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Coenzyme Q10 Depletion: Etiopathogenic or Predisposing Factor in Statin Associated Myopathy?

The role of coenzyme Q10 (CoQ10) in the pathogenesis of statin-associated myopathy has been controversial. We read with great interest the study by Young et al,[1] which demonstrated that oral CoQ10 supplementation does not prevent simvastatin-induced myopathy. Although conflicting with a previous investigation,[2] this study suggests that CoQ10 is not immediately involved in statin-associated myopathy.

CoQ10 is a nonsterol isoprenoid cometabolite in the endogenous biosynthetic pathway of cholesterol with an important biologic role, maintaining the normal function of the respiratory chain within the mitochondria and subsequently the cell viability.[3] Theoretically, statins may inhibit the synthesis of CoQ10 in the mitochondria and through this effect may compromise the function of the mitochondrial respiratory chain, impairing the energy production in skeletal muscle cells, ultimately inducing myopathy.[3] Although statins were found to reduce the serum CoQ10 levels, they showed no effect on CoQ10 levels within the skeletal muscle cells, with the exception of high-dose treatment with simvastatin, which was found to reduce intramuscular CoQ10.[4] Furthermore, a direct association between reduced levels of intramuscular CoQ10 and mitochondrial myopathy has not been conclusively shown.[3]

There is accumulating evidence that statin-associated myopathy is mediated through the reduction of the bioavailability of downstream intermediate isoprenoid cometabolites (i.e., geranyl pyrophosphate and farnesyl pyrophosphate) and the resultant dysprenylation of proteins (e.g., small guanosine triphosphatases, lamins) and selenocysteine transfer ribonucleic acid. This effect results in impaired intracellular trafficking and signaling, induction of apoptosis, altered gene expression, and impaired protein synthesis.[3]

Although CoQ10 depletion does not appear to play an etiopathogenic role in statin-induced myopathy, it is most likely that it is a critical predisposing factor, especially in subjects in whom other CoQ10-depleting conditions coexist. Such conditions include old age, increased doses of statin treatment, increased statin bioavailability due to renal or hepatic dysfunction, hereditary metabolic syndromes, such as familial mitochondrial encephalomyopathy, and other co-morbidities, such as cancer, heart failure, diabetes, familial hypercholesterolemia, and hypothyroidism.[3] Clinicians should be aware of the increased myopathic potential when prescribing statins in patients susceptible to myopathy. After eliminating and treating CoQ10-depleting conditions in such patients, it may be worth prescribing CoQ10 supplementation.[3] However, on the basis of the current evidence, routine CoQ10 supplementation for all patients taking statins to prevent myotoxicity is not recommended.

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doi:10.1016/j.amjcard.2007.12.005

The Value of Exercise-Induced ST-Segment Depression in Asymptomatic Chronic Nonischemic Mitral Regurgitation

I read with interest the report by Supino et al,[1] who performed treadmill exercise tests according to the modified Bruce protocol in a cohort of 38 nonsurgical patients with chronic severe nonischemic mitral regurgitation (MR) and compared them with 46 surgical candidates with severe MR. Exercise duration, but not the prevalence of exercise-induced ST-segment depression, was significantly lower in the surgical candidates at entry. Those with excellent exercise tolerance had relatively benign courses, and exercise-induced ST depression was of no prognostic value. The investigators considered as "positive" additional horizontal or downsloping ST depression of $\geq$0.1 mV, which was found in 26% of their patients. In my opinion, because 84% of the cohort patients had MR due to mitral valve prolapse (MVP), the prevalence and lack of prognostic value of the exercise-induced ST depression were not surprising.

As early as 1976, I commented on ST-T changes at rest in MVP and postulated that they may be due to an autonomic imbalance leading to sympathetic overactivity.[2] Most normalized or markedly reduced the ST-T changes 1 hour after oral propranolol. Moreover, in later studies, we reported exercise-induced "ischemic-like," and at times ominous looking, ST depression in 31.6% and 40% of patients with MVP without coronary disease, in whom repeated exercise testing after β blockade eliminated the ST changes in most patients.[3,4] Thus, the reported prevalence of abnormal exercise tests in MVP varies from 10% to 60%, with an overall prevalence of 33%.[5] Ambulatory electrocardiographic monitoring revealed in 53% of patients with MVP, ST depressions with circadian behavior and early-morning peaks similar to those observed in ischemic patients.[6] These findings support the claimed role of high adrenergic activity, hyperresponse to adrenergic stimulation, and catecholamine regulation abnormality reported in MVP.[7]

Thus, Supino et al's[1] findings agree with previous experience in exercise testing in MVP regarding the nature,