



## REVIEW PAPER

## Nutritional Assessment in Heart Failure Patients

**H**eat failure (HF) is a growing epidemic worldwide with a particularly large presence in the United States. There are approximately 5 million persons in the United States who have HF, with more than 550,000 new patients diagnosed each year.<sup>1,2</sup> In 2010, \$39.2 billion was spent in the United States for the management of HF.<sup>1</sup> Because of the high prevalence and incidence of HF, much research has been devoted to the care of these patients. This research has led to the current guidelines for HF therapy, which include  $\beta$ -blockers, angiotensin receptor blockers, aldosterone antagonists, diuretics, cardiac resynchronization, and implantable cardiac-defibrillators.<sup>2</sup> Although these therapies have been shown to decrease morbidity and mortality and even improve quality of life, additional management strategies need to be studied to further improve the outcomes of these chronically ill individuals. One area of HF management that has limited study and application is nutritional assessment and supplementation. This review will describe the different nutrients that are potentially important for the HF patient and provide some of the supporting evidence (Table).

### Micronutrients

There are extreme metabolic demands on the adult human heart, which is responsible for pumping approximately 5 L of blood per minute at rest and up to 24 L/min during vigorous exercise. The heart will circulate more >7200 L/d and >2.6 million L/y. During the course of 80 years, the average heart will pump more than 3 billion times. The predominant energy source is fatty acids, but the heart can also easily utilize carbohydrates or both carbohydrates and fatty acids simultaneously. Both of these energy sources are con-

*Heart failure (HF) is a growing epidemic worldwide with a particularly large presence in the United States. Nutritional assessment and supplementation is an area that can be studied to potentially improve the outcomes of these chronically ill patients. There have been many studies reporting the effect of various nutrients on HF patients, often with mixed results. Amino acids such as taurine, which is involved in calcium exchange, has been reported to improve heart function. Coenzyme Q10, a key component in the electron transport chain, is vital for energy production. L-carnitine, an amino acid derivative, is responsible for transport of fatty acids into the mitochondria along with modulating glucose metabolism. Thiamine and the other B vitamins, which serve as vital cofactors, can often be deficient in HF patients. Omega-3 fatty acid supplementation has been demonstrated to benefit HF patients potentially through anti-arrhythmic and anti-inflammatory mechanisms. Vitamin D supplementation can potentially benefit HF patients by way of modulating the renin-angiotensin system, smooth muscle proliferation, inflammation, and calcium homeostasis. Although supplementation of all of the above nutrients has the potential to benefit patients with HF, more studies are needed to solidify these recommendations. Congest Heart Fail. 2011;17:199–203. ©2011 Wiley Periodicals, Inc.*

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verted into adenosine triphosphate (ATP), which is hydrolyzed by the heart to continue its pump function. Micronutrients and macronutrients are essential for maintaining this highly efficient machine's parts for the life of the human it occupies by way of renewing enzymes, membranes, and structural elements with amino acids, lipids, and carbohydrates that are either synthesized or consumed in the diet. Micronutrients of importance include coenzyme Q10 (Co Q10), L-carnitine, thiamine, amino acids such as taurine, omega-3 fatty acids, and vitamins. Many of these micronutrients have been noted to be deficient in patients with HF.<sup>3,4</sup>

Amino acids are a vital nutrient for cardiac metabolism in that they are the foundation from which proteins are constructed as well as serve as an intermediary metabolite. Of particular importance is taurine, which is not involved in protein synthesis; however, taurine is reported to make up one fourth of the amino acid pool in the heart and functions as an antioxidant and regulates calcium homeostasis.<sup>4</sup> Taurine modulates a variety of calcium exchange mechanisms to ensure optimal levels and prevent cellular overloads or deficiencies.<sup>5</sup> In a recently published randomized controlled trial of taurine supplementation in HF patients, those who received taurine supplements had

**Table.** Nutrients Important in Heart Failure Patients

Amino acids: taurine
Coenzyme Q10
L-carnitine
Thiamine (vitamin B1)
Riboflavin (vitamin B2)
Pyridoxine (vitamin B6)
Omega-3 fatty acids
Vitamin D
Magnesium, potassium, zinc, selenium

better exercise capacity than those who received placebo.<sup>6</sup> Taurine supplementation has also been shown to lower left ventricular (LV) end-diastolic pressures<sup>6</sup> as well as improve systolic function.<sup>8,9</sup> In a study of taurine transporter knock out mice, it was observed that they reverted to a fetal cardiac phenotype and had cardiomyocyte atrophy, mitochondrial and myofiber damage, and ultimately cardiac dysfunction.<sup>10</sup>

Co Q10, also known as ubiquinone, is an important component of the electron transport chain in the mitochondria and is essential for the production of the heart's major energy source, ATP. Co Q10 has also been shown to act as an antioxidant that decreases low-density lipoprotein oxidation.<sup>11</sup> Unfortunately, in patients with HF, serum and tissue levels of Co Q10 have been shown to be lower.<sup>12</sup> In addition to this fact, statins, commonly used by HF patients, are HMG-CoA reductase inhibitors that can further deplete the body of this vital nutrient.<sup>13</sup> It has been suggested that the degree of Co Q10 deficiency can correlate to worse LV function and mortality.<sup>14,15</sup> For this reason, several studies looked at the supplementation of Co Q10 in HF patients. Significant improvement in ejection fraction,<sup>16</sup> stroke volume,<sup>16,17</sup> cardiac output,<sup>17</sup> pulmonary artery pressure,<sup>17</sup> functional capacity,<sup>18,19</sup> and quality of life<sup>20</sup> has been shown in trials of Co Q10. Although there is a good deal of evidence supporting Co Q10 supplementation, some studies showed no benefit,<sup>21,22</sup> leaving us with mixed results. Recently, however, meta-analyses have shown significant benefit of Co Q10 supplementation in HF patients.<sup>23</sup> Co

Q10 also has been shown in a meta-analysis to lower systolic blood pressure by up to 17 mm Hg and diastolic blood pressure by up to 10 mm Hg, without major adverse side effects in patients with essential hypertension.<sup>24</sup>

L-carnitine is derived from amino acids and is responsible for the transport of fatty acids into the mitochondria from the cytosol.<sup>25</sup> It also has a role in modulating glycolysis, the Krebs cycle, and glucose metabolism. Propionyl-L-carnitine, a derivative of L-carnitine, has also been shown to be involved in the Krebs cycle as well as increased glucose oxidation and improved contractile function.<sup>26</sup> Although L-carnitine can be produced endogenously as well as provided by diet, low levels have been observed in HF patients.<sup>27</sup> In a study by Serati and colleagues,<sup>28</sup> treatment with L-carnitine resulted in improved diastolic parameters by echocardiography when compared with those who received placebo. In a randomized, double-blind, placebo-controlled multicenter trial conducted by Iliceto and colleagues,<sup>28</sup> supplementation of L-carnitine post-myocardial infarction was shown to attenuate LV dilatation. Rizo demonstrated a mortality benefit in New York Heart Association class II or IV patients treated with L-carnitine.<sup>30</sup> Despite the positive results in studies investigating the effect of L-carnitine on HF, there have been others that have shown no benefit.<sup>31</sup> In summary, L-carnitine supplementation has been shown to improve exercise capacity, maximum exercise time, peak heart rate, and peak oxygen consumption as well as hemodynamic and echocardiographic parameters in HF patients in a variety of studies.<sup>4</sup> However, more studies are needed to truly demonstrate the benefits of L-carnitine supplementation in HF patients.

Thiamine, otherwise known as vitamin B1, serves as a key cofactor in carbohydrate metabolism. It is not synthesized in humans, and little thiamine is stored endogenously. As such, continual ingestion is required to prevent thiamine deficiency.<sup>3</sup> The effects of thiamine deficiency and the benefit of thiamine supplementation are disease- and

medication-dependent.<sup>3</sup> Severe thiamine deficiency can result in severe vasodilatation and high-output HF, known as wet beriberi. This form of thiamine deficiency clearly warrants thiamine supplementation; however, wet beriberi is increasingly uncommon.<sup>3</sup> The benefit of thiamine supplementation in less severe forms of thiamine deficiency is still unclear. Thiamine deficiency in HF has typically been attributed to the use of loop diuretics, which promote the excretion of thiamine and other water-soluble B vitamins.<sup>32,33</sup> However, poor dietary intake is likely a contributing factor in many patients.<sup>34</sup> A series of studies have shown thiamine deficiency to be fairly common in the HF population, with prevalence ranging from 13% to 33%.<sup>35,36</sup> The prevalence may be even higher in hospitalized and elderly patients with HF.<sup>36,37</sup> A number of small studies have shown improved markers of LV function after thiamine supplementation. Shimon and colleagues<sup>38</sup> enrolled 30 patients with thiamine deficiency taking loop diuretics and provided 7 weeks of thiamine supplementation.<sup>38</sup> Twenty-seven of the 30 patients showed a mean improvement in LV ejection fraction of 22%. Another study by Seligmann and colleagues<sup>32</sup> treated 23 HF patients with a 7-day course of intravenous thiamine and demonstrated a mean improvement in ejection fraction of 13% and a mean increase in systolic blood pressure of 10 mm Hg. Studies have shown that the use of spironolactone helps to abate the excretion of thiamine and improve serum thiamine levels.<sup>39,40</sup> Moreover, even small doses of thiamine (1.5 mg/d) appear to prevent thiamine deficiency in HF patients.<sup>35</sup> Other studies have shown mixed results from thiamine supplementation in HF.<sup>37,41</sup> Larger studies are necessary to examine the benefit of thiamine supplementation in HF, but it appears reasonable to supplement thiamine in chronic HF patients, especially those taking high-dose loop diuretics.

Riboflavin and pyridoxine are water-soluble B vitamins that play a key role in the beta-oxidation of lipids, carbohydrate metabolism, and red blood cell production. Like thiamine, these

vitamins show increased excretion with loop diuretics.<sup>42</sup> Riboflavin and pyridoxine deficiencies have been demonstrated in chronic HF patients. One study of 100 patients reported riboflavin deficiency in 27% and pyridoxine deficiency in 38%<sup>42</sup>; however, data regarding supplementation and its effect on cardiac function are lacking.

Hyperhomocysteinemia has been established as an independent risk factor for the development of HF even in the absence of myocardial infarction.<sup>43,44</sup> Vitamin B12 and folate deficiencies are the most common cause of elevated plasma homocysteine levels in adults.<sup>45</sup> Supplementation of these vitamins can effectively reverse elevated plasma homocysteine levels.<sup>46</sup> Studies show that levels of B12 and folate correlate poorly with the development of HF, and supplementation with vitamin B12 or folate has not been investigated.<sup>47,48</sup>

Other potential important micronutrients in the HF patient include magnesium, potassium, zinc, selenium, and creatine. Magnesium and potassium deficiencies have been associated with arrhythmias. Zinc and selenium are antioxidants that have also been reported to be low in HF patients.<sup>4</sup> Creatine is a key component of energy metabolism in the heart muscle and has also been reported to be deficient in patients with severe HF.<sup>4</sup>

### **Omega-3 Fatty Acids**

Although reasons for the potential benefits of omega-3 polyunsaturated fatty acids (PUFAs) are not completely understood, omega-3 fatty acids appear to confer cardiovascular benefits largely through docosahexaenoic acid- and eicosapentaenoic acid-enrichment of membrane phospholipids.<sup>49</sup> The incorporation of omega-3 PUFA into the membranes of target cells and tissues is likely to produce a reduction in electrical excitability, thus decreasing the potential for arrhythmic events.<sup>50</sup> Other beneficial physiologic effects include inhibition of thromboxane production, increased production of prostacyclin, increased fibrinolytic activity of plasma, modification of leukotriene and cytokine production to reduce inflammation,

reduction in vasospastic response to catecholamines, reduction in blood viscosity, decreased platelet-activating factor and platelet-derived growth factor, and oxygen free-radical generation.<sup>51</sup> These cumulative effects ultimately lead to increased arrhythmic thresholds, reduction in arterial blood pressure, improvement in arterial and endothelial function, reduced platelet aggregation, and favorable effects on autonomic tone.<sup>52</sup> Fish oils also decrease tumor necrosis factor (TNF) production in HF and improve body weight.

Omega-3 PUFA supplementation may represent a novel therapeutic approach in late-stage HF characterized by cardiac cachexia.<sup>53,54</sup> Supplementation with omega-3 PUFAs has also been of potential interest as a therapy for HF. Trials in primary and secondary prevention of coronary heart disease showed that omega-3 fatty acid supplementation results in a relative risk reduction of 10% to 20% in fatal and nonfatal cardiovascular events.<sup>55</sup> The Cardiovascular Health Study showed an inverse association in the intake of baked or broiled fish and incidence of congestive HF.<sup>56,57</sup> This result was supported by recent data from the Atherosclerosis Risk in Community (ARIC) study, showing an inverse relationship between omega-3 PUFA intake and incident HF in women.<sup>58</sup>

Further evidence on the benefit of omega-3 PUFA in HF was shown by the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico Heart Failure (GISSI-HF) investigators. Almost 7000 patients with New York Heart Association class II through IV chronic HF were randomized to receive 1 g/d of omega-3 PUFAs or matching placebo.<sup>59</sup> Death from any cause was reduced from 29% with placebo to 27% in those treated with omega-3 fatty acids (adjusted hazard ratio, 0.91; 95.5% confidence interval, 0.833–0.998;  $P=.041$ ). The co-primary outcome of death or admission to hospital for a cardiovascular event was also reduced. Although the improvements in clinical outcomes were modest, the therapy was safe, well tolerated, and additive to those of other therapies that are standard of care in HF.

Animal studies in cardiac remodeling suggest that higher doses of omega-3 PUFA may be useful.<sup>60</sup> In a small 18-week study of 14 patients with class II through IV HF, there was marked improvement in inflammatory cytokines, TNF- $\alpha$  and interleukin 1, with 5.1 g/d of eicosapentaenoic acid and docosahexaenoic acid.<sup>53</sup> These findings were echoed in the GISSI-HF study. Effect of n-3 PUFAs in patients with chronic HF in the GISSI-HF trial, a randomized, double-blind, placebo-controlled trial,<sup>59</sup> and a Japanese epidemiological study<sup>61</sup> both suggest that higher pharmacologic doses of omega-3 PUFA are needed to obtain maximal clinical benefits in patients with HF.

Further studies are needed to determine not only the optimal dose of omega-3 PUFA protection in different stages of HF, but also the underlying mechanism of action responsible for these benefits. It is clear that supplementation with omega-3 PUFA provides significant overall benefit with minimal risk. In a recent editorial published in *The Lancet*, Fonarow<sup>62</sup> concludes that "supplementation with omega-3 PUFAs should join the short list of evidence-based life-prolonging therapies for HF."<sup>62</sup>

### **Vitamin D**

Vitamin D deficiency has been reported to be associated with many of the traditional CV risk factors such as diabetes mellitus, hypertension, and dyslipidemia either directly or indirectly.<sup>63</sup> Of particular interest for this review is the association of vitamin D deficiency with increased parathyroid hormone levels and subsequent effect on the modulation of the renin-angiotensin system, cardiac contractility, and smooth muscle proliferation leading to LV hypertrophy.<sup>64</sup> The greatest source of vitamin D is sunlight exposure and endogenous production in the skin. Vitamin D can also be obtained from dietary sources but to a much lesser degree.<sup>63</sup> Vitamin D deficiency has been reported to be a problem in several different populations ranging from the young and healthy to the elderly and is prevalent in HF patients as well. A study published by

Schierbeck and colleagues<sup>65</sup> indicated that both low vitamin D and elevated PTH were independently associated with mortality in HF patients.

## Future of Nutrition in HF

Nutrition is an extremely important part of managing HF patients, particularly because many of them may be malnourished. With the large energy and nutrient demands of the human heart, it is essential to keep up with consumption

to prevent the further fall in heart function in these already disadvantaged patients. There are physiologic reasons to supplement all of the nutrients we have discussed in this review, yet data still do not exist to be able to make solid recommendations. In addition, have many of the studies that have investigated nutrient supplementation simply fulfilled the need of one nutrient to potentially unmask the need for another? As discussed above, some basic treat-

ment modalities of HF patients such as diuretics can, in and of themselves, contribute to some of the nutrient deficiencies. It is time to investigate the benefits of nutrient supplementation by designing a large randomized controlled trial comparing patients with repleted nutrients vs those who receive placebo. The formulation of nutrients in this study should include many if not all of the ones discussed in this review to answer the question of whether there is benefit.

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