Letters to the Editor

Vitamin E Is Not Deficient in Human Atherosclerotic Plaques

To the Editor:

With great interest, we recently read the article entitled “Vitamin E supplementation in patients with carotid atherosclerosis: reversal of altered oxidative stress status in plasma but not in plaque” published in the January 2004 issue of Arterioscler Thromb Vasc Biol.1 This article addresses the endogenous vitamin E status of candidates for carotid endarterectomy as compared with healthy controls and evaluates the effect of supplemental vitamin E on markers of oxidative stress in the circulation and in atherosclerotic plaques. These questions are important in light of several large-scale clinical trials documenting a lack of benefit of dietary vitamin E supplementation relative to the risk of coronary heart disease2–4 (reviewed by Kritharides et al5). The authors reported plasma vitamin E/cholesterol ratios to be lower in patients than in controls, and 7β-hydroxycholesterol/vitamin E ratios to be substantially higher in carotid plaque than plasma.1 Based on these findings, the authors concluded “vitamin E levels are reduced in... atherosclerotic plaques of patients with advanced atherosclerosis.”

In our opinion, this conclusion is not justified, for the following reasons. First, it is based on comparison of vitamin E/cholesterol ratios in plaques versus control plasma1 (Table). Second, 7β-hydroxycholesterol/vitamin E ratios reflect the extent of cholesterol oxidation relative to the concentration of the vitamin, so that changes in either or both compound(s) affect the ratio. Analysis of the data reported1 clearly shows that higher levels of 7β-hydroxycholesterol (330±170 versus 2.1±0.4 nmol/mmol cholesterol for plaque and plasma, respectively) rather than lower concentrations of vitamin E (2.06±0.7 versus 3.05±0.6 μmol/mmol cholesterol for plaque and plasma, respectively) are responsible for the difference in the 7β-hydroxycholesterol/vitamin E ratios. Third, the authors’ data in fact show that the concentrations of vitamin E in plasma and normal vessels are comparable (2.06±0.7 versus 0.54±0.3 μmol/mmol cholesterol for plaques and normal vessels, respectively)9 (Table). Indeed, the lack of a deficit in α-tocopherol in human atherosclerotic plaques has been documented previously (Table).9,10 Moreover, the intra-plaque levels of α-tocopherol do not differ between intermediate, early, and advanced lesions and are comparable to plasma levels of the vitamin (Table).6,8,9 Similar results have been reported for the vitamin E content of lipoproteins isolated from human lesions corresponding to different developmental stages.9,10 In addition, gas chromatography–mass spectrometry analysis suggests that only a fraction (<20%) of vitamin E is oxidized in the lesions.9 Thus, the data of Micheletta et al1 have consistently documented the absence of a deficit of vitamin E in human plaque tissue, even at advanced stages of atherosclerosis.

It is also relevant that a decrease in plasma vitamin E levels in atherosclerotic patients versus controls, as reported by Micheletta at el,1 is not observed consistently. For example, lipid-adjusted plasma levels of vitamin E have been reported to be lower in subjects with myocardial infarction as compared with their respective controls,11,12 By contrast, patients with advanced atherosclerosis,13 unstable coronary syndrome,14 coronary heart disease,15 peripheral vascular disease,16 or hyperlipidemia17 were reported to display normal plasma vitamin E levels (Table).

Interestingly, Micheletta at el1 reported that supplementation of candidates for carotid endarterectomy with α-tocopherol (450 IU/d for 6 weeks) led to elevation in its concentration in plasma but not in carotid plaques. The reasons for this difference are not clear at present. Based on the observed increased circulating concentrations of α-tocopherol,1 and the fact that the vitamin is transported by and enters the vessel wall via lipoproteins, one might expect lesion vitamin E levels to increase with increasing severity of the disease in subjects displaying atherogenic dyslipidemia. However, at advanced stages of plaque development, accumulation of lipoprotein-derived lipids and antioxidants may no longer be substantial, particularly over the relatively short period of six weeks examined,1 or vitamin E may be metabolized faster than (and independently of) lipoprotein-derived lipids. Regarding the latter possibility, it is known that oxidation does not appear to contribute significantly to a putative increase in metabolism of vitamin E in endarterectomy specimens.8 In any case, the findings of Micheletta et al1 suggest that supplemental vitamin E may not have reached its target tissue, and that plasma α-tocopherol is not a suitable surrogate measure for vessel wall vitamin E.

Concomitantly with the increased plasma concentration of α-tocopherol, 7β-hydroxycholesterol levels decreased in plasma but not in lesions. The authors concluded that α-tocopherol supplementation beneficially influenced oxidative stress in plasma but not in atherosclerotic plaques. The apparent inability of therapeutic amounts of

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**Lipid-Adjusted Concentrations of Vitamin E in Arterial Tissue and Plasma from Atherosclerotic Patients and Control Subjects**

<table>
<thead>
<tr>
<th>Arterial tissue</th>
<th>Atherosclerosis</th>
<th>P for the Difference</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial tissue</td>
<td>Patients</td>
<td>Controls</td>
<td>Artery</td>
</tr>
<tr>
<td>Arterial</td>
<td>2.1±0.7</td>
<td>0.5±0.3</td>
<td>Carotid (P), thoracic (C)</td>
</tr>
<tr>
<td></td>
<td>3.6±2.7*</td>
<td>2.4±1.0</td>
<td>Carotid, femoral (P), iliac (C)</td>
</tr>
<tr>
<td></td>
<td>6.3±2.5</td>
<td></td>
<td>Carotid</td>
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<tr>
<td></td>
<td>4.8±2.2</td>
<td></td>
<td>Aorta</td>
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<tr>
<td></td>
<td>4.9±0.8</td>
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<td>Aorta</td>
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<tr>
<td></td>
<td>5.4±1.6</td>
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<td>Aorta</td>
</tr>
<tr>
<td></td>
<td>2.0±1.9</td>
<td></td>
<td>Aorta</td>
</tr>
<tr>
<td>Arterial</td>
<td>Plasma†</td>
<td></td>
<td>Advanced</td>
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<tr>
<td></td>
<td>3.0±0.6</td>
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<tr>
<td></td>
<td>1.9±0.6†</td>
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<td>3.5±1.6</td>
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<td></td>
<td>4.1±1.2</td>
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</table>

*Recalculated using a molar ratio of total cholesterol/free cholesterol of 1.76.

†Data shown are representative of 29 studies on plasma levels of vitamin E in atherosclerosis found in Medline (14 of which show a decrease in the vitamin E in atherosclerosis and 15 do not).

‡μmol/mmol cholesterol + triglycerides.

P indicates patients; C, controls.
supplemental vitamin E to decrease oxidative stress in human atherosclerotic lesions is consistent with earlier studies (reviewed by Upston et al.20) and with the observation that vitamin E is not deficient in human lesions.16,18 In contrast, much higher pharmacological doses of the vitamin have been reported to decrease both aortic lipid oxidation and lesion formation in some19 but not all20 animal studies (see Neuzil et al.21 and Upston et al.22 for review).

The study by Micheletta et al.1 confirms previous reports6-9 that atherosclerotic lesions contain elevated levels of oxidized lipids compared with that in normal arteries and plasma (reviewed by Upston et al.20). Therefore, the available data suggests that in diseased vessels, oxidation of lipids, including those in lipoproteins, occurs in the presence of α-tocopherol.8,18 Mechanistically, such oxidation can be explained readily by the model of tocopherol-mediated peroxidation.23

Oxidative stress is believed to play a key role in the initiation and progression of atherosclerosis, and supplementation with antioxidants is believed to beneficially influence the disease.24 Quantitatively, α-tocopherol is the major antioxidant in organic extracts of LDL,25 and it is therefore not surprising that it was first chosen for large-scale clinical trials.2-4 However, there is accumulating evidence to suggest a major role for two-electron oxidants (such as hypochlorite and peroxynitrite) in lipoprotein oxidation and in other oxidative events in the arterial wall.18,19,26 Importantly, α-tocopherol does not provide protection against these oxidants.27,28 Rather than casting doubt on the concept that antioxidants may be beneficial in the treatment of atherosclerosis, these findings shift attention from vitamin E to agents that could provide protection against physiologically relevant oxidants. The latter may include HDL-associated proteins,29,30 such as those whose precise mechanism of action and relevance to atherosclerosis deserve detailed investigation.

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