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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 apolipoprtoein 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 maintainence haemodialysis. In addition the important therapeutic options are discussed.

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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 hypertrigyceridaemia

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].

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 inititation 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-cysteinelglycine) with major anti-oxidant 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) haemo-dialysis membrane has been reported to reduce lipoperoxidation in plasma and red blood cells. It is suggested that CL-E membranes reduce the effect of bioincompatability 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 erythropoetin 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.

References

1. Halliwell B. Free radicals and antioxidants: a personal view. Nutr Rev 1994; 52: 253-265.
2. Esterbauer H., Gebicki J, PuW H, Jurgens G. The role of lipid peroxidation and antioxidants in oxidative modification of LDL. Free Rad Biol Med 1992; 13: 341-390.
3. Brown JH, Short CD, Mallick NP. Ischaemic heart disease, lipids and the kidney. Contrib Nephrol 1993; 102: 198-219.
4. Steinberg D, Parthasarathy S, Carew TE, Khoo JC, Witztum JL. Beyond cholesterol: modification of lowdensity lipoprotein that increase its atherogenicity. N Engl J Med 1989; 320: 915-924.
5. Maggi E, Bellazzi R, Falasclii F, Frattoni A, Perani G, Finardi G, Gazo A, Nai M, Romariini D, Bellomo G. Enhanced LDL oxidation in uremic patients: An additional

mechanism for accelerated atherosclerosis? Kidney Int 1994; 45: 876-883.
6. Hasselwander O, Young IA. Oxidative stress in chronic renal failure. Free Rad Res 1998; 29: 1-11.
7. Westhuyzen, J. Adams, C E. Fleming, S J.Evidence for oxidative stress during in vitro dialysis. Nephron 1995; 70: 49-54.
8. Fiorillo C, Olivicro C, Rizzuti G, Nediani C, Pacini A, Nassi P. Oxidative stress and antioxidant defenses in renal patients receiving regular haemodialysis. Clin Chem Lab Med 1998; 36: 149-153.
9. Lyons TJ. Oxidised low density lipoproteins:a role in the pathogenesis of atherosclerosis in diabetes? Diabetic Medicine 1991; 8: 411-419.
10. Wolff SP, Jiang ZY, Hunt JV. Protein glycation and oxidative stress in diabetes mellitus and aging. Free Rad Biol and Med 1991; 10: 339-352.
11. Gugliucci A, Bendayan M. Renal fate of circulating advanced glycated end-products (AGE): Evidence for reabscorption and catabolism of AGE-peptides by renal proximal tubular cells. Diabetologia 1996; 39:149-160.
12. Miyata T, van Ypersele C, Kurokawa K. Alterations in nonenzymatic biochemistry in uremia: Origin and significance of 'carbonyl stress' in long-term uremic complications. Kid Int 1999; 55: 389-399.
13. Ranjadayalan K, Umachandran V, Davies SW, Synderc-ombe-Court D, Gutteridge CN, Timmis AD. Thrombolytic treatment in acute myocardial infarction: neutrophil activiation, peripheral leucocyte responses, and myocardial injury. British heart Journal 1991; 66: 10-14.
14. Propai L, Hiramatsu K, Saigusa Y, Nakazawa H. Low superoxide scavenging activity associated with enhanced superoxide generation by monocytes from male hypertriglyceridaemia patients with and without diabetes. Atheroselerosis 1991; 90: 9-47.
15. Hakin RM, Wingard RL, Parker RA. Effect of dialysis membrane in the treatment of patients with acute renal failuire. N Eng J Med 1994; 331: 1338-1342.
16. Sciff H, Lang SM, Konig A, Strasser T, Haider MC, Held E. Biocompatible membranes in acute renal failure: prospective case-controlled study. Lancet 1994; 344: 570-572.
17. Nguyen AT, Lethias C, Zingraff J, Herbelin A, Naret C, Descamps-Latscha B. Hemodialysis membraneinduced activation of phagocyte oxidative metabolism detected in vivo and in vitro within microamounts of whole blood. Kidney Int 1985; 28: 158-167.
18. Ritchey EE, Wallin JD, Shah SV. Cheniiluniinescence and superoxide anion production by leukocytes from hemodialysis patients. Kidney Int 1981; 19: 349-358.
19. Hinnnelfard J, Lazarus M, Hakim R. Reactive oxygen species production by monocytes and polymorphonuclear leukocytes during dialysis. Am J Kidney Dis 1991; 17: 271-276.
20. Cristol JP, Canaud B, Rabesandratana H, Gaillard I, Serre A, Nflon C. Enhancement of reactive oxygen species production and cell surface markers expression during hemodialysis. Nephrol Dial Transplant 1994; 9: 389-394.
21. Foidart JB, Davin JC, Malaise M, Saint-Remy M, MatWeu P. Stimulation of platelet lipoxygenase during hemodialysis. Kidney Int 1988: 33 [Suppl 24]: S80-S81.
22. Cristol JP, Canaud B, Damon M, Chavis C, Mion C. Platelet lipoxygenase stimulation and plateletactivating-factor production during hemodialysis. Prostaglandins Leukotrienes Essent Fatty Acids 1992; 45: 37-42.
23. Epperlein MM, Nourooz-Zadeh J, Jayasena SD, Hothersall JS, Noronha-dutra A, Neild GH. Nature and biological significance of free radicals generated during bicarbonate hemodialysis. J Am Soc Nephrol 1998; 9 (3): 457-463.
24. Van Lenten BJ, Prieve J, Navab M, Hama S, Lusis AJ, Fogelman AM. Lipid-induced changes in intracellular iron homeostasis in vitro and in vivo. J Clin I 1995; 95: 2104-2110.
25. Delmas-Beauvieux MC, Combe C, Penchant E, Carbo-nneau MA, Dubourg L, de Preeigout V, Aparico M, Clerc M. Evaluation of red blood cell lipoperoxidation in hemodialysed patients during erythropoetin therapy supplemented or not with iron. Nephron 1995; 69: 404-410.
26. Toberek M, Wasik T, Drozdz M, Klin M, Magner-Wrobel K, Kopieczna-Grzebieniak E. Effect of hemodialysis on lipid peroxidation and antioxidant system in patients with chronic renal failure. Metabolism 1992; 41: 1229-1232.
27. Loughrey C M, Young, I S, Lightbody J H, McMaster D, McNamee P T, Trimble E R. Oxidative stress in haemodialysis. QJM 1994; 87: 679-683.
28. Mimic Oka J, Siniic T, Ekinescic V, Dragicevic P. Erythrocyte glutatffione peroxidase and superoxide dismutase activities in different stages of chrordc renal failure. Clin Nephrol 1995; 44: 44-48.
29. Bonnefont Rousselot D, Jaudon MC, Issad B, Cacoub P, Congy F, Jardel C, Delattre J, Jacobs C. Antioxidant status of elderly chronic renal patients treated by continuous ambulatory peritoneal dialysis. Nephrol Dial Transplant 1997; 12: 1399-1405.
30. Cristol JP, Bosc JY, Badiou S, Leblanc M, Lorrho R, Descomps B,Canaud B. Erythropoietin and oxidative stress in haemodialysis: beneficial effects of vitamin E supplementation. Nephrol Dial Transplant 1997; 12: 2312-2317.
31. Jacob RA. The integrated antioxidant system. Nutr Res 1995; 15: 755-766.
32. Hultqvist M, Hegbrant J, Nilsson-Thorell C, Lindholm T, Nilsson P, Linden T, Hultqvist-Bengtsson U. Plasma concentrations of vitamin C, Vitamin E and/or malondialdehyde as markers of oxygen free radical production during hemodialysis, Clin Nephrol 1997; 47: 37-46.
33. Bohm V, Tiroke S, Scneider H, Sperschneider G, Stein G, Bitsch R. Vitamin C status of patients with chronic renal failure, dialysis patients and patients after renal transplantation. Internat J Vit Nutr Res 1997; 67: 262-266.
34. Sullivan JF, Eisenstein AB. Ascorbic acid depletion in patients undergoing haemcxfialysis. Am J Clin Nutr 1970; 23: 1339-1346.
35. Descombes E, Hanck AB, Fellay G. Water soluble vitaniins in chronic hemodialysis patients and need for supplementation. Kidney Int 1993; 43: 19-28.
36. Giardirii O, Taccone-Gallucei M, Lubrano R et al. Effects of alpha-tocopherol administration on red blood cell membrane lipid peroxidation in hemodialysis patients. Clin Nephrol 1984; 21: 174-177.
37. Taccone-Gallueei M, Giardini O, Ausiello C et al. Vitan-fin E supplementationin haemodialysis patients: effects on peripheral blood mononuclear cells lipid peroxidation and immune response. Clin Nephrol 1986; 25 (2): 81-86
38. Pastor MC, Sierra C, Bonal J, Teixid AEo J. Serum and erythrocyte tocophercol in uremic patients: effeet of haemodialysis versus peritoneal dialysis. Am J Nephrol 1993; 13: 238-243.
39. Ceballos Picot 1, Witko Sarsat V, Merad Boudia M, Nguyen AT, Thevenin M, Jaudon MC, Zingraff J, Verger C, Jungers P, Descamps Latscha B. Glutatffione antioxidant system as a marker of oxidative stress in chronic renal failure. Free Radic Biol Med 1996; 21: 845-853.
40. Ross EA, Koo LC, Moberly JB. Low whole blood and erythrocyte levels of glutathione in hemoffialysis and peritoneal dialysis patients. Am J Kid Dis 1997; 30: 489-494.
41. Bonkovsky HL. Iron and the liver. Am J Med Sci 1991; 301: 32-43.
42. Bridges KR, Hoffman KE. The effects of ascorbic acid on the intracellular metabolism of iron and ferritin. J Biol

Chem 1986; 261: 14273-14277.
43.Gastaldello K, Vereerstraeten T, Nzame-Nze, Vanhe-rweghem JL, Tielemans C. Resistance to erythropoictin in iron-overloaded haemoffialysis patients can be overcome by ascorbic acid administration. Nephrol Dial Transplant 1995; 10 [suppl 61]: 44-47.
44. Balcke P, Scmidt P, Zazgornik J, Kopsa H, Haubenstock A. Ascorbic acid aggravates secondary hyperoxaluria inpatients on chronic haemodialysis Annal Int Med 1984; 101: 344-345.
45. DeMaio SJ, King SB, Lembo NJ et al. Vitamin E supplementation, plasma lipids, and incidence of restenosis after percutaneous transluminal coronary angioplasty (PTCA). J Am Coll Nutr 1992; 1:68.
46. The ATBC Cancer Prevention Group. The effect of vitamin E and beta carotene on the incidence of lung cancer and other cancers in male smokers. N Engl J Med 1994; 330:1029.
47. Stephens NG, Parsons A, Scofield PM et al. Randoniised controlled trial of vitamin E in patients with coronary disease: Cambridge Heart Antioxidant Study (CHAOS). Lancet 1996; 347:781.
48. Tribble DL, van den Berg JJM, Motchnik PA et al. Oxidative susceptibility of low density lipoprotien subtractions is related to their ubiquinol-10 and alpha-tocopherol content. Proe Natl Acad Sci USA 1994; 91: 1183.
49. Donadio JV Jr, Bergstralh EJ, Offord KP et al. A controlled trial of fish oil in IgA nephropathy. N Engl J Med 1994; 331:1194.
50. Panzetta O, Corriinacini L, Garbin U, Fratta Pasini Ganunaro L, Bioanco F, Davoli A, Campagnola M, De Santis A, Pastorino AM, Lo Cascio V. Increased susceptibilty of LDL to in vitro oxidation in patients on maintenance hemodialysis:effect of fish oil and vitamin E administration Clin Nephrol 1995; 44: 303-309.
51. Cristol JP, Bosc JY, Badiou S, Leblanc M, Lorrho R, Descomps, Canaud B. Erythropoietin and oxidative stress in haemodialysis: beneficial effects of vitamin E supplementation. Nephrol Dial Transplant 1997; 12: 2312-2317.
52. Shurtz-Swirki R, Masffiach E, Kristal B, Shkolnik T, Shasha SM. Antioxidant enzymes activity in polymorphonuclear leukocytes in chronic renal failure. Nephol Dial Transplant 1995; 71 (2): 176-179.
53. Tacoone-Galluci M, Lubrano R, Del Principe D et al. Platelet lipid peroxidation in haemodialysis patients: effects of vitamin E supplementation. Nephrol Dial Transplant 1989; 4: 975-978.
54. Galli F, Rovidati S, CWarantini L, Campus G, Canestrari F, Buoncristiani U. Bioreactivity and biocompatibility of a vitan-iin E-modified multilayer hemodialysis filter. Kidney Int 1998; 54: 580-589.
55. Zachee P, Ferrant A, Deallemans R, Goosens W, Boogaerts MA, Lins RL. Reduced glutathione fro the treatment of anaemia during haemodialysis: A preliminary communication, Nephron 1995; 71 (3): 343-349.
56. Pasaoglu, H. Muhtaroglu, S. Gunes, M. Utas, C. The role of the oxidative state of glutatwone and glutathione-related enzymes in anemia of hemodialysis patients. Clin Biochem 1996; 29:567-572.
57. Penchant E, Carbonneau MA, Dubourg L, Thomas MJ, Perromat A, Vallot C, Clerc M. Lipoperoxidation in plasma and red blood cells of patients undergoing haemodialysis: vitaniins A,E and iron status. Free Radical Biol Med 1994; 16: 339-346.
58. Hassan, MQ. Hussain, SA. Zaki, MA. Alsharif, NZ. Stohs, SJ. Protective effects of antioxidants against uraenija-induced lipid peroxidationand glutatmone depletion in humans. Pharmacol Toxicol 1995; 77: 407-411.
59. Peuchant E, Demas-Beauvieux MC, Dubourg L, Thomas MJ, Perromat A, Aprico M, Clere M, Combe C. Antioxidant effects of a supplemented very low protein diet in chronic renal failure. Free Radic Biol Med 1997; 22: 313-320.