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Betul Kisioglu & Reyhan Nergiz-Unal

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The powerful story against cardiovascular diseases: Dietary factors

Betul Kisioglu and Reyhan Nergiz-Unal

Department of Nutrition and Dietetics, Faculty of Health Sciences, Hacettepe University, Ankara, Turkey

ABSTRACT

Cardiovascular diseases are the underlying cause of most deaths worldwide, and they are expected to rise in the following years. Cardiovascular diseases include diseases that affect the heart, cerebral, and peripheral vessels, resulting in ischemia. On the basis of cardiovascular disease pathophysiology, there are lipoprotein metabolism abnormalities, oxidative stress, chronic inflammation, endothelium damage, and atherothrombosis. Modifiable risk factors for cardiovascular health and diseases are blood pressure, blood lipid profile, oxidative stress, inflammation, and other factors (smoking, obesity, diabetes mellitus). Atherosclerotic plaque development, vascular calcification, and vascular stiffness are caused by a long-term endothelial dysfunction and inflammatory response, which can be prevented and controlled by the diet. Fat and cholesterol are the commonly considered dietary factors in the association of the nutrition and the cardiovascular disease, although other macronutrients, especially carbohydrates and proteins, also have major effects. Nowadays, other macronutrients and micronutrients (minerals and vitamins) have roles in regulating the indicated processes (blood pressure, calcification, oxidative stress, inflammation, etc.) in cardiovascular disease prognosis. Other dietary compounds (sterols, stanols, polyphenols, carotenoids, etc.) that exist in small amounts in foods might have a role in regulating these mechanisms as well. There are also new insights about walnuts, garlic, ginger, and hawthorn as parts of a healthy diet against cardiovascular diseases. So far, there have not appeared any reviews that combine the impact of a wide variety of dietary components on cardiovascular diseases. Thus, the novel nutritional targets and interventions that focus on nutrients and other dietary compounds on potential mechanisms underlying cardiovascular diseases are discussed in this review.

KEYWORDS

Cardiovascular diseases; dietary factors; nutrition

Introduction

Cardiovascular diseases (CVDs) are the underlying cause of one-third of all deaths globally (17.5 million people a year).[1] It is expected that this will rise to 23.6 million in 2030.[1] In the United States, CVDs take up 37.6% of all the noncommunicable mortality,[2] in Europe it causes more than half of all deaths,[3] and in Turkey it takes up 55% of all deaths.[4] CVDs include diseases that affect the heart, cerebral, and peripheral vessels, resulting in ischemia.

CONTACT Reyhan Nergiz-Unal rnergiz@hacettepe.edu.tr; rnergizunal@gmail.com Department of Nutrition and Dietetics, Faculty of Health Sciences, Hacettepe University, Sıhhiye, Ankara 06100, Turkey

These are peripheral vascular disease (PVD), coronary heart disease (CHD), and stroke. Atherosclerosis is a condition that leads to these diseases.[5] On the basis of CVDs' pathophysiology, there are lipoprotein metabolism abnormalities, oxidative stress, chronic inflammation, endothelium damage, and atherothrombosis.[5]

The endothelium regulates vascular tone and inhibits platelet aggregation through nitric oxide (NO) that inhibits cell proliferation, inflammation, and thrombosis.[5] Vascular and endothelial dysfunction occurs when the organ endothelium is damaged, and this acts as a precursor to atherosclerosis, thus CVDs.[5] Atherosclerosis is thickness of the artery walls caused by the development of lesions called plaques. Atherosclerosis may lead to CHD or ischemic heart disease in the heart; cerebrovascular accident (CVA) in the brain, or in the peripheral blood vessels to PVD.[6] In the final process, it might lead to myocardial infarction (MI) or stroke. These ischemic conditions can also cause damage in other tissues by thromboembolism.[6]

It is known that atherosclerosis remains the most common cause of CVDs and that plaque development, vascular calcification, and vascular stiffness are caused by the hyperactivation of a long-term endothelial dysfunction and inflammatory response that are triggered by an inadequate and unbalanced diet and other risk factors. The risk factors or characteristics that contribute to the development of CVDs are gender, age, family history, ethnicity, and previous medical history (nonmodifiable risk factors).[7] On the other hand, modifiable risk factors are hypertension (HT), dyslipidemia, smoking, obesity, diabetes and glucose intolerance, oxidative stress, inflammation, behavioral factors, and physical inactivity.[7] As poor diet is considered a risk factor and HT, dyslipidemia, oxidative stress, and inflammation can be preventable and controlled by the diet; nutrition takes place in lowering the morbidity of CVDs.[8] However, yet there have not appeared any reviews that evaluate the impact of a wide variety of dietary components on CVDs. Thus, the novel nutritional targets and interventions that focus on the nutrients and other dietary compounds on potential mechanisms underlying the CVDs are discussed in this review.

Methods

This study was done by using the databases PubMed, ScienceDirect, Google Scholar, and Scopus with the keywords "*related dietary factor* and cardiovascular disease/cardiovascular health." The authors systematically included only the review articles of the relevant literature from July 2001 to January 2017.

Macronutrients

Carbohydrates

Carbohydrates (CHO) have an important role in the human diet and takes up most of the daily energy intake.[9] There is evidence that CHO type and amount have an important effect on CVDs.[10]

Glycemic index and load

The glycemic index (GI) is a classification of CHO to the glycemic response in the body; glycemic load (GL) is the adjustment of the GI value to the CHO content of the serving.[11–14] It was shown

that high dietary GL and GI increased the risk of CHD in humans.[12,14] Low GI diets are beneficial in the management of hyperglycemia but also have effects on blood lipids. Low GI diets significantly reduce total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) when compared with the high GI diets.[12,14] In some studies, low GI diets have also found to raise blood high-density lipoprotein cholesterol (HDL-C).[15] Especially low GI diets that include beans may reduce systolic blood pressure (BP).[15] Despite all these findings, a study suggests that the effects of GI/GL value of the diet on CVDs risk factors including glucose homeostasis, lipid profile, and inflammatory status were inconsistent.[13] Elevated C-reactive protein (CRP) levels that are an emerging CVDs risk factor seem to be reduced in this context. Additionally, some studies remark that this relationship might be stronger in obese or diabetic patients.[15,16]

Fiber

Dietary fiber, which is in two forms (soluble and insoluble), is a nondigestible CHO polymer.[10,17] Soluble fiber (from legumes, oats, nuts, and some fruits and vegetables) dissolves in water and is fermented in the large intestine, whereas insoluble fiber (from whole grains, wheat and corn barn, some fruits and vegetables) absorbs water and inertly moves through the digestive tract with very little fermentation.[10,17]

Proposed dietary fiber affects plasma lipid reduction, body weight regulation, improved glucose and insulin metabolism, BP control, and reduction of chronic inflammation.[7,17–20] High consumption of dietary fiber significantly decreases TC and LDL-C.[7,18–20] Studies observed lower systolic and diastolic BP with an additional fiber intake of only 10 and 11.5 g/day.[7] Daily 10 g additional dietary total fiber intake from any source was associated with a 10–30% reduction risk of coronary events.[7]

The fiber type is also an essential factor in the association with CVDs as in the amount of fiber. Soluble fiber mainly from whole grains when compared with insoluble fiber from fruit and vegetables has been shown to provide a greater reduction in CVDs' incidence risk.[17] This difference is probably because of its ability to lower blood cholesterol.[7,15]

Soluble fiber plays a greater role in the reduction of BP when compared to insoluble fiber.[7] The cardioprotective effects seen with the consumption of both fiber types should be considered together with the phytochemical, antioxidant, etc., intakes of the diet along with them.[7]

Fructose

Fructose, a monosaccharide that has an important place in the human diet, appears in big amounts in honey, fresh, and dried fruits.[21] For thousands of years, humans have got fructose on average 16–20 g/day in their diets from fresh fruits.[21] Today about 15–20% (85–100 g/day) of the diet's energy comes from artificial fructose from refined convenience foods.[21] Another important source of fructose is high fructose corn syrup (HFCS) that is provided from most of the processed foods.[21]

Current studies suggest that chronic refined sugar consumption can result in cardiovascular dysregulation and soft drink consumption is considered a public health concern with implications on CVDs.[22] High sugar intake directly contributes to structural and functional cardiomyopathy, and myocardial dysfunction, modified growth, and oxidative stress responses are associated with high dietary sugar intake.[23] There is evidence that fructose can be a more harmful sugar component according to glucose in terms of

CVDs.[22] Fructose increases de novo lipogenesis, which might lead to obesity and fatty liver also lead to CVDs by lipoprotein abnormalities.[24] High fructose intake has the potential to adversely influence insulin resistance and glycolytic dysregulation.[23] Rapid hepatic metabolism of fructose generates substrates for lipogenesis and may lead to increased level of uric acid, which is thought to lead to uric acid-mediated HT.[24–27]

High consumption of fructose can provide a high risk in CVDs' development and progression. Fructose dose was positively correlated with TC and LDL-C.[28] A meta-analysis reported that replacing other CHO with fructose at isocaloric conditions increased TC and LDL-C levels when fructose consumption was very high (>100 g/day) via many mechanisms such as increasing endogenous cholesterol synthesis, advanced glycation end products, uric acid, and reduction of cholesterol extraction from LDL-C.[28] Also the high GI of fructose should be considered in its relationship with CVD risk.[11] Controlled feeding trials showed that the cardiometabolic harms of fructose can only be when there is excess energy consumed.[25,26] According to the results of many studies, fructose consumption might lead to many metabolic harms but the type of fructose might also be important. Recent clinical studies showed that relevant doses of sucrose or HFCS along with ad libitum diets increase the risk factors for CVDs.[24–27] Albeit clinical and epidemiological studies have linked fructose consumption with CVDs, further studies are needed to understand this relationship and the difference between animal and human physiology can limit the translation of the findings to humans (Figure 1).[25]

Protein

Proteins that are structured by amino acids are one of the important contents of the human diet and are vital macronutrients.[7,29] Either from animal sources (meat, chicken, fish, etc.) or plant sources (legumes, soy, etc.), proteins consist of amino acids like arginine and bioactive amines, which might be vital contributors to CVDs.[7,29]

Protein type or source

Observational studies showed that there was an association between dietary protein from animal and plant sources in terms of BP and blood lipid profile.[30,31] Few trials found that diets higher in protein from plant sources as from soy was associated with lower BP and lower blood cholesterol.[31] Among milk proteins that are widely studied, both casein and whey proteins (β-lactoglobulin) showed to be antihypertensive via inhibiting angiotensin converting enzyme (ACE).[32,33] Casein fragments also showed antithrombotic effects via inhibiting fibrinogen binding on platelets.[33] Red meat was determined to be associated with a greater risk of morbidity and mortality from CVDs, which can probably be due to its high total and saturated fat content. Recent data suggests that lean red meat can be successfully added to the diets that are recommended for heart health with no detrimental effect on blood lipids.[34] Notwithstanding, dietary animal proteins (whey proteins and casein) are found to be protective against CVDs by lowering BP and optimizing lipid profile. However, it should be considered that they contribute to a higher dietary total fat, cholesterol, and saturated fat intake.

Some plant, animal, and marine-derived protein hydrolysates and peptides also have hypolipidemic properties as shown in mammalian cells and animal models.[35] The hydrolysates and peptides bind bile acids and disrupt cholesterol micelles in the

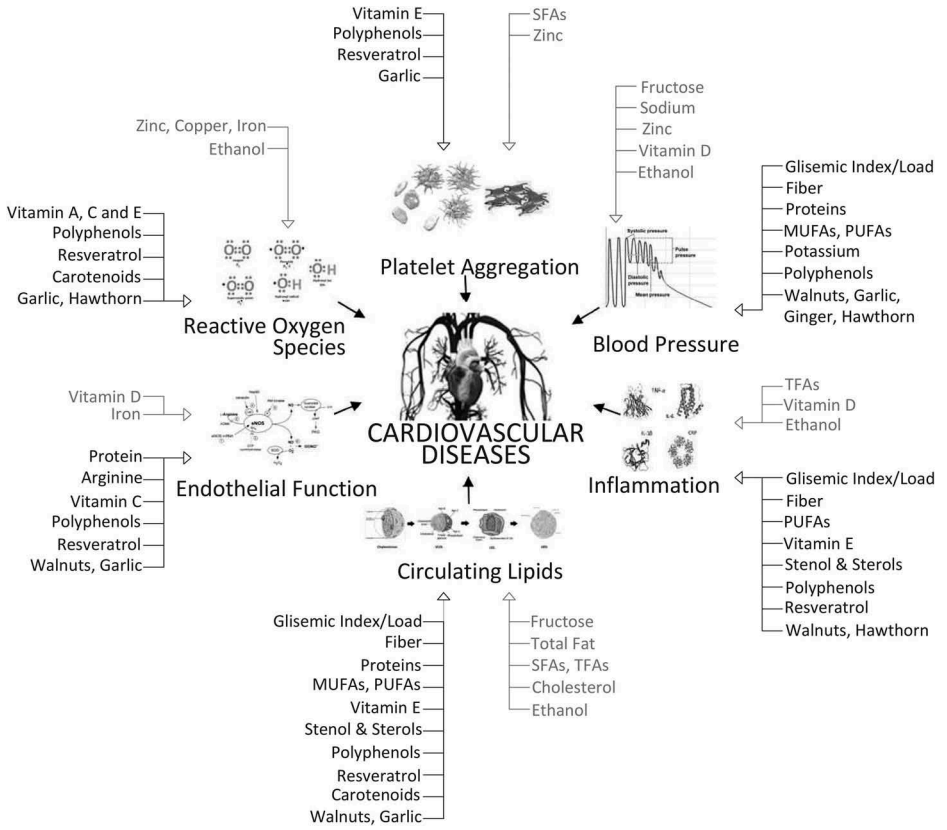

Figure 1. Dietary factors and their possible mechanisms related to cardiovascular health and disease. Dark gray lines and arrows indicate the positive impact on the related pathway. Light gray lines and arrows indicate a negative impact on the related pathway. MUFAs, monounsaturated fatty acids; PUFAs, polyunsaturated fatty acids; SFAs, saturated fatty acids; TFAs, trans fatty acids.

gastrointestinal tract by altering hepatic and adipocytic enzyme activity, and gene expression of lipogenic proteins.[35] Some peptides like alpha-lactalbumins, beta-lactoglobulins, and lactorphins might inhibit ACE and lower BP by normalizing endothelial function or lactorphins by opioid receptors-dependent mechanism.[30]

Recent studies have focused on the idea of the consumption of eggs as a functional food, especially in the prevention and treatment of HT.[36–38] The protein ovokinin was shown to have endothelium-dependent vasodilatory activity. The study determined that ovalbumin hydrolysates and oligopeptides might inhibit the angiotensin I-converting enzyme.[36,39] Several other cardioprotective effects (antiadhesive, antioxidant, anti-inflammatory, etc.) have also been attributed to egg proteins.[37,38] Another up-to-date topic is the protein content of whole-grain wheat.[39] Whole-grain wheat cereal consumption was found to improve BP. The individuals, with antihypertensive medication (no more than one antihypertensive medication – except β-adrenergic blocking agents – and/or one diuretic medication), decreased their drug dose after adding whole-grain wheat cereal (12 weeks of intervention) to their diets.[39]

Arginine

L-arginine is the substrate to form NO with the enzyme NO synthase (NOS).[40] NO is involved in the maintenance of vascular tonus, BP regulation, inhibition of platelet aggregation, leukocyte and endothelial cell interaction, and vascular permeability.[41–43]

When the amino acid arginine is methylated by methyltransferases, it is called asymmetric dimethylarginine (ADMA). Although the role of arginine methylation is unknown, it is known that ADMA competes with NOS and is an inhibitor of the NO synthesis and has a role on starting CVDs by causing endothelial dysfunction, vasoconstriction, high BP, and aggravation of atherosclerosis.[40–43] The fact that arginine is a substrate for NOS l-arginine supplementation can increase NO generation in cells.[44] It is suggested that excessive arginine supplementation reverses the negative effect of reduced NOS activity by antagonizing ADMA.[40]

Studies showed that l-arginine administration has improved endothelial function in animal models with hypercholesterolemia and atherosclerosis. Many studies have been conducted to see if dietary l-arginine supplementation in humans can increase NO production and improve endothelium-dependent vasodilatation. In some studies, the treatment of l-arginine supplementation has been proved as a beneficial treatment of HT, atherosclerosis, and heart disease.[45] Despite these results, arginine supplementation might also show no significant effects and may increase mortality in patients after MI.[44] Human studies have controversial effects, and it is important to identify the individuals that show positive effect of l-arginine supplementation.[44]

Animal studies have shown that high intake of lysine:arginine ratio resulted in elevated levels of blood TC, LDL-C, and HDL-C, therefore considering cardiovascular health; low lysine:arginine could be better.[46] Since the literature about lysine:arginine ratio of the diet was controversial, the whole amino acid profile should be considered.[46]

Lipids

Lipids are a family of compounds that includes triglycerides, phospholipids, and sterols. Dietary lipids circulate in the blood by lipoproteins, which are very low-density cholesterol (VLDL-C), intermediate-density lipoprotein cholesterol (IDL-C), LDL-C, and HDL-C.[47] Lipids are formed by fatty acids that are saturated fatty acids, polyunsaturated fatty acids (PUFAs), monounsaturated fatty acids (MUFAs), and trans fatty acids (TFAs), depending on the existence of double bounds also their number and configuration.[47]

Total fat

Most studies have shown that elevated cholesterol levels are associated with high-fat diets.[48] Though, there is no evidence on and effect of very low-fat diets (less than 20% energy) on hypercholesterolemia [48] and no relationship has been found between very low-fat diets and stroke.[49] Recently, it has been suggested that rather than the quantity the quality of the fat is more important.[47] Studies support the idea of the fat-type modification instead of the fat amount reduction in a diet for cardiovascular health.[47,50,51]

Saturated fatty acids

Fats from animal sources are the major source of saturated fatty acids (SFAs) in the human diet and was found to increase the atherogenic disease risk [52] by elevating LDL-C [53,54] or by promoting blood clotting.[55]

One of the most studied SFAs, stearic acid (18:0) was found to have no or little effect on blood cholesterol.[55] However, it causes lower level of LDL-C and TC:HDL-C ratio compared to other SFAs, and higher LDL-C, higher TC:HDL-C ratio, and lower HDL-C level compared to the unsaturated fatty acids.[55] When compared with CHO, SFAs (with carbons from 12 to 16) raise TC, LDL-C, and HDL-C level without any effect on TC:HDL-C ratio.[52] The US and European advisory committee's results showed that the effect of SFAs on LDL-C linked to CVDs but the effect on HDL-C was ignored.[53]

The replacement of SFAs with different macronutrients can be considered to optimize the blood lipid profile. The replacement with refined CHO can be risky [56] since high CHO intake may stimulate hepatic fatty acid synthesis and the accumulation of fatty acids stimulates chronic systemic low-grade inflammation, which results in atherogenic dyslipidemia.[57] Also when replaced with SFAs, high GI CHO were associated with a CVDs risk by increasing triglyceride levels and small LDL-C particles and reducing HDL-C.[56] However, the replacement with unsaturated fatty acids was published to be beneficial, [9,47,56] especially PUFAs replacement was found to reduce the CVD risk. Replacing 1% of energy from SFAs with PUFAs showed to reduce the CHD risk by lowering LDL-C. The replacement with MUFAs or PUFAs was found to lower LDL-C and TC:HDL-C.[57–59] The benefits of PUFAs seem to be stronger than MUFAs when replaced with SFAs in the diet.

Therefore, reducing red meat and dairy products and increasing nuts, fish, soy products, and nonhydrogenated vegetable oil have been found to have benefits.[51,60] Dairy products that were reduced in the diet lead to a reduction in CHD and stroke.[61] Although when reducing dairy consumption for cardiovascular health there are other dairy components (butyric acid, sphingolipids, rumenic acid, vitamins, etc.), one may need to consider their cardioprotective effects.[54] The consumption of milk and other dairy products with modified fatty acid composition could be a solution instead of excluding them from the diet.[54]

Monounsaturated fatty acids

Oleic acid is a MUFA and is found in olive and canola oils.[62] Populations that consume a Mediterranean diet, rich in olive oil, have a lower incidence of CHD.[62]

Recent studies have shown that the MUFA source (animal fat or vegetable oil) is important in the correlation between MUFAs and CHD risk but animal studies showed that both the sources are not cardioprotective.[62] A study that examined MUFAs in two different diets (MUFAs >12% or ≤ 12%) found that the high-MUFAs diet lowered fat mass, systolic BP, and diastolic BP more than the low-MUFAs diet.[63] High-fat MUFAs-rich diets were found to improve vascular function similarly to low-fat CHO-rich diets, although this effect might be due to other contents of olive oil.[64]

According to epidemiological studies, replacing MUFAs-rich foods for SFAs-rich foods can lower blood TC and CHD incidence but does not lower coronary artery atherosclerosis extent.[62] Another important consideration is which source (animal fat or vegetable

oil) of MUFAs is cardioprotective.[62] To reduce the CHD risk, it has been suggested to replace MUFAs and PUFAs for SFAs in the diet.[62]

Polyunsaturated fatty acids

Long-chain polyunsaturated fatty acids (LC-PUFAs) in the human diet are divided into two groups called n-6 (omega-6) and n-3 (omega-3). n-6 and n-3 LC-PUFAs are both found essential to reduce CVDs[47], n-6 LC-PUFAs [(especially linoleic acid (LA)] might decrease the CVD risk and n-3 LC-PUFAs (especially the long-chain fatty acids eicosapentaenoic acid and docosahexaenoic acid) might decrease the risk of fatal coronary outcomes.[47,52,65] Blood levels reflect the dietary intake, and an n-3 index has been proposed to be a marker for CHD, especially sudden cardiac death.[66–68]

n–3 LC-PUFAs lowers serum TG, resting heart rate, BP, inflammation, and improve myocardial and vascular function.[65,67] However, LC-PUFAs might lead to the oxidation of LDL-C (pro-oxidant effect), platelet aggregation, and interfere with essential fatty acids in phospholipids of the cell membrane.[65] Controlled trials showed that the replacement of n-6 LC-PUFAs with SFAs had no indication of benefit.[51,57]

The n-6/n-3 ratio has been found to be 15/1 to 16.7/1 in Western diets, which is considered to be high and associated with the pathogenesis of many diseases including CVDs.[69–71] Consequently, the lower ratio of n-6/n-3 (10/1 showed consequences) is required for the prevention of chronic diseases and the optimal value varies upon genetic variants.[71] The dietary ratio of n-6/n-3 might be a more sensitive biomarker than n-3 for dyslipidemia and CVDs.[65]

It is clear that n-3 LC-PUFA is important in CVDs, hence fish consumption gets attention.[66,72] n-3 LC-PUFAs in fish have integrative effects on platelet aggregation, arrhythmia, inflammation, endothelial function, and BP.[72] Fish with its other cardioprotective nutrients (protein, vitamin D, selenium) all might provide a synergistic effect on CVDs protection.[72] Fish oil consumption was found to be related to changes in TG (−27 mg/dL), HDL-C (+1.6 mg/dL), and LDL-C (+6 mg/dL), and was found to have no effect on TC.[73] The effect on serum TG was found to be dose-dependent and more significant on people with elevated levels.[73] Although the amount of n-3 LC-PUFAs in fish types varies, fish oil supplement does not have the same effect compared to the whole fish.[67]

Trans fatty acids

TFAs have the structure of a fatty acid when the hydrogens next to the double bonds are on the opposite sides of the carbon chain.[74] The sources are industrial hydrogenation of vegetable or fish oils, the natural digestion process in ruminant animals, hydrogenation of vegetable oils by food manufacturing, and commercial cooking and frying.[75,76] Studies show a clear association between TFA consumption and CVDs.[74,75,77,78]

In the body, TFAs behave like saturated fats and increase blood cholesterol and thereby increase disease risk.[74,76,78] TFAs increase the CVD risk by increasing LDL-C, LDL-C/HDL-C ratio, Lp(a) lipoproteins, and inflammation; they also decrease HDL-C and with its adverse effects on vascular endothelial function.[74,76,78] Also when compared with SFAs, TFAs have stronger adverse effects on CHD,[77] although the replacement of TFAs with stearic acid compared with other SFAs in foods has beneficial effects on LDL-C.[55] There is limited evidence that trans isomers of LA (trans-C18:2) and oleic acid (trans-C18:1) have stronger negative effects than palmitoleic acid (trans-C16:1).[76]

The effect of the source of TFAs might have diverse effect on CVDs.[79] There are studies showing that TFAs from ruminant source might result in less CVDs risk compared to industrial TFAs.[78] However, it was shown that conjugated linoleic acid industrial or luminant may raise plasma LDL-C and the total lipoprotein/HDL-C ratio.[78,79] To conclude, industrial TFAs should be eliminated from the diet because of the adverse effects on CHD.[78,80]

Cholesterol

The harmful effects of cholesterol begin when cholesterol accumulates in the artery walls to foam a plaque.[81] Increased serum TC concentrations are associated with atherosclerosis.[81] However, it is also shown that dietary cholesterol raises plasma cholesterol in only one-third of people[82] and there is a lack of evidence of the significant relationship between cholesterol intake and heart disease risk. Some studies support the hypothesis that dietary cholesterol has a small effect on TC levels but an increase in the cholesterol content of LDL particle and an increase in HDL-C, a small effect on LDL-C: HDL-C ratio.[83] Low cholesterol intake by the diet also is associated to improve dyslipidemia.[84]

The popular idea that dietary cholesterol intake influences the increase in blood cholesterol makes egg consumption questionable. Patients with high CVD risk are recommended to restrict their cholesterol intake, especially by stopping the consumption of egg yolks.[85] Meta-analysis results say that egg consumption does not increase the CVD risk[86]; there is not a relationship between daily egg consumption and increased risk of CHD or stroke,[87] reducing egg consumption is still valid when restricting dietary cholesterol intake[88] and that there is a dose response in the relationship between egg consumption and CVD risk.[89] A focus on postprandial effects of dietary cholesterol and egg intake instead of fasting cholesterol levels is suggested.[85]

Effect of egg intake on different ages and ethnicities on blood lipid concentrations were reported diversely. Therefore, the blood lipid response to dietary eggs may vary in different populations.[90] A diet including eggs more than the recommendations may be safe in the general population and even those at risk (patients with CVDs, CHD, type 2 diabetes).[91] In this context, a diet that includes high egg intake, along with a low SFA intake (PUFAs:SFAs >0.7) or replaced SFAs (with MUFAs and PUFAs), may result in lower or no changes in LDL-C; therefore, it might be considered safe.[91]

Micronutrients

Sodium

Sodium is a major mineral in the body, and high sodium intake correlates with high BP.[92,93] It is known that sodium modulates renal tubule Na^+,K^+-ATPase activity and inhibition of the Na^+,K^+-ATPase activity increases intracellular Na^+ and Ca^{2+} in vascular smooth muscle, and this can lead to an increase in BP so salt intake can be risky for patients who have HT.[94–96]

High salt [sodium chloride (NaCl)] intake does not only increase BP; it also plays a role in endothelial dysfunction, cardiovascular structure and function, and cardiovascular morbidity and mortality.[92,93] High dietary sodium intake from salt is also a risk factor for stroke.[49,95,97–99]

Moderate reduction of salt intake reduces BP and the risk of CVDs [49,92,93,95,97–99] and decreases the number of deaths from HT, CVDs, and stroke.[100,101] Although reducing salt intake improves the CVDs risk, it differs on the hypertensive complication.[102]

The relationship between salt intake and CVD is a J-shaped curve such that a low-salt diet may not be beneficial to everyone and may increase BP in some individuals.[103] More than half of the hypertensives are salt sensitive and a high NaCl intake will respond with a rise in BP.[49,95,97–99] Still salt reduction is essential for the treatment and prevention of HT and CVDs.[102] Today, the population's average salt consumption is 5–10 times greater than physiological requirements.[100,101] Reducing salt consumption, along with high fruit and vegetable consumption, is effective in lowering BP.[49,95,97–99,104]

Potassium

Dietary potassium intake has been shown to lower BP significantly in a dose–responsive manner both in hypertensive and nonhypertensive individuals, although some studies did not display this effect in nonhypertensive adults.[105–107] In hypertensive patients, increased intake of potassium (0.6 g/day) resulted in reduction of systolic and diastolic BP independent from potassium deficiency.[105–107] Potassium that lowers BP also lowers the incidence of stroke, CHD, MI, CVA, and other CVDs.[105–107] The increased intake of potassium had no adverse effects on renal function, blood lipids, and catecholamines in hypertensive patients.[106]

A body that is sodium excess and potassium deficient creates an environment for the pathogenesis of HT by abnormalities in central hemodynamics (renal sodium handling, endothelium-dependent vasodilatation, and oxidative stress). Therefore, it is critical to change the diet to a high potassium–low sodium diet.[49,92,93,108,109] To reduce the CVDs risk, an increase in potassium and a decrease in sodium might be achieved by consuming more fruits and vegetables in the daily diet.[110]

Calcium

Calcium, the most abundant mineral in the human body with many functions, is mostly known for its role in bone health.[111] Supplementation is recommended for osteoporosis, although its role on vascular health is not clear.[111] Because calcium supplementation is common in people over 50, a concern rises whether calcium supplementation and excess calcium intake have detrimental or beneficial effects on CVDs.[111]

Calcium is shown to affect the risk of developing CVDs through many mechanisms (blood cholesterol, insulin secretion and sensitivity, vasodilation, inflammatory profile, thrombosis, obesity, and vascular calcification).[111,112] Large amounts of calcium were shown to lower blood cholesterol by decreasing fatty acid absorption.[111] Benefits to BP regulation by downregulating the activity of the renin–angiotensin system were also shown.[111] Other reported activities of high calcium were decreasing vascular smooth muscle tone, activating lipolysis in adipocytes by inhibiting fatty acid synthase.[111] Relatively low amounts of intracellular calcium may have CVDs' protective effects such as less platelet aggregation, attenuation of cytokine-induces inflammation, and augmentation of vascular relaxation.[111]

High serum calcium was shown to be associated with a higher risk of vascular disease and even mortality.[112] It was reported that high calcium levels could be due to the calcium supplementation,[112,113] which might result in vascular calcification [111,113] and increased MI risk.[112,114] Despite this, the clinical guidelines and the studies concluded that sufficient amount of calcium from food or supplements (with or without vitamin D intake) had no relationship with the CVD mortality, but there is a tolerable upper level.[111,113,115]

Zinc, copper, and iron

Zinc influences cellular signal transduction pathways with the redox status of the cell. Dietary zinc restriction during fetal life, lactation, and postweaning was found to lead to an increase in arterial BP in adult life.[116,117] CVDs (HT, atherosclerosis, congestive heart failure) have been found to be associated with impaired zinc utilization and oxidative stress.[116–118] This might be by the change in zinc homeostasis that may lead to various degrees of deficiency seen in arterial HT.[119] Additionally, ischemia and infarction might lead to a release of zinc from proteins and cause myocardial damage.[120,121] Furthermore, in atherosclerosis, mild zinc deficiency might exist according to current studies.[116,117] Acute zinc depletion in (athero)thrombosis may weaken platelet aggregation and might result with a longer time of bleeding.[120,121] Replenishment with zinc has improved cardiac function,[120,121] although intracellular-free zinc can worsen oxidative stress in CVDs.[116,117] Furthermore, sustained hyperzincemia may influence thrombogenesis.[120,121] Consequently, it is important to evaluate the population's zinc status and develop interventions for zinc deficiency and for better management and prevention in adulthood CVDs.[116,117,122]

Copper, a cofactor for many redox enzymes, might be a risk factor for CVDs when levels are high in the circulation.[123,124] However, limited data show that dietary copper is associated with a better lipoprotein profile, especially with by regulating LDL-C.[124] Experimental studies showed that copper may promote endothelial function.[123] Copper was found to promote angiogenesis.[123] It also can contribute to excess production of reactive oxygen species (ROS) that might lead to various diseases including atherosclerosis and diseases of inflammation.[124,125] Blood homocysteine (Hcy), which can be considered a risk factor for CVDs, when combined with copper (copper–Hcy complexes), may have detrimental effects.[123] These complexes might alter the redox effects of copper.[123] An understanding of a selective modulation of copper to avoid copper–Hcy complexes can improve the CVD condition.[123]

The disruption of iron homeostasis was linked to CVDs.[125–129] Excess iron may contribute to a higher CVDs risk by increasing lipid peroxidation and increasing the production of free radicals.[125–129] Increased iron stores was also associated with vascular endothelial dysfunction and increased CHD event risk.[130,131] In contrast, iron deficiency is one of the comorbidities in heart failure and the severity of heart failure raises the prevalence of iron deficiency.[126–128] Either extreme iron deficiency or iron overload might be associated with increased CVDs risk.[126–128]

Selenium

Selenium is found to have a role in the optimal functioning of the cardiovascular system.[132–135] The antioxidant activity of selenium is considered in the prevention or treatment of CVDs.[132–135] Ecological studies found a relationship between selenium deficiency and atherosclerotic heart disease but epidemiological study results were inconclusive.[132,133]

Selenium, which is an essential trace element found in selenoprotein glutathione peroxidase, is an enzyme responsible of reducing oxidant stress by preventing the oxidation of lipoproteins.[133] Selenium blood levels can be used as a biomarker for oxidative stress-associated diseases.[132] In animal studies, selenium deficiency developed cardiomyopathy and sudden death; therefore, these mechanisms were thought to be the etiology of CVD and other oxidative stress, inflammation-related conditions.[132–135] Selenium might regulate the arachidonic cascade in endothelial cells and its deficiency may lead to enhanced production of 15-hydroperoxyeicostetraaenoic acid and thromboxane A2, and decreased production of prostaglandin I2, E2, and F2, thereby leading to platelet activation.[133]

Reduced selenium levels were found to develop CHD by inadequate prevention of LDL-C oxidation.[132,136] Elevated baseline selenium levels were found to be associated with a lower risk of HT in humans although the opposite was also found.[132,134,135] A 50% increase in selenium concentrations was associated with a 24% reduced risk of coronary events though this relationship is not certain because observational studies have evidence that also include other antioxidants (vitamins, carotene, folate), which makes it harder to address selenium.[136]

The role of selenium in CVDs has not enough evidence to support its supplementation. Interventional studies are currently in progress to assess the benefits of selenium supplements in primary and secondary prevention of atherosclerosis.[132,133] Still selenium supplementation is a target for consumers; therefore, the high intake and toxic effects should be considered. Uncontrolled use can lead to a higher selenium status, which was found to have an adverse effect on the lipid profile.[134,135] Elevated TC levels and high selenium status were found to be associated, but yet there is not any observational prospective evidence to support this.[134,135]

Vitamins A, C, and E

Vitamins A, C, and E are antioxidant vitamins found in fruits and vegetables.[137] The consumption of a diet with large amounts of fruits and vegetables is shown to have lower incidences of CVDs and stroke. This leads to the discussion whether antioxidant vitamin supplements can help prevent CVDs.[138,139] Antioxidant vitamins may improve endothelial function by reducing the concentration of ROS in the vessel walls and prevent the oxidation of LDL-C.[140–144] Animal experiments have showed that vitamin E may prevent the consequences of oxidized LDL-C, whereas vitamin C may provide NOS activity. Prolonged use of vitamin A, C, and E supplementation in pharmaceutical forms might be effective in the prevention of atherosclerosis. However, these animal experiments were performed on young/adult animals with early stage of atherosclerosis while the human patients in clinical trials are much older with late stage of the disease.[142–144]

Tocopherols and tocotrienols both reduce the serum levels of CRP and advanced glycation end products, and expression of cell adhesion molecules, although the CRP-lowering effects of tocotrienols are greater than tocopherol.[145] Tocotrienols also reduce serum lipids and raise serum HDL-C, have greater antioxidant activity than tocopherols, reduce inflammatory mediators, are antithrombotic and suppress the expression of matrix metalloproteinases, and slow the progression of atherosclerosis.[145,146] α-Tocopherol, on the other hand, has no effect on serum lipids. α-Tocopherol is effective in primary prevention of coronary artery disease (CAD).[145] Clinical trials of α-tocopherol showed reduced risk of MI, ischemic stroke, and PVD.[147] The consumption of vitamin-E rich foods in middle-aged to older individuals might lower the risk of CHD, although meta-analyses and randomized cohort studies have not found these beneficial effects.[137,148,149] In contrast, high level of vitamin E supplementation might cause an increase in total mortality, heart failure, and hemorrhagic stroke.[137,148]

Vitamin C (ascorbic acid) was showed to improve endothelial function in patients with endothelial dysfunction by increasing NO bioavailability.[150,151] Epidemiological and prospective studies have found a positive role of ascorbic acid in the prevention of atherosclerosis, although clinical trials have not found a role of ascorbic acid deficiency in the development of hypercholesterolemia and atherosclerosis.[150,151]

Vitamin deficiencies are common in hypertensive individuals and CVD patients; therefore, deficiency treatment might reduce BP, improve vascular health, endothelial dysfunction, vascular biology, and decrease cardiovascular events.[140,141] Nevertheless, randomized controlled trials did not support the long-term use of single antioxidant supplements against CVDs.[152–155] Vitamins may be beneficial in individuals who are antioxidant-deficient or have increased oxidative stress (smokers, diabetics, and the elderly) and it is important to find the optimal vitamin combination for specific target groups.[142–144] All antioxidant-rich foods are recommended instead of single-vitamin supplementation to prevent CVDs.[137,148]

Vitamin D

Apart from calcium homeostasis, vitamin D has a role in the immune/inflammation system by regulating the production of inflammatory cytokines and inhibiting proliferation and proinflammatory cells.[156–159] The possible important effects of vitamin D and its derivatives in the cardiovascular system are promoting endothelial function and suppressing cardiac hypertrophy and fibrosis.[160]

Vitamin D deficiency has been linked to HT, peripheral arterial disease, and heart failure, and low levels of vitamin D (>75 nmol/l) are linked to inflammation, higher coronary artery calcium scores, impaired endothelial function, and increased vascular stiffness.[160–163] Its deficiency could activate the renin–angiotensin–aldosterone system that can predispose to HT, left ventricular hypertrophy.[158,159,164,165] It can also increase the parathyroid hormone that increases HT and inflammation.[158,159,164,165]

The relationship between vitamin D receptor (VDR) and cardiovascular oxidative stress is still unclear, although it is known that CVDs arise from either their insufficiency or intoxication.[160] VDR might promote vasorelaxation by effecting vascular endothelium, inhibiting angiogenesis, and suppressing vascular inflammation, and play a role in

maintaining cardiac structure. Lack of the receptor's signaling was shown to lead to the cardiac hypertrophy and fibrosis.[160]

In the atherosclerosis-related CVDs and other chronic inflammatory diseases, lower vitamin D status was determined.[156–159] Older individuals who had deficient 25(OH)-D concentrations had more than twice CVD mortality than the ones with adequate 25(OH)-D concentrations.[156–159]

Vitamin D supplementation might be used to treat cardiac abnormalities when there is a deficiency.[160] Supplementation leads to vasodilatation and triglyceride suppression.[156–159] Although overdosing may lead to hypercalcemia, hyperphosphatemia, and increased fibroblast growth-factor 23.[158,159,164,165]

Other dietary components

Stenol and sterols

Plant sterols and stenols (PS) are safe and effective agents in reducing cholesterol absorption and reducing circulating levels of cholesterol, thereby reducing the CHD risk.[166,167] PS might activate the pathway where there is a secretion of cholesterol into the intestinal lumen and excretion.[168] A study showed that PS while lowering LDL-C does not change HDL-C or triglyceride levels.[169] Additionally, studies showed effects of PS such as beneficial effects on apolipoprotein B/apolipoprotein AI ratio, HDL-C, and TG.[170] They can also affect inflammatory markers, coagulation parameters, as well as platelet and endothelial function and have a little beneficial effect on oxidative stress.[170] PS-oxidized derivatives (phytosterol oxidation products), which are oxidized during food processing or storage, might contribute to the negative effects of both cholesterol and cholesterol oxidation products.[171] PS effects cannot be seen in humans at usual doses; consequently, there is need for long-term randomized placebo-controlled studies.[170]

Plant sterols might have a potential to exert negative cardiovascular effects especially in atherogenesis.[172,173] In some patients, this may be explained by sitosterolemia.[174–176] Other possible mechanisms are the formation of plant sterol oxidation products or the LDL-C-lowering effect may be only seen in patients with high intestinal cholesterol absorption.[173]

A diet including plant sterols and fibers combined with statin therapy can significantly reduce LDL-C and CRP.[82,177,178] Even a little amount of dietary sterols has an LDL-C-lowering effect and increasing them in the daily diet can prevent dyslipidemia.[166,179] Plant sterols dose dependently could lower LDL-C.[166,180,181] It was concluded that when taking PS to lower LDL-C, the high plasma sterol levels had no adverse effects on health in long-term human studies.[182]

Polyphenols

Polyphenols might decrease the CVD risks by influencing signal pathways and counteract with oxidative stress.[183] Polyphenols have an antioxidant activity, and they enhance the expression of several protective proteins against CVDs, including NOS and paraoxonase 1 in endothelial cells.[184–189] Polyphenols in the human body were shown to have vasodilator, anti-inflammatory effects, and improve oxLDL by certain mechanisms.[184,190]

Studies with anthocyanins, flavonols, procyanidins flavanones, and hydroxycinnamic acids/flavan-3-ols/procyanidins showed different mechanisms related to CVD protection.[191,192]

There are many studies that focused on specific foods with effects on CVDs attributed to their polyphenol contents. Cocoa was shown to have anti-inflammatory effects via its polyphenols.[193] Dark chocolate was shown to lower BP and have anti-inflammatory effect inversely associated with CAD, whereas the effect of coffee and (green) tea was less.[194] Wine and grapes were shown to decrease the risk of CVDs.[195] The possible mechanisms include inhibiting oxLDL, improving endothelial function, lowering BP, inhibiting platelet aggregation, reducing inflammation, and activating novel proteins that prevent cell senescence.[195] A study suggests that the benefits of polyphenols were observable in sufficient intakes while they can disappear in high consumptions.[196]

Resveratrol

Resveratrol is a polyphenol produced in plants that has an antioxidant effect and also known as a pleiotropic agent. It might have many activities in cell proliferation and differentiation, apoptosis, antioxidant defense and mitochondrial energy production.[197–200] Decreasing LDL-C oxidation and platelet aggregation can be counted as antiatherosclerotic and vasorelaxative actions.[201]

Resveratrol was found to prevent the development of atherosclerosis [197], ameliorate MI,[200] and protect against CVDs.[197] Resveratrol's reduction of oxidative stress, production of NO, inhibition of inflammation, and the prevention of platelet aggregation were shown in animals to protect from ischemias and reperfusion injuries in the heart.[198,200–203] Reduction of BP and cardiac hypertrophy by resveratrol in hypertensive animals slowed the advancement of atherosclerosis.[198,200–203] However, clinical studies of resveratrol are limited.

Carotenoids

Carotenoids are shown to have an inverse association with CVDs. The cardioprotective mechanisms may be due to their free radical scavenger activities and improvement of LDL-C.[204,205] Their antiatherosclerotic effect was not determined in some studies in which cardiovascular and cerebrovascular events were investigated.[206] Their antioxidant, antiapoptotic, and anti-inflammatory effects were thought to be due to the intracellular signaling cascades-induced gene expression pathway.[207]

Fruits and vegetables contain various types of carotenoids (β-carotene, α-carotene, β-cryptoxanthin, lycopene, lutein, zeaxanthin, and astaxanthin) although β-carotene is studied predominantly.[208] β-Carotene is thought to reduce the CVD risk by mechanisms including reducing of plasma cholesterol,[205] increasing degradation of LDL-C, inhibiting the production of oxLDL, and reducing inflammation.[209] The other carotenoids like lycopene and alpha-tomatine were found to have anti-inflammatory and cardioprotective effects.[210,211]

Novel studies should focus on these metabolic mechanisms and the dose-dependent response of carotenoids.[206,207] Despite the single carotenoid supplement in the

prevention or treatment of diseases, recent studies have focused on diet quality indexes and the antioxidant properties of the diet all together.[155]

Ethanol

Cardiovascular toxic effects of ethanol (alcohol) include cardiomyopathy, cardiac arrhythmias, sudden cardiac death, HT, stroke, hemorrhagic stroke, and HT.[212,213] High alcohol consumption elevates BP.[214–216] Alcohol induces hypertriglyceridemia by increasing LDL-C secretion, impaired lipolysis, and increased fatty acid fluxes to the liver.[217] Atherogenic effects of alcohol are elevated lipid levels, inflammation, oxidative stress, and endothelial dysfunction.[218–224]

Studies support a J-shaped association between alcohol intake and adverse health outcomes.[225,226] Low-to-moderate alcohol intake may have a protective effect on cardiovascular risk in some populations,[212,219,221–224,227,228] and CAD and ischemic stroke.[213] Low-to-moderate alcohol intake may have benefits on oxidative balance, and [222] intake might be associated with decreased plasma triglycerides.[217] Lipids, platelet aggregation, fibrinogen, tissue-plasminogen activator, plasminogen-activator inhibitor, and omega-3 fatty acids may be the responsible mechanism.[223]

Depending on not only the amount but also the type of alcoholic beverages, the effect of ethanol could be varied. Daily low-to-moderate-dose alcohol intake, especially red wine, before or during the evening meal has the strongest reduction in cardiovascular risk factors.[221,229] The protective effect of moderate alcohol consumption may be due to its alcohol content ethanol or nonalcoholic content that are mainly polyphenols, although this effect is found regardless of the type of drink (red versus white wine, beer, spirits).[228]

Alcohol intake more than 3–4 glasses per day may increase the MI and stroke risk.[228] Individuals who have severe HT had a 12 times more increased CVDs risk when they are binge drinkers.[216] People with cardiomyopathy, cardiac arrhythmias, or hypertriglyceridemia are the ones that should best avoid alcohol,[217,220] and for CVD protection, the dose, age, sex, health status, and lifestyle should be defined to clear this topic.[227,230]

New insights

Walnuts

Bioactive compounds in nuts that form their unique structure are plant protein, fiber, minerals, fatty acids, and phenolic compounds.[231,232] Walnuts were shown to have the highest antioxidant capacity and PUFA content when compared to other nuts.[233,234] The fatty acid profile and polyphenols of walnuts were associated with benefits to protection against the development of CVDs.[235,236] Walnuts also contain l-arginine, which is the precursor of NO and may lead to efficient vascular function.[237]

Diets containing walnuts showed reductions in TC, LDL-C, and triglycerides.[234,236–238] Walnut consumption might stimulate LDL-C receptor activity and promote its removal from the circulation.[238] However, the diets including walnuts did not reduce serum cholesterol in obese patients with metabolic syndrome and their lipid-lowering effects were more significant in the case of patients with higher LDL-C.[237]

The diet high in walnuts was reported to be associated with decreased BP, improvement of endothelial function, decreased oxidative stress and markers of inflammation, and increased cholesterol efflux.[238] Furthermore, recent evidence supported benefits of walnuts on flow-mediated vascular dilatation, reduced circulating endothelial activation/adhesion molecules, and inhibition of proinflammatory cytokine production.[234,238,239] The improved vascular reactivity is thought to be due to the l-arginine, PUFAs, and more unlikely α-linolenic acid, and polyphenols.[234,238,239]

Despite the potential antioxidant activity of walnuts induced by polyphenols, the pro-oxidant effect of PUFAs may lead to oxidation of lipoproteins especially LDL-C.[233] However, studies that compared the consumption of PUFAs-rich walnut or other healthy diets on oxidative markers found no difference.[237]

Intervention studies including walnuts showed a lower relative risk of CHD although more studies should be done. There is limited data about the duration of consumption for the sustainability of the health benefit, adverse effects, and dose response after walnut intake in comparison to the other nuts.[236] Walnuts have been found to be a part of a healthy diet that could not only lower blood cholesterol levels but also other mechanisms underlying CVDs.[236,237]

Garlic

Garlic was proven to help protect against CVDs in clinical and preclinical studies by lowering BP, inhibiting platelet aggregation and adhesion, reducing LDL-C, elevating HDL-C, and preventing LDL-C oxidation.[240,241] It was also shown to improve endothelial function by improving the production of cellular NO and increasing glutathione levels.[242]

Garlic consumption in both humans and laboratory animals resulted in reductions in TC, triglycerides, LDL-C, and increases in HDL-C levels, [242–244] but CVD-induced morbidity and mortality were unclear.[245] Garlic supplementation was shown to improve blood lipid profile[242] and the blood antioxidant potential while reduced BP[244,246,247], blood homocysteine, and nuclear kappa β levels.[247] Decreased platelet aggregation results were significant with garlic.[248] Supplementation of garlic may reduce BP only in patients with uncontrolled HT.[245,247,249–251]

Garlic extract was found to be tolerable with no or little harmful interaction taken with antihypertensive and anticoagulant medication.[247,249,250] Though studies should focus on the dosage, type, and form (fresh, cooked, or aged) of the garlic to develop the CVDs related beneficial effects considering the whole diet.[252]

Ginger

Ginger, which is widely used for many medical purposes, was found to be a strong antioxidant and may lead to the protection against degenerative disorders.[253] Experimental studies have found effects against atherosclerosis such as reducing plasma TC, triglyceride, LDL-C, and VLDL-C.[246,254,255] Some findings support that ginger may enhance plasma fibrinolytic activity and the antiplatelet effect.[254] Inhibition of lipid

peroxidation and ACE activity,[246] antiplatelet,[254] and anti-inflammatory effects were also shown.[254,255]

The content gingerol and shogaol in ginger juice was found to cause vagal stimulation that leads to a decrease in BP and heart rate.[246] Administration of ginger extract in rats increased fecal excretion of cholesterol, thus reducing serum cholesterol and LDL-C levels.[254] It is not clear whether these effects are seen in normal patterns of the daily diet and the amounts are consumable. Ginger may be an alternative with the lowest side effects, hence, there is need for more human studies.[256]

Hawthorn

Hawthorn's benefits on health and disease have been attributed to its flavonoid, anthocyanin (oligomeric procyanidins) contents.[257–260] It might have positive effects on MI by maintaining mitochondrial antioxidant status, thereby preventing mitochondrial lipid peroxidative damage.[257,258] Anticardiac remodeling, antiplatelet aggregation, vasodilating, endothelial protective, reduction of smooth muscle cell migration and proliferation, protection against ischemia/reperfusion injury, antiarrhythmic, lipid-lowering, and decrease of arterial BP effects were also shown.[261,262] Animal studies showed hypolipidemic, hypotensive, antioxidant, radical-scavenging, and anti-inflammatory effects.[258,259,263–265] Antiarrhythmic effects may be due to β-adrenergic receptor blockade.[258,263]

Its extract is processed in capsules or tablets for cardiotonic, hypotensive, and antiatherosclerotic effects in cardiovascular health.[258,259,261,264] Hypertension and hyperlipidemia were also shown to improve by hawthorn.[261] In chronic heart failure, hawthorn extract might be an additional therapeutic agent.[257,262,266,267] However, hawthorn consumption and CVD-induced mortality have not been associated yet and may interact with some pharmaceuticals.[267]

Conclusion

CVDs were induced by the oxidative stress, chronic inflammation, thrombosis, abnormal lipoprotein metabolism, and vascular endothelial dysfunction, which can be prevented and controlled by the diet. The dietary factors in an adequate and balanced diet play an important role in preventing CVDs by regulating the mechanisms (Table 1).

The type and amount of CHO in the diet are underestimated when considering the cardiovascular health. In this context, fructose consumption, which might be a health concern toward many chronic diseases, should be considered. On the other hand, there is not enough evidence about dietary protein type and amount in CVDs, although some peptides might have cardioprotective effects and the amino acid arginine might be a therapeutic agent. In regard to lipids, it is almost certain that the modification of dietary fat, especially lowering SFAs and TFAs and increasing PUFAs and MUFAs, is beneficial in CVDs. Despite the literature and guidelines about sodium, calcium, and potassium suggestions, there is a need for more research about the other micronutrients, especially the antioxidant vitamins (A, C, E) and minerals (selenium, zinc, copper, iron).

Table 1. Dietary factors and their effects on cardiovascular health and disease.

Dietary Factor	Type	Effect	Reference Number
Carbohydrates	Glycemic Index and Load	TC and LDL-C ↓	[12,14]
		HDL-C ↑	[15]
		BP ↓	[15]
		CRP ↓	[15, 16]
	Fiber	TC and LDL-C ↓	[7, 18-20]
		BP ↓	[7, 17-20]
		Inflammation ↓	[7, 17-20]
	Fructose	BP ↑	[24-27]
		TC and LDL-C ↑	[28]
Protein	Plant Protein	BP ↓	[30, 31]
	Whey Protein	BP ↓	[30, 31, 32, 32, 33]
	Egg Protein	BP ↓	[36, 39]
	Arginine	NO ↑	[44]
Lipids	Total Fat	TC ↑	[48]
	Saturated Fat	LDL-C ↑	[53, 54]
		Blood clotting ↑	[55]
	MUFAs	BP ↓	[63]
		TC ↓	[62]
	PUFAs	TG, LDL-C ↓	[65, 67]
		Inflammation ↓	[65, 67]
		BP ↓	[65, 67]
		HDL-C ↑	[73]
	Trans Fatty Acids	LDL-C ↑	[74, 76, 78]
		Inflammation ↑	[74, 76, 78]
		HDL-C ↓	[74, 76, 78]
	Cholesterol	TC ↑	[82]
		Cholesterol content of LDL-C ↑	[83]
		HDL-C ↑	[83]
Micronutrients	Sodium	BP ↑	[92, 93, 94-96]
	Potassium	BP ↓	[105-107]
	Calcium	TC↓	[111]
		Low calcium: Platelet activation ↓	[111]
		Vascular calcification ↑	[111, 113]
	Zinc	Vitamin deficiency: OS ↑	[116-118]
		Vitamin deficiency: BP↑	[116-117]
		Vitamin deficiency: platelet aggregation ↑	[120-121]
	Copper	ROS production ↑	[124, 125]
	Iron	Vitamin overload: Vascular endothelial dysfunction ↑	[130, 131]
		Vitamin overload: Lipid peroxidation ↑	[125-129]
	Selenium	Mineral deficiency: platelet activation ↑	[133]
		Low levels: oxLDL ↑	[132, 136]
	Vitamin A	ROS production ↓	[140-144]
	Vitamin C	ROS production ↓	[140-144]
		NO activity ↑	[150, 151]
	Vitamin E	ROS production ↓	[140-144]
		Inflammatory mediators ↓	[145, 146]
		Thrombosis ↓	[145, 146]
		Serum lipids ↓	[145, 146]
		HDL-C ↑	
	Vitamin D	Vitamin deficiency: inflammation ↑	[158, 159, 164, 165]
		Vitamin deficiency: BP ↑	[158, 159, 164, 165]
		Vitamin deficiency: Endothelial dysfunction ↑	[12160-163]
		Proliferation and proinflammatory cells ↓	[156-159]
		Cardiac hypertrophy and fibrosis ↓	[160]

(*Continued*)

Table 1. (Continued).

Dietary Factor	Type	Effect	Reference Number
Other Dietary Components	Stenol and Sterols	TC, LDL-C ↓	[169, 173, 182, 177]
		CRP ↓	[82, 177, 178]
	Polyphenols	oxLDL ↓	[184, 190]
		Inflammation ↓	[184, 190, 194]
		NOS expression ↑	[184-189]
		BP ↓	[194]
		Platelet aggregation ↓	[195]
	Resveratrol	ROS production ↓	[198, 200-203]
		NO production ↑	[198, 200-203]
		Inflammation ↓	[198, 200-203]
		oxLDL ↓	[201]
		Platelet aggregation ↓	[198, 200-203]
	Carotenoids	ROS ↓	[204, 205]
		LDL-C ↓	[204, 205]
		Apoptosis ↓	[207]
		TC ↓	[205]
	Ethanol	Blood lipids ↑	[218-224]
		Inflammation ↑	[218-224]
		OS ↑	[218-224]
		BP ↑	[214-216]
		Hypertriglyceridemia ↑	[217]
New Insights	Walnuts	TC, LDL-C, and TG ↓	[234, 236-238]
		BP↓	[238]
		Endothelial function ↑	[238]
		OS ↓	[238]
		Inflammation ↓	[238]
New Insights	Garlic	BP ↓	[240, 241, 244, 246, 247]
		Platelet aggregation and adhesion ↓	[240, 248]
		LDL-C, TC and TG ↓	[240]
		HDL-C ↑	[242-244]
		oxLDL ↓	[240, 241]
		NO production ↑	[242]
	Ginger	BP ↓	[246]
		LDL-C, VLDL-C, TC and TG ↓	[246, 254, 255]
		Inflammation ↓	[254, 255]
	Hawthorn	BP ↓	[261, 262]
		Inflammation ↓	[258, 259, 263-265]

BP, blood pressure; CRP, C-reactive protein; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; MUFAs, monounsaturated fatty acids; NO, nitric oxide; NOS, nitric oxide synthase; OS, oxidative stress; PUFAs, polyunsaturated fatty acids; oxLDL, oxidized low density lipoprotein cholesterol; ROS, reactive oxygen species; TC, total cholesterol; TG, triglyceride; VLDL-C, very low density lipoprotein.

In addition to macro and micronutrients, other dietary compounds (stenols, sterols, polyphenols, resveratrol, carotenoids, etc.) that are found in very small amounts in the diet might influence the prevention and treatment of the CVDs. Consumption of different colored fruit and vegetables can be suggested for the intake of different dietary compounds. Some foods like walnuts, ginger, and garlic may be accepted as functional foods for cardiovascular health. Hawthorn, which is consumed abundantly in Turkey, might have cardioprotective effects and may also be listed as a functional food against CVDs. Research and dietary suggestions should focus on traditional foods that are consumed and accessible in countries may be included as part of a healthy diet against CVDs.

Declaration of interest

There are no conflicts of interest to declare.

ORCID

Betul Kisioglu http://orcid.org/0000-0002-7158-9524
Reyhan Nergiz-Unal http://orcid.org/0000-0002-3143-7710

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