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Impact of Coenzyme Q-10 on Parameters of Cardiorespiratory Fitness and Muscle Performance in Older Athletes Taking Statins

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Abstract: Many older athletes take statins, which are known to have potential for muscle toxicity. The adverse effects of statins on muscles and the influence thereof on athletic performance remain uncertain. Coenzyme Q-10 (CoQ_{10}) may improve performance and reduce muscle toxicity in older athletes taking statins. This trial was designed to evaluate the benefits of CoQ_{10} administration for mitochondrial function in this population. Twenty athletes aged $\geq$ 50 years who were taking stable doses of statins were randomized to receive either CoQ_{10} (200 mg daily) or placebo for 6 weeks in a double-blind, placebo-controlled, crossover study to evaluate the impact of CoQ_{10} on the anaerobic threshold (AT). Several secondary endpoints, including muscle function, cardiopulmonary exercise function, and subjective feelings of fitness, were also assessed. The mean (SD) change in AT from baseline was –0.59 (1.2) mL/kg/min during placebo treatment and 2.34 (0.8) mL/kg/min during CoQ_{10} treatment ($P = 0.116$). The mean change in time to AT from baseline was significantly greater during CoQ_{10} treatment than during placebo treatment (40.26 s vs 0.58 s, $P = 0.038$). Furthermore, muscle strength as measured by leg extension repetitions (reps) increased significantly during CoQ_{10} treatment, with a mean (SD) increase from baseline of 1.73 (2.9) reps during placebo treatment versus 3.78 (5.0) reps during CoQ_{10} treatment ($P = 0.031$). Many other parameters also tended to improve in response to CoQ_{10} treatment. Treatment with CoQ_{10} improved AT in comparison with baseline values in 11 of 19 (58%) subjects and in comparison with placebo treatment values in 10 of 19 (53%) subjects. Treatment with CoQ_{10} (200 mg daily) did not significantly improve AT in older athletes taking statins. However, it did improve muscle performance as measured by time to AT and leg strength (quadriceps muscle reps). Many other measures of mitochondrial function also tended to improve during CoQ_{10} treatment.

Keywords: coenzyme Q10; statins; athletes; mitochondria; performance

Introduction

Coenzyme Q-10 (CoQ_{10}) is an important component of mitochondrial biochemistry and a required cofactor for the production of adenosine triphosphate from adenosine diphosphate.[1] Hydroxymethylglutaryl coenzyme A reductase inhibitors (statins) inhibit the production of the CoQ_{10} precursor mevalonic acid, and statins have been associated with reductions in serum and muscle tissue CoQ_{10} levels.[2–5] However, serum and muscle levels of CoQ_{10} are not clearly associated. The elderly appear to be more susceptible to CoQ_{10} deficiency.[6–8] It is biologically plausible that athletes, who require highly efficient oxygen consumption by the mitochondria for peak athletic performance, are very susceptible to mitochondrial dysfunction due to CoQ_{10} deficiency.

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However, previous studies have raised doubts over the uniformity of the effectiveness of CoQ_{10} supplementation.[7,9]

The population that would theoretically stand to benefit most from CoQ_{10} supplementation would be one with all of the previously mentioned characteristics (ie, elderly athletes taking statins). This study was designed to test the hypothesis that CoQ_{10} would effectively improve measures of mitochondrial and muscle function, as well as subjective feelings of well-being in older athletes taking stable doses of statins.

Materials and Methods

A double-blind, randomized, placebo-controlled crossover trial was designed to compare the daily oral administration of CoQ_{10} (200-mg gel capsule) with placebo treatment.

The study protocol was approved by the Ochsner Institutional Review Board. A data safety monitoring committee (DSMC) was also assembled to oversee the ongoing conduct of the study. The DSMC reviewed the unblinded results after each group of 5 patients had completed the study.

The study population consisted of 20 athletes (15 men and 5 women) aged ≥ 50 years who were taking stable doses of statins. Recruitment took place from December 2009 through March 2011. An individual qualified as an older athlete if he or she had participated in a competitive athletic event within the previous year, was currently training for a competitive athletic event to take place within the 6 months following enrollment, or engaged in regular exercise activity for at least 45 minutes per session, 5 times per week. The athletes were engaged in triathlons, running, swimming, and/or cycling.

One participant was excluded from the analysis due to misclassification; therefore, 19 subjects completed the study and were included in the analysis. These were 4 women and 15 men with ages ranging from 50 to 79 years (mean, 63.6; SD, 8.2). The majority of participants (95%) were white, and the mean body mass index was 24.7 (3.6) kg/m^2 (Table 1).

The main exclusion criteria for the study were: (1) use of CoQ_{10} during the preceding 2 months; (2) a baseline creatine phosphokinase (CPK) level > 2 times the upper limit of the normal range; (3) a baseline low-density lipoprotein cholesterol level of > 160 mg/dL for participants without a cardiovascular risk equivalent, or > 130 mg/dL for those with a cardiovascular risk equivalent; and 4) inability to achieve a respiratory gas exchange ratio (RER) of > 1.0 at visit 1a.

Subjects were recruited from community fitness centers, community competitive athletic events, and the practices of primary care physicians in the Ochsner health care system in the greater New Orleans, LA area.

Table 1. Study Participants' Characteristics at Baseline

Participant Characteristic	N = 19
Age, y, mean (SD)	63.5 (8.2)
Body mass index, kg/m^2, mean (SD)	24.7 (3.6)
Race, n (%)	
White	18 (95)
Hispanic	1 (5)
Sex, n (%)	
Male	15 (78.9)
Female	4 (21.1)
Statin, n (%)	
Rosuvastatin	2 (10.5)
Atorvastatin	8 (42.1)
Pravastatin	4 (21.0)
Simvastatin	5 (26.4)

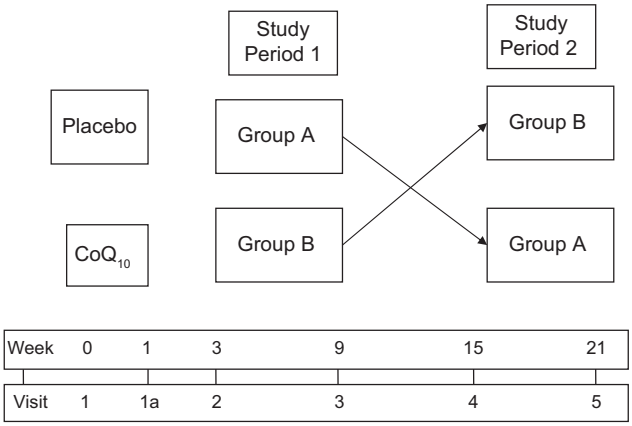
Written informed consent to participate was obtained from all subjects. After meeting the enrollment criteria, eligible participants were randomized to receive either CoQ_{10} (200 mg orally, once daily) or placebo during the 6-week duration of study period 1. After a washout period of 6 weeks, the alternative therapy was administered for the 6-week duration of study period 2. The study design is shown in Figure 1. The types and doses of statins administered remained the same throughout the study.

The subjects were instructed to take the study drug each morning with a light meal in addition to their concomitant conventional therapy. The CoQ_{10} and placebo were provided in tamper-proof bottles in quantities sufficient for each study period at visits 2 and 4. Study compliance was assessed by a pill count and by information provided by the patient at the end of each study period during visits 3 and 5 respectively.

The primary objective of the study was to determine whether oral CoQ_{10} was superior to placebo for improving anaerobic threshold (AT), as measured by cardiopulmonary exercise testing (CPX). The secondary objectives were to determine whether CoQ_{10} was superior to placebo for producing the following effects: (1) improvement in the plasma lactate/pyruvate ratio; (2) improvement in subjectively rated fatigue and fitness levels; (3) increase in oxygen consumption (volume of oxygen consumption [VO_2]); (4) increase in time to AT; (5) decrease in muscle injury, as measured by the CPK level; (6) increase in the RER; (7) increase in muscle strength, as measured by leg extension reps; and (8) decrease in the post-exercise lactate acid level.

At visit 1 (screening), athletes taking a stable dose of statin medications and meeting all inclusion criteria provided informed consent to participate in the study and underwent

Figure 1. Study design.



Abbreviation: CoQ_{10}, coenzyme Q-10.

screening procedures in order to determine their eligibility to participate in the trial.

Visit 1a (Screening)

Preliminary CPX was performed on a GE CASE V6.51 2006 cardiopulmonary exercise treadmill machine. Individuals unable to achieve an RER of $>$ 1.0 were excluded from the study.

Visit 2

Eligible subjects were randomized by the research pharmacist to which study medication (CoQ_{10} or placebo) they would receive in study period 1. Baseline CPX was performed, and the medication for study period 1 was dispensed. The baseline CPX parameters measured included VO_2, AT, time to AT, and RER. Blood samples were drawn for testing CPK, lactic acid, and pyruvate levels immediately prior to CPX testing and again within 5 minutes of finishing CPX. After a $\geq$ 30-minute rest period following CPX, muscle strength testing, which involved recording the number of leg extensions that could be performed using a standardized protocol before exhaustion on a Technogym leg extension weight machine, was performed. The protocol required fitting the subject in the machine and adjusting and recording the seat and lift positions as appropriate. The exercise was performed with a weight of 50% of the subject's body weight on the leg extension machine lift. The fitness questionnaire used was the Rand Short Form 36-item (SF-36) Health Survey 1.0. The physical functioning, energy/fatigue, and pain subsets of the SF-36 were scored.

Visit 3

Cardiopulmonary exercise testing, laboratory test studies, fitness questionnaires, and muscle strength testing were repeated at this visit. The study medication was discontinued after this visit to begin the washout period.

Visit 4

Laboratory studies were repeated, subjects were assessed for continued eligibility to participate in the trial, and medication for study period 2 (placebo or CoQ_{10}) was dispensed. Subjects crossed over to the alternative therapy for the second study period: subjects who had received placebo during study period 1 received CoQ_{10} during study period 2, while subjects who had received CoQ_{10} during study period 1 received placebo during study period 2.

Visit 5

Subjects returned for final CPX and muscle strength testing at visit 5. Laboratory test procedures similar to those performed during visit 2 were repeated. Muscle strength testing and the fitness questionnaires were re-administered. A diagram of the study flow is shown in Figure 2.

To test the hypothesis that CoQ_{10} would improve mitochondrial oxygen use, as measured by AT, in this population, 2 additional parameters were calculated from the measurements recorded during the study. First, the difference between the measurements of AT at baseline and at the end of the placebo treatment period was obtained for each subject by subtracting the AT measurement following the placebo period from the baseline measurement. This difference was designated D_p. The difference between the measurements of AT at baseline and after the CoQ_{10} treatment period was calculated similarly and designated D_q. The parameters D_p and D_q were calculated similarly for each of the endpoints of interest. The lactate/pyruvate ratio score was defined as the post-exercise lactate/pyruvate ratio minus the pre-exercise lactate/pyruvate ratio. The lactic acid score was defined as the post-exercise plasma lactic acid level minus the pre-exercise lactic acid level.

It was estimated that 25 patients would have to be screened to identify 20 patients eligible for randomization. The exclusion rate during the screening period was anticipated to be approximately 10% and the expected discontinuation rate to be 5%. A sample size of 20 was necessary to achieve sufficient power to detect a 10% change in AT.

Each patient was uniquely identified in the study by his/her patient protocol number, which was randomly assigned by a research pharmacist at Ochsner who was not part of the study team and also performed the blinding. The subjects, investigative staff, and individuals performing the assessments were blind to the identity of the treatment

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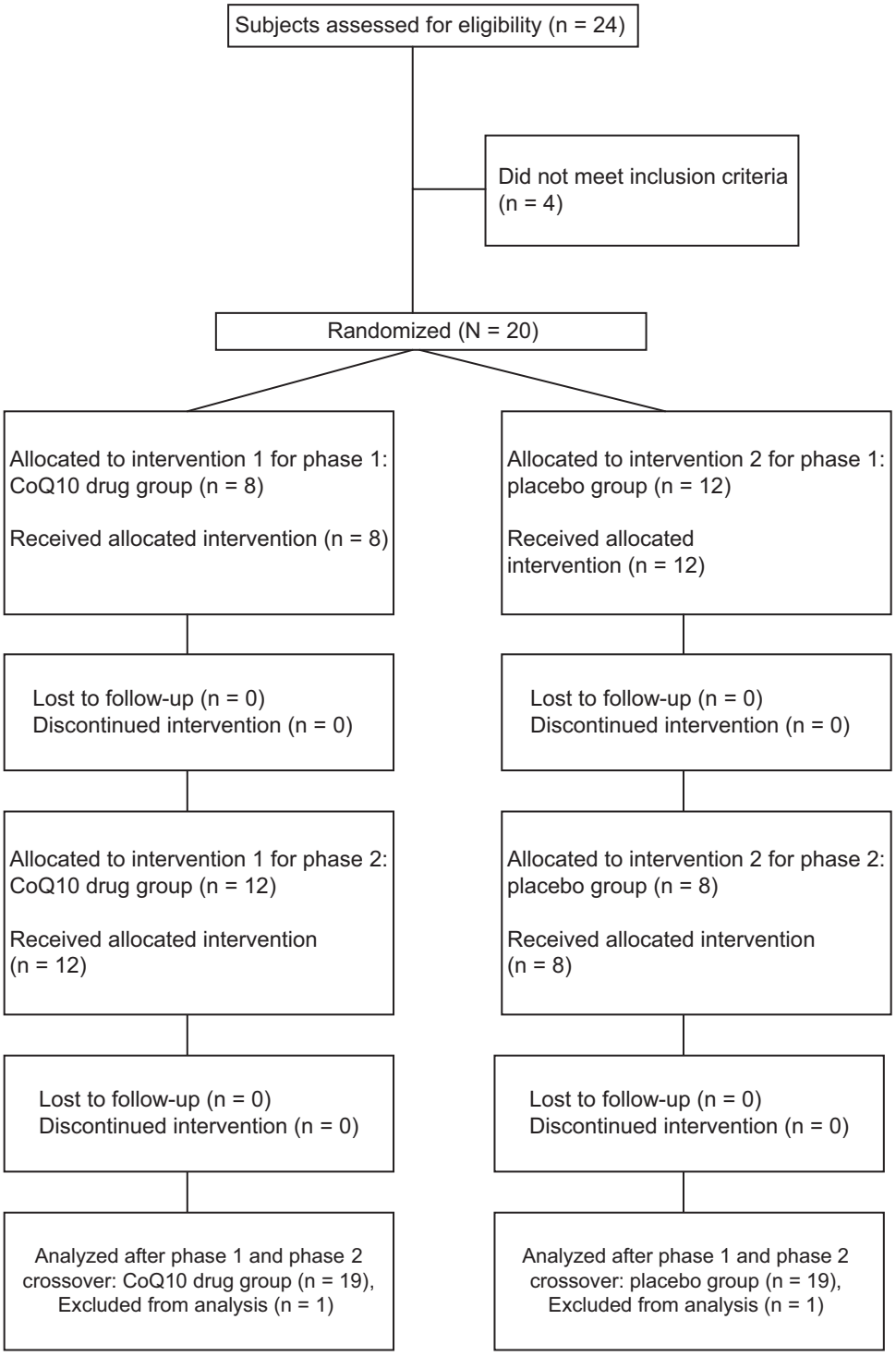
Figure 2. Study flow diagram.



Abbreviation: CoQ10, coenzyme Q-10.

from the time of the computer-generated randomization until the database was locked, and the randomization data were kept strictly confidential until unblinding. The patient randomization list was produced by the research pharmacist using a validated system that automated the random assignment of patient numbers to randomization numbers. These randomization numbers were linked to the different treatment arms, which were linked in turn to medication numbers.

The pharmacist instructed the investigator's team as to which study drug bottles to dispense to which subjects for

study periods 1 and 2. The randomization data were not accessible by anyone involved in the study except for the members of the pharmacy and the DSMC. The research investigators and subjects were blinded to the randomization allocation throughout the study.

The non-parametric t-test for matched pairs (Wilcoxon signed-rank test) was used to assess the difference between D_p and D_q for each of the 9 parameters of interest to detect a positive or negative effect of active treatment. The analysis was performed with 80% power and a 95% CI. A P value of < 0.05 was considered to indicate statistical significance. Data were managed using Microsoft Access and analyzed using STATA/IC Version 10.1 (College Station, TX). Two values derived from a single lactic acid level were missing due to a laboratory error. Because of the random nature of this event, the mean level of lactic acid at visits 2 and 5 was calculated and used to replace the missing measurement from visit 3.

Results

Daily administration of 200 mg of CoQ_{10} resulted in a statistically significant difference in mean CoQ_{10} blood levels between the placebo and treatment groups (749.1 [SD, 280] μg/mL vs 1737 [SD, 705] μg/mL, $P < 0.0001$). The primary endpoint, the difference in AT from the baseline value, did not differ significantly between the CoQ_{10} and placebo treatment periods. The mean (SD) AT increased from baseline by 2.34 (0.8) mL/kg/min during CoQ_{10} treatment and decreased from baseline by 0.59 (1.2) mL/kg/min during placebo treatment ($P = 0.116$). The mean (SD) number of muscle reps increased from baseline by 3.78 (5.0) reps after CoQ_{10} treatment versus 1.73 (2.9) reps after placebo administration ($P = 0.031$). The time to AT also showed a significantly greater improvement following CoQ_{10} administration than following placebo treatment. The mean time to AT (SD) improved from baseline by 40.26 (15.7) seconds after CoQ_{10} treatment versus 0.58 (16.5) seconds after placebo treatment ($P = 0.038$) (Table 2).

Trends indicating a beneficial effect of CoQ_{10} versus placebo on changes from baseline values were noted for a number of secondary endpoints, but none reached statistical significance (Table 2).

The study was designed to compare the differences from baseline values between placebo and active drug treatments for each individual. We performed further analysis to compare the absolute values after active and placebo treatment for each individual. In comparison with placebo treatment, administration of CoQ_{10} improved AT in 10 of 19 subjects (53%). When the secondary endpoints were evaluated, 10 of 19 individuals (53%) exhibited better VO_2 max values after active treatment than after placebo treatment. In addition, 11 of 19 subjects (59%) exhibited better time to AT after CoQ_{10} treatment than after placebo treatment. Overall, 14 of 19 individuals showed improved AT after CoQ_{10} in comparison with the baseline or placebo treatment results, whereas 15 of 19 subjects exhibited improvement in VO_2 after CoQ_{10} treatment in comparison with the placebo treatment or baseline values. Additionally, 16 of 19 individuals demonstrated improvement in time to AT after CoQ_{10} treatment over their baseline or placebo treatment results.

Table 2. Study Results Compared with Baseline Values

Endpoint (N = 19)	Treatment, mean (SD)	Placebo, mean (SD)	P
Difference in anaerobic threshold, mL/kg/min	2.34 (0.8)	–0.59 (1.2)	0.116
Time to anaerobic threshold, s	40.26 (15.7)	0.58 (16.5)	0.038[a]
Lactic acid score	0.77 (1.5)	0.16 (1.7)	0.098
Lactate pyruvate ratio score	–2.35 (18.7)	–5.73 (18.4)	0.295
Fitness questionnaire	1.84 (10.0)	3.68 (9.5)	0.171
CPK, mg/dL	15.68 (9.2)	19.63 (14.2)	0.152
VO_2 max, mL/kg/min	1.13 (3.6)	0.35 (3.8)	0.420
Muscle strength, reps	3.78 (5.0)	1.73 (2.9)	0.031[a]
RER	0.05 (0.1)	0.01 (0.1)	0.468

[a]Statistically significant.
Abbreviations: CPK, creatine phosphokinase; RER, respiratory gas exchange ratio; VO_2max, maximal oxygen consumption.

Of the subjects who responded to active drug treatment (Table 3), 11 showed a mean (SD) improvement in AT of 18.2% (20.7%) over baseline. Furthermore, 10 individuals exhibited a mean improvement in AT of 24.7% (19.7%) after CoQ10 treatment versus placebo treatment.

The time to AT improved by a mean (SD) of 20.3% (16.8%) over baseline in the 13 individuals who responded to CoQ_{10}; this change was not statistically significant ($P = 0.938$). Compared with placebo treatment, CoQ_{10} administration improved the time to AT by a mean (SD) of 19.7% (16.6%) in the 13 responders.

Some individuals showed particular responsiveness to treatment with CoQ_{10}, as indicated by a $> 25\%$ improvement over baseline in the time to AT in 5 of 19 (26%) subjects. A $> 25\%$ improvement in muscle reps after CoQ_{10} treatment was also noted in 12 of 19 (63%) subjects. The mean percent improvement from baseline in muscle reps differed significantly between the CoQ_{10} and placebo treatments ($P < 0.001$).

In comparison with placebo treatment, daily administration of 200 mg of CoQ_{10} showed no significant adverse effects over the course of this study.

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Table 3. Percentage of Improvement in Responders to Oral Administration of CoQ_{10}

Time to AT, s						
Variable	**n**	**Mean, %**	**SD, %**	**Min/Max, s**	**Patients with > 25% Improvement, n**	**Patients with > 10% Improvement, n**
% Improvement over baseline	13	20.3	16.8	0.9/56.1	5	9
% Improvement over placebo	13	19.7	16.6	0.1/54.2	4	10
P[a]		0.938				
AT, mL/kg/min						
Variable	**n**	**Mean, %**	**SD,%**	**Min/Max, mL/kg/min**	**Patients with > 25% Improvement, n**	**Patients with > 10% Improvement, n**
% Improvement over baseline	11	18.2	20.7	1.4/67.7	3	5
% Improvement over placebo	10	24.7	19.7	7.2/65.4	4	7
P[a]		0.469				
Muscle strength, reps						
Variable	**n**	**Mean, %**	**SD, %**	**Min/Max Reps**	**Patients with > 25% Improvement, n**	**Patients with > 10% Improvement, n**
% Improvement over baseline	12	41.0	8.9	21.3/60.7	12	12
% Improvement over placebo	7	26.5	6.5	10.5/42.5	7	7
P[a]		0.001				

[a]Comparison of means between baseline and placebo.
Abbreviations: AT, anaerobic threshold; CoQ_{10} coenzyme Q-10; reps, repetitions.

Discussion

This study found multiple trends suggesting that oral administration of CoQ_{10} improves mitochondrial and muscle function. However, statistically significant improvements were noted for only 2 parameters—time to AT and muscle strength. We attribute the failure of the trends in the other endpoints to reach statistical significance to the relatively small sample size of the study, which may have limited our ability to detect smaller differences. The trends that we detected might have reached statistical significance with a slightly larger sample. Furthermore, the fitness questionnaire may have been too coarse an instrument to adequately detect a subjective improvement in fitness level in this population of highly trained individuals.

The study used a formulation of CoQ_{10} in its most bioavailable form, and the capsules were independently verified to contain 200 mg of CoQ_{10} in each dose. The dose of 200 mg was selected because a review of the literature showed that lower doses resulted in mixed findings regarding the effect of this drug on statin-induced myopathy. The study results confirmed that this dose produced a statistically significant increase in CoQ_{10} levels during administration of the active drug.

The contribution of statin-induced depletion of CoQ_{10} to the myopathy and muscle symptoms associated with statins remains uncertain. Supplementation with CoQ_{10} has been advocated for individuals with other types of myopathy as well as for those with congestive heart failure.[10–12] A recent update on the advantages of CoQ_{10} documented its beneficial effect not only for patients with mitochondrial myopathies but also for those with Parkinson's disease, Huntington's disease, and Friedreich's ataxia.[13]

Aging can increase the CoQ_{10} demand[8] and thus contributes substantially to low CoQ_{10} levels.[14] A study of the contractile force of myocardial trabecular tissue in humans found that the CoQ_{10} content was significantly lower in the tissue of patients aged > 70 years. This lower tissue CoQ_{10} content was associated with a significantly worse contractile performance in vitro that was corrected by pretreatment with CoQ_{10}.[15] Similar differences have also been observed between young and senescent myocardial tissue from rats.[15] CoQ_{10} may also help to improve myocardial performance in older individuals during cardiac surgery and in times of aerobic or ischemic stress.[6,16]

A number of studies have shown that CoQ_{10} improves various parameters related to exercise and athletic performance as well as subjective sensations of fatigue and physical performance during fatigue-inducing workload trials.[17] A study of 18 male Japanese kendo athletes found that CoQ_{10} supplementation decreased exercise-induced muscle injury as measured by the CPK level.[18] Administration of CoQ_{10} to 25 Finnish top-level cross-country skiers improved VO_2, recovery time, and AT.[19]

Other studies, however, have not demonstrated clear benefits of CoQ_{10} administration. A randomized, double-blind, placebo-controlled, crossover study in which 11

young and 8 older athletes received 120 mg of CoQ_{10} daily failed to show any significant difference in VO_2.[20] The mixed results of these studies were underscored in a 2003 review by Rosenfeldt[7] and again more recently by Marcoff.[9]

Aging has a number of effects on both skeletal muscle and cardiac activity. In addition, aging has been associated with a steady decline in the absolute heart rate, which can translate into a decrease in cardiac output and a gradual decline in VO_2. At the same time, the elderly appear to be at greater risk for statin-induced myopathy, which can occur in up to 11% of such patients. The increasing incidence of medical problems such as diabetes, cerebrovascular disease, and cardiovascular disease, all of which warrant more aggressive lipid therapy, has made statin use very common among the elderly.[21,22] Animal models also confirm the deleterious effect of statins on mitochondrial respiration. A recent study in rats showed decreases in exercise capacity and VO_2 and an increase in the muscle levels of reactive oxygen species in atorvastatin-treated mice.[23]

The cohort of older athletes taking statins in this study was a group at high risk of experiencing statin-induced changes in mitochondrial function resulting in a decrease in aerobic performance, an increase in muscle breakdown, or subjective symptoms of impaired exercise performance. CoQ10 administration significantly improved both the time to AT and muscle strength. This study also revealed that daily oral administration of 200 μg of CoQ_{10} tended to improve multiple endpoints in comparison with both baseline and placebo treatment. These results suggest improvements in both mitochondrial function and muscle performance.

In clinical terms, a 10% improvement in athletic performance in highly trained athletes can provide a significant competitive advantage. In this study, CoQ_{10} treatment improved AT by 10% compared with the placebo treatment value in 37% of individuals and time to AT by 10% compared with the placebo treatment value in 53% of individuals.

This study also found that CoQ_{10} administration improved both AT and time to AT by $> 25\%$ in comparison with the placebo treatment values in 21% of athletes, suggesting that there may be certain subgroups that are more likely to benefit. The athletes who experienced the greatest benefit from CoQ_{10} administration may have been those with defects in CoQ_{10} production. Additional analysis of the study data failed to reveal any association of the response to CoQ_{10} with the type or dose of statin used. Likewise, the response was not associated with the subject's gender, age, or type of athletic activity. As new discoveries are made regarding the heterogeneity of the genes coding for the production of CoQ_{10}, individuals who respond to CoQ_{10} administration may benefit from genotype testing for such variants. Individuals deficient in CoQ_{10} production may be at higher risk for statin-induced worsening of myopathy, exercise performance, and congestive heart failure. In particular, exercise-induced variations in the expression of genes involved in the ubiquitin-proteasome pathway in certain individuals taking statins have been shown to result in altered muscle function and injury.[24] A recent study of marathon runners confirmed the susceptibility of athletes taking statins to muscle injury. Significant elevations in CPK levels were noted in runners taking statins, and the strength of this correlation increased with age.[25]

Conclusion

The high prevalence of statin use in the United States and the new recommendations for more aggressive treatment with higher doses of statins warrant close monitoring of the deleterious effects of statins on mitochondrial function. CoQ_{10} treatment is relatively free of significant adverse effects and may thus be a benign approach to reversing statin-induced mitochondrial dysfunction and muscle injury following exercise in older athletes.

Conflict of Interest Statement

Richard E. Deichmann, MD, Carl J. Lavie, MD, and Adriana C. Dornelles, ScD, disclose no conflicts of interest.

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