**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.*

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 disease.

Indeed, the lack 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 et al., 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. By contrast, patients with advanced atherosclerosis, unstable coronary syndrome, coronary heart disease, peripheral vascular disease, or hyperlipidemia were reported to display normal plasma vitamin E levels (Table).

Interestingly, Micheletta et al. 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, 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.

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. In any case, the findings of Micheletta et al. 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.

Concomitant 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 α-tocopherol to reverse the oxidative stress status in carotid plaque relative to control plasma is responsible for the difference in the α-tocopherol/cholesterol ratios in plaques versus control plasma (Table). Second, the authors' data in Table, third, the authors' data in Table, fourth, the authors' data in Table, and seventh, the authors' data in Table, respectively, are responsible for the difference in the α-tocopherol/cholesterol ratios to be substantially lower in patients than in controls, and seventh, the authors' data in Table, respectively, are responsible for the difference in the α-tocopherol/cholesterol ratios to be substantially lower in patients than in controls.

The apparent inability of therapeutic amounts of α-tocopherol to reverse the oxidative stress status in carotid plaque relative to control plasma is responsible for the difference in the α-tocopherol/cholesterol ratios in plaques versus control plasma (Table). Second, the authors' data in Table, third, the authors' data in Table, fourth, the authors' data in Table, and seventh, the authors' data in Table, respectively, are responsible for the difference in the α-tocopherol/cholesterol ratios to be substantially lower in patients than in controls, and seventh, the authors' data in Table, respectively, are responsible for the difference in the α-tocopherol/cholesterol ratios to be substantially lower in patients than in controls.

### 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>Artery</th>
<th>Atherosclerosis</th>
<th>P for the Difference</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>Controls</td>
<td>Artery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arterial tissue</td>
<td>2.1 ± 0.7</td>
<td>Carotid (P), thoracic (C)</td>
<td>Advanced</td>
<td>NS 1</td>
</tr>
<tr>
<td></td>
<td>3.6 ± 2.7*</td>
<td>Carotid, femoral (P), iliac (C)</td>
<td>Advanced</td>
<td>NS 6</td>
</tr>
<tr>
<td></td>
<td>6.3 ± 2.5</td>
<td>Carotid</td>
<td>Advanced</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>4.8 ± 2.2</td>
<td>Aorta</td>
<td>Initial lesions</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>4.9 ± 0.8</td>
<td>Aorta</td>
<td>Fatty streaks</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>5.4 ± 1.6</td>
<td>Aorta</td>
<td>Fibro-fatty lesions</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>2.0 ± 1.9</td>
<td>Aorta</td>
<td>Complex lesions</td>
<td>7</td>
</tr>
<tr>
<td>Plasma1</td>
<td>3.0 ± 0.6</td>
<td>Advanced</td>
<td>&lt;0.001</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>1.9 ± 0.6*</td>
<td>Myocardial infarction</td>
<td>&lt;0.001</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>3.5 ± 1.6</td>
<td>Coronary heart disease</td>
<td>NS 15</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4.1 ± 1.2</td>
<td>Peripheral vascular disease</td>
<td>NS 16</td>
<td></td>
</tr>
</tbody>
</table>

Numerical data is given in μmol/mmol cholesterol unless indicated otherwise.

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^{19}) and with the observation that vitamin E is not deficient in human lesions.\textsuperscript{1,6–9} In contrast, much higher pharmacological doses of the vitamin have been reported to decrease both aortic lipid oxidation and lesion formation in some\textsuperscript{19} but not all\textsuperscript{20} animal studies (see Neuzil et al\textsuperscript{21} and Upston et al\textsuperscript{22} for review).

The study by Michelella at el\textsuperscript{11} confirms previous reports\textsuperscript{6–9} that atherosclerotic lesions contain elevated levels of oxidized lipids as compared with that in normal arteries and plasma (reviewed by Upston et al\textsuperscript{19}). Therefore, the available data suggests that in diseased vessels, oxidation of lipids, including those in lipoproteins, occurs in the presence of \textit{α}-tocopherol.\textsuperscript{9,18} Mechanistically, such oxidation can be explained readily by the model of tocopherol-mediated peroxidation.\textsuperscript{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.\textsuperscript{24} Quantitatively, \textit{α}-tocopherol is the major antioxidant in organic extracts of LDL,\textsuperscript{23} and it is therefore not surprising that it was first chosen for logical doses of the vitamin have been reported to decrease both oxidative events in the arterial wall.\textsuperscript{9,18,26} Importantly, \textit{α}-tocopherol does not provide protection against these oxidants,\textsuperscript{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,\textsuperscript{29,30} such as those whose precise mechanism of action and relevance to atherosclerosis deserve detailed investigation.

Anatol Kontush
M. John Chapman

Dyslipoproteinemia and Atherosclerosis Research Unit (U.551)
National Institute for Health and Medical Research (INSERM)
Paris, France

Roland Stocker

Centre for Vascular Research, University of New South Wales
Department of Haematology, Prince of Wales Hospital
Sydney, Australia

Vitamin E Is Not Deficient in Human Atherosclerotic Plaques
Anatol Kontush, M. John Chapman and Roland Stocker

Arterioscler Thromb Vasc Biol. 2004;24:e139-e140
doi: 10.1161/01.ATV.0000131259.97572.99

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://atvb.ahajournals.org/content/24/7/e139

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Arteriosclerosis, Thrombosis, and Vascular Biology can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Arteriosclerosis, Thrombosis, and Vascular Biology is online at:
http://atvb.ahajournals.org/subscriptions/