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Letters

RESEARCH LETTER

The Effect of Exercise Training on Muscle Coenzyme Q10 in Symptomatic and Asymptomatic Statin Users

Statin-associated muscle symptoms (SAMS) are an important cause of statin nonadherence, which may hamper cardiovascular disease prevention. Statins inhibit the mevalonate pathway and thereby decrease the production of coenzyme Q10 (CoQ10), an important factor for mitochondrial respiration and skeletal muscle function. These reduced CoQ10 levels have been suggested to contribute to SAMS, but studies examining the relation between intramuscular CoQ10 and SAMS are scarce. We recently showed that muscle mitochondrial function improves with exercise training in both symptomatic and asymptomatic statin users,[1] but it is unknown whether this is accompanied with increased CoQ10 levels. Hence, we sought to do the following: 1) compare muscle CoQ10 levels among symptomatic and asymptomatic statin users and nonstatin using control participants; and 2) determine the effect of exercise training on muscle CoQ10 levels.

Percutaneous needle biopsies of the *vastus lateralis* muscle were obtained before and after a 12-week endurance and resistance exercise training program in 16 symptomatic statin users (75% men; age 64 ± 4 years), 16 asymptomatic statin users (69% men; age 64 ± 4 years) and 20 nonstatin using control subjects (50% men; age 63 ± 5 years). Patient characteristics and study design have previously been published.[1] All statin users had used statins continuously for ≥3 months and continued statin therapy during the study. Statin type and dose were not significantly different between symptomatic and asymptomatic statin users.[1] Subjects provided written informed consent as approved by the Local Committee on Research Involving Human Subjects of the Arnhem and Nijmegen region, the Netherlands. This trial is registered in the Netherlands Trial Registry (NL5972/NTR6346). Total CoQ10 content was extracted and quantified using an HPLC-ECD system and expressed as μg CoQ10/g wet muscle tissue.[2] Differences at baseline were assessed by Mann-Whitney *U* test (2 groups) or Kruskal-Wallis test (>2 groups). Linear mixed-effects models were used to evaluate the impact of exercise training on pre-exercise and postexercise training muscle CoQ10 levels, and results are presented as the least-squares mean (LSM) with 95% CI.

Median muscle CoQ10 levels were nonsignificantly lower among symptomatic statin users (49.1 μg/g [Q1-Q3: 35.1-57.6 μg/g]) and asymptomatic statin users (51.4 μg/g [Q1-Q3: 43.3-58.4 μg/g]) than nonstatin control subjects (56.8 μg/g [Q1-Q3: 52.0-63.0 μg/g]) at baseline ($P = 0.066$). Exercise training increased CoQ10 levels in the total study group (LSM: 3.4 μg/g; 95% CI: 0.4-6.3 μg/g; $P = 0.028$), which was not statistically different between symptomatic (LSM: 3.4 μg/g; 95% CI: −3.7 to 10.5 μg/g; $P = 0.34$) or asymptomatic statin users (LSM: 6.0 μg/g; 95% CI: −1.3 to 13.4 μg/g; $P = 0.11$) and control subjects (**Figure 1A**). Correcting for baseline CoQ10 levels and sex did not change these findings.

Statin use overall was associated with lower median muscle CoQ10 levels (50.8 μg/g [Q1-Q3: 39.8-57.7 μg/g]) compared with control subjects (56.8 μg/g [Q1-Q3: 52.0-63.0 μg/g]; $P = 0.023$) at baseline. The increase in CoQ10 levels with exercise was not statistically different in statin users (LSM: 4.7 μg/g; 95% CI: −1.4 to 10.8 μg/g) compared with control subjects ($P = 0.13$) (**Figure 1B**), which did not change after correction for baseline CoQ10 levels and sex.

The present study shows that statin use was associated with lower muscle CoQ10 levels compared with control subjects, but muscle CoQ10 levels were not statistically different between symptomatic and asymptomatic statin users. Reduced CoQ10 levels with statin use have been found predominantly in blood plasma levels, but this may merely reflect reduced levels of lower-density lipoproteins from statin therapy, because plasma CoQ10 is transported in lower-density lipoproteins. Therefore, measuring intramuscular CoQ10 levels is preferred to assess the association between SAMS and CoQ10. The current results propose that CoQ10 depletion is inherent to statin use and not related to the presence of SAMS. Previous

studies examining intramuscular CoQ10 levels did not compare symptomatic and asymptomatic statin users and were merely studied in statin-naïve subjects, which might explain the equivocal results.[3]

As CoQ10 is an essential cofactor in mitochondrial respiration, reductions in muscle CoQ10 may reflect changes in skeletal muscle oxidative capacity caused by changes in mitochondrial volume and/or fiber type composition. We have reported a lower percentage of oxidative type I muscle fibers in symptomatic statin users compared with control subjects,[1] which correlates with baseline CoQ10 levels ($r = 0.37$; $P = 0.020$). This implies that lower baseline CoQ10 levels may reflect a reduction in the mitochondria-rich type I muscle fibers found in symptomatic statin users. Exercise training increased intramuscular CoQ10 levels in all groups, which aligns with the previously observed increase in mitochondrial content and muscle performance.

In conclusion, muscle CoQ10 levels have no diagnostic value for SAMS, but rather may reflect the decrease in skeletal muscle oxidative capacity associated with statins. Moderate-intensity exercise training is an effective way to increase muscle oxidative capacity in statin users, which is accompanied with an increase in muscle CoQ10.

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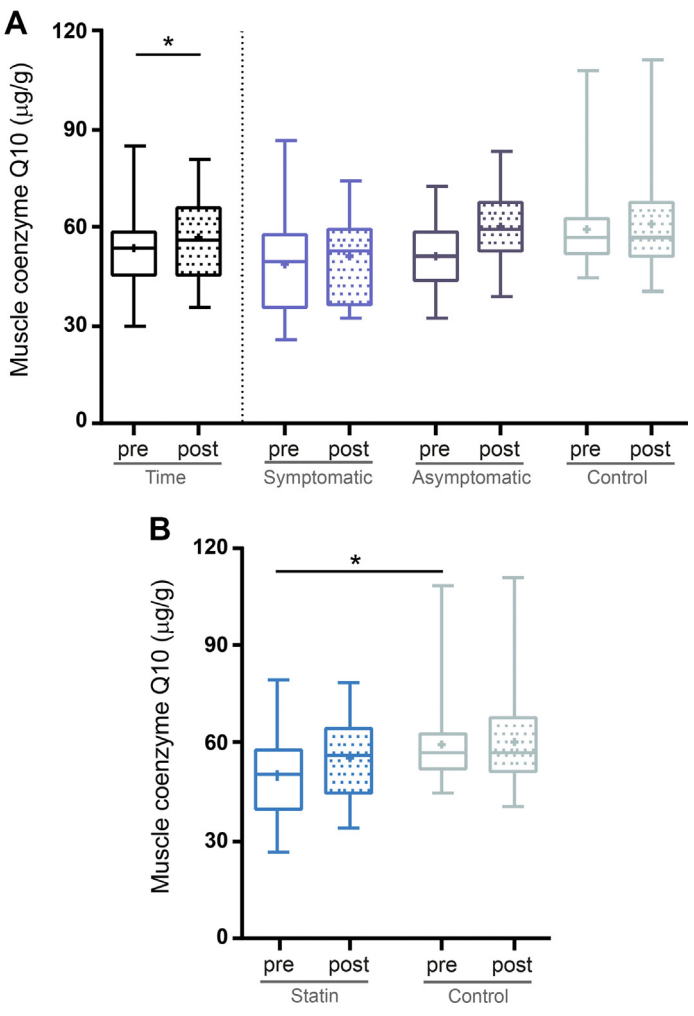
The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

FIGURE 1 Effect of Exercise Training on Muscle Coenzyme Q10



Coenzyme Q10 levels before (pre) and after (post) an exercise training program in (A) all participants and separated into symptomatic or asymptomatic statin users and (B) statin users and nonstatin using control subjects. Data are missing from 1 (post) symptomatic, 2 (pre and post) asymptomatic statin users, and 1 (pre) and 4 (post) control subjects because of insufficient muscle tissue. Boxes represent interquartile ranges, whiskers represent 5th to 95th percentiles, and horizontal line and cross indicate median and mean, respectively. *$P < 0.05$.

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