Statin-associated muscle symptoms:

is it real or is it all in the mind?

XXXXXXXX XXXXXXXXXXXXXXX, Radboud University Nijmegen, XXXX 2023

Abstract

Statins are the most prescribed medication for primary and secondary prevention of cardiovascular disease events by lowering LDL-C through inhibition of HMG-CoA reductase in the mevalonate pathway. There are different statin types based on their pharmacokinetics, including lipophilicity, administration, clearance, and metabolism. Atorvastatin is mostly used in research but since this is an acid type of statin, it has a lower potential to cause myopathy compared to lactone statins. Although statins are safe and effective, statin-associated muscle symptoms (SAMS) cause discontinuation and nonadherence to statin therapy, causing an increased risk of developing cardiovascular events. Suggestions are made that SAMS are associated with negative expectations from patients, and this may have an impact on their experience with SAMS during statin therapy. Are people really statin intolerant or resistant or is it all in their minds? And if the statins are causing these muscle symptoms, what are the underlying mechanisms contributing to these symptoms? Furthermore, how can we tackle this problem and improve the adherence to statins and eventually decrease the risk of developing cardiovascular events? This review will discuss all these questions with existing literature and suggest future directions to improve the cardiovascular treatment with regard to statin therapy.

SAMS include myalgia, myopathy, and rhabdomyolysis. Literature shows little or no significant association between statin use and SAMS, explained by the drucebo effect. However, there are patients who are really statin intolerant or resistant. The underlying mechanisms of statin toxicity is not clear yet, but potential mechanisms are proposed, including cellular and subcellular effects, genetic effects, and the mitochondrial function. In addition, some probable risk factors for the development of SAMS are found, including advanced age, physical disability, female sex, lower body mass index, hypothyroidism, drug-drug interaction, and vitamin D status. For people who are really unable to take statins, other treatment options have to be available. First, the side effects can be treated with supplementation of vitamin D, CoQ10, IGF1, and exercise. However, literature show contradictive and inconclusive evidence for these options. Second, alternative treatment options are treatment with ezetimibe, bile acid resins, PCSK9 inhibitors, and nutraceuticals. These options are also limited, and still statins remain the most effective treatment for lowering LDL-C.

The conclusion of this review is that SAMS exist. Although it is still unclear what the prevalence of statin intolerance and resistance are, since the drucebo effect accounts for a huge part of this prevalence. More awareness of the drucebo effect is needed to increase statin adherence rates. Moreover, more research is warranted to determine the underlying mechanisms of statin toxicity and to identify more effective alternative therapies. In these future studies, a stronger emphasis on the distinction between the various statin types should be made.

Abbreviations

CoQ10	Coenzyme Q10
CYP	Cytochrome P450
FOXO	Forkhead box class O protein group
HMG-CoA	Hydroxymethylglutaryl coenzyme A
IGF	Insulin-like growth factor
LDL-C	Low-density lipoprotein cholesterol
OATP	Organic anion-transporting polypeptide
PCSK9	Proprotein convertase subtilisin/kexin type 9
PI3K	Phosphoinositide 3-kinase
RCT	Randomized controlled trial
RYR	Ryanodine receptor
SAMS	Statin-associated muscle symptoms
SNP	Single-nucleotide polymorphism

Introduction

Statins, also known as hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, are used as medication for primary and secondary prevention of cardiovascular disease events in men and women, and across all age groups (Herrett et al., 2021; Teo et al., 2022). It lowers the concentration of low density lipoprotein cholesterol (LDL-C), which is also called the 'bad' cholesterol since it increases the risk of cardiovascular events. Atherosclerotic cardiovascular events was accounted for the death of approximately 18 million people worldwide (Blazing, 2022). Although more and new effective treatments lowering the LDL-C are discovered, including bempedoic acid, proprotein convertase subtilisin/kexin type 9 (PCSK9) monoclonal antibody inhibitors, and inclisiran, statins remain the first line treatment (Teo et al., 2022). Statins are among the most widely prescribed medication in the world. In 2022, it was estimated that more than 200 million people worldwide are using statins (Needamangalam Balaji, Prakash, Joshi, & Surapaneni, 2022). Statins are proven safe (Collins et al., 2016), but there are some adverse effects, including an increased risk of new-onset type 2 diabetes mellitus, hepatotoxicity, renal toxicity, and neurological and neurocognitive effects (Needamangalam Balaji et al., 2022; N. C. Ward, Watts, & Eckel, 2019). However, the most common side effect of statins are muscle symptoms, like myalgia, myopathy, and rhabdomyolysis. These muscle symptoms are collectively referred to as statin-associated muscle symptoms (SAMS) (Murphy et al., 2022). Due to SAMS, patients often stop their treatment with statin or wanting a lower dosage. This leads again to higher LDL-C levels, increasing the risk of developing major cardiovascular disease events (Herrett et al., 2021; Murphy et al., 2022). It is suggested that SAMS are associated with negative expectations from patients and since the patients are aware of this adverse effect, it may have an impact on their experience with SAMS during statin therapy (Moon, Sedgh, & Jackevicius, 2021). This suggestion is supported by the analysis of Gupta *et al.*, who observed a significant increased incidence of SAMS during the open-label period, yet a no significant increase in SAMS was found in the blinded controlled period in the same population (Gupta et al., 2017).

The most important problem of statins is the adverse effects, mostly shown as SAMS. However, are people really statin intolerant or statin resistant or is it all in their minds? And if the statins are causing these muscle symptoms, what are the underlying mechanisms contributing to these symptoms? Furthermore, how can we tackle this problem and improve the adherence to statins and eventually decrease the risk of developing cardiovascular disease events? This review will discuss all these questions with existing literature and suggest future directions to improve the cardiovascular treatment with regard to statin therapy.

High cholesterol and statin treatment

Cholesterol is a lipophilic molecule which plays a role in many cellular functions. It has an influence on the structural makeup of the membrane, modulates the membrane fluidity, and also influences the susceptibility to gene transcription. Furthermore, cholesterol can cause the induction of carcinogenesis and facilitate the absorption of fat-soluble vitamins A, D, and K. (Huff, Boyd, & Jialal, 2022; Laka, Makgoo, & Mbita, 2022; Schade, Shey, & Eaton, 2020). Cholesterol is transported through the blood, since it is lipophilic, inside lipoprotein particles, also known as high-density lipoprotein (HDL), intermediate-density lipoprotein (IDL), low-density-lipoprotein (LDL), very-low-density lipoprotein (VLDL), and chylomicrons (Huff et al., 2022). High levels of LDL cholesterol (LDL-C), also known as hypercholesterolemia, is a huge risk factor contributing to the formation of atherosclerotic plaques. Damage to the epithelium leads to a dysfunction of the cells, leading to an increased number of LDL particles entering through the vascular wall. Eventually, the atherosclerotic plaques can barricade the vessel, leading to a decreased blood flow and causing ischemia or other cardiovascular diseases. In addition, the atherosclerotic plaque can rupture, causing complete blockage of the blood vessel due to the formation of a thrombus. This can lead to acute myocardial infarctions, or instable angina (Huff et al., 2022).

There are several factors that can lead to increased LDL-C levels, including diet, genetics, medications, sedentary lifestyle, stress, and other disorders like hypothyroidism and nephrotic syndrome. Deficits in genes who regulate

for instance the LDL receptors lead to higher LDL-C levels in our blood. The function of the LDL receptors, who normally mediate the uptake of LDL, will be decreased which results in higher LDL-C levels in the blood (Huff et al., 2022). In addition, our diet can also lead to an increased LDL-C level in the blood, especially in diets high in saturated fats and trans fats (Stefanick et al., 1998).

Cholesterol is synthesized in the mevalonate pathway, shown in Figure 1. The cascade of enzymatic reactions in this pathway is primarily regulated by a rate-limiting step, which involves the conversion of HMG-CoA into mevalonate. This regulatory step is also commonly used as therapeutic target for cardiovascular disorders. (Cruz, Mo, McConathy, Sabnis, & Lacko, 2013). Statins target this regulatory step to lower LDL-C, as they inhibit HMG-CoA reductase. This blocks the underlying mevalonate pathway, resulting in a limitation of the downstream reactions and accumulation of the final products, including cholesterol and isoprenoid (Cruz et al., 2013). It thereby increases the production of microsomal HMG-CoA reductase and the LDL receptor expression on the cell surface in the liver, as a result of the reduced hepatic cholesterol synthesis in the liver. A higher LDL receptor expression on the cell surface results in a higher clearance of the circulating LDL-C levels from the blood (N. C. Ward et al., 2019). This clearance can go up by 20 to 55 percent (Buhaescu & Izzedine, 2007). Reducing LDL-C levels not only has a benefit on the cardiovascular morbidity and mortality, statins also have beneficial effects in the stabilization of atherosclerotic plaques, endothelial function, bone metabolism, anti-inflammatory, immunomodulatory and antithrombotic effects. Furthermore, statins include improvements in a reduced risk for dementia (N. C. Ward et al., 2019). These benefits are thought to be a result of the inhibition of the synthesis of isoprenoid in the mevalonate pathway (Buhaescu & Izzedine, 2007).

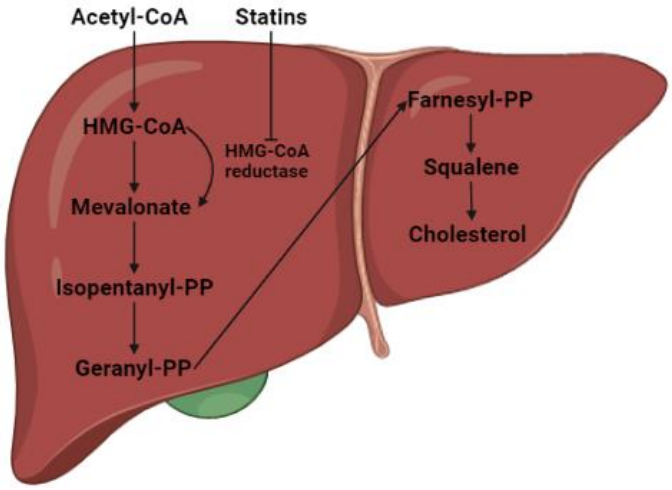

Figure 1. *A simple schematic overview of the mevalonate pathway, where the synthesis of cholesterol takes place and where statins target. Adapted from Bouitbir et al. (Jamal Bouitbir, Sanvee, Panajatovic, Singh, & Krähenbühl, 2020). Created with BioRender.*

The different types of statins have differences in their pharmacokinetics, including the lipophilicity, clearance, administration, and their metabolism. Atorvastatin, fluvastatin, lovastatin, simvastatin, pitavastatin, and cerivastatin belong to lipophilic statins, which means that they are able to passively diffuse through the cell membrane in to the liver. Since these classes are also able to diffuse easily in to other tissues, their hepatoselectivity is low. In addition, the lipophilic statins are overall cleared via oxidative biotransformation. Rosuvastatin and pravastatin are hydrophilic statins, and therefore they need a carrier-mediated uptake to enter the liver. These hydrophilic statins are excreted unchanged. In addition, some statins are administered as a inactive lactone, and in the body it is converted in to the active form, such as lovastatin and simvastatin. Whereas atorvastatin, pravastatin, fluvastatin, pitavastatin, and rosuvastatin are administered in an active acid form. Furthermore, all statin types are metabolised by CYP-enzymes, including CYP3A4 and CYP2C9. CYP3A4 metabolises mainly simvastatin, atorvastatin, and lovastatin, whereas CYP2C9 mainly metabolises fluvastatin (N. C. Ward et al., 2019).

Statin-associated muscle symptoms

SAMS is the most common and most important side effect of statins. Up to 72 percent of all side effects reported are related to the muscles (N. C. Ward et al., 2019). These muscle symptoms can vary from myalgia and myopathy to rhabdomyolysis. The muscle symptoms mostly present symmetrical or bilateral and occur usually within one month of initiation of the statin therapy or within one month after an increase in dose. SAMS usually affects the large proximal muscles, mostly of the lower extremities. Experiencing SAMS happens at rest or directly after exercise (N. C. Ward et al., 2019).

Randomized controlled trials (RCT) have shown that most of the muscle symptoms are not generally a result of statin use. This mechanism is also called the nocebo or drucebo effect (Blazing, 2022). The subjective muscle related symptoms are then experienced as a result of the fact that patients expect them to be there when taking statins (P. E. Penson et al., 2022). A systematic review about the drucebo effect, written by Penson *et al.*, suggest that there is evidence that the drucebo effect is real. They found an increased incidence of SAMS under open-label therapy compared with participants who where blinded to the treatment. This result may explain the low rates of SAMS in RCTs (Penson et al., 2018). For instance, the StatinWISE trials of Herrett *et al.* performed a series of randomized placebo-controlled n-of-1 trails, using 20 mg of atorvastatin. They found no evidence of statins on muscle symptoms. Only a small proportion of the participants were intolerant to statins, and only developed SAMS during the period when taking statins compared with placebo (Herrett et al., 2021). These findings agree with other trials, including the SAMSON trial, which also found no clear effect of statins on the muscle symptoms (Herrett et al., 2021; Wood et al., 2020). In contrast, the GAUSS-3 trial (Nissen et al., 2016) and the ODYSSEY ALTERNATIVE trial (P. M. Moriarty et al., 2014) found only a small proportion of participants who developed SAMS when taking statins compared with placebo. A more recent RCT from Kristiansen *et al.* discovered no effect of atorvastatin on the intensity of muscle symptoms. Some patients even reported to experience more muscle symptoms when taking placebo compared to taking statins (Kristiansen et al., 2021). In contrast, a meta-analysis by Irwin *et al.* included 135 RCTs and found a limited effect of statin therapy on SAMS, while they even included patients with a history of statin intolerance (Irwin, Khalesi, Fenning, & Vella, 2018).

Between the different classes of statin, the prevalence of SAMS differs. The highest risk of developing SAMS is seen in lipophilic statins, including simvastatin, lovastatin, and atorvastatin. These kinds of statin have the ability to diffuse in to the extrahepatic tissues, like skeletal muscle. Hydrophilic statins, including fluvastatin and pravastatin, have a lower risk of causing SAMS since there is less muscle penetration (N. C. Ward et al., 2019). However, the meta-analysis of Irwin *et al.* demonstrated that both the lipophilicity of the statin and the statin dose do not have a clinically significant effect on the development of the muscle symptoms (Irwin et al., 2018). A study by Skottheim *et al.* found that the type of administration contributes to the potential of developing myotoxicity in the human skeletal muscle cells *in vitro*. They showed that the lactone forms, including lovastatin and simvastatin, have a higher potential of developing myotoxicity in the human skeletal muscle cells *in vitro* compared to the acid forms, including atorvastatin, pravastatin, fluvastatin, pitavastatin, and rosuvastatin (Skottheim, Gedde-Dahl, Hejazifar, Hoel, & Asberg, 2008). Besides the differences in the risk of developing SAMS between the statin types, there is also a difference in risk of developing other side effects. Moreover, not all statin types cause the same side effects. Simvastatin and pravastatin are accompanied with fewer side effects compared to other statin types. Thereby, significant results were found that patients taking pravastatin and simvastatin were less likely to stop their treatment because of adverse events. In addition, myalgia was experienced less in patients taking simvastatin compared with patients receiving atorvastatin. Hepatic transaminases is also an adverse effect of statins, whereby patients taking atorvastatin and fluvastatin had significant higher odds of developing hepatic transaminases compared to simvastatin, pravastatin, and rosuvastatin (Naci, Brugts, & Ades, 2013).

The nocebo and drucebo effect

As already mentioned, the nocebo, or drucebo effect is responsible for a part of statin toxicity. The term nocebo effect describes, conversely to placebo, the harm that an inactive drug causes as a result of expectation. However, since statins are not an inactive drug, but have pharmacological actions, this term does not apply very well in this situation. The nocebo effect, even as the placebo effect, is therefore mostly used in clinical trials where an arm is included in which participants do not receive treatment. In the situation of SAMS, where active medication is involved, a new term was introduced. This new term is called the drucebo effect and it is the difference in intensity or frequency of symptoms by comparing them under blinded and under open-label conditions. This gives an insight in what extent the symptoms may result from expectation alone (Peter E. Penson et al., 2022).

Evidence shows that neurobiological processes might contribute to perceived adverse effects. In addition, a lower quality of life, a lower well-being, and currently having symptoms are associated with increased side effect expectations. Moreover, using risk descriptors in verbal language, for instance using the word common, compared to using numerical descriptors, for example giving percentages, are also associated with an increase side effect expectations. A review by Smith *et al.* showed that lower expectations in unrealistic side effects might lead to a decreased experience of side effects. Therefore, it leads to a better adherence to medical treatments (Smith, Webster, & Rubin, 2020). Social modelling, when you observe someone else experience with side effects, is also found related to the drucebo effect, as social modelling of side effects via video lead to increased negative expectations and a higher drucebo effect. This effect is found in a greater extent in females compared to males (Quinn et al., 2023). Also, the other way around is proven to affect the drucebo effect. Mao *et al.* found an association between positive framing of side effects and a reduced drucebo effect. They even conclude that positive framing can prevent the drucebo side effects from happening at all (Mao et al., 2021). The drucebo effect can occur within any type of medication, including statin treatment. In contrast to RCTs on statins, where rates of muscle symptoms and discontinuation owing to any adverse effects are consistently identical in the statin and placebo groups, the drucebo effect is the best explanation for the high prevalence of muscle and other symptoms ascribed to statins in observational studies and clinical practice. Patients who are statin intolerant or statin resistant usually tolerate statin therapy under double-blinded circumstances, which indicates that statin toxicity has little pharmacological basis (Tobert & Newman, 2016). A systematic review of Penson *et al.* even estimated that between 38 percent and 78 percent of SAMS-related statin intolerance could be caused by expectation alone (Peter E. Penson et al., 2022).

Reducing the drucebo effect during statin treatment is needed to decrease the prevalence of statin intolerance and to increase the adherence rate to statins. The communication between the clinician and patient is really important for reducing the drucebo effect, since it can influence the frequency of subjective side effects. Clinicians want to avoid negative expectations about statin treatment in the patient. Moreover, the clinician also need to counter any negative expectation of statin side effects that already exist (Tobert & Newman, 2016). When the clinicians are informing patients about the statin side effects, they need to use numeric descriptors for communication (Smith et al., 2020). The side effects also need to be attributed in a positive way, which decreases the risk of developing drucebo side effects (Mao et al., 2021). Furthermore, evidence shows that clinicians should take extra care when treating patients who currently experiencing symptoms, experienced symptoms previously, or patients with a lower quality of life (Smith et al., 2020).

The mechanisms of statin toxicity

Statin toxicity is important to consider since it can significantly impact the adherence to statin therapy and subsequent cardiovascular risk. Toxicity of statin treatment can lead to statin intolerance or statin resistance in patients. The mechanism underlying SAMS is not known. However, there are proposed mechanisms that contribute to statin toxicity. Since the presentation of SAMS widely varies, it is likely that more than one pathological mechanism contributes to statin toxicity. Proposed mechanisms for SAMS include cellular and subcellular effects, effects on skeletal muscle, the HMG-CoA reductase pathway-mediated effects, and genetic

factors. These factors can alter the muscle cell membrane fluidity, stability, the protein activity and signalling, reduce membrane cholesterol content, and impact mitochondrial function. Differences in statin uptake or metabolism can also lead to a higher exposure on skeletal muscle to statins, leading to an altered calcium signalling, mitochondrial function, and cell cycle pathways (N. C. Ward et al., 2019).

Cellular and subcellular effects

The cellular and subcellular effects include the mitochondrial toxicity and calcium signalling. High statin concentrations in the body are responsible for an overload of calcium and mitochondrial toxicity in the skeletal muscles. Statins lead to the dissociation of the stabilizing FK506 binding protein (FKBP12) from the ryanodine receptor (RYR) in skeletal muscle. The RYR is located on the sarcoplasmic reticulum and is responsible for calcium release. This dissociation causes activation of the apoptotic pathway and the increase in ROS formation resulting in spontaneous calcium release (Lotteau et al., 2019). In addition, the overload of calcium can result in an increase in oxidative phosphorylation, leading to a loss of mitochondrial membrane potential, a decrease in ATP levels, a decreased mitochondrial biogenesis and density, activation of mitochondria permeability transition, calpain-mediated cell death, and apoptosis (Thompson, Panza, Zaleski, & Taylor, 2016). The RYR is found in higher levels in patients with statin intolerance compared to statin tolerant controls. The higher expression of RYR leads to more severe structural damage in skeletal muscle, such as intracellular T-tubular disruption (Turner & Pirmohamed, 2020). This disruption in T-tubule architecture is also seen in analysis of the skeletal muscle of statin users with an electron microscope and is therefore also a proposed mechanism underlying statin toxicity. The T-tubular system is normally involved for the calcium release during muscle contraction (Thompson et al., 2016).

The mitochondrial function

The mitochondrial function appears to be impaired as a result of statin therapy. The coenzyme Q10 (CoQ10) is a mitochondrial transport protein and shuttles electrons from complex I and II to complex III (Hargreaves, 2014). Thereby CoQ10 is also an important antioxidant. CoQ10 is produced by the mevalonate pathway and since this pathway is inhibited by statins, the synthesis of CoQ10 is decreased. This decrease results in an impaired mitochondrial function, resulting in cell damage, a reduced ATP production and oxidative stress. So CoQ10 is proposed as a possible mechanisms underlying SAMS (Jamal Bouitbir et al., 2020; Taylor, Lorson, White, & Thompson, 2015; Thompson et al., 2016).

Moreover, the expression of the atrogin-1 gene is increased according to skeletal muscle biopsies from patients with SAMS and is also associated with mitochondrial dysfunction. The phosphoinositide 3-kinase (PI3K)/Akt pathway controls atrogin-1 production, and it has also been proposed that this pathway contributes to the underlying cause of SAMS. Statins have an effect on the muscles by stimulating this pathway, showed in Figure 2. An active PI3K/Akt pathway can result in muscle hypertrophy or in muscle atrophy. Muscle hypertrophy occur via the activation of rapamycin (mTOR). In

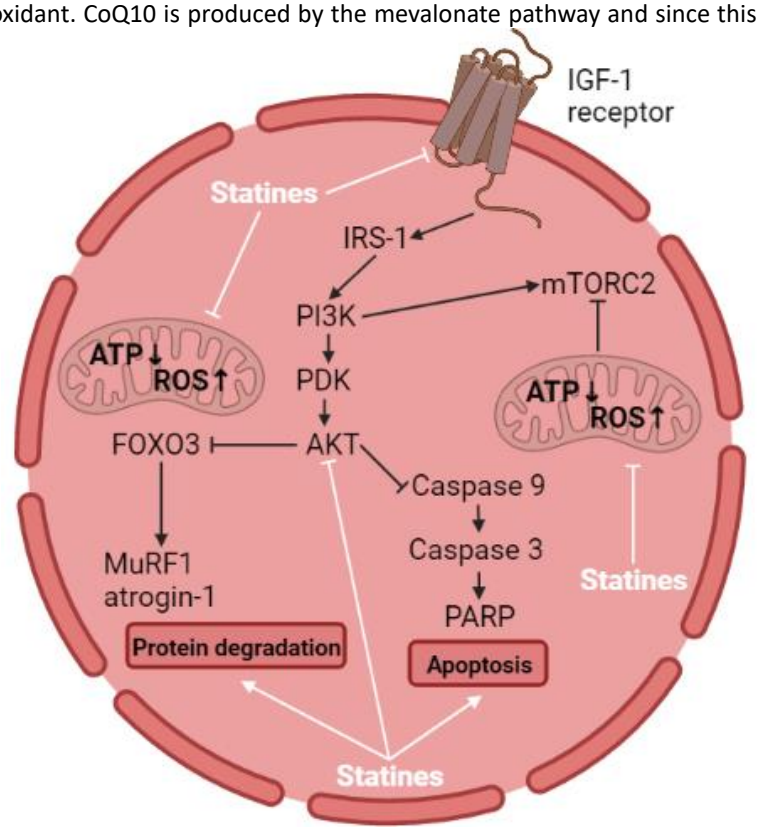

Figure 2. *A simplified scheme of the possible underlying mechanisms of statin toxicity in the PI3K/Akt pathway. Adapted from Bonifacio et al. (Bonifacio et al., 2017). Created with BioRender.*

addition, muscle atrophy occurs via the activation of the forkhead box class O protein group (FOXO). FOXO activates muscle-specific ubiquitin ligases, such as atrogin-1 and MuRF-1, causing degradation of proteins and muscle atrophy (Thompson et al., 2016). Evidence shows that atrogin-1 is found in higher levels in the muscle biopsies from patients with SAMS (Hanai et al., 2007). The phosphorylation of Akt is leading to the phosphorylation of FOXO, preventing FOXO from entering the nucleus. It is proposed that statins reduce farnesyl pyrophosphate (FPP), an enzyme in the cholesterol synthesis pathway. This is leading to a decreased phosphorylation of Akt, whereby the unphosphorylated FOXO can enter the nucleus and there is an increase of the expression of atrogenic proteins. Besides, the transcription of pyruvate dehydrogenase kinase (PDK) is activated by FOXO. By higher PDK levels, the muscle pyruvate dehydrogenase complex is inactivated and this leads to a limited carbohydrate oxidation. As a consequence, there is a possibility that the mechanisms that increase SAMS also produce glucose intolerance as a result of statin use, leading to the adverse effect new onset diabetes mellitus (Thompson et al., 2016). In addition, it is found that simvastatin influences the PI3K/Akt pathway by reducing the Akt phosphorylation via the insulin-like growth factor (IGF)-1 receptor. To support this finding, IGF-1 supplementation resulted in the inhibition of the expression of atrogin-1, leading to preventing and rescuing the simvastatin-induced myotoxicity (Bonifacio et al., 2017; Jamal Bouitbir et al., 2020).

Another observation is a reduction of the oxidative phosphorylation in the mitochondria (OXPHOS) in skeletal muscles in patients using simvastatin compared to healthy controls (Larsen et al., 2013). In this process, mitochondria produce reactive oxygen species (ROS) in the cells. ROS can cause irreversible tissue and cell damage, because of the oxidization of DNA, lipids, and proteins. Evidence shows that statin inhibit complex I and III of the respiratory chain in the mitochondria, which is related to ROS formation, and indeed ROS production in skeletal muscle was increased after statin therapy (J. Bouitbir et al., 2016). A study of Schirris *et al.* agrees with this concept and showed that inhibition of complex III activity is associated with SAMS (Schirris et al., 2015).

Genetic factors

The mechanisms underlying the statin intolerance in some patients can also be related to specific genetic factors. There are variants found in particular genes that increase the probability of experiencing the statin-induced myotoxicity. The organic anion-transporting polypeptide (OATP)1B1 is an influx transporter located on the basolateral membrane of hepatocytes. The OATP1B1 is encoded by the *SLCO1B1* gene, and it controls the hepatic uptake of statins from the blood regulating the serum levels of statins. Two single-nucleotide polymorphism (SNP) variants of the *SLCO1B1* gene are found: rs2306283 and rs4149056 (N. C. Ward et al., 2019). They are negatively related to the OATP1B1 transporter, resulting in a reduced transport activity (Lam, 2019). Furthermore, a strong association was found between the rs4363656 SNP and simvastatin-associated myotoxicity. In addition, the RYR, an intracellular calcium release channel, is encoded by 3 types of genes: *RYR1*, *RYR2*, and *RYR3* (N. C. Ward et al., 2019). An intronic variant in the *RYR2* gene, rs2819742, is found to be associated with rhabdomyolysis. This is a result of an increased expression of the RYR, leading to an increased calcium release and eventually results in apoptosis (Marciante et al., 2011). In addition, the rs12975366 variant in the leukocyte immunoglobulin-like receptor subfamily-B gene (*LILRB5*) is also found to be related with statin intolerant phenotypes. Statins have a positive influence on the number of suppressive immune cells, that will suppress T regulatory cells, which are needed for the repair and regeneration system of the skeletal muscle. This mechanism will lead to elevated CK levels, intolerance to the lowest approved dose, and non-adherence to statin therapy (M et al., 2017; März & Laufs, 2017). SNPs in the UDP glucuronosyltransferases (*UGT*)1A gene were also found associated with muscle toxicity. The lactone statin forms are converted to the acid forms by UDP glucuronosyltransferases. Due to the SNPs in this gene, there is less systemic exposure to the lactone form of atorvastatin (Stormo et al., 2013). Additionally, polymorphisms in the *GATM* gene, including rs9806699 and rs1346268, are found to be protective factors of SAMS. However, the mechanism behind this finding is not well known (Liu, Fan, Zhang, & Li, 2021).

Risk factors for developing SAMS

Beside the possible underlying mechanisms leading to SAMS, there are also risk factors that contribute to an increased risk of developing SAMS during statin therapy. Side effects occur when there is a particular statin concentration in skeletal muscles, which can be the case when someone has a reduced body muscle mass or

when there is an increased serum statin concentration. Similarly, higher statin doses also lead to higher serum concentrations, and eventually to a higher risk for SAMS. In addition, advanced age, physical disability, female sex, and lower body mass index are probable risk factors for developing SAMS since they contribute to lower plasma volumes and a reduced muscle mass. The inhibition of the metabolism of statin will lead to higher drug levels in the body. Hypothyroidism is a condition where the thyroid produce and secrete decreased levels of thyroid hormones. Since the thyroid hormones regulate several metabolic processes, including the metabolism of medication, the statin metabolism alters in a negative way. A reduced metabolism of statins lead to higher serum levels and to an increased risk for SAMS (Thompson et al., 2016). Alcohol has toxic muscle effects, since it increases proinflammatory cytokines and creates an oxidative milieu in the skeletal muscle, besides it can increase the chance of obtaining SAMS during statin therapy (Simon, Jolley, & Molina, 2017). Statins are metabolized by CYP enzymes (mainly CYP3A4). 75 percent of all medications are metabolized by CYP enzymes, whereby most of the drugs are metabolized by CYP3A4. So, there is some competition for metabolism. This competition can result in higher serum concentrations of the drug and high statin concentration in skeletal muscle increase the risk of SAMS. The CYP enzymes are primarily hepatic. However, CYP3A4 is also seen in the intestinal mucosa, where it metabolizes toxins during their absorption. This means that vulnerable statins are inactivated by these intestinal CYP enzymes after their absorption. The inhibition of the intestinal CYP3A4 enzymes will result in a higher absorption rate of statin and therefore higher serum concentrations, as a result of the reduced statin metabolism in the intestine. Some inhibitors of the intestinal CYP3A4 enzymes are grapefruit, starfruit and pomegranate juices (Thompson et al., 2016). Vitamin D deficiency or insufficiency are also contributing to a higher risk of developing SAMS during statin therapy. Insufficient vitamin D decrease the serum calcium level which is important for muscle contraction and the muscle protein synthesis. The receptor of vitamin D is located in skeletal muscle, and it appears that deficiency of 25-OH vitamin D contributes to myopathy. The vitamin D receptor is essential for muscle growth and muscle strength, and a decrease in these processes will lead to myopathy (Shipton & Shipton, 2015; Thompson et al., 2016; Natalie C. Ward, Pang, Ryan, & Watts, 2018).

Treatment options

Patients with high LDL-C levels should reduce these levels to decrease the risk of developing a cardiovascular event. As already said, statins are the first line treatment option when talking about lowering LDL-C levels, and are therefore the most prescribed medication worldwide (Teo et al., 2022). SAMS are the most common reason for patients for stopping statin therapy, even if the patients are not really statin intolerant but because of the drucebo effect. Statins are still the most effective treatment, so studies have been done to find a way to still prescribe statin but without or a lower risk of SAMS. A risk factor for developing SAMS is the vitamin D status, meaning that there is an association between vitamin D and SAMS due to lower calcium levels resulting in a reduced muscle protein synthesis and muscle contraction. The vitamin D receptor is present in skeletal muscle, and suggestions are made that a deficiency of 25-OH vitamin D contribute to myopathy by reducing the muscle strength and muscle growth (Shipton & Shipton, 2015; Thompson et al., 2016; Natalie C. Ward et al., 2018). The trial by Hlatky *et al.* found that supplementation of vitamin D did not reduce statin discontinuation or prevent SAMS (Hlatky et al., 2023). However, other studies found that vitamin D supplementation is related to an improvement of SAMS. Higher vitamin D concentrations lead to a reduced pain intensity and as a result the quality of life in patients with statin intolerance and hypovitaminosis D improved (Carallo, Capozza, & Gnasso, 2022; Teo et al., 2022). So as a result of all the recent studies, supplementation of vitamin D only appears to be beneficial in patients with confirmed vitamin D deficiency or insufficiency (Natalie C. Ward et al., 2018).

A proposed possible mechanism for SAMS was the depletion of the mitochondrial transporter CoQ10. The RCT of Taylor *et al.* studied, therefore, if CoQ10 supplementation would be a suitable and effective treatment to reduce SAMS during statin therapy. The findings showed no reduction in muscle pain in patients with confirmed statin myopathy (Taylor et al., 2015). More randomized placebo-controlled studies show agreement with these results (Bookstaver, Burkhalter, & Hatzigeorgiou, 2012; Rott & Leibowitz, 2013). Contradictory, some studies show opposite findings and report an improvement in SAMS after CoQ10 supplementation (Skarlovnik, Janić, Lunder, Turk, & Šabovič, 2014; Tóth et al., 2017). Even recent meta-analysis do not agree with each other, as one conclude that CoQ10 supplementation ameliorate SAMS (Qu et al., 2018), while the other conclude that CoQ10

supplementation is not beneficial for patients with SAMS (Kennedy, Köller, & Surkova, 2020). So, literature on the supplementation of CoQ10 as treatment option for SAMS seems contradictive and inconclusive.

Exercise is also suggested as a promising treatment option to reduce SAMS, since it reduces muscle atrophy of the skeletal muscle. This atrophy is reduced by hypoxia, which resulted in phosphorylation of FOXO by Akt, and downregulation of atrogin-1 and MuRF-1 (Yu et al., 2022). The downregulation of the expression of the atrogin-1 and MuRF-1 genes is also found in other studies (Al-Nassan, Fujita, Kondo, Murakami, & Fujino, 2012; Moradi, Zehsaz, & Nourazar, 2020; Thompson et al., 2016). Besides, exercise normalizes the binding between FKBP12 and RYR, which was dissociated because of statin therapy. Exercise therefore prevents the ROS formation, the increase in calcium release, and the activation of the apoptotic pathway (Lotteau et al., 2019).

The expression of the atrophy marker atrogin-1 can also be reduced by treatment with growth factors, such as IGF-1. IGF-1 supports the skeletal muscle protein synthesis via the PI3K/Akt pathway shown in Figure 2. IGF-1 supplementation increases Akt activity, leading to a reduction in the FOXO3 gene. The inhibition of FOXO3 results in a decrease in the muscle atrophy factors, including atrofin-1 and MuRF-1 (Bonifacio et al., 2017; Yoshida & Delafontaine, 2020) With this finding by Bonifacio *et al.*, it can be proposed that IGF-1 prevent and rescues simvastatin-induced myotoxicity (Bonifacio et al., 2017).

Beside treating the side effects that come along with statin therapy, other treatment options can be considered. First, and maybe also the most important one, lifestyle should be a therapy adopted for lowering the levels of LDL-C and reduction of the risk of cardiovascular disease events. Improving lifestyle includes following a healthy diet, regular exercise, maintaining a normal weight, and avoiding tobacco products.

Second, the initial pharmacological solution for treating statin intolerance or statin resistance is rechallenge with the same statin or rechallenge with a different statin. Rechallenging is done by patients who stopped using statins because of the adverse effects. The drug is restarted to monitor and determine any signs of the adverse effects. Furthermore, differences in statin treatment can be done by a reduction in statin dose and alter the intermittent or alternate day statin dosing (N. C. Ward et al., 2019). The statin doses prescribed are aligned with the current recommendation, where the benefits and harms of statins are taken into account. So according to these recommendation, there can be assumed that the current statin doses are not too high (Mangione et al., 2022). But some patients who are statin intolerant and are unable to tolerate statins at high doses are able to tolerate statins in lower doses, known as partial intolerance (Cheeley et al., 2022). If these changes in statin treatment do not work, alternative medication will be the next step (N. C. Ward et al., 2019).

Thirdly, another LDL-C lowering medication will be given as replacement of the statin therapy. This first next-line therapy is ezetimibe. This treatment has a an extended half-life and a flat dose-response, suggesting that a lower dosage is needed compared to statin therapy (N. C. Ward et al., 2019). However, ezetimibe mostly do not achieve a greater than 50 percent reduction which is recommend by the current guidelines (Mampuya et al., 2013; Stone et al., 2014). PCSK9 inhibitors, such as evolocumab, have shown potential as an alternative treatment for people who are statin intolerant or statin resistant due to the experience of SAMS. In addition to PCSK9 inhibitors reducing LDL-C levels, are not associated with muscle-related side effects. The GAUSS-3 trial studied the efficacy in reducing LDL-C levels in patients with confirmed SAMS, comparing ezetimibe and evolocumab. They found a significantly greater reduction in LDL-C levels after 24 weeks after the use of evolocumab compared to ezetimibe (Nissen et al., 2016). The ODYSSEY ALTERNATIVE trial by Moriarty *et al.* agreed with these results, as they found a higher reduction in LDL-C levels when using alirocumab compared with ezetimibe. They also found that alirocumab was associated with a significantly lower rate of muscle-associated side effects compared to statins (Patrick M. Moriarty et al., 2015). The adherence to PCSK9 inhibitors is also found to be relatively higher than conventional therapy, such as statins, which is beneficial for reducing the risk of developing cardiovascular events (Moşteoru, Gaiţă, & Banach, 2020). On the other side, the use of PCSK9 inhibitors is limited because of their high costs. It can only be used for high-risk patients who are not able to meet lipid targets at the level of recommendation in America when on maximal medication regimes (Stone et al., 2014).

The second next-line treatment, after ezetimibe, are bile acid resins. Bile acid resins inhibit bile acid in the intestine by binding to them and thereby interrupting the enterohepatic circulation of bile acids. This stimulates the conversion of cholesterol into bile, resulting in decreased hepatic cholesterol. As a result, there will be an increase in expression of LDL receptors causing reductions in the circulation LDL-c (di Gregorio, Cautela, &

Galantini, 2021). Although bile acid resins are very safe, they are limited by a poor acceptance and palatability, the need for separate administration times, worsening the hypertriglyceridemia, and some brands are not included for insurance coverage (N. C. Ward et al., 2019).

Another alternative treatment option are nutraceuticals, which are food components or derivates, and can be given as a monotherapy or in combination with a low-dose statin treatment or non-statin treatment. Some examples of nutraceuticals are berberine, red yeast rice, and policosanol. (N. C. Ward et al., 2019). Berberine improves LDL excretion by inhibiting PCSK9 and increases the expression of the LDL receptor in the liver. In addition, berberine also stimulates the fatty acid oxidation, inhibits oxidative stress and reduces the expression of lipogenic genes. Therefore berberine lowers LDL-c levels, suggesting a possible alternative treatment option. However, berberine has a low bioavailability due to the first-pass metabolism, poor intestinal absorption, and low permeability of the molecule. Besides, there are also side effects which come along with berberine treatment, including constipation, diarrhea, and abdominal distension. Nonetheless, it is demonstrated that berberine is effective in short and long term, and that ezetimibe efficacy is improved by combination therapy with berberine. Increased efficacy of ezetimibe is also seen in combination therapy with red yeast rice. Red yeast rice inhibits HMG-CoA reductase because it is structurally identical to lovastatin, but their pharmacokinetics and bioavailability are different (Cicero et al., 2021). The efficacy of red yeast rice supplementation is therefore not statistically different than statin therapy (Gerards, Terlou, Yu, Koks, & Gerdes, 2015). However, a recent meta-analysis by Fogacci *et al.* showed that red yeast rice supplementation was not associated with an increased risk of SAMS. In addition, a decreased risk of SAMS and serious side effects compared with statin therapy was shown (Fogacci et al., 2019). Policosanols is a plant sterol and it inhibits HMG-CoA reductase and it limits the hepatic synthesis of cholesterol. Policosanols are proven beneficial in reducing LDL-c in combination therapy, for instance together with red yeast rice, artichoke leaves and with ezetimibe (Cicero et al., 2021). Other effects of policosanols that reduce the risk of cardiovascular events are the inhibition of foam cell formation, prevention of LDL peroxidation, inhibition of platelet aggregation, and blocking the effects of cholesterol on smooth muscle proliferation. Although, existing data of the effects of policosanol is still conflicting (Swanson & Keithley, 2009). At the moment, nutraceuticals should not substitute prescribed drugs according to international guidelines, despite their preclinically and clinically evidence for safety and efficacy. However, in the future, implementation of new technologies, such as nutraceuticals and genetically modified technology, leads to better health benefits and better medical treatment. To reach this, more scientific research and newly developed nutraceuticals are warranted (Cicero et al., 2021; Puri et al., 2022).

Discussion and conclusion

Statins are widely used for the primary and secondary prevention of cardiovascular morbidity and mortality by reducing cholesterol levels. However, the nonadherence and discontinuation to statin therapy remains an ongoing and significant clinical problem. The main reason for the nonadherence to statins is the experience of SAMS during statin use. According to the literature, SAMS exists, and people can actually be statin intolerant or statin resistant. However, the drucebo effect is really strong and powerful. Besides, subjective types of SAMS were significantly more commonly reported than objective types of SAMS, which possibly refers to the drucebo effect. The powerful drucebo effect thereby influence the negatively expectations of patients taking statins. This might also be the reason the current literature does not find a significant association between statin use and SAMS. Only a small proportion of patients who are really statin intolerant was found in RCTs. If we can reduce the drucebo effect in statin therapy, less patients will experience SAMS and the adherence will increase, leading to an overall reduced risk of developing cardiovascular disease events. However, it will be hard to reduce the drucebo effect since it will be difficult to alter someone's negative expectations in something more positive. A possible way to achieve this is to create more awareness about the potential drucebo effect in statin therapy. This is also a way to assist clinicians with addressing patients with their concerns about statin therapy (Moon et al., 2021). Creating more awareness can be done by informing patients with sufficient information about the benefits and rationale of statin therapy, and to let them make informed decisions about their care (Peter E. Penson et al., 2022). Clinicians also need to give the patients a positive framing attribution to the side effects and counter the negative expectations that already exist (Mao et al., 2021; Tobert & Newman, 2016). Moreover, they need to use

numeric descriptors for the communication with the patients about the statin side effects and extra care is needed for patients with a low quality of life (Smith et al., 2020).

Patients who are really suffering from statin intolerance or statin resistance need alternative treatments to lower their cholesterol levels to reduce the risk of developing cardiovascular events. Current alternative treatment options include ezetimibe, bile acid resins, PCSK9 inhibitors, and the upcoming nutraceuticals. However, all these treatments have their own downsides and limitations, whereby statins still remain the best and most effective treatment for lowering cholesterol. The alternative treatments are limited in their use because of their costs, efficacy, side effects, and lack of long-term safety (N. C. Ward et al., 2019). Therefore, more research for alternative treatments is warranted. Furthermore, since statins are still the most effective treatment option to lower LDL-C, treatment options for lowering SAMS are existing. The options include supplementation of vitamin D, CoQ10, IGF1, and exercise. However, all these treatment options have limited effect because only suggestions are made, the evidence is contradictive or inconclusive, or it only is effective in particular patients. So further research is necessary to confirm the efficacy and safety of these treatment options, even as the underlying mechanisms for the development of statin toxicity and statin intolerance. There are some potential mechanisms proposed for the development of statin toxicity, but the true identification remains unclear due to a lack of biomarkers and clear definitions.

Most statin-related RCTs in the literature are using atorvastatin. This statin type is lipophilic, which means that atorvastatin is able to diffuse passively through the cell membrane. In addition, atorvastatin is an acid statin, which has a lower potential to cause myopathy compared to lactone statins (Skottheim et al., 2008). In addition, not all the statin types cause the same side effects, and it could even be the case that some patients tolerate one statin type better than others. This indicates that further research of statin myotoxicity should differentiate between acid and lactone statin forms.

This review concludes that SAMS really exist, but the prevalence of statin intolerance and statin resistance is still debatable. A big part of patients who are experiencing SAMS during their statin therapy can be explained by the drucebo effect. To reach higher adherence rates for statin, more awareness of the drucebo effect is needed. In addition, more research to find the underlying mechanism of statin toxicity and to find alternative treatments which are even or more effective than statins, but without the muscle-associated side effects, are warranted. This further research should also be more focused on the differentiation between the different statin types.

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