



Published in final edited form as:

Am Heart J Plus. 2021 May ; 5: . doi:10.1016/j.ahjo.2021.100028.

The impact of statin therapy and aerobic exercise training on skeletal muscle and whole-body aerobic capacity[★]

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Abstract

Background: Statin use is widely recognized for improving cardiovascular health, but questions remain on how statin use influences skeletal muscle, particularly mitochondrial function.

Study objective, design and participants: The influence of statin therapy and exercise (EX) on aerobic capacity was determined. In Study1, skeletal muscle aerobic capacity was measured before and after 80 mg atorvastatin therapy. In Study2, aerobic capacity (skeletal muscle and whole body) was measured before and after a 12-week exercise randomized control trial in older adults (age = 67 ± 5 yrs.), a subset of which were on chronic low-moderate intensity statin therapy.

Main outcome measures: Muscle oxidative capacity was determined from the phosphocreatine recovery rate constant (*k*PCr) using ³¹P Magnetic Resonance Spectroscopy. Whole body peak oxygen uptake (VO₂ peak) was measured during a graded exercise test with indirect calorimetry.

Results: High dose statin therapy resulted in a 12% reduction in muscle oxidative capacity (pre = 1.34 ± 0.34 min⁻¹, post = 1.17 ± 0.25 min⁻¹, $p = 0.004$). Similarly, chronic low-moderate dose statin therapy was associated with lower muscle oxidative capacity at baseline (1.50 ± 0.35 min⁻¹) compared to non-statin users (1.88 ± 0.047 min⁻¹, $p = 0.019$). Following EX, muscle oxidative capacity increased by 35–40% (statin: Pre: 1.39 ± 0.44 vs. Post: 1.88 ± 0.47 min⁻¹, no statin Pre:

[★]Findings presented at American College of Sports Medicine Annual Meeting, Baltimore, Maryland June 2010 and Virtual Meeting June 2020 and the International Society for Magnetic Resonance in Medicine Annual Meeting, Montreal, Quebec April 2019 and Stockholm, Sweden 2010.

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CRediT authorship contribution statement

Jill Slade: Conceptualization, Methodology, Funding Acquisition, Project administration, Supervision, Writing-Original Draft. George Abela: Conceptualization, Supervision, Writing – Review & Editing. Mitch Rozman: Investigation, Writing – Review & Editing. Robert McClowry – Investigation, Writing – Review & Editing. David Hurley: Investigation, Writing – Review & Editing. Sean Forbes: Methodology, Writing – Review & Editing. Ronald Meyer: Conceptualization, Supervision, Writing - Review & Editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

1.86 ± 0.58 vs. Post: 2.58 ± 0.85 min⁻¹) compared to control groups (Pre: 1.74 ± 0.27 vs Post: 1.75 ± 0.49 min⁻¹, $p = 0.001$). VO₂ peak increased by 11% for EX groups (Pre: 18.8 ± 2.8 vs. Post: 20.8 ± 3.0 ml·kg⁻¹·min⁻¹) following training compared to a small decline in controls (Pre: 21.8 ± 3.7 vs. Post: 20.8 ± 3.04 ml·kg⁻¹·min⁻¹, $p = 0.001$).

Conclusions: Statin therapy resulted in reduced muscle oxidative capacity. Aerobic exercise improved skeletal muscle oxidative capacity and whole-body aerobic capacity during statin therapy.

Keywords

Skeletal muscle; Oxidative capacity; Aging; Mitochondria function; Aerobic exercise; VO₂ peak

1. Introduction

Statin medications are widely used to reduce cholesterol and more importantly to improve cardiovascular health [1]. Statin therapy is used by more than 40% of adults over 60 years old and 70% of adults with cardiovascular disease [2]. While important for generally reducing major cardiovascular risk factors and events, there are potential deleterious impacts of statins on skeletal muscle function [3]. Statins have been reported to reduce skeletal muscle oxidative capacity [4,5], oxidative enzyme content [6] and mitochondrial respiration [7-9]. Statin use in middle-aged adults has also been shown to completely block cardiorespiratory and mitochondrial adaptations expected with aerobic exercise training [10]. However, a recent study in rodents showed robust increases in citrate synthase activity and mitochondrial content following exercise with statin treatment in rats [11]. Thus, the effects of statins on mitochondrial adaptations to exercise are still unresolved.

Questions remain on how chronic statin use modifies exercise induced mitochondrial adaptations and whole-body aerobic capacity. The current studies 1) evaluated the effect of high and low-moderate dose statin therapy on skeletal muscle mitochondrial function and 2) evaluated the effect of aerobic exercise training on skeletal muscle mitochondrial function and whole-body aerobic capacity in older adults on low-moderate dose chronic statin therapy.

2. Materials and methods

2.1. Participants

2.1.1. Study 1 participants—Twenty-one healthy adults (20–60 years old) were recruited for a 4-week study of high intensity statin therapy, 80 mg atorvastatin. Exclusion criteria were MRI contraindications (ferromagnetic implants and high BMI), liver disease, elevations of serum liver transaminases, pregnancy or nursing, alcoholism, heart failure or history of heart attack, neurologic disorders, fibromyalgia and current use of statins or red yeast rice as well as medications known to increase risk of myopathy (cyclosporine, fibric acid derivatives, erythromycin, niacin, azole antifungals, and digoxin). Subjects were also excluded if they were participating in strength training. Kidney function (creatinine), liver function (ALT, AST), thyroid function (TSH) and muscle damage (CPK) were assessed prior to enrollment.

2.1.2. Study 2 participants—Thirty healthy older sedentary adults (60–80 years old) were recruited for a 12-week randomized control walking intervention. The presence of chronic statin therapy in half of the participants permitted a small pilot study to examine the influence of low-moderate dose statins on aerobic capacity adaptations. These participants were part of a previous study on microvascular function [12]. Exclusion criteria included prior diagnosis of peripheral vascular disease, cardiovascular disease, current cigarette smoking, history of stroke, advanced diabetes, MRI contraindications and use of ambulatory devices. Medications that exacerbate mitochondrial function (fibrates, niacin, propranolol) and supplementation of coenzyme Q10 (CoQ10) were also exclusionary. Sedentary was defined as aerobic exercise done two or fewer days per week, for 30 min a day or less over the last six months. Statin therapy was determined through a medical history including statin type and dose; chronic statin therapy was defined as ≥ 6 months for primary prevention of atherosclerotic cardiovascular disease.

2.2. Interventions

2.2.1. Study 1 intervention—All subjects were prescribed 80 mg of atorvastatin to be taken daily in the evening. Statin adherence was monitored weekly by telephone survey and blood lipids were assessed every two weeks.

2.2.2. Study 2 intervention—The subjects were randomly assigned to control (CON, $n = 15$) or exercise (EX, $n = 15$). Retrospectively, participants were stratified by chronic statin therapy (+STATIN, $n = 14$) or no statin therapy (–STATIN, $n = 16$). The supervised aerobic exercise intervention undertaken by EX was walking on a graded treadmill for 12 weeks, for four days a week, for 40 min a day at 70% heart rate reserve (HRR) as previously described [12]. In brief, the treadmill grade and speed were increased over the intervention to maintain 70% HRR. CON maintained a sedentary lifestyle.

2.3. Outcome measures

2.3.1. Study 1 outcome measures—The resynthesis rate of phosphocreatine following brief exercise was assessed to measure in vivo skeletal muscle oxidative capacity of the knee extensors using ^{31}P Magnetic Resonance Spectroscopy (MRS) before and after 80 mg statin therapy. The MRS protocol included 60s of rest prior to a 90s burst of moderate intensity knee extension exercise, followed by 300 s of recovery using the methods previously described [13]. For the burst exercise, subjects performed 60 submaximal dynamic contractions over 90 s corresponding to a targeted 25% PCr hydrolysis. The moderate intensity burst exercise enables a high-confidence kinetic analysis without provoking significant muscle acidification [13]. A 10 cm Visual Analogue Scale was used to examine muscle pain at rest and under tension of the thighs, arms, chest and back. A vertical mark was drawn on each horizontal line and the distance was measured; the sum of all body areas is reported. Blood lipids and CPK were measured at baseline and after two and four weeks of statin therapy.

2.3.2. Study 2 outcome measures— ^{31}P MRS was used to quantify muscle oxidative capacity of the plantar flexors before and after exercise intervention. The plantar flexors were selected primarily due to the high level of muscle recruitment of the calf muscles

during uphill walking [14]. The MRS protocol included 30s of resting baseline prior to a 30s burst of plantar flexion followed by 300 s of recovery. For the burst exercise, subjects performed 20 maximal isometric plantar flexion contractions over 30s corresponding to a target of ~25% PCr hydrolysis designed to avoid significant muscle acidification.

Peak oxygen uptake (VO_2 peak) was determined with indirect calorimetry using a modified Balke protocol on the treadmill as previously described [12]. Only a subgroup of participants ($n = 21$) had post-training VO_2 peak assessed (EX = 12, CON = 9) due to scheduling difficulties. Maximal heart rate, RER and RPE (using the Borg 6–20 scale) were measured during the peak exercise test.

2.4. Research ethics statement

This research was approved by the Biomedical and Health Institutional Review Board at Michigan State University. All participants provided written informed consent prior to participation.

2.5. Data acquisition and analysis

Blood serum measures were taken after an overnight fast (8 h) using standard clinical enzyme procedures. MRS data were acquired at 3T using a 15 cm (Study 1, knee extensors) or 12 cm (Study 2, plantar flexors) surface coil (GE Excite, 51.7 MHz, TR = 3 s, 2500 Hz sweep, 60° pulse). MRS data were processed with jMRUI, AMARES algorithm [15]. A monoexponential model was used to fit the rate constant of phosphocreatine (PCr) recovery following exercise using the following equation:

$$Y(t) = Y(\text{Bsl}) + \text{Amp} \times (1 - e^{-k\text{PCr}t}) \quad (1)$$

Y represents PCr at any time (t); Bsl is the baseline Y value; Amp is the amplitude change in PCr; and $k\text{PCr}$ is the recovery rate constant. Muscle pH was determined by the chemical shift of Pi [16]. Measures of PCr had 3 s temporal resolution while pH was quantified by averaging consecutive spectra for 6 s temporal resolution.

2.6. Statistical analysis

For Study 1, repeated measures analysis of variance (ANOVA) was used to examine blood measures before and after high dose statin therapy. Paired t -tests were used to examine changes in muscle oxidative capacity measures and pain before and after high dose statin therapy. For Study 2, ANOVA was used to examine group differences at baseline for +STATIN (+S) vs. -STATIN (-S) and between subgroups (CON-S, CON+S, EX-S, EX+S). Repeated measures ANOVA was used to assess changes in muscle oxidative capacity and VO_2 peak measures over time with between group factors of exercise training (CON vs. EX) and chronic statin therapy (+S vs. -S). Significance was set at $p < 0.05$. Data were analyzed using IBM SPSS version 24. Values are reported as mean \pm SD unless otherwise noted.

3. Results

3.1. Study 1 results

Sixteen subjects completed the 4-week study of high dose statin therapy (Fig. 1). Of the five enrolled subjects who did not complete the study, one subject dropped out primarily due to an unexpected paresthesia of the throat and secondarily reported muscle pain. Subject descriptive characteristics are shown in Table 1. As expected, high dose statin therapy reduced total and LDL cholesterol markedly after two and four weeks compared to baseline ($p < 0.001$, Table 1). There were no changes in muscle pain after four weeks of high dose atorvastatin therapy for those completing the study ($n = 16$, $p = 0.295$). Muscle oxidative capacity was reduced by 12% after four weeks of high dose statin therapy ($p = 0.004$, Table 1). The acute plantar flexion burst exercise resulted in ~28% phosphocreatine hydrolysis with no significant differences in PCr hydrolysis or muscle pH following statin therapy ($p = 0.130$). The burst exercise did not cause significant muscle acidification ($p = 0.349$).

3.2. Study 2 results

Subject enrollment is reported in Fig. 1 and descriptive characteristics are shown in Table 2. Chronic low-moderate dose statin therapy included daily dosages of simvastatin (5 mg, $n = 1$; 10 mg, $n = 6$; 20 mg, $n = 2$), atorvastatin (10 mg, $n = 3$) and pravastatin (20 mg, $n = 2$). +STATIN had lower total and LDL cholesterol compared to -STATIN ($p = 0.006$, Table 2). CON+S had lower LDL compared to EX-S, $p = 0.018$. The subjects in the exercise group on statin therapy (EX+S) were taking 10 mg simvastatin ($n = 3$), 20 mg simvastatin ($n = 2$) or 20 mg pravastatin ($n = 1$). There were no other differences in baseline characteristics.

Twenty-seven subjects completed the 12-week study (Fig. 1). Subjects confirmed no changes in any medication types or dosages for the duration of the study. Compliance to the exercise training intervention was excellent with 95% attendance. Lower baseline LDL in the +STATIN group compared to -STATIN (Table 2, $p = 0.002$) and stable LDL in +STATIN in a sub-group with baseline and post-intervention bloodwork (baseline = 92 ± 17 mg/dL, post = 91 ± 23 mg/dL, $n = 10$, $p = 0.912$) provide support for statin compliance.

Sample experimental data from the assessment of muscle oxidative capacity are shown in Fig. 2. +STATIN had 20% lower muscle oxidative capacity at baseline compared to -STATIN ($n = 30$, $p = 0.019$); (Table 2, Fig. 3). The acute plantar flexion burst exercise resulted in ~25% phosphocreatine hydrolysis associated with an initial muscle alkalinization during the short burst and recovery to baseline pH with little muscle acidification (Fig. 3). Resting muscle pH was not different between groups prior to intervention ($p = 0.311$, Table 2). The overall minimal pH was not different between groups ($p = 0.431$, Table 2, Fig. 3). There were no baseline differences in VO_2 peak ($p = 0.515$, Table 2).

There was a time by exercise group interaction for muscle oxidative capacity following exercise training (Fig. 3, $n = 27$, $p = 0.003$). Muscle oxidative capacity significantly improved by 37% for EX compared to CON who remained stable over time. Exercise training resulted in similar increases in mitochondrial function within the EX groups; muscle oxidative capacity increased by 36% for EX+S and 39% for EX-S. Therefore, chronic low-moderate dose statin therapy (STATIN group factor) did not influence the relative

changes following intervention. There were no group, time or interaction effects for resting muscle pH (pre: see Table 2, post: CON-S = 7.02 ± 0.02 , CON+S = 7.03 ± 0.02 , EX-S = 7.04 ± 0.02 , EX+S = 7.03 ± 0.02) and minimum pH (pre: see Table 2, post: CON-S = 6.96 ± 0.03 , CON+S = 6.97 ± 0.03 , EX-S = 6.99 ± 0.02 , EX+S = 6.98 ± 0.03). The MRS protocol elicited ~25% PCr hydrolysis which was similar between groups ($p = 0.425$) with a trend to be slightly lower with time ($p = 0.053$, Fig. 3).

There was a time by training group interaction for VO_2 peak (Fig. 4, $p = 0.001$). Following exercise training, VO_2 peak increased by an average of 11% following EX, a $2.0 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ increase compared to a 5% decrease or $1.2 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ decrease in CON. Consistent with muscle oxidative capacity, low-moderate dose chronic statin therapy did not significantly influence the VO_2 peak improvement. Maximal heart rate, RER and RPE during VO_2 peak averaged 152 ± 17 beats per minute, 1.08 ± 0.07 , and 18 ± 1 , respectively and were not different between groups or over time (data not shown).

4. Discussion

High dose statin therapy and moderate-low dose chronic statin therapy was associated with reduced skeletal muscle oxidative capacity. Following exercise training, subjects on chronic low-moderate dose statin therapy had increases in aerobic capacity that were roughly equivalent to the relative increases in subjects not on therapy. Therefore, the primary outcome is that chronic statin therapy did not blunt the improvement in aerobic capacity following exercise training.

This study confirms the findings of other research, showing that statin therapy is associated with reduced in vivo muscle oxidative capacity [5]. In the current study we show reduced muscle oxidative capacity using a moderate intensity exercise protocol without inducing substantial muscle acidity. This is an important point as muscle acidification has a direct influence on estimating mitochondrial function as it slows phosphocreatine recovery [17,18]. These data confirm a statin-induced reduction in in vivo oxidative capacity in the distal plantar flexor muscles [5] and show that the proximal quadriceps muscles are also affected. The present study shows the reduction in groups who did not overtly present with muscle pain. For Study 2, although pain was not formally measured, no participant reported muscle pain, weakness or calf cramping during the testing or exercise intervention compared to previous findings in which history of statin-related myalgia was reported [5]. A prior study of statin therapy showed significantly slower metabolic recovery following vigorous exercise using a robust cross-over design. As muscle pain and cramping were used as endpoints for the vigorous calf exercise (up to 7 min in duration) [5], their findings may be associated with significant muscle acidity and contribute to exercise intolerance reported by some patients on statin therapy [19]. Prior studies have also shown a reduction in mitochondrial volume and enzyme content with simvastatin use [6] and reduced mitochondrial respiration in patients on statin therapy [4,9]. Baseline VO_2 peak was not reduced with statin therapy, consistent with prior findings in older adults [20].

Exercise training increased muscle oxidative capacity and VO_2 peak in older adults including older women on statin therapy. Thus, low-moderate intensity statin therapy did

not appear to limit the relative adaptation in plantar flexor oxidative capacity following exercise training. The current data align with recent findings of improved mitochondrial content [21,22] and improved mitochondrial function as measured by improvements in fat oxidation [22] and muscle oxidative capacity [21] following exercise training for individuals treated with chronic statin therapy. Our results extend mitochondrial improvements into older adults. The results are also consistent with exercise data from mice treated with statin medication, which showed both improvements in markers of mitochondria biogenesis and mitochondrial enzyme content [11]. In addition, VO_2 max has been reported to increase following combined aerobic and resistance training for individuals on chronic statin therapy similar to the present findings [21,23].

Two studies have reported reductions in exercise induced aerobic adaptations in middle-aged adults undergoing statin therapy [10,22]. Mikus et al., showed that novel aerobic exercise and 40 mg simvastatin completely blunted increases in both VO_2 peak and skeletal muscle oxidative enzymes compared to exercise therapy alone [10]. We propose that exercise training offset the expected loss in oxidative enzyme content typically observed with statin therapy; our data show reduced muscle oxidative capacity following high dose statin therapy and also show lower capacity in individuals on low dose chronic statin therapy. More recently, Morales-Palomo et al., also reported partially blunted improvements in whole body aerobic capacity in chronic statin users with high intensity interval training [22]. Prior studies have shown that high intensity exercise may not be well tolerated during statin therapy [19] which could theoretically reduce the overall training effort and stimulus or otherwise reduce adaptations in ways not fully understood. The presence of metabolic syndrome [24], a primary focus of the two aforementioned studies in which statin therapy blunted adaptations, may have limited adaptations. In addition, reduced cardiac strain with statin use may be a contributing factor [25]. It is also worthwhile to consider the trends in the post-intervention data of the current study that reflect lower muscle oxidative capacity in the presence of chronic statin therapy despite the similar relative improvement (Fig. 3). Specifically, EX+S tended to have lower oxidative capacity post-training compared to EX-S. Therefore, the overall trend in lower muscle oxidative capacity following exercise training during chronic statin therapy may indicate limits in improvement. The collective findings from the current study and prior results show an important role for aerobic and similar exercise in improving aerobic capacity or preventing anticipated declines during statin therapy while hinting at potential limits in maximal aerobic capacity.

Aerobic exercise training prior to statin therapy has also been explored as a means to protect against statin induced mitochondrial dysfunction. Exercise trained rodent muscle treated with statins showed blunted reductions in mitochondrial respiration compared to muscle from sedentary mice treated with statins [26]. Thus, exercise interventions that begin before statin therapy may help to prevent reductions in mitochondrial capacity occurring with statin therapy. However, this beneficial effect has not been shown in vivo and has yet to be directly investigated in humans. Anecdotally, the introduction of statin therapy in elite athletes training at high exercise intensities was associated with exercise intolerance rather than conferring any notable protection or improvements [19]. Future work in this area may need to parse out the role of the exercise intensity when exploring the potential protective effects of exercise interventions.

There were limitations to acknowledge with this research. The exercise intervention study is limited by a small sample size and no male subjects in the exercise group that were on statin therapy. Additional studies are needed to extend the exercise improvements to patients prescribed higher intensity statin doses targeting lower LDL levels including patients on statin therapy for secondary prevention of cardiovascular events.

5. Conclusions

The outcomes of the study corroborate findings of reduced in vivo skeletal muscle oxidative capacity with chronic statin therapy. The current data show that aerobic exercise training effectively improves whole body and skeletal muscle aerobic capacity in older adults in the presence of chronic statin therapy. The ability to increase aerobic capacity is important as improvements in exercise capacity have been shown to independently and significantly reduce cardiovascular disease mortality [27]. The successful adaptations of the exercise intervention may have occurred in part due to a low-moderate dose of statin therapy. Nonetheless, these results are encouraging, in particular for older adults as 40% or more are likely to be prescribed a statin for control of blood cholesterol, reduction in cardiovascular event risk or prevention of or treatment for metabolic syndrome, likely for a lifetime [2]. Furthermore, these data underscore the importance of aerobic exercise as a tool to help offset reductions in muscle oxidative capacity tied to statin therapy. Our study supports the notion that aerobic exercise can improve baseline levels of aerobic fitness for individuals already on statin therapy, but additional studies are warranted to assess limits that statins may impose on maximal aerobic capacity.

Acknowledgements

The authors would like to thank Linda East, Hillary Vogel and the MSU Cardiology fellows for their assistance with stress testing and physical examinations. Thanks to Ryan Stringer, James Lewis, Ananya Juneja, Stacie Clark, Jeff Cross, Bradley Riedinger, and Ewan Williams for assisting with testing and interventions.

Sources of funding

This work was supported by the National Institutes of Health (R21 AG042041 and R21 AR054117).

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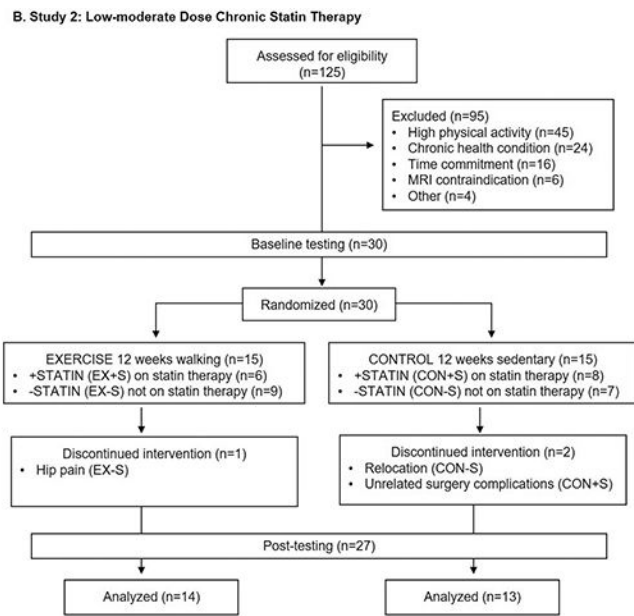
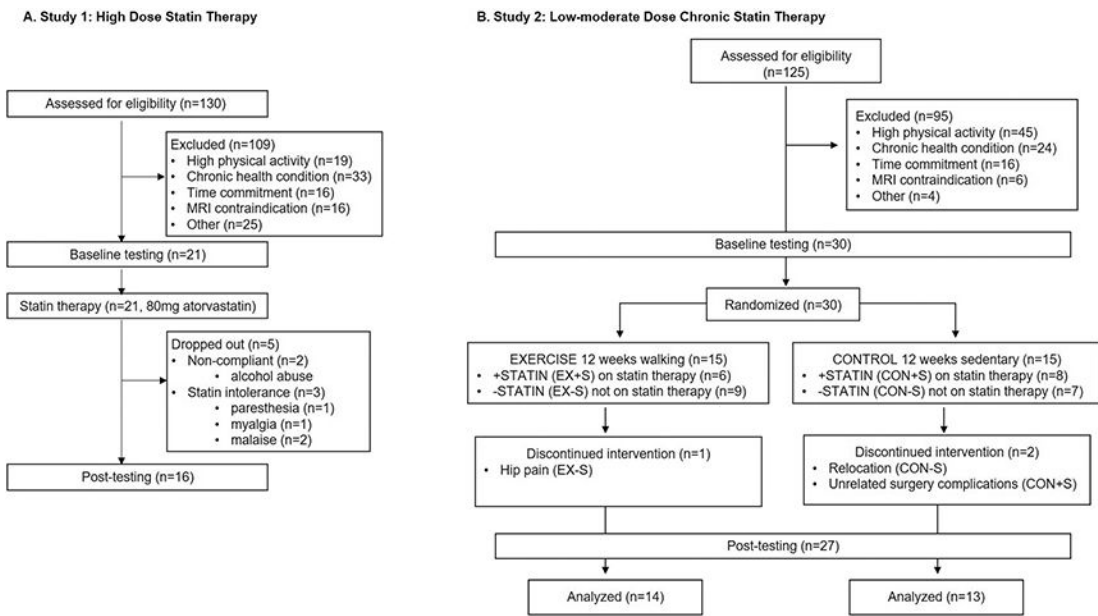


Fig. 1.
CONSORT flow charts for Study 1 and Study 2.

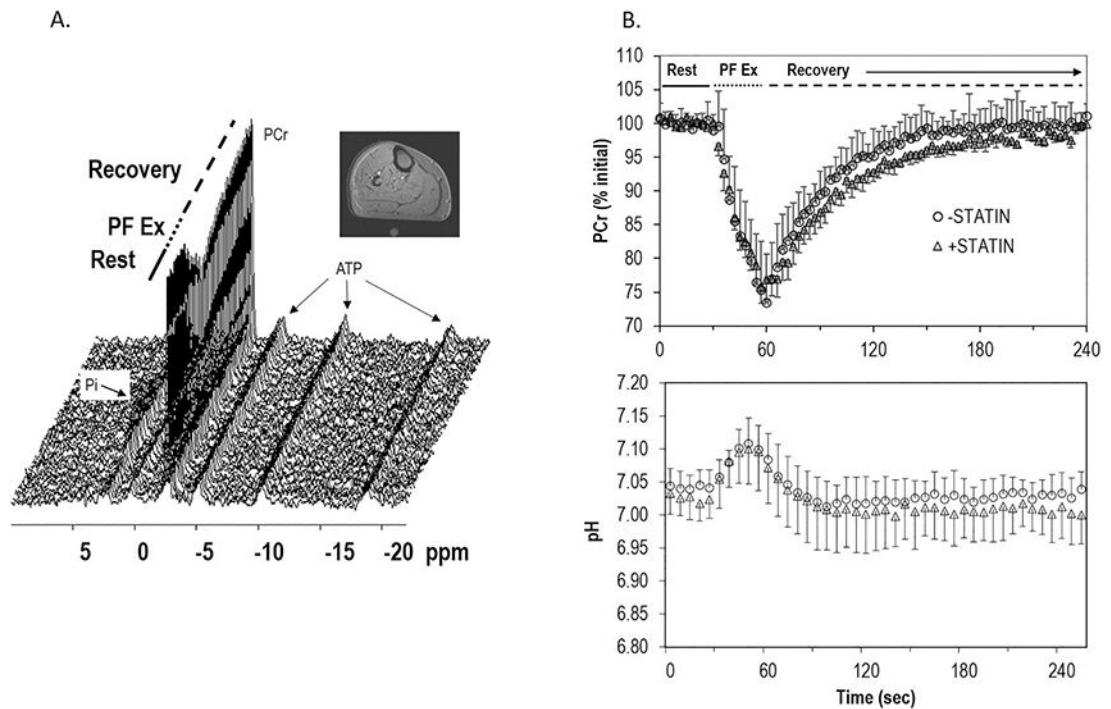


Fig. 2. Baseline muscle oxidative capacity measures. A phosphorus series of spectra at rest, during 30s burst plantar flexor exercise (PF) and immediately following burst exercise (recovery) from a representative subject; inset shows the location of the coil centered at mid-calf (A). Quantification of phosphocreatine and muscle pH during the burst exercise are shown for subjects on chronic statin therapy (triangles, +STATIN) and subjects not taking statins (circles, -STATIN), displayed as group mean \pm SD (B). Baseline measures are prior to exercise intervention.

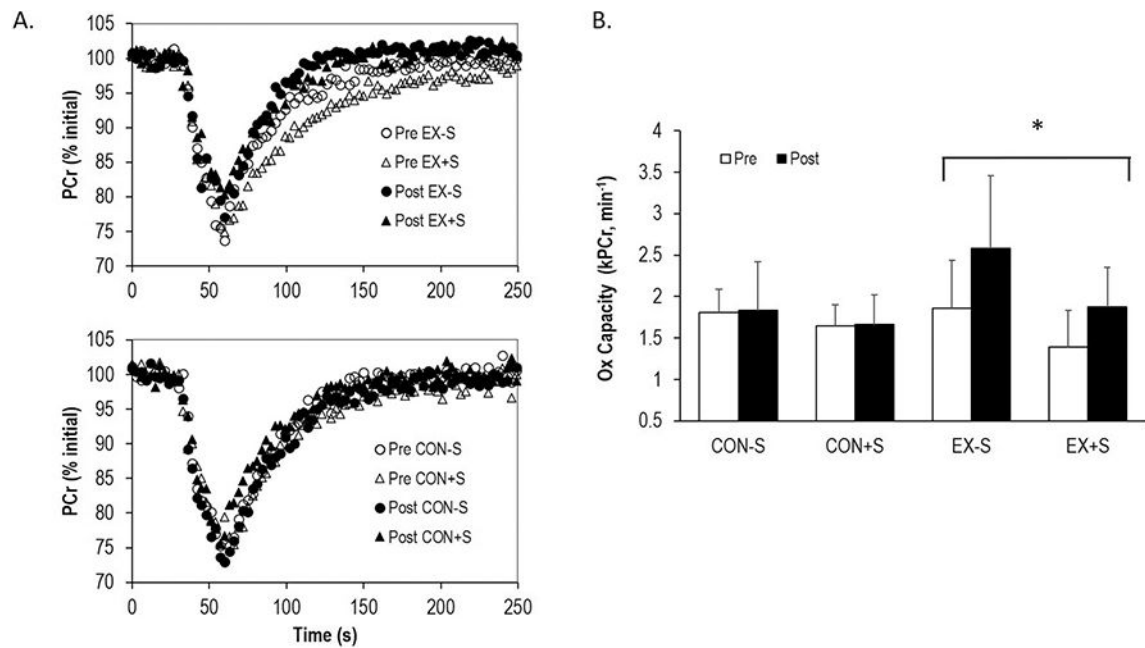


Fig. 3. Changes in phosphocreatine during burst exercise are shown for EX (top) and CON (bottom) (group means, A); circles indicate non-statin therapy group and triangles indicate statin therapy group, with open symbols indicating pre-intervention and closed symbols indicating post-intervention. Muscle oxidative capacity of the calf ($kPCr$) before (pre) and after (post) a 12-week walking exercise intervention; group mean values \pm SD are shown (B). CON-S = non-exercise control group without statin, CON+S = non-exercise control group with chronic statin therapy, EX-S = exercise group without statin, EX+S = exercise group with chronic statin therapy. Only subjects with pre and post data are included ($n = 27$). *significant exercise group \times time interaction, $p < 0.05$.

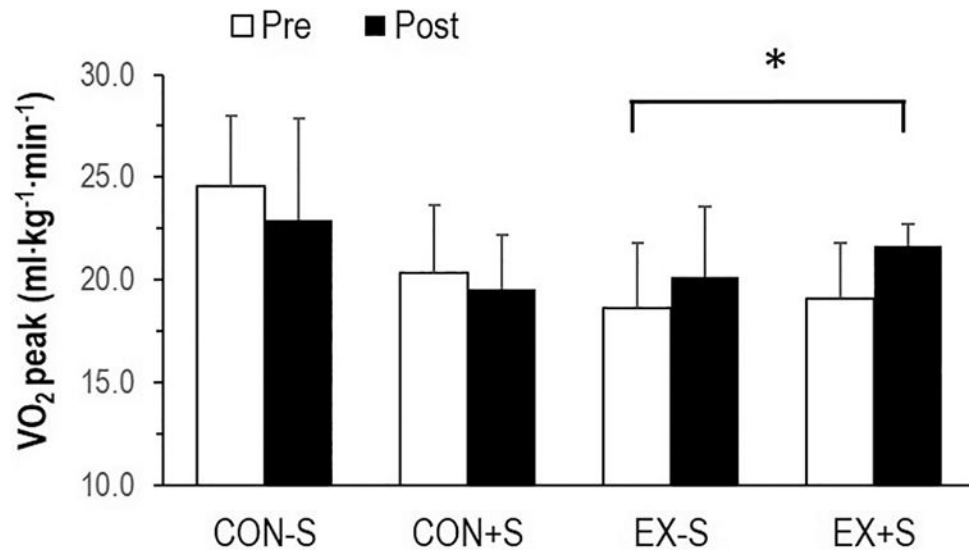


Fig. 4. Whole body peak oxygen consumption (VO_2 peak) before (pre) and after (post) a 12-week walking exercise intervention. CON-S = non-exercise control group without statin, CON+S = non-exercise control group with chronic statin therapy, EX-S = exercise group without statin, EX+S = exercise group with chronic statin therapy. Only subjects with pre and post data are included ($n = 21$). *significant exercise group x time interaction, $p < 0.05$.

Table 1Subject characteristics and outcomes (Study 1, $n = 16$).

Variables	Baseline	Mid	Post	<i>p</i> value
Age (yrs)	45 ± 9	–	–	–
Males (number)	9	–	–	–
BMI (kg/m ²)	27 ± 5	–	–	–
LDL (mg/dl) *	138 ± 40	59 ± 18	58 ± 20	<0.001
HDL (mg/dl)	53 ± 16	51 ± 16	48 ± 15	0.074
Total chol (mg/dl) *	218 ± 45	128 ± 20	126 ± 25	<0.001
Triglycerides (mg/dl)	132 ± 73	90 ± 32	98 ± 33	0.052
CPK	112 ± 38	141 ± 91	143 ± 62	0.083
Oxidative capacity <i>k</i> PCr (min ⁻¹) *	1.34 ± 0.34	–	1.17 ± 0.25	0.004
PCr hydrolysis (%)	72 ± 12	–	71 ± 10	0.769
Muscle pH rest	6.98 ± 0.02	–	6.97 ± 0.01	0.130
Muscle pH minimum	6.98 ± 0.05	–	6.95 ± 0.08	0.245
Muscle pain rest (mm)	4.9 ± 8.4	–	2.6 ± 7.1	0.421
Muscle pain tension (mm)	1.9 ± 3.7	–	4.2 ± 7.1	0.295

Values are mean ± SD. Baseline: prior to statin therapy; Mid: following 2 weeks of 80 mg atorvastatin; Post: following 4 weeks of 80 mg atorvastatin.

* Significant effect of time, $p < 0.05$.

Table 2

Subject characteristics at baseline (Study 2).

Variables	-STATIN n = 16	+STATIN n = 14	CON - S n = 7	EX - S n = 9	CON + S n = 8	EX + S n = 6
Age (yrs)	66 ± 6	69 ± 5	64 ± 4	67 ± 6	69 ± 5	69 ± 5
Males (number)	3	2	1	2	2	0
BMI (kg/m ²)	31 ± 6	29 ± 5	32 ± 7	30 ± 6	31 ± 5	27 ± 5
LDL (mg/dl)	123 ± 25	96 ± 17*	118 ± 22	128 ± 27	92 ± 11 [†]	102 ± 21
HDL (mg/dl)	59 ± 14	57 ± 18	56 ± 9	61 ± 16	56 ± 18	58 ± 19
Total chol (mg/dl)	210 ± 33	175 ± 30*	204 ± 32	215 ± 36	170 ± 24	181 ± 37
Triglycerides (mg/dl)	133 ± 57	116 ± 44	153 ± 61	118 ± 53	130 ± 43	99 ± 42
VO ₂ peak (ml·kg ⁻¹ ·min ⁻¹)	20.7 ± 4.4	19.9 ± 2.8	21.6 ± 4.5	20.0 ± 4.5	20.4 ± 3.1	19.2 ± 2.4
Oxidative capacity <i>k</i> PCr (min ⁻¹)	1.88 ± 0.47	1.50 ± 0.35*	1.81 ± 0.28	1.93 ± 0.59	1.58 ± 0.27	1.39 ± 0.44
Muscle pH rest	7.04 ± 0.02	7.03 ± 0.03	7.05 ± 0.02	7.03 ± 0.03	7.03 ± 0.03	7.03 ± 0.02
Muscle pH minimum	6.98 ± 0.04	6.98 ± 0.04	6.96 ± 0.04	6.99 ± 0.02	6.96 ± 0.05	6.98 ± 0.04

Values are mean ± SD. CON = non-exercise control group, EX = exercise group, -S/-STATIN = subjects not on statin therapy, +S/+STATIN = subjects on chronic low-moderate dose statin therapy.

* Significant difference compared to -STATIN (p < 0.05).

[†] Significant difference compared to EX-S (p < 0.05).