If Oxidative Stress Is an Appropriate and Specific Target, What Reagent Should We Choose?

George A. Kaysen*† and Andrew Chin*

*Division of Nephrology, Department of Medicine, and †Department of Biochemistry and Molecular Medicine, University of California Davis School of Medicine, Davis, California

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Correspondence: Dr. George A. Kaysen, Division of Nephrology, Department of Medicine, University of California Davis School of Medicine, GBSF 451 Health Sciences Drive, Room 6301, Davis, CA 95616. Email: gakaysen@ucdavis.edu

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Inflammation as measured by the levels of IL-6 and acute phase proteins, including C-reactive protein (CRP), and oxidation of specific substrates, including oxidation of lipoproteins, are associated with increased clinical risk.4,5 There are significant data supporting the hypothesis that protein oxidation and thiol oxidation of endothelial cells and mitochondria alter their structure and function. Aging is also associated with increased oxidation of mitochondria and endothelial dysfunction.6,7 Preventing these structural changes offers an attractive target for therapeutic intervention, although data concerning the effect of ALA on mitochondrial structure suggest that mitochondrial injury and permeability may be increased.8 The principal questions that appear to be relevant are as follows: (1) What specific pathways of oxidation are appropriate targets? (2) Will changing the redox potential by administering dietary supplements as potential reducing agents effect meaningful biologic and chemical change? and (3) Are nutrients that have the capacity to act as reducing agents the appropriate reagents to effect change?

Antioxidants may not always produce the desired effects or may function as oxidants. For example, although ascorbate is predominantly considered an antioxidant, it can also favor oxidation depending on its ability to reduce transition metals, such as iron and copper. In addition, the biologic action of ascorbate among species that cannot endogenously synthesize the metabolite, including humans, is not associated with its activity as an antioxidant. Although there were some positive outcomes with tocopherol in a small clinical trial in dialysis patients,9 most large clinical trials in nondialysis patients have either observed no detectable therapeutic effect of tocopherols and other vitamin supplements on outcomes10,11 or, as in the case of β carotene or B vitamins, observed an increase in mortality.12

Vitamin E exerts its protective effects, in part, by incorporating into cell membranes and inhibiting lipid peroxidation by scavenging free radicals. However, many of the biologic actions of tocopherols are independent of their chemical action as antioxidants.13 Vitamin E requires regeneration back to its reduced form by interaction with linked water-soluble redox cycles. The interdependency of these cycles, which include ascorbic acid and thiol (e.g., lipoic acid) cycles, suggests that adequate function of the entire network may be required to achieve the desired antioxidant effect. Supplementation with vitamins C and E or either alone failed to reduce lipid peroxidation associated with aging.14 In addition, accumulation of oxidation products associated with aging is not associated with a decline in antioxidant enzymes.15 Finally, previous studies in healthy populations16 found that doses of ALA similar to those used by Himmelfarb et al.10 reduced urinary F2 isoprostane, suggesting that the dosages used in this study were within...
REFERENCES


DISCLOSURES

None.