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Effects of Statin Therapy on Exercise Levels in Participants in the National Runners' and Walkers' Health Study

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Abstract

Objectives: To determine whether decreases in exercise 1) were greater in individuals who were diagnosed as having hypercholesterolemia than in those without the diagnosis during follow-up and 2) were greater in incident hypercholesterolemic participants starting statins than in those not treated with cholesterol-lowering medications.

Participants and Methods: Regression analyses of changes since baseline (Δ) in exercise vs diagnosis of hypercholesterolemia and its treatment in 66,377 runners and 12,031 walkers not using cholesterol medications at baseline who were resurveyed during the National Runners' and Walkers' Health Study follow-up (January 1, 1991, through December 31, 2006).

Results: A total of 3510 runners began statin treatment, 1779 began other or unspecified cholesterol-lowering drug treatment, and 2583 had untreated hypercholesterolemia; 58,505 runners remained nonhypercholesterolemic controls during the mean 7.2-year follow-up. Usual distance run decreased significantly more in hypercholesterolemic runners who began taking statins (mean ± SE: −0.47±0.06 km/d) than in runners who remained nonhypercholesterolemic during follow-up (−0.08±0.02 km/d) ($P<.001$). However, running distance also decreased significantly more in hypercholesterolemic runners who began unspecified/other (−0.52±0.08 km/d) or no (−0.47±0.07 km/d) cholesterol drugs than in nonhypercholesterolemic runners during follow-up. Moreover, Δrunning distance did not differ significantly between hypercholesterolemic runners who were statin treated vs those treated with other/unspecified ($P=.64$) or no ($P=.94$) cholesterol drugs. Initiating statin therapy was not associated with Δrunning pace in hypercholesterolemic runners or Δwalking distances in hypercholesterolemic walkers.

Conclusion: These results are consistent with the premise that a decrease in running distance is associated with hypercholesterolemia and do not suggest that statins reduce exercise level or intensity.

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Statins are generally well tolerated, but approximately 10% of statin users report symptoms including myalgia, cramps, and weakness.[1,2] Several studies suggest that statins diminish physical activity.[1-3] Impairment of mitochondrial respiration,[4] deregulated muscle calcium homeostasis,[4] and reduced mitochondrial volume[5,6] have been suggested as contributing to statins' skeletal muscle effects. The Osteoporotic Fractures in Men Study reported a greater decline in physical activity during the 6.9-year follow-up in 845 new statin users than in 1467 men who never used statins.[7] Also, at baseline, men who were already statin users performed less physical activity than the other men.[7]

Randomized controlled clinical trials have not demonstrated an increase in myalgia or elevations in creatine kinase (CK) levels from statin use.[8,9] Moreover, muscle strength and performance are not generally decreased with statin-induced myalgia,[10] and atorvastatin 80 mg/d did not decrease muscle strength or exercise performance during 6 months in a randomized study of 420 patients.[11] Mean CK levels increased with maximum-dose atorvastatin treatment,[11] but even marked increases in CK levels did not impair skeletal muscle function or reduce physical activity levels.[12]

The discrepancy between the clinical trial evidence and epidemiologic associations of the Osteoporotic Fractures in Men Study could be

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due to limitations in both approaches. Few clinical trials measured muscle strength, queried patients about muscle pain, or reported mean CK levels.[8] On the other hand, the cross-sectional differences and longitudinal relationships observed in epidemiologic studies do not distinguish cause and effect and may not completely account for confounding variables. Statins could reduce exercise activity, but lower exercise levels could increase the risk of hypercholesterolemia prompting statin treatment. Less running mileage, for example, has been shown to increase the risk of hypercholesterolemia in several prospective epidemiologic analyses.[13-15]

We, therefore, compared changes in exercise and medication use in the National Runners' and Walkers' Health Study, the largest epidemiologic cohort specifically created to study the health benefits of exercise.[13-16] In participants who developed hypercholesterolemia, we examined whether decreases in exercise were greater in those who started statin treatment than in those not treated with cholesterol medications. If statins reduce exercise level, initiating statin treatment should produce significantly greater exercise reductions than no treatment with a cholesterol-lowering drug in hypercholesterolemic individuals. Conversely, if less exercise increases the diagnosis of hypercholesterolemia but is not associated with choice of drug, then reductions in exercise should be similar in statin-treated, nonstatin-treated (ie, treated with a different cholesterol-lowering drug), and untreated hypercholesterolemic individuals.

PARTICIPANTS AND METHODS

We analyzed the combined sample from the National Runners' Health Study I (recruited between 1991 and 1994),[13,16,17] the National Runners' Health Study II (recruited between 1998 and 2001),[14] and the National Walkers' Health Study (also recruited between 1998 and 2001).[14] The earliest baseline survey was January 1, 1991, and the latest follow-up survey was December 31, 2006. The study protocol was reviewed by the University of California Berkeley committee for the protection of human subjects, and all the participants provided a signed statement of informed consent.

Participants completed baseline and follow-up questionnaires on usual distance walked or run, usual walking and running pace, and distance of their longest usual walk or run. Distance run or walked at baseline and follow-up were obtained from the question, "Average miles run per week for:" and then listed the current and preceding 5 years with answer fields for the responses. Pace was determined by the question, "During your usual run, how many minutes does it take for you to run 1 mile?" Walking distance and pace were ascertained using the same questions for walking instead of running. Mileage for the current year was used for the analyses. Walking energy expenditure (metabolic equivalents [METs] or MET hours per day, where 1 MET·h is approximately the energy spent running 1 km[18]) was calculated by converting the usual distance walked per week into duration (ie, distance/miles per hour) and then calculating the product of the average hours walked per day and the MET value corresponding to their reported pace.[19] Running energy expenditure was calculated as 1.02 MET·h/km.[18] A correlation of r=0.89 has been observed between repeated questionnaires for self-reported running distance.

Runners were also requested to provide the number of marathons, best marathon time, and best 10-km race performance during the previous 5 years. Running and walking pace and distance of the longest usual walk or run were requested from all walkers but only from runners recruited from 1998 through 2001. Ten-kilometer race performance was used to assess aerobic capacity in the runners. Ten-kilometer race performance completion times can be used to estimate treadmill-determined maximum oxygen consumption (VO_{2max}) in well-motivated individuals.[20-22] In this paper, exercise dose refers to distance run or walked, exercise energy expenditure, longest usual run or walk, number of marathons per year, or participation in 10-km races. Exercise intensity refers to usual running or walking pace, marathon pace, or 10-km pace.

Participants reported at baseline and follow-up whether they used medications for high cholesterol level, hypertension, and diabetes. They also provided the drug name and dose. Six statins were most commonly listed