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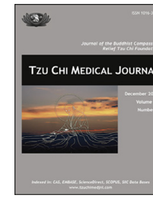

Original Article

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

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A R T I C L E I N F O

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A B S T R A C T

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 $\geq$ 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

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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].

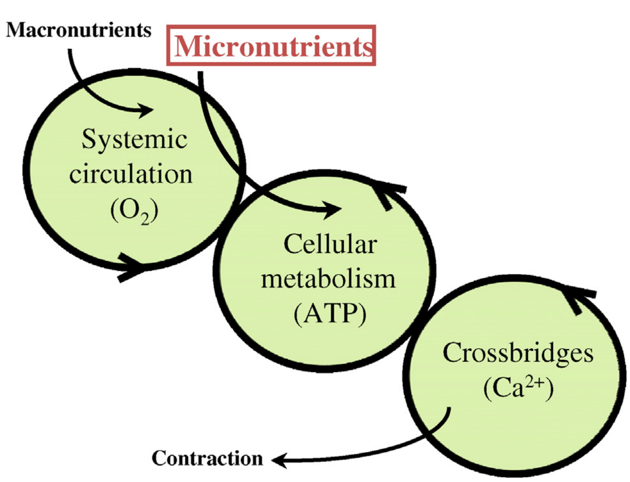

Fig. 1. Energy transfer in a beating heart. ATP = adenosine triphosphate. *Note*. From "Micronutrient deficiencies an unmet need in heart failure" by Victor Soukoulis et al, 2009, *Journal of the American College of Cardiology*, 54, p. 1660–73. Copyright 2009, *Name of Copyright Holder*: Dr. Heinrich 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