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REVIEW ARTICLE

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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.

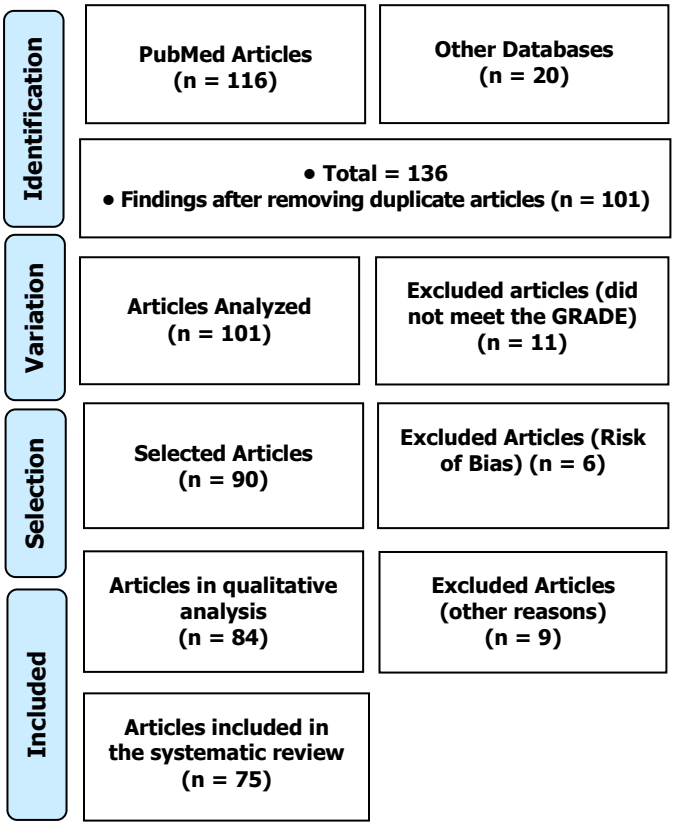
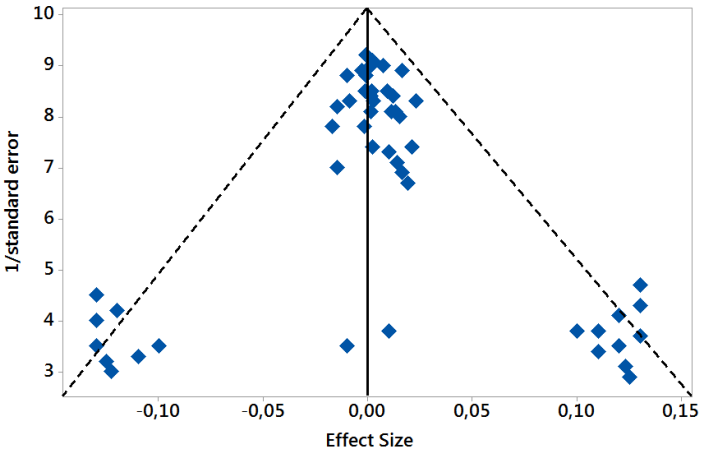


Figure 2 presents the results of the risk of bias of the studies using the Funnel Plot, showing the calculation of the Effect Size (Magnitude of the difference) using the Cohen Test (d). Sample size was determined indirectly by the inverse of the standard error (1/Standard Error). This graph had a symmetrical 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]**.

Figure 2. The symmetrical funnel plot suggests no risk of bias between 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 (NTotal=75 studies evaluated in full in the systematic review).



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.

References

1. Fernandes ADF, Fernandes GC, Mazza MR, Knijnik LM, Fernandes GS, Vilela AT, Badiye A, Chaparro SV. A 10-Year Trend Analysis of Heart Failure in the Less Developed Brazil. Arq Bras Cardiol. 2020 Feb;114(2):222-231. doi: 10.36660/abc.20180321.
2. Virani SS, Alonso A, Aparicio HJ, et al. Heart disease and stroke statis-tics–2021 update: a report from the American Heart Association. Circula-tion. 2021;143:e254–e743.
3. Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, Deswal A, Drazner MH, Dunlay SM, Evers LR, Fang JC, Fedson SE, Fonarow GC, Hayek SS, Hernandez AF, Khazanie P, Kittleson MM, Lee CS, Link MS, Milano CA, Nnacheta LC, Sandhu AT, Stevenson LW, Vardeny O, Vest AR, Yancy CW. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation. 2022 May 3;145(18):e895-e1032. doi: 10.1161/CIR.0000000000001063. Epub 2022 Apr 1. Erratum in: Circulation. 2022 May 3;145(18):e1033. Erratum in: Circulation. 2022 Sep 27;146(13):e185.
4. Vest AR, Chan M, Deswal A, Givertz MM, Lekavich C, Lennie T, Litwin SE, Parsly L, Rodgers JE, Rich MW, Schulze PC, Slader A, Desai A. Nutrition, Obesity, and Cachexia in Patients With Heart Failure: A Consensus Statement from the Heart Failure Society of America Scientific Statements Committee. J Card Fail. 2019 May;25(5):380-400. doi: 10.1016/j.cardfail.2019.03.007.
5. Tangvoraphonkchai K, Davenport A. Magnesium and Cardiovascular Disease. Adv Chronic Kidney Dis. 2018 May;25(3):251-260. doi: 10.1053/j.ackd.2018.02.010. PMID: 29793664.
6. Shrimanker I, Bhattarai S. Electrolytes. 2021 Jul 26. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan–. PMID: 31082167.
7. Kikuchi K, Tanaka H, Gima M, Kashiwagi Y, Shida H, Kawamura Y, Hasebe N. [Abnormalities of magnesium (Mg) metabolism and therapeutic significance of Mg administration in patients with metabolic syndrome, type 2 diabetes, heart failure and chronic hemodialysis]. Clin Calcium. 2012 Aug;22(8):1217-26. Japanese. PMID: 22846358.
8. Voultsos P, Bazmpani MA, Papanastasiou CA, Papadopoulos CE, Efthimiadis G, Karvounis H, Kalogeropoulos AP, Karamitsos TD. Magnesium disorders and prognosis in heart failure: A systematic review. Cardiol Rev. 2021 May 12. doi: 10.1097/CRD.0000000000000397. Epub ahead of

print. PMID: 34001688.

9. Liu M, Dudley SC Jr. Magnesium, Oxidative Stress, Inflammation, and Cardiovascular Disease. Antioxidants (Basel). 2020 Sep 23;9(10):907. doi: 10.3390/antiox9100907. PMID: 32977544; PMCID: PMC7598282.
10. Peter J. Joris, Jogchum Plat, Stephan JL, Bakker, Ronald P. Mensink. Effects of long-term magnesium supplementation on endothelial function and cardiometabolic risk markers: A randomized controlled trial in overweight/obese adults. Scientific Reports 2017, 7: 106.
11. Baker WL. Treating arrhythmias with adjunctive magnesium: identifying future research directions. Eur Heart J Cardiovasc Pharmacother. 2017; 1;3(2):108117.
12. Yu L, Li H, Wang SX. Serum Magnesium and Mortality in Maintenance Hemodialysis Patients. Blood Purif. 2017;43(13): 3136.
13. Amorim AG, Tirapegui J. Aspectos atuais da relação entre exercício físico, estresse oxidativo e magnésio. Rev Nutr, 2008; 21(5):563-75.
14. Vieth R. Vitamin D supplementation, 25-hydroxyvitamin D concentrations, and safety. Am J Clin Nutr 1999;69(5):842–56.
15. Schuch NJ, Garcia VC, Martini LA. Vitamin D and endocrine diseases. Arq Bras Endocrinol Metab 2009;53(5):625–33.
16. Tóth Š, Šajty M, Pekárová T, Mughees A, Štefanič P, Katz M, Spišáková K, Pella J, Pella D. Addition of omega-3 fatty acid and coenzyme Q10 to statin therapy in patients with combined dyslipidemia. J Basic Clin Physiol Pharmacol. 2017.
17. Kumar A, Kaur H, Devi P, Mohan V. Role of coenzyme Q10 (CoQ10) in cardiac disease, hypertension and Meniere-like syndrome. Pharmacology & Therapeutics, 2010, 124: 259-268.Baaij JHF, Hoenderop JGJ, Bindels RJM. Regulation of magnesium balance: lessons learned from human genetic disease. Clin Kidney J, 2012; 5(1):i15-i24.
18. Blanchard A, Vargas-Poussou R. Désordres de la magnésémie. Nephrol Ther, 2012; 8(6):482-91.
19. Elin RJ. Assessment of magnesium status for diagnosis and therapy. Magnes Res, 2010; 23(4):194-8.
20. Hata A, Doi Y, Ninomiya T, Mukai N, Hirakawa Y, Hata J, et al. Magnesium intake decreases Type 2 diabetes risk through the improvement of insulin resistance and inflammation: the Hisayama Study. Diabet Med, 2013; 30(12):1487-94.
21. Oost LJ, van der Heijden AAWA, Vermeulen EA, Bos C, Elders PJM, Slieker RC, Kurstjens S, van Berkel M, Hoenderop JGJ, Tack CJ, Beulens JWJ, de Baaij JHF. Serum Magnesium Is Inversely Associated With Heart Failure, Atrial Fibrillation, and Microvascular Complications in Type 2 Diabetes. Diabetes Care. 2021 Aug;44(8):1757-1765. doi: 10.2337/dc21-0236. Epub 2021 Jun 18. PMID: 34385344.
22. Houillier P. Mechanisms and regulation of renal magnesium transport. Annu Rev Physiol, 2014; 76:411-30. Jahnen-Dechent W, Ketteler M. Magnesium basics. Clin Kidney J, 2012; 5(1):i3–i14.
23. Fang X. et al. Dietary magnesium intake and the risk of cardiovascular disease, type 2 diabetes, and all-cause mortality: a doseresponse meta-analysis of prospective cohort studies. BMC Med. 2016; 14, 210.
24. Del Gobbo LC. et al. Circulating and dietary magnesium and risk of cardiovascular disease: a systematic review and meta-analysis of prospective studies. Am. J. Clin. Nutr. 2013; 98, 160–173.
25. Joosten MM. et al. Urinary and plasma magnesium and risk of ischemic heart disease. Am. J. Clin. Nutr. 2013; 97, 1299–1306.
26. Joris PJ, Plat J, Bakker SJ, Mensink RP. Long-term magnesium supplementation improves arterial stiffness in overweight and obese adults: results of a randomized, double-blind, placebo-controlled intervention trial. Am. J. Clin. Nutr. 2016; 103, 1260–1266.
27. Laurent S. et al. Expert consensus document on arterial stiffness: methodological issues and clinical applications. Eur. Heart J. 2006; 27, 2588–2605.
28. Wilkinson IB. et al. Nitric oxide regulates local arterial distensibility in vivo. Circulation. 2002; 105, 213–217.
29. Guerrero-Romero F. et al. Oral magnesium supplementation improves insulin sensitivity in non-diabetic subjects with insulin resistance. A double-blind placebo-controlled randomized trial. Diabetes Metab. 2004; 30, 253–258.
30. Paolisso G. et al. Daily magnesium supplements improve glucose handling in elderly subjects. Am. J. Clin. Nutr. 1992; 55, 1161–1167.
31. Marken PA. et al. Effects of magnesium oxide on the lipid profile of healthy volunteers. Atherosclerosis. 1989; 77, 37–42.
32. Chacko SA. et al. Magnesium supplementation, metabolic and inflammatory markers, and global

genomic and proteomic profiling: a randomized, double-blind, controlled, crossover trial in overweight individuals. Am. J. Clin. Nutr. 2011; 93, 463–473.

33. Cosaro E. et al. Effects of magnesium supplements on blood pressure, endothelial function and metabolic parameters in healthy young men with a family history of metabolic syndrome. Nutr. Metab. Cardiovasc. Dis. 2014; 24, 1213–1220.
34. Mortazavi M. et al. Effect of magnesium supplementation on carotid intima-media thickness and flow-mediated dilatation among hemodialysis patients: a double-blind, randomized, placebo-controlled trial. Eur. Neurol.2013; 69, 309–316.
35. Shechter M. et al. Oral magnesium therapy improves endothelial function in patients with coronary artery disease. Circulation. 2000; 102, 2353–2358.
36. Ellins EA, Halcox JP. Where are we heading with noninvasive clinical vascular physiology? Why and how should we assess endothelial function? Cardiol. Res. Pract 2011, 870132.
37. Poredos P, Jezovnik MK. Testing endothelial function and its clinical relevance. J. Atheroscler. Thromb. 2013; 20, 1–8.
38. Deanfield JE, Halcox JP, Rabelink TJ. Endothelial function and dysfunction: testing and clinical relevance. Circulation. 2007; 115, 1285–1295.
39. Cohn JN, Quyyumi AA, Hollenberg NK, Jamerson KA. Surrogate markers for cardiovascular disease: functional markers. Circulation. 2004; 109, IV31–IV46.
40. Beijers HJ. et al. Higher central fat mass and lower peripheral lean mass are independent determinants of endothelial dysfunction in the elderly: the Hoorn study. Atherosclerosis. 2014; 233, 310–318.
41. Despres JP, Lemieux I. Abdominal obesity and metabolic syndrome. Nature. 2006; 444, 881–887.
42. Ras RT, Streppel MT, Draijer R, Zock PL. Flow-mediated dilation and cardiovascular risk prediction: a systematic review with meta-analysis. Int. J. Cardiol.2013; 168, 344–351.
43. Seelig M. Cardiovascular consequences of magnesium deficiency and loss: pathogenesis, prevalence and manifestations-magnesium and chloride loss in refractory potassium repletion. Am. J. Cardiol.1989; 63, 4G–21G.
44. Turgut F. et al. Magnesium supplementation helps to improve carotid intima media thickness in patients on hemodialysis. Int. Urol. Nephrol. 2008; 40, 1075–1082.
45. Lorenz MW. et al. Prediction of clinical cardiovascular events with carotid intima-media thickness: a systematic review and metaanalysis. Circulation. 2007; 115, 459–467.
46. Calder PC. et al. A consideration of biomarkers to be used for evaluation of inflammation in human nutritional studies. Br. J. Nutr. 2013, 109, S1–S34.
47. Cunha AR, Umbelino B, Correia ML, Neves MF. Magnesium and vascular changes in hypertension. Int. J. Hypertens. 2012, 754250.
48. Song Y, He K, Levitan EB, Manson JE, Liu S. Effects of oral magnesium supplementation on glycaemic control in Type 2 diabetes: a meta-analysis of randomized double-blind controlled trials. Diabet. Med. 2006; 23, 1050–1056.
49. Simental-Mendia LE, Sahebkar A, Rodriguez-Moran M, Guerrero-Romero F. A systematic review and meta-analysis of randomized controlled trials on the effects of magnesium supplementation on insulin sensitivity and glucose control. Pharmacol. Res.2016; 111, 272–282.
50. Heil W, Ehrhardt V. Reference ranges for adults and children. Pre-analytical considerations in Roche Diagnostics 9th Edition (2008).
51. Moslehi N, Vafa M, Rahimi-Foroushani A, Golestan B. Effects of oral magnesium supplementation on inflammatory markers in middle-aged overweight women. J. Res. Med. Sci. 2012; 17, 607–614.
52. Van Mil AC. et al. Impact of volunteer-related and methodology-related factors on the reproducibility of brachial artery flowmediated vasodilation: analysis of 672 individual repeated measurements. J. Hypertens. 2016; 34, 1738–1745.
53. Maier JA, Malpuech-Brugère C, Zimowska W, Rayssiguier Y, Mazur A. Low magnesium promotes endothelial cell dysfunction: implications for atherosclerosis, inflammation and trombosis. Biochim. Biophys. Acta. 2004; 1689, 13–21.
54. Maier JA. Endothelial cells and magnesium: implications in atherosclerosis. Clin. Sci. (Lond.)2012; 122, 397–407.
55. Santulli G. MicroRNAs and Endothelial (Dys) Function. J. Cell Physiol. 2016; 231, 1638–1644 .
56. Sorriento D. et al. Endothelial cells are able to synthesize and release catecholamines both in vitro and in vivo. Hypertension. 2012; 60, 129–

136.

57. Nesby-O'Dell S, Scanlon KS, Cogswell ME, Gillespie C, Hollis BW, Looker AC, et al. Hypovitaminosis D prevalence and determinants among African American and white women of reproductive age: third National Health and Nutrition Examination Survey, 1988–1994. Am J Clin Nutr 2002;76(1):187–92.
58. Hollis BW. Circulating 25-hydroxyvitamin D levels indicative of vitamin D sufficiency: implications for establishing a new effective dietary intake recommendation for vitamin D. J Nutr 2005;135(2):317–22.
59. Hyppönen E, Power C. Hypovitaminosis D in British adults at age 45 y: nationwide cohort study of dietary and lifestyle predictors. Am J Clin Nutr 2007;85(3):860–8.
60. Wang TJ, Pencina MJ, Booth SL, Jacques PF, Ingelsson E, Lanier K, et al. Vitamin D deficiency and risk of cardiovascular disease. Circulation 2008;117(4):503–11.
61. Salehpour A, Shidfar F, Hosseinpanah F, Vafa M, Razaghi M, Hoshiarrad A, et al. Vitamin D 3 and the risk of CVD in overweight and obese women: a randomized controlled trial. Br J Nutr 2012;108(10):1866–73. S0007114512000098.
62. Hewison M. Vitamin D and the immune system: new perspectives on an old theme. Endocrinol Metab Clin North Am 2010;39(2):365–79.
63. Cantorna MT. Vitamin D and its role in immunology: multiple sclerosis, and inflammatory bowel disease. Prog Biophys Mol Biol 2006;92(1):60–4.
64. Michos ED, Melamed ML. Vitamin D and cardiovascular disease risk. Curr Opin Clin Nutr Metab Care 2008;11(1):7–12. http://dx.doi.org/10.1097/MCO.0b013e3282f2f4dd.
65. Vaidya A. Vitamin D and cardio-metabolic disease. Metabolism 2013;62(12):1697.
66. Wolden-Kirk H, Overbergh L, Christesen HT, Brusgaard K, Mathieu C. Vitamin D and diabetes: its importance for beta cell and immune function. Mol Cell Endocrinol 2011;347(1): 106–20.
67. Kim HJ, Kang CK, Park H, Lee MG. Effects of vitamin D supplementation and circuit training on indices of obesity. and insulin resistance in T2D and vitamin D deficient elderly women. J Exerc Nutr Biochem 2014;18(3):249.
68. Chiu KC, Chu A, Go VLW, Saad MF. Hypovitaminosis D is associated with insulin resistance and β cell dysfunction. Am J Clin Nutr 2004;79(5):820–5.
69. Norman PE, Powell JT. Vitamin D and cardiovascular disease. Circ Res 2014;114(2):379–93.
70. Herrmann M, Sullivan DR, Veillard A, McCorquodale T, Straub IR, Scott R, et al. Serum 25-Hydroxy vitamin D: a predictor of macrovascular and microvascular complications in patients with type 2 diabetes. Diabetes Care 2014;38(3): 521–8.
71. Wellen KE, Hotamisligil GS. Inflammation, stress, and diabetes. J Clin Invest 2005;115(5):1111–9.
72. Cani PD, Delzenne NM. Gut microflora as a target for energy and metabolic homeostasis. Curr Opin Clin Nutr Metab Care 2007;10(6):729–34.. 0b013e3282efdebb.
73. Caricilli AM, Picardi PK, de Abreu LL, Ueno M, Prada PO, Ropelle ER, et al. Gut microbiota is a key modulator of insulin resistance in TLR 2 knockout mice. PLoS Biol 2011; 9(12):e1001212.
74. Moraes ACF, Silva IT, Almeida-Pititto B, Ferreira SRG. Microbiota intestinal e risco cardiometabólico: mecanismos e modulação dietética. Arq Bras Endocrinol Metab 2014;58(4): 317–27.
75. Ridker PM, Buring JE, Shih J, Matias M, Hennekens CH. Prospective study of C-reactive protein and the risk of future cardiovascular events among apparently healthy women. Circulation 1998;98(8):731–3.
76. Calder PC, Ahluwalia N, Albers R, Bosco N, Bourdet-Sicard R, Haller D, et al. A consideration of biomarkers to be used for evaluation of inflammation in human nutritional studies. Br J Nutr 2013;109(S1):S1–S34.
77. Almeida-Pititto B, Ribeiro-Filho FF, Bittencourt MS, Lotufo PA, Bensenor I, Ferreira SR. Usefulness of circulating E-selectin to early detection of the atherosclerotic process in the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil). Diabetol Metab Syndr 2016;8(19).
78. Littaru G, Langsjoen P. Coenzyme Q10 and statins: Biochemical and clinical implications. Mitochondrion, 2007, 7: S168-S174.
79. Littaru G, Langsjoen P. Bioenergetic and antioxidant properties of coenzyme Q10: recent developments. Molecular Biotechnology, 2007, 37(1):31-37. Mitochondrion, 2007, 7: S168-S174.
80. Littaru G, Langsjoen P. Clinical aspects of coenzyme Q10: an update. Nutrition, 2010, 26(3): 250-254.
81. Mas E, Mori T. Coenzyme Q10 and statin myalgia:

What is the evidence? Current Atherosclerosis Reports. 2010, 12(6): 407-413.

82. Pepe S, Marasco S, Haas S, Sheeran F, Krum H, Rosenfeldt F. Coenzyme Q10 in cardiovascular disease. Mitochondrion. 2007, 7(S):154-167.

83. Prakash S, Sunitha J, Hans M. Role of coenzyme Q10 as an antioxidant and bioenergizer in periodontal diseases. Indian Journal of Pharmacology. 2010, 42(6): 334-337.

84. Michley L, Allen J, Bradley R. Coenzyme Q10 deficience in patients with Parkinson' disease. Journal of the Neurological Sciences. 2012, 318: 72-75.

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