Oxidative stress in chronic renal failure

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Introduction

Oxidative stress defines an imbalance between formation of reactive oxygen species (ROS) and antioxidative defence mechanisms. In view of the profound biological effects of ROS, in recent years numerous clinical and experimental studies focused on detection of signs of oxidative stress in renal patients. There is good evidence indicating that uraemia in general is associated with enhanced oxidative stress [1,2], and treatment of uraemic patients with haemodialysis or peritoneal dialysis has been suggested to particularly contribute to oxidative stress and reduced antioxidant levels in these patients [3,4]. The latter may result from haemodialysis membrane-induced activation of macrophages on the surface of dialysis membranes during the dialysis session. Loss or deficiency of antioxidant activity (e.g. vitamin E deficiency) could also contribute to enhanced oxidative stress in uraemia.

In this issue of Nephrology Dialysis Transplantation, Klemm et al. [5] investigate erythrocyte antioxidant capacity and formation of oxygen radicals in haemodialysis patients using the electron paramagnetic resonance method. Klemm et al. identified glutathione peroxidase as the prominent, highly effective radical-eliminating system in erythrocytes. As long as this system was intact, there was no difference between haemodialysis patients and controls; only when glutathione peroxidase was inhibited did erythrocytes of haemodialysis patients show a significant delay in the elimination of free radicals, indicating a defect in the antioxidant forces outside the glutathione peroxidase system.

A series of reports over recent years demonstrated signs of increased oxidative stress in renal and haemodialysis patients. However, the significance of enhanced oxidative stress in renal patients remains to be further elucidated in clinical endpoint studies. The latter is of particular importance since in non-renal patients, studies using antioxidant treatments to prevent vascular and other diseases revealed equivocal effects [6–9].

What generates oxidative stress?

It is generally accepted that ROS such as hydrogen peroxide (H$_2$O$_2$) or hypochlorous acid (HOCl), and free radicals such as superoxide (O$_2^−$), hydroxyl radical (OH), and nitric oxide (NO), are continuously formed in vivo [10]. Thus, detection of ROS per se does not yet define oxidative stress; however, in a situation where antioxidative defence mechanisms are attenuated, it is the imbalance between formation of ROS and defence mechanisms that creates oxidative stress. Renal sources for ROS are activated macrophages, vascular cells and various glomerular cells [1]. The balance between formation of ROS and antioxidative defence mechanisms depends on the activity of enzymes such as superoxide dismutases (SOD), catalase, NO-synthase, and, as emphasized in the study by Klemm et al. [5], glutathione peroxidase. This balance, however, is rather fragile, difficult to predict, and strongly dependent on environmental conditions [10], as illustrated in Figure 1: for example, once O$_2^−$ is formed, the activity of SOD will transform it to H$_2$O$_2$. H$_2$O$_2$, in the presence of sufficient catalase activity, will be converted to harmless H$_2$O and O$_2$. However, too much SOD relative to H$_2$O$_2$-removing catalase can be deleterious, giving rise to the formation of the highly reactive hydroxyl radical in the presence...
Antioxidant studies in uraemia

As mentioned above, studies using antioxidant treatment to prevent vascular and other diseases revealed equivocal effects in non-renal patients [6–9]. Since renal patients live under particularly pro-oxidative conditions [3], the question arises whether there may be particular benefit of antioxidant treatment for this subset of patients. Unfortunately, only a few antioxidant intervention studies with clinical endpoints have been published referring to renal patients. Two studies recently reported beneficial effects of vitamin E treatment on lipid metabolism, atherosclerosis, and cardiovascular disease (CVD) in haemodialysis patients. Mune et al. [27] used vitamin E coated cellulose membrane dialysers in end-stage renal disease patients for 2 years and measured oxidized LDL, LDL-malondialdehyde, and aortic calcification as an index for the progression of atherosclerosis. This treatment resulted in a significant reduction of LDL oxidation and reduced the progression of aortic calcification. In the SPACE study, the effect of high dose vitamin E supplementation (800 IU/day) on CVD was investigated in haemodialysis patients with pre-existing CVD [28]. In this high-risk population, vitamin E supplementation over 2 years resulted in a significant reduction of CVD end-points including myocardial infarction, without significant effects on total mortality and mortality from CVD. Thus, although the final word has not yet been spoken, there is already some evidence that antioxidant treatment is effective in the prevention of CVD in the high-risk population of haemodialysis patients, emphasizing the clinical impact of elevated oxidative stress in these patients.

Conclusion

Our knowledge about stimuli and sources of oxidative stress, and about its role as an important cofactor contributing to endothelial dysfunction, inflammation, atherosclerosis and glomerulonephritis has substantially increased over the last years. However, even though partial prevention of CVD by antioxidant treatment in haemodialysis patients could be achieved, no clinical end-point study using various antioxidant treatments was able to clearly show a beneficial effect on total mortality in non-renal or renal patients. Thus, a major task for the coming years will be to design effective antioxidant protocols and to analyse them in clinical intervention studies with hard end-points, including mortality, to prove whether the concept holds true.

References


23. Steinberg D. Clinical trials of antioxidants in atherosclerosis: are we doing the right thing? *Lancet* 1995; 346: 36–38


**Editor’s note**

See also original article by Klemm et al., pp. 2166–2171