Vitamin E and Atherosclerosis[1,2]

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ABSTRACT Vitamin E was advocated as an effective treatment for heart disease by Dr. Even Shute of London, Ontario more than 50 years ago. His pioneering claims, which were unacceptable to the medical community at large, have been confirmed by recent findings from epidemiologic studies and clinical trials. This review integrates our current knowledge of atherogenesis with the biological functions of vitamin E. The response-to-injury hypothesis explains atherosclerosis as a chronic inflammatory response to injury of the endothelium, which leads to complex cellular and molecular interactions among cells derived from the endothelium, smooth muscle and several blood cell components. Inflammatory and other stimuli trigger an overproduction of free radicals, which promote peroxidation of lipids in LDL trapped in the subendothelial space. Products of LDL oxidation are bioactive, and they induce endothelial expression and secretion of cytokines, growth factors and several cell surface adhesion molecules. The last-mentioned are capable of recruiting circulating monocytes and T lymphocytes into the intima where monocytes are differentiated into macrophages, the precursor of foam cells. In response to the growth factors and cytokines, smooth muscle cells proliferate in the intima, resulting in the narrowing of the lumen. Oxidized LDL can also inhibit endothelial production of prostacyclin and nitric oxide, two potent autacoids that are vasodilators and inhibitors of platelet aggregation. Evidence is presented that vitamin E is protective against the development of atherosclerosis. Vitamin E enrichment has been shown to retard LDL oxidation, inhibit the proliferation of smooth muscle cells, inhibit platelet adhesion and aggregation, inhibit the expression and function of adhesion molecules, attenuate the synthesis of leukotrienes and potentiate the release of prostacyclin through up-regulating the expression of cytosolic phospholipase A_2 and cyclooxygenase. Collectively, these biological functions of vitamin E may account for its protection against the development of atherosclerosis. J. Nutr. 128: 1593–1596, 1998.

KEY WORDS: • vitamin E • endothelium • smooth muscle cell • monocyte • eicosanoids • platelets • oxidized LDL

Atherosclerosis and its complications continue to be the major cause of premature death in the developed world. Centuries of debate over the origin of this condition were finally resolved by the unifying "response-to-injury" hypothesis (Ross 1986). This hypothesis explains atherosclerosis as a process of chronic inflammatory response to injury of the endothelium, which leads to complex molecular and cellular interactions between cells derived from the endothelium, smooth muscle and several blood cell components. Inflammatory stimuli trigger the release of cytokines, growth factors and the generation of free radicals with their metabolic consequences manifested in transmigration and proliferation of vascular smooth muscle cells. The process also triggers the oxidation of LDL, which further potentiates the adhesion and migration of blood monocytes into the vessel walls where they differentiate to macrophages. The rapid uptake of oxidized LDL (ox-LDL)[3] via the macrophage scavenger receptor causes the transformation of macrophages into the lipid-laden foam cells, characteristic of a fatty streak, an early sign of atherosclerosis (Ross 1993 and 1995).

Vitamin E and coronary heart diseases. More than 50 years ago, the Shute brothers in London, Ontario, were the first to advocate vitamin E as an effective treatment of heart diseases (Vogelsang and Shute 1946). Their pioneering claims, which were unacceptable to the medical community at large, have gained considerable support from recent advances in epidemiologic studies and clinical trials. Large-scale prospective studies involving 40,000 men (4 y follow-up) and almost 80,000 women (8 y follow-up) revealed that large doses of vitamin E supplements (>100 IU/d) are associated with a significantly decreased risk of coronary heart disease (Rimm et al. 1993, Stampfer et al. 1993). In a population of postmenopausal women, vitamin E consumption was confirmed to be inversely associated with the risk of death from coronary heart disease (Kushi et al. 1996). Results from clinical intervention trials showed that vitamin E therapy (>400 IU/d for 510 d) significantly reduced the recurrence of heart attacks in over 1000 coronary patients (Stephens et al. 1996). Regression of existing atherosclerosis, determined by an angiographic method, was demonstrated in a group of middle-aged men who had coronary bypass surgery and who had an intake of over 100 IU/d of vitamin E (Hodis et al. 1995). Hence, the protective effect of vitamin E against the development of atherosclerosis and favoring the regression of existing lesions appeared to be well supported by epidemiologic and clinical studies. However, the effective dose was over 100 IU/d, a level that is an order of magnitude above the currently recommended values for this vitamin. This review focuses on recent advances that have revealed the mechanisms by which vitamin E may exert its protection against atherogenesis (**Table 1**). The antiatherogenic property of vitamin E and the overall protective effects of antioxidants on atherosclerotic heart disease are reviewed elsewhere (Diaz et al. 1997, Ferns et al. 1993).

Low density lipoprotein oxidation, cellular response and protection by vitamin E. LDL oxidation plays a key role in atherogenesis (Steinberg et al. 1989, Steinberg 1997) . It is now accepted that the first event in the development of fatty streaks is the transport of LDL into the artery wall, a concentration-dependent process that does not require receptor-mediated endocytosis (Navab et al. 1996). In hypercholesterolemia and hypertensive conditions, it is expected that the rate of LDL trapping will be increased considerably. The oxidation

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[3] Abbreviations used: ELAM, endothelium leukocyte adhesion molecule; 5-HETE, 5-hydroxy-eicosatetraenoic acid; ICAM-1, intercellular adhesion molecule 1; LTB_4, leukotriene B_4; LTE_4, leukotriene E_4; NO, nitric oxide; PGI_2, prostacyclin; PKC, protein kinase C; $cPLA_2$, cytosolic phospholipase A_2; VCAM-1 vascular cell adhesion molecule.

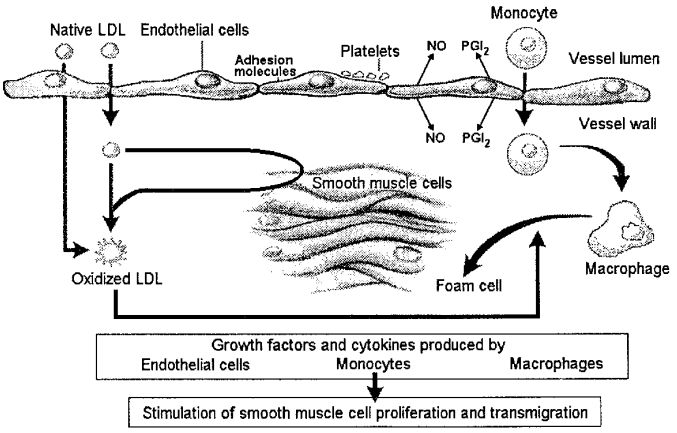

FIGURE 1 Schematic diagram depicting the role of lipid peroxidation in atherogenesis. The entry of LDL into the subendothelial area is followed by its oxidation. Oxidized LDL, inflammatory and other stimuli trigger cellular release of growth factors and cytokines, which stimulate smooth muscle cell proliferation, the release of NO (nitric oxide) and PGI_2 (prostacyclin), and the expression of endothelial adhesion molecules. Oxidized LDL also promotes the migration of monocytes into the vessel wall where they differentiate into macrophages. The rapid uptake of oxidized LDL by the scavenger receptors of macrophages leads to foam cell formation. Protective effects of vitamin E in these cellular events are summarized in Table 1.

can occur in the microenvironment of the subendothelial space or it can be cell mediated (**Fig. 1**). Macrophages, endothelial and smooth muscle cells can oxidize LDL, and the process is known to be dependent on superoxide generated in endothelial cells during mitochondrial respiration (Mabile et al. 1997). The resulting oxidized particles, which contain oxidized apoproteins and varying amounts of oxidized cholesterol esters, polyunsaturated fatty acids, phospholipids and their deacylated products, lysophospholipids, are bioactive. They can induce endothelial expression and secretion of cytokines, growth factors and several cell surface adhesion molecules that are capable of recruiting circulating monocytes and T lymphocytes into the intima (Fig. 1). Ox-LDL activate the development of monocytes into macrophages where the uptake of ox-LDL via the scavenger receptor is rapid. It also inhibits the production of nitric oxide (NO) and prostacyclin (PGI_2), two antithrombotic and vasodilating molecules released by the endothelium (Ross 1993).

LDL is a key carrier of vitamin E in the circulation and it is estimated that, for individuals who are not receiving any supplement, the average LDL particle contains 7 molecules of α- and 0.5 molecule of γ-tocopherol (Halliwell 1995). Evidence to date demonstrates that both cell-mediated and metal-dependent oxidation of LDL can be suppressed by vitamin E supplementation. Enrichment of LDL with vitamin E was reported to protect LDL against ex vivo oxidative modification (Dieber-Rotheneder et al. 1991, Jialal et al. 1995, Reaven et al. 1993). Conversely, enrichment of endothelial cells with vitamin E significantly attenuated their ability to oxidize LDL (Steinbrecher et al. 1984). Similarly, in survivors of myocardial infarction, vitamin E content in LDL was inversely related to the severity of the coronary stenosis score as determined by angiograms (Hodis et al. 1995, Regnstrom et al. 1996). Taken together, these studies clearly demonstrate that as the vitamin E content in LDL or endothelial cells is increased, there is an overall protection against LDL oxidation, with a subsequent reduction in the severity of the coronary stenosis score.

Thrombin, a serine protease that is involved in clot formation, can be generated by circulating lipoproteins. The production of thrombin is mediated by specific phospholipids and is enhanced by oxidation of these phospholipids. In a recent study by Rota and co-workers (1998), it was reported that in a cell free system, ox-LDL caused a 12-fold increase of thrombin generation. Addition of vitamin E markedly reduced this increase.

Adhesion of platelets, monocytes and T lymphocytes to the endothelium. Increased adherence of monocytes to the endothelium constitutes one of the early visible changes in experimental atherosclerosis. Exposure of ox-LDL to endothelial cells stimulates the expression of endothelium-derived adhesion molecules: ELAM (endothelium leukocyte adhesion molecule), ICAM-1 (intercellular adhesion molecule 1) and VCAM-1 (vascular cell adhesion molecule 1). These proteins promote monocyte adhesion and subsequent migration into the intima where monocytes differentiate into macrophages (Holvoet and Collen 1994). When human endothelial cells in culture were enriched with vitamin E, the expression of VCAM-1 was down-regulated (Cominacini et al. 1997). Similar treatment can cause a functional change in the reduction of monocyte adhesion to endothelial cells, presumably due to a decreased expression of adhesive molecules (Devaraj et al. 1996, Faruqi et al. 1994, Martin et al. 1997). Conversely, in vitamin E deficiency, it has been reported that the binding of monocytes to endothelial cells is increased (Molenor et al. 1989). Whether the protective effect of vitamin E is due to its antioxidative property remains unknown at present. It is clear, however, that vitamin E can reduce the interaction of monocytes to the endothelium and thereby down-regulate monocyte migration into vessels (Table 1).

Effects on endothelial arachidonic acid metabolism and smooth muscle cell proliferation. The vascular endothelium is made up of a monolayer of endothelial cells. Although it functions as a barrier for nutrient transport, the endothelium is now considered to be a distinct metabolic and endocrine organ by virtue of its involvement in pathophysiologic processes such as inflammation, thrombosis formation, control of vasomotor tone and cancer cell metastasis. When stimulated, endothelial cells release PGI_2 as the principal metabolite of

TABLE 1

Protective effects of vitamin E on lipoproteins and different cell types involved in atherogenesis

Target	Biologic function
LDL	Inhibits its oxidation[1]
Lipoproteins	Inhibits thrombin generation assembly[2]
Endothelial cells	Potentiates prostacyclin synthesis[3]
	Up-regulates the expression of cytosolic phospholipase A_2 and cyclooxygenase[4]
	Inhibits agonist-induced monocyte adhesion[5]
	Attenuates cell-mediated LDL oxidation[6]
	Decreases endothelial expression of adhesion molecules induced by oxidized LDL[7]
Smooth muscle cells	Inhibits their proliferation[8]
Platelets	Inhibits platelet adhesion, aggregation and platelet release reaction[9]
Neutrophils	Reduces leukotriene synthesis[10]
Monocytes	Reduces monocyte adhesion[11]

[1] Dieber-Rotheneder et al. (1991), Reaven et al. (1993), Jialal et al. (1995). [2]Rotas et al. (1998). [3]Chan and Leith (1981), Szczeklik et al. (1985), Thorin et al. (1994), Tran and Chan (1990). [4]Chan et al. (1998). [5] Faruqi et al. (1994). [6]Steinbrecher et al. (1994). [7]Cominacini et al. (1997). [8]Azzi et al. (1995), Boscoboinik et al. (1991). [9]Freeman et al. (1996), Higashi and Kikuchi (1974), Steiner and Anastasi (1976). [10]Chan et al. (1989), Denzlinger et al. (1995), Kohlschutter et al. (1997). [11]Devarej et al. (1996), Martin et al. (1997), Molenor et al. (1989).

arachidonic acid. The synthesis of PGI_2 commences with the release of arachidonic acid from membrane phospholipids, a rate-limiting step catalyzed by an 85-kDa cytosolic phospholipase A_2 ($cPLA_2$) that was shown to have acyl-selectivity for the arachidonyl-containing phospholipids. Once released, arachidonate is transformed sequentially by cyclooxygenase and prostacyclin synthetase to form PGI_2.

Vitamin E was first recognized to potentiate the release of PGI_2 in rabbit aorta (Chan and Leith 1981, Szczeklik et al. 1985). In ischemic-reperfused rat hearts, the release of PGI_2 by coronary vasculatures was inversely related to the levels of vitamin E in the diet (Pyke and Chan 1990). When human endothelial cells in culture were enriched with different concentrations of vitamin E, PGI_2 synthesis was stimulated in a dose-dependent manner, irrespective of the presence or absence of arachidonate, suggesting that both $cPLA_2$ and cyclooxygenase are up-regulated (Tran and Chan 1990). In disease states in which PGI_2 production is known to be compromised such as in diabetes, megadoses of vitamin E treatment were able to restore the diminished PGI_2 production (Gilbert et al. 1983). The impaired PGI_2 production resulting from exposure of endothelial cells to oxidized LDL can be normalized by vitamin E enrichment (Martin et al. 1997, Thorin et al. 1994). The mechanism by which vitamin E exerts its effect was recently identified as a higher expression of $cPLA_2$ and cyclooxygenase enzymes in endothelial cells and other cell types (Chan et al. 1998, Tran et al. 1996). Therefore, the cardioprotective function of vitamin E is due in part to its augmentation of PGI_2 release (Table 1).

Smooth muscle cells found in the media constitute the bulk of normal arterial cellularity. Many stimuli can induce the migration of smooth muscle cells from the media to the intima where cell proliferation can occur. For example, in response to inflammation or injury, growth and chemotactic factors released by neighboring endothelial cells, monocytes, macrophages or platelets can accelerate smooth muscle proliferation. This results in the thickening of the intima, which represents the intermediate phase of atherogenesis in which narrowing of the vessel lumen becomes evident. Sources of cellular growth factors, cytokines as well as their cellular targets and biologic responses, have been comprehensively reviewed (Raines and Ross 1995).

Vitamin E was reported to inhibit serum-induced smooth muscle cell proliferation in culture, and the effect was apparently mediated by an inhibition of protein kinase C, a signal-transducing enzyme that controls cell division (Boscoboinik et al. 1991). A comparison of other tocopherol isomers showed that the effect of α-tocopherol was not related to its antioxidant property (Azzi et al. 1995, Chatelain et al. 1993, Ozer et al. 1995). Collectively, these results suggest that vitamin E may inhibit the proliferation of smooth muscle cells in vivo and hence retard the narrowing of the artery wall (Table 1).

Effects of vitamin E on leukotriene synthesis and platelet function. The leukotrienes are potent chemotactic factors and mediators of inflammation derived from the 5-lipoxygenase pathway. Dietary vitamin E was showed to inhibit the synthesis of 5-hydroxy-eicosatetraenoic acid (5-HETE) and leukotriene B_4 (LTB_4) in a dose-dependent manner in rat peritoneal neutrophils (Chan et al. 1989). This suppressive effect was recently demonstrated in humans given vitamin E supplementation from which urinary excretion of leukotriene E_4 (LTE_4) was monitored (Denzlinger et al. 1995, Kohlschutter et al. 1997). Irrespective of the mechanism, the anti-inflammatory action of vitamin E in attenuating phycocytic generation of these potent inflammatory mediators could mitigate the development of atherosclerosis.

Vitamin E has been shown to inhibit ex vivo platelet aggregation and the platelet release reaction (Higashi and Kikuchi 1974, Steiner and Anastasi 1976). The mechanism underlying this effect was recently shown to be mediated by the inhibition of platelet protein kinase C activation (Freedman et al. 1996). However, the oxidized products of tocopherol (tocopherol quinone and tocopherol hydroquinone) were also reported to have the same inhibitory effect on platelets at a similar concentration, suggesting that the tocopherol effect is not necessarily due to its antioxidant property (Mower and Steiner 1982).

Factors affecting vitamin E status and future research perspectives. The vitamin E status of an organism is determined by factors other than the level of vitamin intake. Ample evidence, both in vivo and ex vivo, suggests that a high degree of interaction exists among antioxidant nutrients (Chan 1993). The ability of one antioxidant to regenerate another oxidized species is common and appears to be more dependent on their redox potential than on their cellular compartment (Buettner 1993). Hence, in intact animals, a sparing effect of vitamin C on vitamin E status has been noted in guinea pigs (Bendich et al. 1984) and fish (Hamre et al. 1997). In human platelet homogenate, oxidized vitamin E was shown to be regenerated by vitamin C or reduced glutathione (Chan et al. 1991). Recycling of oxidized tocopherol was also shown to be afforded by lipoate (Packer et al. 1997, Podda et al. 1994) and ubiquinol (Stoyanovsky et al. 1995).

Intake of polyunsaturated fatty acids, turnover of polyunsaturated fatty acids by the lipoxygenase pathway and excessive iron are known to reduce the store of vitamin E. Environmental factors such as increased UV radiation or ozone level tend to deplete antioxidant nutrients. Prolonged starvation or other energy-insufficient states could compromise the antioxidant status because the electrons necessary for the regeneration reactions (NADH and NADPH) are ultimately derived from the oxidation of food. Therefore, the maintenance of vitamin E in vivo is subjected to modification by not only the abundance of other cellular antioxidants but also the presence of other dietary and environmental factors and the energy status of the organism.

Future research in this area should focus on the regulation of gene expression by vitamin E and other antioxidants. Recent advances in the area of plant phenolic compounds and bioflavonoids clearly show that some of these compounds are potent antioxidants and have pharmacokinetics similar to those of vitamin E. Their effects on the cardiovascular systems require clarification. In view of the recent finding that vitamin E can attenuate thrombin generation (Rota et al. 1998), further studies to explore the metabolic implications should be conducted. Finally, the HDL-associated paraoxonase, an antioxidant enzyme that can effectively reduce the oxidation of LDL (Navab et al. 1996), should be an interesting target for more investigation as a non-drug approach to combat blood vessel-related disorders.

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