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Nutritional deficiency cardiomyopathy: A review and pooled analysis of pathophysiology, diagnosis and clinical management

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Abstract

The increasing recognition of deficiency of certain essential micronutrients in the failing heart suggests that they may be involved in the pathogenesis of nutritional deficiency cardiomyopathy (NDCM) and ultimately heart failure (HF). Chronic deficits in thiamine, carnitine, selenium, niacin, taurine and Coenzyme Q10 in the myocardial tissues have already been associated with alterations in myocardial energy production, calcium balance or oxidative defences. These pathologic changes may lead to metabolic or myocardial remodelling progressing into NDCM. Due to the severity of potential outcomes of untreated NDCM, it is important for cardiologists to have a good understanding of NDCM. More importantly, NDCM is a treatable phenotype of dilated or hypertrophic cardiomyopathy (CM). Early detection and prompt initiation of nutrient supplementation therapy (NST) has the potential to reverse pathologic myocardial changes and resolve cardiac symptoms. However, current expert consensus guidelines on the treatment of HF do not expressly recommend or are conspicuously silent about the use of NST possibly attributable to inconsistent findings by several small-scale trials and the lack of reliable data by large-scale randomized clinical trials. This review summarizes the existing published data about NDCM with an emphasis on the specific aetiologic micronutrients deficiencies, including their pathophysiology, manifestation, diagnosis and clinical management. This review also identifies gaps in current studies and areas of limited knowledge to move forward with research to fill these critical gaps in knowledge.

Introduction

Nutritional deficiency (ND) is an important cause of morbidity and mortality, particularly in resource-constrained countries. It is a direct cause of 300,000 deaths annually and indirectly involved in about 50% of all deaths in children [1]. Part of the indirect cause of death is the hypothesized involvement of ND in the pathogenesis of heart failure (HF) [2,3]. In healthy conditions, the human heart needs a continuous supply of energy-providing substrates such as carbohydrates, lipids, amino acids or ketone bodies to produce adequate energy to enable uninterrupted maintenance of the primary function of the heart as a pump. In cardiomyopathic patients, defects in myocardial substrate utilization and energy metabolism may contribute to abnormalities in the myocardial structure and contractile function [2]. Several micronutrients such as carnitine, thiamine, selenium, taurine and niacin are essential co-factors of metabolic reactions in the myocardium and contribute to efficient and appropriate energy utilization. Thus, genetic or acquired deficits in any one of these micronutrients has the potential to lead to specific forms of cardiomyopathies (CMs) [4-6].

Several studies on HF suggest the involvement of ND in the pathogenesis of heart diseases through the association of ND with the loss of muscle mass and function (sarcopenia) and/or loss of tissue mass (cachexia) [7-10], impaired cardiac energy metabolism, and persistently high morbidity and mortality rates despite significant advances in medical and device therapies [2-5]. Indeed, two decades since the introduction of the renin-angiotensin-aldosterone system (RAAS) antagonists, beta-blocker and device therapies, clinical outcomes in HF patients have significantly improved although the quality of life and functional capacity have remained poor especially for patients with advanced HF [3]. This may be partly attributable to the standardized HF treatment not fully addressing some unique cardiac requirements for energy [2-4]. A recent meta-analysis of 11 trials enrolling 529 HF patients suggested that correcting micronutrients deficiency might be a promising method to limit or even reverse progressive cardiomyocyte dysfunction and/or necrosis although clinical efficiency of such nutritional intervention remains unclear [4]. This review summarizes the existing literature on ND in cardiomyopathic patients focusing on the evidence regarding specific micronutrients and their pathophysiological role in the development of CM, diagnosis, clinical presentation and management.

Nutritional deficiency

The World Health Organization (WHO) defines nutritional deficiency (also known as malnutrition) as the cellular imbalance between the supply of nutrients and energy, and the body's demand for them to ensure growth, maintenance and execution of other essential body's functions [11]. Throughout medical history, several nutrient deficient states have been identified as an aetiology of CMs raising the question of whether the imbalance of micronutrients such as selenium, thiamine or carnitine can provide the milieu for inefficient energy expenditure and cardiac metabolism in the context of CM [12,13]. To

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date, there is a paucity of evidence in CM and HF literature to confirm this theory. Nevertheless, numerous studies strongly suggest a link between ND, and inefficient energy expenditure and the development of HF. The 2016 scientific statement by American Heart Association on specific forms of dilated cardiomyopathy (DCM) does not classify ND as a specific aetiology of DCM but recognizes its role in the pathogenesis of HF and recommends its exclusion of in the differential diagnosis of certain specific forms of DCMs especially in areas where malnutrition is endemic [14]. Numerous studies based on animal models have already demonstrated genetic-induced micronutrient deficiencies in HF and nutritional or pharmacological correction of these deficiencies has the potential to improve cardiac function [15-21].

Normal cardiac metabolism

In a significant proportion of patients with HF, the heart has a deficit of key micronutrients or nutrient co-factors [7,22-26]. This is despite having adequate cardiac energy because coronary circulation continually provides more substrates than the rate of utilization. Indeed, HF mostly appears to be the consequent of impaired substrate metabolism [27]. The turnover of adenosine triphosphate [ATP] (the main source of cardiac energy) in the failing myocardium may be reduced by up to 30% although whether this reduction is the cause or consequence of HF remains unclear [28]. Under stressful conditions such as in HF, the heart reverts to the foetal gene program, switching from the dominant fatty acid metabolism to the more efficient carbohydrate metabolism to limit additional injury to the myocardium [29-34]. Infants have a decreased ability to biosynthesize carnitine and taurine, and for this reason, these micronutrients are often included in infant formulas but the involvement of foetal gene program in the deficits of carnitine and taurine in HF remains unknown [2]. In HF, pathologic alterations occur at all stages of the production and transfer of energy in the heart: substrate utilization, oxidative phosphorylation and ATP utilization [27]. Inadequate energy conversion in overworked cardiomyocytes may result in cell injury or death mediated by oxidative stress, resulting in mitochondrial damage and cytochrome C release. It also makes the injured myocardium more susceptible to ischemia, accelerating the process of HF [13,35]. Inadequate micronutrients may be intensified by medical interventions such as cholesterol-lowering HMG-CoA reductase inhibitors exacerbate present nutritional deficiency and limiting long-term treatment success [36-41]. However, plasma concentration of micronutrient compounds may not reflect tissue levels because of large transmembrane cellular gradients [42-46].

Micronutrients deficiency associated with cardiomyopathy

Although the deficiencies of many micronutrients can cause CM, the most clinically important ones are coenzyme Q10 (CoQ10), thiamine, carnitine, taurine, selenium, and niacin. These six are (i) essential components for metabolic pathways involved in energy production, myocardial calcium balance or oxidative defences; (ii) have significantly reduced levels in HF patients; (iii) deficits in any one of them can result in cardiac pathology; and (iv) supplementation therapy can reserve their pathological effects on the myocardium [18,47,48].

Thiamine deficiency: Thiamine (or vitamin B_1) is a water-soluble vitamin playing an important role as a co-enzyme in the carbohydrate metabolism as well as produces essential glucose for energy. In the presence of magnesium and ATP, the body converts thiamine into thiamine pyrophosphate through the actions of the enzyme thiamine pyrophosphokinase [49]. Thiamine pyrophosphate is the metabolically active form of thiamine, which serves as a co-factor for the pyruvate dehydrogenase complex and for transketolase, which are both key mediators of energy substrate metabolism. Thus, a deficit in thiamine may causes a decrease in ATP production and an increased in cellular acidosis on a metallic level [50]. The human body stores thiamine in small quantities and cannot be produced endogenously although adequate nutritional intake through a diet of whole grains, legumes and nuts or supplements has been demonstrated to be useful in preventing thiamine deficiency [13].

Thiamine deficiency leads to various clinical manifestations due to resulting dysfunction of the nervous or the cardiovascular (CVD) system. Wet or cardiac beriberi is the clinical condition characterized with severe thiamine deficiency and CVD involvement while a deficit of thiamine with nervous system involvement is termed dry beriberi [51]. Cardiac beriberi or thiamine deficiency CM is a chronic disease characterized by peripheral vasodilation leading to fluid retention through the activation of the renin-angiotensin system and ultimately the development of high-output HF. Wet beriberi is more prevalent in resource-constrained countries whereas in resource-rich countries, the most frequently encountered cases are mild to moderate thiamine deficiency in HF patients [2]. Due to its rarity in resource-rich countries, it is often a missed diagnosis. However, the presence of undernourished dietary history and chronic alcohol intake can raise the clinical suspicion of thiamine deficiency CM. Studies of animal models demonstrate that thiamine deficiency can lead to cardiac dysfunction, hypertrophy and arrhythmias in the absence of beriberi [52-60]. In HF patients, thiamine deficiency affects between 13% and 93% [61-68], with a more severe cardiac manifestation in patients with New York Heart Association (NYHA) functional class III-IV compared to NYHA class I or II [61].

Besides, genetic and dietary causes, furosemide therapy, common in beriberi patients with HF, may precipitate or even aggravate thiamine deficiency through increasing the urinary excretion of thiamine [61,62]. Patients with HF often have an increased need for thiamine mainly because of inadequate nutritional levels compared with controls [61]. In a study of 100 hospitalized HF patients, thiamine deficiency appears to respond to oral supplementation as little as 1.5 mg per day [61]. In a randomized clinical trial of 30 HF patients receiving furosemide and thiamine 200 mg/day or placebo, thiamine levels increased with significant improvement in diuresis and LV systolic function [69]. Although the evidence on thiamine supplementation is inconsistent, the known cardiac effect of thiamine on the heart suggests that pharmacological repletion of thiamine may be of therapeutic benefit if examined on a larger HF trial.

Currently, the diagnosis of thiamine deficiency CM is by exclusion. Definitive diagnosis rests on three main factors: (i) the identification of clinical symptoms related to HF and characteristic history of dietary inadequacy in combination with excessive alcohol intake; (ii) the exclusion of other known aetiologies of heart disease; and (iii) a positive therapeutic response to pharmacological thiamine repletion [70,71]. Although the diagnostic process appears to be straightforward, it is frequently difficult to draw a definitive conclusion of thiamine deficiency CM because clinical manifestations are not usually pathognomonic [72,73]. Even with the support of contemporary non-invasive cardiac imaging modalities such as echocardiography and cardiac magnetic resonance imaging (MRI), diagnosis of thiamine deficiency CM is often missed in resource-rich countries largely due to very low incidence of the disease [74]. Due to widespread use, ease of use, rapidity and non-invasive nature, transthoracic echocardiography is considered the imaging modality of choice in both the initial and follow-up evaluation of a variety of CMs. Typical echocardiographic

findings for thiamine deficiency CM include LV enlargement with or without reduced function and can be accompanied by valvular dysfunction. Empiric therapy with thiamine could be a reasonable option due to non-specific cardiac imaging findings and the lack of real-time lab data [74]. However, since these findings are very similar to those of other forms of DCM, echocardiography evaluation alone cannot establish the diagnosis of thiamine deficiency CM [72-74].

Besides echocardiography, recent studies suggest the potential role of cardiac MRI in the diagnosis of thiamine deficiency CM on the basis that the myocardial disease has characteristic cardiac MRI findings such as decreased LV ejection fraction (LVEF) with LV enlargement, global LV hypokinetic motion and increased T2-weighted signal intensity due to myocardial oedema [75,76]. However, myocardial oedema in the absence of LV systolic function is not a specific finding of thiamine deficiency CM since it is not always present in the affected patients [71]. In addition to diagnostic confirmation, cardiac MRI can be useful for the exclusion of other known causes such as ischemic CM instead of using invasive angiography. However, the absence of pathognomonic features in both echocardiography and cardiac MRI places emphasis on the need for thorough history taking to identify a patient's history of chronic alcoholism and insufficient dietary nutritional intake to confirm diagnosis [71].

Laboratory findings are also useful to confirm thiamine deficiency. Serum levels of thiamine pyruvate, alpha-ketoglutarate, lactate, glycosylate or urinary excretion of thiamine and its metabolites can be measured to support and confirm diagnosis. The scarcity of any of these may help confirm diagnosis of thiamine deficiency. However, the assessment of these chemicals is both cost- and time-consuming and can potentially delay diagnosis and treatment. Therefore, for these clinical reasons, thiamine repletion as a therapeutic trial is considered the most feasible approach. If the patient responds favourable to empirical thiamine repletion therapy, it is safe to conclude that the CM is primarily the consequence of thiamine deficiency. The non-toxic nature of thiamine even at high blood levels supports the approach of thiamine repletion as a therapeutic trial [71]. Moreover, there is virtually no downside to empiric treatment in thiamine deficiency patients with normal renal function since kidneys can rapidly eliminate excess thiamine [70]

Carnitine deficiency: Carnitine (also known as beta-hydroxy-gamma-trimethylaminobutyric acid) is a naturally occurring hydrophilic amino acid derivative produced endogenously in the kidneys and liver or derived from meat and dairy products in the diet. Normal human omnivores (non-vegetarians) derive about 75% of carnitine from the diet while the rest is produced endogenously [77]. Carnitine is eliminated through urine as free carnitine and acylcarnitine although more than 95% is filtered in the kidney and re-absorbed by the proximal tubules in a process that regulates the homeostatic balance of carnitine in the body [78]. Carnitine is a co-factor in the transport of long chain fatty acid into the mitochondria for subsequent beta-oxidation as well as plays a role in glucose metabolism by reversing the inhibition of pyruvate dehydrogenase, allowing for better coupling between glycolysis and glucose oxidation [79,80]. Long-chain fatty acids is the dominant energy substrate for the myocardium and other muscle tissues but cannot diffuse freely in the mitochondria. Thus, deficiency of carnitine blocks mitochondrial oxidation of fatty acids to carbon dioxide in all tissues and to ketones in the liver resulting into accumulation in the cytosol [79-81]. Since cardiac muscle (and skeletal muscle) depend on fatty acid oxidation for most of their energy, deficiency of carnitine has a severe effect on these tissues [82].

The two distinct clinical forms of carnitine deficiency are primary and secondary deficiency. Primary carnitine deficiency (also known as carnitine uptake defect, carnitine transported defect or systemic carnitine deficiency) is an autosomal recessive disorder of the carnitine cycle that leads to defective fatty acid oxidation [78,83,84]. It is the consequence of heterogeneous mutations in the SLC22A5 gene encoding high-affinity carnitine transporter in the plasma membrane, which is strongly expressed in the myocardium, skeletal muscle, renal tubules, intestine and placental tissues. These mutations usually result in urinary carnitine wasting, low serum carnitine levels and decreased intracellular carnitine accumulation. The clinical symptom consists of episodes of hypoketotic hypoglycemia, hepatomegaly, muscle weakness and CM with HF [78]. Secondary carnitine deficiency is either hereditary or acquired as a consequence of a number of organic acidemias, defects of fatty acid oxidation and the carnitine cycle. Carnitine deficiency can also occur as a result of liver disease, renal disease, premature birth, dietary insufficient and drug therapy [85].

Cardiomyopathy with or without skeletal muscle weakness is the most common manifestation of carnitine deficiency, which includes DCM and hypertrophic cardiomyopathy (HCM) with a higher incidence of DCM in children [78]. An earlier study reported a severe form of familial DCM similar to endocardial fibrosis secondary to systemic carnitine deficiency. Post-mortem histological findings reveal massive lipid accumulation with endocardial fibrosis in both ventricles [86]. In a review of clinical features of 20 infants and children with defective carnitine uptake, progressive CM occurred in 60% of the patients with average age of presentation at 2-4 years of age suggesting a longer period for severe cardiac and skeletal muscle to manifest. Infants have a reduced ability to biosynthesize L-carnitine but whether the foetal gene program contributes to this deficit in HF remains unclear [13]. The affected children are normal at birth and may be asymptomatic for several years until overt signs of CM and HF develop. Cardiac function in non-responsive to inotropes or diuretics, and if not correctly diagnosed and without treatment using carnitine supplementation initiated, the disease progresses to HF and eventually to death [78]. Although carnitine deficiency CM is frequent in infantile patients, there are cases of adult onset. In Faroe Islands that has the highest prevalence of carnitine deficiency, 76 adult patients diagnosed with carnitine deficiency were asymptomatic with normal cardiac morphology and function [87].

Definitive diagnosis of carnitine deficiency CM rests on the measurement of plasma carnitine concentration or mutation analysis for defective gene. Significantly reduced carnitine plasma concentration suggests carnitine deficiency. Carnitine deficiency can also be confirmed by mutation analyses of the SLC22A5 gene [84]. Echocardiographic finding of cardiac involvement in carnitine deficiency are usually non-specific with inconsistent findings across studies. Some patients may present with characteristics of DCM while some with features of HCM [88-91]. In a study of six patients with primary carnitine deficiency, Wang et al. [84] reported typical echocardiographic characteristics of carnitine deficiency CM differ with those of DCM or HCM. They include LV enlargement accompanied with decreased LVEF, co-existent with myocardial thickening, as well as thickening of trabecular and mitral valve papillary muscles. Although interventricular septum and ventricular walls may be clearly hypertrophic, the extent of thickening is less than that observed in HCM with no obstruction of the LV outflow tract. These echocardiographic findings support the hypothesis that carnitine deficiency and defective oxidation of fatty acids initially causes the accumulation of fat in the myocardium resulting in ventricular hypertrophy. As the disease progresses, the LV becomes

impaired and dilated. The key to diagnosis is thus the measurement of plasma carnitine [84].

The approved treatment of carnitine deficiency CM is carnitine supplementation, which can lead to dramatic resolution of severe HF within a short period thereby altering the naturel history of the disease and reducing or eliminating signs of CM [79]. The Food and Drug Administration was the first to approve carnitine at 100 to 400 mg/kg/day during life-threatening events while carnitine 100 to 300 mg/kg/day administered orally recommended for chronic cases [92]. The multicentre trial, CEDIM (Carnitine Ecocardiografia Digitalizzata Infarto Miocardico) study, show the benefit of carnitine on cardiac remodelling after myocardial infarction [93]. Carnitine supplementation is also associated with increased exercise capacity, maximum exercise time, peak heart rate and peak oxygen consumption [94-97]. Hemodynamic and echocardiographic studies on the effects of carnitine supplementation therapy reveal reduced pulmonary artery pressure, LV systolic, diastolic, left atrial and end-diastolic dimensions [95] as well as improvement in LVEF, although inconsistently reported [95,97]. One trial suggested carnitine supplementation shows promising results in improving mortality demonstrating improvement in 3-year survival in DCM patients in NYHA functional class III to IV [98]. However, carnitine supplementation therapy warrants further study in CM and HF patients to determine its precise therapeutic value and the effect on clinical hard endpoints such as death and hospitalization.

Selenium deficiency: Selenium is a trace element present as selenocysteine residue at four catalytic sites in the enzyme glutathione peroxidase. Selenium content in adults is estimated at 6 mg varying between 3 mg and 14 mg reflecting the profound influence of the natural environment on selenium contents of soils, crops and human tissues. In the human body, selenium occurs in the muscle (30%), liver (30%), kidney (15%) and blood plasma (10%) [99]. Much of metabolic active forms of selenium tissue is found in proteins as seleno-analogues of sulphur amino acids as well as seleno-trisulphides and other acid-labile selenium compounds [99]. Selenium is an essential micronutrient for the biosynthesis of selenocysteine needed for the synthesis of selenoproteins. Selenoproteins play an important role in the pleiotropic biological activities including antioxidant activity, anti-inflammatory activity, and deiodinase activity (required for the synthesis of active thyroid hormone) [100].

Selenium deficiency is endemic in some regions of China where the soil has a low content of selenium [101]. Chronic selenium deficiency also occurs in individuals with malabsorption and long-term selenium-deficient parental nutrition in a shorter period, at times even with selenium supplementation [99]. There is also a clinical association between selenium deficiency and epilepsy [102]. Ketogenic diet (a low carb diet based on 4:1 ratio of fat to carbohydrates) has proved beneficial to patients with drug-resistance epilepsy. However, ketogenic diet is low in selenium compared to a normal balanced diet and has been associated with the development of CM [101,103]. Selenium deficiency causes CM due to the depletion of selenium-associated antioxidant enzymes (selenoenzymes), which protect cell membranes from damage by free radicals. The CM manifests by insidious onset of HF or a complication of sudden cardiac death or thromboembolic phenomena. The deficiency of selenoproteins deiodinases, thioredoxin reductases (TRxR) and glutathione peroxidase (GPx) have been implicated in the pathogenesis of selenium deficiency CM.

Deiodinases play an essential role in thyroid hormone metabolism and function. It activates thyroid hormone (TH) T_3 from its precursor T_4 as well as inactivates both T_3 and T_4 by removing specific iodine atoms [104]. Deficiency of deiodinase affects TH functions and can be confused with primary hypothyroidism that is characterized by reduced T_3 concentrations. Since TH regulates a plethora of organs metabolic functions including the heart, its dysregulation due to the deficiency of selenium or defects in deiodinases increases the risk of pathological myocardial perturbations [105]. Reactive oxygen species can also cause damage to all cell types including vascular endothelial cells and cardiomyocytes [106].

GPx uses glutathione to detoxify hydroperoxides into water thereby providing cells with anti-oxidant protection [107]. In a mice model, GPx1 inhibited ischemia induced apoptosis of cardiomyocytes [108] and targeted deletion of GPx1 gene resulted into heart and vascular dysfunction [109]. Other forms of GPx (GPx3 and GPx4) provide protection against thrombosis and atherosclerosis [110,111]. A positive correlation between selenium and GPx activities or expression alludes to selenium's indirect CVD protective role. For instance, selenium supplementation increases GPx activities in vascular endothelial cells resulting in reduced oxidative stress [101]. Chronic selenium deficiency leads to a decrease in GPx expression and activity and CVD damage, which can be reversed by dietary supplementation [112,113].

TRxR is critical for the control of cellular redox homeostasis. It detoxifies peroxides, prevents deleterious disulphide bond formation within and between biomolecules, reduces thioredoxin and regulates the redox state of transcription factors [114]. In mice model studies, systemic inactivation of TRxR lead to embryonic fatality associated with anaemic embryos, thinning of the ventricular heart wall and malformation of the heart, and cardiac tissues selective knock-out of the mitochondrial TRxR gene resulted in fatal DCM [115]. Human studies have also demonstrated the protective role of TRxR in the CVD system as well as identified loss-of-function mutations of TRxR that cause DCM [116]. Thus, the loss of cardiac mitochondrial TRxR activity is a pathogenetic factor for the development of DCM.

Keshan disease is the classical clinical presentation of cardiac disease due to selenium deficiency, often presenting with clinical features characteristic of DCM: cardiogenic shock, cardiac arrhythmias, ECG abnormalities, enlarged heart, and/or heart failure [117]. There is also echocardiographic evidence of biventricular enlargement and histologically defined oedema, mitochondrial swelling, hypercontraction bands, widespread myocytolysis and extensive fibrosis [6]. The possibility of selenium deficiency should be considered in all malnourished patients who receive parenteral nutrition. Selenium status should be monitored in all such patients with serum selenium levels and erythrocyte glutathione peroxidase activity measured at initiation of intravenous feeding. The primary treatment of selenium deficiency CM is selenium supplementation and parenteral nutrition. Patients with borderline or low selenium status should receive supra-normal selenium supplementation. Patients with demonstrated evidence of cardiac dysfunction and HF can receive furosemide (preload reduction), enalapril (afterload reduction), and carvedilol (antioxidant effects). Carvedilol is a non-selective beta-blocker that suppresses ROS and has antioxidant and ant-inflammatory effects [118].

Niacin deficiency: Severe niacin (vitamin B_3) deficiency (due to problems affecting absorption of niacin or its amino acid precursor tryptophan) presents in humans as the disease pellagra, characterized by the 3D's: dermatitis, dementia and diarrhoea, which if left untreated often leads to death [119]. Other symptoms of pellagra include anorexia, anxiety, psychosis, cheilosis, constipation, delirium, diminished strength, glossitis, intermittent stupor, melancholia, nausea, paralysis of extremities, peripheral neuritis, stomatitis, weight loss, and vomiting

[119,120]. Secondary causes includes but not limited to chronic alcoholism and a variety of chronic bowel disorders [119]. Pellagra used to be a disease of epidemic proportions in Africa and Asia, where the staple food is corn-based diet as well as related to poverty. Corn has a low tryptophan content and the niacin is tightly bound, requiring alkaline food processing to make it bioavailable [120]. However, at present, niacin deficiency is a very rare condition confined to certain at-risk groups such as refugees or displaced people [120-122]. Little progress has been made on the clinical understanding of pellagra since its initial description in 1735 [123,124] and since the discovery that nicotinamide is a preventive factor in 1926 [125]. In fact, since the past nine decades, there has been no changes in the treatment or diagnostic criteria of niacin deficiency. Insight into the role of niacin and various nicotinamide adenine dinucleotide (NAD)-related diseases ranging from cancer, aging and metabolic diseases to CVD problems has shifted the current perspective of niacin as a vitamin to the current perspective exploring its potential therapeutic role [121].

Niacin consists of nicotinic acid and nicotinamide, which serve as precursors of two important co-enzymes of cellular metabolism: NAD and NAD-phosphate (NADP). The deficiency of these two enzymes is the basis of the pathogenesis of pellagra. NAD and NADP participate in multiple mechanisms in cell metabolism: the metabolism of amino acids and proteins (tryptophane and niacin absorption), the generation of high-energy phosphate bonds and glycolysis [126,127]. Thus, NAD and NADP are important co-factors for most cellular redox reactions and thus are essential for the maintenance of cellular metabolism and respiration [119,121]. The deficiency of NAD and NADP affects tissues with a high rate of cell turnover such as the digestive tract and the skin, and tissues with high-energy needs such as the brain and the myocardium [128,129].

Cases of CVD involvement in niacin deficiency are very rare and in most cases asymptomatic. Although electrocardiographic (ECG) changes are common, symptomatic cardiac involvement is rare in patients diagnosed with severe niacin deficiency. ECG may be normal or with ST-T changes, and in some cases, the Q-T interval and mechanical systole may be prolonged [130]. Deformation of the ventricular complex (low voltage or notching) is frequent in niacin deficient patients [131]. In literature, the case of niacin deficiency with DCM has been described in general [132,133] with a few published case reports suggesting CM may develop in some patients with niacin deficiency. The main recommended treatment is niacin supplementation therapy. Vitamin B tablets compound contains 20 mg of nicotinamide, and pyridoxine and riboflavin, which are needed in the synthesis of niacin from dietary tryptophan. LV dysfunction may be reversible if treated with niacin replacement at appropriate time [122]. Additional management strategies include stopping alcohol intake and ensuring a diet rich in protein and niacin and avoiding sun exposure. Food sources rich in niacin and/or tryptophan include yeast, eggs, bran, peanuts, poultry, fish, legumes and whole grain cereals. Maize contains significant amounts of niacin but it is in bound form thereby not readily bioavailable [120].

Taurine deficiency: Taurine (also known as 2-aminoethanesulfonic acid) is a semi-essential non-codified amino acid derived from cysteic acid decarboxylation. Taurine can be synthesized endogenously from methionine or cysteine and as such is not an essential amino acid. However, a majority of taurine is obtained from dietary sources such as fish and milk [134,135]. The heart extracts its taurine supply through active transport by taurine transporter [136]. Infants and the elderly have decreased taurine biosynthesis with an increased dependency on dietary sources [135]. Taurine is an essential ingredient in infant formula and a larger dose is the central component of many popular caffeine energy drinks [2]. Taurine is highly concentrated in the cardiomyocytes but its function has not been completely clarified [137] although it believed to be an endogenous regulator of intracellular calcium homeostasis, and contributes to the function of mitochondrial enzymes [138-140]. Taurine modulates voltage-dependent calcium channels, sodium-calcium exchange and sodium-taurine co-transport and the net effect of protection of myocardial cells from calcium overload or calcium low calcium state. Cardiomyocyte calcium levels increase in HF and contributes to cellular injury. Taurine also possesses antioxidant properties and reacts with a variety of potentially toxic intracellular aldehydes [141]. Cytokine activity, particularly TNF-alpha is increased in HF. TNF-alpha decreases with taurine levels [142]. Taurine deficiency in cardiomyocytes potentiates taurine deficiency CM [143].

Taurine-deficient hearts often exhibit impaired aerobic metabolism, reduced oxygen consumption, increased glycolysis and lactate concentration and a decline in ATP activity. Taurine may prevent HF progression and reduce cardiotoxicity induced by detrimental activation of the sympathetic nervous system and angiotensin II [144]. Some studies in humans have demonstrated a beneficial effect of taurine supplementation in HF patients, associating a few weeks of therapy with improved exercise capacity, LVEF and NYHA class [145-147]. In a study of 24 HF patients, 2 mg oral taurine for 4-8 weeks was effective in 19 patients with a significant improvement in clinical signs and symptoms, and 15 patients in NYHA III/IV improved to NYHA II [145]. In a double blind randomized crossover trial, taurine added to conventional treatment in 14 HF patients for 4 weeks compared with placebo found taurine significantly improved NYHA class ($p<0.001$) with no observed side effect during taurine treatment [146]. In a randomized single-blind placebo-controlled clinical trial enrolling 29 HF patients (LVEF < 50%' mean = 29.27%) and in NYHA II/III, there was a significant improvement in exercise time, metabolic equivalents, exercise distance in patients who received taurine for 2 weeks ($p< 0.0001$ for all) but did not increased significantly in patients who received placebo ($p = 0.379$, 0.244 and 0.577 respectively) [147]. These findings suggest that taurine added to conventional therapy is safe and efficacious for the treatment of HF patients. Japan has approved taurine supplementation for HF treatment based on the known pathological effect of taurine deficiency on the heart structure and function. However, to date there is no clear association between taurine supplementation, and cardiac function and hard clinical endpoints such as mortality outcomes.

Coenzyme Q10: Coenzyme Q10 (CoQ10; also called ubiquinone) is an endogenously synthesized and diet supplied lipid-soluble co-factor that acts in the mitochondrial inner membrane. CoQ10 is present in high concentrations in the mitochondrial electron transport chain (ETC) as compared to other tissues [149]. It acts as an essential co-factor in the oxidative phosphorylation in mitochondria, playing a key role in the formation of ATP. CoQ10 mediates electron transfer in the ETC from complex 1 (NADH coenzyme Q reductase) to complex 3 (cytochrome bc1 complex), and from complex 2 (succinate dehydrogenase) to complex 3. In addition, CoQ10 has an antioxidant effect preventing membrane oxidation and lipid peroxidation, stabilizing LDL particles and promoting recycling of alpha-tocopherol thereby supporting CVD health [2,149]. Although its precise role in the pathogenesis of CM remains unclear, myocardial CoQ10 depletion has been hypothesized to be pathologic mechanism in the development and progressions of HF. Folkers et al. [150] demonstrated association between myocardial CoQ10 levels and symptomatic severity of HF,

with the lowest levels seen in patients with NYHA class IV and the highest in NYHA class I. In addition, the antioxidant effect of CoQ10 reduces oxidative stress that is known to adversely affect LVEF and alter disease outcomes [151]. CoQ10 may also stabilise caecum dependent channels in the myocardium thereby enhancing the effectiveness of ATP synthesis [152].

The literature on CM has not elucidated the association between CoQ10 deficiency and the pathogenesis of CM. The basis of the current evidence are findings on therapeutic benefits of CoQ10 supplementation therapy on signs and symptoms of HF and improvement in cardiac function. CoQ10 is deficient in myocardial tissues of biopsies taken from DCM hearts. In a study of 30 patients with histological diagnosis of DCM orally treated with CoQ10 for 2 months, Manzoni et al. [153] described 47% of the patients with regressed clinical symptomatology with improvement in NYHA class, LEVF (0.31 to 0.37, $p<0.001$) and CoQ10 plasmatic levels improved in 95% of the patients. Patients with lower myocardial levels appeared to have better therapeutic response. The findings suggest that CoQ10 deficiency in DCM may be reversible and that the therapeutic effects depends on the basal plasmatic and myocardial levels. Therapy with CoQ10 is a potentially efficacious complementary treatment to the traditional treatment of chronic HF [153]. Despite a high number clinical trials showing favourable effects of CoQ10 supplementation, a recent systematic review underlines the frailty of the evidence in HF patients [149]. The systematic review including seven studies comparing CoQ10 with placebo, despite minimal improvements in LVEF values and symptoms, the improvement in outcomes, functional capacity and brain natriuretic peptides (BNP) were not confirmed. In light of the evidence supporting CoQ10 supplementation as an attractive option in the management of HF, it merits additional evaluation in larger randomized studies to clarify previous conflicting results.

Meta-analysis of diagnosis/management

The current expert consensus guidelines developed for the diagnosis and treatment of CMs largely depend on morphological and functional abnormalities demonstrated by non-invasive cardiac imaging techniques. The impact of this is the lack of generally acceptable criteria for aetiology-based diagnosis for specific forms of CMs. Already, chronic deficiency of certain types of micronutrients have been implicated as key pathogenic factors in certain forms of CMs but lack pathognomonic cardiac features to confirm diagnosis. In patients diagnosed with micronutrient deficiency, diagnosis is usually a clinical challenge resting on a combination of tests, which includes history taking to identify clinical signs and symptoms related to HF, the exclusion of other known aetiologies of heart diseases and a positive therapeutic response to micronutrient supplementation therapy. Indeed, due to the cost- and time-intensive nature of determining the deficient micronutrient or mutational analysis for defective genes, a positive response to micronutrient supplementation therapy is emerging as a key factor used to support the diagnosis of nutritional deficiency CM. The present systematic review and meta-analysis aggregates current evidence on the diagnosis and treatment of nutritional deficiency CM to identify common diagnostic features as well as treatment strategies and outcomes.

A systematic search was conducted to identify and select randomized controlled trials (RCTs) that evaluated diagnosis and treatment of NDCM using different micronutrient therapies. The databases used in the search were PubMed, Embase, Scopus and Google Scholar. The key words used in the search included the following, "cardiomyopathy" OR "heart failure", "nutritional deficiency", "nutrient deficiency", and the names of individual micronutrients, "diagnosis" and "treatment" and its cognates. Included studies were RCTs that reported diagnostic features, and micronutrient intake and outcomes. On the other hand, the excluded studies investigated animals, health conditions that influence dietary intake, studies without a random sample and enrolled virtual populations. Data extracted from each study included the following: author, year of publication, number of randomized patients per each study arm, sex proportion, mean age in years, diagnostic methods used, micronutrient used and dose, and the impact on cardiac outcomes and duration of follow-up. The outcome of interest were non-invasive cardiac features used in the diagnosis and the effect of treatment on cardiac function.

Findings: In total, the electronic search retrieved 122 potentially relevant studies from which 13 studies that met the inclusion/exclusion criteria were include in the present meta-analysis [154-166]. The year of publication of individual trials ranged between 1992 [154,161] and 2016 [166]. Seven studies [154-160] evaluated CoQ10 deficiency and supplementation while the remaining six [161-166] evaluated carnitine. Study characteristics of the included trials are described in Table 1. All the 113 studies were randomized controlled trials (RCTs) consisting of 14 double blind studies [154-162,164,166] and two non-blinded open-label studies [163,165]. Treatment duration ranged between 0.2 (7 days) [166] to 12 months [162,165]. Parallel trials had longer duration and enrolled more patients compared to crossover trials. Although the clinical history of enrolled patients in each trial differed among trials, all the trials included patients diagnosed with HF. The total population of enrolled patients in the 13 trials was 1,264, with a greater proportion (more than three quarters) being male patients (76.6%). The patients were generally older, with the mean age ranging between 49.8 and 70.1 years. In the nine parallel studies [158,159,161-166], the total population was 1,101 patients consisting of almost an equal representation of patients in the treatment arm (n=557; 50.6%) and in the placebo arm (544; 49.4%). The baseline LVEF ranged between 22.0% and 52%, including patients in NYHA functional classes II to IV.

The primary outcome of interest was non-invasive cardiac parameters used to support the diagnostic and therapeutic efficacy in NDCM patients. Common cardiac structure and function assessed by the 13 trials was LV systolic function (LV ejection fraction: LEVF) and hemodynamics (LV systolic volumes and diameters). LVEF was the most common diagnostic parameter and therapeutic outcomes assessed in a majority of the studies. However, the majority of the studies on nutritional deficiency have centred on CM patients with HF or HF in the setting of other non-CM causes. As such, the diagnostic value of non-invasive cardiac imaging did not emerge clearly. In addition to laboratory determination of the deficiency of certain essential micronutrients, most of the patients had severe systolic dysfunction (LVEF < 40%) and in NYHA functional class II-IV. The outcome of interest were non-invasive cardiac features used in the diagnosis and the effect of treatment on cardiac function.

Nutrient supplementation as a therapy for cardiomyopathic patients with HF. In a pooled analysis of all the 13 trials, there was a slight but statistically significant increase in LVEF for HF patients on nutritional supplementation in addition to the standard HF medication compared to placebo (weighted mean difference [WMD] 1.93%; 95% CI: 0.251 to 3.612; $p = 0.02$: Figure 1). A similar increase was observed in a pooled analysis of six studies [154-157,159,160] on patients on CoQ10 supplementation (WMD: 1.83%; 95% CI: -0.403 to 4.075: Figure 2) and in six studies [161-166] on patients on carnitine supplementation, the increase in LVEF was relatively and

Table 1. Characteristics of studies included in this meta-analysis

Author [Ref #]	Year	Study Design	Sample (Trt/Ctl)	Age (Trt/ Ctl)	Male (n) (Trt/Ctl)	Inclusion Criteria	Main Nutrient	Non-Invasive Diagnostic Test	B/Line LVEF	Treatment Duration (month)	Main Findings
Permanetter [154]	1992	X-over	25	51	20	iDCM, NYHA I-III	CoQ10	Echo, chest x-ray, radionuclide ventriculography	39.5	4	T/P and P/T: ↑ LVEF 39.5±11.5/37.6±17.0; ↓ LVEDD 65±9/67±8; CO 5.1±1.41/5.1±1.11
Morisco [155]	1994	X-over	6	49.8	NR	Clinically documented HF	CoQ10	Ambulatory radionuclide detector	27.0	4	↑ LVEF At rest 33±13/27±11; at peak exercise 30±12/24±8
Hofman-Bang [156]	1995	X-over	79	61	69	Stable Chronic HF	CoQ10	Nuclear angiography	22.0	3	↑ LVEF 24±12/22±10
Watson [157]	1999	X-over	30	55	26	Ischemic CM or iDCM and chronic LV dysfunction	CoQ10	Nuclear angiography	26.0	3	LVEF 31±9/31±9; ↓ LVEDV 209±75/220±68; ↓ LVESV 149±61/155±58
Khatta [158]	2000	Parallel	46 (23/23)	64	39	HF, NYHA III/ IV, LVEF < 40%	CoQ10	Radionuclide ventriculography	28.5	6	↓ LEVF 0.3±8 (-3.7 to 3.1)
Jeejeebhoy [159]	2002	Parallel	38 (20/18)	62/69	19/18	Elective aortocoronary bypass surgery, LVEF ≤ 40	CoQ10, Taurine, Carnitine	Radionuclide ventriculography	42.8	NR	↑ LEVF 43.7±12.5/42.8±12.2; ↓ LVEDV 158.9±51/170.5±50; ↓ LVESV 94.2±46.4/99.8±42.5
Belardinelli [160]	2006	X-over	23	59	20	HF due to ischemic CM/ heart disease NYHA II-III	CoQ10	Echo dobutamine stress	37.0	1	↑ LEVF 43±8.7/37.9±8
Mancini [161]	1992	Parallel	60 (30/30)	59.8/60.7	23/21	HF, NYHA II-III, LVEF < 50% at rest	Carnitine	2D-Echo	41.8	6	↑ LEVF 47.43±6.25/39.98±4.97
Iliceto [162]	1995	Parallel	472 (233/239)	60/58	195/204	Acute MI	Carnitine	2D-Echo	48.7	12	↑ LEVF 45.8±0.57/45.2±0.52; ↓LVEDV 99.3±2.06/104.5±2.37; ↓ LVESV 55.0±1.63/58.9±1.75
Gurlek [163]	2000	Parallel	51 (31/20)	64.3/66.2	27/17	Ischemic CM	Carnitine	2D-Echo	37.8	1	NS change: LEVF 42.3±8.9/43.8±8.3
Cheng [164]	2013	Parallel	120 (60/60)	57.9/70.1	34/36	Chronic HF, NYHA III-IV	Carnitine	2D-Echo	34.0	0.5	↑ LEVF 50±21/38±19
Nishimura [165]	2015	Parallel	53 (27/26)	64.3/64.7	28/14	HF, NYHA IV	Carnitine	2D-Echo	52.0	12	↑ LEVF 53.7±9.5/51.9±6
Jing [166]	2016	Parallel	261 (133/128)	51.9/52.4	84/70	HF, NYHA II-IV, LVEF ≤ 45%	Carnitine	2D-Echo	41.1	0.2	NS change: 44.12±8.3/44.9±8.6

Ctl: Control; Echo: Echocardiography; HF: Heart Failure; iDCM: Idiopathic Dilated Cardiomyopathy; LVEF: Left Ventricular Ejection Fraction; LVEDD: Left Ventricular End Diastolic Diameter; LVEDV; Left Ventricular End Diastolic Volume; LVESV: Left Ventricular End Systolic Volume; MI: Myocardial Infarction; NYHA: New York Heart Association; NS: Not Significant; Trt: Treatment; X-over: Cross-over

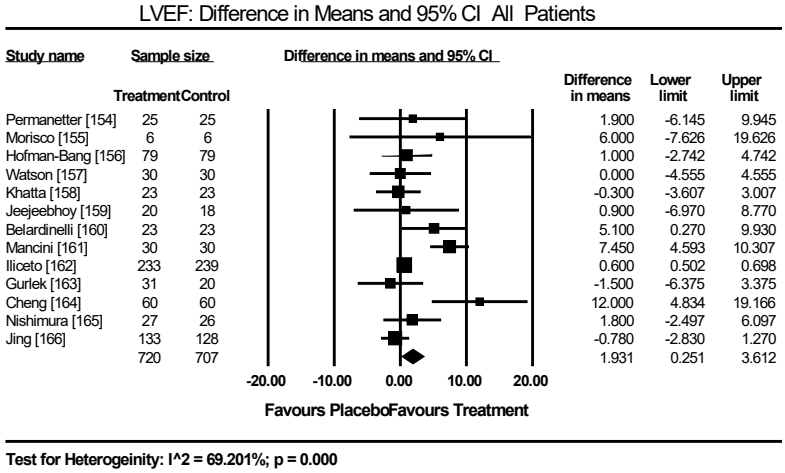

Figure 1. Forest plot for mean difference for LVEF all studies 26

significantly higher (2.455%; 95% CI: 0.229 to 5.139; Figure 3). CoQ10 supplementation was also associated with a trend towards improved cardiac hemodynamics. Pooled analysis of two studies [157-159] there was a non-significant decrease in LVEDV (WMD: -11.335 ml; 95% CI: -35.393 to 12.722; p = 0.356; Figure 4) and LVESV (WMD: -5.788; 95% CI: -26.452 to 14.875; p = 0.583; Figure 5). In addition, individual studies also reported an insignificant decrease in LVEDD (65±9 from 67±8 mm) and no change in cardiac output (5.1±1.41 from 5.1±1.11 min^{-1}) [154].

Discussion

In the present meta-analysis, the focus was on changes in cardiac function at baseline and after the treatment by nutrient supplementation in cardiomyopathic patients with HF. In the search for relevant studies, it emerged that there is a conspicuous lack of data on the diagnosis of CM (changes in cardiac structure and function) in patients with nutrient deficiency. In the included studies, almost all the patients had chronic and severe HF in NYHA class III or IV secondary to CM

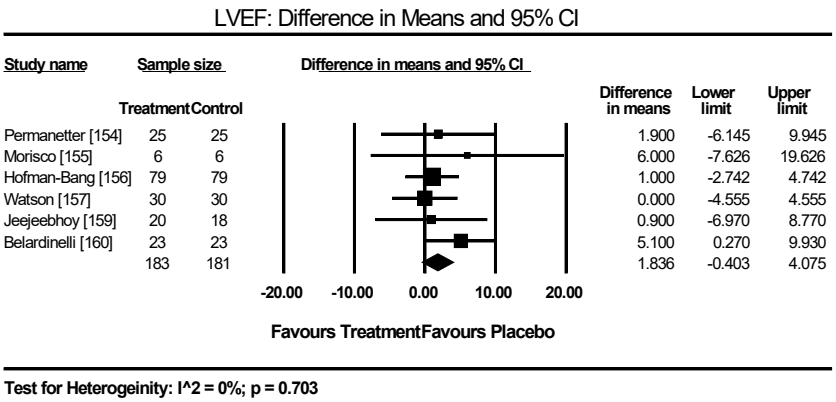

Figure 2. Forest plot for mean difference in LVEF after CoQ10 supplementation

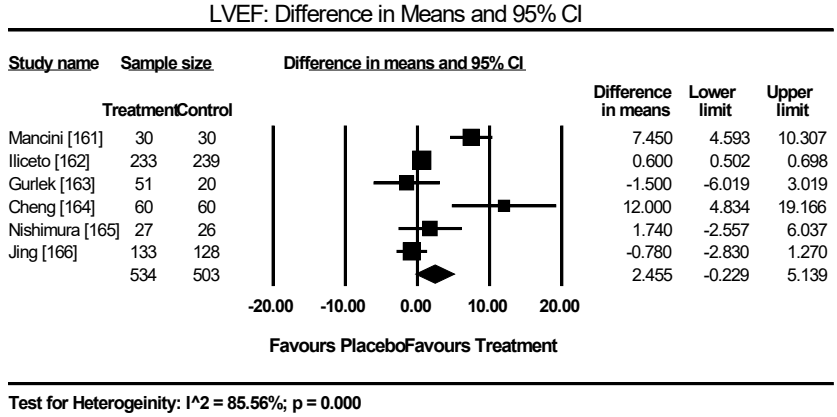

Figure 3. Forest plot for mean difference in LVEF after carnitine supplementation

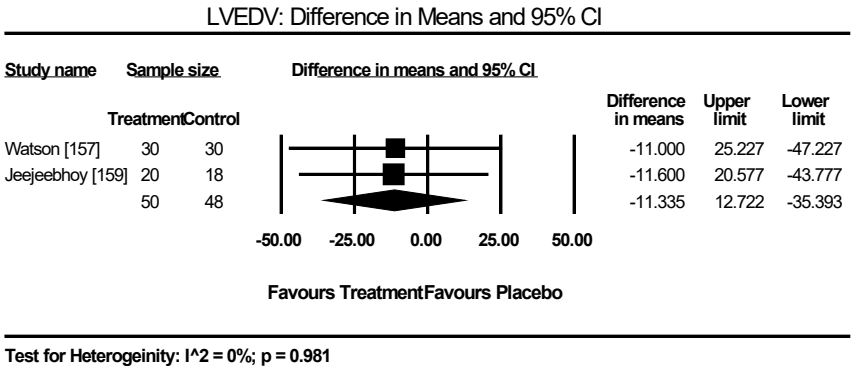

Figure 4. Forest plot for mean difference in LVEDV after CoQ10 supplementation

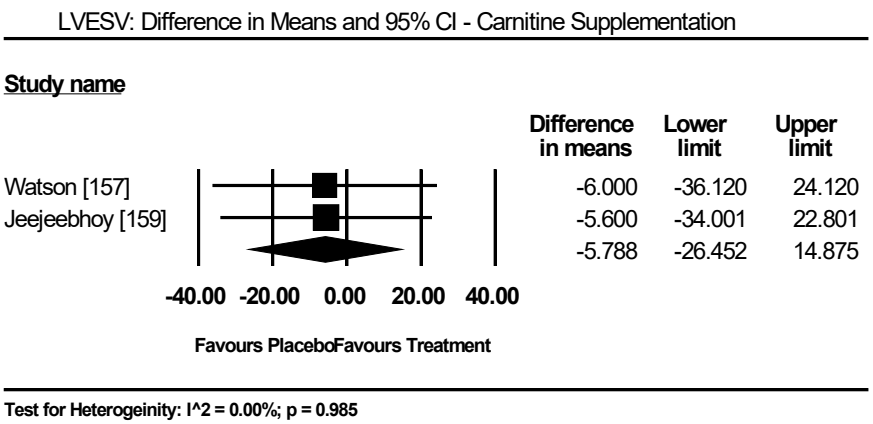

Figure 5. Forest plot for mean difference in LVESV after CoQ10 supplementation

or ischemic heart diseases. As such, the evidence on diagnosis based on cardiac imaging that is specific to nutrient deficiency is lacking. However, in terms of treatment, cardiac imaging is emerging are a promising technique for monitoring the therapeutic efficacy of nutrient supplementation in patients in the late stages of CM. The present analysis finds nutrition supplementation has a significant effect on LV systolic function (demonstrated by a marked increase in LVEF) compared to patients receiving placebo with a trend towards improvement in cardiac hemodynamics demonstrated by a non-significant decrease in LV diastolic and systolic volumes as well as diastolic diameter.

One of the drawbacks of the present meta-analysis is that the majority of clinical trials evaluated only two micronutrients: CoQ10 and carnitine supplementation, which undermined a holistic understanding of the therapeutic value of all the major micronutrients whose deficiency can result in cardiomyopathy. Nevertheless, five additional studies were identified that evaluated the effect of taurine [145,146] and thiamine supplementation [167,168] on cardiac function but were excluded due to incompatibility of type of data or the aim of the study relative to that of the present meta-analysis. Azuma et al. [145] investigated 24 patients with congestive HF administered with oral taurine for eight weeks. The study expressed the severity of HF by a score based on clinical signs and symptoms and roentgenographic data, with 23 points indicating the worst possible HF score. Taurine treatment was effective demonstrated by a decrease in the severity scores from 7.3±0.6 pre-treatment to 4.4±0.5 post-treatment and a re-classification of 15 patients from NYHA class III or IV to class II after the completion of the study. In a double cross-over placebo-controlled trial investigating the effect of adding taurine to the conventional HF treatment in 14 HF patients, taurine significantly improved NYHA class ($p<0.02$), pulmonary crackles ($p<0.02$) and chest film abnormalities ($P<0.01$). Moreover, patients receiving taurine did not experience any side effects [146].

Three clinical trials on thiamine supplementation were also identified during the initial search for relevant studies but were excluded for limited data provided or did not satisfy the inclusion criteria. The first was a randomized, double blind, placebo-controlled, cross-over pilot trial enrolling nine patients with symptomatic HF (LVEF <40%) who received thiamine for four weeks. Thiamine treatment improve LVEF by 3.9% in absolute terms compared to placebo [167]. In the second randomized placebo-controlled study of 49 patients (25 on thiamine and 24 on placebo), thiamine treatment reduced re-hospitalization for cardiac reasons by 35% compared to placebo [168]. However, in a recent randomized controlled trial of 118 patients with acute HF, Smithline et al. [169] reported that in patients with mild to moderate acute HF without thiamine deficiency, a standard dosing regimen of thiamine did not improve dyspnoea, biomarkers or other clinical parameters. This finding suggests that a diagnosis of nutrient deficiency is important to inform the decision to initiate nutrient supplementation therapy.

Consistent with two previous systematic reviews and meta-analyses [170,171], the present analysis finds micronutrients supplementation has beneficial outcomes on cardiac function in HF patients without any demonstrable adverse side effect. Micronutrient supplementation appears to work synergistically with standard HF therapy by correcting the deficits in energy metabolism and providing the failing heart with the deficient co-factors that may limit cellular energy transfer. Indeed, micronutrient supplementation therapy is emerging as a promising paradigm for the treatment of CM and HF, which merits further investigation by large prospective clinical trials to confirm its therapeutic value. A previous systematic review study reports that micronutrient supplementation therapy offers the opportunity to correct deficiencies in critical cardiomyocytes pathways such as those associated with providing ATP (CoQ1o, carnitine and thiamine) and intracellular calcium homeostasis (CoQ10 and taurine) [2]. Another literature review study on nutritional deficiencies links poor dietary behaviours with adverse clinical outcomes and poor quality of life among HF patients [3].

The current research evidence on the role of nutritional deficiency and supplementation in the pathogenesis and treatment of specific forms of CM and HF has almost exclusively focused on a single micronutrient. Although such a singular focus allows the investigation of the effect of each individual micronutrient, it has the drawback of potentially limiting the understanding of the pathogenesis of CM as well as clinical outcomes. Often HF patients may exhibit multiple nutrient deficiencies. As such, correcting one deficiency may unmask one of the many other deficiencies or the need for a certain micronutrient (such as carnitine) may not be apparent because plasma levels do not always indicate deficiency in a failing myocardium. Animal models have already demonstrated multiple-nutrient deficiencies in failing hearts [18,23,172]. A study of cardiomyopathic hamsters found deficiencies in CoQ10, carnitine and taurine in the myocardium during the late stages of the disease, and multiple-nutrient supplementation for three months compared to placebo diet improved myocardial structure, contractility and cardiac function [18]. In a recent study, triple nutrient supplementation in rats prior to coronary artery litigation showed

marked improvement in survival, cardiac function and reduced infarct size compared to placebo [172].

Fewer studies have investigated multiple-nutrient supplementation in HF in humans [160,173,174]. Belardinelli et al. [160] examined the effect of a nutrient energy drink that included CoQ10, carnitine, thiamine and taurine on 41 patients with ischemic CM (LVEF < 40%) scheduled for elective bypass surgery. Analysis of LV biopsies revealed 40 to 144% higher levels of these micronutrients on the myocardium, a decrease in LV end-diastolic volume (LVEDV) and a trend towards decreased LV end-systolic volume (LVESV) but LVEF was unaffected. However, at the onset of the trial, many patients did not have clinical HF symptoms and thus the study could not assess the effect on symptoms. Witte et al. [173] analysed the effect of a combination of 10 different micronutrients on LV function and quality of life in 30 elderly patients with stable systolic HF secondary to ischemic heart disease compared to controls and found significant improvement in quality of life and LVEF. A subsequent randomized placebo-controlled trial investigating 74 HF patients administered with several macronutrients (vitamins and minerals) showed an increase in serum concentrations of supplemented micronutrients but with no change in LVEF, quality of life, natriuretic peptides and inflammatory marker levels [174]. These conflicting results warrants larger RCTs to confirm the benefits of multiple-nutrient therapy on HF patients.

The approach to evaluate multiple micronutrient therapy is compelling because it is a more comprehensive method of supplementation that promises to overcome some limitations inherent in a single-supplementation method. Theoretically, multiple-micronutrient supplementation may correct several deficiencies and improve multiple metabolic pathways. However, conflicting findings indicates that need for further research to clarify the best composition and the possible role of multiple-micronutrient supplementation in HF. In addition, current single and multiple nutritional studies enrolling a small sample have significant design drawbacks, which merit the need for larger and more comprehensive micronutrient trials in HF.

Implications

The current evidence indicate micronutrient supplementation is a promising complementary therapy to the standard HF medication for patients diagnosed with CM and HF. Despite this evidence, the current HF guidelines have not recommended a specific nutritional strategy for HF patients. The ESC guidelines omit nutrient supplementation [175]. The Heart Failure Society of America (HFSA) recommends HF patients, especially those on diuretic therapy and restricted diets should be considered for daily multivitamin-mineral supplementation to ensure adequate intake of the recommended daily value of essential nutrients [176]. The Canadian Cardiovascular Society (CSC) does not recommend the use of CoQ10, vitamin and herbal supplements as HF therapy [177]. The ACC/AHA does not recommend routine use of nutritional supplements of unproved value [178]. The omission of nutrient supplementation may possibly be due to lacking support by large randomized trials and limited (and even conflicting) evidence regarding outcomes. Since the evidence of nutrient deficiency has been associated with the failing heart, further large trials may clarify the benefits of nutrient supplementation for consideration for inclusion in the current treatment guidelines by the leading heart and cardiology associations particularly in regions and countries where nutritional deficiency is prevalent.

Conclusion

Nutritional deficiency (ND) is an imbalance between the body's supply and demand for certain essential nutrients. In the heart, ND potentially leads to various metabolic and myocardial compensatory mechanisms leading to cardiomyopathy (NDCM) and ultimately heart failure (HF). Although the deficiency of numerous nutrients may result in NDCM, in particular, chronic deficits in thiamine, carnitine, selenium, niacin, taurine and CoQ10 has a deleterious effect on the myocardium leading to various morphological forms of CM – DCM, HCM or RCM. Possibly, ND may cause the development of CM through altering metabolic pathways involved in energy production, myocardial calcium balance or oxidative defences. Clinical signs and symptoms, including ECG and echocardiographic changes, are non-specific. However, the possibility of NDCM should be considered in all CM patients presenting with malnourishment. Diagnosis is usually based on a combination of a history of dietary inadequacies, physical examinations, and contemporary cardiac imaging modalities to assess changes in cardiac structure and function. Laboratory tests may confirm deficits in micronutrients to support diagnosis but these tests are often cost- and time-consuming, and thus, nutrient repletion as a therapeutic trial is the most feasible strategy to support diagnosis. Treatment targets correcting the underlying cause and relieving signs and symptoms of cardiac dysfunction. Nutrient supplementation acts synergistically with the standard HF therapies to improving energetic metabolism and energy transfer. Although multiple micronutrient supplementation may overcome limitations inherent in the single supplement method as well as correct several deficiencies, the current evidence is limited and inconsistent. Larger clinical trials are warranted to clarify diagnostic parameters and the therapeutic value of multiple nutrient supplementation in CM and HF patients.

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