Invited Comment

Has the time come to use antioxidant therapy in uraemic patients?

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Keywords: antioxidants; arteriosclerosis; cardiovascular disease; dialysis; oxidative stress; vitamin E

Introduction

Oxidative stress and inflammation currently resound throughout the scientific community as risk factors for arteriosclerosis and cardiovascular diseases. Already more or less reasonable recommendations appear in various lay-media, providing suggestions of how to prevent arteriosclerosis by antioxidative strategies, including, for example, daily consumption of red wine containing antioxidative tannins, or daily administration of vitamin E. What currently is the evidence for antioxidative treatment? Are there any validated recommendations particularly for uraemic patients bearing a high risk for arteriosclerosis and cardiovascular diseases? These questions will be addressed in the following.

Pathophysiological background

In the western world, cardiovascular diseases are the most common cause of death, not only for the general population but also for renal patients. Although development of cardiovascular diseases emerges from various factors, arteriosclerosis is accused of playing a crucial role in most of these patients. In recent years, arteriosclerosis has been recognized more and more as a chronic inflammatory process [1]. There is convincing clinical and experimental evidence that formation of reactive oxygen species (ROS) is augmented during this chronic inflammatory process due to an imbalance between synthesis of ROS and neutralizing antioxidative defence mechanisms [2]. During inflammation, increased synthesis of ROS, for example, results from myeloperoxidase-catalysed reactions in phagocytes. In this context, ROS production reflects a host defence mechanism against pathogens. Antioxidative potential is also impaired during inflammation, for instance through decreased $\alpha$-tocopherol levels or reduced thiol groups associated with proteins such as serum albumin [3]. Enhanced oxidative stress has a major impact on cardiovascular function. It is a crucial factor responsible for endothelial dysfunction in cholesterol-fed animals [4]. The same mechanisms seem to induce diminished flow-dependent vasodilatation in forearm arteries of hypercholesterolaeamic patients [5]. Endothelial dysfunction, further characterized by increased endothelial permeability, expression of adhesion molecules, and attachment and invasion of monocytes, is deemed to represent an early stage of arteriosclerosis, appearing long before noticeable macroscopic signs of advanced arteriosclerotic lesions. Associated with these early stages of arteriosclerosis is the oxidative modification of low-density lipoproteins (LDLs) within the vessel wall, a prerequisite for the formation of foam cells seen in arteriosclerotic lesions resulting from the uptake of oxidized LDL by monocytes/macrophages [6].

Oxidative stress and cardiovascular diseases in renal patients

Established cardiovascular risk factors such as hypercholesterolaemia and hypertension were found to have only a low predictive value in the subset of dialysis patients [7]. Instead, inflammation and malnutrition were found to be strongly correlated with cardiovascular events in these patients [8]. Although these findings are not completely understood, elevated C-reactive protein (CRP) levels, found in 30–50% of dialysis patients as an inflammation marker, emerge increasingly as a predictive factor with high power, and are also associated with increased oxidative stress in these patients [9]. Potential sources of inflammation in dialysis patients

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Antioxidant therapy in uraemic patients

are not only catheters, grafts and shunts, but also the activation of macrophages by dialysis membranes [10]. Furthermore, malnutrition contributes to increased oxidative stress in renal and dialysis patients [11]. Adding to this harmful situation, diminished uptake of exogenous antioxidants such as tocopherol and ascorbate reduces the antioxidative potential in dialysis patients. Dialysis treatment aggravates decreased antioxidant levels by their filtration into the dialysate [12]. Additionally, malnutrition leads to reduced endogenous synthesis of antioxidants such as albumin, usually containing large amounts of antioxidative thiol groups [13]. Consequently, hypoalbuminaemia results in increased lipid peroxidation initiated by oxidative stress. Therefore, in renal patients with proteinuria, the disastrous combination of hypercholesterolaemia, hypoalbuminaemia and increased lipid peroxidation may contribute to their high cardiovascular risk. Taken together, many renal patients have to deal with enhanced oxidative stress early in the course of their disease and throughout renal replacement therapy, making antioxidative treatment a reasonable therapeutic approach particularly for uraemic patients. But is it really effective?

Clinical investigations with antioxidative treatment and endothelial dysfunction as end point

Antioxidants indeed can improve endothelial dysfunction as demonstrated for vitamin C in patients with coronary vascular disease [14], renovascular hypertension [15] or hypercholesterolaemia [15]. Considering the predictive value of endothelial dysfunction for the incidence of cardiovascular diseases, one could be encouraged by these results to treat those patients at risk with antioxidants. But what is the evidence for antioxidative treatment when looking at hard endpoints such as mortality and cardiovascular events in prospective controlled trials?

Clinical investigations with antioxidative treatment and hard end points in the general population

Since observational studies in the 1990s suggested a beneficial impact of nutritional vitamin E consumption on cardiovascular event rates [16], several large placebo-controlled studies were attempted to investigate the effect of vitamin E alone and in combination with other antioxidants on cardiovascular event rates. For the general, non-renal population, the vast majority of these studies failed to demonstrate a positive effect of antioxidants on cardiovascular event rates, as shown by the GISSI study [17], the HOPE study (Heart Outcomes Prevention Evaluation Study) [18], the SECURE study (Study to Evaluate Carotid Ultrasound changes in patients treated with ramipril and vitamin E) [19] and the HPS study (Heart Protection Study). The latter even investigated the combined effect of 600 mg of vitamin E, 250 mg of vitamin C and 20 mg of β-carotene administered daily in 20,536 patients, but nonetheless failed to show a benefit of this treatment [20]. Only the CHAOS study (Cambridge Heart Antioxidant Study) [21] suggested a beneficial effect of α-tocopherol on cardiovascular event rates. Recently, it has been reported that antioxidative treatment with vitamins E and C may even be potentially harmful because these vitamins blunt the protective HDL cholesterol response to HDL cholesterol-targeted therapy [22].

Clinical investigations with antioxidative treatment and hard end points in dialysis patients

As a result of the combination of the underlying, often inflammatory, disease, of uraemia and of the treatment modalities, dialysis patients are particularly exposed to enhanced oxidative stress [23–25]. Thus, this group of patients might have a greater benefit from antioxidative treatment as compared with the general population. Accordingly, several trials were undertaken to test the effectiveness of antioxidative treatment on surrogate parameters of oxidative stress in uraemic patients. As an example, use of a vitamin E-coated cellulose membrane dialyser for up to 2 years resulted in a significant reduction in oxidatively modified LDL compared with the ordinary cellulose membrane dialyser, and significantly reduced the percentage increase of the aortic calcification index after 24 months compared with the controls [26]. In another study, haemodialysis by vitamin E-coated membrane prevented dialysis-induced endothelial dysfunction and increased in oxidized LDL [27]. However, to our knowledge, controlled studies with hard cardiovascular end points using vitamin E-coated dialysers are not available at present.

Therefore, the SPACE study (Secondary Prevention with Antioxidants of Cardiovascular disease in End-stage renal disease) attracted great attention when it was published in the Lancet 3 years ago, because it was the first study with hard end points using oral antioxidative treatment. An Israeli group administered 800 IU of vitamin E daily in 196 haemodialysis patients [28]. The primary end point of this placebo-controlled study was a combination of myocardial infarction, angina pectoris, cerebral ischaemia and peripheral vascular sclerosis. Secondary end points were these cardiovascular events individually and overall mortality. Although this study demonstrated no significant difference on overall mortality, there was a significant decrease in combined cardiovascular events in the group treated with vitamin E. Further studies will have to confirm these results in a larger group of uraemic patients, although the difference in outcome compared with the general population could be explained by increased oxidative stress in the end-stage renal disease population that may...
counterbalance potentially harmful effects as discussed above [22]. However, it should be pointed out that the safety aspect of antioxidative treatment must be analysed further. Potential danger can come not only from a negative influence of vitamin E on the level of protective HDL$_2$ cholesterol, but also from, for example, vitamin C overdosing. It has been reported already many years ago that vitamin C in food or as supplementation may lead to excessive serum levels of vitamin C, resulting in hyperoxalae- mia that may contribute to vascular disease in uraemic patients [29].

Open questions

In view of the largely negative results with anti- oxidant trials—at least in the general population—one might be tempted to close the book on the antioxidative treatment issue. However, before doing so, one has to ask the question of whether we are doing the right thing. Steinberg, who was actively involved in the development of the initial concepts on which the antioxidative treatment trials were based, criticized the reports on antioxidative treatment in an article published recently in Circulation [30]. Accordingly, there are several crucial questions still unanswered:

(i) Have the clinical trials been done with the right antioxidants at the right dosages?
(ii) Was the effectiveness of these antioxidants investigated properly?
(iii) Are the right markers for oxidative stress and for the effectiveness of the antioxidants identified?
(iv) Were the patients for the antioxidative therapies chosen accurately?
(v) Have the trials been started early enough, and have they lasted long enough?
(vi) Are there species differences such that the results in animal models do not extrapolate to humans?

These questions have to be addressed to develop the scientific basis for the design of further studies necessary finally to prove, or disprove, the effectiveness of antioxidative treatment in the prevention of cardiovascular events.

Conclusion

Currently, one would have to advise against anti- oxidative therapies in the general population for primary/secondary prevention of cardiovascular events. In view of the SPACE study, one could be more optimistic in recommending antioxidative treatment for prevention of cardiovascular diseases for the subset of uraemic patients. At least a treatment with 800 IU of vitamin E daily appears to be safe. It might even be beneficial in the prevention of primary/secondary cardiovascular events in renal patients. However, it has to be pointed out that the chapter of antioxidative treatment is by no means closed at present. New studies with a better design and/or more appropriate statistical power are needed for the general population, and also for the subset of uraemic patients.

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