study is the first of many in the field to examine the impact of AKI on cardiovascular disease, an exciting new dimension.

ACKNOWLEDGMENTS

We thank Alan Go and the ASsessment, Serial Evaluation, and Subsequent Sequelae of Acute Kidney Injury Biomarker Consortium for useful discussions.

K.D.L. and C.-y.H. are funded by National Institutes of Health Grant U01-DK082223.

DISCLOSURES

C.-y.H. declares no conflict of interest. K.D.L. has been a member of a Data Safety Monitoring Board for Cytophex and a member of the Clinical Events Adjudication Committee for Astute. K.D.L. has previously done consulting work for Abbvie and Complexa and owns stock in Amgen. K.D.L. has received gifts of reagents for biomarker assays from Abbott and CMIC.

REFERENCES


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 1Department of Biochemistry and Molecular Medicine, University of California Davis School of Medicine, Davis, California


Cardiovascular disease is prevalent in a disproportionately high percentage of patients on maintenance hemodialysis (MHD) and is responsible for much of the mortality in this population.1 In addition, MHD patients express markers of oxidative stress and inflammation at significantly higher levels than

Published online ahead of print. Publication date available at www.jasn.org.

Correspondence: Dr. George A. Kaysen, Division of Nephrology, Department of Medicine, One Shields Avenue, University of California Davis School of Medicine, GBSF 451 Health Sciences Drive, Room 6301, Davis, CA 95616.

Email: gakaysen@ucdavis.edu

Copyright © 2014 by the American Society of Nephrology
those in the general population. Increased oxidation of LDLs is associated with adverse cardiovascular outcomes, and evidence of protein and lipid oxidation (oxidative stress) seems to be closely linked with markers of inflammation. Within the MHD patient cohort, higher markers of inflammation and oxidative stress are associated with greater adverse outcomes. For these reasons, oxidative stress is theorized to play a large role in the morbidity and mortality of this population. It is logical, then, to consider the use of antioxidants in mitigating oxidative stress in these patients in order to improve cardiovascular outcomes.

In this issue of *JASN*, Himmelfarb et al. concluded a well-powered clinical trial to test the hypothesis that two dietary supplements (a mixture of tocopherols and α-lipoic acid [ALA], presumably a racemic mixture, administered in an appropriate dose) would alter secondary outcomes (products of oxidation and inflammatory biomarkers) in a cohort of MHD patients. This study resulted in a negative outcome, with regard to an effect not only on downstream inflammatory biomarkers but also on metabolites that should reflect an effect on oxidation, regardless of whether or not inhibition of the redox state of proteins should effect changes in inflammation or other downstream effects, such as sensitivity to erythropoietic agents.

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. 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. 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. 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, most large clinical trials in nondialysis patients have either observed no detectible therapeutic effect of tocopherols and other vitamin supplements on outcomes or, as in the case of β carotene or B vitamins, observed an increase in mortality.

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. 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. In addition, accumulation of oxidation products associated with aging is not associated with a decline in antioxidant enzymes. Finally, previous studies in healthy populations found that doses of ALA similar to those used by Himmelfarb et al. reduced urinary F2 isoprostane, suggesting that the dosages used in this study were within what would be expected to have a demonstrable antioxidative chemical effect, even if no therapeutic endpoints were achieved if MHD patients behaved as did patients without ESRD. However, alterations in the regulation of gene expression in aging and in CKD by mechanisms such as the reduction in NRF2, found both in aging and in CKD, may make the addition of exogenous antioxidants alone less effective as a way to reduce oxidative stress in these populations.

This study was designed to establish the effect of vitamin E and ALA on CRP, IL-6, and F2 isoprostanes and isofuranes, surrogate outcomes for clinical events known to be closely associated with these markers of oxidative stress and inflammation. The assumption that administration of an antioxidant would have an effect on IL-6 and CRP presumes a cause-and-effect link requiring that increased oxidation is responsible for initiation of the acute phase response. In MHD patients, the causes of inflammation are likely multifactorial and include, but certainly are not limited to, vascular disease, less than sterile water in dialysate, and alterations in gut perfusion lending toward change in permeability. An effect on erythropoietin response is further downstream from the inflammatory cascade, so again a lack of a change in erythropoietin sensitivity may not be unexpected. The lack of an effect on F2 isoprostanes and isofuranes suggests that more specific reducing reagents or more selective targeting for agents responsible for oxidative injury may be needed in this population. These findings suggest that oxidative injury associated with disease processes and aging are specific and are likely reflective of underlying imbalances in homeostatic processes, which are unlikely to respond to the introduction of nutrients that happen to be reducing agents not linked to the causal pathway of oxidative injury. The data from Himmelfarb et al. suggest that more basic research regarding the cause of increased protein and lipid oxidation is necessary to effectively design treatment strategies to reverse these processes.
DISCLOSURES

None.

REFERENCES


