How to Select Patient Candidates for Antioxidant Treatment?

To the Editor:

In their excellent review, Steinberg and Witztum \(^1\) focused their attention on the different reasons why treatment with natural antioxidants has so far not convinced us that they may prevent atherosclerotic progression and its cardiovascular complications. The use of reliable biological markers of oxidative stress, identification of a population suitable for antioxidant treatment, and the choice of an adequate daily regimen of antioxidants are important points that would help us plan future trials with antioxidants. In accordance with the authors, we believe that knowledge of the intrinsic mechanism leading to LDL oxidation in vivo and the balance between oxidant stress and natural antioxidant defense is likely a crucial element for exploring the role of oxidative hypothesis in human pathology.

So far, many efforts have sought to obtain reliable markers of oxidant stress, whereas evaluation of the antioxidant capacity of the human body has been scarcely taken into account. This is quite surprising, because the logical background of a trial with natural antioxidants should be based on the concept that patients included in such a trial have reduced levels of natural antioxidants. Among the trials that studied the effect of antioxidants in patients with cardiovascular disease, only the ATBC study and the CHAOS study reported the baseline values of circulating vitamins.\(^2\) However, it was unclear whether the population included in these trials had low circulating levels of vitamins. It is also unfortunate that neither the SPACE trial, nor the more recent trial that examined the effect of vitamins E and C in transplant-associated atherosclerosis, demonstrated that circulating levels of vitamins E and C were reduced compared with levels in healthy subjects in specific clinical settings characterized by enhanced oxidant stress.\(^3,4\)

In our opinion, identification of patients with enhanced oxidant stress should be integrated with the analysis of the antioxidant status, including, in particular, the measurement of circulating levels of vitamin E and vitamin C. The potential relevance of this suggestion is based on the fact that we have no evidence about whether some defensive mechanisms have been activated in patients with enhanced oxidant stress. A recent report demonstrated, for instance, that cardiovascular aging is associated with increased circulating and tissue levels of vitamin E.\(^5\) Assuming that this might occur also in human atherosclerosis, the evidence of an enhanced oxidant stress alone could perhaps not justify a supplementation with such vitamins. Therefore, in our opinion, the simultaneous detection of both enhanced oxidant stress and reduced plasma levels of natural vitamins could represent a useful approach for selecting patients who are candidates for supplementation with antioxidant vitamins.

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Response

We thank Violi et al for their generous comments. We of course agree that future clinical trials of antioxidants should try to include some assessment of the susceptibility of the subjects to oxidative damage ("antioxidant status"). However, as Dr Violi and his colleagues point out in their recent review,\(^6\) plasma levels of vitamins (or of other antioxidants) may not be sufficient, although that would at least pick up obvious differences. Measurements of the amounts of oxidized end products in plasma or urine (eg, isoprostanes) may be preferable, as suggested by animal studies. However, these are global measurements of oxidation occurring anywhere in the body and need not reflect what is happening specifically at the level of the artery wall or other sites relating to atherogenesis. The hard fact is that no proposed biomarker will be acceptable as a surrogate end point until it has been shown to correlate with lesion progression or with coronary events.

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