Possible Effects of Simvastatin on Skeletal Muscles

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Abstract
Nearly one-third of American people have hyperlipidemia, or high blood cholesterol, putting them at increased risk for cardiovascular disease. The risks of cardiovascular disease can be reduced with the use of statins, which are lipid-lowering drugs that are both widely prescribed and effective. Among the most prevalent adverse effects of statins are muscular cramps, aches, weakness, and, in extremely rare instances, death due to fast muscle breakdown. These negative effects often manifest themselves during or after intense physical activity. Even though we still don't fully understand how statins influence muscular performance, new studies have pointed to a few common components. Physical therapists are in a prime position to detect statin-related side effects because of their expertise in musculoskeletal and exercise disorders. This perspective article aims to accomplish the following goals: (1) to provide a rundown of statin metabolism and action mechanisms; (2) to talk about how statins affect skeletal muscle function; (3) to describe the symptoms and signs of statin-induced myopathies; (4) to explain the tests used to diagnose these conditions.
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Introduction
Hyperlipidemia, or high blood cholesterol, is a prevalent issue in the cardiovascular system. Among American adults, 35.6% have received the diagnosis of hyperlipidemia.[1] A significant risk factor for coronary artery disease—the top cause of death and disability in the US—is hyperlipidemia.[2]
Hyperlipidemia has multiple etiologies. As people become older and gain weight, their blood cholesterol levels tend to rise. On the other hand, cholesterol levels in women's blood are typically lower before menopause and greater following the transition. Certain risk factors for hyperlipidemia include alcohol consumption, race, and educational attainment. The lack of a single identifiable cause for hyperlipidemia suggests that a multipronged approach is necessary in its management [3-4]
Hyperlipidemia can be treated in a number of ways. Treatment for hyperlipidemia typically involves medication, patient education, adjustments to the patient's diet, and physical activity. A wide range of issues related to the blood lipid profile, which hyperlipidemia represents, must be taken into account while formulating a treatment strategy. Medications, in contrast to alternative

treatments, frequently produce unwanted side effects. The use of drugs to treat hyperlipidemia is, nevertheless, supported by their efficacy. The 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor class of lipid-lowering medications has the best track record of reducing cardiovascular disease risks with a reasonable risk-benefit ratio; these treatments are commonly referred to as statins. [6-9]

The treatment of hyperlipidemia often involves the use of statins. The statin atorvastatin, brand name Lipitor, was the most popular prescription and over-the-counter drug in the US in 2006. The percentage of individuals with hyperlipidemia who used medication to decrease their cholesterol rose from 11.7% in 1988 to 40.8% in 1994. Since statins are given to lower cholesterol levels, physical therapists will most likely assess and treat patients who take these medications. [10]

Recently, there has been an increased interest regarding the side effects of statin use on patients being seen by physical therapists. Approximately 25 million Americans use statins, and 5% to 18% of these patients report some form of myalgia.[14] Skeletal muscle side effects that are associated with statin use involve muscle cramping, soreness, fatigue, weakness, and, in rare cases, rapid muscle breakdown that can lead to death (ie, rhabdomyolysis).[15,16] Side effects have been associated with all commonly used statins and are dose dependent.[17,18] Advancing age, the presence of renal or hepatic disease, the use of concurrent medications, and being female are predisposing risk factors for statin-related myopathy.[17,19] Although serious skeletal muscle side effects are rare,[15] researchers and physicians with expertise in statin therapy have highlighted the importance of developing a reliable method for early diagnosis.[20] However, because definitions of myopathy vary widely, it is difficult to draw reliable conclusions among studies and to determine accurate diagnostic critera.[20,21]

Using statins safely requires regular monitoring for side effects. However, it has recently been suggested that routine examinations for side effects may not be cost-effective.[20,21] Armitage suggested that, currently the "best means of detecting myopathy clinically is awareness of the main risk factors"[22(pp1784–1785)] such as drug interactions, high-dose prescriptions, and being at high risk and that once "statin myopathy or rhabdomyolysis is detected, statin treatment should be immediately stopped."[22(p1785)] Statin withdrawal, however, carries serious vascular risk,[21,23–25] so the relative risk must be considered.

Physical therapists are well trained to evaluate abnormal muscle soreness. Muscle soreness after exercise that is caused by statin use may go undetected by patients.[26] Physical therapists are in a unique position to differentiate between muscle soreness normally experienced after exercise and the side effects from statins. Although some clinicians may have extensive experience with identifying the side effects of commonly used medications, many physical therapists may not know the risk factors associated with statin use or the early warning signs of statin-related myopathy. The purposes of this perspective article are: (1) to review the metabolism and mechanisms of action of statin; (2) to discuss the effects of statins on skeletal muscle function; (3) to detail the role of exercise, genetics, and multiple medications on statin-induced myopathies; (4) to outline the testing used to diagnose statin-induced myopathies; and (5) to introduce a role for the physical therapist for the screening and detection of suspected statin-induced skeletal muscle myopathy. However, prior to presentation of the metabolism and mechanism of action of statins, we first need to present the current terminology related to statin-induced myopathies.

Current Terminology

The National Lipids Association's (NLA) Muscle Expert Panel and other statin experts have emphasized the importance of standardizing terms related to myopathy to allow reliable comparisons among research studies and to improve care for statin users. Standard terminology also may encourage additional clinical trials investigating under-represented populations, such as people with mild increases in creatine kinase (CK) levels, people over the age of 75 years, or those with renal or hepatic comorbidities.[27,28] Creatine kinase is an enzyme that acts with phosphocreatine to replenish the stores of ATP in skeletal muscle.[29] Serum CK levels are commonly used determine the presence of skeletal muscle damage.[30] *Myopathy* is the general term used to describe all muscle problems.[15,28] More specifically, symptomatic myopathy is described as muscle pain, weakness, or other complaints that have a skeletal muscle origin.[20] If these symptoms are accompanied by elevations in CK levels, the condition is known as myositis.[12,21,28] Asymptomatic myopathy exists when CK levels are elevated, as can occur with vigorous exercise[31,32] in the absence of other muscle symptoms [20]

The most severe case of statin-induced myopathy is rhabdomyolysis,[15,16,20,25] which includes the presence of muscle cell destruction or enzyme leakage, usually in combination with an increase in CK level.[20] Clinically, rhabdomyolysis is associated with deterioration in renal function and death.[16,33] Due to the unacceptably high incidence of severe muscle myopathies, cervastatin (Baycol[†]) was removed from the commercial market in 2001, and production ceased on a high-dose version of simvastatin in the mid-1990s.[16] The NLA's Muscle Expert Panel has suggested using absolute CK levels in lieu of the broader term “rhabdomyolysis”[20] to further standardize myopathic definitions [20]

Metabolisms and Mechanisms of Action of Statins

Statins are primarily metabolized in the liver. In hepatic metabolism, a large number of diverse enzymes called cytochrome P450s can direct a drug's passage through the system or control its interaction with other enzymes.[25,34] Cytochrome P450s are found most abundantly in the human liver, but also are seen in the gastrointestinal tract and kidneys.[34] Lipophilic statins are metabolized by the enzymes of the CYP3A4 subfamily.[34] With the exception of cervastatin, these statins also are metabolized significantly via first-pass metabolism, which occurs in the gastrointestinal tract and liver.[34] If first-pass metabolism is inhibited by competing drug or food substances using the same pathway, statin toxicity can increase from 5% to 100%.[34] Calcium channel blockers,[34] fibrates,[28] antifungals,[16,28,35] and grapefruit juice[34] are just a few of the known enzyme inhibitors of various statins by way of the CYP3A4 enzyme subfamily.

The production of cholesterol depends on the rate at which the enzyme HMG-CoA reductase reduces HMG-CoA to mevalonate (Figure).[15,28,36] Statins as a group contain molecular side chains that allow them to be absorbed quickly into liver cells, and then bind to and inhibit HMG-CoA reductase.[37] Statins reduce the production of endogenous cholesterol, and other products of the mevalonate pathway. Decreased hepatocyte low-density lipoprotein (LDL) levels cause an upregulation of LDL-specific cell receptors in the liver that work to pull LDL from the blood; this further reduces hyperlipidemia.[38]

Effects of Statins on Skeletal Muscle Function

The mevalonate pathway also is important for protein regulation and skeletal muscle adaptation. Although cholesterol is the intended target for statins, dolichols, ubiquinone, and prenylated proteins production are reduced as well (Figure). Dolichols function to synthesize glycoproteins necessary for tissue growth.[39] Ubiquinone (coenzyme Q10 [CoQ10]) acts within mitochondria to reduce metabolic equivalents in the tricarboxylic acid cycle.[36] Prenylated proteins act to regulate cell growth, intracellular traffic with a specific function between the endoplasmic reticulum and the golgi apparatus,[40] and gene transcription.[41]

The ubiquitin proteasome pathway has been shown to play a key role in the maintenance of skeletal muscle architecture.[42] The ubiquitin proteasome pathway mediates protein turnover via several enzymes and, in the presence of catabolic disease states, upregulation of this pathway can lead to muscle atrophy.[43,44] One of these enzymes, a ubiquitin protein ligase known as atrogin-1, is increased as a result of statins[45] and is associated with muscle wasting secondary to disease or fasting.[46,47]

Statin-induced myopathy may be multifactorial, the result of impaired signal transduction, cell trafficking, gene transcription, structural protein formation and regulation, and oxidative phosphorylation.[8,28] Also, a genetic tendency toward abnormal muscle and drug-induced mitochondrial dysfunction may be exacerbated by statins.[25,34,48] Abnormal fat oxidation or mitochondrial dysfunction may be the primary mechanism underlying statin myopathy.[44] Other possible mechanisms are reduced sarcolemmal cholesterol[25] and isoprenoids involved in muscle fiber apoptosis.[25,49] Cellular metabolism is negatively affected by statins alone through the inhibition of a cellular pathway (Figure).

Commonly prescribed statins are identified by their lipophilic or hydrophilic nature[49] and have different recommended dosages[50] (Tab. 3). Lipophilic statins demonstrate a concentration-dependent adverse effect on muscle cell viability and promote cell disruption via proteolysis and apoptosis.[15,49] *In vitro* studies confirm that lipophilic statins have greater myopathic effects than hydrophilic statins.[15,28,49] Ease of diffusion via passive transport across the bilipid membrane layer by lipophilic statins has been associated with higher toxic effects.[16,28] For example, cervastatin, which was a commonly prescribed lipophilic statin[37,49] before its removal from the commercial market, has been shown to have the highest incidence of rhabdomyolysis and other myopathic complaints compared with other statins.[9] Rosuvastatin is a hydrophilic statin that has demonstrated a propensity to reduce LDL levels more effectively than lipophilic atorvastatin, while having positive effects on high-density lipoprotein levels.[51] It is worth noting, however, that pravastatin, another hydrophilic statin, can cause increases in plasma concentration 10 times greater than those of other lipophilic statins due to poor penetration into muscle cells.[28]

Each statin can be further classified into its lactone or acid forms.[15] Both forms, for all statins, interconvert to achieve equilibrium *in vivo.*[15] Researchers in Norway[15] evaluated the potency on muscle cells of the lactone forms versus the more active acid forms of several commonly prescribed statins. Morphological analysis revealed that both lactone and acid forms of statins reduced the number of living muscle cells.[15] Although myopathy was found to be time and concentration dependent, based on the number of remaining viable cells, lactone forms consistently showed more extensive myopathic effects compared with their respective acid forms.[15] The mechanism of the

higher myopathic potential of the lactone forms of statins is unclear,[15] but researchers surmise that the lipophilic nature of the lactone versions may enhance their passive transport across the muscle membrane, yielding a greater propensity for damage.[16]

Although cholesterol is the target of statins, CoQ10 also is affected. Coenzyme Q10 is produced within the mevalonate pathway and is involved in the electron transport during oxidative phosphorylation in mitochondria.[36,41] Coenzyme Q10 acts as a mobile component of the respiratory chain in mitochondria.[28] A reduction in CoQ10 levels has been suggested to mediate statin myopathy as a result of its proposed ill effect on mitochondrial function.[25,52] It is suggested that depleted serum levels of CoQ10 play a more integral role as a predisposing factor, rather than a primary role, in statin-induced myopathies.[28] Statin treatment may impair mitochondrial oxidative metabolism and alter resting substrate utilization, shifting the balance toward carbohydrate metabolism.[39] Statins have been associated with a decrease in CoQ10 synthesis that leads to impaired oxidative phosphorylation and impaired energy production.[28] Although there have been inconsistent findings of altered mitochondrial dysfunction in the presence of reduced CoQ10, there is a lack of evidence supporting the mitigating results of myopathy with CoQ10 supplementation.[25,28] Depleted CoQ10 as a result of statin use, therefore, may affect mitochondrial oxidative metabolism and impair energy production during exercise. Skeletal muscle impairments related to the combined effects of exercise and statin use are not thoroughly understood and are currently under investigation.

Role of Exercise, Genetics, and Multiple Medications on Statin-Induced Myopathies

Statins and Exercise

Statin treatments have been shown to exacerbate exercise-induced skeletal muscle injury.[53] The extent of statin-influenced myopathies during exercise is still under investigation. Thus, because statins are a commonly prescribed cholesterol-lowering intervention, it is likely that a clinician or physical therapist may come across signs and symptoms of an adverse side effect during treatment. Exercise-induced muscle damage and increased serum levels of CK increase as a result of damage to the muscle tissue following intense, prolonged exercise, especially exercises that are weight bearing and include eccentric muscular contractions.[18,31,32] Myocytes that are affected by exercise-induced muscle damage release intracellular substances, such as CK, into the blood; therefore, CK levels are a commonly used marker to determine skeletal muscle damage.[30] Individual CK level responses vary and may be influenced by multiple factors, such as genetics, level of athletic performance, and types of exercises being performed.[18,30] Individuals with significant CK level increases as a response to exercise have been labeled as “high responders,” but there is no clear clinical definition of a high responder, and the phenomenon is not well understood.[30] Exertional rhabdomyolysis is a clinical syndrome that may occur as a result of severe skeletal muscle destruction in response to exercise.[30]

Thompson et al[53] compared the CK response to downhill treadmill walking and bicep curl exercises in young men who were healthy taking lovastatin or a placebo. These men were physically inactive, exercising less than once per week during the preceding 6 months, consumed fewer than 2 alcoholic drinks per day, and had lipid-lowering medications, probuchol, and supplemental vitamins discontinued 6, 12, and 4 weeks, respectively, prior to the beginning of the study. Thompson et

al[53] found that the mean CK concentrations were 62% and 77% higher 24 and 48 hours after treadmill exercise in subjects who received lovastatin versus those who received a placebo, respectively. Thompson et al[53] also found elevated CK levels in the subjects who received lovastatin versus those who received a placebo following the completion of a biceps curl exercise protocol, although these differences were not significant. Although baseline CK levels were different between the randomized groups, statistical analyses accounted for these differences, and the authors concluded that statins and eccentric exercise together exacerbated muscle injury more than exercise alone.

Adverse effects of statins on the skeletal muscle during exercise are widely accepted by many professionals and investigators to be dose dependent.[37] Kearns et al[32] examined the contrasts in the effects of different statin doses (atorvastatin, 10 mg versus 80 mg) on skeletal muscle during eccentric exercise. Seventy-nine men completed both the 5-week treatment and a downhill treadmill protocol during the fifth week of treatment. Using inclusion criteria similar to those of Thompson et al,[53] Kearns and colleagues randomly assigned 42 men to the 10-mg atorvastatin group and 37 men to the 80-mg atorvastatin group. Baseline values were used as the control. Plasma CK levels were significantly elevated from baseline 24, 48, and 72 hours after the completion of the exercise protocol in both treatment groups. There was no significant difference in the postexercise CK levels or muscle soreness between the 2 dose-dependent treatment groups.[32] Interestingly, these findings contradict other literature that suggests the side effects of statins during exercise are dose dependent. Pretreatment CK values were slightly, but significantly, higher in the 10-mg atorvastatin group than in the 80-mg atorvastatin group. This finding may have obscured any effects due to the higher dosage, as baseline CK levels are used as a marker for the predisposition to statin toxicity or muscle injury.[32] However, the results from this study showed an increase in CK values during exercise with statin use occurred in both treatment groups, regardless of dosage.[53]

The exact mechanisms or pathways through which statins adversely affect the skeletal muscles during exercise are not fully understood.[8,32,53] The ubiquitin proteasome pathway is one possible mechanism for statin-induced muscle myopathy during exercise. Upregulation of the ubiquitin proteasome pathway during eccentric exercise has been shown to be associated with increased muscle injury, decreased muscle strength, and a decrease in myofibrillar protein.[54] Atrogin-1 is a ubiquitin protein ligase strongly induced by any stimulus that induces muscle atrophy and may be a key effector in muscle degradation during catabolic states.[47] Atrogin-1 may be referred to as FBX32, because it is classified as a muscle F-box family protein. Increases in FBX03, another F-box family protein, has been observed after statin treatment and exercise; this finding suggests that the ubiquitin ligase machinery may be altered by exercise with statin treatments, which, in turn, may affect protein degradation and repair.[8]

Changes in ubiquitin proteasome pathway gene expression in skeletal muscle as a result of exercise and statin use were investigated by Urso et al.[8] In that study, subjects performed 300 eccentric exercises with one leg before and after the completion of an 80-mg atorvastatin or placebo treatment. The unexercised leg was used as a control. With the statin treatment alone, only 5 genes were differentially expressed compared with the unexercised leg or the exercised leg of the placebo group, indicating that the use of statins has little effect on skeletal muscle gene expression.

Furthermore, eccentric exercise alone presented 80 genes that were differentially expressed compared with the nonexercised leg of the placebo group. According to the gene ontology classification database used in the study, the authors concluded that the genes that were differentially expressed due to eccentric exercise alone often were involved in cell functions. They found that eccentric exercise along with statin treatment had the greatest effect on transcription factors and genes involved in the ubiquitin proteasome pathway when compared with eccentric exercise or statin use alone. These results indicate that altered gene expression resulting from a combination of statins and exercise may be one explanation for observed side effects on skeletal muscle with statin treatments.

Exercise provides a well-defined stimulus for skeletal muscle oxidative metabolism.[55] Respiratory exchange ratio (RER) is the ratio of carbon dioxide production to oxygen consumption (RER=CO_2 production/O_2 consumption)[56] and indicates the types of fuel sources used for energy production. The relative contributions from fatty acids versus carbohydrates to oxidative energy production can be measured under controlled conditions using ventilatory gas exchange.[56] Impaired fat oxidation at rest, represented by a higher RER value, may indicate increased carbohydrate use, which would be a limiting factor during exercise, leading to lower levels of exercise tolerance, increasing fatigue, and possibly causing other symptoms during exercise.[57] Phillips et al[58] found statin-induced increases in fasting RER at rest. Patients postmyositis, who were off statins, had a significantly increased RER compared with a control group. Interestingly, Phillips et al[58] also found that a 6-week statin treatment increased the fasting RER within the control group. These findings may be explained by a reduction in mitochondrial utilization of fatty acids. Contrary to the results of other investigations, Chung et al[55] did not see any changes in resting energy expenditure or resting RER in 13 subjects who were administered 40 mg per day of atorvastatin. Eight weeks of a 40-mg atorvastatin treatment did not have an effect on steady-state RER, fatty acid oxidation, or oxygen consumption. Based on these results, Chung et al[55] concluded that atorvastatin at 40 mg per day does not impair fatty acid oxidation or muscle mitochondrial capacity in people who are healthy.

Statins and Related Genetic Factors

Genetic predisposition testing may become an integral component of personalized medicine and may influence the efficacy and safety in which medications are selected.[41] Muscle toxicity related to statin use may be influenced by genetic factors or the presence or absence of specific genotypes. Genetic risk factors contributing to the development of statin-induced myopathies that are of interest relate either to drug metabolism or to muscle metabolism.[41] According to Vladutiu,[41] the SEARCH collaborative group found that more than 60% of 85 patients with myopathic symptoms had variations of the C allele of the SLCO1B1 gene. Encoded polypeptides within the SLCO1B1 gene are involved in the regulation of the hepatic uptake of statins.[59]

Genomic variations or reductions of specific coenzymes, such as CoQ10, may be another possible mechanism for statin-induced myopathy. Oh et al[48] compared 133 subjects who were statin intolerant with 158 matched controls who were statin tolerant and found that genomic variation in CoQ10 was associated with an increased risk of statin intolerance, defined through muscle symptomatology. Coenzyme Q2 is the second enzyme in the CoQ10 biosynthetic

pathway.[25] These findings reinforce the concept that adverse muscle symptoms or statin intolerance may be associated with a genomic variation in the CoQ10 pathway.

Effects of Multiple Medications

The occurrence of drug interactions between statins and other medications have been well documented.[7,25,34,60] Either the medication itself or its metabolic products can pose the largest threat of harmful effects to the user.[34] Recently, mechanisms underlying the effects of multiple medications have gained attention due to the effects severe myopathies have on some statin users.[7,37]

For many patients, additional lipid-lowering medication often is needed to reduce their risk of adverse cardiovascular events.[61] Niacin, bile acid sequestrants, and plant stanols are supplemental lipid-lowering agents often used in combination with statins to maximize efficacious management of high LDL cholesterol levels.[60,61] Stein et al[60] found that atorvastatin combined with ezetimibe, which inhibits cholesterol absorption in the intestine, is more effective at reducing LDL cholesterol levels compared with double doses of atorvastatin. Although the safety and tolerability of both treatments were found to be similar in this study,[60] other researchers have shown that myopathic effects are dose dependent.[37]

In contrast, there is evidence that statins will interact in a negative way with other medications that are broken down through the same metabolic process in the liver.[7,62] Many patients who are taking statins for hyperlipidemia also may be taking other medications that could interact.[63] Varying degrees of myopathy, including rhadomyolysis, have occurred with the concomitant use of statins with other medications, including colchicine,[64] digitoxin and amiodarone,[65] nefazodone,[66] and others.[67–69] Obtaining a detailed medical history that includes current medications is imperative for physical therapists to facilitate the management of skeletal muscle dysfunction in statin users.

Fibrates are another class of medication used to mitigate high cholesterol and, when used with statins, can effectively modulate complex hyperlipidemias.[28] This combination therapy, however, increases the incidence of statin-induced myopathies.[9,28,33,58] McClure et al[9] reported the increased risk of myositis (moderate CK levels as per the NLA's Muscle Expert Panel) with statins, fibrates, and other patient-related variables. These researchers showed that the average time to the onset of myositis was ≤2 years with both statin-fibrate combination therapy and statin use alone.[9] Statins, fibrates, pre-existing renal disease, and hepatic disease are all significantly associated with myositis.[9] Molokhia et al[7] reported a significant increase in the risk of myopathies and myalgias with prolonged statin exposure at both 26 and 52 weeks and that the risk for myopathy for all statins and fibrates increases significantly after 12 months of use.

Despite recent research regarding increased risk with the combined use of statins and fibrates, fibrates do not inhibit the P-450s during hepatic metabolism. A process known as glucuronidation has been suggested not only as a means for statin metabolism but also as a possible mechanism for statin toxicity in the presence of multiple medications.[16,20] When statins are administered as stable, lactone forms, they are quickly converted to more active acid forms. Glucuronidation is the statin-metabolizing process by which these active acid forms become unstable glucuronides that, in turn, quickly become inactive lactone forms.[16] Fibrates, like gemfibrozil, are proposed to inhibit this

glucuronidation pathway, thus increasing the concentration of the acid forms of some statins, and potentially, the risk of myopathy.[28]

Testing Used to Diagnose Statin-Induced Myopathies

Creatine kinase levels, liver function testing, and myoglobin levels.

Historically, CK levels have been used to assist in the diagnosis of statin-related myopathy.[20] Utilizing CK levels as the sole marker to identify the presence of myopathy may be misleading.[7,16,20,45] Elevated CK levels can occur without myopathic effects and often are seen as a result of exercise.[31,32] Clarkson et al[31] monitored several indicators of muscle damage, including CK, myoglobin, LDH, and other measures of renal function, following an eccentric exercise protocol. No subjects with moderate to marked increases in CK levels had signs or symptoms of renal failure. The results of this study confirm that large increases in CK and myoglobin as a result of exercise in individuals who are healthy are not sufficient to induce renal damage.[31] In the presence of statin therapy, therefore, clinicians using a strength program for their patients should exercise caution when evaluating the presence of elevated CK levels.[31,32] Clarkson and colleagues[31,32] also showed that simply maintaining adequate hydration in the presence of these elevated serum concentrations is adequate in preventing renal compromise. Because the onset of myopathy can be multifactorial, the need for more judicious monitoring of patients using statins, as well as more nontraditional screening methods, is indicated.

The efficacy and cost-effectiveness of liver function testing for patients using statins has been discussed by several experts.[20,21] Elevated transaminases, as regularly seen with statin use, in the absence of muscle symptoms and increased bilirubin are not indicative of serious risk to the patient.[21,34] It has been suggested that transaminase elevations may be a normal and transient pharmacological effect of the reduction of cholesterol within the hepatocytes and that the costs of screening and monitoring would be staggering.[21] Elevated myoglobin is yet another marker used to identify damage to myocytes and often accompanies elevated circulatory CK levels.[16,31] The release of myoglobin from damaged cells can instigate renal failure via accumulation in the renal tubules.[31] Researchers have shown that despite elevations in myoglobin and CK levels after an eccentric exercise protocol, evidence of renal compromise was not evident.[31]

Phosphodiesters.

Several procedures previously suggested as efficacious testing measures to identify the presence of statin-related myopathy have been re-evaluated.[15,20,21,45] Glycerophosphocholine, the primary phosphodiester in skeletal muscle, is a key factor in cell membrane turnover as a result of lipid layer breakdown. Evaluation of this metabolite can give valuable information to researchers exploring the energetic mechanisms of physiological stresses.[70] Elevation of phosphodiesters has been reported in other muscle disorders, including muscular dystrophies.[70] It is thought that the elevation of this metabolite and associated myopathy are present with statin use due to accelerated myocyte membrane turnover or reduction in cholesterol synthesis.[70] These researchers also found that even in the presence of statin-induced elevated levels of phosphodiesters, muscle symptoms were absent.[70] Testing of phosphodiesters may assist physicians in identifying those patients who may have adverse effects due to statin use.

Skeletal muscle.

Evaluation of skeletal muscle composition[45] and function[71] has been used to assess the presence of myopathy in statin users. Muscle biopsies are an invasive procedure that may be used in research to assess histochemical and morphological changes but are not clinical tests for muscle myopathy. Phillips et al[45] used muscle biopsies in a small sample of statin users to confirm the presence of myopathy in the absence of elevated CK levels. Four of the initial 21 patients were able to identify statin therapy versus placebo treatment based on the presence or absence of their reported muscle symptoms.[45] Although different statins were used by each subject, biopsies showed myopathic effects, including diffuse lipid droplet accumulation vacuoles, cytochrome oxidase-negative myofibers, and an increased number of ragged red fibers.[45] These findings were verified as myopathic effects by absence of carnitine deficiency and thyroid dysfunction.[45]

In addition to muscle biopsies, investigators have measured muscle performance as an alternative method of identifying the presence of myopathy.[11,71] Dobkin[71] found that functional lower-extremity weakness of the hip flexors and abductors was related to myopathy and could be independent of CK level. Dobkin evaluated several patients, all of whom were on statin therapy and sought outpatient care several months after neurological insult due to unsteadiness during walking. Proximal upper- and lower-extremity muscle weakness were identified and, in one third of the cohort, affected the neurologically intact side. Difficulty standing from a chair, functional hip abductor weakness, and altered gait were observed even after completion of a 6-week strengthening protocol.[71] Interestingly, no evidence of myopathy was seen with CK testing. Three months after cessation of statin therapy, subjects' complaints of weakness resolved, and all subjects regained 5/5 manual muscle testing strength of their proximal musculature.[71] Recently, Chatham and colleagues[11] found that the inhibited inspiratory muscle performance of one statin user resolved and even improved after cessation of statin use and in conjunction with high-intensity inspiratory muscle training. These researchers demonstrated that noninvasive and inexpensive muscle performance testing can be effective measures to identify and track muscle function and recovery after statin-induced myopathy.[11,71]

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