

High-dose statin use does not impair aerobic capacity or skeletal muscle function in older adults

Tinna Traustadóttir · Anthony A. Stock ·
S. Mitchell Harman

Received: 2 April 2008 / Accepted: 4 July 2008 / Published online: 21 August 2008
© American Aging Association 2008

Abstract 3-Hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins) are lipid-lowering agents widely employed for atherosclerosis prevention. HMG-CoA reductase blockade reduces skeletal muscle coenzyme Q₁₀ (CoQ₁₀) levels and mitochondrial respiratory chain activities and may produce mild to severe skeletal muscle myopathy. This study investigated whether high-dose statin treatment would result in measurably decreased exercise capacity in older men and women. Maximal oxygen consumption, aerobic endurance, oxygen uptake kinetics, maximal strength, muscular power, and muscular endurance were measured before and after 12 weeks of statin treatment (simvastatin, 80 mg/day) in nine men and one woman, ages 55–76 years, with LDL-cholesterol levels >3.3 mmol/l (mean=4.2±0.2 mmol/l). Myalgia symptoms were assessed every 4 weeks. As expected, statin treatment resulted in significant decreases in LDL- and total-cholesterol levels ($P<0.01$) with no significant changes in HDL-cholesterol or triglyceride levels. No significant changes were observed in aerobic capacity, endurance, oxygen kinetics or any measures of muscle function. No subject reported symptoms of myalgia, cramps, or weakness during the study. In the absence of myalgia or myopathic symptoms, high-dose simvastatin treatment did not impair exercise capacity in hyperlipidemic older individuals. We conclude that

decreases in intramuscular CoQ₁₀, in most patients on high dose statin treatment may not be clinically relevant, due to inter-individual variability in the degree of CoQ₁₀ depletion, sensitivity of muscle to decreases in CoQ₁₀, or both.

Keywords Aging · Simvastatin · Vo₂max · Strength · O₂ uptake kinetics · Myalgia

Introduction

3-Hydroxy-3-methylgluteryl-coenzyme A (HMG-CoA) reductase inhibitors (statins) are the most effective available pharmaceutical agents to lower cholesterol and thereby reduce risk for coronary artery disease (Johannesson et al. 1997; Pedersen 2001). Evidence from clinical trials indicates that higher doses of statins are more effective in reducing the relative risk of cardiovascular events compared with moderate or low doses (Davidson and Robinson 2007). However, blocking HMG-CoA reductase also reduces endogenous synthesis of other metabolites in the mevalonate pathway, including coenzyme Q₁₀ (CoQ₁₀) also known as ubiquinone. CoQ₁₀ is an important co-factor for oxidative phosphorylation as an electron shuttle between complex I and III in the mitochondrial electron transport chain. Reduced levels of CoQ₁₀ can decrease electron flux through the respiratory chain and impair aerobic ATP synthesis.

It has recently been shown that high-dose simvastatin treatment depletes CoQ₁₀ levels in muscle tissues

T. Traustadóttir (✉) · A. A. Stock · S. M. Harman
Kronos Longevity Research Institute,
2390 E. Camelback Rd, Suite 440,
Phoenix, AZ 85016, USA
e-mail: tinna.traustadottir@kronosinstitute.org

(Paiva et al. 2005). Substantial reduction in intramuscular CoQ₁₀ levels were associated with decreased citrate synthase activity as well as decreased respiratory chain enzymes, suggesting diminished mitochondrial number and/or volume (Paiva et al. 2005).

The effect of statin-induced reduction in CoQ₁₀ levels may not result in detectable changes in aerobic metabolism under resting conditions. However, during exercise, as the heart and skeletal muscles are required to perform increased amounts of work, it is more likely that a compromise due to CoQ₁₀ depletion would become evident.

We hypothesized that, because CoQ₁₀ levels have been shown to decrease with age (Kaikkonen et al. 1999; Lass et al. 1999; Turunen et al. 2004), older individuals may be more susceptible to statin-associated CoQ₁₀ depletion. Aging is associated with decreased skeletal muscle reserve, which may be related in part to cumulative mitochondrial damage and lower mitochondrial ATP production rate (Conley et al. 2007; Petersen et al. 2007). This is an important issue, as it is anticipated that the elderly will constitute an increasing proportion of patients for whom statins are prescribed to reduce hyperlipidemia and mortality from coronary heart disease (CHD) (Pasternak et al. 2002).

To explore whether high-dose statin would result in detectable impairment of exercise capacity, we measured maximal oxygen consumption (VO_{2 max}), kinetics of O₂ uptake, aerobic endurance, maximal strength, power output, and high intensity muscular endurance in an open-label pilot study of older men and women before and after 12 weeks on 80 mg of simvastatin.

Materials and methods

Study population

We recruited 12 healthy men and women, ages 55–76 years for this pilot study. Criteria for inclusion included LDL-cholesterol levels above 3.3 mmol/l (130 mg/dl), not overly obese as determined by body mass index (BMI) < 32 kg/m², no contraindications to exercise testing, and not currently on any cholesterol-lowering medications. Exclusion criteria included any clinical signs and symptoms of coronary artery disease, diabetes mellitus, liver or renal diseases, elevated liver enzymes, any disease or musculoskeletal problems that

would limit ability to perform the exercise testing, or contraindications to statin treatment. Furthermore individuals currently taking medications known to potentially increase the risk of developing myopathy were excluded from participation. All subjects gave written informed consent, and the study was approved by the Institutional Review Board of Arizona State University.

Experimental design

The study design was a 12-week single-group open-label trial using a high-dose (80 mg/day) of simvastatin. Recent trials have demonstrated greater reductions in LDL-cholesterol, C-reactive protein, and a reduced progression of atherosclerosis using high-dose statin therapy (Cannon et al. 2004; Nissen et al. 2004, 2005). Subjects underwent screening prior to participating in the study which included health history, physical examination, resting EKG, and a fasting blood sample for routine laboratory screening (SMA-24, CBC, TSH, lipid and lipoprotein profile, fasting glucose, liver enzymes, creatine kinase). The exercise testing was divided between 2 days (see Table 1). On the first day, subjects underwent testing of maximal oxygen consumption, maximal strength (upper and lower body) and aerobic endurance. On the second day, they completed measures of oxygen uptake kinetics, repeated maximal strength tests, followed by measures of muscular power and muscular endurance. These tests are described in detail below. Creatine kinase (CK) levels were also measured 24-h after the completion of the exercise testing. After pre-testing was completed, statin therapy was initiated at 40 mg/day for the first 2 weeks and then increased to 80 mg/day for the remaining 10 weeks. This up-titration from a moderate to a high dose is associated with lower rates of adverse effects (Davidson et al. 2007). Liver enzymes and CK were measured after 4 weeks for safety monitoring. Additionally, we administered a questionnaire on myalgia

Table 1 Exercise testing sequence (*LP* leg press, *CP* chest press, *TTE* time to exhaustion)

Day 1	Day 2
1. VO ₂ max test	1. O ₂ kinetics test
2. 1-RM test (LP/CP)	2. 1-RM test (LP/CP)
3. Aerobic endurance (TTE)	3. Muscular power (LP/CP)
	4. Muscular endurance (LP/CP)

symptoms at baseline and every 4 weeks thereafter. All exercise testing was repeated at 12 weeks, as well as measures of lipid profile, liver enzymes, and creatine kinase levels.

Maximal oxygen consumption ($\text{VO}_2 \text{ max}$)

Maximal aerobic capacity was measured using a graded exercise test (GXT). The GXT was performed on an electronically-braked stationary cycle ergometer (Ergoline 900) with an integrated metabolic measurement cart (SensorMedics Vmax Series 229, Yorba Linda, Calif.) that measured oxygen uptake via open-circuit indirect calorimetry throughout the test. A continuous 12-lead EKG (Marquette CardioSoft, Milwaukee, Wis.) was recorded, and blood pressure was measured every 3 min throughout exercise and recovery (SunTech Tango, Raleigh, N.C.). The initial workload during the GXT was 15 or 20 W (chosen based on the individual's predicted maximal workload so that the test would be completed in 7–12 min), followed by an incremental increase in workload (same watts as the initial workload) every minute thereafter until the subject was at a point of volitional fatigue. Maximal oxygen uptake was considered to be achieved if two of the following three criteria were met: (1) a plateau in VO_2 with an increase in workload, (2) a respiratory exchange ratio (RER) ≥ 1.10 or (3) heart rate within ten beats of the age-predicted maximal heart rate (Kohrt et al. 1991). Standard contraindications to exercise testing and termination criteria as outlined by the ACSM were followed (American College of Sports Medicine 1991).

Maximal muscle strength (1-RM)

Maximal strength via a standard one-repetition maximum (1-RM) test was determined for upper and lower body using a Keiser pneumatic bi-axial chest press and seated leg press fitted with a Keiser A420 electronic package. This equipment allows determination of force, velocity, and power output per repetition performed and automatically downloads this data to a personal computer (Keiser, Fresno, Calif.). All subjects were instructed on the proper techniques for each weight-lifting exercise, followed by a warm-up set (ten repetitions) with light resistance to enhance preparedness of the respective muscle groups. As per NSCA guidelines (Baechle et al.

2000), resistance was increased to an estimated load such that the subject could perform five repetitions (40–60% of the subjects estimated maximum). After a 2-min rest, the resistance was increased by 5–10% for the upper body and 10–20% for the lower body to a 'conservative, near-maximum' load and the subject was asked to perform two repetitions. Following 2-min rest, the resistance was increased similarly and the subject attempted a 1-RM. Another 2-min rest was allowed, and resistance was progressively increased until a 1-RM was achieved (Baechle et al. 2000). As maximal strength is effort dependent (Ploutz-Snyder and Giamis 2001), the 1-RM was reassessed on the second day of each test battery. The highest force produced during the 2 days was determined to be the subject's 1-RM.

Aerobic endurance (time to exhaustion)

Following assessment of maximal muscular strength and a 10-min rest period, subjects completed an aerobic endurance test on the stationary cycle ergometer and equipment previously described. After a 1-min warm up at 10 W, the resistance was increased to 80% of the maximal workload achieved during the $\text{VO}_2 \text{ max}$ test. Subjects were asked to maintain a pedaling cadence of 60 rpm at this work rate until they were no longer able to tolerate the work. Breath-by-breath gas exchange and heart rate were measured throughout the procedure. The total exercise time (time to exhaustion) was used as a marker of aerobic endurance.

Kinetics of O_2 uptake

Subjects came to the Kronos Longevity Research Institute following an overnight fast. The VO_2 kinetics response was determined during sub-maximal exercise on the bicycle ergometer at a pedaling frequency of 60 rpm. Briefly, the subject cycled at a 10-W workload for 3 min and immediately thereafter the workload was increased to 50% of the maximal workload achieved during the $\text{VO}_2 \text{ max}$ test, and kept constant for 6 min. The time-point of the change in workload occurred without prior warning to the subjects, to minimize any feed-forward responses. Each subject completed three trials, with 12 min of seated rest in-between each trial. The raw data from breath-by-breath measurement of O_2 consumption during the trial was linearly interpolated to provide VO_2 values

at 1-s intervals. The time-constants (τ) of the VO_2 kinetics on-response were calculated after fitting the data to a mono-exponential equation using data analysis software (GraphPad Prism, 4.0, San Diego, Calif.). Attainment of 'steady state' was assessed by calculating the difference in VO_2 at minute 6 and minute 3 ($\Delta\text{VO}_2^{\text{min } 6-3}$). Steady state was defined as $\Delta\text{VO}_2^{\text{min } 6-3} < 8\%$. Results from trials that did not meet the criteria for steady state were excluded from analyses. The outcome variable was the τ , averaged from the two best trials. Respiratory exchange ratios (RERs) were determined during the steady state phase of the O_2 kinetics test, to assess whether statin treatment induced changes in fuel selection during sub-maximal exercise.

Muscle power output

After re-assessing 1-RM, power output for each subject was determined using the Keiser pneumatic bi-axial chest press and seated leg press previously described. Power was determined at 30%, 40%, 50%, 60%, and 70% 1-RM for the chest press and 40%, 50%, 60%, 70% and 80% 1-RM for the leg press. Subjects were instructed to complete the concentric portion of the exercise movement as rapidly as possible. Each workload included five individual trials with a 30-s rest between each attempt. The highest score achieved was taken as the power score for that workload. The procedure was then repeated for the next workload.

High-intensity muscular endurance

Each subject performed as many repetitions as possible, through a full range of motion, at a workload set to 80% of 1-RM for the leg press and 70% of 1-RM for chest press. Failure to complete the full range of motion for two consecutive repetitions ended the test. The number of repetitions completed was used as a marker of muscular endurance.

Myalgia questionnaire

The subjects were interviewed every 4 weeks regarding adverse effects and symptoms related to myalgia, using a questionnaire adapted from Franc et al. (2003). The questionnaire includes questions relating to the characteristics of muscle pain (location, time pattern, type and intensity, triggering and aggravating factors, and the impact of muscle pain on daily activities).

Laboratory analyses

Lipid profile, HgbA1C, creatine kinase and Chem 24 (including aspartate aminotransferase and alanine aminotransferase) were determined using standard clinical methodology on a Synchron Clinical System LX20 (Beckman Coulter, Fullerton, Calif.). Complete Blood Count was obtained on a Coulter GEN-S utilizing the Coulter Principle (Beckman Coulter, Fullerton, Calif.). Thyroid stimulating hormone (TSH) was measured using standard clinical methodology on a DPC Immulite 2000 Immunoanalyzer (Diagnostic Products, Los Angeles, Calif.).

Statistical power and analyses

Based on power analyses using the within-subject reproducibility of $\text{VO}_{2 \text{ max}}$ in our Exercise Testing Center, we determined that 12 subjects would provide an 80% probability of detecting a difference of 0.5 SD with significance at the 0.05 level.

Data analyses were performed with SPSS software, version 11.5 (SPSS, Chicago, Ill.). Comparisons between values at baseline and 12 weeks were tested using the paired *t*-test. Statistical significance was set at $P < 0.05$. Data are presented as means \pm SE unless otherwise stated.

Results

Of 12 subjects enrolled, two were excluded from participation, one due to a borderline-positive stress test at screening and the other due to a $\text{BMI} > 32$. Thus, ten subjects completed the study, nine men and one woman. Baseline characteristics of these ten subjects are shown in Table 2. There were no significant changes in body weight or BMI from baseline to the end of the study (see Table 2).

Laboratory measures

Table 2 shows the changes in blood and serum measures from before and after the statin treatment. After 12 weeks, simvastatin treatment (80 mg/day) resulted in a significant lowering of LDL-cholesterol by 51% (from 4.18 ± 0.21 to 2.12 ± 0.15 mmol/l) and total cholesterol by 60% (6.40 ± 0.49 vs 3.82 ± 0.17 mmol/l). There were no significant changes in HDL-cholesterol

Table 2 Subject characteristics and laboratory measures taken before (baseline) and after 12 weeks of statin treatment. Age is presented as mean (\pm SD); all other data presented as means \pm SE, ranges in parentheses. Comparison made with paired *t*-test*C* cholesterol, *TG* triglycerides, *CK rest* creatine kinase at rest, *CK exercise* creatine kinase after exercise, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *AP* alkaline phosphatase, *GGTP* gamma-glutamyltranspeptidase)

	Baseline	12 weeks	<i>P</i>
Subject characteristics			
Age (years)	66 \pm 6 (55–76)		–
Height (cm)	171 \pm 6 (165–183)		–
Weight (kg)	81.3 \pm 3.9 (72.2–112.7)	82.0 \pm 4.1 (71.8–115.0)	0.201
BMI (kg/m ²)	28 \pm 1 (23–34)	28 \pm 1 (23–37)	0.207
VO ₂ max (ml·kg ⁻¹ ·min ⁻¹)	22.1 \pm 1.3 (17.1–30.1)	23.3 \pm 1.9 (17.0–34.4)	0.129
Laboratory measures			
LDL-C (mmol/l)	4.18 \pm 0.21	2.12 \pm 0.15	<0.01
Total C (mmol/l)	6.40 \pm 0.49	3.82 \pm 0.17	<0.01
HDL-C (mmol/l)	1.30 \pm 0.08	1.18 \pm 0.14	0.31
TG (mmol/l)	1.97 \pm 0.64	1.29 \pm 0.26	0.16
LDL-C:HDL-C	3.3 \pm 0.3	2.0 \pm 0.3	<0.01
Total C:HDL-C	5.2 \pm 0.6	3.6 \pm 0.4	<0.01
CK rest (IU/l)	108 \pm 16	143 \pm 20	0.04
CK exercise (IU/l)	189 \pm 38	167 \pm 39	0.61
ALT (IU/l)	23 \pm 1	33 \pm 3	<0.01
AST (IU/l)	25 \pm 1	32 \pm 2	<0.01
AP (IU/l)	59 \pm 4	58 \pm 4	0.64
GGTP (IU/l)	27 \pm 5	26 \pm 4	0.75

or triglycerides. Creatine kinase levels at rest were significantly increased at 12 weeks (108 \pm 16 vs 143 \pm 20 IU/l, respectively) but remained within normal range at both time points. Creatine kinase levels at 24-h post exercise testing were not significantly different between baseline and 12 weeks.

Two of the liver enzymes, alanine aminotransferase and aspartate aminotransferase, were significantly increased from baseline during statin treatment but all individual values remained within normal ranges. There were no changes in the other liver enzymes measured, alkaline phosphatase and gamma-glutamyl-transpeptidase.

Exercise measures

Overall, there were no significant changes in any of the measures of exercise capacity or muscular function (see Table 3). Mean maximal oxygen consumption values are presented in Fig. 1a. All subjects met the criteria for achieving a true VO₂ max, at both pre- and post-testing [see Table 3 for test duration and heart rate, blood pressure, and respiratory exchange ratio (RER) at maximum]. The mean VO₂ max at baseline and 12 weeks were 1,785 vs 1,901 ml/min, re-

spectively. As shown in Fig. 1b, the non-significant upward trend in the mean VO₂ max after treatment was due to increases in three of the ten subjects shown. Similarly, statin treatment did not change high-intensity endurance (time to exhaustion), O₂ uptake kinetics (τ), or fuel selection during mild sub-maximal exercise (RER). Muscular strength, power, and endurance were also not affected by the statin treatment (Table 3).

Myalgia

None of the study participants reported any symptoms of myalgia (muscle weakness, cramping, or non-specific muscle aches or pains).

Discussion

The central finding of the present study is that, contrary to our hypothesis, high-dose simvastatin treatment did not reduce exercise capacity in older adults. As expected, lipid profile improved.

An obvious limitation of our study was that we did not measure changes in CoQ₁₀ levels in our subjects.

Table 3 Exercise measures. Data are presented as means \pm SE. Comparison made with a paired *t*-test (*TTE* time-to-exhaustion, *RER* respiratory exchange ratio, *HR* heart rate *SBP* systolic blood pressure, *DBP* diastolic blood pressure)

	Baseline	12 weeks	<i>P</i>
VO ₂ max (ml/min)	1,785 \pm 113	1,901 \pm 152	0.09
Test duration (min:s)	8:37 \pm 0:24	8:50 \pm 0:32	
HR _{max} (bpm)	151 \pm 5	147 \pm 6	
RER _{max}	1.29 \pm 0.04	1.26 \pm 0.04	
SBP _{max} (mm Hg)	192 \pm 4	200 \pm 7	
DBP _{max} (mm Hg)	88 \pm 5	85 \pm 4	
Time to exhaustion (min:s)	5:55 \pm 1:00	6:20 \pm 1:18	0.57
O ₂ -kinetics test			
τ (s)	58 \pm 4	57 \pm 5	0.63
RER	0.94 \pm 0.02	0.95 \pm 0.02	0.82
1-RM (Newtons)			
Leg press	1,955 \pm 130	1,698 \pm 141	0.79
Chest press	421 \pm 24	446 \pm 25	0.50
Power leg press (watts)			
40%	922 \pm 57	988 \pm 82	0.33
50%	1,049 \pm 62	1,113 \pm 128	0.42
60%	1,073 \pm 84	1,115 \pm 119	0.51
70%	990 \pm 73	1,027 \pm 95	0.45
80%	884 \pm 100	917 \pm 83	0.60
Power chest press (watts)			
30%	276 \pm 18	297 \pm 23	0.05
40%	303 \pm 21	319 \pm 25	0.10
50%	307 \pm 25	315 \pm 29	0.42
60%	286 \pm 21	285 \pm 27	0.96
70%	231 \pm 31	240 \pm 24	0.63
Muscular endurance (repetitions)			
Leg press	13 \pm 1	13 \pm 1	0.75
Chest press	12 \pm 1	13 \pm 1	0.26

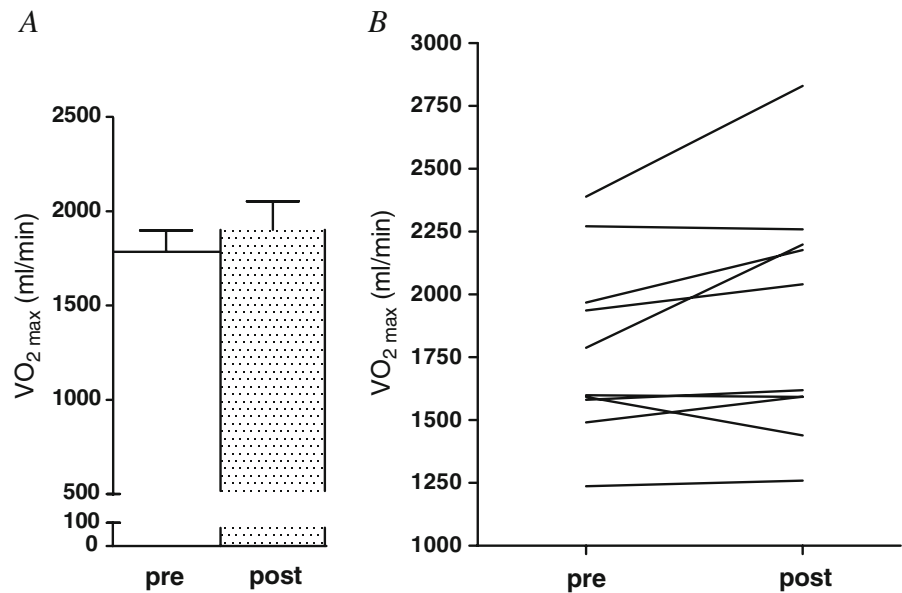
Päivä et al. (2005) have previously shown that simvastatin, at the same dose as used in the present study, significantly reduced mean CoQ₁₀ levels in skeletal muscle after 8 weeks of treatment. Furthermore, their patients had significant depletion of mtDNA, suggesting inhibition of mitochondrial function (Schick et al. 2007). Because the aim of our study was to collect preliminary data for a larger randomized trial, we elected not to perform muscle biopsies. Serum CoQ₁₀ was not measured because it is well known that CoQ₁₀ levels in blood correlate poorly with intramuscular levels (Paiva et al. 2005).

In contrast to Thompson et al. (1997), we did not find an exacerbation of exercise-induced skeletal muscle injury after statin treatment. In fact, the acute changes in CK levels from rest to 24 h after completing the exercise testing were only significant at baseline (mean change=80 IU/l or 79.8%, $P<0.05$) and not at 12 weeks (mean change=15 IU/l or 9.5%, NS).

Our prediction of greater reliance on carbohydrate oxidation during sub-maximal exercise (as indicated by higher RER) after statin treatment was also not supported. In a previous study there were changes in fasting substrate utilization after 6 weeks of statin therapy as the RER increased from 0.74 to 0.85, indicative of a decrease in fatty-acid oxidation (Phillips et al. 2004). To be able to directly compare results, we examined the resting data from the O₂ uptake kinetics trials, which were performed after an overnight fast. Similar to the exercise data, the fasting RER in our study did not change from pretreatment values (0.79 vs 0.80).

Two individuals in the present study showed a marked improvement in VO₂ max after the statin treatment. Although participants were asked not to change their physical activity levels during the course of the study, one admitted to an increase in his habitual cycling activity for an upcoming event and the other had started

Fig. 1 Maximal oxygen consumption ($VO_{2\text{ max}}$) before and after 12 weeks of statin treatment: (a) mean values (\pm SE) pre- and post-treatment and (b) individual changes



exercising during the treatment period. The fact that they were able to increase their aerobic capacity during the treatment further strengthens the conclusion that the high-dose statin treatment did not impair the oxidative phosphorylation pathway.

The most clinically relevant adverse effects of statin treatment are myopathy (Nawarskas 2005; Phillips et al. 2002c) and rhabdomyolysis (Omar et al. 2001). Patients taking statins often complain of myalgia, weakness, muscle tenderness, and decreased exercise tolerance, which may contribute to reduced patient compliance (England et al. 1995; Sinzinger et al. 1999). Despite the high dose of statin used in our study, none of our ten participants complained of myalgia or other myopathic symptoms. Although clinical trials have not reported a high incidence of adverse effects from statin therapy, a recent population-based cohort study found that statin users were at an eight-fold greater risk of myopathy compared with the general population (Gaist et al. 2001). In a large French observational study on high-dose statin therapy, the rate of myalgia was 10.5% overall, and 18% of patients on simvastatin experienced muscular symptoms (Phillips et al. 2004; Bruckert et al. 2006). It is possible that individuals who experience statin-induced myopathy may be genetically predisposed. A recently published preliminary analyses found a genetic variation in the CoQ₁₀ biosynthesis gene *COQ2* to be associated with statin intolerance (Oh et al. 2007).

Studies where patients presented with myopathy during statin therapy, found decreased muscle strength in those patients (Phillips et al. 2002b; Caso et al. 2007; Phillips et al. 2004). In addition, muscle biopsies showed mitochondrial dysfunction as evidenced by increased lipid droplet accumulation during the drug phase, while these abnormalities were not seen during the placebo phase (Phillips et al. 2002a). In one of these studies, patients with statin-induced myopathy treated with CoQ₁₀ compared with placebo had improvements in muscle pain severity and interference with daily activities (Caso et al. 2007) suggesting that the myopathy was related to CoQ₁₀ deficiency.

In summary, high-dose statin therapy in older individuals who did not experience myalgia or myopathic symptoms did not negatively affect exercise capacity or muscular function.

We conclude that decreases in intramuscular CoQ₁₀, in most patients on high-dose statin treatment may not be clinically relevant, due to inter-individual variability in the degree of CoQ₁₀ depletion, sensitivity of muscle to decreases in CoQ₁₀, or both. Further studies on changes in exercise capacity in *statin-intolerant* individuals are warranted.

Limitations of the study

There are limitations that need to be acknowledged regarding the present study. These include the small

sample size, with only one woman, and the lack of a placebo control group. Because there were no discernable effects of the high-dose statin treatment on exercise capacity or muscular function, it is unlikely that a placebo group would have changed the interpretation of the results. However, the learning/familiarization effect of repeated testing could have influenced these results. Thus, a modest decline in strength or endurance post-statin treatment could have been offset by a familiarization effect. An additional limitation, as mentioned earlier in the discussion, was that we did not perform muscle biopsies to measure CoQ₁₀ levels. If the rate of myalgia and muscle symptoms is in the range of 10–18%, as reported by previous studies, it is likely that the current sample was not powered to detect myalgia. Nevertheless, the primary aim of this study was to test the hypothesis that exercise capacity would be decreased in response to high-dose statin treatment due to decrements in mitochondrial function, regardless of whether myalgia occurred.

Acknowledgements This work was supported by funding from the Aurora Foundation. The results of this study were presented at the Annual Meeting of the American College of Sports Medicine, New Orleans, June 2007. We would like to acknowledge KLRI staff for their assistance with this study, as well as all of our participants.

References

- American College of Sports Medicine (1991) Guidelines for exercise testing and prescription, 4th edn. Lea & Febiger, Philadelphia
- Baechle TR, Earle RW, Wathen D (2000) Resistance training. In: Baechle TR, Earle RW (eds) Essentials of strength training and conditioning. 2nd edn. Human Kinetics, Champaign, pp 406–409
- Bruckert E, Hayem G, DeJager S, Yau C, Begaud B (2006) Mild to moderate muscular symptoms with high-dosage statin therapy in hyperlipidemic patients—The PRIMO Study. *Cardiovasc Drugs Ther* 19:403–414
- Cannon CP, Braunwald E, McCabe CH, Rader DJ, Rouleau JL, Belder R et al (2004) Comparison of intensive and moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med* 350:1495–1504
- Caso G, Kelly P, McNurrian MA, Lawson WE (2007) Effect of Coenzyme Q10 on myopathic symptoms in patients treated with statins. *Am J Cardiol* 99:1409–1412
- Conley K, Jubrias S, Amara CE, Marcinek DJ (2007) Mitochondrial dysfunction: Impact on exercise performance and cellular aging. *Exerc Sport Sci Rev* 35:43–49
- Davidson MH, Robinson JG (2007) Safety of aggressive lipid management. *J Am Coll Cardiol* 49:1753–1762
- England J, Walsh J, Stewart P, Boyd I, Rohan A, Halmagyi G (1995) Mitochondrial myopathy developing on treatment with the HMG CoA reductase inhibitors—simvastatin and pravastatin. *Aust N Z J Med* 25:374–375
- Franc S, DeJager S, Bruckert E, Chauvenet M, Giral P, Turpin G (2003) A comprehensive description of muscle symptoms associated with lipid lowering drugs. *Cardiovasc Drugs Ther* 17:459–465
- Gaist D, Rodriguez L, Huerta C, Hallas J, Sindrup S (2001) Lipid-lowering drugs and risk of myopathy: a population-based follow-up study. *Epidemiology* 12:565–569
- Johannesson M, Jönsson B, Kjekshus J, Olsson AG, Pedersen TR, Wedel H (1997) Cost effectiveness of simvastatin treatment to lower cholesterol levels in patients with coronary heart disease. Scandinavian Simvastatin Survival Study Group. *N Engl J Med* 336:332–336
- Kaikkonen J, Nyssönen K, Tuomainen T-P, Ristonmaa U, Salonen JT (1999) Determinants of plasma coenzyme Q10 in humans. *FEBS Lett* 443:163–166
- Kohrt W, Malley M, Coggan A, Spina R, Ogawa T, Ehsani A et al (1991) Effects of gender, age, and fitness level on response of VO₂ max to training in 60–71 yr olds. *J Appl Physiol* 71:2004–2011
- Lass A, Kwong LK, Sohal RS (1999) Mitochondrial coenzyme Q content and aging. *Biofactors* 9:199–205
- Nawarskas JJ (2005) HMG-CoA reductase inhibitors and coenzyme Q10. *Cardiol Rev* 13:76–79
- Nissen S, Tuzcu E, Schoenhagen P, Brown BG, Ganz P, Vogel R et al (2004) Effect of intensive compared with moderate lipid-lowering therapy on progression of coronary atherosclerosis. A randomized controlled trial. *JAMA* 291:1071–1080
- Nissen S, Tuzcu E, Schoenhagen P, Crowe T, Sasiela WJ, Tsai J et al (2005) Statin therapy, LDL cholesterol, C-reactive protein, and coronary artery disease. *N Engl J Med* 352:29–38
- Oh J, Ban MR, Miskie BA, Pollex RL, Hegele RA (2007) Genetic determinants of static intolerance. *Lipids Health Dis* 6:7–11
- Omar MA, Wilson JP, Cox TS (2001) Rhabdomyolysis and HMG-CoA reductase inhibitors. *Ann Pharmacother* 35:1096–1107
- Paiva H, Thelen KM, Van Coster R, Smet J, De Paepe B, Mattila KM et al (2005) High-dose statins and skeletal muscle metabolism in humans: A randomized, controlled trial. *Clin Pharmacol Ther* 78:60–68
- Pasternak RC, Smith SC Jr, Bairey-Merz CN, Grundy SM, Cleeman JI, Lenfant C (2002) ACC/AHA/NHLBI Clinical Advisory on the Use and Safety of Statins. *Stroke* 33:2337–2341
- Pedersen TR (2001) Pro and con: low-density lipoprotein cholesterol lowering is and will be the key to the future of lipid management. *Am J Cardiol* 87:8–12
- Petersen KF, Befroy D, Dufour S, Dziura J, Ariyan C, Rothman DL et al (2007) Mitochondrial dysfunction in the elderly: Possible role in insulin resistance. *Science* 300:1140–1142 doi:10.1126/science.1082889
- Phillips PS, Haas RH, Bannykh S, Hathaway S, Gray NL, Kimura BJ et al (2002a) Statin-associated myopathy with normal creatine kinase levels. *Ann Intern Med* 137:581–585

- Phillips PS, Haas RH, Bannykh S, Hathaway S, Gray NL, Kimura BJ et al (2002b) Statin-associated myopathy with normal creatine kinase levels. *Ann Intern Med* 137:581–585
- Phillips PS, Haas RH, Bannykh S, Hathaway S, Gray NL, Kimura BJ et al (2002c) Statin-associated myopathy with normal creatine kinase levels. *Ann Intern Med* 137:581–585
- Phillips PS, Phillips CT, Sullivan MJ, Naviaux RK, Haas RH (2004) Statin myotoxicity is associated with changes in the cardiopulmonary function. *Atherosclerosis* 177:183–188
- Ploutz-Snyder LL, Giamis EL (2001) Orientation and familiarization to 1RM strength testing in old and young women. *J Strength Cond Res* 15:519–523
- Schick BA, Laaksonen R, Frohlich JJ, Paiva H, Lehtimäki T, Humphries KH et al (2007) Decreased skeletal muscle mitochondrial DNA in patients treated with high-dose simvastatin. *Clin Pharmacol Ther* 81:650–653
- Sinzinger H, Schmid P, O’Grady J (1999) Two different types of exercise-induced muscle pain without myopathy and CK-elevation during HMG-Co-enzyme-A-reductase inhibitor treatment. *Atherosclerosis* 143:459–460
- Thompson PD, Zmuda JM, Domalik LJ, Zimet RJ, Staggars J, Guyton JR (1997) Lovastatin increases exercise-induced skeletal muscle injury. *Metabolism* 46:1206–1210
- Turunen M, Olsson J, Dallner G (2004) Metabolism and function of coenzyme Q. *Biochim Biophys Acta* 1660:171–199