

Nutritional Impact on Lipid Oxidation and Coronary Artery Disease

Victor B. Klausner, DO

Atherosclerotic heart disease remains the number one cause of death in the Western world. In 1996, 476,800 deaths were attributed to this disease. Including associated vascular pathology such as stroke and peripheral vascular disease, the annual health care cost of atherosclerotic heart disease is estimated at 51 billion dollars.¹ The trend in medicine has been to recognize and treat atherosclerosis by identifying negative risk factors that directly correlate with the prevalence of coronary artery disease (CAD), such as low-density lipoprotein (LDL), hypertension, diabetes mellitus, and smoking. Although these risk factors identify most people with CAD, identification of these factors still does not answer all the questions that must be addressed from a preventive medicine standpoint. What is the physiologic effect of each negative risk factor that manifests as CAD? Why do some people with a significant risk of atherosclerosis not manifest CAD? Are there factors that can be identified to protect patients from manifesting CAD? How can physicians help those patients at risk for CAD to slow the disease progression and reverse the effects of CAD by maximizing protective factors? These questions are but a few of those left unanswered.

The traditional approach to medical management of vascular diseases has only partially answered these questions. This article proposes that complete answers can be found by focusing on the pathophysiology of atherosclerosis and the influence that nutrition plays on this process. Over the past two decades a significant amount of research has been performed, revealing the full spectrum of factors that affect the complicated process of CAD. Based on this research, most of the medical community has focused on three forms of primary prevention: LDL cholesterol reduction, β -blocker



therapy, and anti-platelet therapy. Although these interventions have prolonged lives, physicians have yet to significantly lower the incidence of mortality caused by ischemic heart disease during the past 10 years.¹ Why is this the case? This article proposes that, in order for primary prevention of atherosclerosis to move to a new level, physicians must focus on the effects of nutrition. The purpose of this article is to

review the latest research and identify harmful as well as protective nutritional factors that may aid in the prevention and treatment of CAD.

PATHOPHYSIOLOGY OF CORONARY ARTERY ATHEROSCLEROSIS

The Oxidation Hypothesis of Atherosclerosis

An elevated level of plasma LDL is a major risk factor for developing atherosclerosis; however, the quantity of plasma LDL exposed to the vascular endothelium does not fully explain the occurrence of this disease. The mechanism that promotes the development of an early fatty streak, the initial phase of atherosclerosis formation, involves the oxidation of LDL. The oxidative modification of LDL is an important and possibly necessary step in the formation of an atherosclerotic lesion.²

The initial event that begins the process of LDL oxidation is damage or dysfunction of the vascular endothelial layer. Researchers know that this step must occur because LDL must migrate into the subendothelial space where oxidation most likely occurs. Injury to the endothelial cell causes an influx of calcium that disrupts the electrical monolayer resistance and hence disrupts the integrity

Dr. Klausner is a Sports Medicine Fellow, Columbia-Olympia Fields Osteopathic Medical Center, Olympia Fields, IL.

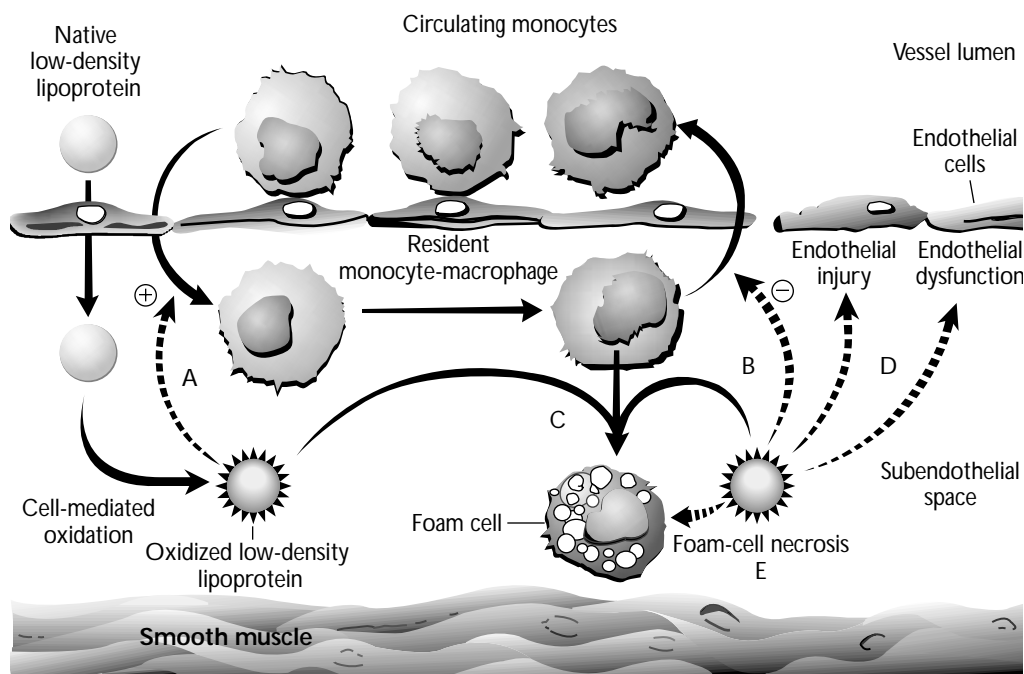


Figure 1. Early events in atherogenesis. Native low-density lipoprotein (LDL) becomes trapped in the subendothelial space where it can be oxidized by resident vascular cells such as smooth muscle cells, endothelial cells, and macrophages. A) Oxidized LDL stimulates (plus sign) monocyte chemotaxis and B) inhibits (minus sign) monocyte egress from the vascular wall. C) Monocytes differentiate into macrophages that internalize oxidized LDL, leading to foam-cell formation. D) Oxidized LDL also causes endothelial dysfunction and injury, as well as E) foam-cell necrosis, resulting in the release of lysosomal enzymes and necrotic debris. Broken arrows indicate adverse effects of oxidized LDL. Adapted with permission from Diaz MN, Fji B, Vita JA, Keaney JF Jr: Antioxidants and atherosclerotic heart disease. *N Engl J Med* 1997;337:408-416.

of the endothelial barrier. Increased intracellular calcium also stimulates lipid peroxidation, release of von Willebrand's factor, and activation of phospholipases and proteases. Elevated levels of the following compounds can induce direct endothelial cell injury: glucose, linoleic acid, homocysteine, reduced iron or copper, and oxysterols (oxidized products of cholesterol).³

Once the LDL particle has entered the subendothelial space, the next step is the actual process of LDL oxidation. **Figure 1** shows a schematic illustration of LDL oxidation. The process by which LDL oxidation occurs is not fully understood, but theories point to three mechanisms. In vitro studies show that reduced forms of iron and copper (or complexes of these metals) can bind to LDL and promote rapid lipid peroxidation. Release of superoxide anions from endothelial or smooth muscle cells and release of 15-lipoxygenase from macrophages may also contribute to lipid peroxidation. The end result of these events is exactly the same—formation of oxidatively modified LDL. An important point to realize is that, in controlled animal studies, antioxidant com-

pounds were shown to effectively inhibit atherosclerosis by protecting the LDL particle at this crucial step.⁴

The next step in the process of LDL oxidation is as follows: the modified LDL induces local endothelial cells to produce monocyte chemotactic protein and monocyte colony-stimulating factor, which stimulates monocyte recruitment to the subendothelial space and subsequent phenotypic differentiation to macrophages. The accumulating macrophages further accelerate the process of oxidation and cause alteration of the apolipoprotein B receptor on the LDL particle. This altered receptor is recognized by scavenger receptors on macrophages, which induce internalization of the oxidized LDL. The uptake of modified LDL is not subject to the same negative feedback by cholesterol concentration that is present in native LDL. The result is massive uptake of cholesterol by macrophages and the subsequent formation of foam cells. These foam cells become trapped in the subendothelial space because of the inhibition of macrophage migration. This cycle becomes self-perpetuating by continued

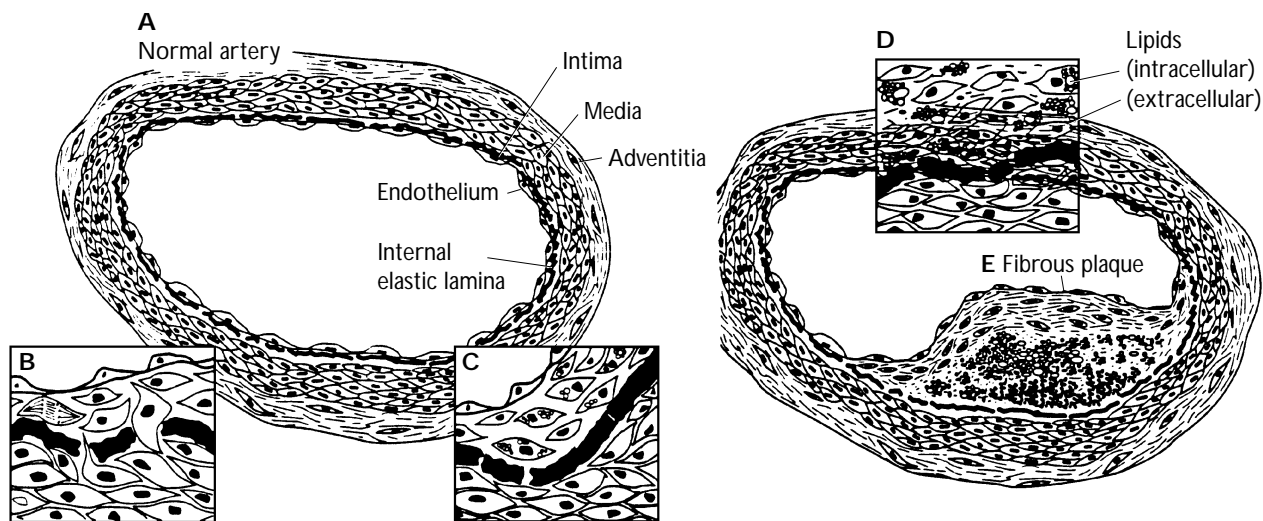


Figure 2. A series of possible stages in the development of the various lesions of atherosclerosis. A) The appearance of a normal muscular artery and its component layers; the intima bounded by endothelium and internal elastic lamina, the media, and the adventitia. In children and young adults, the intima is thin and contains only an occasional smooth muscle cell; with age, the intima slowly and uniformly increases in thickness and cell content. Note that no fibroblasts are present in either the intima or the media of mammalian arteries. Fibroblasts are found only in the adventitia. B) The first phase of a developing lesion in atherosclerosis: a focal thickening of the intima consists of an increase in smooth muscle cells and extracellular matrix. Smooth muscle cells are shown proliferating within the intima; two cells are in the process of migrating through fenestrae of the internal elastic lamina. Subsequent to or possibly concomitant with internal smooth muscle proliferation, accumulation of intercellular lipid deposits (C) or extracellular lipid (D) or both occurs, resulting in a fatty streak. E) A fibrous plaque may result from a continued accumulation of a connective tissue cap covering increased numbers of smooth muscle cells laden with lipids, extracellular lipid, and cell debris overlying a deeper extracellular pool of lipid. A complicated lesion may form as a result of continuing cell degeneration, ingress of blood constituents, and calcification superimposed upon the elements present in the fibrous plaque. Observations made at necropsy and experiments such as those described in the text suggest that this may represent the sequence of events that occurs in humans. Adapted with permission from Glomset JA, Ross R: Atherosclerosis and the arterial smooth muscle cell. *Science* 1973;180:1332.

chemotactic activity of macrophages, which by itself causes further oxidation of LDL.^{5,6}

The early stage of LDL oxidation forms a pathologic finding in the arterial wall, termed a *fatty streak*. Within the fatty streak, an increase in the concentration of oxidized LDL has many effects, including endothelial cytotoxicity, release of lysosomal enzymes, and formation of autoantibodies, all of which contribute to arterial denudation. Specifically, monocytes and macrophages produce metalloproteinases that degrade components of the extracellular matrix and weaken the plaque wall. Progression of the atherosclerotic lesion develops as increased amounts of necrotic debris develop in the subendothelial cap, eventually ending in rupture. **Figure 2** shows the anatomy of an advanced atherosclerotic lesion.⁵ The period of time necessary for the progression from a fatty streak to the rupture of plaque is unknown, but autopsy studies indi-

cate that this time is on the magnitude of approximately 20 years. As would be expected, the multifactorial nature of this process would make the course extremely variable within any given population.⁷

Other Factors Involved in Atherosclerosis

Smooth muscle proliferation is another pathologic factor observed within the atherosclerotic lesion. Smooth muscle proliferation has been shown to be a major factor in restenosis after coronary artery balloon angioplasty. The replication of smooth muscle not only produces significant bulk to the atherosclerotic lesion within the arterial media, but smooth muscle cells are also a significant component of the fibrous cap. Two factors have been implicated in triggering smooth muscle proliferation: interleukin-1 and homocysteine. Oxidized LDL can stimulate monocytes to produce interleukin-1, which is a potent stimulator of smooth

muscle proliferation.⁵ The clinical significance of this factor has been elucidated in a recent study in which the restenosis rate after angioplasty was reduced by 47% after pretreating patients with probucol, a potent antioxidant drug.⁸ Homocysteine is an amino acid intermediate that acts in two ways to stimulate smooth muscle replication. First, elevated levels of homocysteine have been shown to directly stimulate smooth muscle cell DNA synthesis and proliferation. Second, homocysteine, as well as oxidized LDL, prevents the release of nitric oxide from endothelial cells, a substance that, when present, acts to inhibit smooth muscle proliferation.⁹

Because vascular endothelial cells are involved in regulation of vascular tone, permeability, inflammation, and platelet adhesion, damage or dysfunction of endothelium integrity is a critical event in atherosclerosis. As previously discussed, oxidized LDL can cause cytotoxicity and damage to endothelial cells. The first significant event that results from this injury is platelet aggregation to the damaged endothelium. This process is normally inhibited by the release of nitric oxide and prostaglandin E₂ (PGE₂), both potent vasodilators and inhibitors of platelet adhesion. In the presence of endothelial dysfunction and oxidized LDL, release of these two substances is significantly hindered. The results are platelet aggregation, especially while in the presence of other compounds such as arachidonic acid and homocysteine, triggering of the coagulation cascade, thrombus formation, and unrestricted arterial vasospasm. The final result is an acute vascular thrombotic event that may result in total arterial occlusion.^{3,4}

EFFECT OF ANTIOXIDANTS ON CORONARY ARTERY DISEASE General Considerations

Dietary micronutrients with antioxidant properties, such as vitamin E (α -tocopherol), vitamin C (ascorbate), β -carotene, and certain minerals, could prove to be a safe and effective way to limit the oxidation of LDL and consequently prevent CAD. Several factors may potentially influence the ability of LDL to undergo oxidation, including the magnitude of oxidative stress, concentration of lipid and aqueous soluble vitamins, composition of lipids within LDL, and serum concentration of divalent cations. Thus, controlled research is potentially difficult.¹⁰ The research performed in this area has been extensive over the past two decades and predominantly focuses on vitamins E and C and β -carotene. The research can be divided into six categories: randomized double-blind trials, prospective studies, case-controlled studies, epidemiologic studies, animal studies, and in vitro experimental

tion. The type of study must be considered when reviewing the data.

Vitamin E

Vitamin E is the primary lipid-soluble, chain-breaking antioxidant present in human blood and cell membranes. Because vitamin E is the predominant antioxidant within the LDL particle, this vitamin seems to be a prime candidate for atherosclerosis prevention. One of the main functions of vitamin E is to terminate lipid peroxidation chain reactions generated by free radicals, a major step in the formation of oxidized LDL. In addition to the antioxidant properties of vitamin E, this vitamin also modulates PGE₂ release and indirectly inhibits platelet activation by inhibiting the effect of arachidonic acid on protein kinase C.³

Interest in antioxidant research began when early epidemiologic studies in the 1970s and 1980s, primarily the Basel study,¹¹ found an inverse relationship between antioxidant vitamin intake/plasma levels and mortality from CAD.¹² In 1989, Gey and Puska¹³ reported a cross-sectional study with a strong inverse correlation between plasma vitamin E levels and death from ischemic heart disease in a population from 16 European regions. Since this study, the number of human research studies involving vitamin E has greatly multiplied. **Table 1** outlines the results from one case-controlled study, three prospective studies and two randomized, double-blind trials. The vitamin E dosage in these studies ranges from 50 to 800 IU per day.

A significant amount of evidence links vitamin E with a protective effect against CAD. The one trial that did not show an effect was the α -Tocopherol, β -Carotene Cancer Prevention Study, which was actually designed to study cancer prevention in smokers.¹⁴ The results from this trial must be critically interpreted based on two points as the findings relate to CAD. The dose of vitamin E was relatively small (50 IU/day) compared with other studies that showed a dose higher than 100 IU/day to be effective. In addition, the lower dose may be particularly significant when considering the study population of male smokers who have a higher level of oxidative stress and endothelial damage.¹⁵ Considering the majority of positive data, a strong case can be made for use of vitamin E as a preventative therapy for CAD.

Vitamin C

Vitamin C is a water-soluble, chain-breaking antioxidant that reacts directly with superoxides, hydroxyl radicals, and singlet oxygen. Because of its hydrophilic nature, vitamin C does not reside within the LDL particle. Hence, the effects of vitamin C occur in the serum

Table 1. Selected Studies Showing a Relationship Between Vitamin E Intake and Coronary Artery Disease

Study*	Population Studied	Vitamin E Dosage	Results
Case-control studies			
Riemersma et al	110 patients with angina and 394 healthy patients	Not available	Lower plasma level of vitamin E in patients with angina compared with healthy patients
Prospective studies			
Nurse's Health Study (Stampfer et al)	87,245 female nurses with 8-year follow-up	Average intake 200 IU/day	With respect to vitamin E intake, patients in the top fifth had a relative risk of 0.66 compared with the patients in the lower fifth
Health Professional Follow-Up Study (Rimm et al)	39,910 male health care workers over 5 years	Intake > 100 IU/day	Patients with intake of vitamin E > 100 IU/day had a relative risk of 0.63 compared with < 7.5 IU/day (in smokers)
Losonczy et al	11,178 elderly United States citizens	Intake > 100 IU/day	Lower coronary artery disease mortality in patients taking vitamin E compared with control group (relative risk, 0.59)
Randomized, double-blind trials			
α -Tocopherol β -Carotene Cancer Prevention Study	29,133 Finnish male smokers over 8 years	50 IU/day	No effect of vitamin E intake on coronary artery disease events
Cambridge Heart Antioxidant Study (CHAOS) (Stephens et al)	2002 British patients with angiographically proven coronary artery disease	400–800 IU/day	A 77% reduction in nonfatal myocardial infarction in patients taking vitamin E as compared with placebo (relative risk, 0.23)

*Riemersma RA, Wood DA, Macintyre CC, et al: Risk of angina pectoris and plasma concentrations of vitamins A, C, and E and carotene. *Lancet* 1991;337:1–5.

Stampfer MJ, Malinow MR, Willett WC, et al: A prospective study of plasma homocyst(e)ine and risk of myocardial infarction in US physicians. *JAMA* 1992;268:877–881.

Rimm EB, Stampfer MJ, Ascherio A, et al: Vitamin E consumption and the risk of coronary heart disease in men. *N Engl J Med* 1993;328:1450–1456.

Losonczy KG, Harris TB, Havlik RJ: Vitamin E and vitamin C supplement use and risk of all-cause and coronary heart disease mortality in older persons: the Established Populations for Epidemiologic Studies of the Elderly. *Am J Clin Nutr* 1996;64:190–196.

The effect of vitamin E and beta carotene on the incidence of lung cancer and other cancers in male smokers. The α -Tocopherol, β -Carotene Cancer Prevention Study Group. *N Engl J Med* 1994;330:1029–1035.

Stephens NG, Parsons A, Schofield PM, et al: Randomised controlled trial of vitamin E in patients with coronary disease: Cambridge Heart Antioxidant Study. *Lancet* 1996;347:781–786.

and cellular cytoplasm where the vitamin interacts with tocopheroxyl radical (oxidized vitamin E), resulting in the regeneration of α -tocopherol. This effect seems to be the key role that vitamin C plays in prevention of LDL oxidation. However, an in vitro study showed that vitamin C was as effective as probucol in preventing copper-catalyzed LDL oxidation independent of vitamin E.² This finding lends credence to the theory that vitamin C can act as a free radical scavenger interacting directly with LDL particles. Also, vitamin C has been shown to stimulate the synthesis of PGE₂ in endothelial

cells.³ A recent in vivo study showed that oral intake of 2 g of vitamin C significantly improved nitric oxide-mediated vasodilation of the brachial artery in CAD patients.¹⁶

Large epidemiologic studies have correlated vitamin C intake with a decreased risk of CAD; however, the results of controlled studies have been mixed.^{17,18} Two case-controlled studies have found significantly lower levels of ascorbate in leukocytes and aortic tissue in subjects with CAD compared with controls.^{19,20} Losonczy et al²¹ reported a decreased risk of cardiovascular mortality

with vitamin E and C supplementation (relative risk, 0.52) compared with vitamin E alone (relative risk, 0.59). A prospective study published from the National Health and Nutritional Examination Survey with 11,348 patients showed an inverse correlation between vitamin C intake and cardiovascular disease mortality.²² One subset of patients who consumed more than 750 mg/day of vitamin C ($n = 227$) showed a 60% reduction in cardiovascular mortality.²² However, the results of the Health Professionals' Follow-Up Study failed to show any correlation between vitamin C intake and CAD events.¹⁹

At this time, the author of this article believes enough data support a recommendation for vitamin C supplementation, especially considering its excellent safety profile. However, the need remains for a randomized, double-blind, placebo-controlled trial using adequate dosages of vitamin C to arrive at a firm conclusion.

β -Carotene and Vitamin A

β -carotene is a precursor of vitamin A that is present in the plasma as retinol, a less potent antioxidant. A plant-derived, lipid-soluble carotenoid, β -carotene is the most effective biological scavenger of singlet oxygen. β -carotene can also inactivate hydroxyl radicals and lipid peroxides but is only effective at physiologic oxygen pressure. In vitro studies have shown that β -carotene is present within the LDL particle and does inhibit LDL oxidation.³ Other effects of β -carotene and vitamin A include maintenance of endothelial cell integrity and modulation of cellular proliferation.³

The results of β -carotene intake in controlled human studies have been discouraging. The Health Professionals' Follow-Up Study was the only trial to show a clear benefit.¹⁹ This prospective study showed an inverse association between CAD events and intake of β -carotene (greater than 14,000 IU/day) in smokers (relative risk, 0.3) and previous smokers (relative risk, 0.6); however, the study failed to show any benefit for non-smokers. The Physicians' Health Study, a randomized, double-blind, controlled trial, analyzed a group of 333 male physicians with stable angina.²³ The subgroup taking 50 mg (8300 IU) of β -carotene every other day showed 40% fewer coronary events compared with the control group. Despite this promising data, the statistical significance was negligible when the trial was completed with 22,000 subjects. The α -Tocopherol, β -Carotene Cancer Prevention Study also failed to show any correlation with 20 mg (3300 IU) of β -carotene per day in 29,000 male smokers.¹⁴

Because the data on β -carotene is contradictory at this time, it seems prudent to not recommend supplementation. However, if future trials show a clear benefit

that cannot be achieved by dietary intake alone, then the issue of β -carotene should be reconsidered.²⁴

Minerals

Selenium. Selenium is an integral cofactor for an important antioxidant enzyme, glutathione peroxidase. This enzyme catalyzes the reduction of hydrogen peroxide and lipid hydroperoxides to less reactive alcohols in the plasma and on membranes. The main role of this enzyme as it relates to CAD is to protect endothelial cells against oxidative stress. Epidemiologic studies have shown that low levels of selenium in serum appear to be associated with an increased risk of atherosclerotic heart disease.²⁵

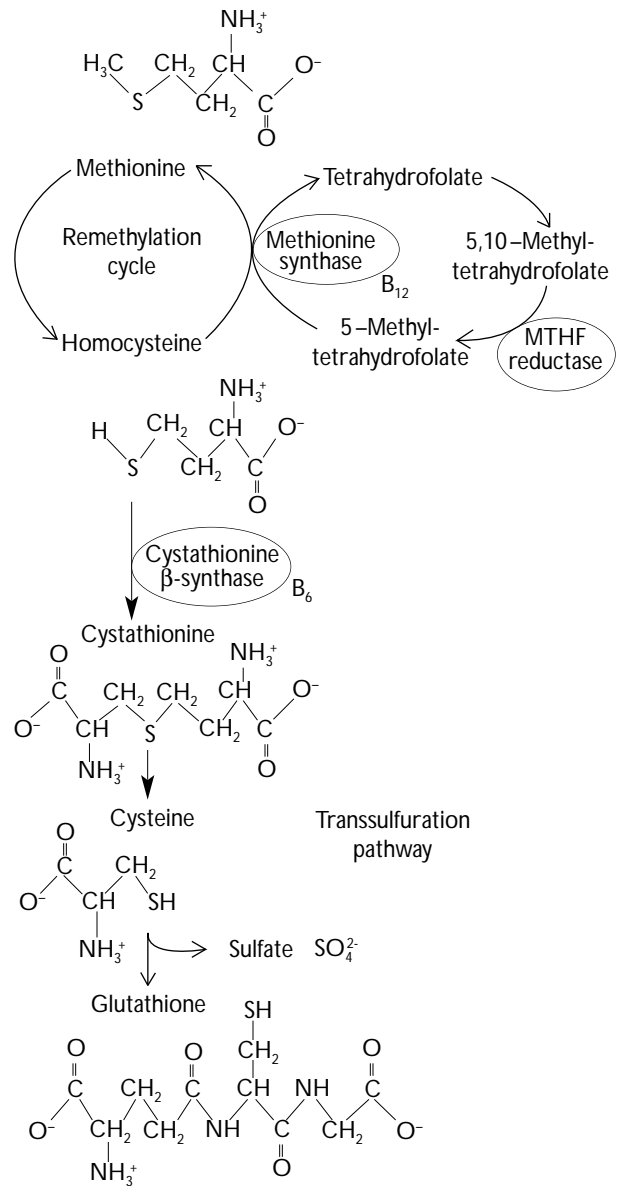
Zinc. Zinc is an integral part of all biomembranes and is necessary for maintenance of membrane structure and function. This mineral has two major functions relating to the vascular endothelium. Zinc is essential for maintaining endothelial barrier function, and zinc protects endothelial cells from cell-destabilizing agents, such as cytokines and polyunsaturated lipids. Animal and in vitro studies have shown that zinc deficiency causes decreased levels of serum vitamin E, impairment of endothelial barrier integrity, alteration of membrane-bound enzymes, and endothelial cell injury.³

Magnesium. The effect of magnesium on cardiovascular disease is primarily related to a deficiency state. Clinically, magnesium deficiency frequently occurs with cardiovascular disease. The biologic activity of magnesium is caused in part by its close relationship with calcium metabolism, acting as a calcium antagonist. Magnesium deficiency causes calcium influx into cells, vasospasm, release of cytokines from macrophages, and alterations in lipid metabolism. The result is significant endothelial cell injury from interleukin-1, interleukin-6, tumor necrosis factor, and free radicals. Animal studies have shown that antioxidants can prevent myocardial injury caused by magnesium deficiency.²⁶

EFFECT OF HOMOCYSTEINE ON CORONARY ARTERY DISEASE Causes of Elevated Homocysteine

Homocysteine is an amino acid intermediate that is formed from the metabolism of methionine to cysteine. **Figure 3** is a schematic illustration of this pathway. The balance between homocysteine and methionine is governed by a remethylation cycle catalyzed by methionine synthase. The methyl donor in this reaction is 5,10-methyltetrahydrofolate (derived from folic acid), of which vitamin B₁₂ is an essential cofactor. If an excess of methionine is present, cysteine is produced in a transsulfuration pathway by cystathionine β -synthase, of which vitamin B₆ is a necessary cofactor. Understanding

Figure 3. Homocysteine is formed during the metabolism of methionine, an essential amino acid derived from dietary protein. After formation, homocysteine may enter the remethylation cycle or the transsulfuration pathway. In the remethylation cycle, homocysteine is recycled to methionine in a reaction catalyzed by methionine synthase. The methyl donor in this reaction is 5,10-methyltetrahydrofolate (MTHF); vitamin B₁₂ is an essential cofactor, and 5,10-MTHF reductase acts as a catalyst in the remethylation process. If excess methionine is present or cysteine synthesis is required, homocysteine can enter the transsulfuration pathway, in which the vitamin B₆-dependent enzyme cystathionine β-synthase catalyzes the formation of cystathionine, which is subsequently hydrolyzed to yield cysteine. Cysteine can be incorporated in glutathione or, in another vitamin B₆-dependent reaction scheme, be metabolized to sulfate and excreted in the urine. Adapted with permission from Welch GN, Upchurch GR Jr, Loscalzo J: Homocysteine, oxidative stress, and vascular disease. *Hosp Pract (Off Ed)* 1997;32:81-82, 88-92.



this biochemical pathway is important when considering the genetic causes and vitamin deficiencies that could contribute to elevated plasma homocysteine. **Table 2** lists potential factors that may cause elevated serum homocysteine levels, including genetic diseases, age, gender, renal function, nutritional status, systemic diseases, and medications.⁹

Effect of Homocysteine on Vascular Endothelium

Homocysteine influences almost every facet of CAD pathophysiology. The primary cytotoxic effect that homocysteine has on vascular endothelium is oxidative damage. Homocysteine oxidizes in the plasma to form super-

oxide radicals and hydrogen peroxide, which cause endothelial cell damage and lipid peroxidation, eventually leading to oxidized LDL formation. Also, homocysteine thiolactone reacts with LDL and forms an aggregate LDL that is taken up by subendothelial macrophages and creates foam cells in the vascular intima. Other effects of homocysteine include: inhibition of glutathione peroxidase activity (a potent antioxidant), impairment of nitric oxide-dependent vasodilation, increase in vascular smooth muscle proliferation, platelet adhesion/activation, and subsequent thrombus formation. Considering the consequences, it is not surprising that elevated serum homocysteine level is a major risk factor for CAD.⁹

Table 2. Factors That Contribute to Elevated Plasma Homocysteine Concentration

Cause	Effect
Genetic cause	Cystathionine β -synthase deficiency (most common genetic cause) 5,10-methylenetetrahydrofolate reductase deficiency Methionine synthase deficiency
Age	Homocysteine level increases with age (probably caused by vitamin deficiencies)
Gender	Homocysteine level higher in men and postmenopausal women compared with premenopausal women (estrogen has a beneficial effect on homocysteine metabolism)
Renal function	Homocysteine level rises with increasing serum creatinine
Nutritional status	Vitamin B ₁₂ , Vitamin B ₆ , or folate deficiency
Systemic disease	Hypothyroidism, chronic renal failure, carcinoma (breast, ovary, pancreas)
Medications	Methotrexate and phenytoin (altered folate metabolism), theophylline (decreases B ₆ synthesis)

Adapted with permission from Welch GN, Upchurch GR Jr, Loscalzo J: Homocysteine, oxidative stress, and vascular disease. *Hosp Pract (Off Ed)* 1997;32:81-82, 88-92.

Homocysteine and Coronary Artery Disease

The link between homocysteine and atherosclerosis was first postulated in 1969 by McCulley,²⁷ whose post-mortem findings in patients with genetic diseases of homocysteine metabolism showed extensive atherosclerotic vascular disease. After many research studies, homocysteine has recently been identified as a major independent risk factor for CAD.²⁸ Notably, the Physicians' Health Study showed significantly higher levels of homocysteine in patients that died of myocardial infarction (relative risk for the highest 5% homocysteine level, 3.1).²⁹ Another prospective study by Nygard et al¹⁸ showed a strong relation between plasma homocysteine levels and mortality in 587 patients with angiographically proven CAD. Compared with patients with a homocysteine level less than 9 $\mu\text{mol/L}$, the mortality risk was 1.9 for patients with a homocysteine level of 9 to 14.9 $\mu\text{mol/L}$, 2.8 for patients with a level of 15 to 19.9 $\mu\text{mol/L}$, and 4.5 for patients with a level of 20 $\mu\text{mol/L}$ or higher. This study confirms the fact that the risk of vascular disease mortality increases directly with plasma homocysteine levels, even when levels are within the normal range (6 to 10 $\mu\text{mol/L}$ for women and 8 to 12 $\mu\text{mol/L}$ for men).

The therapeutic implication is that physicians should be monitoring and treating elevated homocysteine levels in all patients at risk for CAD. In hyperhomocysteinemic patients, 1 to 5 mg of folate can normalize homocysteine levels in most cases.⁹ Vitamins B₁₂ and B₆ only lower homocysteine levels if the patient has a vitamin-deficient state.²⁸

CONCLUSIONS

The recommended daily allowance requirements

were developed by the United States Food and Drug Administration to prevent vitamin deficiency syndromes and purposefully do not reflect health-promoting benefits of vitamins at higher doses. Clearly, the data outlined in this review article prove that benefits may be gained by taking large doses of certain vitamins and minerals. **Table 3** recommends a series of nutritional considerations and supplement doses that are specifically geared towards the prevention of CAD. These recommendations are based on the material presented in this article and from clinical experience (these recommendations have not all been proven by controlled research trials). When implementing these nutritional recommendations, it is imperative to treat each patient individually. Factors that must be considered include comorbid conditions, magnitude of heart disease risk, variety/quality of dietary intake as it relates to specific nutrients, and patient compliance.

One question that must be addressed is, "Can patients achieve these levels of vitamins and minerals through dietary intake alone or is vitamin supplementation necessary?" Achieving sufficient levels by dietary intake alone is easy for certain vitamins and minerals and difficult for others (**Tables 4** and **5** list the vitamin content of common foods). For example, more than 10,000 IU of β -carotene can be ingested by eating one raw carrot or two mangos. In contrast, 2 lb of sunflower seeds or 100 tbs of safflower oil are required to achieve 400 IU of vitamin E intake. The average American diet must also be considered. A national nutrition survey published in 1991 by Block³⁰ showed that, of 12,000 adults on 1 day, 17% of subjects ate no vegetables and 41% ate no fruit, whereas only 10% ate the recommended five servings of fruits and vegetables. In this context, the decision to

Table 3. Nutritional Recommendations for Patients at Risk for Coronary Artery Disease

Supplement	Supplement Dose/Day	Recommended Daily Allowance	Toxic Dose	Nutritional Considerations
Vitamin E	400 IU	30 IU	12,000 IU	May potentiate effect of warfarin and raise INR Diet source: primarily vegetable oil
Vitamin C	500–1000 mg	60 mg	10,000 mg	Doses more than 10 g may cause renal calculi Diet source: primarily fruits and vegetables
β-Carotene	None	3300 IU	None	Current evidence does not support supplementation Recommended daily allowance easily achieved via diet rich in fruits and vegetables
Vitamin A	None	5500 IU	25,000 IU	Current evidence does not support supplementation Recommended daily allowance easily achieved via diet rich in fruits and vegetables
Selenium	0–0.1 mg	0.07 mg	0.70 mg	Use caution with renal failure patients Diet source: whole grains, fish, and lean red meat
Zinc	10–60 mg	15 mg	10,000 mg	May potentiate copper deficiency Diet source: peas, beans, fish, and lean red meat
Magnesium	0–400 mg	400 mg	None	Use caution with renal failure patients Diet source: vegetables, nuts, legumes, and whole grains
Folic acid	1–5 mg	0.4 mg	15 mg	Initiate treatment if serum homocysteine level > 9 μmol/L Can mask pernicious anemia if low vitamin B ₁₂ level
Vitamin B ₁₂	Supplement if deficient	0.006 mg	None	Check vitamin B ₁₂ level if serum homocysteine is elevated Supplement with vitamin B ₆ if low serum vitamin B ₁₂ level

General considerations

Gaining nutrients from natural sources is preferred to supplementation.

Most studies have shown that a minimum of 2 years of nutrient intake is necessary before the benefits of supplementation are achieved.

Avoid high doses of iron and copper because these minerals act as pro-oxidants.

Avoid potential dietary sources of oxidized lipids including: all frying oils, precooked meat products, margarine, butter, dried dairy products, and dried egg products.

Avoid excessive amounts of linoleic acid (polyunsaturated fatty acid found in vegetable oils) because certain studies have shown this acid to disrupt the endothelial barrier function.⁴

Monounsaturated fatty acids (eg, olive oil, canola oil) are the preferred dietary choice because these acids do not interfere with the endothelial barrier and they improve lipid profiles (decrease low-density lipoprotein).

Address all factors associated with cardiovascular risk including exercise, weight loss, tobacco use, and control of comorbid conditions (eg, hypertension, diabetes, renal failure).

INR = international normalized ratio.

Table 4. Natural Sources of Antioxidant Vitamins*

Food Source	Amount	Vitamin A, IU [†]	Vitamin C, mg	Vitamin E, mg
Fruits				
Apple, raw with skin	1 medium	74	8	0.81
Apricot				
Raw	3 medium	2769	11	–
Dried	10 halves	2534	1	–
Banana	1 medium	92	10	0.31
Cantaloupe	1 cup, cubed	5158	68	0.22
Grapefruit				
Red/pink	Half, medium	318	47	0.30
White	Half, medium	12	39	–
Guava	1 medium	713	165	–
Honeydew melon	1 cup, cubed	68	42	–
Mango	1 medium	8060	57	2.32
Orange				
Raw	1 medium	256	80	0.30
Juice	8 fl oz	194	97	0.10
Papaya	1 medium	6122	188	–
Pear	1 medium	33	7	0.83
Prunes, dried	10 whole	1669	3	–
Strawberries, raw	1 cup	41	85	0.18
Vegetables				
Broccoli, cooked	½ cup	1082	58	0.20
Brussels sprouts, cooked	½ cup	561	48	0.66
Carrots				
Raw	1 medium	20,253	7	0.32
Cooked	½ cup	19,152	2	0.33
Celery, raw	1 stalk	54	3	0.14
Green peas, cooked	½ cup	478	11	0.10
Pepper, sweet				
Green	½ cup	316	45	0.34
Red	½ cup	2850	95	0.34
Potato, baked	1 medium	–	26	0.05
Spinach, cooked	½ cup	7371	9	0.02
Sweet potato, baked	½ cup	24,877	28	5.93
Winter squash, baked	½ cup	3628	10	0.12

*Quantities of vitamins found in natural sources are useful only as rough estimates. Actual vitamin content depends on freshness, food preparation, and storage factors.

[†]The vitamin A content in fruits and vegetables comes from provitamin A carotenoids, including β-carotene, not retinol. One IU of provitamin A carotenoids roughly equals 0.1 retinol equivalent.

Adapted with permission from Pennington JAT, ed: *Bowes and Church's Food Values of Portions Commonly Used*, 16th ed. Philadelphia: JB Lippincott, 1994.

Table 5. Vitamin E and Fat Content in Common Foods

Food Source	Amount	Vitamin E, mg	Saturated Fat, %	Monounsaturated Fat, %	Polyunsaturated Fat, %
Almonds	1 oz*	6.7	10	65	21
Canola oil	1 tbsp	—	7	59	29
Corn oil	1 tbsp	1.9	13	24	59
Cottonseed oil	1 tbsp	4.8	26	18	52
Mayonnaise†	1 tbsp	11	15	30	54
Olive oil	1 tbsp	1.7	13	73	8
Peanuts, dry roasted	1 oz	2.2	14	50	32
Peanut butter, creamy	2 tbsp	3	19	47	29
Safflower oil	1 tbsp	4.6	9	12	74
Sunflower seeds, dried	1 oz	14.2	10	21	69
Wheat germ oil	1 tbsp	20.3	19	16	62

*Equals approximately 24 nuts.

†Also contains 51 mg of cholesterol.

Adapted with permission from Pennington JAT, ed: *Bowes and Church's Food Values of Portions Commonly Used*, 16th ed. Philadelphia: JB Lippincott, 1994.

supplement certain vitamins and minerals becomes obvious—first, to reach the necessary serum concentrations, and, second, to achieve patient compliance in a population that already has poor dietary intake.

Much of the data in this article is not new—why is it not standard practice to recommend nutritional supplementation to prevent CAD? Many clinicians believe that data is insufficient to conclusively make recommendations for nutritional supplementation. Another reason for failure to recommend supplementation may be that, because this type of treatment for CAD is preventive, patients are slow to realize the full effects. For this reason, physicians as well as patients may not feel that any benefit is derived because the results are not instant or identifiable. To recommend nutritional supplementation, the medical community must view antioxidant treatment similarly to aspirin therapy, in which positive results are viewed as prevention of mortality. Lastly, the medical community in general may have a bias towards high-dose vitamin supplementation. Vitamins may be viewed as an alternative therapy or not as part of standard medicine because patients can purchase supplements in health-food stores or catalogs. All of these biases are refutable, and the author hopes this article may diffuse any hesitations that still exist.

Physicians must now look more closely at the effects of nutrition for the prevention of CAD. Based on the individual patient, the clinician should carefully tailor

nutritional recommendations based on the potential benefits and side effects of such treatment and the nutritional status of the patient. The potential side effects from vitamin and mineral supplementation are restricted to a small patient population; for example, vitamin E can potentiate the effects of warfarin, and magnesium and selenium can reach toxic levels in patients with renal compromise. If patients are screened adequately and educated about proper dosages, then vitamin/mineral supplementation is relatively risk free. Antioxidant therapy is one of the most exciting areas in medicine and probably entails the future of preventive medicine. Now is the time to implement this treatment with patients on a large scale to reduce mortality and possibly eliminate a major cause of death, coronary artery atherosclerosis. **HP**

REFERENCES

1. Bureau of the Census: *Statistical Abstract of the United States*, 118th ed. Austin, TX: The Reference Press, 1998.
2. Jialal I, Grundy SM: Influence of antioxidant vitamins on LDL oxidation. *Ann N Y Acad Sci* 1992;669:237-248.
3. Hennig B, Toborek M, Cader AA, Decker EA: Nutrition, endothelial cell metabolism, and atherosclerosis. *Crit Rev Food Sci Nutr* 1994;34:253-282.
4. Witztum JL: The oxidation hypothesis of atherosclerosis. *Lancet* 1994;344:793-795.
5. Diaz MN, Frei B, Vita JA, Keaney JF Jr: Antioxidants and atherosclerotic heart disease. *N Engl J Med* 1997;337:408-416.

6. Luc G, Fruchart JC: Oxidation of lipoproteins and atherosclerosis. *Am J Clin Nutr* 1991;53(suppl 1): 206S-209S.
7. Steinberg D: Clinical trials of antioxidants in atherosclerosis: are we doing the right thing? *Lancet* 1995;346:36-38.
8. Tardif JC, Cote G, Lesperance J, et al: ProbucoI and multivitamins in the prevention of restenosis after coronary angioplasty. Multivitamins and ProbucoI Study Group. *N Engl J Med* 1997;337:365-372.
9. Welch GN, Upchurch GR Jr, Loscalzo J: Homocysteine, oxidative stress, and vascular disease. *Hosp Pract (Off Ed)* 1997;32:81-82, 88-92.
10. Illingworth DR: The potential role of antioxidants in the prevention of atherosclerosis. *J Nutr Sci Vitaminol (Tokyo)* 1993;39:S43-S47.
11. Stahelin HB, Eichholzer M, Gey KF: Nutritional factors correlating with cardiovascular disease: results of the Basel Study. *Bibl Nutr Dieta* 1992;49:24-35.
12. Verlangieri AJ, Kapeghian JC, el-Dean S, Bush M: Fruit and vegetable consumption and cardiovascular mortality. *Med Hypotheses* 1985;16:7-15.
13. Gey KF, Puska P: Plasma vitamins E and A inversely correlated to mortality from ischemic heart disease in cross-cultural epidemiology. *Ann N Y Acad Sci* 1989;570: 268-282.
14. The effect of vitamin E and β -carotene on the incidence of lung cancer and other cancers in male smokers. The α -Tocopherol, β -Carotene Cancer Prevention Study Group. *N Engl J Med* 1994;330:1029-1035.
15. Levine GN, Frei B, Koulouris SN, et al: Ascorbic acid reverses endothelial vasomotor dysfunction in patients with coronary artery disease. *Circulation* 1996;93:1107-1113.
16. Simon JA: Vitamin C and cardiovascular disease: a review. *J Am Coll Nutr* 1992;11:107-125.
17. Dubick MA, Hunter GC, Casey SM, Keen CL: Aortic ascorbic acid, trace elements, and superoxide dismutase activity in human aneurysmal and occlusive disease. *Proc Soc Exp Biol Med* 1987;184:138-143.
18. Nygard O, Nordrehaug JE, Refsum H, et al: Plasma homocysteine levels and mortality in patients with coronary artery disease. *N Engl J Med* 1997;337:230-236.
19. Rimm EB, Stampfer MJ, Ascherio A, et al: Vitamin E consumption and the risk of coronary heart disease in men. *N Engl J Med* 1993;328:1450-1456.
20. Ramirez J, Flowers NC: Leukocyte ascorbic acid and its relationship to coronary artery disease in man. *Am J Clin Nutr* October 1980:2079-2087.
21. Losonczy KG, Harris TB, Havlik RJ: Vitamin E and vitamin C supplement use and risk of all-cause and coronary heart disease mortality in older persons: the Established Populations for Epidemiologic Studies of the Elderly. *Am J Clin Nutr* 1996;64:190-196.
22. Enstrom JE, Kanim LE, Klein MA: Vitamin C intake and mortality among a sample of the United States population. *Epidemiology* 1992;3:194-202.
23. Hennekens CH, Buring JE, Manson JE, et al: Lack of effect of long-term supplementation with β -carotene on the incidence of malignant neoplasms and cardiovascular disease. *N Engl J Med* 1996;334:1145-1149.
24. Steinberg D: Antioxidants in the prevention of human atherosclerosis. Summary of the proceedings of a National Heart, Lung, and Blood Institute Workshop: September 5-6, 1991, Bethesda, Maryland. *Circulation* 1992;85:2337-2344.
25. Oster O, Prellwitz W: Selenium and cardiovascular disease. *Biol Trace Elem Res* 1990;24:91-103.
26. Hennig B, Alvarado A: Nutrition and endothelial cell integrity: implications in atherosclerosis. *Prog Food Nutr Sci* 1993;17:119-157.
27. McCulley KS: Vascular pathology of homocystinemia: implications for the pathogenesis of atherosclerosis. *Am J Pathol* 1969;56.
28. Parnetti L, Bottiglieri T, Lowenthal D: Role of homocysteine in age-related vascular and non-vascular diseases. *Aging (Milano)* 1997;9:241-257.
29. Stampfer MJ, Malinow MR, Willett WC, et al: A prospective study of plasma homocyst(e)ine and risk of myocardial infarction in US physicians. *JAMA* 1992;268:877-881.
30. Block G: Dietary guidelines and the results of food consumption surveys. *Am J Clin Nutr* 1991;53(suppl 1): 356S-357S.

Copyright 1999 by Turner White Communications Inc., Wayne, PA. All rights reserved.