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Dietary Supplements and Cardiovascular Disease: What is the Evidence and What Should We Recommend?

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1. Introduction

1.1 Importance of cardiovascular disease and scope of this chapter

Cardiovascular disease, diabetes, and obesity are important causes of morbidity and mortality. Cardiovascular disease affects 80 million Americans and is the leading cause of death (Lloyd-Jones et al., 2009). Diabetes and obesity are also increasing at alarming rates, and together, the three conditions have a significant impact on public health (Ogden et al., 2006). Cardiovascular disease, diabetes and obesity can be influenced by lifestyle changes, including diet and physical activity (McCullough et al., 2000). The American Heart Association recommends a diet rich in vegetables and fruits, whole grains, high-fiber foods, with lean meats and poultry, moderate consumption of fish, an emphasis on fat-free or low fat dairy products, and limiting the amount of saturated fat, trans fat and cholesterol (Lichtenstein et al., 2006).

Among natural products found in food, fish oils, vitamin E, and soy isoflavones have been studied for their effects on cardiovascular disease. Many of these compounds are available as food supplements. There is a great interest among the public and in the lay press about the use of these compounds to treat or prevent disease. The scope of this chapter is to review the evidence for the effects of these compounds on cardiovascular disease, so that physicians and patients may better understand their health effects, in an effort to reduce the risk for cardiovascular disease, diabetes and obesity.

1.2 Types of evidence: Epidemiologic, mechanistic, and randomized clinical trials

It is important to realize the different kinds of evidence in support of health benefits of natural products. One type of evidence is *epidemiologic evidence*. Epidemiologic information may offer the first suggestion that certain natural products in the diet may influence the risk and course of chronic diseases like cardiovascular disease, diabetes, and cancer. Cross-cultural studies might indicate that populations that have high or low intake of certain compounds have different incidence of cardiovascular disease. This does not prove that supplementation with these compounds would necessarily change the course of

cardiovascular disease. Genetic and environmental factors may all contribute to the effects observed in the epidemiologic studies. Cohort studies, which follow groups of people and their intake of certain compounds, also provide suggestive evidence for their effects.

A second type of evidence comes from *mechanistic studies* in the laboratory or in animal models. Here, the natural products or compounds in question are added to cells or enzyme reactions, to see what their effects are. Studies may be done in animal models of human disease, for example apoE knockout mice that develop diet-induced atherosclerosis. They may be carried out on blood vessels from animals to see whether the compounds affect vascular function. Mechanistic studies help determine the possible molecular and cellular mechanisms and pathways involved in biological function. However, just because a compound has an effect in these experiments or animals models does not mean that taking them will necessarily reduce disease in people. Many of these experiments are done *in vitro*, not *in vivo*.

A third type of evidence comes from *randomized controlled clinical trials*. In these trials, compounds are administered to a large population, which is then followed for clearly defined disease events. Randomized clinical trials offer the strongest scientific evidence for or against health benefits. These studies often use pure compounds or standardized preparations. Often, compounds for which epidemiologic studies suggest benefit, and mechanistic studies show effects, fail to do so in large randomized clinical trials. There have also been surprising results of increased disease risk from certain natural products, suggesting the need for caution and for ongoing studies to obtain evidence of the best possible quality. It is important to approach results of studies with a critical eye, and to always consider the quality of the information and how strongly it supports an effect.

In this article, three specific classes of compounds—omega-3 fatty acids, vitamin E, and soy isoflavones—are reviewed. Evidence for their biological effects are presented, categorized separately according to type of evidence: epidemiological studies, mechanistic studies, and where available, randomized controlled trials. It is hoped that this review will provide the basis for evidence-based recommendations to patients regarding these compounds and food supplements.

2. Fish oils: Omega-3 fatty acids

2.1 Structure and food sources

While many fatty acids serve as energy stores that are broken down by the body to generate energy, *omega-3* and *omega-6* fatty acids are two types of polyunsaturated fatty acids that serve as precursors to biologically active molecules, including prostaglandins, leukotrienes, and thromboxanes. This role gives them particular importance in the diet.

Polyunsaturated fatty acids are a family of long-chain (typically 18-24 carbon atoms) fatty acids containing two or more double bonds. Omega-3 and omega-6 refer to the position of the last double bond. The convention in chemical nomenclature is to label the COOH carbon as the first carbon, and the one furthest from this as the last, or *omega*, carbon. Thus, omega-3 fatty acids contain a double bond three carbons from the end of the molecule furthest from the COOH group. Given that the length of the hydrocarbon chain is variable, the length is sometimes referred to as "n," so omega-3 fatty acids are also known as n-3 fatty acids, and omega-6 fatty acids as n-6 fatty acids.

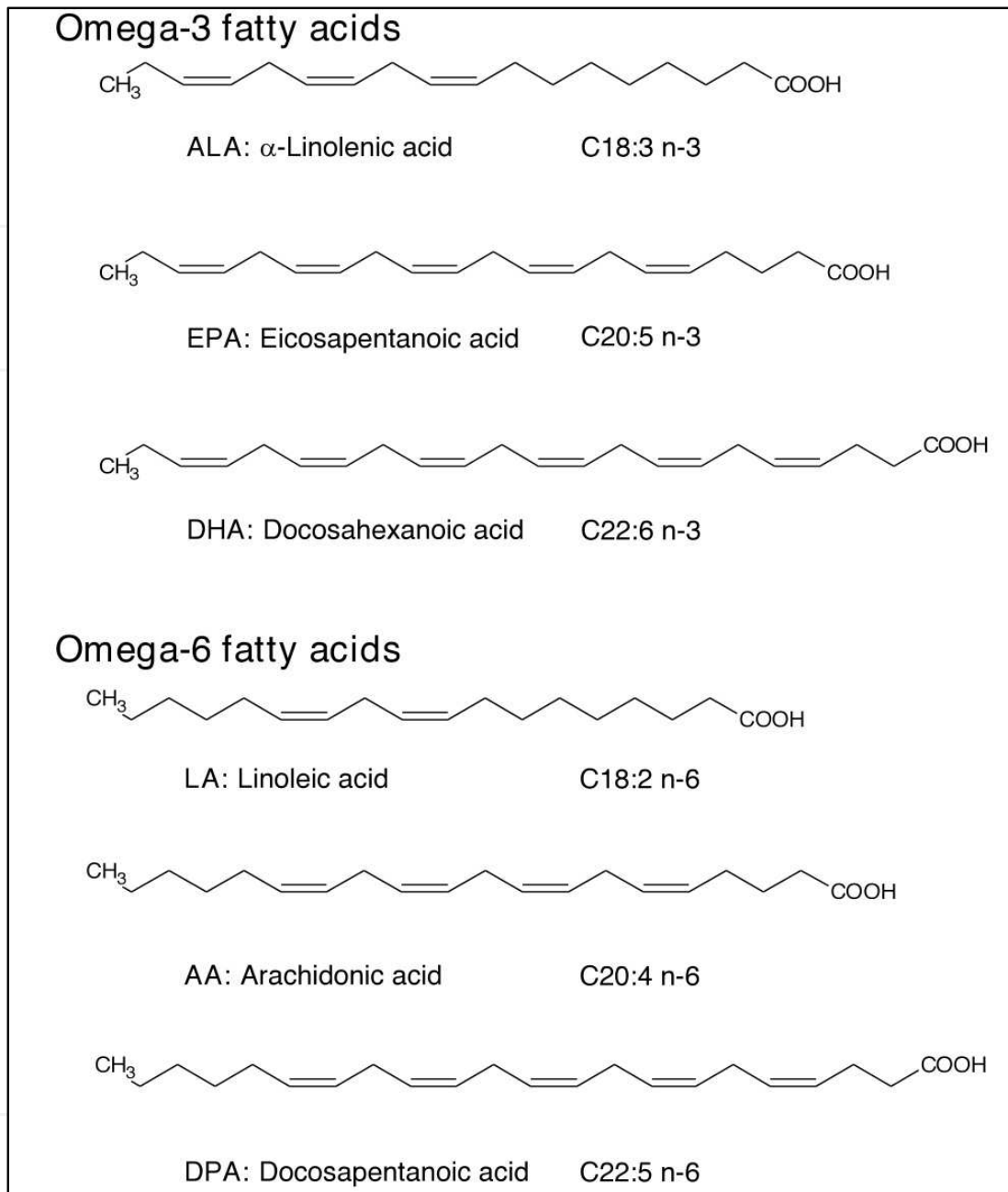


Fig. 1. Structures of omega-6 and omega-3 fatty acids

Omega-3 fatty acids differ from omega-6 fatty acids by the location of their first double bond from the methyl (CH₃) end of the fatty acid. Omega-3 fatty acids include α -linolenic acid (ALA), eicosapentanoic acid (EPA), and docosahexanoic acid (DHA). Omega-6 fatty acids include linoleic acid (LA), arachidonic acid (AA), and docosapentanoic acid (DPA). In the chemical names, the number of carbon atoms is given first, separated by a colon from the number of double bonds, followed by the position of the first double bond.

The structures of omega-3 and omega-6 fatty acids are shown in Figure 1. Representative omega-3 fatty acids are α -linolenic acid (ALA), eicosapentanoic acid (EPA), and docosahexanoic acid (DHA). Of these, the parent omega-3 fatty acid is ALA, an 18 carbon fatty acid with three double bonds, the last of which is located between carbons 15 and 16

(the n-3 position). Therefore, in shorthand, ALA is C18:3 n-3. ALA serves as the precursor to the omega-3 fatty acids EPA (C20:5 n-3) and DHA (C22:6 n-3) by the addition of carbons to the chain (elongation) and by the replacement of single bonds by double bonds (desaturation). Likewise, representative omega-6 fatty acids are linoleic acid (LA), arachidonic acid (AA), and docosapentanoic acid. LA is an 18 carbon fatty acid with two double bonds, with the last one located at the n-6 position (C18:2 n-6). LA serves as a precursor to AA (C20:4 n-6) and docosapentanoic acid (C22:5 n-6), which are formed by elongation and desaturation.

The parent fatty acids of the omega-3 family (ALA) and omega-6 family (LA) cannot be made by the human body, so they are *essential* fatty acids. They must be supplied in the diet. LA is found in vegetable oils like soybean and canola, and also in nuts, seeds, vegetables, legumes, grains, and fruit. ALA is found in vegetable sources like flaxseed, but only 5% of ALA is converted to DHA and EPA. The richest sources of DHA and EPA are fish and fish oils.

2.2 Biological roles of omega-3 and omega-6 fatty acids

Omega-3 and -6 fatty acids are important biologically because they influence production of prostaglandins, leukotrienes, and thromboxanes. These mediators affect many diverse processes, and are involved in inflammation, pain, and thrombosis (Calder, 2006). Moreover, omega-3 and omega-6 fatty acids are separate families that cannot be interconverted by the human body. Because they compete for the same enzymes, the ratio of omega-3 to omega-6 fatty acids in the diet influences the relative amounts of prostaglandins and leukotrienes that are synthesized from arachidonic acid.

2.3 Epidemiologic data on fish oils and cardiovascular disease

Epidemiologic data from fish-eating populations like the Greenland Inuits established a link between fish oil consumption and lower incidence of cardiovascular disease (Dyerberg et al., 1975). Fish oil consumption was also linked with low levels of triglycerides, plasma cholesterol and very low-density lipoproteins (VLDL) and high levels of high-density lipoproteins (HDL), all of which would protect against cardiovascular disease.

2.4 Mechanistic studies

Omega-3 fatty acids may influence cardiovascular disease through effects on lipid profiles, eicosanoid pathways, and susceptibility to arrhythmias.

2.4.1 Lipid profiles

Omega-3 fatty acids decrease plasma cholesterol concentrations in animal models (Fernandez & West, 2005). They increase hepatic LDL receptor number and LDL turnover *in vivo* (Fernandez & McNamar, 1989, Fernandez et al., 1992), and bind to peroxisome proliferator activated receptors (PPARs), liver X receptors (LXRs), hepatic nuclear factor-4 (HNF-4), and sterol regulatory element binding proteins (SREBPs) (Jump, 2002). Omega-3 fatty acids suppress SREBP-1 expression, leading to decreased lipogenesis and VLDL secretion (Field et al., 2003), increased LPL activity (Illingworth & Schmidt, 1993), and

decreased apoC3 levels (Shachter, 2001). They also decrease lipogenesis and VLDL secretion while increasing reverse cholesterol transport (Vasandani et al., 2002).

2.4.2 Eicosanoid metabolism

Omega-3 and omega-6 fatty acids are precursors to a broad array of structurally diverse and potent bioactive lipids, including eicosanoids, prostaglandins, and thromboxanes. Eicosanoids are produced from arachidonic acid, EPA, and dihomo- γ -linolenic acid when these fatty acids are released from membranes by phospholipase A₂ (Zhou & Nilsson, 2001). The availability of these eicosanoid precursors depends on dietary levels of these molecules, as well as the parent fatty acids of each family: ALA for omega-3 fatty acids, and LA for omega-6 fatty acids. Because omega-6 and omega-3 fatty acids cannot be interconverted, their relative ratios are important.

Arachidonic acid, an omega-6 fatty acid, is a precursor of prostaglandins, leukotrienes and related compounds that mediate inflammation. Because omega-3 fatty acids compete with omega-6 fatty acid metabolism, increased consumption of omega-3 fatty acids (particularly DHA and EPA) results in the partial replacement of arachidonic acid in cell membranes by EPA and DHA, and a decrease in the production of biological mediators derived from AA. Intake of 6 g DHA/d decreased production of prostaglandin E₂ by 60% and leukotriene B₄ by 75% in endotoxin-stimulated mononuclear cells (Kelley et al., 1999). Other studies have shown a shift in the relative amounts of prostaglandin I₂ and thromboxane A₂, resulting in vasodilation and reduced thrombosis (von Schacky et al., 1985, Goodnight et al., 1989). Omega-3 fatty acids, particularly DHA and EPA in fish oil, may themselves reduce expression of ICAM-1 on the surface of stimulated blood monocytes (Hughes et al., 1996), and decrease hydrogen peroxide production (Fisher et al., 1990).

2.4.3 Antiarrhythmic effects

DHA and EPA may be preferentially incorporated into membrane phospholipids, accounting for an antiarrhythmic effect after dietary intake (Nair et al., 1999). These fatty acids directly influence conduction of several membrane ion channels (Leaf et al., 2003), inhibit voltage-gated sodium currents and L-type calcium currents (Kang et al., 1995), and shift the steady-state inactivation potential to more negative values in cardiomyocytes. These results provide an electrophysiological basis for antiarrhythmic effects.

2.5 Clinical studies

Dietary intake of omega-3 fatty acids, particularly DHA and EPA found in fatty fish or fish-oil supplements, reduces risk of CVD (Kris-Etherton et al., 2002, Wang et al., 2006). The strongest evidence comes from the Italian GISSI trial (1999), a secondary prevention study in over 11,000 patients with recent myocardial infarction. Supplementation with 0.85 g EPA and DHA per day reduced all-cause mortality by 21%, cardiac death by 35%, and sudden death by 45%. No effect was found on stroke. In contrast, a Norwegian study of 300 patients following MI, randomized to a higher intake of omega-3 fatty acids (3.4 g EPA and DPA per day), failed to show a difference in CVD events, but there was a high background of fish oil intake in both groups. Several other small studies suggested beneficial trends in CVD and PVD, but these were not statistically significant (Sacks et al., 1995, Nilsen et al., 2001).

In these studies, patients with implantable cardiac defibrillators (ICD) were excluded. Several randomized controlled trials, ranging in size from 200 to over 500 patients, studied fish oil consumption in patients with ICDs (Raitt et al., 2005, Brouwer et al., 2006). These studies showed no change in mortality from fish oil consumption. It is possible that the beneficial effects of fish oils may not be observed in the ICD population, because these patients all have defibrillators and therefore cardiac arrhythmic sudden death would be removed from both groups.

Primary prevention trials, which study patients in the general population who do not have known heart disease, have not shown as strong an effect as the GISSI trial. Most primary prevention data on fish oils comes from large cohort studies from China, Japan, and the United States (Dolecek, 1992, Nagata et al., 2002) and others. In aggregate, these studies included over 343,000 subjects, and showed reductions in all-cause mortality, cardiac mortality, and sudden death. Interestingly, in one of these studies (Mozaffarian et al., 2003), the protection was found with tuna and other nonfried fish, while consumption of fried fish or fried fish sandwiches was associated with increased cardiovascular events.

3. Vitamin E

3.1 Structure and food sources

Vitamin E is a fat-soluble vitamin that exists in at least eight naturally occurring forms, as shown in Figure 2. Tocotrienols differ from tocopherols by the presence of three double bonds in their isoprenoid side chains. The α -, β -, γ -, and δ - forms are defined by the identity of the R groups on the chromanol rings. Vitamin E found naturally in food is primarily γ -tocopherol, but α -tocopherol is the predominant form found in supplements, and is also the most biologically active form.

Vitamin E is an essential vitamin because it cannot be synthesized by the body. Sources of vitamin E include nuts and seeds, such as almonds, peanuts, sunflower seeds, and filberts.

Tocopherols are similar in structure to tocotrienols, except that tocotrienols have three double bonds in the phytyl side chains. There are three positions on the chromanol ring, denoted R_1 , R_2 , and R_3 . The particular identity of the tocopherol or tocotrienol is determined by the identities of these side chains. Vitamin E found naturally in food is primarily γ -tocopherol. α -tocopherol, which is the most biologically active, is the predominant form found in supplements.

Vitamin E is also found in vegetable oils (soy, corn or sunflower), and their derivatives (margarine), cereals and grains. Vitamin E is found in potato chips and tomato products because of the vegetable oils that they contain.

3.2 Biological roles of vitamin E

Vitamin E is an antioxidant, because it breaks chain reactions that are propagated by free radicals. Vitamin E is present in biological membranes, and serves as an important lipid soluble antioxidant. It reacts with oxidant molecules and protects cell membranes from lipid peroxidation by trapping peroxy radicals. One molecule of α -tocopherol per 1,000 phospholipids can protect cellular membranes. α -tocopherol can also be regenerated from its tocopheroxyl radical by an electron donor like vitamin C.

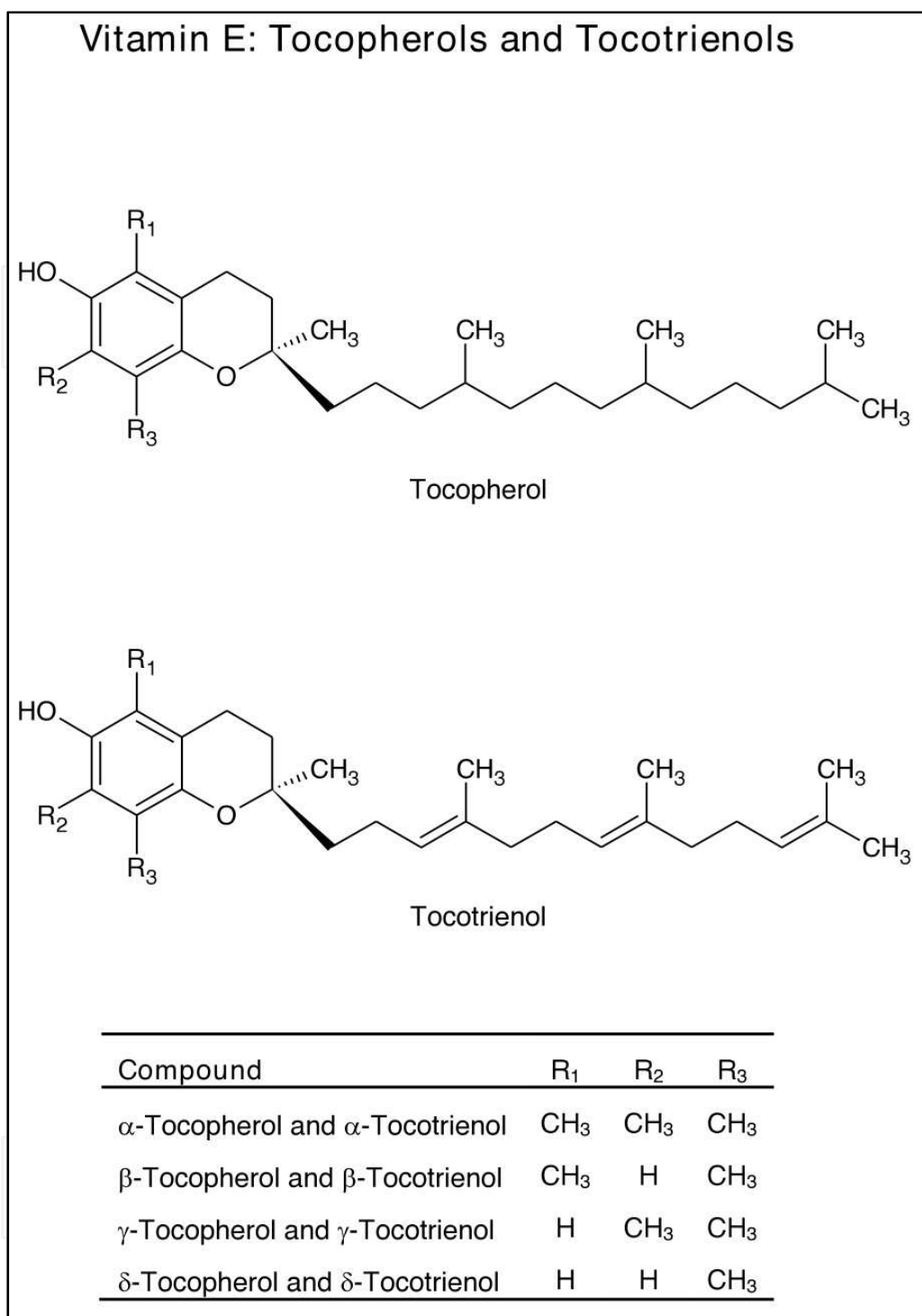


Fig. 2. Structures of tocopherols and tocotrienols

3.3 Epidemiologic data on vitamin E and cardiovascular disease

High intake of vitamin E is epidemiologically associated with lower cardiovascular disease risk. The World Health Organization/Monica project performed cross-cultural analysis on vitamin intake in populations with different incidence of coronary heart disease mortality. Differences in cardiovascular mortality were primarily attributable to plasma levels of

vitamin E in middle-aged men representing 16 European study populations (Gey et al., 1991).

Several cohort studies showed similar results. The US Nurse's Health Study followed a cohort of 87,245 female nurses between the ages of 34 and 59 years, over an eight year period. Supplementation with α -tocopherol for at least two years was associated with reduced risk of cardiovascular disease (Stampfer et al., 1993). Incidence of heart disease was 30-40% lower in those with the highest intakes of vitamin E. Another cohort study followed 39,910 male health professionals between the ages of 40 and 75. Consumption of more than 60 IU/d of vitamin E was associated with a 40% relative risk reduction of cardiovascular disease (Rimm et al., 1993). Vitamin E intake from food was inversely associated with CVD risk in 34,486 postmenopausal women (Kushi et al., 1996).

3.4 Mechanistic studies

In *ex vivo* human studies, monocytes isolated from healthy human subjects supplemented with α -tocopherol showed decreased LDL oxidation (Devaraj et al., 1996). In other studies, vitamin E supplementation failed to affect lipid oxidation, including isoprostanes and 4-hydroxynonenal (breakdown products of fatty acid autooxidation) (Meagher et al., 2001).

One animal study showed that vitamin E intake inversely correlates with atherosclerotic lesions and liver peroxidation in apoE knockout mice (Ferre et al., 2001). In another study, vitamin E and coenzyme Q (CoQ) supplementation significantly reduced tissue lipid hydroperoxide formation and limited the development of atherosclerosis in apoE knockout mice (Thomas et al., 2001). However, still other studies found that vitamin E did not reduce atherosclerosis in apoE knockout mice (Paul et al., 2001), or fatty streak formation in C57/Bl6 mice (Munday et al., 1998). The degree of lipid oxidation in vascular tissue also failed to correlate with the extent of the lesions in apoE knockout mice (Wu et al., 2006). Thus, animal studies do not show uniform benefit of vitamin E supplementation in preventing LDL oxidation or reducing atherosclerosis.

3.5 Clinical trials on vitamin E

3.5.1 Vitamin E and cardiovascular disease

Some clinical trials suggest a benefit of vitamin E in reducing cardiovascular disease. The Cambridge Heart Antioxidant Study (CHAOS) randomized 2,002 patients with coronary disease to α -tocopherol (400 to 800 IU) or placebo. The vitamin E treated groups showed 1.9 fold reductions in cardiovascular death and nonfatal myocardial infarction (Stephens et al., 1996). The Secondary Prevention with Antioxidants of Cardiovascular Disease in End-stage Renal Disease (SPACE) trial randomized 192 renal failure patients undergoing hemodialysis to 800 IU vitamin E or placebo. The vitamin E treated group showed a significant decrease in both fatal and nonfatal cardiovascular endpoints (Boaz et al., 2000).

Other clinical trials failed to show benefit. In the GISSI study, 11,324 patients were given omega-3 fatty acids, vitamin E at 300 mg per day, both, or neither, and followed over a 3½ year period. Two-way analysis did not show any reduction in fatal or nonfatal cardiovascular events from vitamin E supplementation (Marchioli et al., 2002), (1999). The Heart Outcomes Prevention Evaluation (HOPE) trial was a multinational study of over 9,500

patients with known cardiovascular disease, randomized to the angiotensin converting enzyme inhibitor ramipril, natural source vitamin E at 400 IU per day, both, or neither. Over a 4½ year follow-up, there was no reduction in fatal or nonfatal cardiovascular events in the vitamin E treated groups (Yusuf et al., 2000). In an extension study (HOPE -TOO), almost 4000 subjects continued to take vitamin E or placebo for an additional 2½ years (Lonn et al., 2005). Despite this 7 year total follow-up period, there was no significant protection against cardiovascular disease, stroke, or death.

Of concern, the HOPE-TOO study showed a higher incidence of heart failure in the treated group. In the Women's Angiographic Vitamin and Estrogen Study, 423 postmenopausal women with coronary disease took supplements with 400 IU vitamin E or placebo (Waters et al., 2002). Not only did women taking vitamin E not show cardiovascular benefit, but there was an increase in all-cause mortality. In the Physicians Health Study II, 15,000 health physicians age 50 or over were randomized to α -tocopherol (400 IU), 500 mg vitamin C, both, or placebo (Sesso et al., 2008). Over a follow-up period of 8 years, neither vitamin E nor vitamin C resulted in a decrease in cardiovascular events, stroke, or cardiovascular mortality. In contrast, α -tocopherol was associated with an increase in hemorrhagic stroke. Taking the results of all of these results together, including a meta-analysis (Miller et al., 2005), vitamin E is not recommended for the purpose of reducing cardiovascular risk.

3.5.2 Vitamin E and diabetes

Oxidative stress and inflammation have been implicated in the pathogenesis of diabetes (Ho & Bray, 1999). Vitamin E treatment (600 mg per day) improved insulin-mediated glucose disposal in 36 healthy, nondiabetic volunteers (Facchini et al., 2000). A prospective cohort study showed that plasma concentration of α -tocopherol was inversely related to fasting plasma glucose concentration and oxidative stress markers in 101 women at high risk of type 2 diabetes in Finland (Ylonen et al., 2003). In secondary prevention trials, 600 mg/day of vitamin E supplementation significantly decreased markers of oxidative stress and improved brachial artery reactivity in 40 patients with diabetes (Paolisso et al., 2000). However, the Insulin Resistance and Atherosclerosis Study (IRAS) cohort study showed no protective effect for either reported intake of vitamin E or plasma concentration of α -tocopherol in 895 nondiabetic adults (Mayer-Davis et al., 2002). In another study, high levels of α -tocopherol and β -carotene were associated with decreased risk of non-insulin dependent diabetes mellitus, but the association disappeared after adjustment for cardiovascular risk factors (Reunanen et al., 1998). Whether vitamin E influences the development of diabetes is not clear and warrants further investigation.

4. Phytoestrogens

4.1 Structure and food sources of phytoestrogens

Phytoestrogens are flavonoids that have similar chemical structure to estrogen. They include isoflavones, coumestans, and lignans (Kurzer & Xu, 1997). Figure 3 shows a comparison of the chemical structures of estradiol (a naturally occurring human estrogen), genistein (an isoflavone), and coumestrol (a coumestan). A number of these compounds have been identified in fruits, vegetables, and whole grains commonly consumed as food. Soybeans,

clover and alfalfa sprouts, and oilseeds (such as flaxseed) are the most significant dietary sources.

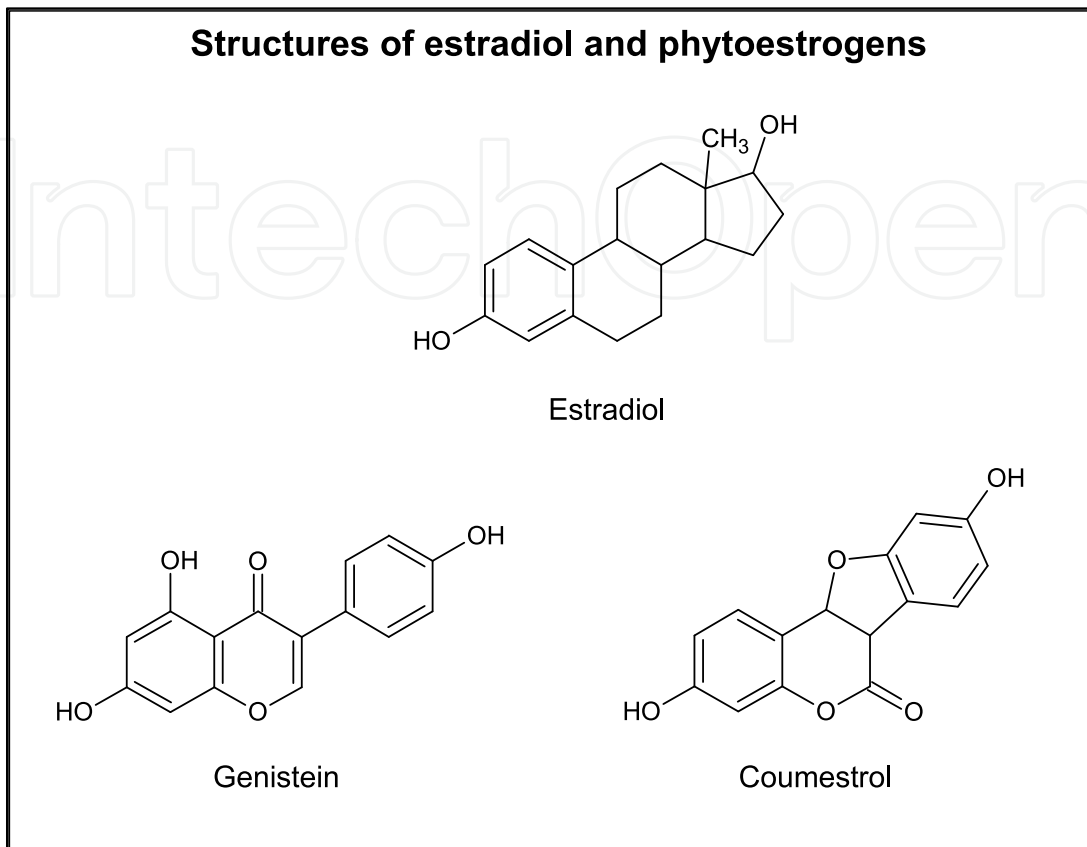


Fig. 3. Structures of isoflavones and coumestans compared with estrogen. The structure of estradiol, a natural estrogen, is shown along with the structures of genistein, a prototypic isoflavone found in soy, and coumestrol, a prototypic coumestan.

4.2 Epidemiology data on phytoestrogens and cardiovascular disease

While typical isoflavone intake is less than 1 mg per day in Western countries, intakes of 20–50 mg per day are common in Asian countries such as China and Japan, where soy is a traditional staple food (Adlercreutz & Mazur, 1997). These countries also have shown reduced incidence of cardiovascular disease compared with Western countries, an effect that is diminishing as Western eating habits and diets are adopted.

4.3 Biological activities of phytoestrogens

Dietary phytoestrogens may play an important role in prevention of menopausal symptoms, osteoporosis, cancer, and cardiovascular disease. The major mechanisms of biological action for the phytoestrogens are those mediated by estrogen receptors (estrogenic and antiestrogenic effects), effects on tyrosine kinase and DNA topoisomerase activities, suppression of angiogenesis, and antioxidant effects.

Although not as active as 17β -estradiol, phytoestrogens compete with estradiol for binding to estrogen receptors (ER), particularly $ER\beta$ (Kuiper et al., 1998). $ER\beta$, present in high

concentrations in ovary and testis, binds phytoestrogens with higher affinity, and may mediate some of their biological effects (Kuiper et al., 1998). Alternatively, soy isoflavones may be natural selective estrogen receptor modulators (SERMs) with both agonist and antagonist activities (Setchell, 2001).

Soy isoflavones decrease total cholesterol, LDL, and triglycerides, and increase HDL levels (Clarkson et al., 2001). They also lower blood pressure and improve endothelial reactivity (Teede et al., 2001, Steinberg et al., 2003). Supplementation of isoflavones derived from red clover containing genistein, daidzein, biochanin, and formononetin significantly improved arterial compliance in elderly men and women (Nestel et al., 1999).

Several studies reveal the potential of phytoestrogens to induce hormone-dependent cancers (e.g. breast and endometrium) (McMichael-Phillips et al., 1998), leading to safety concerns. Because of this, a maximum daily intake level for phytoestrogens has been suggested in several countries (Sirtori et al., 2005).

Summary of key points

Omega-3 fatty acids

- Important omega-3 fatty acids include EPA and DHA
- Mechanisms for omega-3 fatty acids include
 - reduced inflammation due to decreased prostaglandin and leukotriene synthesis
 - reduced thrombosis and platelet aggregation
 - direct antiarrhythmic effects in cell membranes
- Large studies confirm that omega-3 fatty acid intake reduces cardiovascular disease and sudden death
- The American Heart Association recommends eating fish twice a week, and daily intake of 1 g EPA and DHA to reduce cardiovascular disease

Vitamin E

- Vitamin E is an essential fat soluble vitamin that is an antioxidant
- Animal studies do not uniformly show beneficial effects
- Vitamin E reduced cardiovascular risk in two studies (CHAOS and SPACE), but not in others (GISSI, HOPE-TOO)
- Vitamin E supplementation has been associated with higher incidence of heart failure, so routine supplementation with vitamin E is *not* recommended

Phytoestrogens

- Phytoestrogens, including soy isoflavones, are plant compounds with chemical structures that resemble estrogens
- Mechanisms include improved lipid profiles and improved endothelial reactivity
- Phytoestrogens may induce hormone dependent cancers (breast and endometrial), leading to recommendations on maximum daily intake

5. Conclusions and evidence-based recommendations

Omega-3 fatty acids have been clearly shown in epidemiological studies and clinical trials to reduce the incidence of cardiovascular disease. Thus, the American Heart Association recommends eating fish (particularly fatty fish) at least twice a week. They also recommend foods rich in ALA (flaxseed, canola, and soybean oils; flaxseed and walnuts). For patients with documented coronary heart disease, the recommended level of consumption is 1 g of EPA+DHA per day, either from fish (preferably), or supplementation. For subjects with elevated triglyceride levels, 2-4 grams of EPA+DHA is recommended as supplementation (Kris-Etherton et al., 2002).

At this time, the evidence does not justify the use of vitamin E supplements for CVD risk reduction, both because of lack of evidence for benefit and possible adverse effect reflected in the increases in all-cause mortality and hemorrhagic stroke. However, a balanced diet with emphasis on antioxidant-rich fruits, vegetables, and whole grains is recommended (Kris-Etherton et al., 2004). Whether antioxidant vitamin supplements including vitamin E influence the development of diabetes, in which oxidative stress plays an important role, is not clear and warrants further investigation.

Supplementing the diet with soy protein has failed to confirm phytoestrogens as the responsible agent for beneficial cardiovascular effects. Furthermore, soy phytoestrogens may increase carcinogenesis. Thus, isoflavone supplements are not currently recommended (Sacks et al., 2006). Soy foods may still be beneficial to cardiovascular and overall health because of their high content of polyunsaturated fats, fiber, vitamins, and minerals and low content of saturated fat (Krauss et al., 2000).

Epidemiologic evidence has suggested an array of potentially beneficial compounds in foods. While there have been many mechanistic studies in the laboratory or in animal models, large scale randomized controlled clinical trials are necessary to prove or disprove their effects on health and safety, particularly in light of possible toxicities. Until the results of such studies are available, a diet consistent with American Heart Association recommendations (Kris-Etherton et al., 2004), with emphasis on antioxidant-rich fruits, vegetables, and whole grains, appears to be the most sensible approach.

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7. References

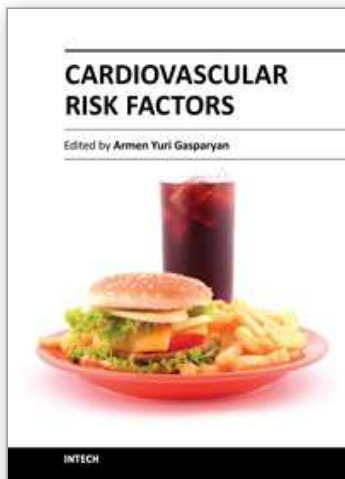
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Cardiovascular risk factors contribute to the development of cardiovascular disease from early life. It is thus crucial to implement preventive strategies addressing the burden of cardiovascular disease as early as possible. A multidisciplinary approach to the risk estimation and prevention of vascular events should be adopted at each level of health care, starting from the setting of perinatology. Recent decades have been marked with major advances in this field, with the emergence of a variety of new inflammatory and immune-mediated markers of heightened cardiovascular risk in particular. The current book reflects some of the emerging concepts in cardiovascular pathophysiology and the shifting paradigm of cardiovascular risk estimation. It comprehensively covers primary and secondary preventive measures targeted at different age and gender groups. Attention is paid to inflammatory and metabolic markers of vascular damage and to the assessment of vascular function by noninvasive standardized ultrasound techniques. This is a must-read book for all health professionals and researchers tackling the issue of cardiovascular burden at individual and community level. It can also serve as a didactic source for postgraduate medical students.

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