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Simvastatin Impairs Exercise Training Adaptations

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Objectives This study sought to determine if simvastatin impairs exercise training adaptations.

Background Statins are commonly prescribed in combination with therapeutic lifestyle changes, including exercise, to reduce cardiovascular disease risk in patients with metabolic syndrome. Statin use has been linked to skeletal muscle myopathy and impaired mitochondrial function, but it is unclear whether statin use alters adaptations to exercise training.

Methods This study examined the effects of simvastatin on changes in cardiorespiratory fitness and skeletal muscle mitochondrial content in response to aerobic exercise training. Sedentary overweight or obese adults with at least 2 metabolic syndrome risk factors (defined according to National Cholesterol Education Panel Adult Treatment Panel III criteria) were randomized to 12 weeks of aerobic exercise training or to exercise in combination with simvastatin (40 mg/day). The primary outcomes were cardiorespiratory fitness and skeletal muscle (vastus lateralis) mitochondrial content (citrate synthase enzyme activity).

Results Thirty-seven participants (exercise plus statins: $n = 18$; exercise only: $n = 19$) completed the study. Cardiorespiratory fitness increased by 10% ($p < 0.05$) in response to exercise training alone, but was blunted by the addition of simvastatin resulting in only a 1.5% increase ($p < 0.005$ for group by time interaction). Similarly, skeletal muscle citrate synthase activity increased by 13% in the exercise-only group ($p < 0.05$), but decreased by 4.5% in the simvastatin-plus-exercise group ($p < 0.05$ for group-by-time interaction).

Conclusions Simvastatin attenuates increases in cardiorespiratory fitness and skeletal muscle mitochondrial content when combined with exercise training in overweight or obese patients at risk of the metabolic syndrome. (Exercise, Statins, and the Metabolic Syndrome; NCT01700530) (J Am Coll Cardiol 2013;62:709–14) © 2013 by the American College of Cardiology Foundation

The metabolic syndrome is a cluster of inter-related factors, including insulin resistance, central adiposity, hypertension, and dyslipidemia, that are associated with increased risk of cardiovascular disease, stroke, type 2 diabetes, and early death (1,2). Obesity and a sedentary lifestyle are closely linked to the metabolic syndrome. Currently, over 70% of adults in the United States are overweight or obese, whereas 98% do not meet current physical activity guidelines (3). An estimated 23% have metabolic syndrome (4).

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Abbreviations and Acronyms

BMI = body mass index

LDL-C = low-density lipoprotein cholesterol

Vo_2peak = peak oxygen consumption

Therapeutic lifestyle changes, including exercise, are the first line of treatment for patients with metabolic syndrome. The health benefits of exercise have been widely described, the most notable of which is an increase in cardiorespiratory fitness. Importantly, cardiorespiratory fitness has been identified as the strongest independent predictor of both all-cause and cardiovascular disease mortality in nearly every population in which it has been examined (5–7).

Statins, a class of hydroxymethylglutaryl-coenzyme A reductase inhibitors that lower low-density lipoprotein cholesterol (LDL-C), are commonly prescribed to patients with metabolic syndrome or those with multiple cardiovascular disease risk factors when lifestyle changes fail to achieve LDL-C targets to reduce the risk of coronary heart disease morbidity and mortality. Indeed, statins are the most widely prescribed drug in the United States and around the world. Many patients are advised to continue daily exercise when statin therapy is initiated. In recent years, there has been a growing movement to begin prescribing statins to low-risk patients and to all patients over the age of 50 years for the primary prevention of cardiovascular disease (8), making the case for statins to be used in primary prevention. This concept is gaining momentum as inexpensive generic statins have become available.

Although reports from pharmaceutical trials indicate that statins are generally well-tolerated, statins have been linked to skeletal muscle cramping, pain, myalgia, and, in rare cases, rhabdomyolysis (9). Statins are poorly tolerated among elite athletes (10) and may increase susceptibility to muscle damage during exercise (11,12). Although the mechanisms are poorly understood, some statins (simva-, atorva-, fluva-) have been shown to reduce skeletal muscle mitochondrial content and oxidative capacity in humans (13–16). In rodents, atorvastatin lowers running capacity (17,18) and impairs exercise-mediated mitochondrial adaptations in skeletal muscle (18). Despite the potential public health implications, studies examining the benefits and risks of combining statins and exercise in humans are limited.

This randomized, controlled trial was designed to compare the effects of exercise training to those of simvastatin in combination with exercise on changes in cardiorespiratory fitness and skeletal muscle citrate synthase activity, a marker of skeletal muscle mitochondrial content, in previously sedentary, overweight, or obese patients with at least 2 metabolic syndrome risk factors.

Methods

Participants. Volunteers were recruited through advertisements and word-of-mouth and underwent a thorough medical screening to determine eligibility. Volunteers were eligible if they were between 25 and 59 years of age, overweight, or obese (body mass index [BMI]: 26 to 39 kilograms of body weight per height in meters squared), sedentary (no more than 30 min of structured physical activity per week during the previous 6 months), weight stable (change in body weight of no more than 5% during the previous 3 months), and had at least 2 of the 5 metabolic syndrome risk factors as defined by the National Cholesterol Education Program's Adult Treatment Panel III. Exclusion criteria included smoking, the use of statins or other medications or supplements that affect lipid profiles or body weight (e.g., fibric acids, bile acid sequestrants, nicotinic acids, fish oil), changes in the use or dose of other medications or supplements during the previous 3 months, diagnosis of chronic diseases including cardiovascular disease, diabetes mellitus, other metabolic diseases (e.g., thyroid), cancer, human immunodeficiency virus or acquired immunodeficiency syndrome, positive graded exercise stress test, or musculoskeletal or other problems that result in an inability to walk on a treadmill. The study was approved by the Health Sciences Institutional Review Board at the University of Missouri. All volunteers provided written informed consent.

Study design. We used a block-randomized design to assign eligible participants to a 12-week supervised aerobic exercise training program or to the exercise program in combination with daily simvastatin use. Group assignment was stratified according to age, sex, and BMI.

The supervised exercise training program began with 30 min of treadmill walking or jogging at 60% to 75% of heart rate reserve (equivalent to approximately 60% to 75% of peak oxygen consumption [Vo_2peak]) on 3 days during the first week and on 5 days during the second week, where 60% of heart rate reserve = [(peak heart rate during treadmill test − resting heart rate) × 0.60] + resting heart rate. During the remaining 12 weeks, participants completed 45 min of treadmill walking or jogging at 60% to 75% of heart rate reserve 5 days per week. Exercise intensity was monitored via Polar heart rate monitors as previously described (19). Adherence was calculated as the number of exercise sessions completed divided by the number of sessions prescribed. Exercise sessions were performed in a fitness facility on the University of Missouri campus under close supervision by study staff.

Participants assigned to the combination group participated in the exercise training program and were given 40 mg simvastatin per day (20).

Assessments. Assessments were completed at baseline and at the end of the 12-week intervention. Body weight, height, and waist circumference were measured, and body composition was determined using a QDR-4500A dual X-ray absorptiometry (Hologic, Shelby Township, Michigan). Blood pressure was measured using a mercury sphygmomanometer following 10 min of seated rest.

Blood samples were collected after a 12-hr overnight fast. Fasting glucose was determined using the glucose oxidase method. Fasting insulin was measured by enzyme-linked immunosorbant assays. Total cholesterol, high-density lipoprotein cholesterol, LDL-C, and triglycerides were measured by immunocalorimetric assays by a commercial labororatory. LDL-C was calculated using the Friedewald equation (21).