Symposium: Molecular Mechanisms of Protective Effects of Vitamin E in Atherosclerosis

Vitamin E and Atherosclerosis: Beyond Prevention of LDL Oxidation[1,2]

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ABSTRACT Atherosclerosis is a chronic inflammatory disease of the arterial wall. Observational and experimental studies indicate that dietary vitamin E supplementation is associated with reduced risk of atherosclerosis. Evidence indicates that vitamin E, in addition to inhibition of oxidative modification of LDL, may inhibit atherogenesis through several other mechanisms at the molecular and cellular levels, which also include its nonantioxidant functions. J. Nutr. 131: 366S–368S, 2001.

KEY WORDS: • *α-tocopherol* • *cardiovascular disease* • *atherosclerosis* • *molecular mechanism*

Atherosclerosis, a chronic inflammatory disease of the arterial wall, is the major cause of morbidity and mortality from cardiovascular disease (CVD) in much of the world's population. A substantial body of evidence has indicated oxidation of LDL as one of the major mechanisms for the pathogenesis of atherogenesis. Over the past decade, a large body of experimental and epidemiologic data has indicated that dietary antioxidants might reduce the risk of atherosclerosis. The reduction of oxidative stress and inhibition of LDL oxidation by vitamin E are thought to be major actions for which it has received considerable attention as a health benefit in reducing the risk of CVD. In addition to the inhibition of oxidative modification of LDL, vitamin E has been identified recently as a favorable modulator of other atherogenic processes at the molecular and cellular levels.

Vitamin E, mainly α-tocopherol, is the major fat-soluble antioxidant present in the LDL particle. On average, 5–9 vitamin E molecules are carried by each LDL particle and are believed to protect LDL from oxidative damage. In vivo, free radicals generated by endothelial cells of the arterial wall and activated macrophages are thought to oxidize LDL particles (Carr et al. 2000), making them chemotactic to attract monocytes. The oxidized LDL particles are recognized by macrophage scavenger receptors and taken up by the macrophages, forming lipid-laden foam cells in the fatty streak lesions. In vitro studies have indicated that increasing the vitamin E content of LDL particles increases LDL resistance to oxidation and decreases their uptake by macrophages. Vitamin E supplementation has also been reported to suppress macrophage uptake of oxidized LDL in human arterial lesions (Iuliano et al. 2000). Vitamin E in LDL particles acts as a chain-breaking antioxidant and prevents lipid peroxidation of polyunsaturated fatty acids and modification of proteins in LDL by reactive oxygen species (ROS) (Carr et al. 2000).

Vitamin E and atherosclerosis

Prevention of oxidative modification of LDL by dietary vitamin E has been hypothesized as a plausible mechanism for its favorable effects in CVD. The effect of dietary vitamin E has been examined in several studies, many of which have reported a clear association between the reduction in the relative risk of CVD with high intake or supplementation of vitamin E, although some have shown no such association. Cross-cultural studies in Europe reported that a higher level of plasma vitamin E is associated with a lower mortality rate from CVD (Gey et al. 1993). Prospective cohort studies in men and women also reported a lower risk of CVD with long-term vitamin E supplementation (Rimm et al. 1993, Stampfer et al. 1993). The reduced relative risk of death from heart disease has been reported also in elderly subjects who were supplemented with vitamin E (Losonczy et al. 1996). An inverse association between CVD and vitamin E supplement usage (Meyer et al. 1996) or vitamin E from a food source (Kushi et al. 1996) has also been reported. Several other studies have found inverse association of blood vitamin E with angina or myocardial infarction (Miwa et al. 1996, Riemersma et al. 1991, Salonen et al. 1985).

Earlier studies also reported that vitamin E helped to reduce intermittent claudication (Haeger 1974, Livingstone and Jones 1958, Tornwall et al. 1999, Williams et al. 1971). As

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clinical indices of CVD, ultrasound measurements of intima-media thickness of the carotid artery wall and angiographic scores of coronary artery stenosis have been reported to be inversely related to vitamin E status (Kirtchevsky et al. 1995, Rengestrom et al. 1996). High levels of vitamin E in RBC were associated with less thickening of the arterial wall in French patients (Bonithon-Kopp et al. 1997) and low vitamin E status in Eastern Finnish men who had accelerated atherosclerosis (Salonen et al. 1993). In Finnish men who were heavy smokers, 50 mg/d of synthetic vitamin E supplementation for 6 y provided a slight protection against ischemic heart disease mortality (The Alpha-Tocopherol Beta-Carotene Cancer Prevention Study Group 1994). These observational data are further supported by the positive effect of vitamin E in high risk CVD patients. (Hodis et al. 1995) reported that less progression of coronary lesion was observed when patients received vitamin E supplements. Supplementation with 400 or 800 IU/d natural vitamin E substantially reduced the rate of nonfatal myocardial infarction, with beneficial effects apparent after 1 y of supplementation (Stephens et al. 1996).

In contrast, two recent studies (GISSI and HOPE trials) (GISSI-Prevenzione Investigators 1999, The Heart Outcomes Prevention Evaluation Study 1999) reported that vitamin E treatment of CVD patients had no effect on reducing the primary end points, which included death, nonfatal myocardial infarction or stroke. It was suggested that the genetic background, type and dose of vitamin E and dietary habit and lifestyle of study subjects might have contributed to the differential results in these studies (Brown 1999, Jialal et al. 1999).

Although these two recent studies have raised some doubts on the efficacy of vitamin E in the prevention of progression of atherosclerotic lesions, the overwhelming observational and experimental studies strongly support its positive effect on the reductions of risk of atherogenesis. Investigators of the HOPE study suggested that a longer treatment time and follow-up might be necessary to suppress early events and observe a positive effect of vitamin E. In many observational studies in which the beneficial effects of vitamin E have been noted, intake of other vitamins and micronutrients and their interaction with vitamin E might have contributed to the observed positive effects. Accordingly, trials using a combination of vitamin E with other micronutrients are currently underway and will reveal the role of such interactions in the prevention or regression of atherosclerosis.

Mechanism of vitamin E

Vitamin E, in addition to being carried in an LDL particle and protecting it from oxidative modification, is incorporated into the other components of the vascular system, including endothelial cells, smooth muscle cells, platelets and immune cells, and has been shown to modulate a variety of inflammatory processes that are involved in atherogenesis (**Table 1**). Vitamin E inhibits production of proinflammatory cytokines by endothelial cells and immune cells (Cannon et al. 1991, Devaraj et al. 1996, Wu et al. 1999). Vitamin E suppresses expression of adhesion molecules on endothelial cells and ligands on monocytes and reduces their adhesive interactions, which is an important early event in the initiation of fatty streak formation and atherogenesis. This interaction has been shown to be reduced by vitamin E supplementation in cell culture systems and in both animal and human studies (Devaraj et al. 1996, Fruebis et al. 1999, Wu et al. 1999). Soluble adhesion molecules are regarded as a marker for atherosclerosis. Vitamin E supplementation reduced production of intracellular adhesion molecule-1 by endothelial cells (Martin et al. 1997). Vitamin E may also inhibit production of chemokines by endothelium, such as interleukin-8 and MCP-1 (Wu et al. 1999), and reduce the attraction of monocytes to inflammatory sites at the arterial wall. Modulation of cytokine release and expression of adhesion molecules by vitamin E appears to be through inhibition of ROS-sensitive signaling pathways, which include protein kinase C and DNA-binding activity of nuclear transcription factor-κB. Studies have also indicated that vitamin E may function through its nonantioxidant properties to inhibit smooth muscle cell proliferation (Ricciarelli et al. 1998) and platelet aggregation (Freedman et al. 1996), which are important processes in plaque formation and atherogenesis. Vitamin E also modulates cyclooxygenase-2 activity and inhibits thrombaxane formation, which has platelet aggregation and vasoconstrictive properties, and increases production of prostacyclin, which has antiaggregatory and vasodilatory properties (Chen et al. 1998, Meydani et al. 1993). These effects of vitamin E together with modulation of NO production by the endothelium can modulate vascular reactivity in response to physical stress and thus may contribute to the reduction of risk of ischemic heart disease (Kinlay et al. 1999, Newaz et al. 1999). In this symposium, the current understandings of several molecular and cellular mechanisms by which vitamin E may exert its beneficial effects in the prevention of atherogenesis will be reviewed.

TABLE 1

Potential mechanisms by which vitamin E inhibits atherosclerosis[1]

↓ LDL oxidation, ↓ macrophage uptake of oxLDL
↓ Endothelial cell injury
↓ Adhesion molecule expression
↓ Immune/endothelial cell adhesion
↓ Inflammatory cytokines and chemokines
↓ Smooth muscle cell proliferation
↓ Platelet aggregation
↑ NO production, ↑ arterial dilation
↑ PGI_2 ↓ TXA_2

[1] PGI_2, prostacyclin; TXA_2, thromboxane A_2.

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