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

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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 heart 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
produced when a patient remains for a long time with impurities in
the body following a long illness. The flesh is consumed and be-
comes 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 are 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].

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 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 multi-vitamin–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...
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.

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: 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        | Single micronutrient                | 3              |
| [25]  | Germany                  | 15 | 1:14            | 61 ± 6            | Unclear              | Single micronutrient                | 6              |
| [26]  | Italy                    | 23 | 3:20            | 59 ± 9            | Unclear              | Single micronutrient                | 9              |
| [27]  | United Kingdom & Poland  | 35 | 10:25           | 63 ± 12           | Unclear              | Single micronutrient                | 16             |
| [28]  | United Kingdom           | 70 | 15:55           | 57 ± 2            | Unclear              | Single micronutrient                | 1              |
| [29]  | Germany                  | 15 | Unclear         | 59 ± 4            | Unclear              | Single micronutrient                | 1              |
| [30]  | Ukraine                  | 98 | Unclear         | 21:102            | Unclear              | Single micronutrient                | 1              |
| [31]  | Germany                  | 123| 21:102          | 55 ± 3            | Unclear              | Single micronutrient                | 15             |
| [32]  | Iran                     | 64 | 10:54           | 63 ± 8            | Unclear              | Multiple micronutrients             | 3              |
| [33]  | United Kingdom           | 32 | Unclear         | 75 ± 4            | Unclear              | Multiple micronutrients             | 25             |
| [34]  | Canada                   | 41 | Unclear         | 65 ± 8            | Unclear              | Multiple micronutrients             | 4              |

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   | Year | Intervention | Dose | N  | Primary & secondary outcomes                                      | EF | ET | FC | LVSF | QOL | Others                                      |
|-------|------|--------------|------|----|---------------------------------------------------------------|----|----|----|------|-----|--------------------------------------------|
| [24]  | 2014 | Amino Acid   | 4 g  | 13 | Peak VO$_2$, VO$_2$ at anaerobic threshold improved significantly, reduction of NT-proBNP levels | Y  | Y  | Y  | No   | No  |                              |
| [25]  | 2003 | D-Ribose     | 5 g  | 15 | Enhances diastolic function                                  | Y  | Y  | No | No   | No  |                              |
| [26]  | 2006 | Coenzyme Q10 | 100 mg | 23 | Improves endothelial function, LV contractility              | Y  | No | No | No   | No  |                              |
| [27]  | 2008 | Iron         | 200 mg | 35 | Improved exercise capacity & symptoms                        | Y  | Y  | No | No   | No  |                              |
| [28]  | 2000 | Vitamin C    | 2 g twice daily | 70 | Reduces oxidative stress, increases flow-mediated dilation    | No | No | No | No   | No  |                              |
| [29]  | 1998 | Vitamin C    | 25 mg/min IA | 15 | Improves endothelial function                                | No | No | No | No   | No  |                              |
| [30]  | 2013 | Magnesium    | 1000 mg 3 times/d | 98 | Normalizes endothelial dysfunction & carbohydrate metabolism | No | No | No | No   | No  |                              |
| [31]  | 2014 | Vitamin D    | 50 g Vitamin D3 | 123 | Anti-inflammatory agent, suppress serum PTH                  | No | No | No | No   | No  |                              |

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.
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].

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

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**Table 4**

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

| Ref  | Y   | Intervention/dose                                                                 | N   | Primary & secondary outcomes                  |
|------|-----|----------------------------------------------------------------------------------|-----|-----------------------------------------------|
| [32] | 2015| Selenium 200 µg & Coenzyme Q 30 mg                                                | 64  | EF No No Y                                      |
|      |     | Calcium 250 mg Magnesium 150 mg                                                   |     | ET No No Y                                     |
|      |     | Zinc 15 mg                                                                        |     | FC Y No                                        |
|      |     | Copper 1.2 mg                                                                     |     | LVSF No                                        |
|      |     | Selenium 50 mg                                                                   |     | QOL No                                         |
|      |     | Vitamin A 800 mg                                                                  |     | Others Improvement of NYHA classes             |
| [10] | 2005| Calcium 250 mg Magnesium 150 mg                                                   | 32  | EF No No                                        |
|      |     | Zinc 15 mg                                                                        |     | ET No No                                       |
|      |     | Copper 1.2 mg                                                                     |     | FC No No                                       |
|      |     | Zinc 15 mg                                                                        |     | LVSF No                                        |
|      |     | Sodium 108 mg                                                                     |     | QOL No                                         |
|      |     | Potassium 750 mg; Chloride 203 mg                                                 |     |                                             |
| [10] | 2005| Calcium 315 mg                                                                    |     |                                             |
|      |     | Magnesium 20 mg                                                                  |     |                                             |
|      |     | Iron 1.0 mg                                                                       |     |                                             |
|      |     | Zinc 15 mg                                                                        |     |                                             |
| [33] | 2002| MyoVite per 250 mL contains:                                                      | 41  | EF No No                                        |
|      |     | Energy 200 kcal                                                                   |     | ET No No                                       |
|      |     | Protein 15 g                                                                      |     | FC No No                                       |
|      |     | Carbohydrates 17.7 g                                                             |     | LVSF Y                                         |
|      |     | Fat 7.8 g                                                                         |     | QOL No                                         |
|      |     | 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                                                 |     |                                             |
| [33] | 2002| Calcium 315 mg                                                                    |     |                                             |
|      |     | Magnesium 20 mg                                                                  |     |                                             |
|      |     | Iron 1.0 mg                                                                       |     |                                             |
|      |     | Zinc 15 mg                                                                        |     |                                             |
| [33] | 2002| 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                                                                   |     |                                             |

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.

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**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                      | D                       | E        |                  |
| [25] | 2003| A             | C                      | A                       | E        |                  |
| [26] | 2006| A             | C                      | D                       | A        |                  |
| [27] | 2008| A             | C                      | D                       | C        |                  |
| [28] | 2000| C             | C                      | D                       | E        |                  |
| [29] | 1998| C             | C                      | D                       | E        |                  |
| [30] | 2013| C             | C                      | D                       | E        |                  |
| [31] | 2006| A             | C                      | C                       | A        | D                 |
| [32] | 2015| A             | A                      | A                       | A        |                  |
| [33] | 2002| A             | A                      | A                       | E        |                  |

A – XX; B – XX; C – XX; D – XX; E – XX.
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...
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 prostehond hormone [36], which plays an important role in the osteological and nonpharmacological treatment.

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