Moderate Intensity Exercise Training Improves Skeletal Muscle Performance in Symptomatic and Asymptomatic Statin Users

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ORIGINAL INVESTIGATIONS

Moderate Intensity Exercise Training Improves Skeletal Muscle Performance in Symptomatic and Asymptomatic Statin Users

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ABSTRACT

BACKGROUND The combination of statin therapy and physical activity reduces cardiovascular disease risk in patients with hyperlipidemia more than either treatment alone. However, mitochondrial dysfunction associated with statin treatment could attenuate training adaptations.

OBJECTIVES This study determined whether moderate intensity exercise training improved muscle and exercise performance, muscle mitochondrial function, and fiber capillarization in symptomatic and asymptomatic statin users.

METHODS Symptomatic (n = 16; age 64 ± 4 years) and asymptomatic statin users (n = 16; age 64 ± 4 years) and nonstatin using control subjects (n = 20; age 63 ± 5 years) completed a 12-week endurance and resistance exercise training program. Maximal exercise performance (peak oxygen consumption), muscle performance and muscle symptoms were determined before and after training. Muscle biopsies were collected to assess citrate synthase activity, adenosine triphosphate (ATP) production capacity, muscle fiber type distribution, fiber size, and capillarization.

RESULTS Type I muscle fibers were less prevalent in symptomatic statin users than control subjects at baseline ($P = 0.06$). Exercise training improved muscle strength ($P < 0.001$), resistance to fatigue ($P = 0.01$), and muscle fiber capillarization ($P < 0.01$), with no differences between groups. Exercise training improved citrate synthase activity in the total group ($P < 0.01$), with asymptomatic statin users showing less improvement than control subjects ($P = 0.02$). Peak oxygen consumption, ATP production capacity, fiber size, and muscle symptoms remained unchanged in all groups following training. Quality-of-life scores improved only in symptomatic statin users following exercise training ($P < 0.01$).

CONCLUSIONS A moderate intensity endurance and resistance exercise training program improves muscle performance, capillarization, and mitochondrial content in both asymptomatic and symptomatic statin users without exacerbating muscle complaints. Exercise training may even increase quality of life in symptomatic statin users. (The Effects of Cholesterol-Lowering Medication on Exercise Performance [STATEX]; NL5972/NTR6346)
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ABBREVIATIONS AND ACRONYMS

ATP = adenosine triphosphate

CS = citrate synthase

QoL = quality of life

SAMS = statin-associated muscle symptoms

Vo_2peak = peak oxygen uptake

Hydroxymethylglutaryl-coenzyme A reductase inhibitors or statins, are among the most widely prescribed medications because they reduce the incidence of cardiovascular events by lowering low-density lipoprotein cholesterol (1). Statins are well-tolerated but may produce statin-associated muscle symptoms (SAMS) in some patients (2). Statins reduce mitochondrial oxidative capacity and content in human skeletal muscle (3-5), which suggests that mitochondrial dysfunction contributes to SAMS.

Increased physical activity is associated with reduced cardiovascular disease risk, and this reduction with physical activity is increased by statin treatment (6). It is unclear if the mitochondrial dysfunction associated with statin therapy reduces the increases in exercise capacity and muscle performance from exercise training (7-10). We have observed that mitochondrial dysfunction is more pronounced in statin users with SAMS compared with asymptomatic statin users (3). This suggests that exercise training adaptations could be different between statins users with and without SAMS, a confounder often overlooked by other exercise training studies in statin users (7-10). SAMS may also be exacerbated by physical activity, thereby prohibiting a physically active lifestyle for statin users (11).

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We sought to compare the impact of moderate intensity endurance and resistance exercise training on mitochondrial content and function between symptomatic and asymptomatic statin users, and nonstatin using control subjects. Our secondary aims examined the effect of this training program on muscle fiber composition, exercise performance, and muscle complaints. We hypothesized that the combination of endurance and resistance exercise training would improve mitochondrial function in all groups and thereby alleviate skeletal muscle complaints and reduce the statin-associated myocellular changes we noted previously (12).

METHODS

PARTICIPANTS. Participants were recruited via advertisements in local newspapers, pharmacies, and physician offices. Statin users were included if they had used statins continuously for ≥3 months. Statin users could be included if the statin dose or type had been changed within these 3 months. We calculated 'atorvastatin' equivalence to standardize the statin dose potency, as 1 atorvastatin equivalent = 5 mg of atorvastatin = rosuvastatin 1.25 mg = simvastatin 10 mg = lovastatin 20 mg = pravastatin 20 mg (13,14). Statin users were considered symptomatic or asymptomatic based on the presence, localization, and onset of muscle cramps, pain, and/or weakness, using the statin myalgia clinical index score (15). Exclusion criteria included familial hypercholesterolemia, known hereditary skeletal muscle defects, diabetes mellitus, hypo- or hyperthyroidism, and use of other medications known to cause muscle symptoms or mitochondrial dysfunction (eg, steroids or metformin). Subjects were not recruited if they had contraindications to maximal aerobic exercise testing (16), muscle biopsy (eg, anticoagulant therapy), or if they engaged in sports activities ≥2 hours weekly. Subjects provided written informed consent as approved by the Local Committee on Research Involving Human Subjects of the region Arnhem and Nijmegen, the Netherlands. This trial is registered in the Netherlands Trial Registry (STATEX [The Effects of Cholesterol-Lowering Medication on Exercise Performance]; NL5972/NTR6346).

STUDY DESIGN. Participants were enrolled in an endurance and resistance exercise training program. Exercise sessions were supervised and performed in groups of 2-3 subjects. Endurance exercise was performed biweekly on a cycling ergometer and consisted of a 10-min warmup, 40 min at 70%-80% of maximal heart rate, and a 5-min cool down. Heart rate was monitored using heart rate monitors (Polar RS800; Polar Electro Oy) and documented in a training log. The ergometer workload was changed to maintain target heart rate. Resistance exercise was performed once a week for 60 minutes and included leg presses, leg extensions, leg curls, chest and shoulder presses, seated rows, latissimus dorsi and triceps pull downs, and cable curls and hovers. Each exercise consisted of 3 sets of 12 repetitions with 1 minute rest between sets. Workloads were increased when participants could perform >12 repetitions in 2 of the 3 sets. Participants were encouraged to maintain their dietary intake and physical activity habits throughout the intervention period. All

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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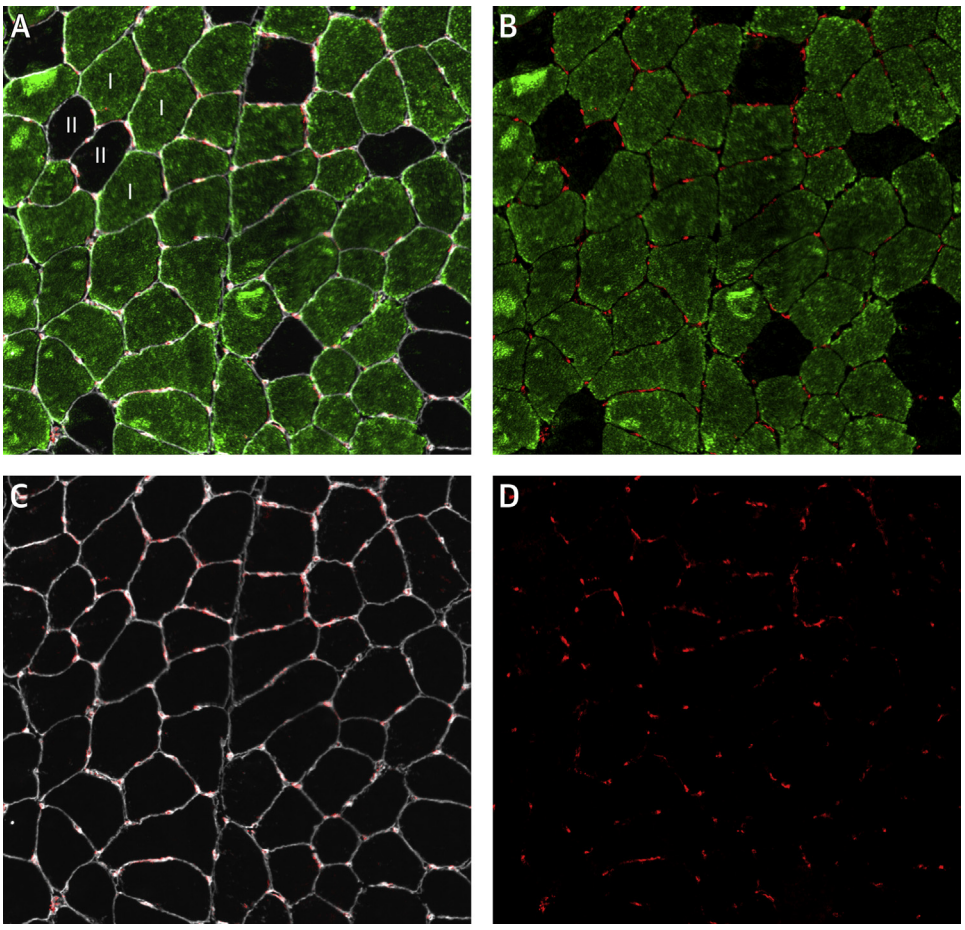
FIGURE 1 Immunohistochemical Analyses of Muscle Biopsies



Immunohistochemical analyses of type I and type II muscle fiber characteristics. **(A)** Myosin heavy chain I (MHCI) **(green)** + laminin **(white)** + CD31 **(red)** staining. **(B)** MHCI + CD31 staining. **(C)** Laminin + CD31 staining. **(D)** CD31 staining only.

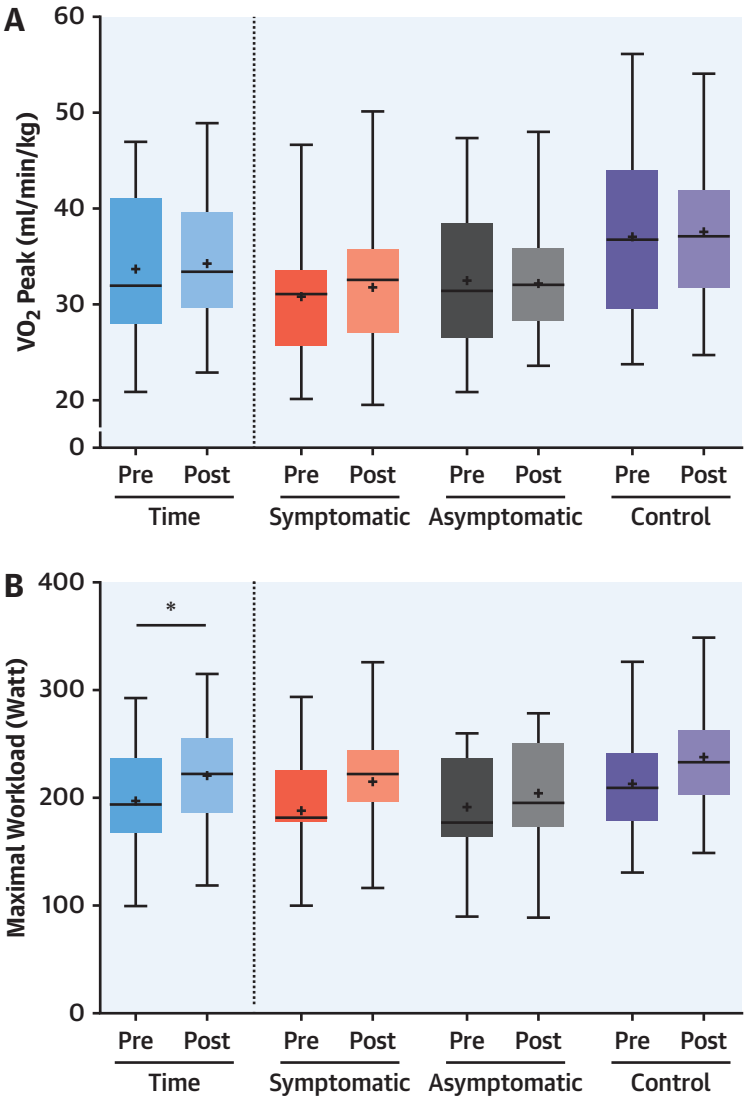
measurements were completed during the 14 days before and 7 days after the training program.

MEASUREMENTS. Weight, height, and waist and hip circumference were measured. Body composition was determined using a dual-energy x-ray absorptiometry scan (QDR 4500 densitometer, Hologic Inc). Fasting venous blood was collected to measure serum lipids and creatine kinase levels. The Short Questionnaire to Assess Health-enhancing physical activity was used to determine physical activity (17). Total physical activity levels at the end of the intervention did not include study training sessions. Muscle pain scores were measured by pain-rating index scores (18) and visual analogue scales. The Brief Fatigue Inventory was used to measure fatigue and the short-form McGill Pain Questionnaire was used to measure QoL index scores (18,19).

Maximal voluntary contraction and muscle fatigue resistance were determined in the quadriceps femoris of the dominant leg (3). Maximal exercise performance was measured with an incremental cycle ergometer test (Lode Excalibur) with continuous electrocardiographic monitoring (20). Peak oxygen uptake (Vo_2peak) was defined as the highest 30-second averaged Vo_2 uptake (3).

A percutaneous needle biopsy of the vastus lateralis muscle was obtained under local anesthesia after an overnight fast (21). Fresh muscle tissue was used to determine ATP production capacity normalized for protein content and citrate synthase (CS) activity as a proxy measure for mitochondrial density (22). The remaining biopsy sample was embedded in Tissue-Tek (Sakura Finetek, Zoeterwoude), frozen in liquid nitrogen-cooled isopentane, and stored at −80 °C for

FIGURE 2 Effect of Exercise Training on Exercise Performance



(A) Peak oxygen consumption (Vo_2peak), **(B)** maximal workload, and **(C)** maximal voluntary contraction (MVC) of the m. quadriceps femoris were measured before (pre) and after (post) 12 weeks of combined aerobic and strength training in all included participants (time effect) and separated by group. **(D)** Muscle force decline and **(E)** increase in half relaxation time (RT) were determined by repetitive electrical stimulation and expressed as percentage of prefatigue value. **Boxes** represent interquartile (25th to 75th percentile) ranges, **whiskers** represent 5th to 95th percentiles, and the **horizontal line and cross** indicate the median and mean, respectively. *Significant effect of time ($P < 0.05$).

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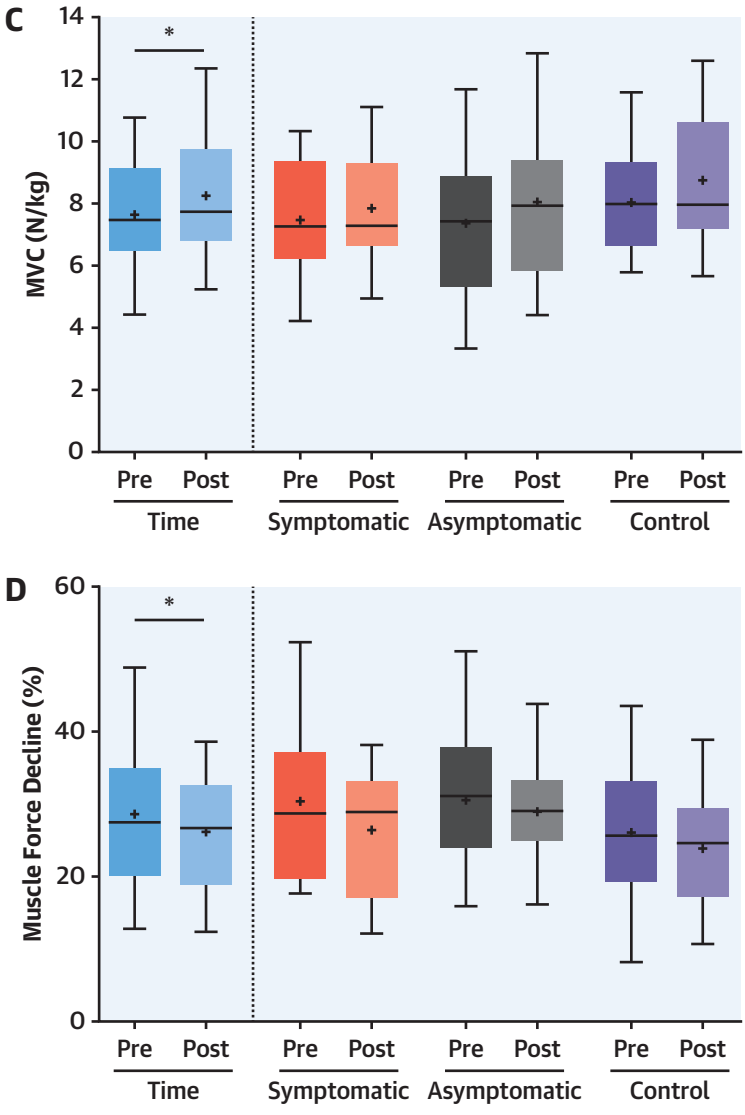
subsequent analyses. Muscle biopsy samples were cut into 5-μm-thick cryosections at −20 °C, with pre- and postsamples from individual participants mounted on the same slide. Type I and type II muscle fiber type distribution, fiber size (cross-sectional area), and indexes of fiber capillarization were determined by immunohistochemistry (23). The number of capillaries was manually counted and expressed as capillary count (number of capillaries in contact with each fiber), sharing factor (number of fibers sharing each capillary), C/Fi (where the C/Fi is the number of the capillary count divided by the mean sharing factor for each fiber), capillary density (numbers of capillaries per square millimeter), and CFPE index (number of capillaries per 1,000-μm perimeter) (24). Representative images of immunohistochemical analyses are shown in **Figure 1**.

FIGURE 2 Continued



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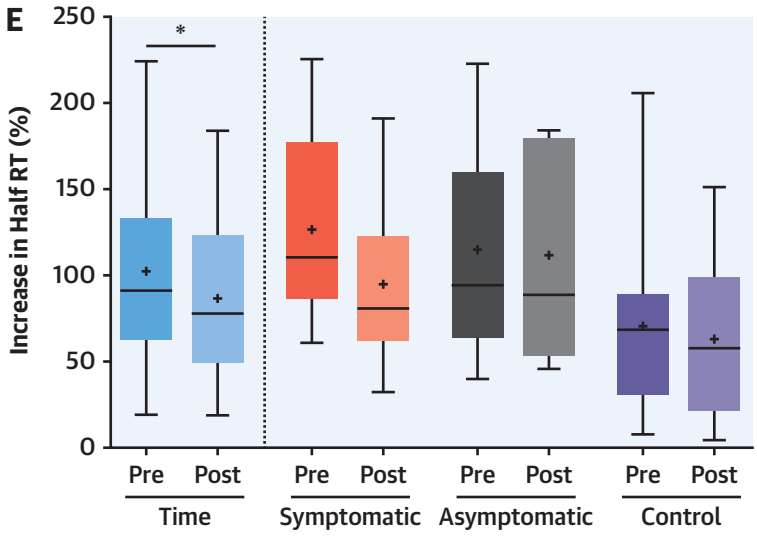
STATISTICAL ANALYSIS. Continuous variables were reported as mean ± SD or median (25th and 75th quartiles). Categorical variables were reported in proportions and tested by chi-square test. Differences at baseline were assessed by 1-way analysis of variance for normally distributed variables and by Kruskal-Wallis 1-way analysis of variance for skewed variables, followed by Bonferroni post hoc tests to identify specific pairwise comparisons. Linear mixed models and generalized linear model analyses were used to evaluate the impact of exercise training. This design was used to adjust for baseline differences between the groups and a regression to the mean effect, which is associated with repeated measures. First, the overall effect of the training intervention in all 3 groups together (time) was determined using linear mixed models with random intercept. Second, an interaction term for group and time was added to investigate differences in training adaptations among the 3 groups (time × group). Finally, a generalized linear model was used to correct for baseline and sex differences between the groups. Pearson's or Spearman's correlation analyses were conducted to identify correlations between variables. Statistical significance was set at $P < 0.05$. Analyses were performed using SPSS 24.0 (IBM).

FIGURE 2 Continued



RESULTS

PARTICIPANTS. Seventeen symptomatic statin users, 17 asymptomatic statin users, and 20 nonstatin using control subjects participated. One symptomatic and 1 asymptomatic statin user withdrew from the study because of the physical burden of the exercise training and because of time constraints, respectively. Fifty-two participants (33 men and 19 women) completed the study. Statin type, atorvastatin equivalence, and duration of the current statin treatment were not significantly different between the statin groups (Table 1). Individual data on statin use can be found in Supplemental Table 1. Physical activity levels were not different among groups at baseline and did not change with exercise training (Table 1). Adherence to exercise training was high, and only 1 asymptomatic statin user missed an endurance session that could not be rescheduled.

BODY COMPOSITION. There were no significant differences in body mass index or body composition among the groups at baseline (Table 1). Body mass index ($P = 0.004$) and hip ($P = 0.04$) and waist ($P < 0.001$) circumferences decreased with training in all groups. Fat mass ($P = 0.006$) and percent body fat ($P = 0.004$) decreased with exercise training. Asymptomatic statin users experienced a greater decline in fat mass (fixed effect estimate: -0.9 kg; 95% CI: -1.7 to -0.05 kg; $P = 0.04$) compared with control subjects. Whole body lean tissue mass did not change in any group over time, whereas appendicular lean mass increased (fixed effect estimate: 0.3 kg; 95% CI: 0.05-0.5 kg; $P = 0.02$) with exercise training, with no group differences (Table 1).

MUSCLE SYMPTOMS. Symptomatic statin users had higher pain-rating index and visual analogue scale pain scores at baseline than control subjects ($P < 0.01$) and asymptomatic statin users ($P < 0.001$), and higher fatigue scores than control subjects ($P < 0.05$). Pain and fatigue scores did not change with exercise training (Table 1). At baseline, QoL index scores were significantly higher in symptomatic than in asymptomatic users ($P < 0.001$) and control subjects ($P < 0.001$). QoL index scores correlated with pain-rating index ($r = 0.70$), visual analogue scale pain ($r = 0.68$) and fatigue scores ($r = 0.52$) (all $P < 0.001$). QoL index scores were maximized and therefore unchanged in the asymptomatic users and control subjects (Table 1), whereas these scores improved in symptomatic statin users with training (fixed effect estimate: -2.4 AU; 95% CI: -4.13 to -0.62 AU; $P < 0.01$).

EXERCISE PERFORMANCE. V_{O_2}peak was not different among groups at baseline and did not change with training in any group (Figure 2A), whereas maximal workload increased significantly in the total group by 12 ± 8% (Figure 2B) and similarly in the separate groups. After correcting for baseline workload and sex, asymptomatic statin users increased their maximum workload less than the control subjects ($P = 0.02$) (Supplemental Table 2). Quadriceps maximal voluntary contraction (per kg bodyweight) increased significantly by 9% ± 14% with exercise training

TABLE 1 Subject Characteristics

	Symptomatic (n = 16)		Asymptomatic (n = 16)		Control (n = 20)		Effect of Exercise Training *P* Value		
	Pre	Post	Pre	Post	Pre	Post	Time	S vs C	A vs C
Sex, M/F	12/4		11/5		10/10				
Age, y	65 (60-67)		65 (61-68)		64 (58-68)				
Statin type									
Simvastatin	7 (43.8)		10 (62.5)		N/A				
Atorvastatin	3 (18.8)		5 (31.3)		N/A				
Rosuvastatin	4 (25.0)		1 (6.3)		N/A				
Pravastatin	2 (12.5)		0 (0)		N/A				
Atorvastatin equivalents[a]	4 (2-7)		4 (2-4)		N/A				
Duration current statin, months	30 (13-81)		42 (11-133)						
Total physical activity, METmin/week	3,045 (1,445-4,483)	3,876 (2,442-5,096)	3,101 (1,931-5,263)	3,993 (1.863-5,639)	4,206 (1,671-6,161)	3,566 (1,487-6,840)	0.81	0.27	0.58
Body mass index, kg/m^2	27.3 ± 3.7	27.0 ± 3.7	26.5 ± 4.4	26.0 ± 3.7	25.1 ± 4.1	25.0 ± 3.9	0.004	0.29	0.09
Hip circumference, cm	101.8 ± 7.2	101.0 ± 7.7	99.6 ± 8.4	98.2 ± 7.5	98.4 ± 9.2	98.4 ± 8.0	0.04	0.37	0.06
Waist circumference, cm	99.4 ± 11.3	97.1 ± 10.8	96.2 ± 13.5	94.0 ± 10.9	90.5 ± 13.6	90.0 ± 13.3	<0.001	0.06	0.07
Fat mass, kg	27.8 ± 7.7	27.1 ± 7.3	26.3 ± 8.7	25.3 ± 7.8	24.0 ± 7.7	23.9 ± 7.7	0.006	0.24	0.04
Body fat, %	32.3 ± 5.0	31.7 ± 4.7	31.3 ± 6.8	30.7 ± 6.9	30.9 ± 6.0	30.5 ± 6.0	0.004	0.45	0.51
Lean body mass, kg	55.3 ± 11.5	55.8 ± 11.9	54.2 ± 9.6	53.9 ± 9.1	50.8 ± 11.4	51.3 ± 10.9	0.27	0.98	0.14
Appendicular lean mass, kg	24.2 ± 5.8	24.5 ± 6.0	23.9 ± 4.6	24.0 ± 4.5	22.2 ± 5.6	22.6 ± 5.5	0.02	0.91	0.37
Pain rating index, AU	24.9 (21.4-35.2)[b,c]	26.4 (15.8-37.8)	2.0 (0.0-20.0)	0.0 (0.0-4.1)	0.0 (0.0-23.7)	0.0 (0.0-27.8)	0.34	0.23	0.10
Fatigue score, AU	3.5 (0.5-7.8)[b]	3.0 (2.0-6.5)	2.0 (0.3-3.0)	1.5 (0-4.5)	0.5 (0.0-2.8)	1.5 (0.0-2.0)	0.72	0.63	1.00
VAS pain score, AU	1.7 (0.4-2.6)[b,c]	2.2 (0.4-4.7)	0.0 (0.0-0.6)	0.0 (0.0-0.1)	0.0 (0.0-1.4)	0.0 (0.0-1.0)	0.24	0.53	0.33
Quality of life index, AU	4.5 (2.3-6.0)[b,c]	2.0 (0.0-5.0)	0.0 (0.0-0.8)	0.0 (0.0-2.3)	0.0 (0.0-1.8)	0.0 (0.0-2.0)	0.85	0.009	0.57
Total cholesterol, mmol/L	4.3 ± 0.9[b]	4.3 ± 0.9	4.4 ± 1.0[d]	4.2 ± 1.1	5.3 ± 0.8	5.2 ± 0.8	0.16	0.55	0.60
LDL cholesterol, mmol/L	2.3 ± 0.7[b]	2.4 ± 0.7	2.3 ± 0.7[d]	2.3 ± 0.7	3.0 ± 0.7	2.9 ± 0.7	0.28	0.18	0.89
HDL cholesterol	1.3 ± 0.4[b]	1.3 ± 0.3	1.4 ± 0.4	1.4 ± 0.3	1.7 ± 0.6	1.8 ± 0.6	0.87	0.20	0.22
Creatine kinase, U/L	134 (92-256)	133 (113-256)	92 (77-126)	105 (80-166)	115 (77-131)	105 (81-152)	0.73	0.91	0.57

Values are n, median (interquartile range), n (%), or mean ± SD. [a]1 atorvastatin equivalent (5mg) = rosuvastatin 1.25 mg = simvastatin 10 mg = lovastatin 20 mg = pravastatin 20 mg. When significant differences between groups were found, pairwise comparisons were made by Bonferroni post-hoc testing. [b]Prevalues were significantly different between symptomatic statin users and control subjects ($P < 0.05$). [c]Prevalues were significantly different between symptomatic and asymptomatic statin users ($P < 0.05$). [d]Prevalues were significantly different between asymptomatic statin users and control subjects ($P < 0.05$). The effect of the exercise training was determined in the total group (time), in symptomatic statin users compared with control subjects (S vs C) and in asymptomatic statin users compared with control subjects (A vs C) using linear mixed models with a random intercept.

AU = arbitrary units; HDL = high-density lipoprotein; LDL = low-density lipoprotein; MET = metabolic equivalent of task; VAS = visual analogue scale.

(**Figure 2C**), with no differences among groups. Muscle fatigue resistance increased with training, illustrated by a smaller relative decline in muscle force (fixed effect estimate: -2.51%; 95% CI: -4.42% to -0.61%; $P = 0.01$) (**Figure 2D**) and a smaller relative increase in half relaxation time (fixed effect estimate: -17.96%; 95% CI: -31.35% to -4.57%; $P = 0.01$) (**Figure 2E**) during repetitive electrical stimulation. The increase in muscle fatigue resistance was not different among groups (Supplemental Table 2). Absolute values on exercise performance are shown in **Table 2**.

SKELETAL MUSCLE MITOCHONDRIAL FUNCTION. There were no differences in muscle CS activity or ATP production capacity among the 3 groups at baseline. Training increased muscle CS activity in the total study group (fixed effect estimate: 34.8 mU/mg protein; 95% CI: 15.7-53.9 mU/mg protein; $P = 0.001$) (**Figure 3A**). The increase in CS activity was less in asymptomatic statin users than in control subjects (fixed effect estimate: -52.0 mU/mg protein; 95% CI: -96.8 to -7.1 mU/mg protein; $P = 0.02$). Correcting for baseline CS activity and sex eliminated this difference (Supplemental Table 3). Training did not change ATP production capacity in the total group ($P = 0.49$) (**Figure 3B**) or among groups (Supplemental Table 3). Absolute values on skeletal muscle mitochondrial function are shown in **Table 2**.

MUSCLE FIBER TYPE DISTRIBUTION, SIZE, AND CAPILLARIZATION. Slow-twitch type I muscle fibers were less prevalent in symptomatic statin users than in control subjects at baseline ($P = 0.06$). The percent of type I fibers was inversely related to the relative decline in muscle force ($r = -0.58$; $P < 0.05$) and with the increase in half relaxation time ($r = -0.58$; $P < 0.05$) during repetitive electrical stimulation in symptomatic statin users at baseline, demonstrating that type I fiber prevalence was associated with fatigue resistance in this group. Type I muscle fiber

TABLE 2 Clinical Outcome Measures Pre- and Post-Training

	Symptomatic (n = 16)		Asymptomatic (n = 16)		Controls (n = 20)	
	Pre	Post	Pre	Post	Pre	Post
Vo_2peak, mL/min/kg	30.5 ± 7.4	31.3 ± 7.4	32.0 ± 7.3	32.3 ± 6.8	36.5 ± 8.2	37.1 ± 6.4
Maximal workload, W	188 ± 54	216 ± 58	190 ± 47	205 ± 49	214 ± 48	238 ± 48
MVC, N/kg	7.5 ± 1.8	7.9 ± 1.9	7.4 ± 2.2	8.1 ± 2.2	8.1 ± 1.6	8.8 ± 2.1
Muscle force decline, %	30.3 ± 10.0	26.5 ± 8.8	30.5 ± 9.8	28.9 ± 7.3	26.1 ± 9.8	24.0 ± 7.6
Increase in half RT, %	125.5 ± 52.7	93.8 ± 44.3	113.6 ± 59.4	110.6 ±57.7	69.8 ± 48.8	62.4 ± 43.9
Citrate synthase activity, mU/mg protein	186 ± 59	214 ± 70	200 ± 55	209 ± 37	164 ± 39	224 ± 68
ATP production capacity, nmoL/h/mg protein	3,838 ± 1.561	4,340 ± 2,110	4,597 ± 2,322	3,714 ± 959	3,185 ± 1,109	3,841 ± 1,517
Proportion type I fibers, %	48.3 ± 16.2	64.7 ± 16.1	56.8 ± 14.8	57.2 ± 17.1	61.1 ± 11.1	63.4 ± 17.1
Type I muscle fiber size, μm^2	5,302 ± 1,355	5,528 ± 1,276	5,504 ± 1,389	5,618 ± 1,750	5,537 ± 1,289	5,793 ± 1,945
Type II muscle fiber size, μm^2	4,726 ± 1,091	4,736 ± 1,497	4,825 ± 2,162	4,902 ± 2,230	4,272 ± 1,277	4,374 ± 1,800
CFPE type I muscle fibers, capillaries × 1,000 μm^{-1}	5.8 ± 1.5	6.5 ± 1.1	6.2 ± 1.2	7.0 ± 1.3	6.2 ± 1.1	6.9 ± 1.3
CFPE type II muscle fibers, capillaries × 1,000 μm^{-1}	4.8 ± 1.8	5.4 ± 0.9	4.7 ± 1.1	5.5 ± 0.8	4.9 ± 1.2	5.5 ± 1.3

Values are mean ± SD.
ATP = adenosine triphosphate; CFPE = capillary-to-fiber perimeter exchange index; MVC = maximal voluntary contraction; RT = relaxation time; Vo_2peak = peak oxygen consumption.

prevalence tended to increase in the total study group with training ($P = 0.08$) (Figure 4A). The increase in the prevalence of type I fibers was associated with improved fatigue resistance in symptomatic statin users, evidenced by an inverse correlation between the increase in type I fibers and the decline in muscle force development during repetitive electrical stimulation ($r = -0.65$; $P = 0.03$). Type I and II fiber size was not different among groups at baseline and was unchanged with exercise training (Figures 4B and 4C). Capillary count, C/Fi, CFPE, and capillary density were not different among the groups at baseline. Only type I fiber capillary count increased with training in the total study group ($P < 0.01$), whereas C/Fi, capillary density (Table 3), and the CFPE index increased significantly in both type I and II fibers after training (Figures 4D and 4E). The increase in muscle fiber capillarization was not different between groups (Table 3, Supplemental Table 4). Absolute values on muscle fiber type, size, and capillarization are shown in Table 2.

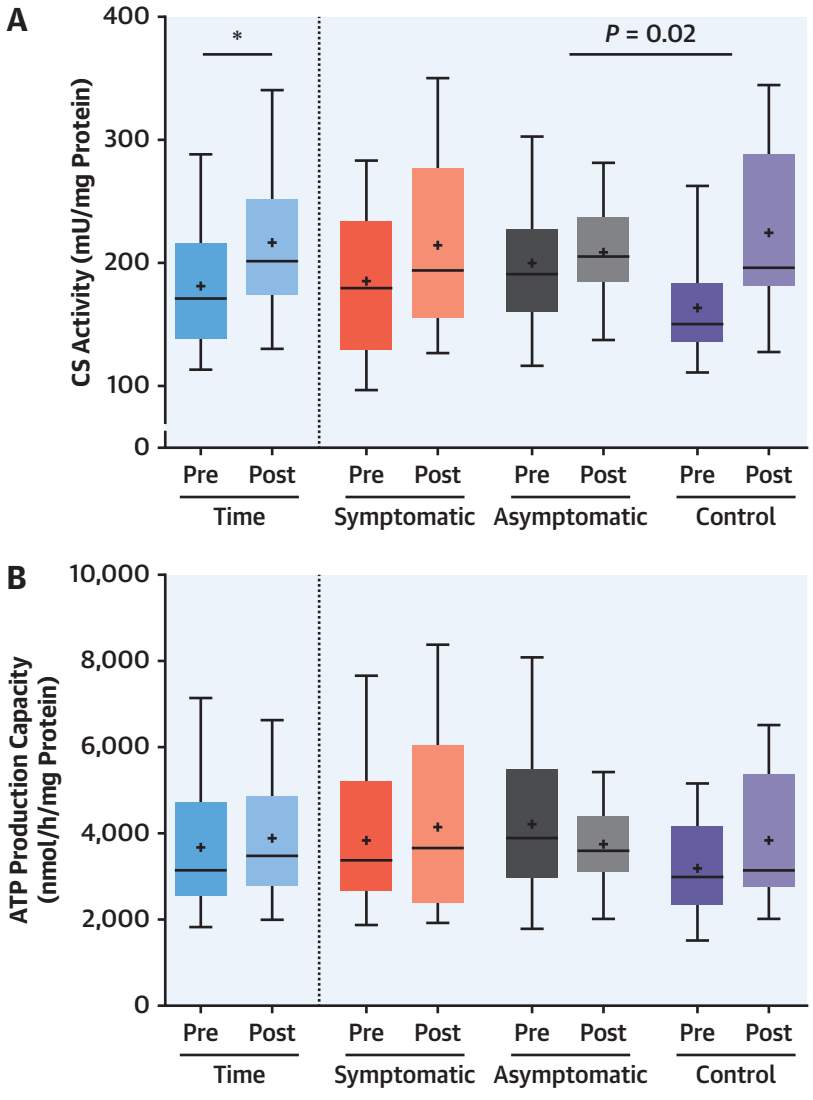
DISCUSSION

Statin-induced mitochondrial dysfunction might interfere with skeletal muscle adaptations to exercise training (8), thereby reducing increases in cardiovascular fitness and muscle performance. The present study demonstrated that 12 weeks of endurance and resistance exercise training improved muscle performance, skeletal muscle mitochondrial content, and muscle fiber capillarization in both statin- and nonstatin using adults. Moreover, we demonstrated that improvements in muscular performance with training were not different between symptomatic and asymptomatic statin users. Pain scores were not exacerbated by exercise training in symptomatic and asymptomatic statin users, demonstrating the feasibility of the exercise program for statin users. Exercise training might even contribute to an increased QoL in symptomatic statin users (Central Illustration). Statin use and physical activity are key components of both primary and secondary cardiovascular diseases risk reduction. The present results indicate that the response to exercise training is similar in symptomatic and asymptomatic statin users and nonstatin using control subjects.

EXERCISE AND MUSCLE PERFORMANCE. The present study demonstrated that both symptomatic and asymptomatic statin users could increase muscle strength and resistance to fatigue with exercise training, without increasing muscle complaints. Although resistance exercise was only performed once a week, appendicular lean mass increased in all groups. These findings were in line with previous studies that reported improved muscle strength in statin users after 10-12 weeks of combined endurance and resistance exercise training (7,10). Because muscle strength is an important factor for functional performance (25), and statin users might experience an accelerated loss of skeletal muscle mass and strength during ageing (26), these improvements in muscle strength and appendicular lean mass are of critical importance for statin users.

Maximal workload during the exercise performance test increased in all groups (12% ± 8%) following exercise training, which indicated improved exercise tolerance. Yet, Vo_2peak remained unchanged following exercise training. The lack of increase in Vo_2peak also in the control group argues that our aerobic training stimulus might have been

FIGURE 3 Effect of Exercise Training on Mitochondrial Energy Metabolism

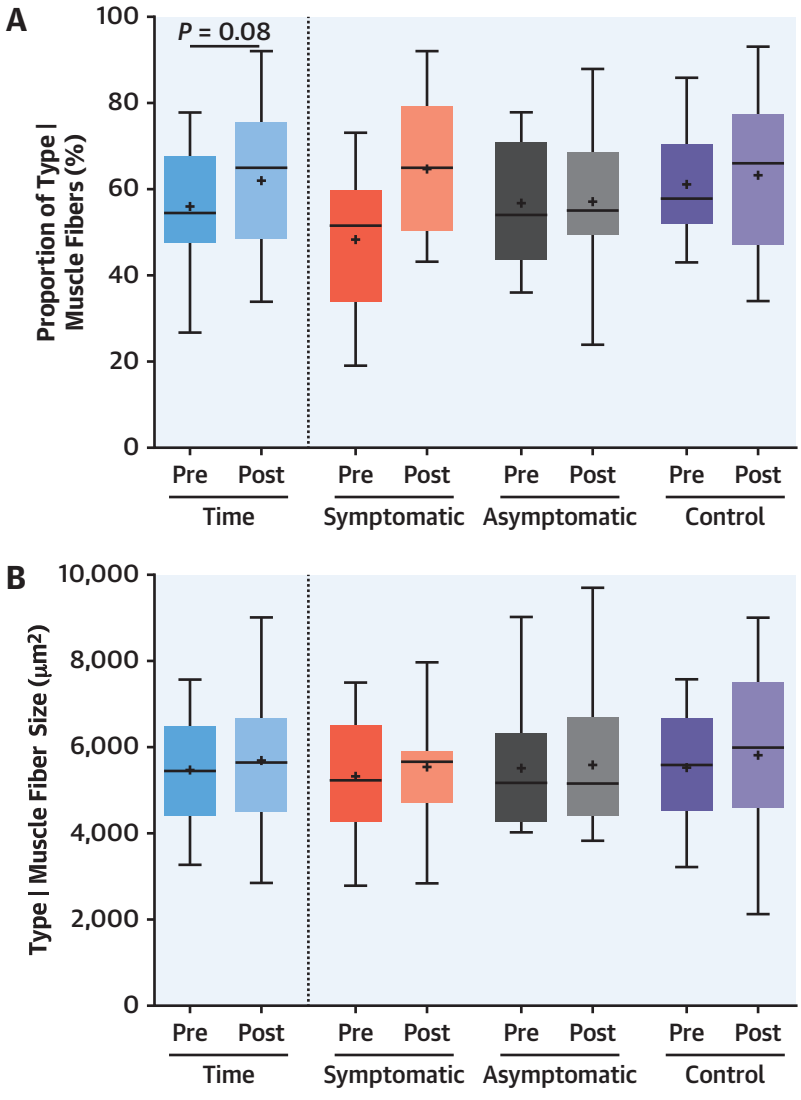


Mitochondrial fractions were prepared from fresh muscle biopsies. **(A)** Citrate synthase (CS) activity and **(B)** adenosine triphosphate (ATP) production capacity were measured before (pre) and after (post) 12 weeks of combined aerobic and strength training in all included participants (time effect) and separated by group. **Boxes** represent interquartile (25th to 75th percentile) ranges, **whiskers** represent 5th to 95th percentile, and the **horizontal line and cross** indicate the median and mean, respectively. *Significant effect of time ($P < 0.05$).

too moderate to improve Vo_2peak in our study population. Previous reports that demonstrated increases in aerobic capacity in statin users showed similar (7,10,27) or lower (8,9) increases in aerobic capacity in statin users compared with control subjects with 10-16 weeks of exercise training. Our participants had a higher initial physical fitness level and were older than participants in these previous exercise intervention studies (7-10,27). Moreover, our training program consisted of concurrent endurance and resistance training, which is known to minimize increases in maximal aerobic capacity compared with endurance training alone (28,29). As a result, we could not conclude if statin use affected increases in aerobic capacity with training.

SKELETAL MUSCLE MITOCHONDRIAL FUNCTION. Improvement in CS enzyme activity was reported to be attenuated in participants who took simvastatin compared with nonstatin users after 12 weeks of

FIGURE 4 Effect of Exercise Training on Muscle Fiber Type, Size, and Capillarization

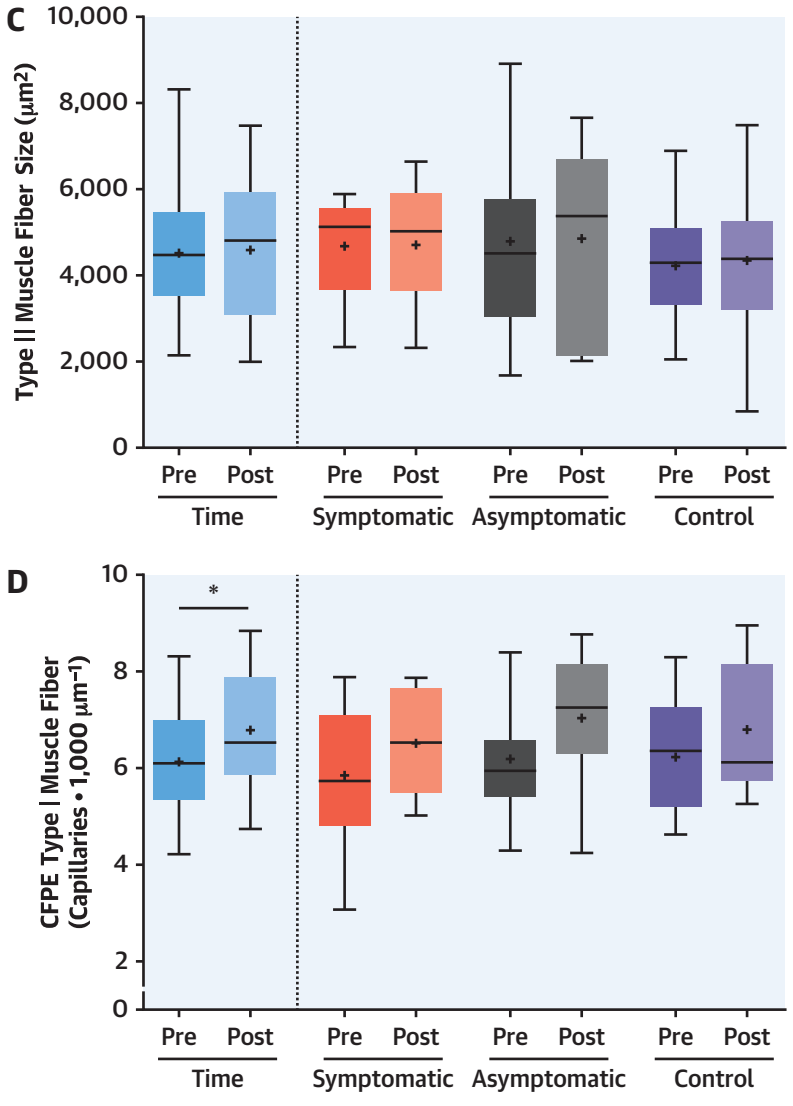


(A) Muscle fiber type distribution, **(B and C)** muscle fiber size, and **(D and E)** capillarization were measured before (pre) and after (post) 12 weeks of combined aerobic and strength training in all included participants (time effect) and separated by group. **Boxes** represent interquartile (25th to 75th percentile) ranges, **whiskers** represent 5th to 95th percentile, and the **horizontal line and cross** indicate the median and mean, respectively. *Significant effect of time ($P < 0.05$). CFPE = capillary-to-fiber perimeter exchange index.

Continued on the next page

moderate aerobic exercise training (8). However, that study included previously statin-naive participants, who might have experienced an initial decline in mitochondrial content with statin treatment, which potentially masked the exercise training effect (8). Our combined exercise program led to an increase in CS activity in the total study group, whereas ATP production capacity remained unchanged. This might be explained by the observation that endurance exercise primarily increases the number of subsarcolemmal mitochondria (30), which show lower levels of oxidative phosphorylation proteins and respiratory chain complex activities compared with intermyofibrillar mitochondria (31). We did not differentiate subsarcolemmal and intermyofibrillar mitochondria in this study. The lower increase in CS activity in asymptomatic statin users compared with control subjects might be explained by the higher

FIGURE 4 Continued



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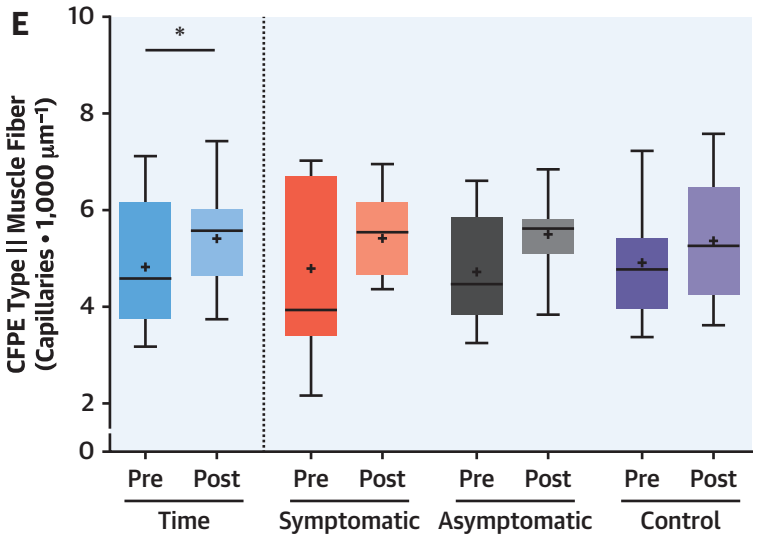
pretraining values in this group, because differences with training were no longer observed after correcting for baseline CS activity. These findings agree with previous exercise intervention studies, in which statins did not prevent improvements in mitochondrial content or markers of function (7,9), and suggest that statin use does not prevent mitochondrial proliferation with exercise training.

SKELETAL MUSCLE FIBER SIZE AND CAPILLARIZATION. Although appendicular lean tissue mass increased significantly in response to exercise training, we were not able to detect a change in type I and type II muscle fiber size over time. The gain in leg lean mass (78 ± 638 g) was likely too small to detect muscle hypertrophy on a myocellular level. The present study did show a significant improvement in muscle fiber capillarization, with an average increase of 16% ± 24% in CFPE index following exercise training. To our knowledge this is the first study to show that the muscle fiber angiogenic response is not different between symptomatic and asymptomatic statin users or nonstatin using control subjects. This training-induced angiogenic response is of importance for optimal metabolic function and muscle fiber adaptation to exercise training by allowing sufficient delivery of nutrients, oxygen, and growth factors (32).

SKELETAL MUSCLE FIBER TYPE COMPOSITION. Skeletal muscle fibers consist of bundles containing both slow-twitch (type I) oxidative and fast-twitch

FIGURE 4 Continued



(type II) muscle fibers. The current view is that type II fibers are most vulnerable to statin-induced muscle injury (33,34). Type II fibers contain more calcium in the sarcoplasmic reticulum than type I fibers (34), and statin therapy possibly leads to higher calcium release from mitochondria and sarcoplasmic reticulum stores (35). This results in sustained increases in cytosolic calcium levels, which ultimately results in atrophy,

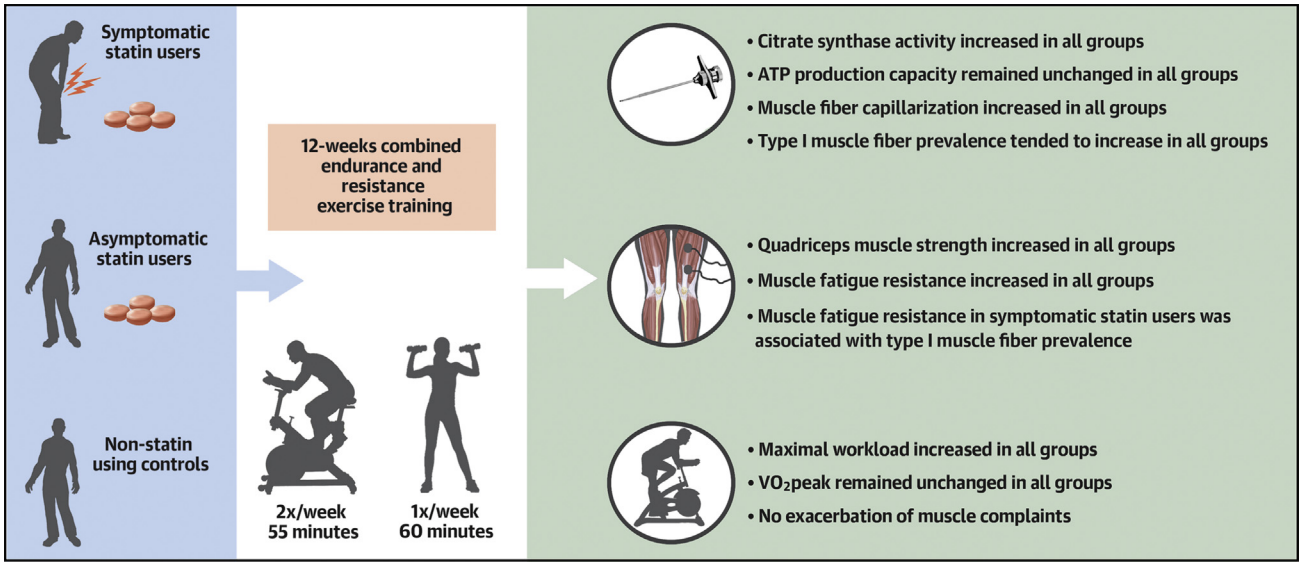
TABLE 3 Effect of Exercise Training on Muscle Fiber Capillarization

	Time		Time × Group		Model 1[a]		Model 2[a]	
	Fixed Effect Estimate (95% CI)	*P* Value	Fixed Effect Estimate (95% CI)	*P* Value	β (95% CI)	*P* Value	β (95% CI)	*P* Value
CC type I muscle fiber	0.55 (0.18 to 0.92)	0.004						
Control subjects			Reference		Reference		Reference	
Asymptomatic			0.04 (−0.84 to 0.92)	0.93	0.12 (−0.65 to 0.89)	0.76	−0.06 (−0.80 to 0.67)	0.87
Symptomatic			0.24 (−0.70 to 1.18)	0.60	0.16 (−0.68 to 0.99)	0.71	−0.17 (−0.99 to 0.66)	0.69
CC type II muscle fiber	0.21 (−0.30 to 0.73)	0.41						
Control subjects			Reference		Reference		Reference	
Asymptomatic			0.60 (−0.63 to 1.82)	0.33	0.53 (−0.29 to 1.34)	0.20	0.16 (−0.53 to 0.85)	0.66
Symptomatic			0.44 (−0.86 to 1.74)	0.49	0.39 (−0.49 to 1.26)	0.39	−0.08 (−0.83 to 0.67)	0.84
C/Fi type I muscle fiber	0.29 (0.09 to 0.49)	0.005						
Control subjects			Reference		Reference		Reference	
Asymptomatic			0.01 (−0.47 to 0.49)	0.97	0.08 (−0.36 to 0.51)	0.73	−0.00 (−0.41 to 0.40)	0.99
Symptomatic			0.03 (−0.48 to 0.54)	0.91	0.04 (−0.42 to 0.50)	0.87	−0.14 (−0.59 to 0.31)	0.54
C/Fi type II muscle fiber	0.22 (0.02 to 0.43)	0.03						
Control subjects			Reference		Reference		Reference	
Asymptomatic			0.11 (−0.38 to 0.59)	0.66	0.20 (−0.21 to 0.61)	0.34	0.09 (−0.24 to 0.43)	0.59
Symptomatic			−0.11 (−0.63 to 0.41)	0.68	0.02 (−0.42 to 0.45)	0.94	−0.14 (−0.50 to 0.22)	0.45
CD type I muscle fiber	51.89 (23.73 to 80.05)	0.001						
Control subjects			Reference		Reference		Reference	
Asymptomatic			5.26 (−63.23 to 73.75)	0.88	−0.11 (−60.92 to 60.70)	1.00	19.76 (−9.58 to 49.10)	0.19
Symptomatic			−9.09 (−81.96 to 63.78)	0.80	−15.22 (−79.85 to 49.42)	0.65	−4.36 (−30.68 to 21.97)	0.75
CD type II muscle fiber	62.35 (22.54 to 102.15)	0.003						
Control subjects			Reference		Reference		Reference	
Asymptomatic			−27.73 (−123.99 to 68.53)	0.56	−32.99 (−126.79 to 60.81)	0.49	4.24 (−57.83 to 66.31)	0.89
Symptomatic			3.75 (−98.59 to 106.09)	0.94	0.07 (−100.32 to 100.46)	1.00	−10.06 (−76.45 to 56.33)	0.77

Overall effect of training in total study group (time) and differences between groups (time x group) were analyzed using linear mixed models with control subjects set as reference group. [a]Differences between groups (time x group) corrected for baseline (pre) value (model 1) or baseline (pre) and sex (model 2) using generalized linear models analysis.

β = β-coefficient; CI = confidence interval; CC = capillary count; C/Fi = individual muscle fiber capillary-to-fiber ratio; CD = capillary density.

CENTRAL ILLUSTRATION **Exercise Training Effects on Skeletal Muscle Performance in Long-Term Statin Users**



Allard, N.A.E. et al. J Am Coll Cardiol. 2021;78(21):2023–2037.

A moderate intensity endurance and resistance exercise training program improves muscle performance, capillarization, and mitochondrial content in both asymptomatic and symptomatic statin users and nonstatin using adults, without exacerbating muscle complaints in symptomatic statin users. ATP = adenosine triphosphate; Vo_2peak = peak oxygen consumption.

myocellular damage, and apoptosis (36). We found a trend toward a lower percentage of type I muscle fiber at baseline in symptomatic statin users (48% ± 16%) compared with that of control subjects (61% ± 11%), with asymptomatic statin users showing intermediate percentages (57% ± 15%). Few human studies assessed if statins affected muscle fiber composition, although fewer type I muscle fibers in statin users were observed by 1 study (32) but not confirmed by others (37). These studies did not differentiate between symptomatic and nonsymptomatic statin users or included only statin-tolerant subjects, which might explain the conflicting results. Furthermore, skeletal muscle atrophy from disuse appears to primarily affect type I muscle fibers, whereas atrophy caused by cachexia or ageing primarily reduces type II glycolytic fibers (38). How or even if statins alter skeletal muscle fiber type distribution remains unclear. However, the lower percentage of type I fibers and thus higher percentage of type II fibers found in our symptomatic statin users might increase their susceptibility for muscle dysfunction and complaints. The present study showed a tendency for an increase in proportion of type I fibers with training, which was correlated with enhanced fatigue resistance in symptomatic statin users.

MUSCLE SYMPTOMS. Physical activity may exacerbate SAMS, making a physically active lifestyle difficult for some statin users. Our moderate intensity exercise program did not exacerbate muscle symptoms in statin users because pain and fatigue scores remained unchanged in all groups with training. This confirmed previous findings, in which moderate endurance and resistance training was well-tolerated by participants taking rosuvastatin (10). Moreover, QoL index scores improved significantly in our symptomatic statin users with exercise. These scores were maximized at baseline in our asymptomatic users and control subjects, and therefore, could not change. These results demonstrate that moderate exercise training does not worsen muscle complaints in statin users and can improve QoL scores in symptomatic statin users.

STUDY LIMITATIONS. There is no diagnostic test for SAMS, so we could not certify that our symptomatic statin users' complaints were caused by statins. A double-blind, randomized cross-over design with statins and placebo has been used to verify SAMS before therapeutic intervention, but such a design adds considerable subject burden to any study (39). Although our symptomatic statin users had higher pain and fatigue scores than our asymptomatic statin

users and control subjects, it is possible that more severely affected statin users would not have participated in our study. Further studies that include statin users with more severe symptoms or frailty are warranted to extrapolate these results to frail statin users. Our symptomatic and asymptomatic statin subjects used different statins (Supplemental Table 1) which could have affected SAMS (40) and skeletal muscle adaptations to exercise training, but differences in statin type and dose were not statistically significant. A key limitation of our results was that the exercise training regimen did not increase V_{O_2}peak, ATP production capacity, and skeletal muscle fiber size. We elected to use moderate intensity exercise training to mimic that recommended for patients at risk for cardiovascular disease. The intensity of 70%-80% V_{O_2}peak was similar to that used in other exercise training studies in statin users (8,10), but our subjects exercised only twice weekly compared with 3 (10) or 5 (8) times weekly in other statin studies. Thus, the exercise volume might have been insufficient to increase V_{O_2}peak. Our study participants had higher initial physical fitness levels and were older than participants in these previous exercise intervention studies (8,10), which might have also limited the increase in these exercise training parameters. Similarly, our resistance exercise training regimen was only once weekly, which likely accounts for the lack of improvement in muscle hypertrophy in our subjects. The key observation of our data, therefore, was that despite limitations in the exercise regimens, there were no differences in the exercise training results among control subjects and symptomatic and asymptomatic statin users. Our subjects did not increase their physical activity habits during the study because they were requested to maintain their previous activity levels, and the exercise training sessions were not recorded as habitual physical activity. Our sample size was necessarily small because of subject burden, including repetitive muscle biopsies and extensive exercise testing. Previous exercise intervention studies that involved statin treatment used similar size groups (7,8,10). For example, 1 study examined 21 control subjects and 20 statin subjects but performed muscle biopsies in only 13 and 17 subjects per group, respectively (8). A nonexercise control group was not included in the study because it would have been difficult to motivate participants to undergo repeated muscle biopsies without providing them with an exercise training program. Moreover, physical activity habits throughout the intervention did not change, which reduced the need for a nonexercise control group.

CONCLUSIONS

A moderate intensity endurance and resistance exercise training program improves muscle performance, capillarization, and mitochondrial content in both asymptomatic and symptomatic statin users and nonstatin using adults, without exacerbating muscle complaints in symptomatic statin users. Exercise training might even increase QoL in symptomatic statin users. This has important clinical implications because combining statin therapy with physical activity is known to produce substantial health benefits. These results indicate that statin use is unlikely to alter the exercise training response, and statin use should not be a factor limiting clinicians from prescribing exercise to statin users.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Statin use does not prevent patients with or without statin-associated muscle symptoms from participating in a moderate intensity training program. Both symptomatic and asymptomatic statin users can improve skeletal muscle performance, muscle fiber capillarization, and mitochondrial content by participating in a combined exercise training program without exacerbating symptoms.

TRANSLATIONAL OUTLOOK: The distribution of muscle fiber types may be an important factor contributing to muscle complaints in statin users. Further research is needed to examine whether increasing the proportion of type I muscle fibers by exercise training is an effective strategy to improve muscle performance in symptomatic statin users.

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KEY WORDS combined exercise training, exercise performance, mitochondrial dysfunction, muscle fiber type distribution, statin-associated muscle symptoms

APPENDIX For supplemental tables, please see the online version of this paper.