK concentration in two different populations treated with 40 mg/day simvastatin for 6 weeks.¹¹⁸ Although no causal mechanism can be inferred, it was speculated that reduced phosphocreatine storage impairs adenosine monophosphate-activated protein kinase signalling, in a way that could be protective against glucose and/or cholesterol deprivation.^{118,119} However, these data were not replicated in subsequent studies.^{120,121} Areas of uncertainty still exist on this topic.

Mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes syndrome

Mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes syndrome is an archetypical model of mitochondrial genome inheritable disease. Because all mtDNA genes encode

for mitochondrial proteins, these pathologies are characterized by dysfunctions in organs and tissues with high-energy requirements.¹²² Statin treatment has been shown to disclose several cases of previously asymptomatic mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes syndrome, possibly as a consequence of reduction in mitochondrial number and volume^{79,123} or as a consequence of CoQ10 depletion,^{123,124} as discussed previously.

Carnitine palmitoyltransferase-2 deficiency

Carnitine palmitoyltransferase-2 (CPT-2) is an IMM enzyme that allows acyl-CoA to undergo β -oxidation in mitochondrial matrix. CPT-2 deficiency is the most common disorder of lipid metabolism and shows up with recurrent myalgia, rhabdomyolysis, and myoglobinuria that is precipitated by physical exercise, cold, infections, emotional stress, or fasting, usually during adulthood. Laboratory tests display high plasma acylcarnitine levels and acylcarnitine/carnitine ratio.¹²⁵ Such laboratory findings were found in a rabbit model treated with 30 mg/day lovastatin for 16 weeks, whereas the liver, heart, and skeletal muscle carnitine concentrations decreased after treatment. Interestingly, CPT-2 activity was significantly increased in the heart and liver but not in skeletal muscle.¹²⁶ In a case-control study, the frequency of the CPT-2 heterozygous mutation was 13-fold higher over the expected general population rate in patients affected by SIM. Statin treatment in those patients could be responsible for an impairment in CPT-2 activity, leading to a critical reduction of the enzyme overall activity and eliciting homozygous-like clinical manifestations.¹¹⁴ These results corroborate the hypothesis that statin-induced mitochondrial dysfunction could also occur as impaired fatty acid oxidation, as suggested by histopathological findings.⁵⁷ The abnormally increased respiratory exchange ratio in patients who had experienced myositis¹²⁷ but not in those without SAMS¹²⁸ provides further evidence. Moreover, in high-fat-fed apoE knockout mice experiencing impaired exercise training adaptation after statin treatment, the administration of trimetazidine, a β -oxidation inhibitor, was successful in reversing statin-induced muscle injury,¹²⁹ suggesting that lipid metabolism disruption could be one of the several pathological mechanisms for SAMS.

Statin-induced diabetes and mitochondrial function

In the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER), the use of pravastatin (40 mg/day) in old patients was associated with an increased incidence of T2DM.¹³⁰ Similarly, in the Justification for the Use of Statins in Primary

Prevention: Intervention Trial Evaluating Rosuvastatin (JUPITER) trial, a significantly higher incidence of new-onset diabetes occurred in the rosuvastatin group when compared with the placebo group during the 2 years of statin administration.¹³¹ A large meta-analysis of 13 trials including 91 140 patients reported a significant 9% increase in the risk of T2DM among patients treated with statins.¹³² Because of these findings, FDA imposed to report the risk of new-onset diabetes on statin safety labels.

In an experimental setting, rats treated with 80 mg/kg/day lovastatin or 20 mg/kg/day atorvastatin for 2 weeks displayed increased glucose levels and decreased insulin secretion compared with controls.¹³³ Statin-treated rats also showed increased pancreatic cells ROS production, disrupted membrane potential, mitochondrial swelling, and reduced complex IV activity.¹³³ Administration of CoQ10 and L-carnitine separately or together was able to partially but significantly blunt these statin-induced abnormalities.¹³³

We herein discuss the mitochondria-related mechanisms potentially explaining the increased risk of T2DM in statin-treated patients.

Impaired insulin secretion

ATP levels are crucial in beta cells because they regulate the K_{ATP} channel closure that leads to cell depolarization and to insulin secretion. Mitochondrial dysfunction in beta cells could impair insulin secretion.¹³⁴ In a study on human pancreatic islets and in rat insulinoma INS-1 cells, atorvastatin—but not pravastatin—impaired both basal and glucose-induced insulin secretion.¹³⁵ This phenomenon is likely to be attributed to a significant decrease in ATP basal levels and ATP production rate, which is subsequent to a time and dose-dependent reduction in complexes I, III, and IV, and ATP synthase expression in atorvastatin-exposed cells.¹³⁵ Both mevalonate administration and *N*-acetylcysteine, an antioxidant agent, were able to rescue the impaired insulin secretion in statin-exposed cells.¹³⁵ In rat isolated pancreatic mitochondria, exposure to $>75 \mu\text{M}$ atorvastatin significantly impaired complex II activity and reduced ATP levels.¹³⁶

Nevertheless, experiments with patch clamping suggested that statins might impair insulin secretion by inhibiting L-type voltage-dependent Ca^{2+} channel as well, preventing the Ca^{2+} cytosolic concentration increase that is fundamental for insulin secretion.¹³⁷ The contrasting results obtained with atorvastatin and pravastatin account for their different diabetogenic potential.¹³⁸

Atorvastatin exposure determined a significant increase in ROS levels both in human pancreatic islets and in INS-1 rat insulinoma cells¹³⁵ and in rat isolated pancreatic mitochondria¹³⁶ in a time and dose-dependent manner. Because pancreatic beta cells have weak antioxidant systems, oxidative stress may be crucial for beta-cell dysfunction, thus

increasing the risk of new-onset diabetes during statin treatment.¹³⁶

Finally, CoQ10 concentration was reduced by atorvastatin administration as well, leading to ETC activity impairment.¹³⁵ As a consequence of ETC activity disruption, atorvastatin caused a decline in mitochondrial membrane potential, mitochondrial swelling, and cytochrome *c* release,¹³⁶ thus leading to intrinsic apoptosis induction in the pancreas.

Peripheral insulin resistance

Statins could also induce peripheral insulin resistance via different pathways. Simvastatin determined a reduction in insulin-dependent glucose transporter GLUT4 expression in 3T3-L1 adipocytes, and this phenomenon could be rescued by CoQ10 administration.¹³⁹ The accumulation of non-esterified fatty acids in skeletal muscle cells is responsible for insulin resistance.¹⁴⁰ Mitochondrial uncoupling protein (UCP)-3 is a protein located in the IMM that acts as a fatty acid carrier, favouring their β -oxidation.¹⁴¹ Patients affected by T2DM show lower expression of UCP3.¹⁴² A case-control study pointed out a significantly reduced UCP3 expression in patients treated with simvastatin.¹⁴³ The complex relationship among statins, UCP3, and insulin resistance has not been fully clarified yet. Though no causative mechanisms can be inferred, it can be hypothesized that statins could play a role in determining skeletal muscle insulin resistance by down-regulating UCP3 expression.

Cognitive impairment and dementia

Many studies have been published in the last two decades about the relationship between statin treatment and cognitive function. Like skeletal muscle, brain tissue has a high metabolic demand and hence suffers from mitochondrial vulnerability.¹⁴⁴

A large retrospective study showed an increased risk for both Alzheimer's disease and vascular dementia in hypercholesterolaemic patients after a three-decade follow-up.¹⁴⁵

Intriguingly, several case reports^{146,147} and two randomized controlled trials^{148,149} suggested a potential association between statin treatment and cognitive impairment, leading FDA to include in the warning section of all statin labels a statement about the risk for reversible memory loss or impairment. Contrariwise, large trials,^{130,150} a Cochrane database systematic review,¹⁵¹ a consensus statement by the Statin Cognitive Safety Task Force,¹⁵² and more recent meta-analyses^{153,154} failed to demonstrate any effect of statin treatment on cognitive function, while a large meta-analysis even showed a great risk reduction for dementia associated with statin treatment.¹⁵⁵ An extensive and

punctual review about the state of the art on this topic has been recently published.¹⁵⁶

It is plausible that these contradicting results derive from different mechanisms that might be responsible for both cognitive protective effect of statins and treatment-related adverse cognitive effects.¹⁵⁶

In terms of mitochondrial function, the pathological basis for these contradictory results is completely to be elucidated. It is conceivable that the mechanisms implicated in SAMS, such as CoQ10 depletion, ROS accumulation, and mitochondrial membrane depolarization, could account for cognitive impairment too. Accordingly, genetic disorders, dysthyroidisms, or the metabolic syndrome, which all underlie mitochondrial dysfunction, are well-known risk factors for statin-related cognitive adverse effects.^{15,157} However, it must be underlined that simvastatin was able to protect a neuroblastoma cell line (i.e. SH-SY5Y) from amyloid- β neurotoxicity by improving several aspects of mitochondrial function (e.g. cytochrome *c* release, ROS production, Bcl-2/Bax ratio, and membrane potential).¹⁵⁸ In addition, in a cellular model of mitochondrial dysfunction (i.e. cybrid), low-dose (1 μ M) simvastatin reduced hypoxia-inducible factor 1 α and β -site amyloid precursor protein cleaving enzyme, the latter molecules promoting amyloid- β production. However, higher dose of simvastatin (10 μ M) increased hypoxia-inducible factor 1 α and β -site amyloid precursor protein cleaving enzyme expression both in the cybrid and control cell models,¹⁵⁹ thus suggesting that statin dose might differentially affect neuronal function irrespective of mitochondrial activity.

Conclusions

Besides the well-known beneficial effects in primary and secondary prevention of CVD, statins may induce adverse effects, like myopathy. Mitochondrial dysfunction is likely to play an important role in the pathogenesis of these adverse reactions due to CoQ10 depletion, inhibition of ETC complexes, depletion of mevalonate pathway end products,

membrane depolarization and induction of intrinsic apoptosis, dysregulation of calcium metabolism, and fatty acid oxidation. Chronic statin treatment has been associated with increased risk for T2DM and cognitive impairment. The beneficial effects of statin treatment are not questionable; however, the widespread usage of these drugs and the considerable prevalence of side effects require the underlying pathological mechanisms to be carefully studied.

Acknowledgements

The authors certify that they comply with the ethical guidelines for publishing in the *Journal of Cachexia, Sarcopenia and Muscle*.¹⁶⁰ The authors also thank Dr Andy Gitsham for his help in editing the manuscript.

Conflict of interest

Dr M.B. has served on the speakers bureau of Abbott/Mylan, Abbott Vascular, Actavis, Akcea, Amgen, Biofarm, KRKA, MSD, Sanofi-Aventis, Servier, and Valeant and has served as a consultant to Abbott Vascular, Akcea, Amgen, Daichii Sankyo, Esperion, Lilly, MSD, Resverlogix, and Sanofi-Aventis; he also received grants from Sanofi and Valeant. S.v.H. has been a paid consultant for and/or received honoraria payments from Bayer, Boehringer Ingelheim, BRAHMS, Chugai, Grünenthal, Helsinn, Hexal, ovartis, Respicardia, Roche, Sorin, and Vifor; owns shares in Actimed. SvH; and reports research support from IMI and the German Center for Cardiovascular Research (DZHK).

Other authors have no competing interests to declare.

Funding

None.

References

- Mensah GA, Roth GA, Fuster V. The global burden of cardiovascular diseases and risk factors. *J Am Coll Cardiol* 2019;**74**:2529–2532.
- Forouzanfar MH, Afshin A, Alexander LT, Anderson HR, Bhutta ZA, Biryukov S, et al. Global, regional, and national comparative risk assessment of 79 behavioural, environmental and occupational, and metabolic risks or clusters of risks, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet* 2016;**388**:1659–1724.
- Sampson UK, Fazio S, Linton MF. Residual cardiovascular risk despite optimal LDL cholesterol reduction with statins: the evidence, etiology, and therapeutic challenges. *Curr Atheroscler Rep* 2012;**14**:1–10.
- Ference BA, Ginsberg HN, Graham I, Ray KK, Packard CJ, Bruckert E, et al. Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European Atherosclerosis Society Consensus Panel. *Eur Heart J* 2017;**38**:2459–2472.
- Ference BA, Majeed F, Penumetcha R, Flack JM, Brook RD. Effect of naturally random allocation to lower low-density lipoprotein cholesterol on the risk of coronary heart disease mediated by polymorphisms in NPC1L1, HMGCR, or both. *J Am Coll Cardiol* 2015;**65**:1552–1561.
- Kapur NK, Musunuru K. Clinical efficacy and safety of statins in managing cardiovascular risk. *Vasc Health Risk Manag* 2008;**4**:341–353.

7. Franklin BA, Durstine JL, Roberts CK, Barnard RJ. Impact of diet and exercise on lipid management in the modern era. *Best Pract Res Clin Endocrinol Metab* 2014;**28**:405–421.
8. Pirro M, Vetrani C, Bianchi C, Mannarino MRR, Bernini F, Rivellese AAA. Joint position statement on “Nutraceuticals for the treatment of hypercholesterolemia” of the Italian Society of Diabetology (SID) and of the Italian Society for the Study of Arteriosclerosis (SISA). *Nutr Metab Cardiovasc Dis* 2017;**27**:2–17.
9. Bianconi V, Mannarino MR, Sahebkar A, Cosentino T, Pirro M. Cholesterol-lowering nutraceuticals affecting vascular function and cardiovascular disease risk. *Curr Cardiol Rep* 2018;**20**:53.
10. Pirro M, Mannarino MR, Bianconi V, Simental-Mendía LE, Bagaglia F, Mannarino E, et al. The effects of a nutraceutical combination on plasma lipids and glucose: a systematic review and meta-analysis of randomized controlled trials. *Pharmacol Res* 2016;**110**:76–88.
11. Johnston TP, Korolenko TA, Pirro M, Sahebkar A. Preventing cardiovascular heart disease: promising nutraceutical and non-nutraceutical treatments for cholesterol management. *Pharmacol Res* 2017;**120**:219–225.
12. Sahebkar A, Simental-Mendía LE, Reiner Ž, Kovanen PT, Simental-Mendía M, Bianconi V, et al. Effect of orlistat on plasma lipids and body weight: a systematic review and meta-analysis of 33 randomized controlled trials. *Pharmacol Res* 2017;**122**:53–65.
13. Endo A, Kuroda M, Tsujita Y. ML-236A, ML-236B, and ML-236C, new inhibitors of cholesterol synthesis produced by penicillium citrinum. *J Antibiot (Tokyo)* 1976;**29**:1346–1348.
14. Stancu C, Sima A. Statins: mechanism of action and effects. *J Cell Mol Med* 2001;**5**:378–387.
15. Golomb BA, Evans MA. Statin adverse effects. *Am J Cardiovasc Drugs* 2008;**8**:373–418.
16. Sahebkar A, Serban C, Ursoniu S, Mikhailidis DP, Undas A, Lip GYH, et al. The impact of statin therapy on plasma levels of von Willebrand factor antigen. *J Thromb Haemost* 2016;**115**:03:520–532. <https://doi.org/10.1160/th15-08-0620>
17. Afshari AR, Mollazadeh H, Henney NC, Jamialahmad T, Sahebkar A. Effects of statins on brain tumors: a review. *Sem Cancer Biol* 2020. <https://doi.org/10.1016/j.semcancer.2020.08.002>
18. Bagheri H, Ghasemi F, Barreto GE, Sathiyapalan T, Jamialahmadi T, Sahebkar A. The effects of statins on microglial cells to protect against neurodegenerative disorders: A mechanistic review. *BioFactors* 2020;**46**:3:309–325. <https://doi.org/10.1002/biof.1597>
19. Parizadeh SMR, Azarpazhooh MR, Moohebbati M, Nematy M, Ghayour-Mobarhan M, Tavallaie S, et al. Simvastatin therapy reduces prooxidant-antioxidant balance: results of a placebo-controlled cross-over trial. *Lipids* 2011;**46**:333–340.
20. Chruściel P, Sahebkar A, Rembek-Wieliczko P, Serban M-C, Ursoniu S, Mikhailidis DP, et al. Impact of statin therapy on plasma adiponectin concentrations: a systematic review and meta-analysis of 43 randomized controlled trial arms. *Atherosclerosis* 2016;**253**:194–208.
21. Mohammadzadeh N, Montecucco F, Carbone F, Xu S, Al-Rasadi K, Sahebkar A. Statins: Epidrugs with effects on endothelial health? *Eur J Clin Invest* 2020;**50**:12. <https://doi.org/10.1111/eci.13388>
22. Calabrò P, Yeh ETH. The pleiotropic effects of statins. *Curr Opin Cardiol* 2005;**20**:541–546.
23. Li M, Losordo DW. Statins and the endothelium. *Vascul Pharmacol* 2007;**46**:1–9.
24. Blanco-Colio LM, Tuñón J, Martín-Ventura JL, Egido J. Anti-inflammatory and immunomodulatory effects of statins. *Kidney Int* 2003;**63**:12–23.
25. Stoll LL, McCormick ML, Denning GM, Weintraub NL. Antioxidant effects of statins. *Drugs of Today* 2004;**40**:975–990.
26. Mahley RW, Berson TP. Drug therapy for hypercholesterolemia and dyslipidemia. *Goodman Gilman's Pharmacol Basis Ther* 2006;933–966.
27. Gazzerro P, Proto MC, Gangemi G, Malfitano AM, Ciaglia E, Pisanti S, et al. Pharmacological actions of statins: a critical appraisal in the management of cancer. *Pharmacology* 2012;**64**:102–146.
28. McTaggart F. Comparative pharmacology of rosuvastatin. *Atheroscler Suppl* 2003;**4**:9–14.
29. Thompson PD, Panza G, Zaleski A, Taylor B. Statin-associated side effects. *J Am Coll Cardiol* 2016;**67**:2395–2410.
30. Lemstra M, Blackburn D, Crawley A, Fung R. Proportion and risk indicators of nonadherence to statin therapy: a meta-analysis. *Can J Cardiol* 2012;**28**:574–580.
31. Mann DM, Woodward M, Muntner P, Falzon L, Kronish I. Predictors of nonadherence to statins: a systematic review and meta-analysis. *Ann Pharmacother* 2010;**44**:1410–1421.
32. Maningat P, Gordon BR, Breslow JL. How do we improve patient compliance and adherence to long-term statin therapy? *Curr Atheroscler Rep* 2013;**15**:291.
33. Venturini CD, Engroff P, Ely LS, de Araújo Zago LF, Schroeter G, Gomes I, et al. Gender differences, polypharmacy, and potential pharmacological interactions in the elderly. *Clinics* 2011;**66**:1867–1872.
34. Apostolopoulou M, Corsini A, Roden M. The role of mitochondria in statin-induced myopathy. *Eur J Clin Invest* 2015;**45**:745–754.
35. Auer J, Sinzinger H, Franklin BARRY, Berent R. Muscle- and skeletal-related side-effects of statins: tip of the iceberg? *Eur J Prev Cardiol* 2016;**23**:88–110.
36. Scott RS, Lintott CJ, Wilson MJ. Simvastatin and side effects. *N Z Med J* 1991;**104**:493–495.
37. Wierzbicki AS, Lumb PJ, Semra Y, Chik G, Christ ER, Crook MA. Atorvastatin compared with simvastatin-based therapies in the management of severe familial hyperlipidaemias. *QJM* 1999;**92**:387–394.
38. Stroes ES, Thompson PD, Corsini A, Vladutiu GD, Raal FJ, Ray KK, 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.
39. Thompson PD. In Thompson PD, Taylor BA, eds. *The Clinical Presentation of Statin-Associated Muscle Symptoms (SAMS)*. Cham: Springer; 2020. p 21–26.
40. Zaleski AL, Taylor BA, Thompson PD. Coenzyme Q10 as treatment for statin-associated muscle symptoms—a good idea, but *Adv Nutr* 2018;**9**:519S–523S.
41. Parker BA, Capizzi JA, Grimaldi AS, Clarkson PM, Cole SM, Keadle J, et al. Effect of statins on skeletal muscle function. *Circulation* 2013;**127**:96–103.
42. Krishnan GM, Thompson PD. The effects of statins on skeletal muscle strength and exercise performance. *Curr Opin Lipidol* 2010;**21**:324–328.
43. Thompson PD, Clarkson P, Karas RH. Statin-associated myopathy. *JAMA* 2003;**289**:1681–1690.
44. Toth PP, Harper CR, Jacobson TA. Clinical characterization and molecular mechanisms of statin myopathy. *Expert Rev Cardiovasc Ther* 2008;**6**:955–969.
45. Magni P, Macchi C, Morlotti B, Sirtori CR, Ruscica M. Risk identification and possible countermeasures for muscle adverse effects during statin therapy. *Eur J Intern Med* 2015;**26**:82–88.
46. McKenney JM, Davidson MH, Jacobson TA, Guyton JR. Final conclusions and recommendations of the National Lipid Association Statin Safety Assessment Task Force. *Am J Cardiol* 2006;**97**:S89–S94.
47. Pasternak RC, Smith SC, Bairey-Merz CN, Grundy SM, Cleeman JI, Lenfant C. ACC/AHA/NHLBI clinical advisory on the use and safety of statins. *Circulation* 2002;**106**:1024–1028.
48. Maji D, Shaikh S, Solanki D, Gaurav K. Safety of statins. *Indian J Endocrinol Metab* 2013;**17**:636. <https://doi.org/10.4103/2230-8210.113754>
49. Newman CB, Tobert JA. Statin-related myopathy and rhabdomyolysis. *Endocr Metab Med* 2018;**760**–774.
50. Chavez LO, Leon M, Einav S, Varon J. Beyond muscle destruction: a systematic review of rhabdomyolysis for clinical practice. *Crit Care* 2016;**20**:135.
51. Bindoff L. Mitochondria and the heart. *Eur Heart J* 2003;**24**:221–224.
52. Rich PR, Maréchal A. The mitochondrial respiratory chain. *Essays Biochem* 2010;**47**:1–23.

53. Brookes PS. Mitochondrial H⁺ leak and ROS generation: an odd couple. *Free Radic Biol Med* 2005;**38**:12–23.
54. Raha S, Robinson BH. Mitochondria, oxygen free radicals, disease and ageing. *Trends Biochem Sci* 2000;**25**:502–508.
55. Chan K, Truong D, Shangari N, O'Brien PJ. Drug-induced mitochondrial toxicity. *Expert Opin Drug Metab Toxicol* 2005;**1**:655–669.
56. Arenas J, Fernández-Moreno MA, Molina JA, Fernández V, Del Hoyo P, Campos Y, et al. Myoglobinuria and COX deficiency in a patient taking cerivastatin and gemfibrozil. *Neurology* 2003;**60**:124–126.
57. 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**:581–585.
58. De Pinieux G, Chariot P, Ammi-Saïd 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* 2003;**42**:333–337.
59. Wu JS, Buettner C, Smithline H, Ngo LH, Greenman RL. Evaluation of skeletal muscle during calf exercise by 31-phosphorus magnetic resonance spectroscopy in patients on statin medications. *Muscle Nerve* 2011;**43**:76–81.
60. Liantonio A, Giannuzzi V, Cippone V, Camerino GM, Pierno S, Camerino DC. Fluvastatin and atorvastatin affect calcium homeostasis of rat skeletal muscle fibers in vivo and in vitro by impairing the sarcoplasmic reticulum/mitochondria Ca²⁺-release system. *J Pharmacol Exp Ther* 2007;**321**:626–634.
61. Asping M, Stride N, Søggaard D, Dohlmann TL, Helge JW, Dela F, et al. The effects of 2 weeks of statin treatment on mitochondrial respiratory capacity in middle-aged males: the LIFESTAT study. *Eur J Clin Pharmacol* 2017;**73**:679–687.
62. Galtier F, Mura T, Raynaud de Mauverger E, Chevassus H, Farret A, Gagnol J-P, et al. Effect of a high dose of simvastatin on muscle mitochondrial metabolism and calcium signaling in healthy volunteers. *Toxicol Appl Pharmacol* 2012;**263**:281–286.
63. Hou T, Li Y, Chen W, Heffner RR, Vladutiu GD. Histopathologic and biochemical evidence for mitochondrial disease among 279 patients with severe statin myopathy. *J Neuromuscul Dis* 2017;**4**:77–87.
64. Marcoff L, Thompson PD. The role of coenzyme Q10 in statin-associated myopathy. *J Am Coll Cardiol* 2007;**49**:2231–2237.
65. Garrido-Maraver J, Cordero MD, Oropesa-Ávila M, Fernández Vega A, de la Mata M, Delgado Pavón A, et al. Coenzyme Q₁₀ therapy. *Mol Syndromol* 2014;**5**:187–197.
66. Sahebkar A, Simental-Mendia LE, Stefanutti C, Pirro M. Supplementation with coenzyme Q10 reduces plasma lipoprotein(a) concentrations but not other lipid indices: a systematic review and meta-analysis. *Pharmacol Res* 2016;**105**:198–209.
67. Åberg F, Appelkvist EL, Dallner G, Ernster L. Distribution and redox state of ubiquinones in rat and human tissues. *Arch Biochem Biophys* 1992;**295**:230–234.
68. Salviati L, Trevisson E, Doimo M, Navas P. Primary Coenzyme Q10 Deficiency. In Pagon RA, Adam MP, Ardinger HH, Wallace SE, Amemiya A, Bean LH, et al., eds. *GeneReviews*®. Seattle, WA: University of Washington; 2017.
69. Saha SP, Whyne TF. Coenzyme Q10 in human health: supporting evidence? *South Med J* 2016;**109**:17–21.
70. Bouitbir J, Charles A-L, Echaniz-Laguna A, Kindo M, Daussin F, Auwerx J, et al. Opposite effects of statins on mitochondria of cardiac and skeletal muscles: a 'mitohormesis' mechanism involving reactive oxygen species and PGC-1. *Eur Heart J* 2012;**33**:1397–1407.
71. Kaufmann P, Török M, Zahno A, Waldhauser KM, Brecht K, Krähenbühl S. Toxicity of statins on rat skeletal muscle mitochondria. *Cell Mol Life Sci* 2006;**63**:2415–2425.
72. 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**:60–68.
73. du Souich P, Roederer G, Dufour R. Myotoxicity of statins: mechanism of action. *Pharmacol Ther* 2017;**175**:1–16.
74. Laaksonen R, Jokelainen K, Laakso J, Sahi T, Härkönen 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**:851–854.
75. 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**:62–66.
76. Lamperti C, Naini AB, Lucchini V, Prella A, Bresolin N, Moggi M, et al. Muscle coenzyme Q10 level in statin-related myopathy. *Arch Neurol* 2005;**62**:1709–1712.
77. Banach M, Serban C, Sahebkar A, Ursoniu S, Rysz J, Muntner P, et al. Effects of coenzyme Q10 on statin-induced myopathy: a meta-analysis of randomized controlled trials. *Mayo Clin Proc* 2015;**90**:24–34.
78. Qu H, Guo M, Chai H, Wang W, Gao Z, Shi D. Effects of coenzyme Q10 on statin-induced myopathy: an updated meta-analysis of randomized controlled trials. *J Am Heart Assoc* 2018;**7**:e009835.
79. Schick BA, Laaksonen R, Frohlich JJ, Päivä H, Lehtimäki T, Humphries KH, et al. Decreased skeletal muscle mitochondrial DNA in patients treated with high-dose simvastatin. *Clin Pharmacol Ther* 2007;**81**:650–653.
80. Stringer HAJ, Sohi GK, Maguire JA, Côté HCF. Decreased skeletal muscle mitochondrial DNA in patients with statin-induced myopathy. *J Neurol Sci* 2013;**325**:142–147.
81. Mikus CR, Boyle LJ, Borengasser SJ, Oberlin DJ, Naples SP, Fletcher J, et al. Simvastatin impairs exercise training adaptations. *J Am Coll Cardiol* 2013;**62**:709–714.
82. Singla M, Rastogi A, Aggarwal AN, Bhat OM, Badal D, Bhansali A. Vitamin D supplementation improves simvastatin-mediated decline in exercise performance: a randomized double-blind placebo-controlled study. *J Diabetes* 2017;**9**:1100–1106.
83. Mullen PJ, Zahno A, Lindinger P, Maseneni S, Felser A, Krähenbühl S, et al. Susceptibility to simvastatin-induced toxicity is partly determined by mitochondrial respiration and phosphorylation state of Akt. *Biochim Biophys Acta – Mol Cell Res* 2011;**1813**:2079–2087.
84. Bonifacio A, Sanvee GM, Bouitbir J, Krähenbühl S. The AKT/mTOR signaling pathway plays a key role in statin-induced myotoxicity. *Biochim Biophys Acta – Mol Cell Res* 2015;**1853**:1841–1849.
85. Vaughan RA, Garcia-Smith R, Bisoffi M, Conn CA, Trujillo KA. Ubiquinol rescues simvastatin-suppression of mitochondrial content, function and metabolism: implications for statin-induced rhabdomyolysis. *Eur J Pharmacol* 2013;**711**:1–9.
86. Singh F, Zoll J, Duthaler U, Charles A-L, Panajatovic MV, Laverny G, et al. PGC-1 β modulates statin-associated myotoxicity in mice. *Arch Toxicol* 2019;**93**:487–504.
87. Liu A, Wu Q, Guo J, Ares I, Rodríguez J-L, Martínez-Larrañaga M-R, et al. Statins: adverse reactions, oxidative stress and metabolic interactions. *Pharmacol Ther* 2019;**195**:54–84.
88. Kwak H-B, Thalacker-Mercer A, Anderson EJ, Lin C-T, Kane DA, Lee N-S, et al. Simvastatin impairs ADP-stimulated respiration and increases mitochondrial oxidative stress in primary human skeletal myotubes. *Free Radic Biol Med* 2012;**52**:198–207.
89. Sirvent P, Mercier J, Lacampagne A. New insights into mechanisms of statin-associated myotoxicity. *Curr Opin Pharmacol* 2008;**8**:333–338.
90. Schirris TJJ, Renkema GH, Ritschel T, Voermans NC, Bilos A, van Engelen BGM, et al. Statin-induced myopathy is associated with mitochondrial complex III inhibition. *Cell Metab* 2015;**22**:399–407.
91. Sirvent P, Bordenave S, Vermaelen M, Roels B, Vassort G, Mercier J, et al. Simvastatin induces impairment in skeletal muscle while heart is protected. *Biochem Biophys Res Commun* 2005;**338**:1426–1434.
92. 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.

93. Schaefer WH, Lawrence JW, Loughlin AF, Stoffregen DA, Mixson JA, 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.
94. Duncan AJ, Hargreaves IP, Damian MS, Land JM, Heales SJR. Decreased ubiquinone availability and impaired mitochondrial cytochrome oxidase activity associated with statin treatment. *Toxicol Mech Methods* 2009;**19**:44–50.
95. Murlasits Z, Radák Z. The effects of statin medications on aerobic exercise capacity and training adaptations. *Sports Med* 2014;**44**:1519–1530.
96. Herminghaus A, Laser E, Schulz J, Truse R, Vollmer C, Bauer I, et al. Pravastatin and gemfibrozil modulate differently hepatic and colonic mitochondrial respiration in tissue homogenates from healthy rats. *Cell* 2019;**8**:983.
97. Ramachandran R, Wierzbicki A. Statins, muscle disease and mitochondria. *J Clin Med* 2017;**6**:75.
98. Sirvent P, Fabre O, Bordenave S, Hillaire-Buys D, Raynaud De Mauverger E, Lacampagne A, et al. Muscle mitochondrial metabolism and calcium signaling impairment in patients treated with statins. *Toxicol Appl Pharmacol* 2012;**259**:263–268.
99. Sirvent P, Mercier J, Vassort G, Lacampagne A. Simvastatin triggers mitochondria-induced Ca^{2+} signaling alteration in skeletal muscle. *Biochem Biophys Res Commun* 2005;**329**:1067–1075.
100. Taha DA, De Moor CH, Barrett DA, Lee JB, Gandhi RD, Hoo CW, et al. The role of acid-base imbalance in statin-induced myotoxicity. *Transl Res* 2016;**174**:140–160.e14.
101. Skottheim IB, Gedde-Dahl A, Hejazifar S, Hoel K, Åsberg A. Statin induced myotoxicity: the lactone forms are more potent than the acid forms in human skeletal muscle cells in vitro. *Eur J Pharm Sci* 2008;**33**:317–325.
102. Nakahara K, Yada T, Kuriyama M, Osame M. Cytosolic Ca^{2+} increase and cell damage in L6 rat myoblasts by HMG-CoA reductase inhibitors. *Biochem Biophys Res Commun* 1994;**202**:1579–1585.
103. Hermann M, Bogsrud MP, Molden E, Åsberg A, Mohebi BU, Ose L, et al. Exposure of atorvastatin is unchanged but lactone and acid metabolites are increased several-fold in patients with atorvastatin-induced myopathy. *Clin Pharmacol Ther* 2006;**79**:532–539.
104. Dirks AJ, Jones KM. Statin-induced apoptosis and skeletal myopathy. *Am J Physiol Physiol* 2006;**291**:C1208–C1212.
105. Suzuki K, Hata S, Kawabata Y, Sorimachi H. Structure, activation, and biology of calpain. *Diabetes* 2004;**53**:S12–S18.
106. Sacher J, Weigl L, Werner M, Szegeci C, Hohenegger M. Delineation of myotoxicity induced by 3-hydroxy-3-methylglutaryl CoA reductase inhibitors in human skeletal muscle cells. *J Pharmacol Exp Ther* 2005;**314**:1032–1041.
107. Bouitbir J, Singh F, Charles A-L, Schlagowski A-I, Bonifacio A, Echaniz-Laguna A, et al. Statins trigger mitochondrial reactive oxygen species-induced apoptosis in glycolytic skeletal muscle. *Antioxid Redox Signal* 2016;**24**:84–98.
108. Hosseinzadeh A, Bahrampour Juybari K, Kamarul T, Sharifi AM. Protective effects of atorvastatin on high glucose-induced oxidative stress and mitochondrial apoptotic signaling pathways in cultured chondrocytes. *J Physiol Biochem* 2019;**75**:153–162.
109. Novelli G, D'Apice MR. Protein farnesylation and disease. *J Inherit Metab Dis* 2012;**35**:917–926.
110. Guijarro C, Blanco-Colio LM, Ortego M, Alonso C, Ortiz A, Plaza JJ, et al. 3-Hydroxy-3-methylglutaryl coenzyme A reductase and isoprenylation inhibitors induce apoptosis of vascular smooth muscle cells in culture. *Circ Res* 1998;**83**:490–500.
111. Johnson TE, Zhang X, Bleicher KB, Dysart G, Loughlin AF, Schaefer WH, et al. Statins induce apoptosis in rat and human myotube cultures by inhibiting protein geranylgeranylation but not ubiquinone. *Toxicol Appl Pharmacol* 2004;**200**:237–250.
112. Mutoh T, Kumano T, Nakagawa H, Kuriyama M. Involvement of tyrosine phosphorylation in HMG-CoA reductase inhibitor-induced cell death in L6 myoblasts. *FEBS Lett* 1999;**444**:85–89.
113. Mutoh T, Kumano T, Nakagawa H, Kuriyama M. Role of tyrosine phosphorylation of phospholipase C γ 1 in the signaling pathway of HMG-CoA reductase inhibitor-induced cell death of L6 myoblasts. *FEBS Lett* 1999;**446**:91–94.
114. 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**:153–162.
115. Oh J, Ban MR, Miskie BA, Pollex RL, Hegele RA. Genetic determinants of statin intolerance. *Lipids Health Dis* 2007;**6**:7.
116. Rúaño G, Windemuth A, Wu AHB, Kane JP, Malloy MJ, Pullinger CR, et al. Mechanisms of statin-induced myalgia assessed by physiogenomic associations. *Atherosclerosis* 2011;**218**:451–456.
117. Humm A, Pritsche E, Steinbacher S. Structure and reaction mechanism of L-arginine:glycine amidinotransferase. *Biol Chem* 1997;**193**–197.
118. Mangravite LM, Engelhardt BE, Medina MW, Smith JD, Brown CD, Chasman DI, et al. A statin-dependent QTL for GATM expression is associated with statin-induced myopathy. *Nature* 2013;**502**:377–380.
119. Ballard KD, Thompson PD. Does reduced creatine synthesis protect against statin myopathy? *Cell Metab* 2013;**18**:773–774.
120. Floyd JS, Bis JC, Brody JA, Heckbert SR, Rice K, Psaty BM. GATM locus does not replicate in rhabdomyolysis study. *Nature* 2014;**513**:E1–E3.
121. Carr DF, Alfirevic A, Johnson R, Chinoy H, van Staa T, Pirmohamed M. GATM gene variants and statin myopathy risk. *Nature* 2014;**513**:E1–E1.
122. Schon EA, Bonilla E, DiMauro S. Mitochondrial DNA mutations and pathogenesis. *J Bioenerg Biomembr* 1997;**29**:131–149.
123. Ghatak A, Faheem O, Thompson PD. The genetics of statin-induced myopathy. *Atherosclerosis* 2010;**210**:337–343.
124. Chariot P, Abadia R, Agnus D, Danan C, Charpentier C, Gherasdi RK. Simvastatin-induced rhabdomyolysis followed by a MELAS syndrome. *Am J Med* 1993;**94**:109–110.
125. Bonnefont JP, Djouadi F, Prip-Buus C, Gobin S, Munnich A, Bastin J. Carnitine palmitoyltransferases 1 and 2: biochemical, molecular and medical aspects. *Mol Aspects Med* 2004;**25**:495–520.
126. 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**:867–870.
127. Phillips PS, Phillips CT, Sullivan MJ, Naviaux RK, Haas RH. Statin myotoxicity is associated with changes in the cardiopulmonary function. *Atherosclerosis* 2004;**177**:183–188.
128. Traustadóttir T, Stock AA, Harman SM. High-dose statin use does not impair aerobic capacity or skeletal muscle function in older adults. *Age (Omaha)* 2008;**30**:283–291.
129. Song M, Chen F, Li Y, Zhang L, Wang F, Qin R, et al. Trimetazidine restores the positive adaptation to exercise training by mitigating statin-induced skeletal muscle injury. *J Cachexia Sarcopenia Muscle* 2018;**9**:106–118.
130. Shepherd J, Blauw GJ, Murphy MB, Bollen ELEM, Buckley BM, Cobbe SM, et al. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. *Lancet* 2002;**360**:1623–1630.
131. Ridker PM, Danielson E, Fonseca FAH, Genest J, Gotto AM, Kastelein JJP, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med* 2008;**359**:2195–2207.
132. Sattar N, Preiss D, Murray HM, Welsh P, Buckley BM, de Craen AJ, et al. Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials. *Lancet* 2010;**375**:735–742.
133. Sadighara M, Joktaji J, Hajhashemi V, Minaiyan M. Protective effects of coenzyme Q 10 and L-carnitine against statin-induced pancreatic mitochondrial toxicity in rats. *Res Pharm Sci* 2017;**12**:434.
134. Supale S, Li N, Brun T, Maechler P. Mitochondrial dysfunction in pancreatic β cells. *Trends Endocrinol Metab* 2012;**23**:477–487.
135. Urbano F, Bugliani M, Filippello A, Scamporrino A, Di Mauro S, Di Pino A,

- et al. Atorvastatin but not pravastatin impairs mitochondrial function in human pancreatic islets and rat β -cells. Direct effect of oxidative stress. *Sci Rep* 2017;**7**:11863.
136. Sadighara M, Amirshardost Z, Minaiyan M, Hajhashemi V, Naserzadeh P, Salimi A, et al. Toxicity of atorvastatin on pancreas mitochondria: a justification for increased risk of diabetes mellitus. *Basic Clin Pharmacol Toxicol* 2017;**120**:131–137.
 137. Yada T, Nakata M, Shiraiishi T, Kakei M. Inhibition by simvastatin, but not pravastatin, of glucose-induced cytosolic Ca^{2+} signalling and insulin secretion due to blockade of L-type Ca^{2+} channels in rat islet β -cells. *Br J Pharmacol* 1999;**126**:1205–1213.
 138. Cederberg H, Stančáková A, Yaluri N, Modi S, Kuusisto J, Laakso M. Increased risk of diabetes with statin treatment is associated with impaired insulin sensitivity and insulin secretion: a 6 year follow-up study of the METSIM cohort. *Diabetologia* 2015;**58**:1109–1117.
 139. Ganesan S, Ito MK. Coenzyme Q10 ameliorates the reduction in GLUT4 transporter expression induced by simvastatin in 3T3-L1 adipocytes. *Metab Syndr Relat Disord* 2013;**11**:251–255.
 140. Moro C, Bajpeyi S, Smith SR. Determinants of intramyocellular triglyceride turnover: implications for insulin sensitivity. *Am J Physiol Metab* 2008;**294**:E203–E213.
 141. Schrauwen P, Hesselink MKC, Blaak EE, Borghouts LB, Schaart G, Saris WHM, et al. Uncoupling protein 3 content is decreased in skeletal muscle of patients with type 2 diabetes. *Diabetes* 2001;**50**:2870–2873.
 142. Liu J, Li J, Li W-J, Wang C-M. The role of uncoupling proteins in diabetes mellitus. *J Diabetes Res* 2013;**2013**:1–7.
 143. Larsen S, Stride N, Hey-Mogensen M, Hansen CN, Bang LE, Bundgaard H, et al. Simvastatin effects on skeletal muscle. *J Am Coll Cardiol* 2013;**61**:44–53.
 144. Sastre J. The role of mitochondrial oxidative stress in aging. *Free Radic Biol Med* 2003;**35**:1–8.
 145. Solomon A, Kivipelto M, Wolozin B, Zhou J, Whitmer RA. Midlife serum cholesterol and increased risk of Alzheimer's and vascular dementia three decades later. *Dement Geriatr Cogn Disord* 2009;**28**:75–80.
 146. Wagstaff LR, Mitton MW, Arvik BM, Doraiswamy PM. Statin-associated memory loss: analysis of 60 case reports and review of the literature. *Pharmacotherapy* 2003;**23**:871–880.
 147. Rojas-Fernandez CH, Cameron J-CF. Is statin-associated cognitive impairment clinically relevant? A narrative review and clinical recommendations. *Ann Pharmacother* 2012;**46**:549–557.
 148. Muldoon MF, Ryan CM, Sereika SM, Flory JD, Manuck SB. Randomized trial of the effects of simvastatin on cognitive functioning in hypercholesterolemic adults. *Am J Med* 2004;**117**:823–829.
 149. Muldoon MF, Barger SD, Ryan CM, Flory JD, Lehoczy JP, Matthews KA, et al. Effects of lovastatin on cognitive function and psychological well-being. *Am J Med* 2000;**108**:538–546.
 150. Collins R, Armitage J, Parish S, Sleight P, Peto R. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20 536 high-risk individuals: a randomised placebocontrolled trial. *Lancet* 2002;**360**:7–22.
 151. McGuinness B, Craig D, Bullock R, Passmore P. Statins for the prevention of dementia. *Cochrane Database Syst Rev* 2016;**2016**.
 152. Rojas-Fernandez CH, Goldstein LB, Levey AI, Taylor BA, Bittner V. An assessment by the Statin Cognitive Safety Task Force: 2014 update. *J Clin Lipidol* 2014;**8**:S5–S16.
 153. Ott BR, Daiello LA, Dahabreh IJ, Springate BA, Bixby K, Murali M, et al. Do statins impair cognition? A systematic review and meta-analysis of randomized controlled trials. *J Gen Intern Med* 2015;**30**:348–358.
 154. Swiger KJ, Manalac RJ, Blumenthal RS, Blaha MJ, Martin SS. Statins and cognition: a systematic review and meta-analysis of short- and long-term cognitive effects. *Mayo Clin Proc* 2013;**88**:1213–1221.
 155. Song Y, Nie H, Xu Y, Zhang L, Wu Y. Association of statin use with risk of dementia: a meta-analysis of prospective cohort studies. *Geriatr Gerontol Int* 2013;**13**:817–824.
 156. Schultz BG, Patten DK, Berlau DJ. The role of statins in both cognitive impairment and protection against dementia: a tale of two mechanisms. *Transl Neurodegener* 2018;**7**:5.
 157. Müller WE, Eckert A, Kurz C, Eckert GP, Leuner K. Mitochondrial dysfunction: common final pathway in brain aging and alzheimer's disease—therapeutic aspects. *Mol Neurobiol* 2010;**41**:159–171.
 158. Li Y, Liu Q, Sun J, Wang J, Liu X, Gao J. Mitochondrial protective mechanism of simvastatin protects against amyloid β peptide-induced injury in SH-SY5Y cells. *Int J Mol Med* 2018;**41**:2997–3005.
 159. Jeong J-H, Yum KS, Chang JY, Kim M, Ahn J, Kim S, et al. Dose-specific effect of simvastatin on hypoxia-induced HIF-1 α and BACE expression in Alzheimer's disease cybrid cells. *BMC Neurol* 2015;**15**:127.
 160. von Haehling S, Morley JE, Coats AJS, Anker SD. Ethical guidelines for publishing in the Journal of Cachexia, Sarcopenia and Muscle: update 2019. *J Cachexia Sarcopenia Muscle* 2019;**10**:1143–1145.