The Egyptian Journal of Hospital Medicine (July 2024) Vol. 96, Page 2578-2583

Impact of Micronutrients on Cardiovascular Health: A Review Article

Tasneem Bakheet [1*], Nagah Abo El-Fetoh [1], Ayat Ahmed [2], Magda Ali [1]
[1] Public Health and Community Medicine Department,
[2] Family Medicine Department, Faculty of Medicine, Sohag University, Sohag, Egypt
***Corresponding Author:** Tasneem Bakheet, **Email:** Tasnimmohamed@med.sohag.edu.eg, **Phone:** +20 103 081 0189

ABSTRACT

Background: Cardiovascular diseases (CVD) account for 31% of global mortality, with major contributors including heart attacks and strokes. The development of CVD is influenced by a combination of dietary, lifestyle, and genetic factors.

Objective: The review aimed to clarify the benefits and potential risks associated with micronutrient supplementation, including vitamins and minerals, in the context of CVD prevention and management and modulating risk factors associated with CVD.

Methods: We searched Google Scholar, Science Direct, PubMed and other online databases for vitamins and minerals supplementation and their impact on cardiovascular health. The authors also reviewed references from pertinent literature, however only the most recent or comprehensive studies from 2010 to February 2023 were included. Documents in languages other than English were disqualified due to lack of translation-related sources. Papers such as unpublished manuscripts, oral presentations, conference abstracts, and dissertations that were not part of larger scientific studies were excluded.

Conclusion: Micronutrients play significant roles in cardiovascular health through mechanisms involving inflammation, oxidative stress, and endothelial function. While certain micronutrients, such as calcium, zinc, vitamin D, and selenium, show promise in supporting cardiovascular health, excessive levels may pose risks. Supplementation with folic acid and B vitamins has been associated with reduced stroke risk, whereas niacin and antioxidants may increase all-cause mortality risk. The evidence does not support the routine use of vitamin supplements for reducing cardiovascular risk, highlighting the need for balanced micronutrient intake through diet rather than supplementation.

Keywords: Vitamins, Minerals, Cardiovascular health, Micronutrients supplementation.

INTRODUCTION

Cardiovascular disease (CVD) stands as the sole etiological factor for a substantial 31% of worldwide mortality. About 85% of these fatalities are attributed to stroke and myocardial infarction. An unhealthy diet and obesity, physical inactivity, hyperlipidemia, stress, and hereditary elements all contribute to the confluence of risk factors that initiate CVD [1]. In CVD prevention, the identification of modifiable risk factors and treatments remains a primary concern. The multifaceted influence of trace elements and micronutrients on health and disease has prompted an innumerable number of scientific inquiries [1].

Micronutrients, which include numerous minerals and vitamins including selenium and zinc, are believed to decrease the danger of CVD because they modulate oxidative damage and inflammation via pathways. Deficiencies in vitamins and minerals have been associated with well-documented clinical disease states, as these substances are not producible in the body and must be consumed via diet [2].

Due to the fact that both hydrosoluble and liposoluble vitamins have been reported to be intimately involved in the regulation of various metabolic processes for energy production and cellular biosynthesis, changes in their concentration are believed to cause cardiovascular abnormalities. Vitamins A, D, and E, as well as vitamins B6 (pyridoxine), B9 (folic acid), and C, which are hydrosoluble, have been found to have a substantial impact on cardiovascular function, according to four separate studies [3].

Despite the fact that plasma concentrations of the majority of vitamins remain within normal ranges in healthy human and animal subjects, liposoluble and hydrosoluble vitamin deficiencies have been identified in patients with various forms of heart disease. Therefore, a multitude of vitamins are frequently advocated to enhance cardiovascular well-being [3]. The aim of this review was to assess the functions of the micronutrients mentioned above in relation to all cardiovascular events and risk factors.

Vitamins and cardiovascular health

On the basis of their effects on homocysteine, lipoproteins, oxidative stress, inflammation, and nitric oxide levels, among others, vitamins have been associated with cardiovascular disease. While liposoluble and hydrosoluble vitamins do not directly impact cardiovascular function, their influence on distinct cardiovascular diseases is believed to be through the modulation of their respective risk factors [4].

Vitamin A is a fat-soluble vitamin composed of three active forms (retinoids): retinal, retinol, and retinoic acid. Carotene, which has a significant antioxidant effect, is the most important of the 3 retinoids. β-Carotene exhibited a notable enhancement in cardiac function in rat models during times of reduced reperfusion, but this protective effect was lost

Received: 15/02/2024
Accepted: 16/04/2024

with increasing dosage and prolonged reperfusion. A large randomized clinical trial (RCT) investigated the effect of individual vitamins and minerals - including beta-carotene, vitamin E, vitamin C, selenium, and B vitamins, among others - with the vast majority showing no effect on CVD endpoints [5]. Eleven years of follow-up on a beta-carotene supplement with more than 14,000 males failed to identify a statistically significant difference in mortality or major cardiovascular disease[6].

Although certain reviews and meta-analyses failed to establish a correlation among CVD and vitamin A supplementation, other research has demonstrated that increased consumption of β-carotene is linked to a substantially reduced likelihood of dying from any cause (Respiratory rate highest vs. lowest group = 0.83, 95% CI 0.78–0.88). Furthermore, elevated levels of β-carotene in serum or plasma are also associated with a significant decrease in the risk of all-cause mortality. Moreover, a meta-analysis has proposed that the administration of high-dose vitamin A substantially elevates the likelihood of mortality from any cause [6].

B vitamins, including folate, vitamin B6, and vitamin B12, have been shown in observational studies to decrease homocysteine levels, an independent CVD risk factor. Randomized controlled trials found that supplementation with folic acid (2.5 mg), vitamin B6 (50 mg), and vitamin B12 (1 mg) reduced homocysteine levels by 18% compared to placebo. Conversely, interleukin-6, C-reactive protein, fibrinogen, and intercellular adhesion molecule 1 did not exhibit any discernible changes as endothelial damage indicators. Some reports suggest that carotid intima-media thickness, a marker for cardiovascular disease, might decrease in correlation with vitamin B group consumption [7].

Conversely, factorial design studies that administered folic acid, vitamin B6, and vitamin B12 supplements revealed a trend indicating that patients receiving these vitamins experienced an elevated incidence of cardiovascular events. Although diabetic patients who had suffered myocardial infarction (MI) exhibited comparable outcomes, those who received the supplement experienced a noteworthy 24% decrease in the incidence of stroke [7].

The administration of niacin (nicotinic acid or vitamin B3) to individuals who have atherosclerotic CVD or are at risk for developing the condition does not yield significant reductions in cause-specific mortality, recurrent cardiovascular events, or overall mortality. Moreover, it exhibited a 10% increase in all-cause mortality when administered at pharmacological doses ranging from 1 to 3 g per day in combination with statins ($p = 0.05$). One plausible rationale for this phenomenon is its deleterious influence on glycemic response [8].

Although some studies have established a link between inadequate vitamin C consumption and increased CVD risk, the exact relationship between plasma vitamin C levels and the current incidence of cardiovascular events is still unknown. The observed correlation between vitamin C deficiency and an elevated risk of coronary artery disease in women can be attributed to heightened oxidation of low-density lipoproteins and the development of atherosclerosis, respectively. On the contrary, in the elderly population, a deficiency in vitamin C was linked to a higher mortality risk from stroke rather than coronary artery disease. An increase in the sensitivity of C-reactive proteins and a deficiency in vitamin C were noted to transpire as heart failure (HF) advanced in adult individuals. Moreover, due to their antioxidant properties, plasma vitamin C levels may serve as a predictor of heart failure incidence [9].

Prominent complications associated with congestive heart failure (CHF) in individuals deficient in vitamin D encompass peripheral vascular disease, hypertension, as well as compromised systolic and diastolic functions. There is evidence to suggest that vitamin D deficiency accelerates the development of atherosclerosis and myocardial infarction via mechanisms including inflammation, autoimmunity, endothelial dysfunction, foam cell formation, and smooth muscle cell proliferation. Hypertension, diabetes, obesity, dyslipidemia, and metabolic syndrome have also been associated with insufficient vitamin D [10].

In addition to diabetes and hypertension, vitamin D deficiency has been linked to the activation of the renin-angiotensin system, increased oxidative stress, and the inflammatory pathway; glucose intolerance and insulin resistance are also among the complications associated with vitamin D deficiency [11].

Vitamin E deficiency is relatively rare among humans, as opposed to deficiencies in other nutrients, owing to the abundant accessibility of readily available foods. Conversely, it has been determined that infants and those with specific genetic disorders or fat malabsorption issues are susceptible to vitamin E deficiency. The antioxidant and anti-inflammatory properties of vitamin E are regarded as effective against CVD. Proposed mechanisms include reductions in lipid peroxidation, radical production, and scavenger receptor expression—all of which are essential for cell formation and arteriosclerosis [12].

A link has been established between vitamin K, which inhibits the production of proinflammatory cytokines, and CVD. While the precise protective mechanism by which this vitamin operates within the human body remains unclear[13].

According to the available evidence, a high intake of vitamin K is associated with a reduced risk of CVD, including CAD and vascular calcification. RCTs have indicated potential advantages in relation to the mitigation of arterial stiffness, elastic properties of the carotid artery, and progression of arteriosclerosis. Increased consumption of vitamin K through diet is

marginally correlated with a decreased risk of coronary artery disease (CAD), but does not appear to have any significant effect on mortality from CVD or any other cause [13].

Minerals and cardiovascular health

Zinc, owing to its extensive range of physiological functions within the human body, is universally recognized as an essential trace element. As an essential antioxidant, it hinders the formation and reactive reaction of free radicals, which are detrimental to cells and have the potential to induce degenerative diseases. Zinc is prescribed at recommended daily allowances of 8 mg for females and 11 mg for males, with a maximum daily intake of 40 mg. The principal sources of zinc in the diet are meats including beef, veal, pork, and lamb, in addition to cereals, grains, fish, vegetables, nuts, milk, and dairy products [14].

A correlation between zinc deficiency and the development of cardiovascular disease, specifically atherosclerosis, has been identified. A deficiency in superoxide dismutase activity may be due to zinc deficiencies observed in the patients studied, leads to oxidative stress by increasing the production of nitric oxide (NO), a highly effective vasodilator that can induce fluctuations in blood pressure. Additionally, oxidative stress may play a role in the pathogenesis of atherosclerosis. The antioxidant characteristics of zinc and its impact on calcium ion transport may both contribute to its potential role in blood pressure regulation [15].

Oxidative stress possesses the capacity to cause irreparable harm to molecules and cells, as well as to aid in the advancement of insulin resistance, a predisposing element for type 2 diabetes mellitus, a cardiovascular disorder. Vitamin C is indispensable for the process of insulin maturation and synthesis. Zinc has the potential to impede the secretion of cytokines IL-1b, TNF-a, and IL-6 by monocytes and macrophages, which may result in pancreatic beta cell apoptosis [14].

In addition to being an essential trace element, selenium also exerts an influence on cardiovascular health. It is indispensable for the synthesis of selenoproteins; to date, an estimated thirty have been identified. The incorporation of selenium into essential amino acid derivatives, such as selenomethionine, selenocysteine, methylselenocysteine, and selenocystathionine, has attracted recent interest. Selenoproteins fulfill essential physiological functions, including but not limited to facilitating the reduction of hydrogen and organic peroxides, regulating cellular proliferation and apoptosis, controlling levels of thyroid hormone, and adjusting the function of the cardiovascular system [16].

Long associated with CVD is selenium deficiency; Keshan disease, a form of cardiomyopathy observed in specific regions of China with selenium-deficient soil, is one example. The precise mechanism through which selenium deficiency induces cardiomyocyte deterioration and an increased susceptibility to damage is currently unknown. A correlation between selenium deficiency and an elevated risk of myocardial infarction and acute coronary syndrome has been established by a number of additional studies [16].

Minerals perform an extensive array of functions within the human body due to the inorganic nature of their composition. These include facilitating the regulation of nerve and muscle activity and preserving the acid-base and water balances. Electrolyte imbalances, which include magnesium (Mg), calcium (Ca), potassium (K), and sodium (Na), are common and potentially fatal. A variety of cardiovascular ailments, including hypertension, coronary heart disease, cardiomyopathy, and HF, are caused by these imbalances [17].

As well as its critical role in the biological system, Ca is an indispensable mineral for cardiovascular health and bone health. The recommended daily Ca intake for both genders is 1,200–1,500 mg. Fortified flour, milk and milk products, and green leafy vegetables (spinach, kale, etc.) are the primary supplies of Ca. It is quite difficult to attain the required serum levels solely through diet. For this reason, many individuals choose to supplement with Ca either alone or in combination with vitamin D, in order to improve bone health and ensure adequate serum levels. The impact of calcium and Ca supplements on cardiovascular health has been the subject of conflicting findings from a multitude of observational and clinical trial investigations conducted throughout history. The extracellular Ca concentration has a direct effect on the cell membrane potentials of all excitable tissues, particularly the heart and nerves. Calcium is vital for myocardium and other muscle contractions.[18].

Micronutrients supplementation and cardiovascular health

Vitamins, which consist of the B vitamins and chemicals A, C, D, E, and K, are indispensable for sustaining regular cellular metabolism. Minerals, such as zinc, calcium, and iron, are essential inorganic substances for the maintenance of healthy human function. Dietary supplements frequently contain vitamins and minerals due to their potential health benefits and disease prevention properties [19].

In postmenopausal women, there is an inverse correlation between vitamin E consumption and the risk of coronary heart disease (CHD), whereas no such correlation has been identified in relation to vitamins A and C. Furthermore, the preventive attributes of B vitamins and folic acid with regard to the mitigation of stroke are documented. The risk of CVD cannot be reduced significantly through the use of multivitamins, vitamins C and D, β-carotene, calcium, and selenium. Indeed, excessive consumption of vitamin supplements may potentially elicit distinct adverse effects. Vitamin and mineral supplementation in healthy adults was evaluated for its benefits and drawbacks through a

systematic review conducted by the US Preventive Services Task Force. The results suggest that supplementation does not provide a significant or any preventive effect against CVD [20]. Therefore, the existing body of evidence is inadequate to support the notion that vitamins and minerals effectively prevent CVD [21].

Vitamin D, which is fat-soluble, operates as a steroid hormone. Vitamin D predominantly aids in the absorption of calcium, a vital element in the process of bone mineralization. Previous cross-sectional research has demonstrated a correlation between vitamin D deficiency and an increased risk of CVD. The National Health and Nutrition Examination Survey reveals that hypovitamin D is common among adults with certain conditions (e.g., CHD and HF) in the United States [22]. A significant correlation exists between insufficiency of 25-hydroxyvitamin D and an increased risk of myocardial infarction and HF. Cohort and RCT studies have investigated the correlation between vitamin D deficiency and the risk of cardiovascular disease. Individuals with 25-hydroxyvitamin D levels below 15 ng/mL have a 1.62 hazard ratio for developing cardiovascular events, whereas those with 25-hydroxyvitamin D levels at or above 15 ng/mL have no association with incident CVD [23].

Suggested individual nutrient consumption according to the evidence on the association between dietary choices and cardiovascular disease are shown in figure 1[24].

Figure 1: Suggested individual nutrient consumption according to the evidence on the association between dietary choices and cardiovascular disease management. (A) Fat; (B) Carbohydrate; (C) Protein; (D) Vitamins and minerals; (E) Dietary fibers [24].

Consistently, a nonlinear Mendelian randomization analysis substantiates the hypothesis that an inadequate intake of vitamin D could potentially elevate the likelihood of developing CVD [25].

However, recent randomized controlled trials have failed to establish a correlation between vitamin D supplementation and a decreased risk of cardiovascular disease. A daily supplementation regimen consisting of 2000 IU of high-dose vitamin D3 for five years did not produce a statistically significant reduction in the incidence of major cardiovascular events, including myocardial infarction, stroke, and mortality from CVD. Supplementing elderly Finnish participants with vitamin D3 at doses of 1600 IU/day or 3200 IU/day for five years failed to prevent the occurrence of major CVD events in another randomized controlled trial [26]. Therefore, the available evidence fails to substantiate any significant advantages or drawbacks of vitamin D with regard to cardiovascular risk [24].

CONCLUSION

Based on an extensive review of observational studies and the data at our disposal, we are able to assert unequivocally that calcium, zinc, vitamin D, and selenium are indispensable micronutrients in maintaining cardiovascular health. Nevertheless, a scarcity of research has demonstrated that heightened concentrations of these micronutrients in the circulatory system have an adverse effect on cardiovascular health, although the exact mechanism through which this transpires is still unknown. An extended period of time, several hours, passes during which serum levels of micronutrients remain elevated when taken in the form of supplements.

The evidence does not support the routine use of vitamin supplements to reduce cardiovascular risk. There was no consistent benefit observed with the continued administration of vitamin C, vitamin D, and calcium in relation to the prevention of CVD, myocardial infarction, stroke, or all-cause mortality. Folic acid alone reduced the incidence of stroke, as did folic acid supplementation with B6, and B12. In contrast, niacin and antioxidants were linked to an increased risk of death from any cause.

Financial support and sponsorship: Nil.
Conflict of interest: Nil.

REFERENCES

1. **Narayanam H, Chinni S, Samuggam S (2021)**: The impact of micronutrients-calcium, vitamin D, selenium, zinc in cardiovascular health: A mini review. Front Physiol., 12(3):742425.
2. **Sunkara A, Raizner A (2019)**: Supplemental vitamins and minerals for cardiovascular disease prevention and treatment. Methodist Debakey Cardiovasc J., 15(3):179-84.
3. **Shah A, Dhalla N (2021)**: Effectiveness of some vitamins in the prevention of cardiovascular disease: A narrative review. Front Physiol., 12(5):729-55.
4. **Barteková M, Adameová A, Görbe A *et al.* (2021)**: Natural and synthetic antioxidants targeting cardiac oxidative stress and redox signaling in cardiometabolic diseases. Free Radical Biology and Medicine, 169446-77.
5. **Sesso H, Christen W, Bubes V *et al.* (2012)**: Multivitamins in the prevention of cardiovascular disease in men: The physicians' health study II randomized controlled trial. JAMA, 308(17):1751-60.
6. **Carazo A, Macáková K, Matoušová K *et al.* (2021)**: Vitamin a update: Forms, sources, kinetics, detection, function, deficiency, therapeutic use and toxicity. Nutrients, 13(5):22-9.
7. **Christen W, Cook N, Van Denburgh M *et al.* (2018)**: Effect of combined treatment with folic acid, vitamin B_6, and vitamin B_{12} on plasma biomarkers of inflammation and endothelial dysfunction in women. J Am Heart Assoc., 7(11): e008517.
8. **Ying H, Gao L, Liao N *et al.* (2022)**: Association between niacin and mortality among patients with cancer in the NHANES retrospective cohort. BMC Cancer, 22(1):1173-9.
9. **Morelli M, Gambardella J, Castellanos V *et al.* (2020)**: Vitamin C and cardiovascular disease: An update. Antioxidants (Basel), 9(12):54-8.
10. **Latic N, Erben R (2020)**: Vitamin D and cardiovascular disease, with emphasis on hypertension, atherosclerosis, and heart failure. Int J Mol Sci., 21(18):6483-9.
11. **Cosentino N, Campodonico J, Milazzo V *et al.* (2021)**: Vitamin D and cardiovascular disease: Current evidence and future perspectives. Nutrients, 13(10):3603-8.
12. **Violi F, Nocella C, Loffredo L *et al.* (2022)**: Interventional study with vitamin E in cardiovascular disease and meta-analysis. Free Radic Biol Med., 178(4):26-41.
13. **Popa D, Bigman G, Rusu M (2021)**: The role of vitamin k in humans: Implication in aging and age-associated diseases. Antioxidants, 10(4):72-81.
14. **Maywald M, Rink L (2022)**: Zinc in human health and infectious diseases. Biomolecules, 12(12):33-9.
15. **Shen T, Zhao Q, Luo Y *et al.* (2022)**: Investigating the role of zinc in atherosclerosis: A review. Biomolecules, 12(10):33-6.
16. **Zhang F, Li X, Wei Y (2023)**: Selenium and selenoproteins in health. Biomolecules, 13(5):21-7.
17. **Jomova K, Makova M, Alomar S *et al.* (2022)**: Essential metals in health and disease. Chem -Biol Interact, 367(6):110-73.
18. **Cainzos-Achirica M, Miedema M, McEvoy J *et al.* (2020)**: Coronary artery calcium for personalized allocation of aspirin in primary prevention of cardiovascular disease in 2019: the MESA Study (Multi-Ethnic Study of Atherosclerosis). Circ., 141(19):1541-53.
19. **Ofoedu C, Iwouno J, Ofoedu E *et al.* (2021)**: Revisiting food-sourced vitamins for consumer diet and health needs: a perspective review, from vitamin classification, metabolic functions, absorption, utilization, to balancing nutritional requirements. PeerJ., 9(3):11940-6.
20. **O'Connor E, Evans C, Ivlev I *et al.* (2022)**: Vitamin and mineral supplements for the primary prevention of cardiovascular disease and cancer: Updated evidence

report and systematic review for the US preventive services task force. JAMA, 327(23):2334-47.

21. **Simsek B, Selte A, Egeli B *et al.* (2021)**: Effects of vitamin supplements on clinical cardiovascular outcomes: Time to move on! - A comprehensive review. Clin Nutr Espen, 42(6):1-14.
22. **Kim D, Sabour S, Sagar U *et al.* (2008)**: Prevalence of hypovitaminosis D in cardiovascular diseases (from the National Health and Nutrition Examination Survey 2001 to 2004). Am J Cardiol., 102(11):1540-4.
23. **Zhang S, Miller D, Li W (2021)**: Non-musculoskeletal benefits of vitamin D beyond the musculoskeletal system. Int J Mol Sci., 22(4):2128-32.
24. **Chen W, Zhang S, Hu X *et al.* (2023)**: A review of healthy dietary choices for cardiovascular disease: From individual nutrients and foods to dietary patterns. Nutrients, 15(23):4898-105.
25. **Zhou A, Selvanayagam J, Hyppönen E. (2022)**: Non-linear Mendelian randomization analyses support a role for vitamin D deficiency in cardiovascular disease risk. Eur Heart J., 43(18):1731-9.
26. **Virtanen J, Nurmi T, Aro A *et al.* (2022)**: Vitamin D supplementation and prevention of cardiovascular disease and cancer in the Finnish Vitamin D Trial: a randomized controlled trial. Am J Clin Nutr., 115(5):1300-10.