

## Moving Conventional Heart Micronutrient Supplementation have a Role?

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### Abstract

HF is a burgeoning problem worldwide, which affects almost 23 million people. Despite many recent advances in the evaluation and management of HF, the development of symptomatic HF still carries a poor prognosis. The recommended pharmacological therapy includes the use of angiotensin converting enzyme inhibitors, angiotensin receptor blocker, beta-blockers, diuretics, and aldosterone antagonists. The impact of heart failure and its treatment on specific nutrient requirements is unknown. Anorexia, malnutrition, advanced age, and frequent hospitalization are all factors that have been identified as contributing to increased risk of nutrient deficiencies in patients with congestive heart failure. Micronutrient supplementation in heart failure patients has been found to improve outcomes.

more than 550,000 people are diagnosed with this condition each year.

### General Nutrition

Nutrition plays an important role in heart failure patients. Heart failure is a catabolic state [3]. Weight loss or frank cachexia is commonly seen, the prevalence increasing with worsening symptoms [4]. Cardiac cachexia was described by Hippocrates: "The flesh is consumed and becomes water ... the abdomen fills with water; the feet and legs swell; the shoulders, clavicles, chest and thigh melt away" [5]. Nutritional status of patients with heart failure also is important-those with poor nutritional status tend to have a poor long-term prognosis.

### Vitamins

**Thiamine:** Thiamine is a water-soluble vitamin that plays an important role as a coenzyme in carbohydrate metabolism [6]. Through the addition of magnesium and ATP, thiamine is converted to thiamine pyrophosphate by the enzyme thiamine pyrophosphokinase. As the metabolically active form of thiamine, thiamine pyrophosphate serves as a cofactor for pyrophosphate dehydrogenase complex and for transketolase, both key mediators of energy-substrate metabolism. Thiamine deficiency results in decreased ATP production and increased cellular acidosis on a metabolic level [7]. Thiamine itself is stored in the body in only small amounts and cannot be produced endogenously. Adequate nutritional intake through diet (whole grains, legumes, and nuts) or supplements is therefore critical in preventing deficiency.

Thiamine deficiency causes cardiovascular and neurological damage that presents clinically as Beriberi. When the circulatory system is predominantly involved (Wet Beriberi), patients predominantly present with high-output biventricular heart failure, peripheral vasodilatation, volume overload, tachycardia, and wide pulse pressure, as well as relative depression of left ventricular function with low ejection fraction. Thiamine supplementation improves cardiac function as well as functional status in heart failure patients [8].

### Abbreviations

HF: Heart Failure; ATP: Adenosine Triphosphate; LVEF: Left Ventricular Ejection Fraction

**Keywords:** Nutrition; Thiamine; Micronutrients; Heart Failure; Selenium

### Introduction

Micronutrients are dietary components, often referred to as vitamins and minerals, which although only required by the body in small amounts, are vital to development, disease prevention, and wellbeing. Micronutrients are not produced in the body and must be derived from the diet. The required amount is generally less than 100 mg/day. Microelements may be either trace elements like iron or vitamins.

Chronic heart failure (CHF) is a common and leading cause of death in industrialized countries [1,2]. Heart failure (HF) is a serious public health concern, with an estimated 5 million people in the United States having the condition. Additionally,

Sofi et al., showed significant improvement in end systolic and diastolic left ventricular volumes as well as ejection fraction and six minute walk test after 4 weeks of thiamine supplementation in patients of heart failure [9]. Schoenenberger et al., in their randomized, double blind, crossover study to assess the effect of thiamine supplementation in patients with heart failure concluded that high-dose thiamine supplementation (300 mg/day) for 28 days was associated with improvement in LVEF. LVEF was significantly higher in the Thiamine group as compared with the Placebo group (32.8% with thiamine and 28.8% with placebo,  $p = 0.024$ ) [10]. DiNicolantonio et al., did a meta-analysis of randomized, double-blind, placebo-controlled trials that revealed thiamine supplementation results in a significant improvement in net change in LVEF (3.28%; 95% confidence interval, 0.64–5.93%) in patients with systolic heart failure.

Although current therapies have addressed hemodynamic, neurohormonal modulation, and electrophysiological aspects of heart failure, these therapies have not targeted the metabolic needs of the failing heart. Depletion of water-soluble B-vitamins that play key roles in the production of cellular energy in patients with heart failure can contribute to depletion of energy in failing heart. Anorexia, malnutrition, advanced age, frequent hospitalization, and diuretic medications are all factors that have been identified as contributing to increased risk of nutrient deficiencies in patients with congestive heart failure. Thiamine supplementation improves cardiac function and functional capacity of heart failure patients.

**Vitamin D and Calcium:** Vitamin D and calcium deficiency is common in patients with HF, particularly elderly individuals. The reasons are multiple. Elderly individuals may absorb less calcium as their gut is less responsive to calcitriol; besides lesser amounts of calcitriol are manufactured in kidney. Also loop diuretics used in heart failure are calciuretic [11]. Although Vitamin D deficiency is known to cause muscle weakness and Vitamin D repletion has been shown to result in improvements in strength, achieving robust levels of Vitamin D3 did not improve physical performance in patients with HF in a study done by Boxer et al.

**Vitamin E:** Vitamin E refers to a group of compounds that include both tocopherols and tocotrienols.  $\alpha$ -tocopherol, the most biologically active form of vitamin E, is the second-most common form of vitamin E in the diet. Vitamin E has many biological functions, the antioxidant function being the best known. As an antioxidant, vitamin E acts as a peroxy radical scavenger, disabling the production of damaging free radicals in tissues, by reacting with them to form a tocopheryl radical, which will then be reduced by a hydrogen donor (such as vitamin C) and thus return to its reduced state [12-14].

A growing body of evidence suggests that not only free radical-mediated reactions but also inflammatory responses play a major role in atherogenesis [15-17]. Although earlier trials showed that vitamin E prevented second heart attacks but subsequent larger trials largely did not show any benefit.

**Vitamin B12 and Folic Acid:** Vitamin B12 [18] and folate deficiency are relatively rare in patients with chronic HF and levels are not associated with prognosis [19,20]. However Vitamin B12 deficiency is associated with elevated homocysteine and, thereby, an elevated risk for coronary artery disease [21]. Similarly there is epidemiological evidence of an inverse link between folate consumption and risk of coronary heart disease.

**Vitamin C:** Heart-failure patients consuming a diet high in vitamin C are about half as likely to suffer a cardiac event within a year as patients with low vitamin-C levels, according to results of a study presented at the American Heart Association 2011 Scientific Sessions. Low Vitamin C levels portend worse heart failure outcomes [22]. In a study done by Song et al., out of 212 heart-failure patients, 82 patients (39%) had an inadequate vitamin-C intake.

One year after enrolment, 61 patients (29%) had an adverse cardiac event or died. Low vitamin-C intake was associated with higher levels of hs-CRP and both low vitamin-C intake and hs-CRP  $>3$  mg/L were associated with a shorter event-free survival.

## Minerals

**Magnesium:** Magnesium [23] is important as a cofactor in several enzymatic reactions contributing to stable cardiovascular hemodynamics and electrophysiologic functioning. Its deficiency is common and can be associated with risk factors and complications of heart failure. Magnesium therapy, both for deficiency replacement and in higher pharmacologic doses, has been beneficial in improving hemodynamics and in treating arrhythmias [24]. Hypomagnesemia is associated with a worse prognosis in HF and an increase in the rate of ventricular ectopic beats, both in the presence of left ventricular (LV) dysfunction and normal cardiac function.

**Selenium:** Selenium [25] deficiency has been identified as a factor in the etiology of heart failure syndromes in areas of very low selenium intakes, such as China, where an endemic selenium-responsive cardiomyopathy is called Keshan disease.

Selenium is a constituent of the antioxidant enzyme glutathione peroxidase [26]. Selenium-deficient cardiomyopathy has also been described in Western countries, for example, in patients on long-term total parenteral nutrition.

**Copper and Zinc:** Copper deficiency leads to hypertrophic cardiomyopathy in various experimental models which ultimately leads to systolic and diastolic failure. Copper deficiency is the only nutritional insult that elevates cholesterol, blood pressure, homocysteine, and uric acid, has adverse effects on electrocardiograms and arteries, impairs glucose tolerance, and promotes thrombosis and oxidative damage.

Zinc is a vital element in maintaining the normal structure and physiology of cells [27]. It appears to have protective effects in coronary artery disease and cardiomyopathy and has

been shown to improve cardiac function and prevent further damage (**Table 1**).

**Table 1:** Sum and substance of the literature.

S. No	Micronutrient	Established Role
1	Thiamine	Established role as a supplement in heart failure treatment and used widely all over the world owing to its low cost.
2	Vitamin D	No role found.
3	Vitamin E	Some studies have shown role in preventing second heart attack.
4	Vitamin B12 and Folic Acid	Deficiency is rare in HF patients, although folate supplementation may be beneficial in CAD patients.
5	Vitamin C	Lower levels associated with worse outcomes in CAD and HF.
6	Magnesium, Selenium, Zinc, Copper	Beneficial in improving heart failure outcomes and preventing CAD.

## Others

**Co-enzyme Q10:** CoQ10 is an essential cofactor for energy production and is also a powerful antioxidant. A low level of myocardial CoQ10 is related to the severity of HF [28]. Mortensen et al., showed that long-term CoQ10 treatment of patients with chronic HF is safe, improves symptoms, and reduces major adverse cardiovascular events.

**Carnitine and Creatinine Phosphate:** Carnitine supplementation is thought to improve the utilization of pyruvate in the Krebs's cycle and, thereby, improve muscle metabolism. However several trials failed to show a significant beneficial effect of Carnitine supplementation in heart disease patients.

Cardiac creatine levels are depressed in chronic heart failure. Oral supplementation of creatine to healthy volunteers has been shown to increase physical performance [29]. In a study done by Gordon et al., one week of creatine supplementation to patients with chronic heart failure did not increase ejection fraction but increased skeletal muscle energy-rich phosphagens and performance as regards both strength and endurance.

Micronutrients have long been considered of medical benefit particularly in cardiovascular disease. As early as 1989 DeFelice hypothesized about the protective role of "nutraceuticals" defined as 'a food (or part of a food) that provides medical or health benefits, including the prevention and/or treatment of a disease' [30]. The Bureau of Nutritional Sciences of the Food Directorate of Health Canada defines nutraceutical as "a product isolated or purified from foods that is generally sold in medicinal forms not usually associated with food. It is demonstrated to have a physiological benefit or provide protection against chronic disease." Several micronutrients are now manufactured as nutraceuticals and used in the management of heart failure. The largest evidence is for thiamine supplementation in heart failure. Thiamine has proved as an inexpensive add on therapy in heart failure and it has not only improved symptoms of the patient but also functional and physiological parameters in heart failure.

## Conclusion

Heart failure is a complex clinical situation and despite different therapeutic modalities heart failure treatment remains inadequate. Nutrition is important in heart failure as it is in any other chronic disease. Besides heart failure patients are at an added disadvantage due to drug and disease related micronutrient deficiency. Supplementation with micronutrients may thus prove as an inexpensive way of improving heart function and physical quality of life (**Figure 1**).



**Figure 1:** Representative figure.

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