NUTRICEUTICALS IN HEALTH AND DISEASE PREVENTION

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INTRODUCTION

Traditionally in medicine, nearly all prescribing decisions were made by the treating physician. Now, all that has changed and patients are increasingly vocal participants in the prescribing decision, on both clinical and economic grounds. The recently coined term "nutraceutical" is enjoying increasing popularity for describing a variety of non prescription products that are used to enhance health. This term is best reserved to describe the products that are naturally occurring substances (e.g., vitamins, amino acids, herbals) or formulations of these substances. Nutraceutical is a useful term for a physician to know because it is appearing more frequently in the lay press. Most "nutraceuticals" are dietary supplements, although a smaller percentage are medical foods and food additions. Recognizing the need to control the balance between environmental stress causing agents and human health, this brief review presents role and benefit of nutraceuticals in health. The nutraceuticals to be discussed include vitamin E, vitamin C, coenzyme Q₁₀, carotenoids (beta carotene, lycopene) L-arginine, S-adenosyl methionine, lipoic acid, and flavonoids.

VITAMIN E

Vitamin E is a potent and is the most readily available naturally occurring, lipid-soluble antioxidant carried in LDL and is particularly effective in protecting it from oxidation (1,2). Several short-term randomized, placebo-controlled trials have shown that vitamin E supplementation can reduce the susceptibility of LDL to oxidation (2). This effect has been demonstrated among healthy subjects as well as those with preexisting cardiovascular disease (2). Vitamin E has other beneficial actions on vascular reactivity, such as antiplatelet properties and inhibition of smooth muscle cell proliferation and protein kinase C, an important component in atherogenesis (3). One potential

mechanism for vitamin E in reducing clinical events is regression of atherosclerotic lesions, and there is evidence that people on vitamin E supplements (> 100 IU/day) demonstrated less atherosclerotic lesion progression than those who do not consume supplement (4). However, the magnitude of this effect is quite small and out of proportion to the 77% reduction in clinical events seen in the CHAOS trial, suggesting that vitamin E may have some effect (perhaps on atherosclerotic plaque activity) other than simply reducing lesion progression (5). In ARIC (Atherosclerosis Risk Communities Study), use of vitamin E slowed the progression of atherosclerosis, as measured by intima-media thickness of the carotid artery wall (6). Thus results from observational and experimental studies consistently support an effect of vitamin E supplementation on reducing risk of coronary heart disease.

VITAMIN C

The major aqueous-phase antioxidant, vitamin C (ascorbate) traps peroxy radicals in the aqueous phase before they can initiate lipid peroxidation (1). Vitamin C is not found in appreciable concentrations in LDL, it too has strong antioxidant capacity and may function to regenerate or spare vitamin E, and in some, but not all studies, lead to reduced LDL oxidizability (2,7). Vitamin C improves and normalizes endothelial vasodilator function in patients with chronic heart failure by increasing the availability of the potential vasodilator nitric oxide (7,8). Improved endothelial functions with vitamin C has also been observed in patients with hypertension hypercholesterolemia, and diabetes mellitus (7,9).

COENZYME Q₁₀

The lipid phase antioxidant coenzyme Q₁₀ is a free radical scavenger that regenerates vitamin E (1). It inhibits the oxidation of low-density lipoprotein in plants and animal models. Coenzyme Q₁₀ protects left ventricular function from ischaemia-reperfusion injury (10) via an antioxidant effect. At present, although coenzyme Q₁₀ is a fairly popular (yet expensive) dietary supplement, there are insufficient clinical data to recommend the use of coenzyme Q₁₀ as a cardiovascular agent.

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CAROTENOIDS

More than 600 naturally occurring carotenoids have been identified and β -carotene is the most prominent of the 600 carotenoid compounds, atleast 40 have been isolated from food stuff; β -carotene, α -carotene, lycopene, β -cryptoxanthin, lutein, and zeaxanthin are the most common (2,11). Carotenoids are transported in body via lipoproteins and they prevent lipid peroxidation by singlet oxygen-quenching (2,11).

BETA CAROTENE

In the Health professionals follow-up study (2,12), men in the highest quintile of β -carotene intake had a significantly lower risk of coronary intake. The strong association was limited exclusively to men who were former or current smoker. These results were corroborated in the initial report of a large European Collaborative case-control study of a adipose carotenoid concentration and risk of non-fatal myocardial infarction and in a small nested case-control study in the United States (2,13).

In the Nurses' Health Study (14), women in the highest quintile of intake had a 22% reduction in risk of coronary artery disease compared with those in the lowest quintile.

Several long-term clinical trials of β -carotene have shown no benefit, among either smokers or nonsmokers. In the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (ATBC) (15) and Carotene and Retinol Efficacy Trial (CARET) (16) high doses of β -carotene correlated with an increased risk of lung cancer. In ATBC, men assigned to β -carotene had 11% higher mortality from ischaemic heart disease than men taking placebo (16).

Clinical trials convincingly demonstrate that β -carotene supplements do not lower the risk of coronary heart disease among men. However, some have suggested that β -carotene supplementation still may be beneficial at lower doses or among poorly nourished populations (2). A trial initiated in Paris is expected to provide evidence of effectiveness of β -carotene supplementation at lower doses (2).

LYCOPENE

Lycopene provides the familiar red colour to tomato products and is one of the major carotenoids in the diet of North Americans and Europeans. Lycopene appears to be a more potent antioxidant than β -carotene and may be responsible for many of the cardiovascular attributes originally claimed for β -carotene (11-13). In the European Community Multi Center Study on Antioxidants, myocardial Infarction, and Cancer of the Breast (EURAMIC), high tissue levels of lycopene were associated with a low risk of

myocardial infarction (13). Recent epidemiological studies have implicated lycopene in prevention of cardiovascular disease and cancers of the prostate or gastrointestinal tract (11,13). Low intake of lycopene is associated with macular degeneration (11). Dietary lycopene is usually provided using tomato juice, sauce and cooking them with vegetables in Indian diet and average consumption of tomatoes in Indian diet is fairly good. Experimental studies have shown that dietary supplementation of lycopene significantly increased serum lycopene level and decreased serum lipid peroxidation and LDL oxidation (12).

FLAVONOIDS

Flavonoids are polyphenolic antioxidants naturally present in vegetables, fruits, red wine and tea, for which they provide colour, texture, and taste (12,17). The most important groups of flavonoids are anthocyanins, flavonols, flavones, catechins, and flavanones. As free radical scavengers, flavonoids inhibit lipid peroxidation, promote vascular relaxation, and help prevent atherosclerosis (18). In addition, flavonoids inhibit cyclooxygenases, which may reduce thrombosis (17,18). Quercetin a major flavonoid inhibits oxidation and cytotoxicity of LDL *in vitro* (19). The Zutphen Elderly Study found a strong inverse association between the intake of various flavonoids and coronary heart disease, with a >50% reduction in mortality risk (19).

SOYBEAN PRODUCTS

Soybeans are rich in flavonoids, the most prevalent of which is genistein and diadzein and glycitin are minor component (20). Isoflavones have structural similarity with female sex hormone estrogen and they can be termed 'phytoestrogens' because they are derived from plant sources. Direct beneficial effects of isoflavone include antioxidant effects and metabolic regulation of cell growth and behaviour via tyrosine kinase inhibition (20). Substitution of soy protein for animal protein in human diet decreases the levels of both total cholesterol and low-density lipoprotein cholesterol.

RED WINE

Quercetin, the most common food flavonoid, is found in abundance in red wine (17). Quercetin, is responsible for the cardioprotective effect of moderate intake of red wine, although ethanol itself may have cardioprotective attributes (17). Quercetin inhibits platelet aggregation and oxidative modification of LDL, both of which processes are involved in the development of atherosclerotic lesions (17).

BLUE BERRIES

Aqueous extract of *Vaccinium myrtillus* (blue berry) is rich in antioxidants and prevents oxidation of LDL (21).

LICORICE ROOT

Chinese licorice (*Glycyrrhiza glabra*) has been used for medicinal purposes for several centuries. It has antioxidant, antiplatelet, anti-inflammatory, and antiviral properties (22).

ARGININE

Accumulating clinical evidence indicates that this semi-essential amino acid may be useful in patients with cardiovascular disease. L-arginine exerts its beneficial effect via its metabolism to nitric oxide (NO) and citrulline by the enzyme NO synthases (23). NO not only is a potent vasodilator, but, also inhibits the adherence of circulating blood elements to the vessel wall and suppresses the proliferation of vascular smooth muscle cells (24). NO also inhibits by processes involved in atherogenesis, including platelet aggregation, monocyte adherence and infiltration, vascular smooth muscle cell proliferation, and oxidative enzyme activity (23-24). Administration of L-arginine can improve coronary and peripheral blood flow in humans (25). A recent Mayo Clinic Trial revealed that oral supplementation with L-arginine (9 g/day) improved coronary blood flow response to acetylcholine by 150% and significantly decreased angina in patients with coronary artery disease (26).

Since the dosage of L-arginine required to have a beneficial effect is not convenient to take in the form of capsules (e.g. eighteen 500-mg capsules per day were used in the Mayo Clinic Study). Recently an arginine- enriched nutrient bar (The Heart Bar) has been developed in California that may be a palatable way for patients to incorporate this supplement into their diets.

CONCLUSION

Available evidence suggests that we can not dismiss the potential value of nutraceuticals in disease and inhibition of atherosclerosis. Epidemiologic data suggest that antioxidant supplementation may be associated with a reduced risk of clinical events from atherosclerosis; however, interventional trials only support a role for vitamin E in this regard. Many studies suggest that a link between fruit and vegetables in diet or the amounts of plasma antioxidant vitamins (ascorbic acid, tocopherols and carotenoids) and risk of death from cancer or coronary heart disease. The usefulness of antioxidant for prevention of cardiovascular disease is yet to be proven. However, studies offer important insights that together with the development of methods to identify individuals most likely to benefit, provide hope to clinicians seeking to use antioxidant vitamins with safety and efficacy for the treatment and prevention of cardiovascular disease. Only continued investigation into the mechanism (s) of action of candidate agents will determine whether

they hold promise as a therapeutic intervention and only then, they can be recommended routinely to the patients. Thus, nutraceuticals are becoming more widely accepted as an adjunct to conventional therapies.

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