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Review Article

The therapeutic implications of oxidative stress in patients receiving haemodialysis

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Introduction

Oxygen-derived free radicals are highly reactive chemical species containing an unpaired electron. They are capable of reacting with lipids, proteins and nucleic acids and are thought to have a major role in the pathogenesis of a variety of diseases including atherosclerosis, diabetes and cancer. Antioxidants protect and limit free radical damage and it is the balance between free radical activity and antioxidant mechanisms that determine the potential for tissue damage [1,2]. Oxidative stress exists when there are either low levels of these antioxidants or increased production of reactive oxygen species (ROS).

In chronic renal failure patients there is a high incidence of premature cardiovascular disease [3] which despite advances in renal therapy, remains one of the leading causes of death in patients with end-stage renal failure. This can be partly explained by the increased prevalence of the major cardiovascular risk factors, including diabetes, hypercholesterolaemia and hypertension. However despite this, a significant proportion of the increased cardiovascular risk remains unexplained.

Oxidative stress may play a role in atherogenesis as it is thought that oxidation of polyunsaturated fatty acids in plasma lipids, particularly in low density lipoproteins (LDL), leads to modification of lysine residues on apolipoprotein B. The resulting modified LDL particle can be taken up by the

macrophage scavenger receptor in the arterial wall [4,5], resulting in the formation of foam cells, a key early step in the initiation of the atherosclerotic plaque.

This paper reviews the evidence for oxidative stress in patients with chronic renal failure, notably in those requiring maintenance haemodialysis. In addition the important therapeutic options are discussed.

Evidence for ROS production

Many studies have shown that chronic renal failure (CRF) patients exhibit an increased production of ROS [6]. This process is exacerbated by haemodialysis (HD) [7,8]. There are a number of potential sources of increased radical production in CRF.

Advanced glycation endproducts (AGE) and hypertriglyceridaemia

Diabetes and chronic renal failure share similar disease mechanisms. Diabetes is known to be associated with glycated proteins undergoing reactions leading to increased radical production [9,10]. Advanced glycation endproducts are also increased in patients with CRF and may participate in oxidative reactions [11]. The accumulation of AGEs in uraemic plasma proteins is not correlated with increased glucose. This can be explained by increased plasma concentrations of small reactive carbonyl precursors of AGEs resulting from increased oxidation of carbohydrates and lipids [12].

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Hypertriglyceridaemia in diabetics can increase monocyte free radical production [13,14]. CRF patients frequently have hypertriglyceridaemia which may contribute to production of ROS.

HD membrane bioincompatibility

There is evidence that exposure to particular HD membranes can cause an inflammatory reaction and bioincompatibility. In one study 37 patients with acute renal failure using a polymethylacrylate (PMA) membrane were compared with 35 using a cuprophane membrane [15]. 62% of patients using the PMA membrane recovered renal function independent of dialysis compared with 37% in the cuprophane group and median days of dialysis was 5 compared with 17. A further report comparing cuprophane membranes with a noncellulosic membrane (polyacrylonitrile AN 69, PAN) revealed a reduction of complement C3a and leukotriene B4 in the PAN group [16]. HD membrane-induced activation of phagocytes and the production of ROS has been shown to increase using chemiluminescence [17,18].

This indicates that membrane incompatibility activates complement and neutrophils which in turn triggers the release of ROS. Bioincompatibility represents an important source of ROS formation: namely the superoxide anion and its metabolites (hydrogen peroxide and the hydroxyl radical) [19,20] and hydroperoxides released enzymatically from arachidonic acid [21,22].

In addition, it has been suggested that the superoxide generated during HD can react with bicarbonate to form the toxic carbonate and formate radicals which are capable of causing lipid peroxidation and endothelial injury [23].

Iron supplementation

Iron supplementation is often indicated for the treatment of anaemia in CRF patients. The oxidative metabolism of LDL is related with intracellular iron metabolism [24] and there is increased lipid peroxidation in red blood cells in patients on HD treated with iron [25].

Depletion of antioxidants

Despite the above mechanisms for the generation of ROS, LDL oxidation would be minimised if it were adequately protected by antioxidants.

Antioxidant enzymes such as superoxide dismutase, catalase and glutathione peroxidase are preventive antioxidants, because they eliminate species involved in the initiation of free radical chain reactions. There is some controversy in the literature as to whether activity of these enzymes is increased

or decreased or unchanged with decline in renal function [26-30].

Vitamin C

Vitamin C is considered to be the first line of defence against ROS. Vitamin C has been shown to scavenge aqueous superoxide and hydroxyl radicals and act as a chain-breaking antioxidant in lipid peroxidation. Vitamin E will not be affected until vitamin C is depleted [31].

There is a low basal plasma concentration of vitamin C in HD patients, which further decreases during an HD session [27,32]. During HD plasma vitamin C drops to approximately 50% of the basal value and takes 44 hour to return to initial levels [33]. Therefore there is an increased need of vitamin C supplementation in HD patients to avoid critically low vitamin C concentrations [27,34,35].

Vitamin E

Vitamin E is a generic term to describe at least eight compounds that exhibit the biological activity of alpha-tocopherol. Vitamin E deficiency may be exacerbated by a deficiency of selenium (a necessary cofactor for glutathione peroxidase). ROS generated during lipid peroxidation extract hydrogen ions from vitamin E. Following interaction with ROS, vitamin E can be regenerated using ubiquinol, reduced glutathione or vitamin C. Vitamin E concentration in erythrocytes and mononuclear cells are low in HD patients despite normal plasma levels [36-38].

Glutathione

Reduced glutathione (GSH) is a tripeptide (structure L-glutamyl-L-cysteinylglycine) with major antioxidant properties. It protects tissues from xenobiotic oxidants and reactive electrophiles that result in free radical injury. In all mammalian cells the concentration of GSH is high (millimolar range) despite variation in the biological half-life; less than one hour in kidney compared to several days in erythrocytes.

GSH concentration closely correlates with the degree of renal failure [39]. There is evidence of low levels of whole blood and erythrocyte levels of glutathione in haemodialysis and peritoneal dialysis patients [40]. Therefore, oxidative stress may occur as a result of the GSH deficiency in CRF.

Treatment with antioxidants

Vitamin C

Vitamin C has complex interactions with iron metabolism, leading to enhanced mobilization from

storage sites. Vitamin C acts as a reducing agent, allowing iron release from ferritin [41] and haemosiderin [42] pools. As a result it has been reported that vitamin C supplementation may alleviate resistance to erythropoietin that sometimes occurs in iron overloaded patients [43]. However care with dosage is important as supplementation with 3 grams per week or more of vitamin C can lead to complications with deposition of calcium oxalate [44].

Vitamin E

Thus far, three clinical trials have studied the effect of vitamin E supplements on coronary heart disease and have shown evidence of reduced morbidity [45-47]. The enhanced oxidative susceptibility of small dense LDL appears to be related to reduced content of vitamin E or a reduced vitamin E to polyunsaturated fatty acid ratio [48].

Fish oil has been thought beneficial to many clinical studies with suggested actions on alteration in cytokine and eicosanoid production and decreased platelet aggregation [49]. Fish oil supplements (15g/day) reduce circulating vitamin E levels via increased vitamin E utilization and decreased gastrointestinal absorption. Fish oils are also highly enriched in unsaturated fatty acids. Thus, greater quantities of vitamin E may be needed to protect LDL from oxidation in these patients. Utilization of fish oil and vitamin E improves the plasma lipid and lipoprotein profile in HD patients [50] and the combination may prove a means of reducing atherosclerosis-related morbidity and mortality in HD patients.

Oral supplementation with vitamin E has been reported to improve the haematocrit [36] and reduction in dosage of erythropoietin needed to maintain a stable haemoglobin in HD patients [51]. Intracellular vitamin E in HD patients are lower than in healthy subjects and erythrocyte vitamin E concentrations are further decreased with erythropoietin treatment. This may be explained by a direct effect from erythropoietin per se or most probably due to iron supplementation administered to the patients [25].

Similarly lipid peroxidation in both platelets and peripheral blood mononuclear cells is increased in patients on HD; vitamin E supplementation results both in improved platelet function and altered immune response [37,52,53].

A vitamin-E-modified cellulose (CL-E) haemodialysis membrane has been reported to reduce lipoperoxidation in plasma and red blood cells. It is suggested that CL-E membranes reduce the effect of bioincompatibility on the generation of ROS and resulting oxidative stress [54].

Glutathione

Administration of reduced glutathione appears to ameliorate the intraerythrocyte oxidative defence. One study suggests glutathione increases red blood cell survival and reduces the dose of erythropoietin in the treatment of anaemia in CRF [55]. Increased oxidised glutathione in CRF may react with haemoglobin and cause protein aggregation in erythrocytes. These alterations cause haemolysis and could play a role in the pathogenesis of anaemia in haemodialysed patients [56].

Others antioxidants

Carotenoids are also chain breaking antioxidants but have yet to prove of value in supplementation. Less than 10% of these compounds can be metabolised to retinal and function as vitamin A. Vitamin A concentrations are significantly raised in HD patients due to reduced renal excretion [57]. Vitamin A has been shown to be at least as effective as vitamin E as an antioxidant in vitro studies. However this has not been proven clinically. Vitamin A has been given to CRF patients but in combination with vitamins C and E with improvement in markers of oxidative stress [58,59].

Conclusion

The generation of ROS and depletion of key chain-breaking and enzymatic antioxidants present in HD patients produces oxidative stress and subsequent increase in the development of atherosclerosis. Supplementation with antioxidants improves markers of oxidative stress. Although the number of studies are small, there is evidence of a beneficial effect of antioxidants on clinical outcome. An antioxidant cocktail should therefore be considered for clinical trials in patients with CRF who require HD.

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