Editorials

Coenzyme Q_{10} and Creatine in Heart Failure: Micronutrients, Macrobenefit?

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Heart failure (HF) therapy over the last 3 decades has primarily focused on neurohormonal, hemodynamic, and electrophysiologic dimensions to reduce morbidity and mortality. Considerably less emphasis has been placed on energy substrate and micronutrient deficiencies in patients with HF. Micronutrient deficiencies have been identified in the failing human heart and have been associated with defective energy metabolism in cardiac myocytes.[1] Plasma and myocardial levels of various micronutrients are known to be reduced in HF patients as compared to control populations. However, considerable debate continues as to whether low levels of micronutrients, such as coenzyme Q_{10} or creatine, are markers of or causes for systolic heart failure.[2]

Coenzyme Q_{10} (also known as ubiquinone) and creatine are both endogenously produced and acquired in a diet higher in red meat, poultry, and fish. Coenzyme Q_{10} is an important mediator of mitochondrial adenosine triphosphate production, is an antioxidant, and is thought to stabilize cell membranes. Creatine is an important mediator of energy metabolism in all muscle types. Dietary supplementation with either agent increases tissue concentrations and improves delivery to the myocardium. A host of small observational studies have shown benefit for coenzyme Q_{10} in regard to surrogate end points like ejection fraction, cardiac index, quality of life, and exercise capacity. However large, well-designed trials of coenzyme Q_{10} and creatine supplementation in HF are lacking, and hard end points (such as mortality and HF hospitalizations) have not been studied. The largest trial of coenzyme Q_{10} supplementation in HF patients to date was observational in nature.[3]

A recent meta-analysis of coenzyme Q_{10} supplementation in HF was undertaken in 2006.[4] Eleven trials were included, all of which were double-blind, prospective, and placebo-controlled. The outcome measures studied in these trials included ejection fraction, cardiac output, cardiac index, stroke volume, and stroke index. Ten trials assessed ejection fraction, which improved by 3.7% (95% confidence interval [CI] 1.6–5.8). Two trials found a significant improvement in cardiac output (0.28 L/min [95% CI 0.03–0.53]) and stroke index (5.7 mL/m2 [95% CI 1.02–10.3]). Cardiac index and stroke volume showed trends for improvement, but were nonsignificant. On subgroup analyses, improvement in ejection fraction was more pronounced in trials (n = 5) excluding New York Heart Association class IV patients, in trials (n = 4) without angiotensin-converting enzyme inhibitor use, and in trials (n = 2) assessing only patients with idiopathic cardiomyopathy. Doses of coenzyme Q_{10} in all included trials ranged from 60 to 200 mg per day with treatment duration from 1 to 6 months.

The data with creatine is much less impressive, with only a handful of studies available and most using high doses. Results of these studies have not revealed improvement in surrogate markers of HF; however, skeletal muscle strength and endurance have shown improvement with creatine supplementation. Adverse effects are not common, but renal failure has been associated with creatine use. Moreover, assessment of renal function can be complicated with creatine use as serum creatinine levels often increase with its supplementation. This can be especially problematic in the HF population, which is prone to experience frequent fluctuations in renal function and to develop the cardiorenal syndrome.

In the current issue of *Clinical Cardiology*, Fumagalli et al present a trial of coenzyme Q_{10} and creatine supplementation in 67 patients with mild to moderate HF.[5] This was a randomized, double-blind, placebo-controlled trial of a commercially available formulation of coenzyme Q_{10}, which has greater bioavailability than other preparations and was given in conjunction with creatine for a period of 8 weeks. The authors noted an improvement in total work capacity and peak oxygen consumption as measured by symptom limited cardiopulmonary bicycle exercise testing. Additionally, a benefit was seen in 1 component of a health-related quality of life survey among the treated patients.

This well-done study adds to the small but growing number of investigations on micronutrients in HF. The current trial does maintain some advantages over preceding trials. First, the studied formulation of coenzyme Q_{10} was much more water soluble, and therefore more bioavailable than previously studied formulations. This may also explain the improved tolerability of coenzyme Q_{10} supplementation in the current study, without any reported gastrointestinal (GI) adverse effects. Additionally, coenzyme Q_{10} was given in combination with creatine, potentially revealing an additive effect of these agents in HF. Several investigators have postulated that micronutrients should be given in combinations to demonstrate any sustained benefit in HF patients.[1]

The authors have no funding, financial relationships, or conflicts of interest to disclose.

Clin. Cardiol. 34, 4, 196–197 (2011)
Published online in Wiley Online Library (wileyonlinelibrary.com)
DOI:10.1002/clc.20892

Received: January 9, 2011
Accepted: January 11, 2011

The results from Fumagalli et al are intriguing, but as alluded to by the authors, could be secondary to benefits in diseased skeletal muscle as opposed to a direct effect on the myocardium. This skeletal muscle effect may be exaggerated in an older population, as was present in this trial, with presumably more dysfunctional skeletal muscle. Moreover, it is unclear if the measured benefits in surrogate outcomes as were seen in this trial will translate into clinical significance. Given its small size and relatively short follow-up period, the current study must therefore be kept in perspective. As the authors suggest, results of the Q-Symbio trial, with larger enrollment, longer follow-up, and harder end points should help to more clearly define the benefit of micronutrient supplementation in HF.

Although this trial suggests that micronutrient supplementation is safe, use of these agents is not without concern for adverse effects or drug interactions. Coenzyme Q_{10} has been commonly associated with GI upset. Levels of coenzyme Q_{10} are also reduced with concurrent statin use due to inhibition of endogenous coenzyme Q_{10} production, and additionally, the anticoagulant effects of warfarin are reduced by coenzyme Q_{10} because coenzyme Q_{10} is structurally similar to vitamin K. Coenzyme Q_{10} may also potentiate the antihypertensive effects of some blood pressure-lowering drugs. Creatine should be used cautiously with nephrotoxic agents due to its effects on renal function, and with stimulants, such and caffeine or ephedra, because stimulants may reduce the ergogenic effects of creatine on skeletal muscle.

The study by Fumagalli et al adds to the important body of literature on micronutrient supplementation in HF. Although the authors should be commended for their well-designed efforts to help clarify this issue, further study is warranted before the routine use of either coenzyme Q_{10} or creatine can be recommended for our patients.

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Published online in Wiley Online Library (wileyonlinelibrary.com)
DOI:10.1002/clc.20892