MAYO CLINIC

Impact of Statins on Physical Activity and Fitness: Ally or Adversary?

See also page 1338

Statin drugs, in my view, are the best cardiovascular drugs ever created, in that they have the greatest potential to prevent atherosclerotic plaques and their complications, and they also have the greatest potential to arrest plaque formation, and therefore, to prevent additional atherosclerotic events. The statin drugs are to atherosclerosis what penicillin was to infectious diseases.

—William C. Roberts[1]

Since their introduction nearly 3 decades ago, statins (ie, 3-hydroxy-3-methylglutaryclo enzyme A reductase inhibitor drugs) have become widely prescribed in the primary and secondary prevention of cardiovascular (CV) disease (CVD) because of their favorable impact on lipid/lipoprotein metabolism and patient survival.[2] Recent randomized controlled trials and meta-analyses[2-4] have reported 20% to 44% reductions in cardiac events after the initiation of statin therapy, with comparable cardioprotective benefits for men and women. Despite the salutary effects, there are some unintended consequences of statins, including being linked to muscle pain, cramps, and fatigue, which may lead to reduced levels of physical activity (PA) and/or structured aerobic exercise. Moreover, statins have been associated with a higher incidence of diabetes mellitus (DM),[5] elevation in serum creatine kinase concentrations (a widely used biomarker of muscle tissue injury), liver dysfunction, inflammation, and myopathy,[6-8] as well as attenuated training-induced increases in cardiorespiratory fitness (CRF) levels.[9] Reductions in PA and/or CRF levels—whether drug related or not—are particularly troubling, in view of their strong inverse relation with CV and all-cause mortality,[10] and the fact that structured aerobic exercise and the positive aspects of drug therapy appear to offer similar mortality reductions in the secondary prevention of coronary heart disease (CHD).[11]

In this issue of *Mayo Clinic Proceedings*, Williams and Thompson[12] provide an insightful epidemiological report on these aforementioned issues by evaluating a large cohort of physically active individuals who were diagnosed with hypercholesterolemia and whether a potential decrease in the level or intensity of exercise was greater in those treated with statins than in those who were not.

To clarify the impact of statin therapy on levels of habitual PA, the investigators used the well-established National Runners' and Walkers' Health Study database, the largest epidemiological cohort specifically created to assess the health outcomes associated with long-term participation in moderate-to-vigorous exercise regimens (ie, walking or running) in men and women with and without CVD, including CHD. The study population included 66,377 runners and 12,031 walkers not using cholesterol medications at baseline, who were initially surveyed and resurveyed over a mean follow-up of 7.2±1.7 years.[12] The standardized survey questionnaires included extensive queries on (1) exercise practices; (2) whether study participants used specific medications to treat high cholesterol levels, hypertension, or DM; and (3) whether they developed "incident hypercholesterolemia" during follow-up, defined as initiating drug therapy for the condition or self-reported physician diagnosis of high cholesterol levels. Additional questions included demographic information (eg, age, sex, height, and weight), smoking status, dietary practices, alcohol consumption, and comorbid conditions, including a history of CHD.

The investigators found that statins per se were not associated with a reduced exercise level or intensity (which Williams and Thompson[12] suggest is good news for patients and the physicians who counsel them). Specifically, among individuals who were diagnosed with hypercholesterolemia, and with the passage of time, exercise levels decreased comparably in patients in whom statins were and were not used. These intriguing results raise the potential for reverse causality; that is, a decrease in exercise levels potentially resulted in adverse physiological and

Mayo Clin Proc. ■ October 2015;90(10):1314-1319 ■ http://dx.doi.org/10.1016/j.mayocp.2015.08.014
www.mayoclinicproceedings.org ■

TABLE. Interactive Effects of Physical Activity, Cardiorespiratory Fitness, and Statin Treatment in Young, Middle-Aged, and Older Adults

Reference, year	Population	Age (y)	Study design	Major findings
Sinzinger and O'Grady,[13] 2004	22 highly trained athletes with FH	13-35	Descriptive/observational	~20% of professional athletes with FH tolerate statin treatment without adverse effects.
Traustadóttir et al,[14] 2008	9 men, 1 woman with LDL-C levels >3.3 mmol/L (130 mg/dL)	55-76	Descriptive/observational	After 12 wk of simvastatin treatment (80 mg/d), no significant changes were observed in $\dot{V}o_2$max, endurance, or measures of muscle function.
Parker et al,[15] 2013	420 healthy, statin-naive men and women	41-47	RCT; atorvastatin (80 mg/d) vs placebo	After 6 mo, there was no adverse effect of atorvastatin on muscle strength or exercise capacity; however, increased myalgia and CK levels were noted.
Mikus et al,[9] 2013	37 inactive, overweight/obese adults with ≥2 MS risk factors	25-59	RCT; exercise vs exercise plus statins	$\dot{V}o_2$max increased 10% in the exercise-only group, but only 1.5% in the exercise-plus-simvastatin group. Similarly, SMCSA increased, respectively, by 13% and decreased by 4.5% in these groups.
Kokkinos et al,[16] 2013	10,043 veterans with dyslipidemia	59±11	Descriptive/observational	Statin treatment and increased CRF are independently associated with lower mortality in veterans with dyslipidemia (see Figure 2).
Lee et al,[17] 2014	5994 participants in the Osteoporotic Fractures in Men Study	≥65	Descriptive/observational	Over a 6.9-y follow-up, men receiving statins engaged in modestly less moderate and vigorous physical activity (~10%) and more sedentary behavior.
Rengo et al,[18] 2014	1201 patients undergoing exercise-based cardiac rehabilitation	65±11	Descriptive/observational	Improvements in $\dot{V}o_2$peak were 3.2 and 3.1 mL/kg per minute for statin users and nonusers, respectively. Long-term statin use does not attenuate aerobic training effects.
Terpak et al,[19] 2015	749 adult masters swimmers and 558 controls	≥35	Descriptive/observational (survey, self-reported)	Statin use was not associated with decreased self-reported swimming performance, considering the frequency, duration, or intensity of workouts.
Qureshi et al,[20] 2015	17,264 participants in the FIT Project	59±8	Descriptive/observational	Statin use was not significantly associated with lower peak METs in this large multiracial cohort of men and women.
Panza et al,[21] 2015	418 statin-naive adults	44±16	RCT; atorvastatin vs placebo	Sedentary time increased and physical activity decreased in the total study population during 6 mo of drug treatment, independent of group assignment.
Williams and Thompson,[12] 2015	66,377 runners and 12,031 walkers in the NRWHS	~21-82	Descriptive/observational (survey, self-reported)	Decreased exercise activity occurred similarly in runners and walkers who developed hypercholesterolemia, irrespective of statin treatment.

CK = creatine kinase; CRF = cardiorespiratory fitness; FH = familial hypercholesterolemia; FIT = Henry Ford Exercise Testing Project; LDL-C = low-density lipoprotein cholesterol; MET = metabolic equivalent (1 MET = 3.5 mL/kg per minute); MS = metabolic syndrome; NRWHS = National Runners' and Walkers' Health Study; RCT = randomized controlled trial; SMCSA = skeletal muscle citrate synthase activity; $\dot{V}o_2$max = maximal oxygen consumption; $\dot{V}o_2$peak = peak oxygen consumption.

clinical responses, including hypercholesterolemia, which prompted the initiation of statin therapy, rather than statin therapy reducing the level of habitual PA.

Limitations of the observational study included analyses that were based on self-reported survey data and the fact that most participants were taking low-dose statins, which may have been less likely to adversely impact their walking and running regimens. Other potential confounding variables include the adherence to, or the duration of statin use, and intercurrent illness or injury.