'The Heart Never Grows Better by "AGE"; I Fear Rather Worse...'

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Patients with renal failure and in particular patients with end-stage renal disease under chronic hemodialysis are exposed to oxidative stress [1], which contributes to their increased risk for cardiovascular disease and accelerated atherosclerosis, major causes of death in these patients [2, 3]. In fact, a major consequence related to oxidative stress, which is amplified by hemodialysis, is the oxidation of lipoproteins, which is of critical importance for the dramatic increase of atherogenic risk in these patients [3]. In addition, increased oxidative stress, particularly the increased production of reactive oxygen species, which results from the hemodialysis-induced activation of endothelial cells lining the lumen of the blood vessels, affects vascular tone via its destruction of vasodilatory nitric oxide. This reduced availability of nitric oxide contributes to hypertension and cardiovascular remodeling, further increasing these patients' risk of cardiovascular disease.

A dialyzer with a membrane coated with vitamin E has been proposed for reducing oxidative stress [4], based on the ability of vitamin E to inhibit lipid peroxidation, which should then reduce oxidative stress and atherosclerosis [5–7]. This has been confirmed by another study [8], which used a molecular biology approach and documented that 6 months of treatment with a vitamin E-modified dialyzer resulted in reduced gene expression of p22^{phox} (a

subunit of NAD(P)H oxidase critical for superoxide generation), reduced plasma hydroperoxide and increased total antioxidant power.

In this issue, Baragetti et al. [9] evaluate the effect of vitamin E-coated dialyzers on the circulating level of advanced glycation end products (AGEs) in dialysis patients in a long-term clinical study. These authors report that shifting hemodialysis patients from the modified cellulose membrane to the vitamin E-coated membrane results in a significant reduction of total AGEs and pentosidine (free and protein-bound). Given the major role played by AGEs in endothelial dysfunction and cardiac remodeling of dialysis patients [10, 11], the study's assessment of flow-mediated dilatation to document the effect of vitamin E-coated membranes on the AGE level and the relationship of AGEs reduction with flow-mediated dilatation, albeit weakened by the lack of a baseline assessment, further strengthens the favorable impact of vitamin E-coated dialyzers on oxidative stress and endothelial dysfunction. The study of Baragetti et al. [9], however, leaves some areas unaddressed and questions that remain to be answered. While Baragetti et al. [9] show that vitamin E-coated dialyzers are effective in reducing the AGE level in treated patients, they suggest no possible mechanism for this reduction. Therefore studies should be set up starting from their results and examining patients on vitamin E-

coated dialyzers, in the light of reports regarding the effects of both vitamin E and vitamin E-coated dialyzers on oxidative stress and inflammation-related proteins at molecular and cellular levels, and how those might be linked both to reduction in AGEs levels and to the clinical consequences of this reduction, such as reduced cardiovascu-

lar complications, and to improved prognosis. The recent availability of a more biocompatible vitamin E-coated polysulphone membrane [12] may provide further information to improve heart and vascular health in hemodialysis patients.

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