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γ-Tocopherol, the new vitamin E?[1,2]

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ATHEROSCLEROSIS, OXIDATIVE STRESS, AND INFLAMMATION

Several lines of evidence support a role for oxidative stress and inflammation in atherogenesis. Epidemiologic studies suggest that low levels of antioxidants are associated with an increased risk of cardiovascular disease and that increased intakes appear to be protective. In supplementation studies in humans, α-tocopherol, the major form of vitamin E, decreased lipid peroxidation (LDL oxidation and F_2-isoprostanes), monocyte proatherogenicity, and platelet aggregation and adhesion and was antiinflammatory (1). α-Tocopherol can modulate the inflammatory response by inhibiting 5-lipoxygenase, which in turn decreases monocyte interleukin 1β release. By decreasing adhesion molecule expression on monocytes and endothelial cells, α-tocopherol also decreases monocyte–endothelial cell adhesion in vitro, possibly by α-tocopherol–mediated inhibition of nuclear factor κB activation (2). α-Tocopherol inhibits signaling pathways through protein kinase C (PKC)-mediated mechanisms in model systems such as monocyte superoxide production, smooth muscle cell proliferation (3), and platelet aggregation and adhesion (4). Another key function regulated by α-tocopherol is vascular homeostasis. Normal vascular function requires responsiveness to nitric oxide (NO). α-Tocopherol mediates NO production, and α-tocopherol supplementation in hypercholesterolemic men and smokers preserves endothelium-dependent vasorelaxation (5).

The results of prospective vitamin E clinical trials, however, have been disappointing. Ten previous studies examined the effects of various combinations of antioxidants, including α-tocopherol, ascorbate, and β-carotene, on cardiovascular events. Of these 10 studies, 3 showed a benefit for the primary endpoint and 4 for a secondary endpoint (6). Many factors could account for the lack of benefit for the primary endpoint in most of the studies, such as the lack of any measurement of compliance (such as vitamin E concentrations) or of biomarkers of oxidative stress or inflammation. Furthermore, most of the studies with negative results used *all-rac*-α-tocopherol and not *RRR*-α-tocopherol at doses that are not antiinflammatory (< 800 IU/d). Furthermore, the antioxidant β-carotene was shown to increase lung cancer and cardiovascular disease mortality and should not be used in conjunction with α-tocopherol.

All of the studies discussed above were carried out with supplements containing α-tocopherol. It is well known that α-tocopherol supplements decrease plasma γ-tocopherol concentrations (7), as a result of the function of the hepatic α-tocopherol transfer protein, which preferentially incorporates α-tocopherol into the plasma (8). Few studies have tested γ–tocopherol, but those that have done so suggest that it may have potent physiologic actions.

MECHANISMS OF γ-TOCOPHEROL ACTION

Serum γ-tocopherol concentrations have been reported to be significantly lower in coronary heart disease patients than in healthy control subjects (9). Although α- and γ-tocopherols are both potent lipophilic antioxidants, γ-tocopherol has a unique function. Because it has an unsubstituted 5-position on the chromanol ring, γ-tocopherol scavenges reactive nitrogen species (10). 5-Nitro-γ-tocopherol may be a useful in vivo marker for estimating the physiologic relevance of such reactions. γ-Tocopherol is also more potent than α-tocopherol with respect to inhibition of cyclooxygenase in cell systems (11).

In rats, although both α-tocopherol–enriched and γ-tocopherol–enriched diets decreased platelet aggregation, delayed time to occlusive thrombus, decreased arterial superoxide anion generation, decreased lipid peroxidation and LDL oxidation, and increased endogenous superoxide dismutase (SOD) activity, the effects of γ-tocopherol were more potent (12). Furthermore, α- and γ-tocopherol feeding increased not only SOD activity in plasma and arterial tissues but also Mn SOD and Cu/Zn SOD protein expression in arterial tissues. Again, γ-tocopherol was more potent than was α-tocopherol. Both α- and γ-tocopherols increased NO generation and endothelial nitric oxide synthase (eNOS) activity; however, only γ-tocopherol increased eNOS protein expression (13).

By contrast, α-tocopherol has greater antiatherogenic effects than does γ-tocopherol in human coronary smooth muscle cells with respect to effects on the kinase cascades; α-tocopherol is also more protective with respect to apoptotic genes of the *Bcl-2* family (14). However, data in humans are lacking in this regard; thus, a comparison of the effects of α- and γ-tocopherols on oxidative stress and inflammation in humans clearly will be instructive and should advance the field.

γ-TOCOPHEROL CLINICAL TRIALS

Despite the numerous antioxidant and antiinflammatory properties of α-tocopherol, the results of large, prospective clinical trials assessing vitamin E efficacy in heart disease progression have been disappointing for the reasons delineated above. Thus, it is important that carefully controlled γ-tocopherol intervention

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studies with the right dose and population are conducted and that measurement of compliance is recorded, including biomarkers of oxidative stress and inflammation. This will help to delineate the role of γ-tocopherol in treating cardiovascular disease and in maintaining optimum human health.

In a study published in this issue of the Journal (15), platelet aggregation was inhibited more potently in platelets isolated from humans supplemented with a mixed tocopherol preparation (100 mg γ-tocopherol, 40 mg δ-tocopherol, and 20 mg α-tocopherol) than in platelets isolated from humans supplemented with α-tocopherol alone. Importantly, both tocopherol supplementation strategies decreased PKC and increased eNOS activation and increased NO and SOD in platelets. Compliance with the supplementation regimen was monitored by measuring α- and γ-tocopherol concentrations in platelet-rich plasma.

The study would have been even more interesting had platelet aggregation in response to supplementation with γ-tocopherol alone been compared with that in response to supplementation with α-tocopherol. Also, supplementation with low and high doses might have shown whether there was an optimal intake for decreasing ADP-induced platelet aggregation and PKC activity. Nonetheless, the study emphasizes that we really do not know the mechanisms by which different tocopherols function and that there may be specific functions mediated by the various dietary tocopherols that urgently need to be explored in clinical studies. Such studies would facilitate the conduct of clinical trials to study the efficacy of these treatment regimens in preventing the progression of atherosclerosis.

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