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Review Article

Myocardial energetics and the role of micronutrients in heart failure: a critical review

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Abstract: Heart failure is a multifactorial disease with poor prognosis. There are many hypotheses regarding the cause of heart failure. Leading among them are the hemodynamic and the neuro-hormonal hypotheses. Although the energy depletion hypothesis has been fairly recent, there is evidence suggesting that declining bioenergy plays a major role in heart failure. This review explored the myocardial energy depletion hypothesis from the role of micronutrients in correcting and alleviating symptoms of heart failure. Even though focus was on key nutrients such as coenzyme Q10, thiamine, riboflavin, L-carnitine, and taurine, emphasis was on the combined effect of multiple micronutrients as a whole. Search from databases from 2000 to 2015 produced four clinical studies using multiple micronutrients on heart failure. Evidence from the studies show that using high doses of multiple micronutrients may have positive effects on heart failure and simultaneously support the myocardial energy depletion hypothesis.

Keywords: Heart failure, myocardial energetics, adenosine triphosphate, Krebs cycle

Introduction

Heart failure (HF) is a progressive, complex, end-stage disease condition of all maladies of the heart resulting in loss of function of the cardiac myocytes. As a consequence, heart-pumping function weakens impairing blood circulation and the body's cells are unable to receive enough oxygen and nutrients to meet the body's needs. This results in symptoms of fatigue and shortness of breath, and for an affected person this makes everyday activities such as walking, climbing stairs or carrying groceries difficult.

Due to its high prevalence, and with estimated cases of over 23 million worldwide [1], a steady increase in HF diagnosis, poor prognosis, and high cost, HF has become a major societal burden [2]. Fifty percent of HF patients die within five years from the initial diagnosis [3].

HF is a multifactorial disease and its various mechanisms have been investigated from a variety of perspectives. These pathogenetic mechanisms (also referred to as models) include increased hemodynamic overload, ischemic-related dysfunction, ventricular remodeling, excessive neuro-hormonal stimulation, abnormal myocyte calcium cycling, excessive or inadequate accumulation of extracellular matrix (fibrosis), accelerated apoptosis, and genetic mutations [4].

Although there are many hypotheses regarding the cause of HF, and with the hemodynamic and the neuro-hormonal as the two leading ones, there is no single unifying pathogenetic theory explaining HF. There are different concepts regarding the underlying causes of the disease, however consensus regarding the definition of HF is lacking [5]. The available evidence suggests that declining bioenergy plays a major role in the failing heart. Accordingly, current conventional treatments for HF include energy-sparing medications like beta-receptor blockers, ACE inhibitors, or angiotensin II blockers, but these are demerits.

Treatment for HF includes pharmacological agents (diuretics, beta-blockers, ACE inhibitors, and neuro-hormonal antagonists), as well as

mechanical devices (left ventricular assist devices) and, finally, transplantation for end-stage HF. These treatment strategies are designed to increase inotropic function of the heart or reduce one or more compensating mechanisms. They are not intended to assure functional recovery or the regeneration of normal cardiac myocytes. This perhaps can be an underlying reason why HF has such poor prognosis.

Therefore, we propose that the most promising therapeutic strategy in achieving partial or total functional recovery of cardiac myocytes should involve the enhancement of bio-energy metabolism in the heart, the myocardial energetics. The concept of the failing heart due to energy depletion was first proposed by Herrmann and Decherd in 1939 [6], but it was not adequately investigated. Our aim is to explore the myocardial energy depletion hypothesis/model of HF from the role of micronutrients in correcting and alleviating symptoms of HF.

Hemodynamic hypothesis

From the beginning, the HF syndrome has been considered as a hemodynamic disorder. Thus, it was defined as a pathologic state where the heart muscle fails to pump blood at a rate to meet the requirements of the metabolizing tissues during ordinary activity [7]. In addition, it was defined as the failure of the heart to deliver oxygen at a rate commensurate with requirements of the metabolizing tissues despite normal filling pressure, or only at the expense of increased filling pressure [8]. HF is initiated by an event, most often myocardial infarction, after a prolonged ischemia. This results in death of cardiac myocytes and eventually diminished pumping capacity of the heart muscle, and is clinically viewed as left ventricular dysfunction.

Based on this hemodynamic concept, the pathophysiology of HF is understood from the perspectives of cardiac contractility, preload, afterload, volume, flow, and the left ventricular ejection fraction. Therefore, treatment is tailored to increase cardiac output by reducing the systemic and pulmonary vascular pressure. Whether it is inotropic, chronotropic, vasodilation or diuretics, the pharmacotropic agents like beta-blockers, digoxin, enalapril, losartan, furosemide, spironolactone, and the like, are aimed to correct the symptoms of hemodynamic abnormalities. Consequently, symptoms like high blood pressure, fatigue, angina, pulmonary edema, and edema of the lower extremities may be partially or fully alleviated and the patient can gain temporary respite. However, despite increase in contractility, vasodilation and reduced ischemia, the disease continues and ultimately the patient dies.

Neuro-hormonal hypothesis

The inability to fully explain why HF continues to progress led researchers to look at the pathogenesis of HF from the role of biologically active molecules which initially contribute to alleviating HF symptoms, but later exert toxic effects hastening the degeneration of HF. This mechanism is known as the neuro-hormonal model.

When a myocardial infarction event occurs, cardiac dysfunction and decreased cardiac output lead to activation of several neuro-hormonal mechanisms to offset the diminished heart contractions, such as activation of the sympathetic nervous system, and increased sodium and water retention [9]. As a result, natriuretic peptides, prostaglandins, and nitric oxide molecules are released to enhance vasodilation [10, 11] in order to improve blood flow.

These neuro-hormonal mechanisms are initially adaptive, compensatory and beneficial, and patients remain asymptomatic, but when sustained they eventually become deleterious and patients become overly symptomatic [12]. After some time the continuous excessive secretion of biologically active molecules is capable of exerting toxic effects on the heart [13]. Some of these proteins that are known to contribute to the disease progression in HF are norepinephrine, angiotensin II, endothelin, aldosterone, and tumor necrosis factor. Their long-term detrimental effects include overgrowth of cardiac myocytes, fibroblast hyperplasia, myocyte damage/myopathy, fetal gene induction, apoptosis of myocytes, pro-arrhythmic effects, vasoconstriction [12], and increased cardiac energy expenditure [14, 15].

Energy depletion hypothesis

The heart has the highest resting energy expenditure than any other organ in the body and has a constant high demand for bio-energy to sustain its workload. The requirement of biochemical energy to support excitation, contraction,

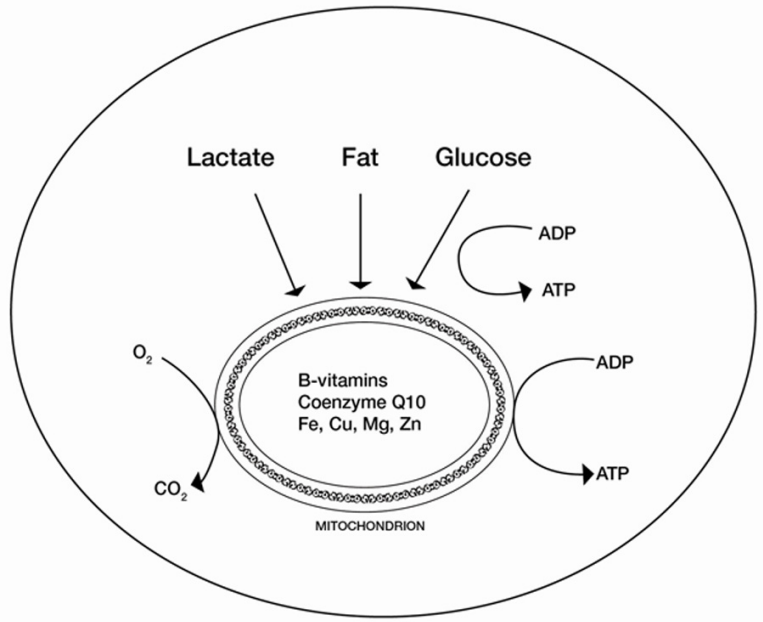

Figure 1. Schematic representation of the ATP synthesis sources and key micronutrients utilized in mitochondrial electron transport system.

relaxation and the molecular synthesis and degradation is absolute. Its production relies mainly on the aerobic oxidation of substrates such as fatty acids, glucose, lactate, and ketone bodies, converting them into energy units called adenosine triphosphate (ATP). The two main substrates for the heart muscle energy generation are fatty acids and glucose (**Figure 1**).

Under normal physiological conditions, the heart relies mainly on fatty acids as substrates for beta-oxidation that contributes 60% to 70% of total ATP production, while the remaining 30% to 40% is provided by glucose and lactate oxidation [16]. Fatty acid oxidation produces more ATP per molecule oxidized than glucose oxidation. However, fatty acid oxidation requires more oxygen per molecule of ATP produced. The ratio of useful energy produced to oxygen consumed is defined as mechanical efficiency. The complete oxidation of 1 fatty acid molecule generates 105 molecules of ATP and consumes 46 atoms of oxygen, whereas the complete oxidation of 1 molecule of glucose generates 31 molecules of ATP and consumes 12 atoms of oxygen [17]. Therefore, fatty acid oxidation is less efficient than glucose oxidation with regards to ATP production based on oxygen consumption.

In ischemic heart disease and HF, oxygen supply is diminished as a result of insufficient tissue perfusion. Therefore, mechanical efficiency is reduced. To compensate, the production of ATP in the myocardium switches from aerobic to anaerobic mode, and from beta-oxidation to glycolysis as the latter yields 11% to 13% more ATP per unit of consumed oxygen [18, 19]. In chronic HF and cardiac hypertrophy, there is a switch in primary substrate utilization from fatty acids to glucose [20] for supporting mechanical efficiency and to conserve energy.

During the initial acute phase of HF, metabolic adaptation and compensation enable the heart to function without compromising mechanical efficiency. Reduction in myocardial oxygen consumption and contractile function are matched [21]. As HF becomes more chronic and the process of remodeling progresses towards an uncompensated state, metabolic adaptation becomes insufficient and the capacity to oxidize glucose decreases along with decreased mechanical efficiency [22]. In HF the ATP is about 25% to 30% lower than its normal values [23, 24].

Energy depletion caused by drugs

In cardiotonic medications, it has been established that vasodilation therapy may reduce myocardial oxygen demand, whereas inotropic stimulation therapy may increase myocardial oxygen demand. Inotropic stimulation consumes energy. Therefore in chronic ischemic conditions and compromised oxygen supply, inotropes may render the failing heart in a more disadvantaged condition, contributing to increased rather than decreased heart failure mortality.

In terms of cardiac output, inotropic agents are known to increase energetic costs of non-mechanical work, which is often referred to as the oxygen-wasting effect [25]. In their study of

30 patients in varying degrees of left ventricular dysfunction, Hayashi and colleagues [26] showed that the oxygen cost of contractility in the severe left ventricular group was significantly greater than in the groups with milder left ventricular dysfunction. Increasing contractility through inotropic agents means increasing oxygen consumption for every beat of the heart.

Beta-blockers are generally considered to be energy sparing in myocardial energetics, however with certain limitations. The study of Hawkins and colleagues [27] showed that metoprolol has a beneficial effect on cardiac efficiency of subjects on mild exercise intensity. However, in subjects on extensive exercise intensity, the cardiac work and calculated cardiac efficiency were reduced. Therefore, caution should be advised for patients with ischemic heart disease who are on beta-blockers and on high intensity exercise, because instead of energy sparing this treatment may hasten energy depletion. Use of ACE inhibitors in patients with impaired cardiac function has been associated with an increase in insulin-like growth hormone factor-1 (IGF-1). However, high levels of IGF-1 predict cardiovascular mortality [28]. It has also been documented in an animal study that IGF-1 increases autophagy and cell death in induced starvation [29].

Nutrients in cardiac metabolism

The contracting heart requires biological fuel in the form of energy units (ATP). As such, it is only logical to analyze the role of nutrients in cardiac metabolism from a reductionist approach. Since the postulation of Herrmann and Dechard in 1939 on energy depletion of the failing heart, the next few decades saw much research on energy metabolism of the heart. However, progress has been slow and almost came to a halt by the first decade of the 21st century.

First, this was because of different views on the cause of HF syndrome. Second, when the neuro-hormonal hypothesis of the cause of HF became more established, pharmacological research mainly targeted the development of drugs modulating substrate utilization as a means to economize and maximize energy production in the failing heart. Studies on nutrients in cardiac metabolism have been sparse and confined mainly to a single nutrient or a combination of a few nutrients. Even much less has been done in addressing cardiovascular endpoints with micronutrient-based approaches.

As discussed earlier, the main energy source of ATP for the heart muscle is fatty acids and carbohydrates. However, the conversion of these macronutrients to biological energy requires micronutrients such as coenzyme Q10 (CoQ10), thiamine, riboflavin, L-carnitine, taurine, and other amino acids that function as essential cofactors for energy production, energy transfer, and maintenance of the physiological heart function [30]. It has been observed that patients with chronic HF do not meet dietary reference values for energy and micronutrients [31]. It was also suggested that nutritional therapy of heart failure should be directed to the replacement of L-carnitine, CoQ10, taurine, antioxidants, and thiamine [32].

Most of the earlier studies on HF and micronutrients have been conducted with a single nutrient or with two-nutrient compounds. However, there have been suggestions to investigate the effects of multiple nutrients on HF [30, 33, 34]. The argument against the use of multiple nutrients is that if improvement is observed, the identification of the active compound and its underlying mechanism will be unclear. Witte and colleagues have argued that using a single nutrient to correct one deficiency when multiple deficiencies exist may be ineffective and could be harmful by causing the accumulation of harmful metabolic products [35]. Soukoulis and colleagues further suggested that using a single micronutrient might potentially shift one metabolic pathway in the energy cascade to another [34], and that correcting one deficiency may unmask other of the many deficiencies present. Indeed, considering that the production and utilization of ATP in the myocyte pathways involves a number of cofactors and intermediary metabolites in energy substrate metabolism, such as CoQ10, thiamine, riboflavin, L-carnitine, taurine and amino acids, it would be appropriate to use multiple nutrients to address multiple nutrient deficiencies especially in HF syndrome. Taking into account a high safety record of micronutrient supplementation and a low risk of their overdosing, this approach does not carry a risk of detrimental side effects as it is in case of pharmaceutical drugs.

Table 1. Clinical studies using multiple micronutrients on heart failure

Study/ Study/ First Author	Study Design	Subjects	Endpoints	Intervention/ Main Micronutrients	Main Outcome
Jeejeebhoy et al. (2002). [36]	RCT	n = 41. HF with IHD EF ≤ 40% Age: 62 ± 11	Primary: Myocardial levels of carnitine, CoQ10, and taurine. Secondary: LVEDV and LVESV.	Daily single dose: Carnitine 3 mg. CoQ10 150 mg. Taurine 3 mg. Thiamine 25 mg. Riboflavin 3 mg. Ascorbate 250 mg. 30 to 45 days.	Significant increase in myocardial levels of carnitine, CoQ10, and taurine. Significant decrease in LVEDV and LVESV. No significant change in EF. No significant difference in cystokine levels. Significant improvement in QOL scores.
Witte et al. (2005). [35]	RCT	n = 30 HF with IHD EF ≤ 35% Age: 75.4 ± 0.7	LV function. Proinflammatory cystokines. QOL.	Daily single dose: CoQ10 150 mg. Thiamine 200 mg. Riboflavin 2 mg. Ascorbate 500 mg. 9 months.	Significant decrease in LVEDV and LVESV. Significant increase in EF. No significant difference in cystokine level. Significant improvement in QOL scores.
McKeag et al. (2014). [37]	RCT	n = 74 HF with IHD EF ≤ 38% Age: 65.8 ± 9.4	Primary: LVEF. Secondary: QOL, 6MWT, NT-proBNP, Proinflammatory cystokines.	Daily single dose: Thiamine 1.5 mg. Riboflavin 1.6 mg. Ascorbate 60 mg. 12 months.	No significant difference in LVEF. No significant difference in QOL score. No significant difference in 6MWT, NT-proBNP, and cystokine levels.
Wong et al. (2015). [38]	Prospec-tive case series.	n = 12 HF with IHD Age: 57.6 ± 9	MLHFQ total score. MLHFQ symptoms score.	Daily three doses: Carnitine 195 mg. CoQ10 27 mg. Taurine 200 mg. Thiamine 22 mg. Riboflavin 22 mg. Ascorbate 2,450 mg. Lysine 1,110 mg. Proline 110 mg. Arginine 790 mg. 4 to 8 months.	Significant decrease in MLHFQ total score. Significant decrease in MLHFQ symptoms score. Improvement in NYHA classification.

EF: ejection fraction; LVEDV: left ventricular end-diastolic volume; LVEF: left ventricular ejection fraction; LVESV: left ventricular end-systolic volume; MLHFQ: Minnesota Living with Heart Failure Questionnaire; NT-proBNP: N terminal prohormone brain natriuretic peptide; QOL: quality of life; RCT: randomized controlled trial; 6MWT: 6 minute walk test.

Studies on heart failure using multi micronutrients

A thorough search through the Cochrane register of controlled trials, Medline, Pubmed, Embase, and Google Scholar databases from 2000 to 2015 revealed only a few studies evaluating HF from a multiple micronutrient approach. These studies are summarized in **Table 1**.

Of the four studies selected, three were randomized controlled trials (RCT), while one was a prospective case series. Even though all four studies used multiple micronutrients, the focus in this review is primarily on L-carnitine, CoQ10, thiamine, riboflavin, and taurine, because the nutrients are known metabolites in the pathways of energy production, oxidative defense, and myocardial calcium balance. There is evidence that L-carnitine [39], CoQ10 [40], taurine [41], and thiamine [42] have a positive effect on HF. There is also evidence of a high prevalence of deficiencies in riboflavin and other B vitamins among patients with HF [43].

Three of the four studies selected showed positive results of micronutrient administration while one showed negative results. The difference in the study outcomes could be explained by differences in micronutrient doses used in the studies. As such, the three studies with positive results used much higher dosages than the study with negative results. In addition, the studies with positive results used CoQ10 and L-carnitine, except for the positive outcome of the study by Witte and colleagues that used only CoQ10 but no amino acids.

Significance of micronutrient dosages

In all previous studies on HF and myocardial energetics, there has been no mention of the significance of dosage of micronutrients. In describing myocardial protein degradation as a consequence of nutrient deprivation, Taegtmeyer and Lubrano [44] proposed restoring fuel homeostasis in order to restore the cycle of protein turnover. The rationale is that there will be substrate deprivation in chronic HF. When there is nutrient deprivation, intracellular concentration of ATP will decline while adenosine monophosphate (AMP) levels rise, resulting in the activation of the enzyme, AMP-activated protein kinase (AMPK). The activation of AMPK results in providing energy by fueling the Krebs cycle with amino acids [45]. AMPK allows for the liberation and recycle of nutrients from the myocytes [46] which maintain a continuous catabolic state for the failing heart.

Refueling the failing heart with metabolites and amino acids supports generation of myocardial energy and it may solve half of the problem. Another therapeutic target should involve arresting the chronic catabolic state and cardiac cachexia. It is reasonable to assume that this can be achieved with supplementation of the necessary nutrients in high dosages. A low micronutrient dosage merely helps maintain basic metabolic needs, but in chronic HF appropriate higher dosages of nutrients are necessary to see therapeutic effect. The positive results of those studies highlighted in **Table 1** provide supporting evidence indicating the significance of using high dosages of multiple micronutrients in achieving therapeutic effects in HF.

Under conditions of ischemic HF and starvation, autophagic activity becomes increased in order to support cellular energy and function by mobilizing endogenous nutritional sources [47]. Organelles and large cellular components are degraded into amino acids, fatty acids, sugars, and nucleotides to be rechanneled for the myocardial energetic and Krebs cycle pathways. AMPK is activated as a mediator for autophagy in the recycling of myocardial energetics [47]. As a remedial measure, it would be appropriate to incorporate a high dosage of micronutrient supplementation to mitigate potential damage caused by chronic HF. For the improved nutrition of the heart, Taegtmeyer and colleagues have proposed that it should go beyond the mere supply of energy-substrates, but also include the supply of amino acids and micronutrients [48].

The role of amino acids

The increased autophagic activity in patients with chronic HF leading to a hyper catabolic state gives an indication of the important role of amino acids in this disease syndrome. In cardiac metabolism, amino acids are necessary for protein synthesis and as intermediate metabolites in energy cycle pathways. In the myocytes, amino acids also act as cofactors or coenzymes for intracellular pathways of energy conversion. In has been mentioned earlier that

the heart requires a large and constant supply of amino acids for protein synthesis and also as intermediates for energy production in the Krebs cycle.

In HF, amino acids have a close relationship with the growth hormone (GH)/insulin-like growth hormone factor-1 (IGF-1) axis. Patients with HF are usually deficient in GH and IGF-1 [49, 50]. When absorbed into the portal system, amino acids stimulate release of IGF-1 and that in turn induces the activation of GH and therefore promotes anabolic metabolism. IGF-1 promotes collagen synthesis by fibroblasts, while GH increases collagen deposition rate in the heart [51, 52]. Thus, amino acids as a group have their important role in maintaining cardiac functions. However, this seems to be a paradox because high levels of IGF-1 predicts cardiovascular mortality [28] and increases autophagy [29]. The possible explanation for this is that IGF-1 during the initial stage of HF is compensatory. When the disease syndrome progresses without a sufficient supply of nutrients to support energy production, the pathology deepens with manifestations in wet beriberi, left ventricular hypertrophy, cachexia, and extreme lethargy. Studies using high daily dosages (8 grams) of the amino acid mixtures in HF, and measuring different outcomes and different endpoints, have produced positive results [53-55]. Single amino acids have been evaluated separately on HF with different endpoints.

L-carnitine has been widely studied in HF and many studies have brought positive results [56-60]. The dosage of L-carnitine used in these studies ranges from 1.5 grams to a high dosage of 6 grams daily. These dosages seem to be well tolerated. Carnitine is not an essential amino acid. Its biosynthesis takes place in the liver and kidneys from the two amino acids, lysine and methionine [61], and it requires ascorbic acid as a cofactor [62, 63]. L-carnitine plays an important role in transporting fatty acid into the mitochondria [64] and, by improving the coupling between glycolysis and glucose oxidation, it improves the utilization of pyruvate in the Krebs cycle [65].

Taurine functions as an antioxidant and a regulator of intracellular calcium homeostasis [41, 66] protecting the myocytes from calcium overload, as in the case in HF. Calcium overload can lead to injury of the myocytes. Studies on the effects of taurine in HF have also produced positive results [41, 67-69]. A daily dosage of 1.5 to 6 grams of taurine was used in these studies, and it was well tolerated.

Other than the one study mentioned in **Table 1** [38], there are no studies involving L-lysine whether used individually or as a component of multiple nutrients in HF. However, this does not mean that its role in HF should be relegated. In the human cells, with a constant flux of biological materials, lysine acetylation plays an important role in a dynamic and reversible post-translational modification of proteins involved in cellular processes including genetic regulations, transcription, survival, apoptosis, and mitochondrial-derived processes in acetyl coenzyme A formation [70, 71]. Almost every enzyme in glycolysis, glucose and fatty acid oxidation are acetylated at least on one lysine residue. Therefore, as lysine is an essential amino acid, and with such myriad cellular processes, the need for its constant supply in the diet or through nutritional supplementation cannot be emphasized enough. In chronic HF, matrix metalloproteinases (MMPs), and other proteolytic enzymes, are overly expressed while tissue inhibitors of MMPs (TIMPs) are under expressed [72]. The disparity in expression between MMPs and TIMPs levels, which favors MMPs activation and proteolysis, contributes to left ventricular remodeling process. While mainstream research has yet to discover a novel strategy to normalize the balance between MMPs and TIMPs, in 1992 Rath and Pauling postulated that L-lysine is a natural inhibitor of proteolysis by MMPs and plasmin [73].

Coenzyme Q10

Coenzyme Q10 (CoQ10), also known as ubiquinone, is present in high concentrations in the mitochondria of the myocardium, liver, and kidneys. It has a vital role in myocardial energetics and the protection of the myocytes. CoQ10, which acts as a mobile electron carrier in the mitochondria, is a cofactor in mitochondrial oxidative phosphorylation leading to ATP production [74]. In addition, it also acts as an antioxidant protecting the cell membrane against oxidation [75] and inhibiting the peroxidation of lipids and lipoproteins [76, 77]. Over the last few decades, there have been numerous studies with CoQ10 supplementation in HF each

using different study designs, dosages, time frame and outcome measures, and often bringing inconclusive results. Of importance are three meta-analyses [78-80] that showed positive results of CoQ10 administration in surrogate endpoints. The meta-analyses of Sander and colleagues [78] and Fotino and colleagues [80] showed significant improvement in ejection fraction using CoQ10 in dosage ranges from 60 to 300 mg/day. Whereas the meta-analysis of Soja and colleagues [79] showed significant improvement in stroke volume, ejection fraction, cardiac output, cardiac index, and end-diastolic volume index.

The B vitamins

The B vitamins are a group of water-soluble vitamins that are important coenzymes in the Krebs cycle and are necessary for ATP production. Of the eight B vitamins, thiamine (vitamin B1) has a direct role in myocardial energetics as a coenzyme in converting carbohydrates to energy. Thiamine is a form of thiamine pyrophosphate and serves as a cofactor of the pyruvate dehydrogenase and transketolase, which are both mediators in energy substrate metabolism [81]. Thiamine is an essential vitamin, therefore it cannot be synthesized endogenously and, as a water soluble vitamin it can be stored only in small quantities. In the clinical trial by Shimon and colleagues [82], patients given 200 mg/day of thiamine showed significant improvements in diuresis and ejection fraction. A recent clinical trial using a high thiamine dosage of 300 mg/day also showed significant improvements in the ejection fraction [42].

Riboflavin (vitamin B2) and pyridoxine (vitamin B6) also play important roles in carbohydrate energy metabolism. Deficiency of riboflavin and pyridoxine has been documented in HF patients [43]. Being water-soluble and essential, these vitamins are subjected to renal loss, have limited tissue storage, and are dependent on dietary intake. Although these B vitamins are known to play an important role in energy metabolism, data to support an effect in HF are lacking.

Conclusion and future direction

Over the last few decades, there have been many clinical studies using mono or multiple micronutrients showing significant positive effects in HF using different surrogate endpoints. These studies used a high dosage of the micronutrients and patients seemed to tolerate well. Taking into account that HF is a syndrome of a chronic failing organ involving multifaceted pathways, treating this disease with a single nutrient may show a temporary positive effect, but the disease as a whole continues. On the other hand, treatments that involve multiple micronutrients may produce better results, but if key micronutrients are applied in low, insufficient doses the positive symptomatic effect may not be immediately demonstrated. Current recommended daily allowances (RDA) for micronutrients are designed to maintain health in a healthy person. However, restoring health in a chronic disease condition may require therapeutic micronutrient doses which are much higher than the RDA. Clinical evidence coming from the studies presented in **Table 1** substantiates the use of multiple micronutrient supplementation in high dosages as an adjunctive therapy for chronic HF.

The case for myocardial bioenergetics as a model for HF has been well established. Current interest has been on modulation of substrates to maximize energy production or energy sparing. Despite research advances in understanding the role of substrate metabolism and pharmacological cardio tonics, morbidity and mortality in HF remain high.

Perhaps it is time that research returns to the basics and refocuses on myocardial energetics with its special emphasis on the role of specific micronutrient combinations. It is a matter of urgency for HF therapy especially if such a repertoire of therapeutics includes safe and affordable micronutrients.

More long-term studies in HF are warranted with larger patient populations and vigorous designs, using high dosage multiple micronutrients with different surrogate and cardiovascular endpoints.

Disclosure of conflict of interest

None.

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