The role of mitochondria in statin-induced myopathy

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Abstract

Statins represent the primary therapy for combatting hypercholesterolemia and reducing mortality from cardiovascular events. Despite their pleiotropic effects in lowering cholesterol synthesis, circulating cholesterol, as well as reducing the risk of other systemic diseases, statins have adverse events in a small, but significant, population of treated patients. The most prominent of these adverse effects is statin-induced myopathy, which lacks precise definition but is characterised by elevations in the muscle enzyme creatine kinase alongside musculoskeletal complaints, including pain, weakness, and fatigue. The exact aetiology of statin-induced myopathy remains to be elucidated, although, impaired mitochondrial function is thought to be an important underlying cause. This may result from or be the consequence of several factors including statin induced inhibition of coenzyme Q_{10} (CoQ_{10}) biosynthesis, impaired ca^{2+} signalling, and modified reactive oxygen species (ROS) generation. The purpose of this review article is to provide an update on the information available linking statin therapy with mitochondrial dysfunction and to outline any mechanistic insights, which may be beneficial in the future treatment of myopathic adverse events.

Key points

- Statins are an effective drug to reduce cardiovascular risks.
- There is a clear role for mitochondrial dysfunction in mediating some of the statin-induced adverse events.
- Targeting mitochondrial therapeutically is a logical mechanistic inference to combat statin-induced myopathy.
- Lack of consensus on therapeutic means (e.g., CoQ10), with a need for adequately powered RCTs.

Introduction

Cardiovascular diseases (CVDs) represent a significant contributor to global mortality, accounting for an estimated 17.9 million deaths in 2017(1). An important causal link between cholesterol levels and CVDs was established following decades of evidence (2-4), namely that dyslipidaemia – in this case, high total cholesterol, low-density lipoprotein cholesterol (LDL-C), and triglyceride, as well as low high-density lipoprotein cholesterol – is the primary risk factor.

The management of hypercholesterolemia has been significantly improved since the discovery of 3-hydroxy-3-methylgutaryl coenzyme A (HMG-CoA) reductase inhibitors (i.e., statins), which have proven a highly effective treatment (5). Although generally well-received, statin usage may cause adverse muscular, neurological, and metabolic adverse events; the most frequently reported of these are statin-associated muscle symptoms (SAMS) (6). Emerging evidence suggests that mitochondrial impairment by statins may be an important contributor to SAMS, rather than being due to the inherent lipid-lowering properties of statins (5, 7).

This review aims to provide a detailed overview of statin pharmacology, and their role in SAMS as a key example of a common adverse effect. It will also explore how muscle mitochondrial function and morphology are directly and indirectly affected by statin usage, through a summarisation of studies *in vitro*, in both animal and human models, and *in vivo*. These mechanistic relationships will be discussed, to show that an interference in mitochondrial activity by statins may be an important causative agent.

Methods

This review article is based on the accumulated literature within the field. We utilised PubMed as the main source for articles, screening for studies associated with the search terms: statins, myopathy and mitochondria, reactive oxygen species, oxidative stress. We did not constrain our search based on article type or publication date.

Statins

Statins are a well-established and central treatment for hypercholesterolemia and are important in cardiovascular medicine due to their proven benefits in reducing cardiovascular events (7). Statins act on the mevalonate pathway, a crucial part in the biosynthesis of cholesterol, and target specifically HMG-CoA reductase, a rate-controlling enzyme in this pathway (**Figure 1**). Inhibition of HMG-CoA reductase reduces mevalonate synthesis, and consequently affects the synthesis of several isoprenoid compounds, of which cholesterol is the most prominent.

The statin family of drugs is a heterogenous group, which differ markedly in their absorption and metabolism (8). They are amphiphilic drugs and are classified as either hydrophilic or lipophilic; these affinities are demonstrated in **Table 1**. Cerivastatin, although a prominent statin in clinical studies, has not been included due to its withdrawal as a treatment resulting from severe incidences of myopathy (9). Lipophilic statins can enter cells more easily via direct interactions with membranes, whereas hydrophilic statins require the use of protein transporters due to their association with the polar surface of the cell membrane (10, 11). All lipophilic statins are metabolised by numerous cytochrome P450 (CYP) enzyme isoforms located in the cell membrane and endoplasmic reticulum of hepatocytes (12), which brings

systemic bioavailability to between 5–30% of the administered dose for most statins (**Table 1**). Conversely, hydrophilic statins undergo little-to-no modification by CYP. The hydro- or lipophilic status of statins and their respective metabolic handling may explain, in part, the variations in lipid-lowering properties, as well as beneficial adverse events (8, 13).

Statins have numerous pleiotropic effects, which have been described and evaluated to account for their clinical impact (14). Their primary role as HMG-CoA reductase inhibitors has two important effects: the direct impediment of cholesterol production, as well as the promotion of complementary reactions which result in a reduction of existing LDL-C in blood plasma (15). One complementary mechanism occurs via an enhanced expression of LDL receptors in hepatic cells, which aid in clearing circulating LDL-C(8) [9]. However, some studies have noted a possibility that statins can increase expression of the enzyme proprotein convertase subtilisin-kexin type 9 (PCSK9), a protease which catabolises these hepatic LDL receptors, thereby limiting LDL-C reduction (16, 17). Studies have also demonstrated that statin therapy lowers the production rate of lipoproteins containing apolipoprotein B100 (apoB100), the primary apolipoprotein responsible for carrying cholesterol, resulting in lower concentrations of cholesterol and triglyceride (18). Statins have been noted to improve endothelial function by preserving endothelial nitric oxide synthase (eNOS), which is important in protecting vasculature (19), although this is independent of any impact on cholesterol levels.

Statin-induced muscle symptoms - mechanisms

Despite being generally well tolerated by most patients, statins may produce an array of adverse events, greatly limiting their clinical use (20). The discontinuation of, or otherwise nonadherence to, statin treatment has marked consequences ranging from loss of the decrease in mortality rate (21), to an elevated incidence of harmful cardiovascular events (22). The severity and risk of these adverse effects may vary between statins, potentially due to the differences in their pharmacological profiles (**Table 1**). Musculoskeletal symptoms, however, form the most frequently observed adverse effect, with large-scale observational studies demonstrating an incidence among statin-treated patients of 10-20% (23-25).

There is not yet a consensus on the definition for SAMS, with a precise classification still heavily debated by various panels worldwide (26). All definitions include the presence of inexplicable muscle pain, weakness, or fatigue, with the distinction between cases of myalgia, myopathy (or myositis), and the more severe rhabdomyolysis depending on the presence of elevated creatine kinase (CK) levels (27); clinically, CK is an enzyme expressed by many tissues and cells – notably skeletal muscle – and acts, in part, as a biomarker of muscular injury or damage when found in circulation (28). However, patients presenting with musculoskeletal complaints and an absence of increased CK may be acknowledged as having SAMS (6). For the purpose of this review, the term myopathy will be used to denote musculoskeletal symptoms and an elevated CK >10x the upper limit of normal (ULN), as recommended by the NLA Task Force(29).

Statins clearly have a beneficial therapeutic effect to combat hyperlipidaemia and to improve cardiovascular outcomes. However, there a significant adverse events or side-effects reported by patients – which we refer to as statin-associated muscle symptoms. There are multiple cellular and molecular mechanisms reported in the field, which may underpin SAMS.

Mitochondrial dysfunction.

In a broad sense, mitochondrial dysfunction is defined as the inability to generate appropriate or adequate energy in the form of ATP and its associated precursors, to meet the metabolic

needs of the cell (30). In a more nuanced sense, this can arise from several mitochondrial perturbations, such as altered membrane potential and proton gradient, oxidative damage to ETC complexes and uncoupling (30). There is clear evidence of mitochondrial dysfunction, in that patients with statin-associated muscle symptoms display reduced mitochondrial content. Analysis of biopsies from patients with SAMs, revealed a significant decline in mitochondrial DNA to nuclear DNA ratio (31).

Thus, logical inferences can be made, that statins may impact the lifecycle or the dynamic nature and turnover of mitochondria. In rodent studies, treatment with atorvastatin revealed a decline in PGC1-alpha expression in the *plantaris* muscle, which ameliorated in the presence of a polyphenolic compound with antioxidant properties (quercetin) (32). There is clear mechanistic evidence of a ROS-mediate axis, affecting mitochondrial biogenesis. In that same study, evaluation of deltoid biopsy tissue, in patients treated with statins and those with SAMs, revealed similar decline in PGC1-alpha expression (32). Thus, there is clear clinical and pre-clinical mechanistic evidence, giving credence to the impact of statins on mitochondrial dysfunction.

Strikingly, there appears to be a differential impact of statins, where oxidative muscle has a more robust activation of ROS generation, which promotes beneficial activation of mitochondrial biogenesis. In contrast, glycolytic muscle lacks that antioxidant response, with reported declines in PGC1-alpha/beta (33). Further pre-clinical evidence has shown elevated OPA1 protein levels in atorvastatin treated $ApoE^{-/-}$ mice (34). OPA1 is involved in regulating mitochondrial fusion, these findings suggest that cell stress in the form of increased energetic demand, may be driven by statins in this model and an overall contributor to mitochondrial dysfunction. In contrast, low dose atorvastatin has been shown to be beneficial in male mice, fed a high-fat diet. Data showed a decreased in mitophagy and an increase in mitochondrial fusion markers (MFN1/2 and OPA1) and improved mitochondrial morphology (35).

Direct effects on electron transport chain complexes have been observed in several experimental settings. *In vitro* studies in rat L6 myocytes and human myoblasts, have revealed inhibition of complexes I, III and IV in response to a range of statins (36, 37). Mitochondrial complex inhibition is an established mechanism for ROS generation (38). Thus, the complex activity inhibition, may be a contributor to the ROS-mitochondrial dysfunction axis in SAMs. The generation of ROS is an important lynchpin in SAMs.

Reactive oxygen species (ROS)

Several studies have evaluated the role that modified reactive oxygen species (ROS) generation is associated with mitochondrial dysfunction. As Ca^{2+} represents a key regulator of mitochondrial function, the aforementioned Ca^{2+} efflux is likely to mediate these observed impairments (39). A study by Bouitbir et al., 2012, examined the effects of statins on ROS generation and mitochondrial biogenesis in cardiac and skeletal muscles (32). The deltoid muscles of patients with statin-induced myopathy demonstrated a highly increased ROS production when compared with age-matched controls, with the process of dihydroethidium staining used in this observation indicating an increase of superoxide and/or hydrogen peroxide (40). Moreover, reduced levels of peroxisome proliferator-activated receptor gamma co-activator-1α (PGC-1α), the major regulator of mitochondrial biogenesis, were observed. A reduced expression of PGC-1α and -β mRNA was noted in rat skeletal muscle cells treated with atorvastatin, further indicating impaired mitochondrial biogenesis. Expression of cytochrome oxidase 1 mRNA was also largely decreased, which could be seen to affect mitochondrial metabolism. Interestingly, the study also examined the effects of statins on

cardiac muscle and found opposing results; the mechanisms governing mitochondrial biogenesis were unaltered, or even, in some cases, activated (32). This provides an important indication that statins have varying effects on different types of muscle.

Increased ROS generation was also noted in a study by Kwak et al., 2012. In human skeletal myotubes cultured with simvastatin, generation of mitochondrial superoxide and hydrogen peroxide was greatly increased following simvastatin treatment. This increase in ROS generation is suggested to initiate mitochondrial-mediated apoptosis, which may prove to be a potential contributor to myopathy (41). Furthermore, increases of 53% in Bcl-2-associated X (Bax) protein – a regulatory protein which plays a key role in promoting apoptosis – and consequent elevations of PTP opening by 44% were observed (41, 42). This aids the aforementioned cytosolic Ca^{2+} efflux, as well as apoptosome formation and subsequent DNA fragmentation and cell death (43); the increased levels noted in this study indicate Bax may act as a mediator for statin-induced apoptosis. The up-regulation of these mitochondrial-mediated apoptotic mechanisms demonstrated in this study supports previous postulations that apoptosis during statin treatment may be directly linked to myopathy (44).

The study by Kwak et al., 2012, also suggests a reduced oxygen consumption in myotubes treated with simvastatin, which is thought to be mediated by an inhibition of complex I (**Figure 2**) (41). This was demonstrated by a 32-37% reduction in ADP-stimulated, state 3 respiratory capacity, and is consistent with previous studies (45). This impairment was not due to a difference in mitochondrial content, as CS activity was noted to be identical between treated and untreated myotubes. Decreased oxygen consumption and respiration were also noted in previous studies. In isolated rat L6 cells exposed to fluvastatin, atorvastatin, and simvastatin, glutamate-driven state 3 respiration was inhibited. This accounted for an observed depression of the respiratory control ratio (37), the ratio between ADP and the rate of oxygen consumption in the presence of a substrate (46). This decrease occurred at statin concentrations above those encountered therapeutically (47). In mitochondria isolated from simvastatin-treated (10μM/6h) C2C12 myotubes, state 3 respiration was significantly reduced by 12.2%, but only in the presence of succinate as a substrate (48). The insulin growth factor 1/protein kinase B (IGF-1/Akt) signalling pathway is well-described to maintain mitochondrial health and be dysregulated by statins (49, 50); its relationship with lowered mitochondrial respiration was also tested. Dephosphorylated Akt was observed in the treated myotubes, which indicates a lack of mitochondrial function maintenance; however, when incubating the myotubes with IGF-1, mitochondrial respiration appeared restored (48). These results reinforce previous studies which describe the importance of the IGF-1/Akt pathway in the aetiology of statin-induced myopathy, such that reductions in signalling via this pathway increase levels of atrogin-1, an atrophy-inducing protein, in muscle (51).

The study by Kaufmann et al., 2006, further describes a decrease in mitochondrial membrane potential ($\Delta\Psi m$), which can also contribute to apoptosis of muscle cells (37, 52). Over half of L6 rat cells exposed to 100μmol/L of fluvastatin exhibited a dissipated $\Delta\Psi m$, with 100μmol/L of atorvastatin and simvastatin also affecting $\Delta\Psi m$ in a smaller, but still significant, proportion of cells (20% and 26%, respectively). The decreases in $\Delta\Psi m$ are associated with other mitochondrial alterations noted in the study, namely impairment of the ETC, and subsequent mitochondrial swelling. Swollen mitochondria were also observed in a study by Obayashi et al., 2011, which preceded necrosis of muscle in rats treated with cerivastatin. Mitochondrial swelling as a result of lowered $\Delta\Psi m$ can culminate in the rupture of the outer mitochondrial membrane and allows for the leaking of pro-apoptotic proteins – e.g., cytochrome c (**Figure 2**) – from mitochondria (53). This contributes to the apoptotic mechanism of myopathy; therefore, the maintenance of this potential is critical in preventing myocyte death (37).

Coenzyme Q_{10} depletion

The mitochondrial electron transport chain (ETC) is one of the primary mechanisms of cellular energy generation. Located in the inner mitochondrial membrane, the ETC is comprised of five enzyme complexes which function to drive the process of oxidative phosphorylation, which results in ATP formation (54); this process is demonstrated in **Figure 2**. Electron carriers are crucial to this process, and are found in the form of CoQ_{10} and cytochrome c. Of particular importance to this review, CoQ_{10} shuttles electrons from complexes I and II to complex III but may also play a secondary role as a potent antioxidant (55). Natural deficiencies in CoQ_{10} biosynthesis represent a treatable type of ETC disorder, and CoQ_{10} supplementation can prove a relevant therapy(56).

The relationship between mitochondria and statin-induced myopathy was originally postulated following studies which demonstrated decreased CoQ_{10} levels in statin-treated, hypercholesterolemic patients, both in circulation and in muscle (57, 58). Several studies since have reported depletion of plasma CoQ_{10} levels in statin-treated patients and have been previously reviewed at length (59). A study by Païva et al., 2005, noted a 30% decrease in muscle CoQ_{10} in hypercholesterolemic patients treated with simvastatin (80mg/day/8 weeks), and a similar decrease in plasma CoQ_{10} (39%) in patients treated with atorvastatin (60). However, as atorvastatin had no impact on muscle CoQ_{10} concentration, the decrease in plasma CoQ_{10} was not significant, and was likely due to reduced LDL as a result of statin treatment, as LDL transports CoQ_{10} in circulation (61). Further analysis of human skeletal muscle biopsies by Duncan et al., 2009, also noted significant decreases in muscle CoQ_{10} concentration after statin treatment. Two patients undergoing simvastatin treatment (40mg/day) demonstrated a decreased CoQ_{10} status in muscle (77 and 132pmol/mg, respectively), and further CoQ_{10} reduction in primary astrocytes cultured with 100μM lovastatin (62). These studies also demonstrated a reduction in ETC complex activity concurrent to CoQ_{10} depletion. Complex IV activity was also found to be decreased in both studies. A reduction in complex I, and II+III activities were also noted by Païva et al., 2005, but were within reference limits in the study by Duncan et al., 2009. However, the loss of ETC complex function observed by Païva et al., 2005, was thought to be due to a loss of mitochondrial volume, unlike in the study by Duncan et al., 2009, as concluded via a decrease in citrate synthase (CS), but a lack of observed change in complex activities relative to CS activity. CS is a quantitative enzyme marker of mitochondrial content (63).

As previously mentioned, a decrease in LDL by statins may represent one mechanism of CoQ_{10} depletion in statin-treated patients. The transport of CoQ_{10} critically requires LDL, due to the inability of CoQ_{10} to circulate in significant concentrations unbound (64). An alternative mechanism exists in the inhibition of the mevalonate pathway (**Figure 1**). One early study examining the effect of statins on plasma CoQ_{10} concentrations was based on the rationale that statins inadvertently block the CoQ_{10} biosynthetic pathway in their attempt to reduce cholesterol synthesis (65). HMG-CoA reductase represents a vital regulatory step in the synthesis of CoQ_{10}, and its inhibition impinges on this process (66). Inherited defects of CoQ_{10} synthesis may also contribute to the development of SAMS, despite not resulting from statin treatments. Several studies, such as that by Oh et al., 2007, demonstrated an association between the occurrence of SAMS and genetic variation in CoQ_2 – the gene which encodes para-hydroxybenzoate-polyprenyl transferase, the second enzyme in the CoQ_{10} synthetic pathway (67). A further study by Ruaño et al., 2011, genotyped patients with SAMS and asymptomatic statin-treated patients (377 and 416, respectively), and noted CoQ_2 as being statistically significant between the groups (68). This validated the CoQ_2 gene as a marker of myopathy in statin-treated patients. Polymorphisms in the CoQ2 gene, which encodes for the CoQ10 biosynthetic enzyme 4-hydroxy-benzoate polyprenyl transferase, have been

suggested as a predictive marker of possible muscular side effects in patients treated with statins. Genetic variation in CoQ2, is associated with increased odds of statin intolerance, defined primarily through muscle symptomatology. Clearly, additional mechanistic and genetic studies are required to confirm these observations. But these preliminary pharmacogenetic results are consistent with the idea that statin intolerance which is manifested primarily through muscle symptoms is associated with genomic variation in CoQ2 and thus perhaps with the CoQ10 pathway (67).

Impaired calcium signalling

Statins have been shown to induce calcium (Ca^{2+}) release in myocytes, and subsequent cellular damage. A study by Nakahara et al., 1994, demonstrated the potential of an increased cytosolic free calcium concentration ($[Ca^{2+}]i$) to cause damage to muscle cells (69). Cultured rat L6 myoblasts treated with simvastatin (20–30 µg/ml), but not pravastatin, initiated an increase in $[Ca^{2+}]i$ via Ca^{2+} release from intracellular stores, across two waves. As the sarcoplasmic reticulum (SR) represents a primary Ca^{2+} store in muscle cells, Sirvent et al., 2005, hypothesised that statins would induce SR-Ca^{2+} release (45). Human skeletal muscle cells were treated with an inhibitor (ryanodine; 100µM) of ryanodine receptors (RyR), which are responsible for SR-Ca^{2+} release. Although simvastatin-induced $[Ca^{2+}]i$ release was largely abolished, weak elevations remained, indicating an alternative pathway of Ca^{2+} release. Mitochondria, another important store of Ca^{2+} (70), were noticed to rapidly unload Ca^{2+} in muscle fibres receiving acute treatment of simvastatin. This early efflux of Ca^{2+} from mitochondria as a result of simvastatin treatment represented the first wave of $[Ca^{2+}]i$ increase, followed by the SR-Ca^{2+} release responsible for the second, delayed increase in $[Ca^{2+}]i$. Mitochondrial efflux of Ca^{2+} can occur via either the Na^{+}-Ca^{2+} exchanger (NCE) or permeability transient pore (PTP) (71, 72). Pre-treatment of muscle fibres with inhibitors specific to these routes (0.2µM clonazepam and 0.5µM cyclosporine, respectively) blocked mitochondrial Ca^{2+} release, and further inhibition of RyR abolished transient release of Ca^{2+} altogether. This study suggests the initial mitochondrial release of Ca^{2+} acts to initiate the larger, delayed SR-Ca^{2+} efflux. These results were further vindicated by a study on human THP-1 cells, conducted by Hattori et al., 2009, in which a significant Ca^{2+} release by both RyR and mitochondria was noted after treatment with simvastatin (100µM) (73).

The mechanisms described in the aforementioned studies provide a potential explanation for the adverse effects encountered by statin users. The robust increase in $[Ca^{2+}]i$ as a result of mitochondrial Ca^{2+} release via PTP and NCE may cause Ca^{2+}-activated protein dysregulation, apoptosis, degradation of proteins, and muscular remodelling (45). One mechanism of protein degradation utilises calpains – proteases located in cytosol and mitochondria – which are activated by increased $[Ca^{2+}]i$ and aid in the release of apoptosis-inducing factors from mitochondria (74). The increase in cytosolic Ca^{2+} may also have knock-on effects, in the form of increased Ca^{2+}- and phospholipid-dependent protein kinase C (PKC). Increased PKC expression promotes the overregulation and closing of ClC-1, a chloride channel found in cell membranes. A large resting chloride channel conductance (gCl) is important in maintaining resting membrane potential and polarisation (75), and this depends on the expression of ClC-1. The closing of ClC-1 causes a decline in gCl and results in hyperexcitability of muscle membranes and reduced skeletal muscle function in rats treated with lipophilic statins (76, 77).

It may be possible that statin-treated patients who experience myopathic symptoms are temporarily exposed to a concentration of statin similar to those experimental doses, as the concentrations required to produce this significant Ca^{2+} efflux are close to therapeutic doses of various statins (45). Furthermore, lipophilic statins, like simvastatin, are expected to cause

this phenomenon more effectively, due to their stronger affinity to cell membranes. This may explain why the study by Nakahara et al., 1994, did not demonstrate any effect of pravastatin on $[Ca^{2+}]i$, nor its ability to cause cellular damage.

Statin treatment may not impair muscle mitochondrial function.

Despite the plethora of existing evidence implicating mitochondrial impairment in statin-induced myopathy, some studies conclude that statin treatment has no significant effect on mitochondrial morphology or function. A study by Laaksonen et al., 1996, showed no change from baseline in CoQ_{10} levels in skeletal muscle biopsies of hypercholesterolemic patients treated with simvastatin (20mg/day/6 months), compared to control (78). The study also noted no changes in high-energy phosphate concentrations in muscle, which represents an important indication of ATP production (79). These results may, however, be accounted for by the low dose of statin used in the study.

Rat skeletal muscle examined by Schaefer et al., 2004, exhibited necrosis and inflammation following 15 days of cerivastatin treatment (0.1, 0.5, or 1.0mg/kg/day) (80). However, mitochondrial dysfunction was not shown to precede these effects, as structural characterisation revealed mitochondrial alterations in degenerating myofibers, and not those unaffected by treatment. Moreover, CoQ_{10} levels did not significantly decrease between treated and control rats, and no observable adverse mitochondrial effects were noted. This concluded that neither mitochondrial damage, nor decreased CoQ_{10} concentrations, represent the primary cause of statin-induced myopathy (80).

Lack of evidence for Coenzyme Q10 in statin-induced myopathy

As CoQ_{10} represents an important component of mitochondrial function, as well as its role as a potent antioxidant, it is unsurprising that CoQ_{10} therapy may be considered for patients with statin-induced myopathy. Numerous studies have assessed the capability of CoQ_{10} in combatting two key aspects of statin-induced myopathy: elevated CK concentrations, and complaints of pain, weakness, fatigue, or cramp. Most of the trials conducted concluded that CoQ_{10} has no significant effect on the biochemical markers of myopathy, such as CK; in these cases, CK concentration remained similar baseline, across both the treatment and placebo groups. Complaints of muscle pain, weakness, fatigue, and cramp were assessed by a visual analog scale (VAS) questionnaire, a validated measure of acute and chronic pain (81). The studies that utilised the VAS were split in their results, and thus no definitive conclusion can be made of the efficacy of CoQ_{10} in relieving pain symptoms. Previous meta-analyses have been conducted using similar trial data. Qu et al., 2018, concluded that while CoQ_{10} supplementation had no significant benefit in lowering CK concentrations, it did ameliorate SAMS, suggesting it as a possible complementary therapy for statin-induced myopathy (82). However, a more recent and up-to-date meta-analysis, robustly challenges the assertions of Qu et al., (83). Specifically, Kennedy et al., identified key flaws in the analysis by Qu et al., in terms of an overestimation in the treatment effect, stemming from a misinterpretation of change in pain score data for two studies. There is a clear gap in knowledge remaining, which can only be addressed through undertaking a robust and appropriately powered RCT.

Conclusion

This review has explored the relationship between statin usage and mitochondrial impairment, and the subsequent role played in the mechanism of statin-associated myopathy, which affects a significant number of statin-treated patients despite the drug's well-tolerated profile. Data clearly demonstrates a plethora of statin-induced impairments of mitochondrial morphology and function, including direct interference in the mitochondrial ETC, and inhibition

of important functional molecules; however, conflicting studies prevent a definitive conclusion being made on whether mitochondrial impairment is a consistent result of statin treatment. The exact mechanism for the development of statin-induced myopathy remains unknown, but the studies presented in this review provide some indication that mitochondrial function plays a partial role in what is likely to be a multifactorial aetiology. Perhaps seen as an obvious potential treatment for myopathy, CoQ_{10}, with its ability to boost ETC function and antioxidant status, has not been shown to have any significant effect in ameliorating myopathy, despite some studies indicating an improvement in muscle pain post-supplementation. In view of its limited therapeutic efficacy, alternative candidate therapies to CoQ10 may be judicious that target the ETC and ameliorate oxidative stress.

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Figure Legends

Table 1: Summary of basic statin pharmacology.

Figure 1: A schematic overview of the melvonate pathway. Created with BioRender.com.

Figure 2: Overview of the oxidative phosphorylation mechanism in the mitochondria. Created with BioRender.com.

Figure 3: Schematic summary of the contributory mechanisms centred around mitochondrial dysfunction, which play a key role in statin-induced myopathy. Abbreviations: bcl-2-like protein 4 (BAX); Insulin-like growth factor (IGF) 1; protein kinase b (Akt); Coenzyme Q10 (CoQ10); chloride channel 1 (ClC-1); protein kinase c (PKC); permeability transition pore (PTP). Created with BioRender.com.