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REVIEW ARTICLE

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Metabolic effects of coenzyme Q10, magnesium and vitamin D in cardiovascular diseases: a systematic review

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Abstract

Introduction: Cardiovascular diseases (CVD) are the main causes of death in the population. According to data from the World Health Organization for 2020, of the 20.8 million deaths from these diseases, 9.2 million are due to atherosclerotic coronary disease. In this context, the beneficial metabolic effects of magnesium, vitamin D, and coenzyme Q10 can be highlighted. **Objective:** It was to scientifically analyze, through clinical and experimental studies, the influence of the three elements Magnesium, Vitamin D, and Coenzyme Q10 concerning cardiovascular diseases and metabolic syndrome, highlighting the improvement of metabolic disorders and heart failure. **Methods:** The systematic review rules of the PRISMA Platform were followed. The research was carried out from September to November 2022 in Scopus, PubMed, Science Direct, Scielo, and Google Scholar databases. The quality of the studies was based on the GRADE instrument and the risk of bias was analyzed according to the Cochrane instrument. **Results and Conclusion:** A total of 154 articles were found, and 80 articles were evaluated and 78 were included in this systematic review. Considering the Cochrane tool for risk of bias, the overall assessment resulted in 18 studies with a high risk of bias and 26 studies that did not meet GRADE. Most studies showed homogeneity in their results, with I2 =95.7% >50%. It was concluded that magnesium plays a fundamental role in glucose metabolism, insulin, and glycemic homeostasis, in the synthesis of adenosine triphosphate, proteins, and nucleic acids. However, 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. 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 immune-mediated disorders, cancer, and cardiometabolic diseases. Coenzyme Q10 exerts an important protective antioxidant action. Clinical studies carried out showed that pathologies such as acute myocardial infarction, arterial hypertension, myopathies induced by statins, physical fatigue inherent to physical exercise, male infertility, pre-eclampsia, Parkinson's disease, periodontal diseases, and migraines had low plasma concentrations of Q10. In addition, Coenzyme Q10 reduces the amount of lipid peroxide found in atherosclerotic lesions. Thus, Q10 protects the lipids present in cell membranes, as well as plasma lipoproteins.

Keywords: Cardiovascular diseases. Magnesium. Vitamin D. Coenzyme Q10. Metabolic processes.

Introduction

Cardiovascular diseases (CVD) are the main causes of death in the population. According to data from the World Health Organization for 2020, of the 20.8 million deaths from these diseases, 9.2 million are due to atherosclerotic coronary disease (ACD) **[1]**. ACD is the most common cause of mortality in developed countries **[1,2]**. Comparing Brazilian patients with stable ACD aged 40 to 75 years per 1,000 inhabitants with those from European countries, Brazil (58.4%) is surpassed only by England (59.0%) and Spain (81.5%) **[1]**. This disease is the main cause of death in some countries in

South America, such as Argentina (12.0%), Bolivia (11.0%), and Ecuador (8.0%) **[3]**. In Brazil, it is responsible for a large number of deaths and health expenses **[1]**.

In this context, one can highlight the beneficial metabolic effects of magnesium, as it acts as a cofactor in more than 300 metabolic reactions, playing a fundamental role in glucose metabolism, insulin, and glucose homeostasis; in the synthesis of adenosine triphosphate, proteins, and nucleic acids, more studies are needed to clarify the role of magnesium in the prevention and treatment of cardiovascular diseases, mainly concerning higher concentrations and longer treatment time **[4-12]**.

In this scenario, 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 immune-mediated disorders, cancer, and cardiometabolic diseases. An inverse correlation between their concentrations and the prevalence of obesity and type 2 diabetes mellitus has been described **[13-16]**.

Moreover, coenzyme Q10 is part of the electron transport chain and is found in high concentrations in mitochondria, mainly in muscles, the brain, and the heart **[17, 18]**. However, as they are more vulnerable organs 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 **[19]**.

Clinical studies have shown that pathologies such as acute myocardial infarction, arterial hypertension, myopathies induced by statins, physical fatigue inherent to physical exercise, male infertility, pre-eclampsia, 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 **[17, 19, 20]**.

In this sense, the present study aimed to scientifically analyze, through clinical and experimental studies, the influence of the three elements Magnesium, Vitamin D, and Coenzyme Q10 on cardiovascular diseases and metabolic syndrome, highlighting the improvement of metabolic disorders and heart failure.

Methods

Study Design

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

Search Strategy and Search Sources

The literary search process was carried out from September to November 2022 and was developed based on Scopus, PubMed, Science Direct, Scielo, and Google Scholar, addressing scientific articles from various eras to the present day. The descriptors (MeSH Terms) were used: "Cardiovascular diseases. Magnesium. Vitamin D. Coenzyme Q10. Metabolic processes" (Cardiovascular diseases. Magnesium. Vitamin D. Coenzyme Q10. Metabolic processes), and using the Boolean "and" between MeSH terms and "or" between 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, accuracy, and consistency of analyses. The most evident emphasis was on 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 graph (Sample size versus Effect size), using Cohen's test (d).

Results and discussion

Summary of Findings

As a corollary of the literary search system, a total of 154 articles were found that were submitted to the eligibility analysis, and, then, 78 of the 80 final studies were selected to compose the results of this systematic review. The listed studies showed medium to high quality (Figure 1), considering in the first instance the level of scientific evidence of studies in types of study 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=95.7%>50%. Considering the Cochrane tool for risk of bias, the overall assessment resulted in 18 studies with a high risk of bias and 26 studies that did not meet GRADE.

Figure 1. Flowchart showing the article selection process.

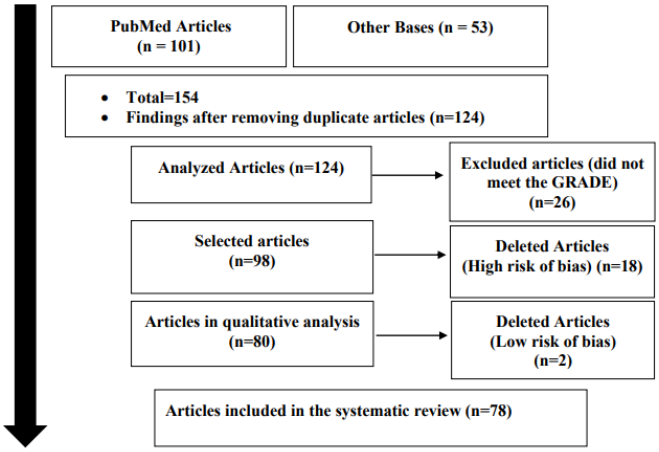
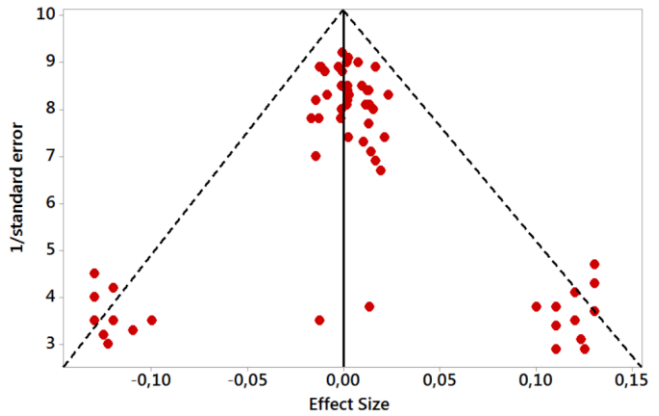


Figure 2 presents the results of the risk of bias of the studies through the Funnel Plot, showing the calculation of the Effect Size (Magnitude of the difference) using the Cohen Test (d). Precision (sample size) was indirectly determined by the inverse of the standard error (1/Standard Error). This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

Figure 2. The symmetrical funnel plot does not suggest a risk of bias among the small sample size studies that are shown at the bottom of the plot. High confidence and high recommendation studies are shown above the graph (n=78 studies).



Source: Own authorship.

Main Clinical Findings

Evidence for Magnesium Salts

Magnesium acts as a cofactor in over 300 metabolic reactions, playing a key role in glucose metabolism, insulin, and glucose homeostasis; in the synthesis of adenosine triphosphate, proteins, and nucleic acids **[4, 5]**. It also acts in the stability of the neuromuscular and cardiovascular membrane, in the maintenance of the vasomotor tonus, and as a physiological regulator of the hormonal and immunological function **[4-8]**.

The Recommended Dietary Allowance (RDA) for magnesium is 400 to 420 mg per day for adult men and 310 to 320 mg per day for adult women. However, consumption is well below this recommendation and the high prevalence of this deficiency has been associated with several chronic diseases **[9, 10]**.

The mineral magnesium is the second most abundant intracellular cation and is involved in several important biochemical reactions **[11, 21]**. It is known that magnesium has an antiarrhythmic effect, and acts on vascular tone, as changes in the extracellular content of magnesium are capable of modifying the formation and release of nitric oxide (NO), resulting in changes in the tone of the smooth muscle artery and the contractility 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, pre-eclampsia, insulin resistance, and diabetes **[22-24]**. Lower magnesium concentrations are associated with reduced HDL cholesterol, increased LDL cholesterol, and triglycerides **[25]**. Furthermore, the deficiency of this mineral has already been related to oxidative stress, pro-inflammatory state, endothelial dysfunction, platelet aggregation, insulin resistance, and hyperglycemia **[26]**.

Besides, magnesium supplementation can increase intracellular adenosine triphosphate (ATP) production and glucose utilization, as magnesium acts as a cofactor for all reactions involving ATP transfer **[27]**. In addition, magnesium also activates the Na-K ATPase pump that controls the balance of these minerals, thus contributing to electrolyte homeostasis in cells **[28]**. Magnesium's action as a calcium channel blocker may also contribute to reducing calcium release and thus reducing vascular resistance **[29-31]**.

Regarding insulin homeostasis, there is a hypothesis that, in hypomagnesemia, there would be an increase in insulin and adrenaline secretion in an attempt to maintain the concentration of cellular magnesium and cAMP (cyclic adenosine 3',5'-monophosphate) **[32]**. In addition, the intracellular concentration of magnesium seems to be dependent on the extracellular level, with its influx through voltage-dependent calcium channels **[33-36]**. Extracellular magnesium can competitively inhibit these channels and 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, increasing insulin secretion **[37]**.

Experimental, clinical, and epidemiological studies have observed a close and inverse relationship between dietary or supplemental magnesium intake and BP level, indicating the potential role of magnesium deficiency in the pathogenesis of primary hypertension **[38]**. Patients with hypertension without BP control presented hypomagnesemia, and Ambulatory BP Measurement (ABPM), is considered an important tool in the evaluation of treatments that affect the circadian pressure cycle, Lasaridis et al. It demonstrated that magnesium supplementation was associated with a slight reduction in blood pressure levels in patients with mild hypertension **[39, 40]**.

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 by reducing oxidative stress and its anti-inflammatory action **[41]**.

The role of magnesium in endothelial dysfunction has been discussed in the literature **[42]**. 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 **[43]**. Peripheral vascular resistance can also be modified by magnesium, through the regulation of responses to vasoactive agents, mainly angiotensin II, endothelin, and prostacyclin **[44]**.

A study that followed more than 90,000 menopausal women showed that dietary magnesium intake was inversely associated with plasma concentrations of inflammatory markers such as IL-6, Creactive protein (CRP), and TNF-alpha. This same study reinforced that magnesium intake would improve the inflammatory process and endothelial dysfunction, and may play a role in preventing metabolic syndrome **[41]**.

Furthermore, hypomagnesemia is associated with type 2 diabetes mellitus and its complications. This study was conducted among 150 types 2 diabetic patients and 150 non-diabetic controls between May and September 2016. Relevant demographic, anthropometric, physiological, and biochemical variables were measured using standardized protocols. Half of type 2 diabetic population studied had hypomagnesemia regardless of the method of diabetes control. Advanced age and poor glycemic control were significant predictors of low serum magnesium levels in these patients **[24]**.

Thus, dietary supplementation with magnesium, in addition to classical diabetes therapies, may help to prevent or delay diabetic complications **[45-53]**. Another study aimed to assess serum Mg status in children with type 1 diabetes and to assess its relationship with glycemic control and lipid profile **[4]**. Then, to evaluate the effect of oral supplementation of Mg salts on glycemic control and lipid parameters. Seventy-one children were enrolled at the Pediatric Endocrinology Outpatient Clinic at the University of Zagazig, Egypt, with type 1 diabetes and assessed for HBA1c, lipid profile, and serum and ionic Mg levels at baseline. 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 hypomagnesemia diabetic 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 of the protective lipid fraction **[4]**.

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 longer treatment times.

Vitamin D

The primary source of vitamin D depends on skin exposure to sunlight and up to 20% comes from intake. It is still controversial whether the consumption of foods containing vitamin D has a direct impact on its circulating levels **[54, 55]**. Vitamin D2 (ergocalciferol) is found in yeast, mushrooms, and some vegetables, and vitamin D3 (cholecalciferol) is in animal foods. The latter is synthesized in the skin through ultraviolet radiation **[56]**.

To be biologically active, vitamin D undergoes hydroxylation in the liver mediated by 25- hydroxylase and in the kidneys by 1α-hydroxylase 1,25(OH) 2 D is recognized by its specific receptors (VDRs) on various cells, mainly in the gut to enhance calcium uptake and bone to regulate skeletal homeostasis **[57,58]**. Altered metabolic patterns result in calcium and phosphorus metabolic disturbances, but well-known vitamin D disturbances have been implicated in some other diseases **[59]**.

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 immune-mediated disorders, cancer, and cardiometabolic diseases **[60-63]**. An inverse correlation between their concentrations and the prevalence of obesity and type 2 diabetes mellitus has been described **[64]**. VDR results on β cells, endothelium, cardiac myocytes, and renin production suggest a role for vitamin D in these diseases **[65-67]**. Furthermore, there is evidence that vitamin D deficiency increases inflammatory cytokines and reduces insulin sensitivity, which has been described as pathophysiological links between cardiometabolic diseases **[68]**.

In addition, the metabolism-induced gut microbiota has been associated with an increase in cardiometabolic risk **[69]**. As vitamin D plays a role in modulating the immune system in the intestine, its deficiency may impair the function of the intestinal barrier, favoring the translocation of endotoxins such as lipopolysaccharides (LPSs) into circulation. LPS are known for low-grade inflammation, which predisposes to insulin resistance **[70]**. Numerous circulating biomarkers have been used to assess clinical and investigational inflammation **[71-73]**.

Coenzyme Q10 (Ubiquinone)

Fredrick Crane, in 1957, discovered Coenzyme Q10 in beef heart mitochondria, and, in 1958, its physical-chemical properties were revealed **[17]**. This compound is a quinone, similar to a vitamin, it is fat-soluble and a crystalline powder in its pure form **[18]**. Coenzyme Q10 is designated as 2,3-dimethoxy5-methyl-6-decaprenyl-1,4-benzoquinone **[19]**. It derives from the conjugation of the benzoquinone ring to a hydrophobic chain of isoprenoids, all in trans configuration and with a double bond, and has a lipophilic character. In humans, Q10 has 10 isoprene units **[20]**.

In this scenario, coenzyme Q10 is part of the electron transport chain and is found in high concentrations in mitochondria, mainly in muscle, brain, and heart **[74]**. However, as they are more vulnerable organs 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 **[75-78]**.

In this context, clinical studies have shown that pathologies such as acute myocardial infarction, arterial hypertension, myopathies induced by statins, physical fatigue inherent to physical exercise, male infertility, pre-eclampsia, Parkinson's disease, periodontal disease, and migraine had low plasma concentrations of Q10 **[20]**. The synthesis of Q10 can occur via the mevalonate cycle, responsible for the production of cholesterol, or it can be obtained through food, but the amount obtained by this route may not be sufficient **[17]**. Clinical studies have shown that the use of Coenzyme Q10 (from 30 mg day1 to 3000 mg day-1) is essential to inhibit the progression and even the reduction of the diseases mentioned above **[20]**.

The dose of Coenzyme Q10 that can be obtained with food intake, about 2-5 mg day-1, is not enough to meet the body's needs **[78]**, as only 10.0% is slowly absorbed by the intestinal tract due to its high molecular weight and its low solubility in water.

Furthermore, the cytotoxicity of natural killer cells in the population of healthy elderly women depends on the plasmatic concentration of Coenzyme Q10 **[17]**. It is also capable of altering the immune response by decreasing the pro-inflammatory cytokines IL-6 and TNF-α that are involved in the progression of myocardial infarction. Additionally, 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 **[17, 20, 75]**.

Conclusion

It was concluded that magnesium plays a fundamental role in glucose metabolism, insulin, and glycemic homeostasis, in the synthesis of adenosine triphosphate, proteins, and nucleic acids. However, 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. 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 immunemediated disorders, cancer, and cardiometabolic diseases. Coenzyme Q10 exerts an important protective antioxidant action. Clinical studies carried out showed that pathologies such as acute myocardial infarction, arterial hypertension, myopathies induced by statins, physical fatigue inherent to physical exercise, male infertility, pre-eclampsia, Parkinson's disease, periodontal diseases, and migraines had low plasma concentrations of Q10. In addition, Coenzyme Q10 reduces the amount of lipid peroxide found in atherosclerotic lesions. Thus, Q10 protects the lipids present in cell membranes, as well as plasma lipoproteins.

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The authors declare no conflict of interest.

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