Nutritional Deficiencies and Sarcopenia in Heart Failure: A Therapeutic Opportunity to Reduce Hospitalization and Death

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There is an expanding prevalence pool of heart failure (HF) due to the increasing prevalence of survivors of myocardial infarction, diabetes, hypertension, chronic kidney disease, and obesity. There is increasing interest in the role of nutrition in all forms of HF, given observations concerning micro- and macronutrient deficiencies, loss of lean body mass or sarcopenia, and their relationships with hospitalization and death. This review examines the relationships among loss of lean body mass, macro- and micronutrient intake, and the natural history of HF, particularly in the elderly, in whom the risks for all-cause rehospitalization, infection, falls, and mortality are increased. These risks are potentially modifiable through strategies that improve nutrition in this vulnerable population.

KEY WORDS

Heart failure • Cardiomyopathy • Lean body mass • Macronutrient supplementation • Hospitalization • Mortality

Heart failure (HF) represents a major healthcare concern worldwide. In the United States alone, it is estimated that approximately 6 million people have HF, and nearly 915,000 more are diagnosed annually.[1] Survival is dependent on the age of onset and is approximately 50% at 5 years; the most common mechanisms of death are pump failure and sudden arrhythmic death.[2] The risk of death or rehospitalization is similar for those with reduced or preserved systolic function, suggesting that, potentially, both cardiac and noncardiac determinants of survival could play a role in the epidemiology of HF.[3]

Despite the common perception that systole requires more energy than diastole, diastole is the more energy-dependent part of the cardiac cycle. The metabolic demands of the myocardium are higher in diastole, requiring more adenosine triphosphate (ATP) to stretch and fill the heart chambers.[4,5] Invariably, as ATP concentrations decline in cardiomyocytes of the failing heart, dysfunction in diastole occurs irrespective of systolic function. Importantly, diastolic dysfunction is related to mortality in a graded manner according to its severity when evaluated in those with preserved or reduced left ventricular ejection fraction (LVEF).[6] Therefore, regardless of its etiology or LVEF, metabolic demands in cardiomyopathy are potentially at risk and should be considered as a target for intervention.

Idiopathic dilated cardiomyopathy (IDCM) describes a group of myocardial diseases of unknown cause, whose common clinical presentation is HF with reduced LVEF. IDCM is probably the result of an underlying genetic predisposition and then a superimposed insult to the heart over the course of time (eg, hypertension, diabetes, chronic kidney disease, viral infection, alcohol).[7] Although the prevalence of IDCM is only estimated to be between 7% and 13% of all patients with systolic dysfunction, the disease can provide helpful hints and insights into some of the biochemical and nutritional determinants involved in myocardial dysfunction and adverse morphologic changes over time. Human nutrition and the intake of both micro- and macronutrients play a role in the provision of energy-containing substrate to the myocardium, as well as the entire body. Thus, oxygen extraction and utilization by skeletal muscles, as well as overall skeletal muscle mass, is considerably influenced by nutritional factors. Sarcopenia is a condition characterized by loss of skeletal muscle mass and function. Although it is primarily a problem of the elderly, its development may be associated with conditions, including HF, that can occur in younger individuals.[8] Low lean body mass or sarcopenia has been consistently associated with an increased risk of morbidity and mortality in HF.[9] Thus, a chain of logic could be constructed that optimization of nutrition would not only improve cardiac energetics, but also increase lean tissue mass, improve respiratory mechanics and oxygen extraction and delivery, enhance functional capacity, improve immune function, reduce the risk of serious falls, and, in a summative fashion, be associated with a reduced risk of death.

Diagnostic and Therapeutic Implications

In the past four decades, much of the research in the field of HF has focused on pharmacotherapeutic management with agents that effect neurohormonal regulation, salt and water balance, hemodynamic abnormalities, and risk of ventricular arrhythmias. The field of cardiac resynchronization therapy and defibrillation has given relatively definitive control over the risk of sudden death. By comparison, the contribution of metabolic abnormalities to the progression of HF has received lesser degrees of attention.[10,11] Micronutrients such as the B vitamins (thiamine, riboflavin, and pyridoxine), L-carnitine, creatine, and taurine, known to be important in myocardial energy production, have been shown to be deficient in HF and may play a role in myocyte energetics (Figure 1). Limited studies in humans have shown that dietary replacement of some of these nutritional factors can result in improvement in myocardial function and exercise capacity.[12-14]

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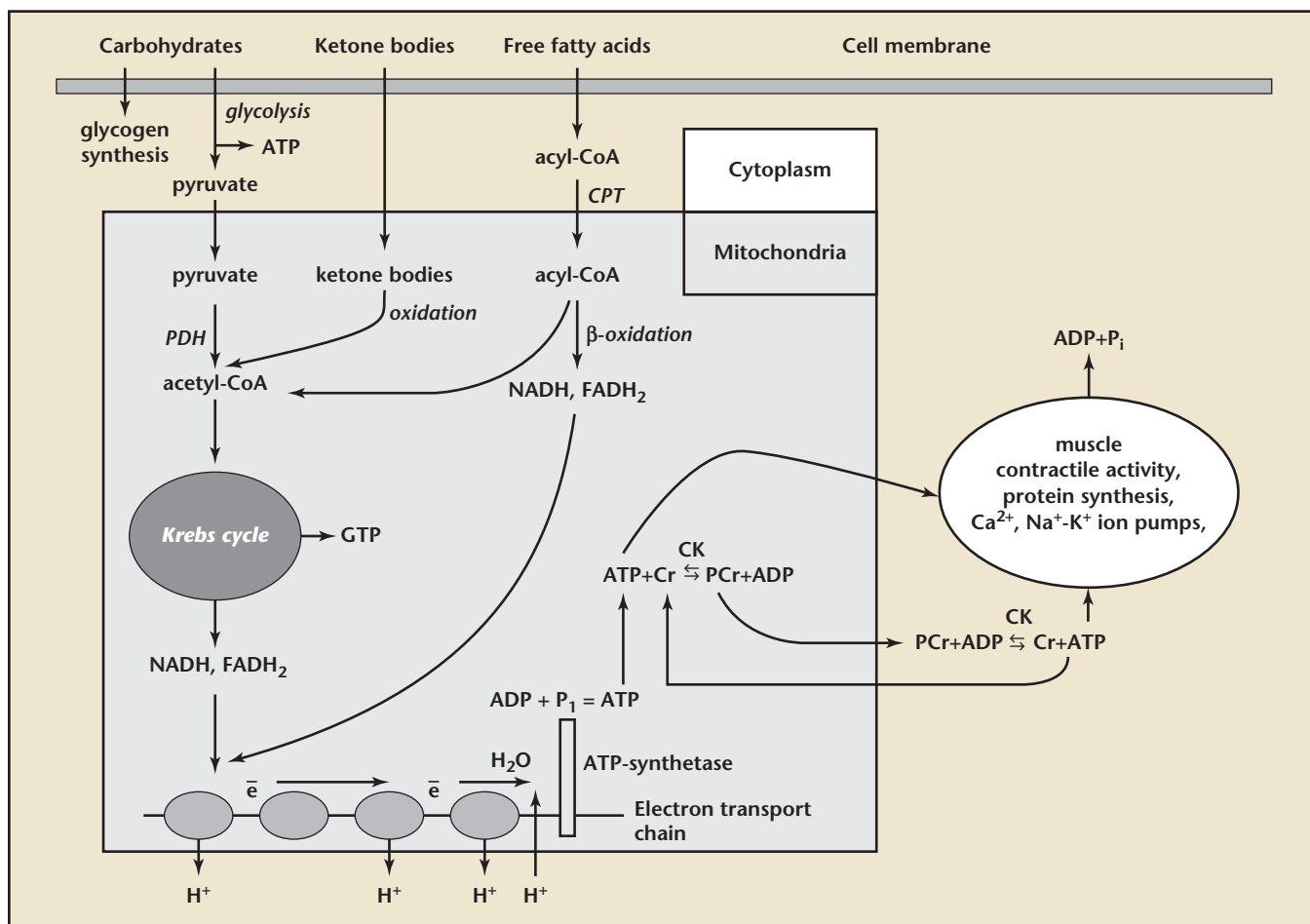
Figure 1. Normal myocardial metabolism. ADP, adenosine diphosphate; ATP, adenosine triphosphate; acetyl-CoA, acetyl coenzyme A; PDH, pyruvate dehydrogenase; NADH, nicotinamide adenine dinucleotide; FADH$_2$, flavin adenine dinucleotide; GTP, guanosine triphosphate; CK, creatine kinase; PCr, creatine phosphate; Pi, inorganic phosphate. Reproduced with permission from Weiss and Maslov.[62]

at least partially treatable through dietary supplementation with modest, preliminary supportive evidence (Table 1). For example, randomized trials of thiamine supplementation have demonstrated improvements in LVEF; however, they have not resulted in differences in functional outcomes or survival.[14-16] Thus, micronutrient deficiencies are a potential cause and at times contributors to HF, and, as such, deserve careful consideration as potentially modifiable factors.

B Complex Vitamins

Referred to as vitamin B complex, the eight B vitamins—B$_1$, B$_2$, B$_3$, B$_5$, B$_6$, B$_7$, B$_9$, B$_{12}$—play important roles in protein and carbohydrate metabolism as well as many other cellular functions. One of

the micronutrients most investigated in IDCM has been thiamine (vitamin B$_1$). Although alcoholic dilated cardiomyopathy is a distinct clinical entity from IDCM, studies on this disease supported a link to thiamine deficiency as early as the 1960s.[17] In this report, 20% of patients presented with cardiac beriberi and thiamine deficiency. The validity of a similar relation between thiamine deficiency and IDCM was highly suggested much later by a 10-year prospective study from New Zealand, which examined the demographic, hemodynamic, and prognostic features of IDCM.[18] The study noted a 9.5% occurrence of an abnormal transketolase test result, which suggests thiamine deficiency is physiologically significant. Additionally, a

cross-sectional study has reported that approximately one-third of hospitalized patients with HF had low thiamine tissue levels.[19] It is important to recognize that thiamine is lost in the urine in response to the use of loop diuretics; thus, there is a need for physiologic replacement in patients with HF.[20]

Riboflavin (vitamin B$_2$) and pyridoxine (vitamin B$_6$) are two other water-soluble B vitamins whose depletions have been shown to play important roles in myocardial energy production. Like thiamine, these B vitamins are subject to limited tissue storage and are renally excreted. In 2009, Keith and colleagues[21] reported that 27% of hospitalized patients with HF had evidence of vitamin B$_2$ deficiency, whereas 38% had low

TABLE 1

Micronutrients With Positive Preliminary Clinical Trial Data on Heart Failure Outcomes

Study	Nutrient	Outcome
DiNicolantonio JJ et al[58] 20 trials	Thiamine	Various, ↑ LVEF
Serati AR et al[59]	L-carnitine	↑ Diastolic performance
Shang R et al[60] 5 trials	L-carnitine	23% risk reduction in all-cause mortality, no effect on HF
Beyranvand MR et al[31]	Taurine	↑ Exercise capacity
Omran H et al[34]	D-ribose	↑ Diastolic performance, quality of life
Jankowska EA et al[40] 5 trials	Iron	↑ Multiple functional capacity and quality of life measures
Stepura and Martynow[44]	Magnesium	↓ All-cause mortality
Ford JA et al[46] 21 studies	Vitamin D	↓ Incident HF

HF, heart failure; LVEF, left ventricular ejection fraction.

concentrations of vitamin B_6.[21] In the same study, the use of B vitamin-containing supplements did not significantly reduce deficiency rates (vitamin B_2 with $P = .38$ and B_6 with $P = .18$), suggesting the need for supplementation may be greater than expected.

Amino Acids

Carnitine is an amino acid that plays an important role in myocardial energy production. L-carnitine plays a role in β-oxidation, transport of long-chain fatty acids from the cytoplasm into mitochondria, and shuttling of toxic acylcarnitines out of cells.[22] L-carnitine availability has been linked to improved cardiac myocyte function.[23] The myocardial concentration of carnitine is approximately 80- to 140-fold higher than the plasma concentration. Nakamura and coworkers[24] demonstrated that serum free carnitine concentrations were significantly higher in patients with IDCM than in normal subjects ($P = .0001$); the ratios of acylcarnitine to carnitine were abnormal, suggesting impairment in carnitine cellular uptake, action, or catabolic fate. These findings are consistent with several studies performed on patients with ischemic cardiomyopathy. A prospective randomized trial of supplementation with carnitine, 2 g/d, resulted in an improved 3-year survival for patients with New York Heart

A prospective randomized trial of supplementation with carnitine, 2 g/d, resulted in an improved 3-year survival for patients with New York Heart Association class III-IV symptoms when compared with placebo.

Association class III-IV symptoms when compared with placebo.[25] Therefore, L-carnitine could be considered a nutritional adjunct to other nutritional interventions in patients with HF.

Creatine is an amino acid that, via phosphate transfer, works to provide energy to all cells in the body, primarily muscle. This is achieved by increasing the formation of ATP. In one report of 39 patients, lower phosphocreatine-to-ATP levels were associated with reduced total and cardiovascular mortality.[26] Creatine supplementation plays a role in reducing lactate production in skeletal muscle during intense exercise in patients with HF, suggesting a possible target for randomized trials.[27] One trial in a mixed population (n = 70) of coronary artery disease and HF patients showed that creatine supplementation had no effect on functional or symptomatic outcomes after 3 months.[28]

Taurine, a nonessential amino acid in humans, is the most abundant free amino acid in the cardiac muscle, and is involved in calcium regulation in the cytosol and mitochondria.[29] Taurine is thought to facilitate calcium release and affect calcium sensitivity of contractile proteins. It may attenuate the intracellular effects of neurohormonal antagonism of the renin-angiotensin and sympathetic nervous systems.[30] In one small randomized trial (n = 29), taurine, 500 mg by mouth three times daily, increased exercise capacity in HF.[31] As a caveat, taurine is a component of high-energy drinks and has been implicated in sudden deaths after large ingestions.[32]

Fatty Acids

There has been great interest in essential fatty acids and their role in cardiovascular disease. Omega-3 and -6 fatty acids have been the subject of many dietary and interventional trials mainly focussed on atherosclerosis or arrhythmias. A recent review by Poudyal and Brown[33] concluded that n-3 polyunsaturated fatty acid trials have not demonstrated significant impact on secondary and other observed outcomes in patients with HF.

Sugars

D-Ribose is a simple sugar that supports the production of ATP. Omran and colleagues[34] performed a double-blind, placebo-controlled, cross-over trial (n = 15) demonstrating that 3 weeks of ribose supplementation significantly enhanced indices of diastolic heart function and exercise tolerance. Given the more recent appreciation for HF due to or worsened by diastolic dysfunction, additional research on D-ribose and myocardial diastolic energetics appears to be warranted.

Minerals

Selenium is an essential nutrient that makes an integral part of the enzyme glutathione peroxide, which, in turn, plays an important protective role in metabolism of cardiomyocytes and all other somatic cells. Several studies have found an association between selenium deficiency and HF, immune deficiency, and diabetes.[35] African-American patients with IDCM appear to have low serum selenium levels.[36] The Selenium Treatment and Chagasic Cardiopathy trial is currently underway, testing the efficacy and safety of selenium supplementation in Chagas cardiomyopathy.[37] There are no completed, definitive trials of selenium treatment in HF.

Both copper and zinc play roles as cofactors in biochemical reactions. IDCM patients most likely also have systemic inflammation, and the acute phase response of inflammation is known to affect serum levels of both copper and zinc, adding an additional layer of complexity to the functional relationships of these spe-

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cific micronutrients in oxidative stress-dependent cardiovascular disease. The role of copper and zinc imbalances in IDCM remains controversial, as there are studies that found no association between copper or zinc deficiency and IDCM.[38]

The deleterious effects of iron-deficiency anemia on the heart must not be overlooked. According to current data, iron deficiency is the most common nutritional deficiency in the developed world; some 2% of US men and 9% of US women have it. One of the extreme results of iron deficiency is cardiomyopathy and HF.[39] In a study by Jankowska and associates,[40] 37% of patients with HF and reduced LVEF had iron deficiency that was associated with worsened severity of heart failure and higher levels of natriuretic peptides. Iron is essential to the structure of both oxygen-carrying myoglobin and hemoglobin. Iron deficiency can result in anemia and cardiac myocyte oxygen deprivation, reduced oxygen storage (myoglobin) and energetic efficiency, increased anaerobic metabolism and mitochondrial dysfunction.[41] A recent meta-analysis of five randomized trials of intravenous iron

therapy showed that iron therapy was associated with a reduction in cardiovascular hospitalization (odds ratio [OR] = 0.44, 95% confidence interval [CI], 0.30-0.64; $P < .0001$), and the combined endpoint of cardiovascular death or hospitalization for worsening HF (OR = 0.39, 95% CI, 0.24-0.63; $P = .0001$).[42] Intravenous iron treatment was associated with improvement in functional class, an increase in 6-minute walking test distance, and an improvement in quality of life.

Hypomagnesemia has been linked to HF and hereditary hypomagnesemia can cause a progressive dilated cardiomyopathy.[43] One small trial (n = 790) demonstrated high-dose chelated oral magnesium was associated with improved survival; however, larger trials have not been planned or completed as of this writing.[44]

Fat-soluble Vitamins

In recent years, vitamin D deficiency has drawn attention in its association to bone and mineral, neurodegenerative, immune, metabolic, and cardiovascular disease. Vitamin D deficiency and secondary hyperparathyroidism are common in patients with HF.[45] Ford and colleagues[46] have published a synthesis of the interventional data to date suggesting benefit of vitamin D supplementation on HF outcomes and other cardiovascular events. In this report, the Randomised Evaluation of Calcium Or vitamin D (RECORD) trial (n = 5292) found a 25% risk

reduction for the HF endpoint, and a meta-analysis of 21 studies found an 18% risk reduction with vitamin D supplementation. Thus, at the time of this writing, vitamin D may be one of the best-supported nutritional interventions for HF patients.

Vitamins A, E, and K are the other fat-soluble vitamins. It is beyond the scope of this review to cover the results of trials in cardiovascular disease with these micronutrients. Although there are important effects on reversal of anticoagulation and they may play a role in the pathophysiology of cardiomyopathy in some extreme malabsorption syndromes, in general these entities have not been implicated in HF.

Figure 2. Constellation of malnutrition, micronutrient deficiencies, and clinical outcomes in heart failure.

Importance of Lean Body Mass

The body can be subdivided into lean (mainly muscle) and fat mass and could be assessed by a variety of methods, including whole-body densitometry.[47] There is a consistent signal in the general medical literature, oncology, critical care, and now in cardiology that lean mass is associated with a variety of cellular and tissue functions that are associated with the ability to survive intercurrent illnesses and are protective against death in the in-

been related to improved outcomes in hospitalized patients.

DiBello and associates[9] studied 402 patients with HF from the National Health and Nutrition Examination Study and found that the 20th percentile of the sex-specific distribution of lean appendicular mass had a statistically significant association with reduced ability to perform household chores, walking one-fourth of a mile, and hospitalization. Narumi and coworkers[49] measured fat-free or lean mass using densitometry in 267 patients with HF and found

… lean mass is correlated with improved endothelial function, vasoreactivity, and the ability to modulate hemodynamic stress. Thus, it is not surprising that lean body mass has been related to improved outcomes in hospitalized patients.

hospital setting (Figure 2).[48] Higher levels of muscle mass are associated with improved oxygen, glucose, and fatty acid metabolism in all tissues and organ systems. In addition, lean mass is correlated with improved endothelial function, vasoreactivity, and the ability to modulate hemodynamic stress. Thus, it is not surprising that lean body mass has
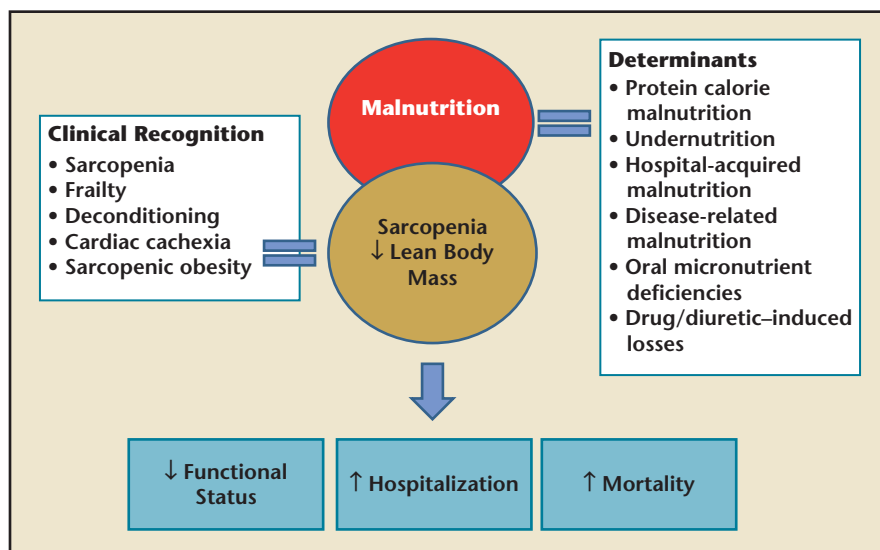
that lean mass was inversely associated with hospitalization and mortality.[49] Related terms *sarcopenia*, *sarcopenic obesity*, and *cachexia* have been used in the recent literature in HF. The important concept is that lean mass and not fat or total body mass is associated with clinically meaningful outcomes. Sarcopenia refers to the

age-associated loss of muscle mass and/or function. Importantly it is possible for an obese individual to have a low muscle mass. Therefore, *sarcopenic obesity* is a state that may be even worse than sarcopenia alone, because all the disadvantages of obesity are present, including insulin resistance, proclivity for thrombosis and venous stasis, and greater degrees of inactivity and musculoskeletal problems.

Nutritional Interventions to Address Low Muscle Mass

Malnutrition and its associated loss of muscle mass exert negative effects on clinical outcome in patients with HF.[50] The loss of muscle mass and function could be addressed by increased intake of dietary proteins, amino acids, their metabolites, and oral nutritional supplements. Dietary protein induces muscle protein synthesis and decreases protein degradation. Interestingly, it was shown that the net protein accretion was significantly higher in elderly individuals consuming 1.5 g/kg/d of dietary

protein rather than the dietary recommended dose of 0.8 g/kg/d. In the same study, protein accretion was not different whether dietary protein was distributed equally through the three daily meals or mainly administered at dinner. Dietary amino acids, especially the branched-chain amino acid leucine and its metabolite, β-hydroxy β-methylbutyrate (HMB), have been shown to stimulate muscle protein synthesis and inhibit protein degradation (Figure 3). Of particular interest to disease-associated low muscle mass, HMB had been shown to inhibit muscle protein degradation in patients with cancer and human immunodeficiency virus cachexia. We recently reviewed the effects of HMB and its potential role in HF-associated cachexia.[51] Oral nutritional supplements providing a mix of macronutrients and micronutrients are effective therapy for malnutrition, especially in elderly malnourished patients. These supplements have been consistently shown to improve weight, muscle function, and clinical outcomes in patients with disease-associated malnutrition.[52] The

overall protein intake appears to be the most important variable in the maintenance or increase in lean tissue mass.[52]

Oral Nutritional Supplement in Older Hospitalized Patients: the NOURISH Trial

In the A Randomized Double Blinded Controlled Trial of an Oral Nutritional Supplement Containing AN 777 in Older Hospitalized Patients (NOURISH) trial, Deutz and colleagues[53] randomized 652 hospitalized adults ≥ 65 years of age, evidence of malnutrition (subjective global assessment [SGA]

class B or C) with diagnoses of HF, acute myocardial infarction, pneumonia, or chronic obstructive pulmonary disease. Patients were randomized to a high-protein oral

nutritional supplement containing HMB (HP-HMB) or usual care. The primary composite endpoint of death or rehospitalization at 90 days was similar between HP-HMB (26.8%) and placebo (31.1%) groups; however, 90-day mortality was significantly lower with HP-HMB as compared with placebo (4.8% vs 9.7%; relative risk 0.49, 95% CI, 0.27-0.90; $P = .018$). The number-needed-to-treat to prevent one death was 20.3 (95% CI, 10.9, 121.4) (Figure 4). Compared with placebo, HP-HMB resulted in improved odds of better nutritional status (SGA class, OR, 2.04, 95% CI, 1.28, 3.25; $P = .009$) at day 90, and an increase in body weight at day 30

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($P = .035$). This trial suggested that improved nutrition and inferred lean tissue mass, although not influencing the rate of intercurrent illness, is associated with improved

Figure 3. Effect of β-hydroxy-β-methylbutyrate (HMB) on lean body mass in elderly patients. Reproduced with permission from Deutz NE et al.[63]
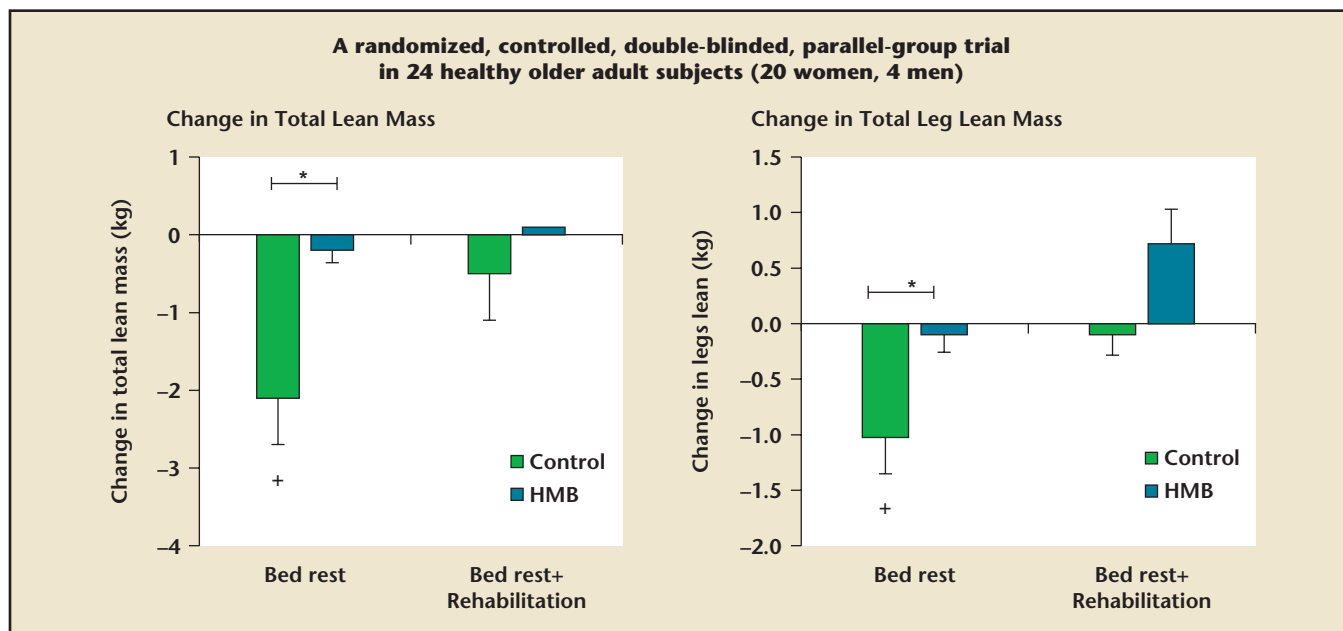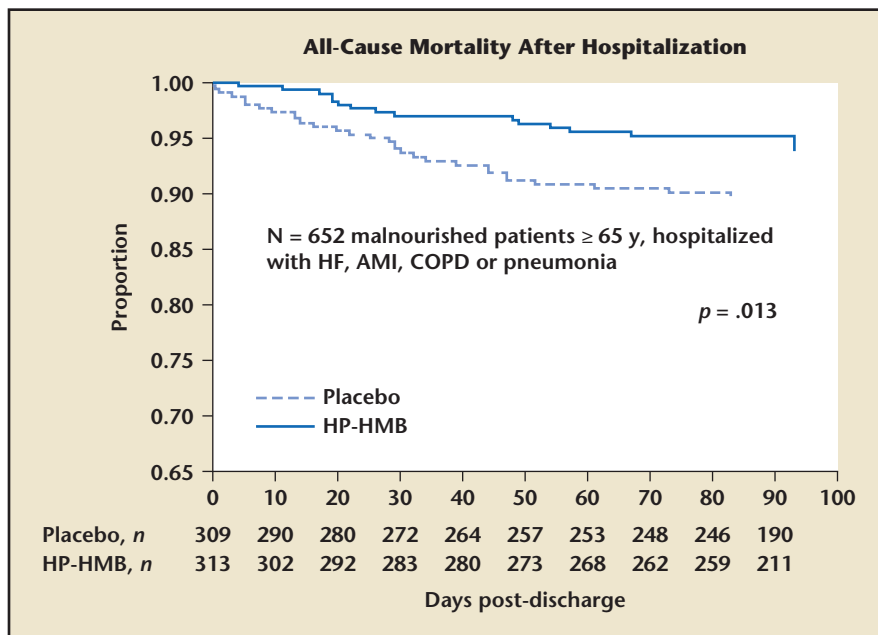
Figure 4. Results from the NOURISH Trial. AMI, acute myocardial infarction; COPD, chronic obstructive pulmonary disease; HF, heart failure; HP-HMB, high-protein β-hydroxy-β-methylbutyrate. HMB supplement given twice daily containing 20 g of protein, 1.5 g of HMB, and 40 IU of vitamin D. Reproduced with permission from Deutz NE et al.[53]

chances of survival should another event occur. Hence, nutritional supplement therapy, particularly high in protein and HMB, should be considered in HF patients with low lean body mass who are at risk for malnutrition.

Clinical Implications for Heart Failure Patients

Metabolic Demands of the Starved Myocardium

The metabolic demands of the myocyte require conversion of the chemical energy from the ATP bond into mechanical energy specific to the cells function (contraction, conduction of electrical charge) (Figure 1). In the case of the normal heart, large fluctuations in workload and energy demand rely on adequate ATP generation and/or recycling mechanisms in the mitochondria. These include oxidative phosphorylation, where fatty acid and carbohydrate metabolism takes place, and creatine kinase (CK) activity, where ATP and free creatine are generated from adenosine diphosphate and

creatine phosphate. Conversely, it is well documented that in the failing heart the balance between energy supply and demand does not function adequately, resulting in a progressively decreasing ATP tissue content.[4,54] In HF, these metabolic mechanisms are disrupted, leading to inefficient energy expenditure and the creation of the term *starved myocardium*. In essence, a chronic energy supply/demand mismatch is created.

Because of the similarities of the energy-starved myocardium with both IDCM and ischemic heart disease, an integrative approach in the treatment of congestive HF has been previously entertained.[55] Relying on nutritional biochemical interventions that preserve and promote ATP production, metabolic cardiology was introduced as an indispensable therapeutic intervention in the context of HF. This approach includes therapeutic options that focus on preservation of energy substrates, such as ribose, or acceleration of ATP turnover, such as carnitine and coenzyme Q10. We argue

that a metabolic intervention in IDCM patients should be expanded to include thorough micronutrient and mineral testing prior to intervention, as this would identify additional therapeutic targets and individualize treatment, most notably iron, magnesium, and vitamin D.

Traditional Heart Failure Therapy and Nutrient Depletion

With the emergence of diuretics, angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) as major components of HF management, the balance of many of the nutrients needs to be monitored. More specifically, ACE inhibitors/ARBs are known to exert their function by binding zinc. Additionally, the use of diuretics has been reported to induce thiamine, selenium, zinc, and coenzyme Q10 deficiencies (Table 2).[56]

Recognition of Sarcopenic Obesity

Increasingly, patients with HF are obese, and thus sarcopenia may be more difficult to recognize. Trends in overall loss in lean body mass may be masked by fluid weight gain. It is important for the clinician to develop a sense of muscle bulk, strength, and functional status in the office and during the bedside examination. Advanced tools such as whole body densitometry, computed tomography of the iliopsoas, and bioimpedance can be used to assist in tracking lean tissue mass.[57] Early intervention with increasing protein intake and HMB should be considered to attenuate the loss of lean body mass and to augment rebuilding of muscle after hospitalization.

Conclusions

There appear to be opportunities for future research and improvements

TABLE 2

Drug-induced Nutrient Deficiencies in Heart Disease Treatment

Class of Drugs	Induced Nutrient Deficiency
Diuretics	B vitamins, thiamine, selenium, potassium, magnesium, folate, homocysteine, calcium
ACE inhibitors/ARBs	Zinc
β-Blockers	Coenzyme Q10
Statins	Coenzyme Q10, carnitine, selenium, omega 3 fatty acids

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker.
Reproduced with permission from Marinescu and McCullough.[61]

in clinical practice for patients with HF with respect to micro- and macronutrient supplementation. Assessment for deficiency states among those with HF seems reasonable. Interventional studies suggest potential benefit with thiamine, L-carnitine, taurine, D-ribose, iron, magnesium, and vitamin D. In terms of macronutrients, protein malnutrition plays a key role in loss of lean body mass and cardiac cachexia. A possible future approach may include assessment of lean body mass, and macronutrient supplementation with high protein and HMB-containing nutritional formulations that appear to reduce the risk of death in elderly hospitalized patients, including those with HF. ■

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MAIN POINTS

- B vitamins (thiamine, riboflavin, and pyridoxine), L-carnitine, creatine, and taurine, may be important in myocardial energy production, and have been shown to be deficient in the heart failure population. These deficiencies could compromise antioxidant defenses, allowing for oxidative stress to impart free radical damage to cardiomyocytes. A small number of human trials have shown that dietary replacement of some of these nutritional factors can result in improvement in myocardial function and exercise capacity.

- Malnutrition and its associated loss of muscle mass exert negative effects on clinical outcome in patients with heart failure. The loss of muscle mass and function can be remedied with increased intake of dietary proteins, amino acids and their metabolites, and oral nutritional supplements.

- Specific metabolic intervention in patients with idiopathic dilated cardiomyopathy should be expanded to include thorough micronutrient and mineral testing prior to intervention, as this will identify additional therapeutic targets and individualize treatment.

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