Tzu Chi Medical Journal 28 (2016) 143–150

Contents lists available at ScienceDirect

Tzu Chi Medical Journal

journal homepage: www.tzuchimedjnl.com

Original Article

Role of micronutrients in congestive heart failure: A systematic review of randomized controlled trials

Chandini Valiyakizha Kkeveetil [a], Grace Thomas [a], Sam Johnson Udaya Chander [b, *]

[a] KG Hospital and Postgraduate Research Institute, Coimbatore, India
[b] Department of Pharmacy Practice, RVS College of Pharmaceutical Sciences, Coimbatore, India

ARTICLE INFO

Article history:
Received 9 May 2016
Received in revised form
20 July 2016
Accepted 23 August 2016
Available online 1 November 2016

Keywords:
Exercise tolerance
Functional Capacity
Heart failure
Micronutrients
Supplementation

ABSTRACT

Objectives: To assess the effect of micronutrients on health outcomes in patients with heart failure.
Materials and Methods: Only randomized controlled trials testing the effectiveness of different micronutrients either singly or combined versus placebo in heart failure patients were included. We conducted a search in different databases such as Medline from PubMed, Embase and Scopus from Elsevier, and Google Scholar. The keywords used in the search were "Heart Failure" and its cognates, "Micronutrient," "Minerals," and names of individual micronutrients.
Results: Out of 3288 titles and abstracts reviewed, only 11 trials comprising 529 individuals were found to be appropriate to be included in the final review. It was found that micronutrients, either single or combined, improved the health outcomes of heart failure patients by improving exercise tolerance, functional capacity, left ventricular function, flow-dependent dilation, and inflammatory milieu, thereby improving the quality of life of health failure patients. Certain micronutrients also normalized endothelial dysfunction.
Conclusion: Overall, this systematic review found sufficient evidence to support a large-scale trial on micronutrient supplementation in patients with heart failure.

1. Introduction

Heart failure (HF) is a chronic progressive disease which has a debilitating impact on an individual patient's life [1]. HF is defined as a syndrome with characteristic symptoms of shortness of breath, fatigue, fluid retention manifesting as pulmonary congestion and ankle edema, and abnormalities of either structure or function of the heart, even at rest [2]. Approximately 1–2% of the adult population in developed countries has HF, with the prevalence rising to 10% or higher among persons aged ≥ 70 years [3]. The prevalence of HF in India, based on disease-specific estimates due to coronary heart disease, hypertension, obesity, diabetes, and rheumatic heart disease, ranges from 1.3 million to 4.6 million with an annual incidence from 491,600 to 1.8 million [4]. The consequences of HF continue to increase with the age of our population [5], as it affects ~10% of those over 80 years old [6]. For HF patients, the age-adjusted mortality is from four- to eight-fold greater than that of the general population [7]. The main troublesome features of the condition are poor prognosis, persistently high readmission rates, and reduced quality of life [6].

HF is a clinical syndrome which can result from any disorder that impairs the ability of the ventricle to fill in or eject blood, therefore making the heart unable to pump blood at a rate sufficient to meet the metabolic demands of the body [8]. This systemic illness includes the presence of oxidative stress with reactive oxygen and nitrogen intermediates that overwhelm endogenous antioxidant defenses in diverse tissues such as the skin, skeletal muscle, heart, peripheral blood mononuclear cells (lymphocytes and monocytes) and blood, a proinflammatory phenotype with activated peripheral blood mononuclear cells and elevations in circulating chemokines and cytokines such as interleukin-6 and tumor necrosis factor-α, and a catabolic state with loss of soft tissues and bone in part due to a negative caloric and nitrogen balance that eventuates in a wasting syndrome termed cardiac cachexia [9]. According to Hippocrates "Dropsy (heart failure) is usually

Conflict of interest: none.

* Corresponding author. Department of Pharmacy Practice, RVS College of Pharmaceutical Sciences, 242-B Trichy Road, Sulur, Coimbatore 641401, Tamil Nadu, India. Tel.: +91 9894676716.
E-mail address: mail2samjohnson@gmail.com (S.J.U. Chander).

http://dx.doi.org/10.1016/j.tcmj.2016.08.001

produced when a patient remains for a long time with impurities in the body following a long illness. The flesh is consumed and becomes water. The abdomen fills with fluid; the feet and legs swell; the shoulders, clavicles, chest and thighs melt away."

Patients with HF may be more susceptible to the effects of micronutrient deficiency because of increased oxidative stress (requiring antioxidant protection), impaired skeletal muscle function (possibly exacerbated by vitamin D deficiency), and impaired myocardial contraction. Some severe micronutrient deficiencies can cause heart failure and, therefore, it is reasonable to expect that less severe deficiency may exacerbate existing cardiac dysfunction [10]. Specific micronutrient deficiencies can cause HF and patients with HF, usually elderly patients with other conditions, have a number of risk factors for micronutrient deficiency, as they have a poor general diet and are prone to excess urinary losses due to diuretic therapy [6]. Due to inadequate intake, altered metabolism, the proinflammatory state, increased oxidative stress, and increased nutrient loss, undernutrition can occur which results in lean body mass depletion (including vital organs such as the myocardium itself), with negative implications on functional capacity and increased postoperative complications and mortality [11].

The adult human heart pumps approximately 5 L of blood per minute at rest and up to 24 L/min during vigorous exercise, which is an extreme metabolic demand. Fatty acids are the predominant energy source. However, carbohydrates can also be easily utilized by the heart or both carbohydrates and fatty acids simultaneously. Adenosine triphosphate (ATP) is formed by converting these energy sources and is hydrolyzed by the heart to continue its pump function [12]. For this pumping function, it is estimated that over 6 kg of ATP is hydrolyzed by the heart daily. The enzymes, membranes, and structural elements of the heart undergo constant turnover and rebuilding to maintain this essential level of efficiency. The entire heart is reconstructed every 30 days with brand-new protein components using a steady supply of nutritional building blocks in the form of amino acids, lipids, and carbohydrates. With a system of interconnected cycles, as shown in Fig. 1, energy transfer in the beating heart can be visualized. The heart receives nutrients through circulation and transfers energy from nutrients to ATP, which in turn is used to support cyclic contractions. By either increasing or decreasing the rate of energy turnover, the system readily responds to environmental changes under normal conditions [13].

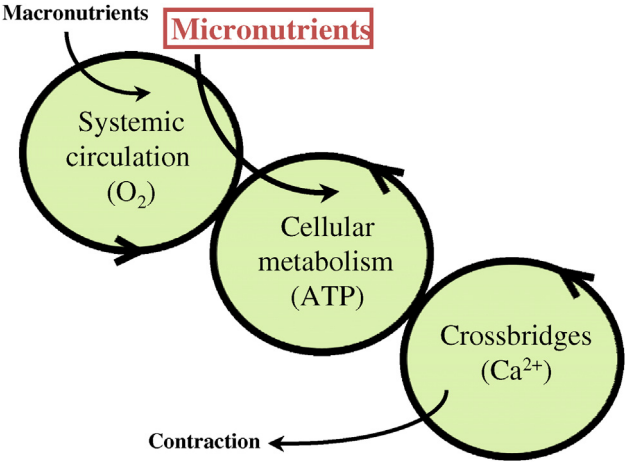

Fig. 1. Energy transfer in a beating heart. ATP = adenosine triphosphate. *Note*. From "Micronutrient deficiencies an unmet need in heart failure" by Victor Soukoulis et al, 2009, *Journal of the American College of Cardiology*, 54, p. 1660–73. Copyright 2009, *Name of Copyright Holder*: Dr. Heinrich Taegtmeyer, Department of Internal Medicine, Division of Cardiology, University of Texas Houston Medical School, 6431 Fannin, MSB 1.246, Houston, Texas 77030. E-mail: Heinrich.Taegtmeyer@uth.tmc.edu. Reprinted with permission.

Nutrition is an important element of health in the older population and affects the aging process [14]. Nutrients are those substances that the body uses to produce energy, to provide building blocks for new molecules, and to function in chemical reactions. Nutrients can be divided into micronutrients, macronutrients, oxygen, and water. Protein, fat, and carbohydrates are the major organic nutrients or macronutrients and are broken down by enzymes into their individual components during digestion [15]. Micronutrients are any essential dietary components and are important trace elements required for growth, metabolism, and the normal functioning of the immune system [16,17]. A decreased intake of macronutrients and micronutrients contributes to the progression of HF. Therefore, not only should the risk factors of coronary heart disease be treated, but malnutrition and nutrient deficiencies should also be corrected [18]. Regardless of whether altered intake or metabolism is responsible, people with chronic disease and/or increased age may require more tailored nutrition than the general population to ensure proper nutrients for cellular repair and metabolism [19]. As HF progresses, nutrient therapy should be individualized according to a patient's particular requirements [20]. However, very little information on nutrition therapy is provided in the treatment guidelines for major heart failure. In the most recent guidelines by of the American Heart Association and American College of Cardiology Foundation, salt restriction was recommended for patients with current or prior symptoms of HF, reduced left ventricular ejection fraction, and evidence of fluid retention [21]. The Heart Failure Society of America provides some comprehensive recommendations on diet and nutrition in their most recent guidelines [22]. According to these guidelines, nutrition assessment and energy supplementation are recommended in patients with advanced HF and muscle wasting. These guidelines also suggest that all patients with HF should be considered for daily evidence-based multivitamin–mineral supplementation, particularly those receiving diuretic therapy or restricted diets. Hence, the present article tries to review the data connecting micronutrients and heart failure. The primary aim of this review is to understand the availability of evidence for and against the use of micronutrients in patients with HF.

2. Materials and Methods

2.1. Search strategy

An extensive search was conducted to select randomized controlled trials that evaluated the utility of different micronutrients in patients with congestive heart failure (CHF). The databases used in the search were Medline from PubMed, Embase and Scopus from Elsevier, and Google Scholar. The keywords used in the search were "Heart Failure" and its cognates, "Micronutrient," "Minerals," and names of individual micronutrients. The inclusion/exclusion criteria for the selection of trials are shown in Fig. 2.

2.2. Recovery of trials

Our initial search returned 3288 articles out of which 143 potentially relevant articles were identified. Potentially eligible studies were identified by one author by screening titles and abstracts by applying the search keywords. All trials were then assessed independently by two authors and potentially relevant studies were selected according to predefined inclusion criteria (Table 1). Any disagreement was reviewed and resolved by the third independent reviewer. Authors of individual trials were contacted if necessary. After reviewing the abstracts, 62 articles did not meet the inclusion criteria and were excluded from the study. Out of 81 articles that met inclusion criteria, 70 trials did not have enough

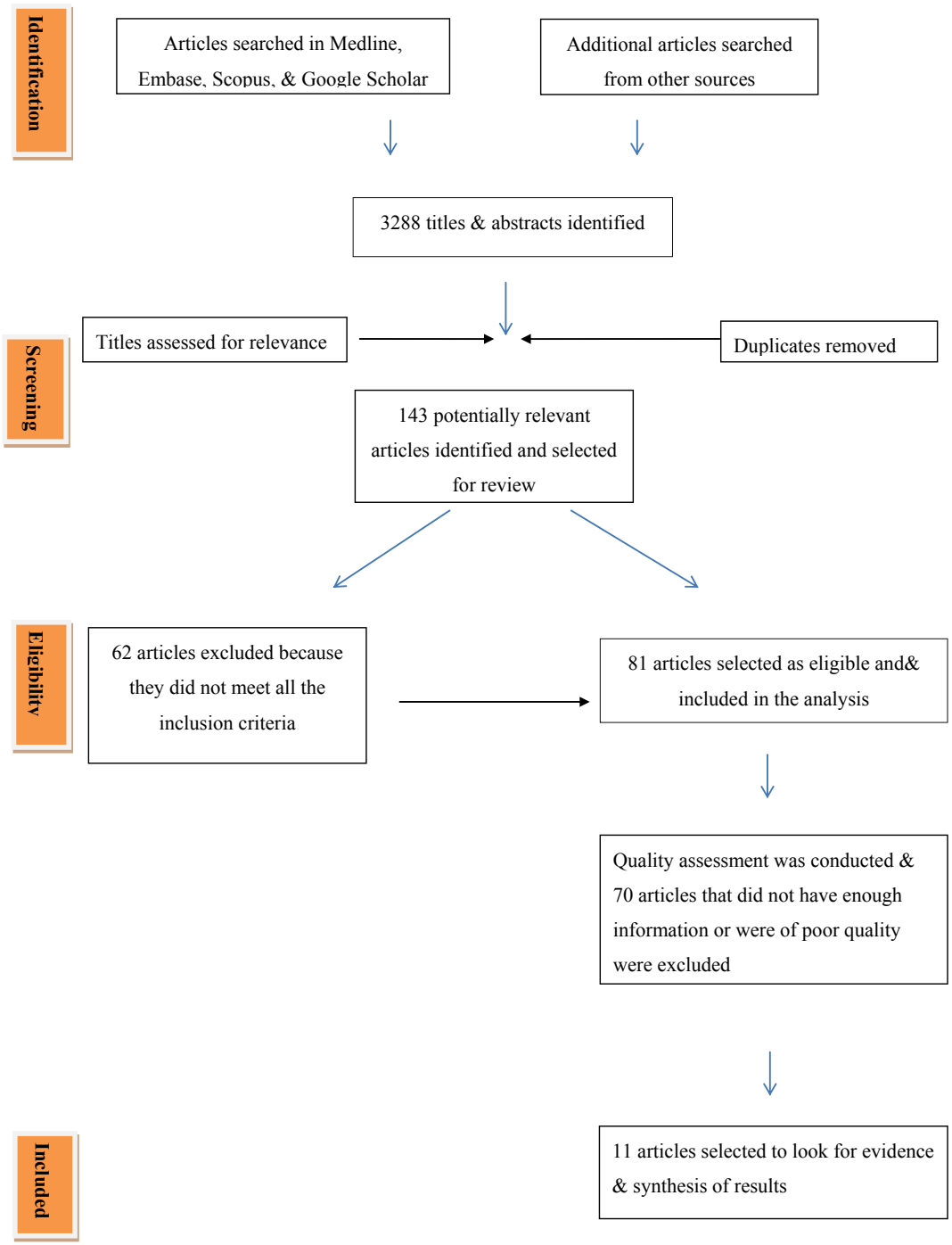

Fig. 2. Flowchart of the article selection process.

information or had poor methodological quality and were excluded. Only 11 trials were included in the final review and synthesis of results.

2.3. Data abstraction and study appraisal

We extracted the following general data from each study: country of origin, year of publication, number of randomized patients per each treatment arm, sex ratio, mean age in years, duration of symptoms, micronutrients used in the trial, dose of each micronutrient, duration of follow up, and outcomes of the study. The primary outcome of interest was the impact of micronutrients on the ejection fraction. Secondary outcomes were the impact of micronutrients on improvement in left ventricular function, exercise capacity, and functional capacity of the patients.

2.4. Methodological quality of included trials

The methodological quality of the trials was assessed based on methods of randomization, allocation concealment, sample size calculation, blinding, and loss to follow up. The letters A through E were used to indicate the quality of the methods used in the trial.

Table 1
Inclusion and exclusion criteria for the selection of studies to review.

Inclusion criteria:
1. Studies that reported micronutrient intake in CHF patients, any age, without date limits.
2. Publications reporting the use of micronutrients either singly or combined in CHF patients.
3. Publications having randomized controlled trials as their study design.
4. Publications for which peer review was conducted.

Exclusion criteria:
1. Studies published in languages other than English or studies for which English translation is not available.
2. Studies in animals.
3. Health conditions that may influence dietary intake (i.e., gestational diabetes, celiac disease, malnutrition, etc.).
4. Studies done in virtual populations.
5. Studies without a random sample.

CHF = congestive heart failure.

For methods of randomization, trials were rated as follows: appropriate randomization procedure (A), inappropriate randomization (B), or unclear (C). Allocation of concealment was rated as: concealed appropriately (A), not concealed (B), or unclear (C). Blinding was rated as: double-blind (A), single blind (B), no blinding (C), or unclear (D). Sample size calculation was assessed as: appropriate calculation procedure (A), inappropriate calculation (B), or unclear (C). The drop-out rate (loss to follow-up) was assessed as: $\leq$ 5.0% (A), 5.1–10.0% (B), 10.1–15.0% (C), > 15.0% (D), or unclear (E) [23].

3. Results

The 11 included studies were classified into trials that included only a single micronutrient and those that included multiple micronutrients, as shown in Table 2.

3.1. Primary and secondary outcomes

Tables 3 and 4 summarize results from all 11 studies. Only eight trials had clearly defined primary and secondary outcomes of interest [10,24–27,31–33]. In the remaining three trials, the reported outcome measures were mostly reduction of inflammatory milieu, improvement in flow-dependent dilation, and normalization of endothelial dysfunction and carbohydrate metabolism [28–30].

Table 2
Details of included studies.

Ref	Country	*N*	Sex ratio (F:M)	Mean age (y) ± SD	Duration of symptoms	Intervention	Follow-up (mo)
[24]	Italy	13	2:11	59 ± 14	HF for ≥ 6 mo in NYHA class II or III, with an ejection fraction 45%	Single micronutrient	3
[25]	Germany	15	1:14	61 ± 6	Unclear	Single micronutrient	6
[26]	Italy	23	3:20	59 ± 9	Unclear	Single micronutrient	Unclear
[27]	United Kingdom & Poland	35	10:25	63 ± 12	Unclear	Single micronutrient	16
[28]	United Kingdom	70	15:55	57 ± 2	Unclear	Single micronutrient	Unclear
[29]	Germany	15	Unclear	59 ± 4	Unclear	Single micronutrient	1
[30]	Ukraine	98	Unclear	Unclear	Unclear	Single micronutrient	Unclear
[31]	Germany	123	21:102	55 ± 3	Unclear	Single micronutrient	15
[32]	Iran	64	10:54	63 ± 8	Unclear	Multiple micronutrients	3
[10]	United Kingdom	32	Unclear	75 ± 4	Unclear	multiple micronutrients	25
[33]	Canada	41	Unclear	65 ± 8	Unclear	Multiple micronutrients	Unclear

F = Female; M = Male; *N* = number of patients in each treatment arm; NYHA = New York Heart Association; SD = standard deviation.

Table 3
Results of studies analyzing the effectiveness of single micronutrient on heart failure patients.

Ref	Y	Intervention	Dose	*N*	Primary & secondary outcomes					
					EF	ET	FC	LVSF	QOL	Others
[24]	2014	Amino Acid L-Leucine L-Lysine L-Isoleucine L-Valine L-Threonine L-Cystine L-Hystidine L-Phenylalanine L-Methionine L-Tyrosine L-Triptophan	4 g 1250 mg 650 mg 625 mg 625 mg 350 mg 150 mg 150 mg 100 mg 50 mg 30 mg 20 mg	13	Y	Y	Y	No	No	Peak VO_2, VO_2 at anaerobic threshold improved significantly, reduction of NT-proBNP levels
[25]	2003	D-Ribose	5 g	15	Y	Y	No	No	Y	Enhances diastolic function
[26]	2006	Coenzyme Q10	100 mg	23	Y	No	Y	No	No	Improves endothelial function, LV contractility
[27]	2008	Iron	200 mg	35	Y	Y	No	No	Y	Improved exercise capacity & symptoms
[28]	2000	Vitamin C	2 g twice daily	70	No	No	No	No	No	Reduces oxidative stress, increases flow-mediated dilation
[29]	1998	Vitamin C	25 mg/min IA	15	No	No	No	No	No	Improves endothelial function
[30]	2013	Magnesium	1000 mg 3 times/d	98	No	No	No	No	No	Normalizes endothelial dysfunction & carbohydrate metabolism
[31]	2006	Vitamin D	50 g Vitamin D3	123	No	No	No	Y	No	Anti-inflammatory agent, suppress serum PTH

EF = ejection fraction; ET = exercise tolerance; FC = functional capacity; LVSF = left ventricular systolic function; *N* = number of patients in each treatment arm; NT-proBNP = N-terminal pro b-type natriuretic peptide; PTH = parathyroid hormone; QOL = quality of life; Y = yes.

Table 4
Results of studies analyzing effectiveness of multiple micronutrients on heart failure patients.

Ref	Y	Intervention/dose	*N*	Primary & secondary outcomes					
				EF	ET	FC	LVSF	QOL	Others
[32]	2015	Selenium 200 μg & Coenzyme Q 30 mg	64	Y	No	No	Y	No	Improvement of NYHA classes
[10]	2005	Calcium 250 mg Magnesium 150 mg Zinc 15 mg Copper 1.2 mg Selenium 50 mg Vitamin A 800 mg Thiamine 200 mg Riboflavin 2 mg Vitamin B6 200 mg Folate 5 mg Vitamin B12 200 mg Vitamin C 500 mg Vitamin E 400 mg Vitamin D 10 mg Co-enzyme Q10 150 mg	32	Y	No	No	Y	Y	
[33]	2002	MyoVite per 250 mL contains: Energy 200 kcal Protein 15 g Carbohydrates 17.7 g Fat 7.8 g Carnitine 3.0 g Coenzyme Q10 150 mg Taurine 3.0 g Creatine 2.25 g Sodium 108 mg Potassium 750 mg; Chloride 203 mg Calcium 315 mg Phosphorus 183 mg Magnesium 20 mg Iron 1.0 mg Zinc 15 mg Copper 1.5 mg Manganese 3.0 mg Fluoride 1.0 mg Molybdenum 50 μg Selenium 50 μg Chromium 33 μg Iodine 100 μg Retinol ester 688 μg Cholecalciferol 5 μg α-Tocopherol acetate 538 mg Thiamin 25 mg Riboflavin 3.0 mg Niacin 20 mg Pantothenate 4.0 mg Pyridoxine 6.0 mg Folate 600 μg Cyanocobalamin 3.0 μg Biotin 100 μg Ascorbate 250 mg	41	Y	No	No	No	No	Reduction in left ventricular end-diastolic volume in patients

EF = ejection fraction; ET = exercise tolerance; FC = functional capacity; LVSF = left ventricular systolic function; *N* = number of patients in each treatment arm; NYHA = New York Heart Association; QOL = quality of life; Y = yes.

3.2. Methodological quality of trials

Table 5 summarizes the quality of the 11 studies. There was a 70% loss to follow up in one study [33] and 25% loss to follow up in another [31]. It was unclear how randomization was carried out in four of the trials [24,28–30]. There were no data available on how allocation concealment was done in any of the studies and it was unclear how blinding was done in six trials [24,26–30].

Table 5
Methodological quality of studies included in the review.

Ref	Y	Randomization	Allocation concealment	Sample size calculation	Blinding	Lost to follow-up
[24]	2014	C	C	C	D	E
[25]	2003	A	C	C	A	E
[26]	2006	A	C	C	D	A
[27]	2008	A	C	C	D	C
[28]	2000	C	C	C	D	E
[29]	1998	C	C	C	D	E
[30]	2013	C	C	C	D	E
[31]	2006	A	C	C	A	D
[32]	2015	A	C	A	A	A
[10]	2005	A	C	C	A	E
[33]	2002	A	C	C	A	D

A = XX; B = XX; C = XX; D = XX; E = XX.

3.3. Heterogeneity of trials

All 11 trials were heterogenous in that they had various inclusion and exclusion criteria and different treatment protocols, which are shown in Tables 2 and 3. The investigated micronutrients were amino acids by Lombardi et al [24], coenzyme Q10 (CoQ10) by

Belardinelli et al [26], ribose by Omran et al [25], iron by Okonko et al [27], magnesium orotate by Krapivko and Omelchenko [30], selenium by Garakyaraghi et al [32], vitamin C by Ellis et al [28], and vitamin D by Schleithoff et al [31]. In the remaining three trials, various combinations of micronutrients were investigated [10,32,33].

3.4. Micronutrients versus no micronutrients

All 11 trials compared the use of micronutrients versus no micronutrients in HF patients. The most commonly used outcome measure was the ejection fraction (EF), which was used in four trials of single micronutrients and three trials of multiple micronutrients. Hence, the mean EF was used as a single parameter to assess the effectiveness of micronutrients in HF patients. The mean EF increased 2% from baseline after iron supplementation, 6% after using CoQ10, 1% after amino acid use, and 1% after D-ribose use. This is depicted in Fig. 3.

In trials using multiple micronutrients, the trial by Jeejeebhoy et al [33], documented a 0.9% increase in mean EF from baseline after treatment compared with a 3.7% increase in the trial by Garakyaraghi et al [32], and a 5.3% increase in the trial of Witte et al [10]. This is illustrated in Fig. 4.

4. Discussion

The data obtained from this review show that many micronutrients including amino acids have a significant role in improving the disease outcome in HF patients. It is evident that different micronutrients display various mechanisms to arrive at this outcome. In HF patients, there is a reduced availability of amino acids leading to abnormalities in cardiac and skeletal muscle metabolism and eventually to a reduction in functional capacity and quality of life [24]. In cardiac metabolism, amino acids play a dual role. They act both as “building blocks” of proteins and are intermediary metabolites in energy substrate metabolism. Taurine

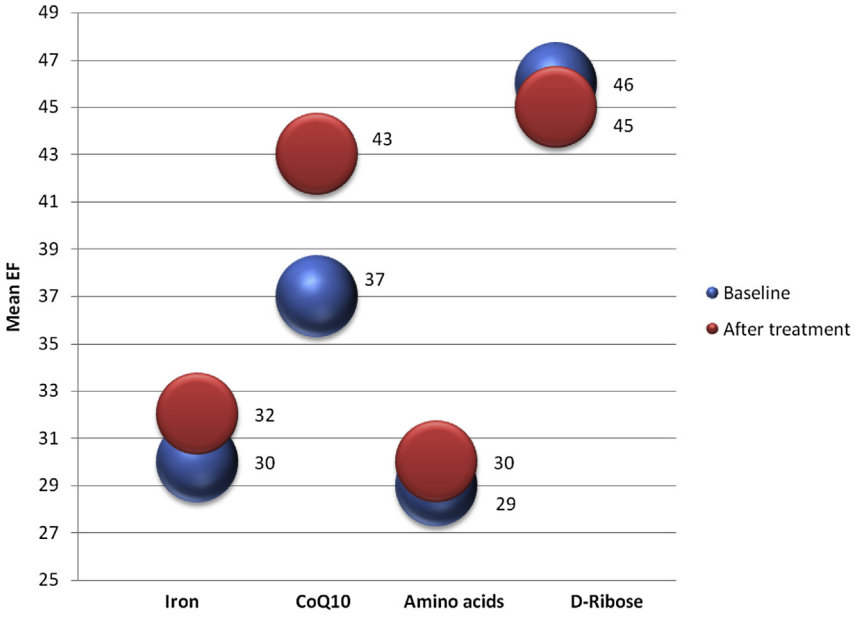

Fig. 3. Mean decrease in ejection fraction (EF) in four trials using a single micronutrient. CoQ10 = coenzyme Q10.

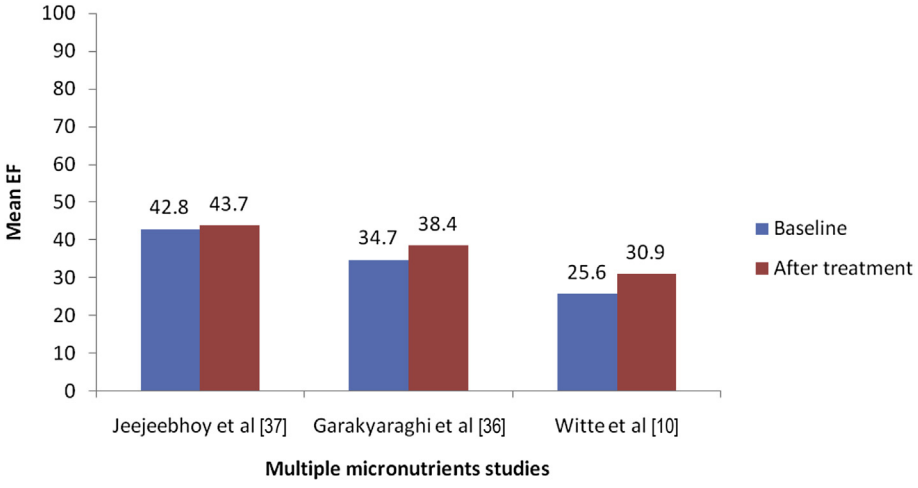

Fig. 4. Mean decrease in ejection fraction (EF) in three trials using multiple micronutrients.

comprises 25% of the cardiomyocyte amino acid pool in humans and can be synthesized from methionine or cysteine, and, as such, is not an essential amino acid. It is an antioxidant and is an important endogenous regulator of intracellular calcium homeostasis [13]. CoQ10, or ubiquinone, is an important component as a redox carrier in the mammalian respiratory transport [34] in mitochondria and serves as a carrier for electrons flowing through complexes I, II, and III. CoQ10 essentially helps in ATP formation in tissues, including the heart, skeletal muscle, brain, kidney, and liver [13]. As the myocardium of patients with HF demonstrates oxidative stress, CoQ10 prevents lipid peroxidation and thus prevents myocardial destruction. Therefore, it acts as an antioxidant scavenger. In HF patients, the concentration of CoQ10 decreases in myocardial cells and the extent of myocardial CoQ10 deficiency correlates with the clinical severity of HF [35]. Vitamin D is a prosteroid hormone [36], which plays an important role in the homeostasis of calcium, which in turn is a key player in cardiac contractility [13]. Witte et al [6] found deterioration of myocardial contraction when patients were given a diet low in vitamin D. Furthermore, after vitamin D supplementation, it was found that the myocardium returned to normal function.

A naturally-occurring pentose sugar, ribose, was shown experimentally to enhance the recovery of depressed myocardial ATP levels and improve myocardial diastolic compliance following ischemia. In cardiac metabolism, D-ribose aids by entering the pentose phosphate pathway to form ribose-5-phosphate and bypasses the rate-limiting enzymes of glucose-6 phosphate dehydrogenase and 6-phosphogluconate dehydrogenase. A reduced level of myocardial ATP leads to diastolic dysfunction [25].

A deficiency of magnesium, which is known to cause significant life-threatening ventricular arrhythmias and sudden death, can be treated with magnesium supplements. In addition, magnesium deficiency may cause myocardial fibrosis and platelet aggregation, thus explaining its overall adverse effect on cardiovascular mortality. Aldosterone, a harmful neurohormone (activated in HF), also increases urinary excretion of magnesium causing low serum magnesium. Thus, low serum magnesium may also be a marker of disease progression in HF [37].

There is documented evidence that deficiencies of CoQ10, B vitamins, and L-carnitine lead to a failing heart. Deficiency in potassium leads to arrhythmia in HF patients. Zinc is an antioxidant found to be deficient in HF, but there is no clear evidence of its association with progression of HF. Deficiency of selenium also leads to endothelial dysfunction and cardiomyopathy [13]. There is evidence that vitamin C inhibits endothelial cell apoptosis in CHF patients [38]. Hence, as in our study, almost all micronutrients play a major role in improving the health outcomes in HF patients.

A clinical trial using micronutrient therapy for HF patients is ongoing with the trial registration number NCT01005303. The study is ongoing so it was not included in this review.

5. Conclusion

Disturbances in minerals and micronutrients are an integral feature of HF and likely contribute to the progressive nature of this disease. These disturbances relate to reduced sunlight exposure and dietary calcium intake along with intake of loop diuretics and angiotensin converting enzyme inhibitors, which are standard in the care of HF patients today. Based on the set of studies included here, micronutrients appear to have a positive impact on the disease outcomes of HF patients. Based on the data presented here, we strongly feel that patients with HF need daily nutrient supplementation in addition to their habitual diet and regular pharmacological and nonpharmacological treatment.

References

[1] Lloyd-Jones D, Adams RJ, Brown TM, Carnethon M, Dai S, De Simone G, et al. Heart disease and stroke statistics—2010 update: A report from the American Heart Association. Circulation 2010;121:e46–215.

[2] Dickstein K, Cohen-Solal A, Filippatos G, McMurray JJV, Ponikowsk P, Alexander P, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). Eur Heart J 2008;29:2388–442.

[3] McMurray JJV, Adamopoulos S, Anker SD, Auricchio A, Böhm M, Dickstein K, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur Heart J 2012;33:1787–847.

[4] Huffman MD, Prabhakaran D. Heart failure: Epidemiology and prevention in India. Natl Med J India 2010;23:283–8.

[5] Krim SR, Campbell P, Lavie CJ, Ventura H. Micronutrients in chronic heart failure. Curr Heart Fail Rep 2013;10:46–53.

[6] Witte KK, Clark AL, Cleland JG. Chronic Heart Failure and Micronutrients. J Am Coll Cardiol 2001;37:1765–74.

[7] Kannel WB. Belanger. Epidemiology of heart failure. Am Heart J 1991;121: 951–7.

[8] Prajapatil SK, Daniel PS, Bhatt PA. Therapeutic role of antioxidants in heart failure. Int J Adv Pharm Res 2011;2:301–6.

[9] Alsafwah S, LaGuardia SP, Arroyo M, Dockery BK, Bhattacharya SK, Ahokas RA, et al. Congestive heart failure is a systemic illness: a role for minerals and micronutrients. Clin Med Res 2007;5:238–43.

[10] Witte KKA, Nikitin NP, Parker AC, von Haehling S, Volk H, Anker SD, et al. The effect of micronutrient supplementation on quality-of-life and left ventricular function in elderly patients with chronic heart failure. Eur Heart J 2005;26: 2238–44.

[11] Pinho CPS, da Silveira AC. Nutritional aspects in heart failure. J Nutr Health Sci 2014;1:1–11.

[12] Lee JH, Jarreau T, Prasad A, Lavie C, O'Keefe J, Ventura H. Nutritional assessment in heart failure patients. Congest Heart Fail 2011;17:199–203.

[13] Soukoulis V, Dihu JB, Sole M, Anker SD, Cleland J, Fonarow GC, et al. Micronutrient deficiencies an unmet need in heart failure. J Am Coll Cardiol 2009;54:1660–73.

[14] Ahmed T, Haboubi N. Assessment and management of nutrition in older people and its importance to health. Clin Interv Aging 2010;5:207–16.

[15] Pretorius SS. Food choices and macro- and micronutrient intake of sowetans with chronic heart failure [dissertation]. Stellenbosch: Stellenbosch University; 2011.

[16] von Haehling S, Doehner W, Anker SD. Nutrition, metabolism, and the complex pathophysiology of cachexia in chronic heart failure. Cardiovasc Res 2007;73:298–309.

[17] Ramkrishna J, Thiagarajah J. Micronutrient deficiencies. In: The Mass General Hospital for Children Handbook of Pediatric Global Health. New York: Spring-Verlag; 2014. p. 337–46.

[18] Pretorius S. The impact of dietary habits and nutritional deficiencies in urban African patients living with heart failure in Soweto, South Africa—A review. Endocr Metab Immune Disord Drug Targets 2013;13:118–24.

[19] Grossniklaus DA, O'Brien MC, Clark PC, Dunbar SB. Nutrient intake in heart failure patients. J Cardiovasc Nurs 2008;23:357–63.

[20] Barney B, Beck GR. Nutrition interventions in heart failure. Chapter 16. Manual of Heart Failure Management. New York: Spring-Verlag; 2009. p. 207–17.

[21] Jessup M, Abraham WT, Casey DE, Feldman AM, Francis GS, Ganiats TG, et al. 2009 Focused Update: ACCF/AHA Guidelines for the Diagnosis and Management of Heart Failure in Adults: A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: Developed in collaboration with the International Society for Heart and Lung Transplantation. JACC 2009;53:1343–82.

[22] Heart Failure Society of America, Lindenfeld J, Albert NM, Boehmer JP, Collins SP, Ezekowitz JA, et al. HFSA 2010 Comprehensive Heart Failure Practice Guideline. J Card Fail 2010;16:e1–194.

[23] Koh CE, Young CJ, Young JM, Solomon MJ. Systematic review of randomized controlled trials of the effectiveness of biofeedback for pelvic floor dysfunction. Br J Surg 2008;95:1079–87.

[24] Lombardi C, Carubelli V, Lazzarini V, Vizzardi E, Quinzani F, Guidetti F, et al. Effects of oral amino acid supplements on functional capacity in patients with chronic heart failure. Clin Med Insights Cardiol 2014;8:39–44.

[25] Omran H, Illien S, MacCarter D, St Cyr J, Lüderitz B. D-Ribose improves diastolic function and quality of life in congestive heart failure patients: a prospective feasibility study. Eur J Heart Fail 2003;5:615–9.

[26] Belardinelli R, Muçaj A, Lacalaprice F, Solenghi M, Seddaiu G, Principi F, et al. Coenzyme Q10 and exercise training in chronic heart failure. Eur Heart J 2006;27:2675–81.

[27] Okonko DO, Grzeslo A, Witkowski T, Mandal AK, Slater RM, Roughton M, et al. Effect of intravenous iron sucrose on exercise tolerance in anemic and nonanemic patients with symptomatic chronic heart failure and iron deficiency

FERRIC-HF: A randomized, controlled, observer-blinded trial. J Am Coll Cardiol 2008;51:103–12.
[28] Ellis GR, Anderson RA, Lang D, Blackman DJ, Morris RH, Morris-Thurgood J, et al. Neutrophil superoxide anion-generating capacity, endothelial function and oxidative stress in chronic heart failure: effects of short- and long-term vitamin C therapy. J Am Coll Cardiol 2000;36:1474–82.
[29] Hornig B, Arakawa N, Kohler C, Drexler H. Vitamin C improves endothelial function of conduit arteries in patients with chronic heart failure. Circulation 1998;97:363–8.
[30] Krapivko SO, Omelchenko AV. Magnesium orotate in the treatment of chronic heart failure. Available at: http://repo.knmu.edu.ua/handle/123456789/3354. [Accessed: August 7, 2016].
[31] Schleithoff SS, Zittermann A, Tenderich G, Berthold HK, Stehle P, Koerfer R. Vitamin D supplementation improves cytokine profiles in patients with congestive heart failure: A double-blind, randomized, placebo-controlled trial. Am J Clin Nutr 2006;83:754–9.
[32] Garakyaraghi M, Bahrami P, Sadeghi M, Rabiei K. Combination effects of selenium and coenzyme Q10 on left ventricular systolic function in patients with heart failure. Iranian Heart J 2015;15:6–12.
[33] Jeejeebhoy F, Keith M, Freeman M, Barr A, McCall M, Kurian R. Nutritional supplementation with MyoVite repletes essential cardiac myocyte nutrients and reduces left ventricular size in patients with left ventricular dysfunction. Am Heart J 2002;143:1092–100.
[34] Berman M, Erman A, Ben-Gal T, Dvir D, Georghiou GP, Stamler A, et al. Coenzyme Q10 in patients with end-stage heart failure awaiting cardiac transplantation: a randomized, placebo-controlled study. Clin Cardiol 2004;27:295–9.
[35] Khatta M, Alexander BS, Krichten CM, Fisher ML, Freudenberger R, Robinson SW, et al. The effect of coenzyme Q10 in patients with congestive heart failure. Ann Intern Med 2000;132:636–40.
[36] DiCarlo C, Schmotzer B, Vest M, Boxer R. Body mass index and 25 hydroxyvitamin D status in patients with and without heart failure. Congest Heart Fail 2012;18:133–7.
[37] Adamopoulos C, Pitt B, Sui X, Love TE, Zannad F, Ahmed A. Low serum magnesium and cardiovascular mortality in chronic heart failure: A propensity-matched study. Int J Cardiol 2009;136:270–7.
[38] Rössig L, Hoffman J, Hugel B, Mallat Z, Haase A, Freyssinet J, et al. Vitamin C inhibits endothelial cell apoptosis in congestive heart failure. Circulation 2001;104:2182–7.