Evaluation of skeletal muscle during calf exercise by ^{31}P MR spectroscopy in patients on statin medications

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Abstract

Introduction—Muscle pain is a common side effect of statin medications, however, the cause is poorly understood.

Methods—We characterized phosphocreatine (PCr) exercise recovery kinetics in 10 patients with hypercholesterolemia before and after a 4 week regimen of statin therapy using ^{31}P magnetic resonance spectroscopy (^{31}P-MRS). [31]P spectra were obtained before, during, and following exercise on a calf flexion pedal ergometer. Creatine kinase (CK) serum levels were drawn before and after statin therapy.

Results—The mean metabolic recovery time constant in subjects increased from 28.1s (SE=6.5s) to 55.4s (SE=7.4s) following statin therapy. The unweighted mean of the pre-post recovery time difference was -27.3s (SE=12.4s); (p-value = 0.02). Pre- and post-therapy CK levels were not significantly different (p-value = 0.50).

Discussion—Metabolic recovery time in the calf is prolonged in patients following statin use. This suggests that statins impair mitochondrial oxidative function, and ^{31}P –MRS is a potential study model for statin-associated myopathy.

Keywords

Statin medications; MR spectroscopy; myopathy; phosphocreatine exercise recovery kinetics; mitochondrial disease

Introduction

Statins, 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG-CoA) inhibitors, are among the most commonly prescribed medications in the world. They are used for the prevention and treatment of atherosclerotic and cardiovascular disease.[1] These drugs are generally safe, however, myotoxicity, including fatal rhabdomyolysis can occur.[2, 3]

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Although severe muscle-related side effects occur in <0.1% of statin users[4], less severe symptoms, such as myalgia and muscle cramps, occur in 1–7% of users.[5–8] Since statins must be taken long-term, muscle pains can affect their tolerability, and adherence is a major concern.[9] Previous studies suggest that <40% of patients take 80% of prescribed statin doses 1 year after starting therapy and about half discontinue the drugs within 6 months of starting them.[10] The mechanisms for statin-associated myopathy remain unclear, and numerous hypotheses exist. Among the most convincing are that the effect of statins on muscle may be due to inhibition of the HMG-CoA reductase pathway which synthesizes not only cholesterol but also isoprenyl end products. These are required for numerous proteins, cofactors and signaling molecules that are important for skeletal muscle cell function. Defects in mitochondrial energy production and/or function have received much attention, because the HMG-CoA reductase pathway is important for the synthesis of the isoprenyl tail of Coenzyme Q10, an integral component of oxidative phosphorylation in mitochondria ATP production.[6, 7, 11, 12] Preliminary studies show that statin therapy may reduce mitochondrial number and/or volume.[13, 14] Additionally, evidence linking the atrogin-1 gene to statin-associated muscle injury shows that the gene and its muscle damaging effects may be blocked by PGC-1alpha, which is thought to be due to its ability to augment mitochondrial number and function.[15, 16]

Non-invasive objective tools to study statin-associated muscle effects and response to treatment are lacking. Creatine kinase (CK) is a biomarker for muscle damage, but it can be normal in patients with symptomatic, biopsy proven statin-associated myopathy.[17, 18] Imaging with MRI and MIBI scintigraphy fail to show visible changes in patients with statin-associated myopathy.[18, 19] There are case reports of radiotracer uptake in skeletal muscle on bone scintigraphy and ^{18}F-FDG PET, but only in patients with severe myotoxicity with rhabdomyolysis.[20, 21] Muscle biopsy with morphological/biochemical analysis is currently the reference standard. Unfortunately, biopsies are invasive, painful, and provide only a metabolic "snapshot" of the muscle. Muscle biopsy cannot evaluate the dynamic nature of the various muscle metabolites.

^{31}P magnetic resonance spectroscopy (^{31}P-MRS) is unique in its ability to study, continuously and non-invasively, the biochemical pathways for the supply and utilization of energy in muscle tissue.[22] The post-exercise metabolic recovery rate of skeletal muscle phosphocreatine (PCr) as measured by ^{31}P-MRS has been used as an index of mitochondrial oxidative capacity in vivo.[23–26] During repeated muscle contraction, the concentration of adenosine triphosphate (ATP) is maintained at a constant level through glycolysis, oxidative phosphorylation, and the CK reaction, which results in a decrease in the concentration of PCr. ^{31}P-MRS in muscle can provide insights into the pathophysiology of certain diseases as well as normal physiology[25] and has been used as an outcome measure for clinical trials.[27] Although not in routine clinical use, ^{31}P-MRS has been used to study muscle metabolite changes in athletes and a wide range of diseases.[22, 24, 28–30] Blunted PCr recovery time has been described in patients with peripheral vascular disease, diabetes, and myopathies,[24, 26] and increased PCr recovery can be seen in professional cyclists[30].

If oxidative phosphorylation and ATP synthesis in mitochondria are impaired by statins, then one may also see prolongation of the metabolic recovery time constant. The purpose of this pilot study was to characterize phosphocreatine (PCr) exercise recovery kinetics in patients with hypercholesterolemia before and after initiation of statin therapy using ^{31}P-MRS.

Materials and Methods

Study Subjects

Ten subjects (5 females and 5 males with a mean age of 52 years, range 35–69) with hypercholesterolemia were recruited from preventive cardiology and primary care clinics at Beth Israel Deaconess Medical Center in Boston Massachusetts. Individuals were eligible if they were statin naïve or had been off statin medication for 2 weeks or longer and had been prescribed a statin by their physician at a dose approximately equivalent to or higher than simvastatin 20 mg daily. A minimum two week period off statin was required in order to allow clearance of the medication from the systemic circulation. All subjects were without muscle symptoms at the time of their baseline measurement. Potential subjects with established peripheral vascular disease, diabetes, or use of other lipid lowering agents or coenzyme Q10 in the last 30 days were excluded. Patients were excluded if they were using medications associated with mitochondrial dysfunction or an increased risk of myopathy, including propranolol, niacin, and fibrates.[2, 31] Moreover, all subjects were instructed to not alter exercise habits or diets during the 4 weeks on statin medication. This study was approved by our institutional review board, and informed consent was obtained from all subjects.

^{31} P MRS equipment/protocol—^{31}P-MRS was performed on the posterior calf using a surface coil during exercise on a custom-built MRI-compatible pedal ergometer. The 10 subjects were studied before and 4 weeks after statin therapy. The exercise ergometer was designed to allow the study subjects to perform plantar flexion exercise by pressing against a foot pedal while lying in the supine position. The subject's lower extremity was secured to the MRI table with straps across the mid thigh and mid lower leg in order to isolate usage of the posterior calf muscles. The force required to depress the pedal was supplied by a pressurized tank of nitrogen gas with an adjustable pressure regulator, which was connected to a piston cylinder attached to the foot pedal (Fig. 1). The maximum pressure (PSI) was determined during 1 trial by incrementally increasing the pressure on the pedal to a point where the subject could only depress the pedal through the full range of motion once. 40% of this maximum pressure was then used for both the pre- and post-therapy studies. The exercise protocol consisted of pressing the pedal down for one second and relaxing back for one second as cued by a metronome with the pressure reduced to 40% of the maximum value. The subjects performed 30 plantar flexions per minute for a maximum of 7 minutes, or until muscle exhaustion or calf pain.

^{31}P-MRS data acquisition—^{31}P-MRS of the posterior calf muscles muscle was performed using a 3-Tesla MR system (General Electric Healthcare, Milwaukee, Wisconsin). A 7.5-cm circular ^{31}P surface coil was centered on the maximum diameter of the calf (approximately 4 to 8 cm below the posterior knee crease). Magnetic field homogeneity was adjusted while observing the ^{31}P signal. Spectra were acquired using a pulse-and-acquire free induction decay (FID) sequence. Localization was accomplished by the surface coil. The ^{31}P-MRS acquisition parameters were: sweep width, 2048 Hz; number of complex points, 1024; TR, 5 s; signal averages, 2; time per acquisition, 10 s. Subjects were studied for: (1) one minute prior to calf exercise, (2) up to 7 minutes during exhaustive exercise, and (3) for 6 minutes following exercise during the recovery period. ^{31}P spectra were acquired at 10 s intervals (Fig. 2).

^{31}P-MRS data analysis—The ^{31}P spectral data were processed using IDL software (Version 6.0. Research Systems, Inc. Boulder, CO). Each FID was processed with 3-Hz exponential line broadening without zero filling. Spectra were manually phased using zero and first-order phase corrections. The areas of the PCr peaks were calculated and normalized

to the pre-exercise value. Monoexponential curve fitting was performed to compare the PCr recovery time between pre- and post-statin therapy. The model fitted is

$$PCr/(PCr+Pi)=1 - b * e^{-1/k*time}$$

where b is *PCr* depletion and k is the *PCr* metabolic recovery time constant.[32, 33] We fitted this nonlinear model to each of the subjects pre- and post-statin therapy using the statistical nonlinear model fitting procedure NLIN of the SAS/STAT software version 9 (SAS Institute Inc., Cary NC). The procedure used nonlinear least squares solution via the Newton method. The two parameters b, and k and their standard errors were estimated for each subject. We were interested in testing the hypothesis that there was a mean difference in the parameter k between pre and post intervention. We calculated both unweighted and weighted mean data, with the weight computed from the inverse of the square of the standard error. With only 10 subjects, we did not have normality for the distribution of the estimates of parameter k, so we were not able to use a weighted paired t-test to obtain inference. Therefore, we used a nonparametric signed rank test on the paired differences.

Creatine kinase (CK)—CK serum levels were drawn on all subjects prior to and 4 weeks after the initiation of statin medications. The following are used as the upper limits of normal CK values at our institution: (Male/Female): Whites 322/201 IU/L; African-Americans 801/414 IU/L; Asians 641/313 IU/L.

Results

Patient Symptoms

Five of the 10 patients had taken statins previously, and 4 of the 5 patients had suspected statin-associated muscle pains that resolved with discontinuation of the medication. Of the 4 patients with a history of muscle pain while on statins, 3 had mild muscle pain while on treatment during the study. Half of the subjects were sedentary or performed light activities only; the other half engaged in moderate to vigorous exercise most or all days of the week. All subjects reported no changes in exercise habits or diets. The patient demographics are summarized in Table 1.

PCr Recovery—The mean metabolic recovery time constant in subjects increased from 28.1s (SE=6.5s) at baseline to 55.4s (SE=7.4s) following statin therapy (Fig. 3). The unweighted mean of the pre-post recovery time difference was −27.3s (SE=12.4s); (p-value = 0.02, using nonparametric signed rank test). The weighted mean was −8.9s (SE=6.0s). Eight out of 10 subjects had an increase in the metabolic recovery time constant, including all 4 patients with reported muscle symptoms during the study. The 2 patients with a small decrease in PCr metabolic recovery time constant did not experience pain while on statin therapy.

Creatine kinase (CK)—CK levels were not significantly different (p-value = 0.50) following 4 weeks of statin medication. The average CK was 107 U/L prior to initiating statin medication and 126 U/L after 4 weeks of treatment.

Discussion

To our knowledge, PCr recovery kinetics in patients with hyperlipidemia before and after statin medication use have not been studied previously. The recovery of PCr concentration in skeletal muscle following exercise relies on the availability of substrates and oxygen as

well as the capacity for the mitochondria to carry out oxidative metabolism within the myocytes. Following statin therapy, participants in this study had a significant drop in the recovery of PCr in their calf muscles when compared to baseline. This suggests impairment of mitochondrial oxidative metabolism as a cause of statin-associated myopathy. Our study had too few participants to compare whether PCr recovery was different among those with and without suspected statin-associated muscle pain. Further investigations are of great interest, as PCr exercise recovery kinetics measured by ^{31}P-MRS may be an effective study tool for diagnosing and evaluating statin-associated myopathy.

Two prior studies have used ^{31}P-MRS to investigate the effect of statins on resting muscle.[34, 35] Slade et al. found a 57% elevation in the phosphodiesterase (PDE), a breakdown product of cell membrane phospholipids, in 10 patients taking statins when compared to normals.[35] Since increased levels of PDE are seen in active tumors, increased age, muscular dystrophies, and non-specific muscle pain syndromes, the authors hypothesize that statin use increases muscle membrane turnover.[35] However, the patients studied did not have muscle symptoms, and MRS was performed at rest. Guis et al performed PCr exercise recovery kinetics in the forearm on 7 patients with a history of statin-associated myalgia and elevated CK.[34] They saw no difference in the PCr recovery between normal subjects and patients with a prior history of statin myopathy.[34] Moreover, the recovery of pH was slower in the patients with a history of statin myopathy versus normal subjects. This suggested reduced proton efflux, which the authors suggest is linked to failure of calcium homeostasis.[34] It is unclear why Guis et al, did not see a blunted PCr recovery in their patients, however, this discrepancy may be because their patients had discontinued statin medications prior to ^{31}P-MRS. Moreover, they performed ^{31}P-MRS in the forearm, a less common site for statin-associated muscle pain in our experience.

The CK did not increase significantly in our patients during the 4 week course of therapy, which was not unexpected. Past studies have shown that CK levels do not correlate well with the degree of muscle pain. Statin-associated muscle symptoms confirmed on blinded statin rechallenge may occur in patients with normal CK levels,[18] while muscle symptoms may be absent or mild, when severe muscle toxicity (i.e., rhabdomyolysis) is present.[36, 37] Damage to the muscle can be seen histologically even when patients are asymptomatic or have normal CK levels. Draeger et al showed that ultrastructural damage (breakdown of the T-tubular system and subsarcolemmal rupture) occurs in skeletal muscle in asymptomatic patients on statin therapy without myalgia.[38] Histologic analysis of patients with statin-associated muscle symptoms following blinded statin rechallenge without elevated serum CK showed microscopic changes of altered myofiber architecture and necrosis, along with signs of mitochondrial dysfunction which are reversible with drug cessation.[18]

A few limitations deserve mention. As with any pilot study, the small number of subjects precludes making firm conclusions, and additional studies with larger patient groups are needed to investigate the ability of ^{31}P-MRS to elucidate the effects of statins on skeletal muscle. Four of our 5 subjects with prior statin use experienced mild-to-moderate muscle pain on a prior statin, which is higher than the general population. Thus there maybe a higher likelihood of a prolong PCr recovery time in our statin subject group when compared to a more normal patient distribution. Another potential limitation is that changes in nutritional status or exercise habits may alter PCr recovery kinetics, however, the subjects did not alter their diet or exercise habits during the 4 week statin course. Moreover, PCr exercise recovery kinetics with ^{31}P-MRS can be difficult to perform, requiring ^{31}P-MRS specific coils, pedal ergometer, and technical expertise in curve fitting and MR spectra data processing. Additional studies to show the reproducibility of the technique are necessary. Moreover, we performed unlocalized ^{31}P-MRS, thus the spectra are believe to be the result

of a summation of muscle tissue. Newer techniques that incorporate localized spectroscopy can be of benefit and should be evaluated.

In conclusion, PCr metabolic recovery time constant in the calf is prolonged in patients following statin use. This supports the hypothesis that statins impair mitochondrial oxidative function. This initial pilot study shows that ^{31}P-MRS is a potential tool in the study of statin-associated myopathy and may be useful for testing of effective treatment options.

Acknowledgments

Abbreviations

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MRS	magnetic resonance spectroscopy
HMG-CoA	3-hydroxy-3-methylglutaryl coenzyme A reductase
PCr	phosphocreatine
CK	creatine kinase

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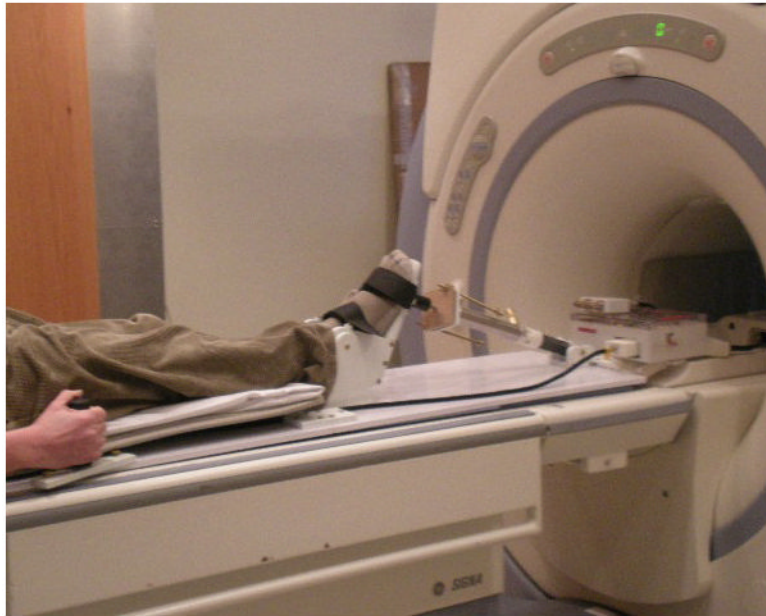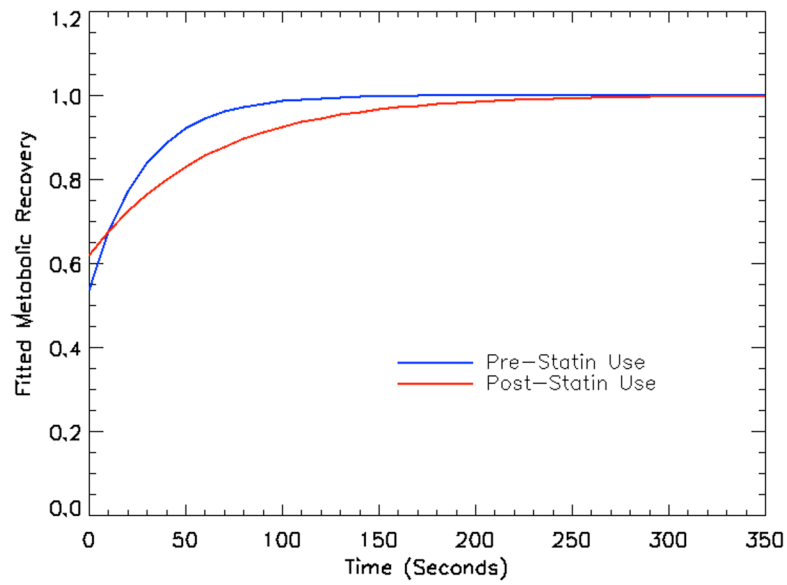
Figure 1.
Photograph of a subject using the custom-built MRI-compatible pedal ankle ergometer during ^{31}P-MRS acquisition.
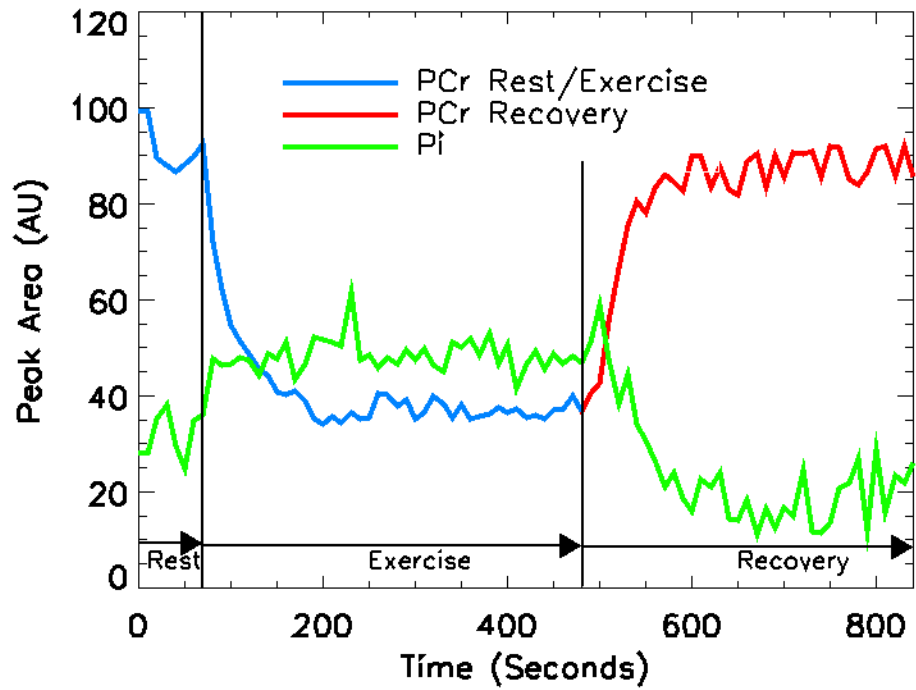
Figure 2.
Graph showing the variability in the amounts of phosphocreatine (PCr) and inorganic phosphate (Pi) during the rest, exercise, and recovery phases of calf exercise as measured by ^{31}P MR spectroscopy in a 44 year old white man prior to statin therapy.

Figure 3.
Graph comparing the fitted cumulative PCr metabolic recovery time constant in 10 subjects before and after statin therapy. There is a prolonged and blunted cumulative recovery curve following 4 weeks of statin therapy when compared to baseline.

Table 1

Subjects undergoing ^{31}P-MRS before and after statin medications

Pt#	Age (yrs)	G	Race	Statin, dose (mg/day)	Prior Statin Use/Pain	Pain during Study	CK Pre/Post (U/L)	Exercise Pre/Post Time (secs)	Recovery Time Pre-Statin Seconds (SE)	Recovery Time Post-Statin Seconds (SE)	Difference in Pre-Post Recovery Seconds (SE)
1	47	F	White	simvastatin, 40	–/NA	–	62/57	120/180	44.1 (4.8)	116.9 (9.1)	–72.7 (8.4)
2	67	F	White	simvastatin, 20	–/NA	–	53/60	440/420	30.2 (6.3)	147.5 (29.4)	–117.2 (27.4)
3	35	M	Asian	simvastatin, 40	–/NA	–	162/263	60/80	21.1 (4.3)	15.0 (3.6)	6.2 (4.3)
4	47	M	Asian	atorvastatin, 10	+/–	–	92/148	90/210	24.0 (4.3)	18.3 (2.7)	5.7 (4.0)
5	47	M	White	simvastatin, 20	+/+	+	80/73	420/410	20.9 (16.8)	36.5 (8.7)	–15.7 (15.4)
6	44	M	White	simvastatin, 40	–/NA	–	205/245	420/420	15.0 (5.6)	35.9 (3.0)	–20.9 (5.2)
7	56	F	White	rosuvastatin, 5	+/+	+	79/89	100/50	26.8 (8.6)	61.6 (6.5)	–34.8 (8.4)
8	69	F	White	atorvastatin, 5	+/+	–	81/92	160/220	34.2 (6.4)	44.5 (5.1)	–10.3 (6.4)
9	54	M	White	atorvastatin, 10	+/+	+	150/145	420/420	14.5 (5.6)	18.0 (2.9)	–3.5 (5.2)
10	50	F	White	simvastatin, 20	–/NA	+	101/88	120/90	50.0 (2.7)	59.6 (3.2)	–9.7 (3.3)

NA-not available; CK-creatine kinase; SE-standard error