

Antioxidants in the treatment of patients with renal failure

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Abstract

Renal failure is accompanied by oxidative stress, which is caused by enhanced production of reactive oxygen species and impaired antioxidant defense. The suggested therapeutic interventions aimed at reducing oxidative stress in chronic renal failure patients are as follows: 1) the use of biocompatible membranes, ultrapure dialysate, and removal of endogenous foci of infection; 2) haemolipodialysis, and electrolysed reduced water for dialysate preparation; 3) administration of antioxidants (α -tocopherol, ascorbic acid, N-acetylcysteine, reduced glutathione); 4) substances possibly affecting oxidative stress indirectly (erythropoietin, sodium selenite). As currently available data have, as yet, provided rather limited evidence for the clinical benefit of antioxidant interventions, at present it is untimely to give practical recommendations with regard to antioxidant treatment of patients with renal failure.

Key words: renal failure, oxidative stress, antioxidant treatment.

Introduction

Renal failure is accompanied by oxidative stress [1,2], which consists in the damage of biological structures by reactive

oxygen species due to their excessive generation and impaired efficiency of antioxidant defense mechanisms.

In renal failure patients enhanced reactive oxygen species production is underlain mainly by inflammation [3,4], malnutrition [3], presence of endogenous stable oxidants in the uraemic plasma [5]. In haemodialysis patients the additional stimulus for increased free oxygen radical production can be the haemodialysis procedure itself [6,7]. It is mainly due to inflammatory cell activation caused by insufficiently biocompatible membranes, which is amplified by various bacterial products passing across from the dialysate to the blood compartment [8,9]. Advanced age and diabetes are further factors increasing pro-oxidant activity in renal failure patients [4]. At the same time, impaired activities of endogenous enzymatic free radical scavengers (superoxide dismutase, glutathione peroxidase, catalase) and deficiency of non-enzymatic antioxidants (reduced glutathione, α -tocopherol, ascorbic acid, transferrin, albumin, 17β -oestradiol) aggravate the oxidative stress [1]. Moreover, antioxidant defenses insufficient to shut down the oxidative stress can lead to a chronic and vicious cycle of free radicals causing production of inflammatory mediators that in turn amplify the generation of reactive oxygen species. Either chronic or acute production of free radicals leads to the oxidative modification of lipids, arachidonic acid derivatives, carbohydrates, amino acids, proteins, and deoxyribonucleic acid [1]. In addition, it activates cellular signaling events regulating cell division [10], differentiation [11], and apoptosis [12].

There is growing evidence from experimental and clinical studies that in chronic renal failure oxidative stress can be considered as a potentially important source of patient morbidity and mortality. It may be implicated in the pathogenesis of atherosclerosis [2,13,14], malnutrition [2,13,14], anaemia [15], dialysis-induced amyloidosis [16], and possibly increased risk of cancerogenesis [17] in these patients. Therefore, for some time past various therapeutic interventions have been attempted in order to reduce oxidative stress in chronic renal failure in the hope to improve patient outcome. Therapeutic approaches to reduce oxidative stress in chronic renal failure patients

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Table 1. Directions of therapeutic interventions considered for reducing oxidative stress in chronic renal failure patients

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| A. Reduction of inflammatory cell activation: | |
| 1) | biocompatible dialysis membranes; |
| 2) | ultrapure dialysate; |
| 3) | removal of focal infections. |
| B. Removal of inflammatory mediators: | |
| 1) | haemolipodialysis; |
| 2) | electrolysed reduced water for dialysate preparation. |
| C. Administration of antioxidants: | |
| 1) | α -tocopherol; |
| 2) | ascorbic acid; |
| 3) | N-acetylcysteine; |
| 4) | reduced glutathione. |
| D. Substances possibly affecting oxidative stress indirectly: | |
| 1) | erythropoietin (?); |
| 2) | sodium selenite (?). |

are focused on the reduction of inflammatory cell activation, removal of inflammatory mediators and the use of antioxidants [8,9]. Measures considered to date to accomplish this aim are presented in *Tab. 1*.

Reduction of inflammatory cell activation

Reduction of inflammatory cell activation can be attained by the use of biocompatible dialysis membranes, ultrapure dialysate, and removal of focal infections.

Biocompatible dialysis membranes. Haemodialysis procedure performed with a biocompatible (e.g. polyacrylonitrile or polysulfone) dialysis membranes is known to reduce significantly intradialytic oxidative stress [7]. Therefore, one can expect that decreased production of active oxygen species would prevent overproduction of oxidized LDL and enhanced endothelial dysfunction, and, consequently, the risk of atherosclerosis with subsequent cardiovascular complications would be reduced. However, this has not, as yet, been confirmed conclusively, and convincing proofs for cause-effect relationship between membrane biocompatibility per se and accelerated atherosclerosis are still lacking.

Ultrapure dialysate. Reactive oxygen species were found to induce oxidative modification of β_2 -microglobulin amyloidosis, and thus, to favour the development of dialysis-induced amyloidosis [16]. Long-term observations disclosed that regular haemodialysis treatment with ultrapure dialysate was associated with a significant decrease in amyloidosis-induced carpal tunnel syndrome compared with pure dialysate [18]. However, it is not, as yet, known whether this phenomenon was affected by the reduction of intradialytic reactive oxygen species production with ultrapure dialysate only or by other factors.

Removal of focal infections. As infections induce oxidative burst of inflammatory cells, removal of focal (i.e. dental,

tonsillar, and other) infections, and preventive measures against vascular access infections are of importance.

Removal of inflammatory mediators

Among suggested measures aimed at removal of inflammatory mediators there are haemolipodialysis, and electrolysed reduced water.

Haemolipodialysis relies on the addition of liposomes to the dialysate during the standard haemodialysis procedure [8,9]. The liposomes of 250-300 nm in diameter are comprised of lyophilized soybean phosphatidylcholine bilayer with incorporated α -tocopherol, which form a unilamellar bilayer upon addition to dialysate [8,9]. At the same time, water-soluble ascorbic acid is added directly to the dialysate. These two antioxidants are used together to increase removal of hydrophobic toxins and inflammatory mediators on the one side, and to synergistically scavenge oxidants on the other side, thereby supporting the host's antioxidant defense system. Maintenance of the appropriate ratio between α -tocopherol and ascorbic acid is of crucial importance to avoid their pro-oxidant action. The preliminary experience with haemolipodialysis for the prevention of intradialytic oxidative stress is, however limited, though promising [9].

Electrolysed reduced water. During electrolysis of raw water the active atomic hydrogen with higher reducing activity is released on the cathode. Administration of the dialysate prepared from this electrolysed reduced water during haemodialysis efficiently scavenged hydrogen peroxide and hypochlorite, and ameliorated antioxidant status during one-month treatment [19].

Antioxidants

Among antioxidants α -tocopherol, ascorbic acid, N-acetylcysteine, and reduced glutathione were tried to modify oxidative stress in renal failure.

A-tocopherol. To date, α -tocopherol (vitamin E) was the most frequently used antioxidant to achieve adequate control of oxidative stress in chronic renal failure patients. Short- or long-term administration of vitamin E orally or intramuscularly has been reported to modify beneficially their oxidative status [20-26]. In addition, haemodialysis procedures performed with vitamin E bonded membrane not only ameliorated antioxidative defense [27-33], but also significantly reduced the percentage increase of the aortic calcification index [30], improved carotid intima-media thickness, viscosity and dysmorphism of the red blood cells [30], and haemolysis [32] with resultant reduction of erythropoietin requirements for the treatment of uraemic anaemia [29]. Haemodialysis by vitamin E-coated membrane also prevented dialysis-induced endothelial dysfunction [33].

Although observational studies suggested possible beneficial effect of vitamin E on cardiovascular complications, except for the CHAOS study [34] the vast majority of large placebo-controlled studies on non-renal population (GISSI [35], HOPE [36], SECURE [37], HPS [38]) were rather discouraging,

because they failed to demonstrate a positive effect of vitamin E on cardiovascular event rates.

Meanwhile, the first double-blind placebo-controlled randomized SPACE study [39] performed on 196 haemodialysed patients disclosed a significant decrease in combined cardiovascular event rates in the group of orally treated with vitamin E 800 IU/day over 2 years, but no significant differences in overall mortality and mortality from cardiovascular disease were observed. However, in view of negative influence of vitamin E on the blood serum level of protective HDL₂ cholesterol, its safety in the long-term antioxidative treatment needs to be determined [2].

Ascorbic acid represents one of the most prominent antioxidants, exerting beneficial effects by an inhibition of lipid peroxidation and by reducing endothelial dysfunction [40]. Although in chronic renal failure patients deficiency of vitamin C can be observed, its administration in these patients requires deliberation. Vitamin C in food or as supplementation may lead to its excessive serum levels, resulting in hyperoxalaemia that may contribute to vascular disease in uraemic patients [41]. In addition, in the presence of transition metals like iron, ascorbate may give rise to an increased generation of antioxidants, and ascorbylation may impose additional carbonyl stress to uraemic patients, particularly in the presence of high blood glucose levels [40]. Therefore, 60 mg of oral vitamin C are currently recommended for chronic kidney patients [42], while in case of suspected subclinical ascorbate deficiency 1-1.5 g of oral vitamin C per week or 300 mg parenteral ascorbate per dialysis session are recommended, respectively [43].

N-acetylcysteine. In the recently published randomized controlled trial [44], treatment with the reduced thiol-containing antioxidant N-acetylcysteine (600 mg orally twice a day for a median of 14.5 months) significantly reduced cardiovascular events by 40% in the treated group compared with the placebo group. However, no effect was reported on total or cardiovascular mortality.

Reduced glutathione. Intravenous administration of exogenous reduced glutathione (tationil) alone [45] or in combination with the use of vitamin E bonded dialysis membrane [46] significantly improved uraemic anaemia. Some investigators [46] believe that combined use of the vitamin E bonded membrane and intravenous reduced glutathione seems to be the best antioxidant therapy so far, with significant saving of recombinant human erythropoietin dose.

Substances with possible indirect antioxidant action

Also some substances with possible indirect antioxidant action, e.g. erythropoietin, and sodium selenite, seem to be helpful for antioxidant treatment in renal failure.

Though erythropoietin is not an antioxidant, it is suggested that in chronic renal failure it can reduce oxidative stress indirectly by the correction of uraemic anaemia, and consequently, the rise in glutathione content in the blood. However, up-to-date reported studies did not provide univocal results. During recombinant human erythropoietin therapy some authors did

not found significant changes in the oxidative stress intensity [47] or antioxidant status [48], while others observed positive effects [49-51].

Selenium deficiency, frequently observed in chronic renal failure patients [48], may contribute to the impairment of activity of glutathione peroxidase, an enzymatic antioxidant belonging to selenoproteins. Correction of selenium deficiency by sodium selenite given intravenously [52] significantly increased red blood cell glutathione peroxidase activity, while seleno-rich yeasts given orally did not affect this enzyme activity [53]. Influence of selenite supplementation on other components of the antioxidant system remains unclear.

Conclusions

There are many prerequisites suggesting possible beneficial effects of therapeutic interventions aimed at reducing oxidative stress in chronic renal failure, and the recently published results of two randomised placebo-controlled clinical trials [39,44] are particularly promising in this respect. However, according to Steinberg and Witztum [54] several crucial questions still remain unanswered: 1) have the clinical trials been done with the right antioxidants at the right doses? 2) was the effectiveness of these antioxidants investigated properly? 3) are the right markers for oxidative stress and for the effectiveness of the antioxidants identified? 4) were the patients for the antioxidative therapies chosen accurately? 5) have the trials been started early enough, and have they lasted long enough? 6) are the species differences such that the results in animal models do not extrapolate to humans? Answering these questions will enable to design suitable antioxidant protocols and to evaluate their effectiveness in chronic renal failure. As currently available data have, as yet, provided rather limited evidence for clinical benefit of antioxidant interventions, at present it is untimely to give practical recommendations with regard to antioxidant treatment of patients with renal failure.

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