The effects of statins on skeletal muscle strength and exercise performance

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Purpose of review

HMG-CoA reductase inhibitors or statins are associated with a variety of muscle side-effects but little is known about the effect of statins on skeletal muscle strength and exercise performance. We performed a literature search to examine these issues.

Recent findings

We identified six studies examining the effect of statins on muscle strength and nine studies examining their effect on exercise tolerance. In general, studies examining both issues were small and used crude measures of strength and exercise performance.

Summary

There is insufficient data to determine if statins affect muscle strength and exercise performance. There is suggestive evidence that these drugs may reduce muscle strength in older patients and alter energy metabolism during aerobic exercise, both possibilities require further study.

Keywords

aerobic capacity, exercise capacity, muscle strength, statin

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Introduction

HMG-CoA reductase inhibitors are the most effective and most frequently prescribed medications to lower low-density lipoprotein (LDL) cholesterol levels. Although generally well tolerated, statins have been associated with a variety of muscle side-effects. These include life-threatening rhabdomyolysis [1], inflammatory myositis [2], asymptomatic creatinine kinase elevations [3], myalgia [1], and weakness. The cause of statin-associated muscle complaints has not been identified, although a number of possible mechanisms have been proposed. Myalgia is the most common complaint and estimated to affect 10% of patients on high-dose treatment [4]. There are limited data on the effects of statins on muscle strength and exercise performance. Consequently, we performed a systematic literature search to examine what is known about the effect of statins on skeletal muscle performance.

Methods

We searched PubMed up to December 2009 using the search terms 'statin', 'muscle', 'muscle strength', 'aerobic', 'aerobic capacity', 'exercise', 'exercise capacity', 'myopathy', and 'rhabdomyolysis'. English language abstracts on the effects of statins on muscle strength and exercise performance in humans were reviewed, and pertinent articles examined in detail.

Results

We examined the effects of statins on muscle strength and exercise performance.

Effects of statins on strength and muscle performance

We identified six articles documenting the effect of statins on skeletal muscle strength in humans (Table 1). To our knowledge, Phillips *et al.* [3] were the first to examine the association of statins and muscle strength in four patients (two women aged 76 and 66 years; two men aged 66 and 62 years) with symptoms of statin myopathy despite normal creatinine kinase levels. They compared hip flexion and abduction strength by unspecified methods on and off statin therapy and noted a decrease in hip abduction and flexion strength during statin therapy in all patients which averaged approximately 25 and 19%, respectively. The patients had normal statin blood levels prompting the authors to conclude that the patients had an underlying metabolic condition that made them susceptible to the drugs.

Agostini *et al.* [5] assessed muscle strength in 756 men, age of all over 65 years, 315 of whom were treated daily with either lovastatin or atorvastatin at a mean ± SD dose of 25 ± 13 or 34 ± 19 mg, respectively. Patients had been treated for an average of 2 years prior to testing. Proximal muscle strength was measured as the time required-to-complete three sit-to-stand maneuvers from a chair.

Table 1 Patient demographics from all studies regarding statins and muscle strength

Author	Sample size (*n*)	Males	Females	Age (years)	Height (cm)	Weight (kg)	BMI (kg/m^2)	Statin type	Statin dose
Phillips *et al.* [3]	4	2	2	67.5	NA	NA	NA	Simvastatin, pravastatin, cerivastatin, lovastatin, atorvastatin	Varied
Agostini *et al.* [5]	756	749	7	74.5	NA	NA	NA	Atorvastatin, lovastatin, pravastatin, simvastatin	Varied
Traustadóttir *et al.* [6]	10	9	1	66 ± 6.0	171	81.3	28	Simvastatin	80 mg/day
Coen *et al.* [7]	46	22	24	51.8	171.2	76.6	26.4	Rosuvastatin	10 mg/day
Scott *et al.* [8••]	774	402	372	62 ± 7.3	167.8	77.7	27.6	NA	NA
Ashfield *et al.* [9]	2987	1572	1415	66.1 ± 2.9	NA	NA	NA	NA	NA

BMI, body mass index; *n*, sample size; NA, not available.

Performance was slightly better in the statin-treated group (-0.5 s, $P = 0.04$), suggesting that low-dose statin therapy improved strength in an asymptomatic cohort.

Traustadóttir *et al.* [6] prospectively examined the effect of 12 weeks of high-dose statin therapy (simvastatin 80 mg/day) on muscle strength and exercise capacity in 10 patients (nine men and one woman) aged 55–76 years. Patients were started on simvastatin 40 mg/day and increased to 80 mg/day after 2 weeks of treatment. Muscle strength was measured as the one repetition maximum using a chest press and seated leg press pneumatic resistance device. Muscle strength did not change during statin treatment, although two patients increased their baseline physical activity during the study.

Coen *et al.* [7] used a randomized, unblinded design to examine the effect of statins with and without exercise training on the lipid profiles of patients (40–65 years old) assigned to rosuvastatin alone (eight women, eight men) or rosuvastatin combined with a resistance and endurance exercise training program (eight women, seven men). Complaints of muscle soreness, stiffness, or fatigue were infrequent in the rosuvastatin and exercise group (an average of three times per person in each of 11 patients) and did not cause any participant to miss training sessions. Muscle complaints did not correlate with increased levels of creatinine kinase, and creatinine kinase levels returned to normal in all patients within 48 h after the fifth bout of exercise. Muscle complaints in the rosuvastatin-alone group were not mentioned. Maximum oxygen consumption increased significantly in the rosuvastatin and exercise group after exercise training ($29 \pm 6\%$, $P < 0.001$) and did not change significantly in the rosuvastatin-alone group. Muscular strength increased in the rosuvastatin and exercise group when compared to the untrained rosuvastatin patients. These results document that gains in muscle strength and aerobic capacity are possible during statin therapy but the absence of a statin-untreated, exercise-trained control group makes it possible that the increase in exercise performance with training is less in statin-treated patients.

Scott *et al.* [8••] employed a prospective cohort design to examine the effect of statin therapy on muscle function, muscle mass, and fall risk in 774 individuals (402 men, 372 women), aged 50–79 years, participating in the Tasmanian Older Adults Cohort Study (TASOAC). Isometric muscle strength of the quadriceps and hip extensors was measured using a dynamometer, and leg muscle quality was computed using leg strength and lower extremity lean muscle mass determined by dual energy X-ray absorptiometry (DEXA) scan. A total of 147 patients reported statin use at baseline 11 of whom had ceased therapy by follow-up. A total of 179 patients reported statin use at follow-up, and 43 nonusers at baseline started statin therapy. Statin users at follow-up had significantly lower mean leg strength than statin nonusers at follow-up [difference in means -5.55 kg; 95% confidence interval (C.I.) -11.01 to -0.10]. Muscle strength and quality decreased significantly in those who reported statin use at baseline and follow-up when compared to all other patients (difference in means -5.02 kg, 95% C.I. -9.65 to -0.40 and -0.30 kg/kg, 95% C.I. -0.59 to -0.01, respectively). Both muscle strength and quality were significantly decreased in statin users at baseline and follow-up compared to those who stopped statin therapy (-16.17 kg; 95% C.I. -30.19 to -2.15 and -1.13 kg/kg; 95% C.I. -2.02 to -0.24, respectively), although the latter group was small ($n = 11$). Such results, determined by dynamometric measurements, suggest that statins decrease muscle strength in older individuals and that this decrease is reversible with treatment cessation.

Ashfield *et al.* [9] used the Hertfordshire Cohort Study; an observational study of 1572 men and 1415 women, aged 59–73, to examine the effect of cardiovascular drugs on hand grip strength and found no association of statin use with handgrip. A total of 204 men and 139 women involved in the study were on statin therapy. Handgrip was measured with a dynamometer and is associated with increased falls [10], fractures [11], and morbidity [12] in the elderly. The type of statins, dosage, or duration of use was not presented.

Effects of statins on aerobic exercise capacity

We identified nine articles examining the effect of statins on exercise capacity, including the Traustadóttir *et al.* and Coen *et al.* reports noted earlier [6,7]. Two studies examined the effects of statins in ostensibly healthy patients [13,14] whereas five articles examined patients with diabetes [15], heart failure [16], and claudication [17,18,19••].

Sinzinger and O'Grady [14] reported *22* professional athletes (15 men, seven women; average age 24.1 ± 5.8 years) with familial hypercholesterolemia requiring statin therapy. Only six tolerated at least one statin and only two tolerated all the statins tried (atorvastatin, fluvastatin, lovastatin, simvastatin, and pravastatin). In all cases, statin therapy was stopped due to muscle pain and symptoms disappeared after withdrawal of therapy. Creatinine kinase and liver enzymes were no higher than levels usually found in professional athletes. This study suggests that physically active individuals may have difficulty tolerating statin therapy.

Castro *et al.* [16] prospectively evaluated 38 patients, mean age 58 ± 12 years, with stable heart failure treated with atorvastatin 20 mg/day for 8 weeks. Average 6 min walking distance increased (431 ± 136 vs. 470 ± 111 m, $P = 0.03$). Myalgia was reported in one patient. The authors concluded that short-term statin therapy increased exercise capacity in patients with stable congestive heart failure but there was no control group to evaluate spontaneous variation or a placebo effect.

Mohler *et al.* [17] conducted a multicenter double-blind, placebo-controlled, parallel-group, randomized study to investigate the effects of atorvastatin (10 mg or 80 mg for 12 months) on treadmill walking distance in 354 patients (273 men, 81 women; average age 68 years) with claudication due to peripheral arterial disease. Although statins did not improve the primary endpoint (maximal walking time), pain-free walk time (PFWT) improved 63% in the atorvastatin 80 mg vs. 38% in the placebo group ($P = 0.025$). When the 80 and 10-mg groups were combined, there was a significant improvement in the PFWT compared with placebo ($P = 0.047$). There was no change in ankle–brachial index with statin treatment suggesting that statins may have improved the endothelial vasodilatory response to exercise.

Mondillo *et al.* [18] conducted a double-blind, placebo-controlled, randomized study to determine the effects of treatment with simvastatin (40 mg/day) for 6 months in 86 patients (62 men, 24 women; average age 67 years) with peripheral arterial disease. At 6 months, the mean pain-free walking distance had increased 90 m more (95% C.I.: 64–116 m; $P < 0.005$) in the simvastatin group than that in the placebo group. Furthermore, total walking distance had increased (+126 m, 95% C.I.: 101–151 m; $P < 0.001$), resting ankle–brachial index had increased (0.09, 95% C.I.: 0.06–0.12; $P < 0.01$), and postexercise ankle–brachial index (0.19, 95% CI: 0.14–0.24; $P < 0.005$) had increased more in the simvastatin group who also had a greater improvement in claudication symptoms. The authors concluded that these positive outcomes may be due to functional effects, such as plaque stabilization and a potential improvement in endothelial function, although endothelial function was not measured in this study.

Momsen *et al.* [19••] conducted a meta-analysis of 43 'robust' ($n > 56$), peer-reviewed, randomized controlled trials to evaluate the efficacy of various pharmacological interventions in improving walking capacity and health-related quality of life for people with intermittent claudication. Vasodilators and phosphodiesterase inhibitors increased maximal walking distance (MWD) by about 50 m compared to placebo but lipid-lowering agents (atorvastatin, simvastatin, policosanol, and avasimibe), increased MWD by about 160 m. The authors concluded that statin therapy was the most efficient pharmacotherapy to improve MWD in patients with peripheral vascular disease.

Phillips *et al.* [13] evaluated exercise capacity and exercise gas exchange in 11 patients (average age 65 ± 12 years; nine men, two women) after statin-associated muscle reactions (either rhabdomyolysis or myositis) and 16 patients (average age 57 ± 10 years; gender not presented) tolerating statin therapy. The control group was given atorvastatin 5–20 mg daily for 6 weeks. Myopathic patients took a variety of statins (lovastatin, cerivastatin, simvastatin, pravastatin, and atorvastatin) at varying doses. Maximum oxygen consumption (V_{O2}max), a measure of exercise capacity, tended to be lower in the group with muscle complaints compared to the control group (20.6 ± 9.6 vs. 31 ± 11, P = not significant) but this could be due to multiple causes including physical deconditioning due to their muscle discomfort. Interestingly, the respiratory exchange ratio (RER), or the production of CO_2 divided by O_2 consumption, was increased in both subject groups during statin therapy and in the myopathic patients off statins. RER is a crude measure of metabolic fuel mix with higher values suggesting a shift from fat to carbohydrate combustion. The authors concluded that statin therapy may impair fat oxidation and increase carbohydrate metabolism. The 'anaerobic threshold' or onset of lactate accumulation, measured by the break in linearity in the CO_2 production curve, was significantly depressed in the myopathic group compared to the control group but there was no significant change in the control group's anaerobic threshold on and off statin therapy.

Paolisso *et al.* [15] examined the effect of statin therapy on respiratory quotient and insulin resistance in 195

(90 women, 105 men, average age 67 ± 4.8 years), dyslipidemic, noninsulin-dependent diabetic individuals in a randomized, single-blind, prospective study. There was a 6% increase in the resting RER on statin treatment (0.78–0.83) but there was no measurement of exercise parameters.

In the study by Traustadóttir *et al.* [6] mentioned earlier, V_{O2}max and RER did not change in 10 patients (nine men, one woman, age 55–76 years) after 12 weeks of simvastatin therapy (80 mg/day). This suggests that short-term high-dose statin therapy does not impair aerobic capacity or alter substrate metabolism in asymptomatic patients. In addition, in the study of Coen *et al.* [7] V_{O2}max increased ($29 \pm 6\%$, $P < 0.001$) in the group simultaneously treated with rosuvastatin and undergoing exercise training suggesting that statins do not eliminate the aerobic training response, but this study did not include an untreated, exercise-trained control group so it is possible that statins may alter the increase in V_{O2}max produced by exercise training.

Discussion

An observational study of 7924 patients treated with high-dose statins reported that, 11% developed muscle symptoms, 4% had muscle symptoms severe enough to interfere with daily activities, and 0.4% were confined to bed with their symptoms [4]. Despite the apparent prevalence of statin muscle complaints and their possible effects on muscle performance, the present systematic review documents that there are few studies examining the effect of statins on muscle strength and exercise capacity. In addition, of those that are available, muscle strength was often measured by crude or poorly described techniques. The two largest studies used a chair to stand [5] and a handgrip [9] both of which are suitable for large population studies, and only one study has performed more sophisticated strength testing with dynamometers [8••]. Interestingly, this later study suggests that statins may deleteriously affect muscle performance in older patients. There is a similar dearth of data on the effect of statins on endurance exercise performance.

The improvement in exercise capacity, documented in patients with claudication [17,18,19••], suggest that statins may improve endothelial function. Endothelial function is often abnormal in patients with increased cardiovascular risk. Consequently, it is possible that statins may actually increase exercise capacity in patients who have endothelial dysfunction due to symptomatic disease or elevated risk factors. It is known that statins can improve endothelial function [20] but to our knowledge, the possibility that such an improvement is associated with improved exercise capacity has not been examined in asymptomatic patients. Future studies examining the effects of statins on exercise capacity should measure cardiovascular risk factors and possibly even endothelial function.

The mechanism by which statins produce myopathic symptoms is not clear but a variety of effects including decreased sacrolemmal [1], or sacroplasmic reticular cholesterol [21], reduced production of ubiquinone or coenzyme Q10 required for mitochondrial electron transport [22], decreased production of prenylated proteins [1], changes in fat metabolism [23], increased uptake of cholesterol [24], or phytosterols [25], failure to replace damaged muscle protein via the ubiquitin pathway [26], disruption of calcium metabolism in the skeletal muscle [27] and inhibition of selenoprotein synthesis [27,28] have all been suggested as possible mediators. Several of these including the effects of statins on fat metabolism, ubiquinone, and the sacroplasmic reticulum could affect exercise performance by altering substrate utilization, mitochondrial function, and calcium-induced contraction, respectively, so it is curious that the effect of statins on muscle performance has not been carefully examined.

Conclusion

There is insufficient data to evaluate the effect of statins on muscle strength and exercise performance. There is suggestive evidence that these drugs may affect strength in older patients [8••] but such results must be confirmed with additional studies. Such studies should employ careful strength measurement techniques and include older patients, since these patients would be likely to be more vulnerable to the deleterious effects of losing muscle strength. There is also suggestive evidence that statins may affect fat and carbohydrate metabolism [13,15] but these reports also require more careful study.

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References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 380–381).

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