Nutrological and metabolic approaches to the action of the some special micronutrients in heart failure and metabolic syndrome: a systematic review

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Abstract

Introduction: In the heart disease scenario, heart failure (HF) is the leading cause of hospitalizations in the United States in patients over 65 years of age, and there is evidence that this pathology affects 26 million people worldwide. Dietary guidance for patients with HF has focused on sodium restriction and fluid intake, but diet quality is often poor in HF patients and can contribute to morbidity and mortality. Restrictive diets can lead to inadequate intake of macro and micronutrients by patients with HF, highlighting deficiencies in calcium, magnesium, coenzyme Q10, zinc, iron, thiamine, vitamins D, E, and K, and folate. Objective: Through a systematic literature review, the main nutrological approaches to the action of the micronutrients magnesium, coenzyme Q10, and vitamin D in heart failure and metabolic syndrome were evidenced. Methods: The present study followed a concise systematic review model (PRISMA). The literary search process was carried out from August 2022 to September 2022 and was developed based on Scopus, PubMed, Science Direct, Scielo, and Google Scholar, using scientific articles from 1998 to 2022. The low quality of evidence was attributed to reports of cases, editorials, and brief communications, according to the GRADE instrument. The risk of bias was analyzed according to the Cochrane instrument. Results and Conclusion: The total of 136 studies were found for eligibility analysis, and then 75 of the 84 total studies were selected for this systematic review. According to the GRADE instrument, most studies showed homogeneity in their results, with I2 =98.7% >50%. The Funnel Plot showed a symmetrical behavior, not suggesting a significant risk of bias in studies with smaller sample sizes. Studies have shown that magnesium deficiency or changes in its metabolism are related to the pathophysiology of heart failure, hypertension, arrhythmias, preeclampsia, insulin resistance, and diabetes. Vitamin D plays an important role in innate and adaptive immune responses, cell cycle, and metabolic processes, evidenced by the reported relationship between its deficiency and the prevalence of immunity-mediated disorders, cancer, and cardiometabolic diseases. The VDR results in β cells, endothelium, cardiac myocytes, and renin production suggesting a role for vitamin D in these diseases. Coenzyme Q10 is part of the electron transport chain and is found in large concentrations in the mitochondrial, especially in the muscles, brain, and heart. Clinical studies have shown that pathologies such as acute myocardial infarction, arterial hypertension, and myopathies induced by statins, physical fatigue inherent in physical exercise, male infertility, preeclampsia, Parkinson’s disease, periodontal disease, and migraine had low plasma concentrations of coenzyme Q10.

Keywords: Dietary therapy. Nutrology. Magnesium. Vitamin D. Coenzyme Q10. Heart Failure. Metabolic syndrome.

Introduction

In the heart disease scenario, heart failure (HF) is the leading cause of hospitalizations in the United States in patients over 65 years of age, and there is evidence that this pathology affects 26 million people worldwide and with increasing prevalence every year [1]. Still, in the United States, about 115 million people have hypertension, 100 million are obese, 92 million have prediabetes, 26 million have diabetes, and 125 million have atherosclerotic cardiovascular disease (CVD) [2,3]. In this context, dietary guidance for patients with
HF has focused on sodium restriction and fluid intake, but diet quality is often poor in HF patients and can contribute to morbidity and mortality. Restrictive diets can lead to inadequate intake of macro and micronutrients by patients with HF, highlighting deficiencies in calcium, magnesium, coenzyme Q10, zinc, iron, thiamine, vitamins D, E, and K, and folate. Furthermore, the elements intravenous iron, thiamine, and coenzyme Q10 have the most data from clinical trials for supplementation [4].

In this sense, it is emphasized that magnesium (Mg) deficiency is related to an increased risk of metabolic syndrome and type 2 diabetes mellitus (T2DM), and to fatal cardiac events in congestive heart failure (CHF) and atherosclerotic vascular calcification in hemodialysis patients. In the heart, Mg plays a key role in modulating neuronal excitation, intracardiac conduction, and myocardial contraction by regulating various ion transporters, including potassium and calcium channels. Magnesium also has a role in the regulation of vascular tone, atherogenesis and thrombosis, vascular calcification, and proliferation and migration of vascular and endothelial smooth muscle cells, influencing the pathogenesis of the cardiovascular disease [5].

Furthermore, Mg acts as a cofactor in more than 300 metabolic reactions, playing a key role in glucose metabolism, insulin, and glucose homeostasis in the synthesis of adenosine triphosphate, proteins, and nucleic acids, further studies are needed to clarify the role of magnesium in the prevention and treatment of cardiovascular diseases, especially concerning higher concentrations and increased treatment time [6-13].

Also, vitamin D plays important roles in innate and adaptive immune responses, cell cycle, and metabolic processes, evidenced by the reported relationship between its deficiency and the prevalence of immunity-mediated disorders, cancer, and cardiometabolic diseases. An inverse correlation between their concentrations and the prevalence of obesity and type 2 diabetes mellitus was described [14,15].

Besides, it is strongly highlighted that coenzyme Q10 is part of the electron transport chain and is found in large concentrations in the mitochondria, especially in the muscles, brain, and heart [16,17]. However, because they are organs that are more vulnerable to the action of oxygen free radicals, Q10 exerts an important protective antioxidant action. However, due to aging, genetics, and statin consumption, the amount of Q10 is decreased [17].

In this sense, clinical studies have shown that in pathologies such as acute myocardial infarction, arterial hypertension, and myopathies induced by statins, physical fatigue inherent in physical exercise, male infertility, preeclampsia, Parkinson's disease, periodontal diseases, and migraine had low plasma concentrations of Q10. In addition, Coenzyme Q10 reduces the number of lipid peroxides found in atherosclerotic lesions. Thus, Q10 protects the lipids present in cell membranes, as well as plasma lipoproteins [16,17].

Therefore, the present study aimed to demonstrate, through a systematic review of the literature, the main nutrological approaches to the action of the micronutrients magnesium, coenzyme Q10, and vitamin D in heart failure and metabolic syndrome.

**Methods**

**Study Design**

The present study followed a systematic review model, following the rules of systematic review - PRISMA (Transparent reporting of systematic review and meta-analysis-HTTP: //www.prisma-statement.org/).

**Search Strategy and Search Sources**

The literary search process was carried out from August 2022 to September 2022 and was developed based on Scopus, PubMed, Science Direct, Scielo, and Google Scholar, using scientific articles from 1998 to 2022, using the descriptors (MeSH Terms): Dietary therapy. Nutrology. Magnesium. Vitamin D. Coenzyme Q10. Heart Failure. Metabolic syndrome, and using the Booleans "and" between the MeSH terms and "or" between the historical findings.

**Study Quality and Risk of Bias**

Quality was rated as high, moderate, low, or very low for risk of bias, clarity of comparisons, precision, and consistency of analyses. The most evident highlight was for systematic review articles or meta-analysis of randomized clinical trials, followed by randomized clinical trials. The low quality of evidence was attributed to case reports, editorials, and brief communications, according to the GRADE instrument. The risk of bias was analyzed according to the Cochrane instrument through the analysis of the Funnel Plot (Cohen test (d)).

**Literary review results**

**Summary of Findings**

It was found 136 studies that underwent eligibility analysis, and then 75 of the 84 total studies were selected for the present systematic review (Figure 1),
considering in the first instance the level of scientific evidence of studies in study types such as meta-analysis, consensus, randomized clinical trial, prospective and observational. The biases did not compromise the scientific basis of the studies. According to the GRADE instrument, most studies showed homogeneity in their results, with I² =98.7% >50%.

**Figure 1.** Flowchart showing the article selection process.

<table>
<thead>
<tr>
<th>Identification</th>
<th>PubMed Articles (n = 116)</th>
<th>Other Databases (n = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variation</td>
<td>Articles Analyzed (n = 101)</td>
<td>Excluded articles (did not meet the GRADE) (n = 11)</td>
</tr>
<tr>
<td>Selection</td>
<td>Selected Articles (n = 90)</td>
<td>Excluded Articles (Risk of Bias) (n = 6)</td>
</tr>
<tr>
<td>Included</td>
<td>Articles in qualitative analysis (n = 84)</td>
<td>Excluded Articles (other reasons) (n = 9)</td>
</tr>
<tr>
<td></td>
<td>Articles included in the systematic review (n = 75)</td>
<td></td>
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</tbody>
</table>

**Figure 2** presents the results of the risk of bias of the studies using the Funnel Plot, showing the calculation of the Effect Size (Magnitude of the difference) using the Cohen Test (d). Sample size was determined indirectly by the inverse of the standard error (1/Standard Error). This graph had a symmetrical behavior, not suggesting a significant risk of bias, both between studies with a small sample size (lower precision) that are shown at the bottom of the graph and in studies with a large sample size that are presented in the upper region.

According to the results collected in this study, it was observed that magnesium acts as a cofactor in more than 300 metabolic reactions, playing a key role in glucose metabolism, insulin, and glucose homeostasis in the synthesis of adenosine triphosphate, proteins, and nucleic acids [10,11]. It also acts on the stability of the neuromuscular and cardiovascular membrane, on the maintenance of vasomotor tone, and as a physiological regulator of hormonal and immunological function [10-20].

The serum concentration of Mg2+ is inversely associated with the risk of developing HF and AF and the occurrence of CKD, diabetic retinopathy, and foot complications in T2DM. Glycemic control partially mediated the association of serum Mg2+ with HF and microvascular complications [21].

The Recommended Dietary Allowances (RDA) for magnesium are 400 to 420 mg daily for adult men and 310 to 320 mg for adult women. However, consumption is well below this recommendation and the high prevalence of this deficiency has been associated with several chronic diseases [18,19].

The mineral magnesium is the second most abundant intracellular cation and is involved in several important biochemical reactions [23-27]. It is known that magnesium has an antiarrhythmic effect, it acts on vascular tone since changes in the extracellular content of magnesium can modify the formation and release of nitric oxide (NO), resulting in the alteration of the tone of the arterial smooth muscle and the contractility by affecting calcium concentrations and also participates in glucose metabolism and insulin homeostasis. Thus, it is suggested that magnesium deficiency or changes in its metabolism are related to the pathophysiology of hypertension, arrhythmias, preeclampsia, insulin resistance, and diabetes [28].

Lower magnesium concentrations are associated with reduced HDL-cholesterol and increased LDL-cholesterol and triglycerides [15]. In addition, the
deficiency of this mineral has previously been related to oxidative stress, pro-inflammatory state, endothelial dysfunction, platelet aggregation, insulin resistance, and hyperglycemia [29].

Also, magnesium supplementation may increase intracellular adenosine triphosphate (ATP) production and glucose utilization, since magnesium acts as a cofactor for all reactions involving ATP transfer [30]. In addition, magnesium also activates the Na-K ATPase pump that controls the balance of these minerals, thus contributing to the homeostasis of electrolytes in cells [31]. The action of magnesium as a calcium channel blocker may also contribute to reducing the release of calcium and thereby reducing vascular resistance [32-37].

Regarding insulin homeostasis, there is a hypothesis that, in hypomagnesemia, there would be an increase in the secretion of insulin and adrenaline in an attempt to maintain the concentration of cellular magnesium and cAMP (3’ adenosine, 5’-cyclic monophosphate) [38]. In addition, the intracellular concentration of magnesium appears to be dependent on the extracellular level, being its influx through voltage-dependent calcium channels [39-41]. Extracellular magnesium can competitively inhibit these channels and the calcium current, causing a decrease in insulin secretion, but when there is a low concentration of magnesium in the extracellular space, this inhibition will not occur, resulting in increased insulin secretion [42,43].

Experimental, and epidemiological studies have observed clinical a close and inverse relationship between dietary intake or magnesium supplementation and blood pressure (BP) level, indicating the potential role of magnesium deficiency in the pathogenesis of primary hypertension [35]. Patients with hypertension without BP control presented hypomagnesemia, and with the Ambulatory BP Measure (ABPM), considered an important tool in the evaluation of treatments that affect the circadian pressure cycle, authors demonstrated that magnesium supplementation was associated with the slight reduction of blood pressure levels in patients with mild hypertension [24,36].

Other possible mechanisms of action of magnesium would be its anti-inflammatory, antioxidant, and cell growth modulating properties since the production of reactive oxygen species is usually increased in the vasculature of hypertensive patients and the participation of magnesium could occur through the reduced oxidative stress and its anti-inflammatory action [40].

The role of magnesium in endothelial dysfunction has been discussed in the literature [39]. Indeed, it has been reported that magnesium modifies vascular tone by regulating endothelium and smooth muscle cell functions and plays an important role in the classical pathway of NO release [41]. Peripheral vascular resistance can also be modified by magnesium, by regulating responses to vasoactive agents, especially angiotensin II, endothelin, and prostacyclin.

A study that tracked more than 90,000 menopausal women showed that dietary magnesium intake was inversely associated with plasma concentrations of inflammatory markers such as IL-6, C-reactive protein (CRP), and TNF-alpha [43]. This same study reinforced that the ingestion of magnesium would improve the inflammatory process and endothelial dysfunction, and may play a role in the prevention of metabolic syndrome.

Also, hypomagnesemia is associated with type 2 diabetes mellitus and its complications [26]. This study was conducted among 150 types 2 diabetic patients and 150 non-diabetic controls between May and September 2016. The relevant demographic, anthropometric, physiological, and biochemical variables were measured using standardized protocols. Half of the type 2 diabetic population under study presented hypomagnesemia without considering the method of diabetes control. Advanced age and low glycemic control were significant predictors of low serum magnesium levels in these patients [26].

In this context, dietary supplementation with magnesium in addition to classical therapies for diabetes may help in the prevention or delay of diabetic complications [26,44-48]. Another study aimed to evaluate the serum Mg status in children with type 1 diabetes and to evaluate its relationship with glycemic control and lipid profile. Then, evaluate the effect of oral supplementation of Mg salts on glycemic control and lipid parameters. Seventy-one children were included in the Pediatric Endocrinology Outpatient Clinic of the University of Zagazig, Egypt, with type 1 diabetes and evaluated HBA1c, lipid profile, and Mg ionic and serum levels at baseline [20]. There was a statistically significant difference in lipid parameters in hypomagnesemia diabetic patients before and after Mg supplementation with a significant reduction in serum triglycerides, LDL, and total cholesterol after Mg supplementation with p<0.001.

Although HDL showed a significant increase after Mg supplementation in diabetic hypomagnesemia children with p <0.001. The correction of hypomagnesemia in type 1 diabetic children with oral supplements of Mg salts is associated with the
optimization of glycemic control and the reduction of the atherogenic lipid fraction, as well as the increase in the protective lipid fraction [5].

Thus, further studies are needed to better clarify the role of magnesium in the prevention and treatment of cardiovascular diseases, especially concerning higher concentrations and increased treatment time [44-55].

Main Nutritional Evidence for Vitamin D

The primary source of vitamin D depends on the skin Exposure to sunlight and up to 20% comes from ingestion. It is still controversial whether the consumption of foods containing vitamin D has a direct impact on its circulating levels [56-60]. Vitamin D2 (ergocalciferol) is found in yeast, mushrooms, and some vegetables, and vitamin D3 (cholecalciferol) in foods of animal origin. The latter is synthesized in the skin using ultraviolet radiation [61].

To be biologically active, vitamin D undergoes hydroxylations in the liver mediated by 25-hydroxylase, and in the kidney, by 1α-hydroxylase 1,25(OH)2D is recognized by its specific receptors (VDRs) in several cells, primarily in the gut to increase calcium uptake, and bone to regulate skeletal homeostasis [62-63]. Altered metabolic patterns result in metabolic disturbances of calcium and phosphorus, but, well-known, vitamin D disorders have been implicated in some other diseases [64].

Besides, vitamin D plays important role in innate and adaptive immune responses, cell cycle, and metabolic processes, evidenced by the reported relationship between its deficiency and the prevalence of immunity-mediated disorders, cancer, and cardiometabolic diseases [61-64]. An inverse correlation between their concentrations and the prevalence of obesity and type 2 diabetes mellitus has been described [65,66].

The VDR results in β cells, endothelium, cardiac myocytes, and renin production suggesting a role for vitamin D in these diseases [67-69]. In addition, there is evidence that vitamin D deficiency increases inflammatory cytokines and reduces insulin sensitivity, which has been described as pathophysiological links between cardiometabolic diseases [69,70].

More recently, metabolism-induced intestinal microbiota has been associated with an increase in cardiometabolic risk [71]. Since vitamin D plays a role in modulating the immune system in the gut, a deficiency could impair intestinal barrier function by favoring the translocation of endotoxins such as lipopolysaccharides (LPSs) into circulation. LPS are known for low-grade inflammation, which predisposes insulin resistance [72,73]. Numerous circulating biomarkers have been used to assess clinical inflammation [74] and investigation [75,76].

Main Nutritional Evidence for Coenzyme Q10

Fredrick Crane, in 1957, discovered Coenzyme Q10 (ubiquinone) in the mitochondria of the ox’s heart, and, in 1958, its physicochemical properties were revealed [77]. This compound is a quinone, similar to a vitamin, and is liposoluble and a crystalline powder in its pure form [78]. Coenzyme Q10 is designated as 2,3-dimethoxy-5-methyl-6-decaprenyl-1,4-benzoquinone. It derives from the conjugation of the benzoquinone ring to a hydrophobic chain of isoprenoids, all in a trans configuration and with a double bond, and is lipophilic. In humans, Q10 has 10 units of isoprenes [79,80].

Besides, coenzyme Q10 is part of the electron transport chain and is found in large concentrations in the mitochondria, especially in the muscles, brain, and heart. However, because they are organs that are more vulnerable to the action of oxygen free radicals, Q10 exerts an important protective antioxidant action. However, due to aging, genetics, and statin consumption, the amount of Q10 is decreased [81,82].

Clinical studies have shown that in pathologies such as acute myocardial infarction, arterial hypertension, and myopathies induced by statins, physical fatigue inherent in physical exercise, male infertility, preeclampsia, Parkinson’s disease, periodontal disease, and migraine had low plasma concentrations of Q10 [83,84].

Its synthesis can occur via the cycle of mevalonate, responsible for the production of cholesterol, or can be obtained by feeding, however, the amount obtained by these means can not be enough. Clinical studies have shown that the use of Coenzyme Q10 (from 30 mg day-1 to 3000 mg day-1) is critical to inhibit the progression and even reduction of the above-mentioned diseases [77].

The dose of Coenzyme Q10 that can be obtained with food intake, about 2-5 mg dia-1, is not sufficient to meet the needs of the organism [76], because only 10.0% is absorbed slowly from the intestinal tract due to its high molecular mass and its low solubility in water [73].

The cytotoxicity of natural killer cells in the population of healthy older women is dependent on the plasma concentration of Coenzyme Q10 [78]. It is also able to alter the immune response by lowering the pro-inflammatory cytokines IL-6 and TNF-α that are involved in the progression of myocardial infarction [79]. In addition, Coenzyme Q10 reduces the number of lipid
peroxides found in atherosclerotic lesions [78-82]. Thus, Q10 protects the lipids present in cell membranes, as well as plasma lipoproteins [80-84].

Conclusion

Studies have shown that magnesium deficiency or changes in its metabolism are related to the pathophysiology of hypertension, arrhythmias, preeclampsia, insulin resistance, and diabetes. Vitamin D plays an important role in innate and adaptive immune responses, cell cycle, and metabolic processes, evidenced by the reported relationship between its deficiency and the prevalence of immunity-mediated disorders, cancer, and cardiometabolic diseases. The VDR results in β cells, endothelium, cardiac myocytes, and renin production suggesting a role for vitamin D in these diseases. Coenzyme Q10 is part of the electron transport chain and is found in large concentrations in the mitochondrial, especially in the muscles, brain, and heart. Clinical studies have shown that pathologies such as acute myocardial infarction, arterial hypertension, and myopathies induced by statins, physical fatigue inherent in physical exercise, male infertility, preeclampsia, Parkinson's disease, periodontal disease, and migraine had low plasma concentrations of coenzyme Q10.

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Data sharing statement

No additional data are available.

Conflict of interest

The authors declare no conflict of interest.

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