Review Article

Vitamins, Minerals, and Flavonoids Intake and the Risk of Cardiovascular Diseases

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Abstract

Diseases of heart and stroke cause most deaths in both sexes of all ethnic groups. For more than 40 years epidemiological studies, experimental studies, and clinical trials have shown that numerous dietary risk factors affect serum lipids, atherogenesis and coronary heart disease (CHD). Substantial interest has recently focused on the hypothesis that the naturally occurring antioxidant vitamins such as vitamin E, vitamin C, and ß-carotene may prevent myocardial infarction, progression of coronary heart disease. Substantial laboratory, animal, and human data suggest that oxidation of low-density lipoprotein (LDL) cholesterol is an important step in the pathogenesis of atherosclerotic lesions. Oxidation of LDL cholesterol is important in both the initiation and progression of plaque or increases the risk for plaque rupture. The major lipid-soluble antioxidant vitamins are vitamin E (α-tocopherol) and ß-carotene, a precursor of vitamin A. The major water-soluble antioxidant vitamin is vitamin C (ascorbic acid). Vitamin E is important in preventing oxidation of LDL cholesterol. ß-Carotene prevents oxidation of LDL cholesterol. Vitamin C prevents oxidation of LDL cholesterol and preserves vitamin E and ß-carotene levels during oxidative stress. It is increasingly recognized that folate and vitamin B6 may play a role in the prevention of cardiovascular disease. The primary mechanism proposed for their effect on coronary vascular disease (CVD) is a reduction in plasma homocysteine concentration by remethylation of homocysteine back to methionine. Minerals like magnesium, Potassium and calcium and also vitamin D have protective effect in blood pressure. Selenium is an important component of antioxidant defence and flavonoids which are derived from plants have been shown to inhibit platelet aggregation and adhesion, which may be another way they lower the risk of heart disease. In this article the role of micronutrients in prevention of cardiovascular diseases will be reviewed.

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Introduction

Heart disease and stroke account for many deaths in both sexes regardless of ethnicity. Clinical trials and epidemiological and experimental studies conducted over the past four decades have shown that numerous dietary risk factors affect serum lipids and contribute to atherogenesis and coronary heart disease (CHD).[1] The public health strategy is

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aimed at the primary prevention of atherosclerosis.[2]

Diet is a cornerstone of cardiovascular disease (CVD) prevention and treatment efforts. At the core of this dietary guidance are the recommendations to decrease saturated fat and cholesterol and to consume more fruit, vegetables, and wholegrain products. Information from a major database indicates that such diets significantly lower blood cholesterol levels, a major risk factor for CVD.[3] There is growing evidence that the oxidative modification of low-density lipoprotein (LDL) may be critical to the development of atherosclerosis. Oxidized LDL is present in atherosclerotic plaques. The oxidation of LDL appears to enhance the uptake of LDL by macrophages, thereby encouraging the formation of foam cells and the development of fatty streaks. In addition, an increased susceptibility to such oxidation is associated with a greater severity of carotid atherosclerosis.[4] Some studies have demonstrated an inverse association between the intake of vitamin E and CHD, whereas others have posited that vitamin C or provitamin A carotenoids may be protective.[5-8] A diet rich in fruit, vegetables, fiber, and minerals; particularly calcium, magnesium, and potassium, has a potent antihypertensive effect. Plant-based diets also provide phytoestrogens, which are vasodilative.[9] In this article, we will review the role of micronutrients in the prevention of CVD.

Vitamins

Vitamin C

Ascorbic acid, or vitamin C, is the main water-soluble antioxidant in the human plasma. A higher dietary intake of vitamin C has been associated with a moderately lower risk of CHD among some study populations. It effectively scavenges superoxide and other reactive oxygen species, and it plays an important role in the regulation of intracellular redox state through its interaction with glutathione. Ascorbic acid spares glutathione from oxidation and may thus preserve intracellular reduced glutathione concentration. The prevention of glutathione oxidation by ascorbic acid could improve endothelium-derived relaxing factor (EDRF) action in the short term by a number of mechanisms. Increasing intracellular ascorbic acid concentration could increase the availability of reduced thiol and thereby improve EDRF action through an increased synthesis of NO and/or stabilization of NO.[10] A large epidemiological study has reported that the dietary intake of ascorbic acid correlates inversely with hypertension and its clinical sequel. In mild-to-moderate hypertensive patients, treatment with ascorbic acid (500 mg/day) significantly improves systolic and diastolic blood pressure and increases plasma HDL cholesterol in female hypertensives. A potent scavenger of free radicals, ascorbic acid stimulates the activation of NOS activity and increases NO synthesis in endothelial cells, contributing to an improved endothelial-dependent vasodilation in hypertensives.[11] Furthermore, strong clinical and experimental evidence suggests that chronic latent vitamin C deficiency leads to hypercholesterolemia and the accumulation of cholesterol in certain tissues. Ascorbic acid is involved in the regulation of cholesterol metabolism in several ways.[12] The possible mechanisms by which ascorbic acid may affect the development of atherosclerosis and the onset of acute coronary events include effects on arterial wall integrity related to the biosynthesis of collagen and GAGs, altered cholesterol metabolism mediated by vitamin C-dependent conversion of cholesterol to bile acids, and effects on triglyceride levels via the modulation of lipoprotein lipase activity. A particularly intriguing possible mechanism for the anti-atherogenic effect of vitamin C is the prevention of atherogenic and oxidative modification of LDL.[13] Endothelial dysfunction and lipid peroxidation are key events in the initiation, progression, and rupture of atheromatous plaques. Lipid peroxidation results from increased oxidative stress, and there is accumulating evidence that this also accounts for endothelial dysfunction.[14] Thus, both metabolic and antioxidant functions may contribute to the possible reduction of CVD risk by vitamin C.[15]

Vitamin E

Vitamin E is the major lipid-soluble antioxidant in humans, and thus plays the largest role in protecting cell membranes. Vitamin E is also the most abundant antioxidant in low-density lipoproteins (LDLs), present at a level of 6 to 8 molecules per LDL molecule, while other antioxidant compounds are present at ratios less than 1 per molecule.[16] The hypothesis that links vitamin E to the prevention of CVD postulates that the oxidation of unsaturated lipids in the LDL particle initiates a complex sequence of events that leads to the development of atherosclerotic plaques. This hypothesis is supported by numerous studies in vitro, in animals, and in humans.[17] As part of its normal circulation, LDL occasionally leaves the antioxidant-replete plasma, entering the subendothelial space of arteries. Here, LDL lipids are oxidized by the local vascular cells, producing chemotactic proteins that attract new monocytes to the area and encourage their differentiation to macrophages. Continuing oxidation of LDL imparts to it a negative charge, which triggers "scavenger receptors" on macrophages to take up LDL. Oxidized LDLs are also directly toxic to the vascular and smooth muscle cells, causing the release of oxidative lysosomal enzymes into the intimal space. This enhances the progression of atherosclerotic lesions. Next, smooth muscle proliferation and fibrous connective tissue secretion occurs, producing lesions that protrude into the vessel lumen. In the absence of vitamin E, endothelial damage continues; and part of this process may be mediated by the body's own immune system reacting against oxidized LDL. The final phenomenon is platelet adhesion and aggregation, causing thrombosis,

and, clinically, infarction. Researchers have demonstrated an in vitro reduction in platelet adhesion and aggregation attributable to vitamin E. The mechanism is different from that of aspirin: vitamin E reduces the development of long, thin pseudopodia, which occurs when platelets adhere to a surface. Platelets enriched in vitamin E produce only short, stubby pseudopodia that appear to anchor the platelets poorly to the adhesive surface. There is evidence that vitamin E can preserve arterial vasodilation in the presence of oxidative stress, perhaps by inhibiting prostaglandin E_2 and by potentiating the production of prostaglandin I_2 and prostacyclin synthesis.[16] The Health Professionals' Follow-up Study has observed that male health professionals with the highest intake of vitamin E, and again only those taking supplements for longer than 2 years, have a 39% lower risk of heart disease, as manifested by ischemic events and the need for cardiac surgery.[5] Two other large prospective studies have supported these results. The Established Populations for Epidemiologic Studies of the Elderly (EPESE) and the Iowa Women's Health Study have also found declines in cardiac mortality with high vitamin E intakes. In EPESE, a long-term use of vitamin E is associated with a 63% decrease in the risk of death from CHD. In addition to the association of vitamin E with atherosclerotic regression, EPESE has also suggested the possibility of a short-term mechanism at work: the use of vitamin E at any time is associated with a 47% reduction in mortality, and there is no 2-year delay in observing the apparent benefit.[18,19]

Folate

It is increasingly recognized that folate may play a role in the prevention of CVD. Over the last few years, several studies have reported the beneficial effects of folate on the endothelial function, a surrogate end point for cardiovascular risk. Consistently, observational studies have demonstrated an association between folate levels and cardiovascular morbidity and mortality.[20] The primary mechanism proposed for the effect of folic acid on CVD is a reduction in the plasma homocysteine concentration by the remethylation of homocysteine back to methionine. Homocysteine harms the vascular endothelium in a variety of ways, impairing the ability of the endothelial to maintain homeostasis. Homocysteine increases platelet aggregation and thrombosis through an enhanced thromboxane synthesis and inactivation anticoagulants. Homocysteine increases oxidative stress by increasing the superoxide production. It also increases leukocyte-endothelium interactions and is believed to be toxic at high concentrations. In addition, homocysteine down regulates the nitric oxide production and acts as a mitogen to increase vascular smooth muscle proliferation. The acute administration of folic acid can restore endothelium function induced by acute hyperhomocysteinemia.[21,22] Apart from the reduction of homocysteine, folates

have recently been reported to have other benefits.[23] In a series of in vitro experiments, it has been demonstrated that folates possess antioxidant potential. It seems that 5-MTHF can reduce the superoxide generation by 2 superoxide-generating systems: xanthine oxidase/hypoxanthine and endothelial NO synthase (eNOS). It has been shown that folates abolish the homocysteine-induced increase in the endothelial superoxide.[20]

Vitamin B6

Lower vitamin B_6 concentrations are reported to confer an increased and independent risk for CVD. Pyridoxal 5'-phosphate (PLP), the active form of vitamin B_6, participates in a wide range of reactions, including the metabolism of homocysteine, a sulfur-containing amino acid that is thought to be a risk factor for occlusive vascular disease.[24,25] The metabolism of homocysteine to cysteine is catalyzed by two vitamin B-6-dependent enzymes: CBS, which catalyzes the condensation of homocysteine with serine to form cystathionine, and cystathionase, which catalyzes the hydrolysis of cystathionine to cysteine and α-ketobutyrate. Therefore, a suboptimal vitamin status is associated with elevated fasting plasma total homocysteine concentrations as well as an increased risk for vascular stenosis and coronary heart disease.[26] Vitamin B_6 deficiency has been associated with the impairment of enzymes involved in determining the structural integrity of the arterial wall, in altering platelet function, and in interfering with cholesterol metabolism.[27] It seems that there is a relationship between PLP and the marker of inflammation C-reactive protein (CRP). Because vitamin B_6 is integrally involved in the synthesis of nucleic acids and consequently in mRNA and protein synthesis, the production of cytokines and other polypeptide mediators during the inflammatory response might require an increased utilization of this coenzyme. Vitamin B_6 deficiency has also been reported to alter the regulation of interleukin-2 production.[28] As inflammation is a major cause of CVD, vitamin B6 deficiency may be an underlying cause of such diseases.

Vitamin D

Calcification is a nearly universal feature of atherosclerosis. Almost all angiographically significant atherosclerotic lesions are calcified, and the presence of calcium within coronary vasculature has been associated with several adverse clinical events including dissection during angioplasty, increased risk of myocardial infarction, and poorer 5-year survival. 1,25-vitamin D has shown a significant association with vascular calcification, and with a negative correlation, revealing that higher serum 1,25-vitamin D levels are associated with lower amounts of vascular calcification. These data suggest a potential role for endogenous 1,25-vitamin D in the inhibition of vascular calcification. 1,25-vitamin D is known to regulate the deposition of calcium in the axial skeleton, and it may regulate the deposition of calcium in the vascular wall as

well. This may be one factor to explain the long observed association between osteoporosis and vascular calcification.[29-31] Animal studies have demonstrated that IL-6 accelerates arteriosclerosis. Calcitriol can suppress the secretion of TNF-α and IL-6 in vitro in a dose-dependent manner. Some studies have shown an inverse association between TNF-α and 25 (OH)D levels in human subjects. Epidemiological investigations have brought forward evidence for an inverse association between myocardial infarction and plasma 25-hydroxyvitamin D_3 levels.[32] The renin-angiotensin system (RAS) plays a central role in the regulation of blood pressure, volume and electrolyte homeostasis. Inappropriate activation of the RAS may lead to hypertension. Clinical and epidemiological studies have suggested a correlation between vitamin D-deficiency and high blood pressure. Our recent studies have demonstrated that vitamin D is a potent endocrine suppressor of renin biosynthesis to regulate the RAS. Mice lacking the vitamin D receptor (VDR) have elevated production of renin and angiotensin (Ang) II, leading to hypertension, cardiac hypertrophy, and increased water intake. Research has also revealed the critical role of the vitamin D endocrine system in the regulation of blood pressure and volume homeostasis, suggesting that low calcemic vitamin D analogs may potentially be developed into a new class of anti-hypertensive agents to control renin production and blood pressure.[33]

Carotenoids

Carotenoids are natural pigments which are synthesized by plants and are responsible for the bright colors of various fruits and vegetables. A number of studies have shown that ß-carotene and others carotenoids have lipid-soluble antioxidant activity.[34] Several epidemiologic studies have shown an inverse association between serum/adipose ß-carotene levels and CHD risk. A body of evidence indicating that the oxidation of low density lipoproteins (LDL) plays an important role in the development of atherosclerosis has led investigators to consider a preventive role for dietary constituents with antioxidant activity. Early in vitro studies of LDL oxidation showed that ß-carotene carried in LDL was oxidized prior to the onset of oxidation of LDL polyunsaturated fatty acids, suggesting a possible role in delaying the onset of LDL oxidation.[35-37] The antioxidant actions of carotenoids are based on their singlet oxygen quenching properties and their ability to trap peroxyl radicals. This results in an excited carotenoid, which has the ability to dissipate newly acquired energy through a series of rotational and vibrational interactions with the solvent, thus regenerating the original unexcited carotenoid, which can be reused for further cycles of singlet oxygen quenching. The quenching activity of a carotenoid mainly depends on the number of conjugated double bonds of the molecule and is influenced to a lesser extent by carotenoid end groups (cyclic or acyclic) or the nature of substituents in carotenoids containing cyclic end groups. Lycopene (eleven conjugated and two nonconjugated double bonds) is among the most efficient singlet oxygen quenchers of the natural carotenoids. The prevention of lipid peroxidation by carotenoids has been suggested to be mainly via singlet oxygen quenching.[34]

Minerals

Calcium

Supplemental dietary calcium is associated with reduced membrane permeability, increased Ca (2+)-ATPase and Na,K-ATPase, and reduced intracellular calcium. Supplemental calcium may limit the calcium influx into the cell and improve the ability of the vascular smooth muscle cells (VSMC) to extrude calcium. This could be a direct effec of calcium on the VSMC or an indirect effect mediated hormonally. The calcium-regulating hormones have all been found to have vasoactive properties and therefore may influence blood pressure. The modulation of the sympathetic nervous system is another important way that dietary calcium can influence blood pressure. There is evidence of altered norepinephrine levels in the hypothalamus as a consequence of the manipulations of dietary calcium as well as changes in central sympathetic nervous system outflow. Dietary calcium has also been shown to specifically modify alpha 1-adrenergic receptor activity in the periphery.[38] The regulation of the intracellular calcium plays a key role in hypertension, and the dysregulation of calcium homeostasis appears to be a fundamental factor linking these conditions. The regulation of the intracellular calcium in key disease-related target tissues by calcitrophic hormones provides the opportunity to modulate disease risk with dietary calcium. The effects of dietary calcium on blood pressure regulation appear to be paradoxical, as increasing intracellular calcium increases vascular smooth muscle tone, peripheral vascular resistance, and blood pressure; while increasing dietary calcium exerts the opposite effect. The protective effect of calcium on blood pressure can be explained in part by the influence of calcitrophic hormones on the intracellular calcium.[39]

Magnesium

Magnesium is related to various physiological functions, including cardiovascular regulation. It has been suggested that deficiency in magnesium and abnormalities in magnesium metabolism play pathophysiological roles in ischemic heart disease, congestive heart failure, sudden cardiac death, arrhythmias, preeclampsia and eclampsia, insulin resistance and diabetes, and hypertension. An inverse relationship between the dietary magnesium intake and the

level of blood pressure or the prevalence of hypertension has been observed in epidemiological studies. It has also been shown that hypertensive patients often have reduced serum and intracellular levels of magnesium compared with normotensive subjects.[40]

Magnesium modulates mechanical, electrical, and structural functions of cardiac and vascular cells, and small changes in the extracellular magnesium levels and/or intracellular free magnesium concentration may have significant

effects on cardiac excitability and on vascular tone, contractility, and reactivity. Thus, magnesium may be important in the physiological regulation of blood pressure, whereas alterations in the cellular magnesium metabolism could contribute to the pathogenesis of blood pressure elevation.[41,42]

Proposed mechanisms for the blood-pressure-lowering effect of magnesium include an inhibition of sympathetic nervous activity and peripheral vasodilation via the control of sodium and calcium metabolism. Cytosolic calcium in the vascular smooth muscle cell, which is mediated by movements of calcium across the membrane, determines the degree of the tension. Calcium influx to the vascular smooth muscle cell occurs through potential operated channels, receptor operated channels, and leak operated channels. The release of intracellular stored calcium in the cytoplasm is also important for the developed tension of vascular smooth muscle cells. Magnesium inhibits the release of calcium from sarcoplasmic reticulum by the competition for calcium receptor on a calcium regulated efflux channel and derives calcium into the sarcoplasmic reticulum. It consequently reduces the tension of muscle. In addition, magnesium supplementation may reduce triglyceride and total cholesterol. In magnesium deficiency, triglyceride and total cholesterol are elevated; and disordered lipid metabolism improves the risk of cardiovascular diseases.[43]

Potassium

High rates of potassium intake are associated with protection from CVD in populations consuming primitive diets and in vegetarians living in industrialized cultures.[44] Humans are prone to sodium overload and potassium depletion. This electrolyte imbalance is important in the pathogenesis of cardiovascular disease and sudden cardiac death. Avoiding hypokalemia is beneficial in several CVD states including acute myocardial infarction, heart failure, and hypertension Hypokalemia causes cellular hyperpolarity, increases resting potential, hastens depolarization, and increases automaticity and excitability. Because cardiac repolarization relies on potassium influx, hypokalemia lengthens the action potential and increases QT dispersion (reflecting electrical inhomogeneity). Hypokalemic ventricular ectopy is suppressed by potassium replacement. Thus, hypokalemia increases the risk of ventricular arrhythmia and sudden cardiac death.[45] In humans, intravenous potassium ameliorates hypertensive endothelial dysfunction. Potassium partly mediates vasodilation via strong inwardly rectifying potassium channels and the sodium-potassium-ATPase pump of vascular smooth muscle cells (VSMCs).[46] This may be important when NO bioavailability is low. Potassium also blunts angiotensin-II–induced vasoconstriction.[47,48] Potassium ameliorates oxidative stress by reducing free-radical formation, impairing VSMC proliferation, and reducing monocyte adherence to vessel walls. Therefore, potassium retards the progression of atherosclerosis.[44] Populations ingesting potassium-rich diets exhibit lower rates of hypertension. This antihypertensive effect may be mediated by increased natriuresis, vasodilation, heightened baroreflex sensitivity, and reduced cardiac sensitivity to catecholamines and angiotensin II.[49] The ratio of sodium excretion to potassium excretion is more closely related to BP than either measure individually. Interventions that increase sodium excretion while conserving potassium may, therefore, be particularly effective treatment for hypertension.[50]

Selenium

Selenium is an essential trace element that is an integral part of many proteins with catalytic and structural functions. The antioxidant properties of some selenoproteins, such as glutathione peroxidase, may be particularly important in carcinogenesis and heart disease. Selenium is an important component of antioxidant defence.[51] Selenium dependent glutathione peroxidase can efficiently reduce hydroperoxides of phospholipids and cholesterol eater associated with LDL and HDL in vivo, indicating that this selenium containing enzyme could act as a physiological antiatherogenic.[52,53] In selenium deficiency, an accumulation of lipid peroxides in the heart may occur, especially under ischemic conditions and if ischemic tissue is reperfused. Lipid peroxides in the heart may damage the cell membrane and may lead to an impaired calcium transport with an uncontrolled calcium accumulation in the cell. This may result in an activation of phospholipids, and, in consequence, to an enhanced formation of arachidonic acid. An increased concentration of lipid peroxides owing to selenium deficiency may shift the prostaglandin synthesis from prostacyclin to thromboxane, causing enhanced blood pressure and platelet aggregability. From animal experiments, it is known that selenium protects against cardiotoxic elements, cardiotoxic xenobiotics, and viral infections that affect the heart. Selenium deficiency may also be a secondary factor in the causation of hypertension and myocardial ischemia.[54]

Recently selenium has also been reported to affect homocysteine levels being reported in selenium deficient rats.[55]

Flavonoids

Epidemiological studies have often shown relationships

between vegetable/fruit intake and CHD that are not clearly attributable to major macronutrients or known vitamins and minerals. This suggests that other components of plants may be important in lowering the risk of CVD. The plant kingdom contains a number of sterols that differ from cholesterol by having ethyl or methyl groups or unsaturation in the side chain. Flavonoids are present in fruits, vegetables, nuts, and seeds.[56] The major flavonoid categories are flavonols, flavones, catechins, flavanones, and anthocyanins. The main dietary sources of these compounds are tea, onions, and soy. The link between flavonoids and atherosclerosis is based partly on the evidence that some flavonoids possess antioxidant properties and have been shown to be potent inhibitors of LDL oxidation in vitro. Flavonoids have also been shown to inhibit platelet aggregation and adhesion, which may be another way they lower the risk of heart disease. Isoflavones in soy foods and flavonoids in tea have been reported to lower plasma cholesterol and also to have estrogen-like effects.[57-61]

These polyphenols are effective scavengers of reactive oxygen species and can inhibit lipid peroxidation through the chelation of transition metal ions or their action as chain-breaking antioxidants.[62-64] These properties suggest that flavonoids might prevent LDL oxidation, a key early event in the development of atherosclerosis. Experimental evidence also suggests that flavonoids may favorably affect the endothelial function.[57,58] Normal endothelium regulates vasomotor tone, platelet activity, leukocyte adhesion, and vascular smooth muscle proliferation via the release of several paracrine factors, including nitric oxide (NO). These endothelial functions are impaired with atherosclerosis and its risk factors.[65] Platelet aggregation is a central mechanism in the pathogenesis of acute coronary syndromes, including myocardial infarction and unstable angina. For these reasons, the observed effects of flavonoids on endothelial and platelet function might explain, in part, the observed beneficial effects of flavonoids on CVD risk.[56]

Conclusion

Substantial evidence suggests that antioxidant vitamins, folic acid, flavonoids, and some minerals have been effective in the endothelial function. The mechanisms by which these nutrients influence endothelial function are likely to be multiple and complex, including the inhibition of monocyte adhesion and platelet activation, increased nitric oxide production, and blockage of lipid peroxidation. To conclude, diet is a major determinant of cardiovascular health. Dietary modification is an important component of primary and prevention of CHD and hypertension. Proper nutrition includes an appropriate intake of the essential micronutrients which can either accelerate or retard the development of CVD.

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