Free Rad. Res., Vol. 29, pp. 1–11
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Invited Commentary

Oxidative Stress in Chronic Renal Failure

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Accepted by Prof. B. Halliwell

(Received 3 October 1997; In revised form 28 October 1997)

Cardiovascular disease is the major cause of morbidity and mortality in chronic renal failure. The aim of this review is to summarise current evidence suggesting that there is increased free radical production, antioxidant depletion and changes in lipoprotein composition in renal failure which will lead to oxidation of LDL and hence to accelerated development of atherosclerosis.

INTRODUCTION

Cardiovascular disease is the main cause of death in patients with end-stage renal failure receiving renal replacement therapy.[1–5] In part this is attributable to an increased prevalence of the major cardiovascular risk factors, including diabetes, dyslipidaemia and hypertension. However, even after taking this into account a substantial proportion of the increased cardiovascular risk remains unexplained. It is now generally accepted that oxidation of LDL within the microenvironment of the arterial wall is a key early stage in the development of atherosclerosis.[6–8] Many of the cells present in the arterial wall can oxidise LDL, including endothelial cells, vascular smooth muscle cells and macrophages.[7] Alternatively, oxidation may be initiated by lipoxygenase enzymes[9,10] and promoted by transition metals which are available within plaques.[11] Other mechanisms which may be important contributors to LDL oxidation *in vivo* include myeloperoxidase, hypochlorous acid and peroxynitrite.[12] The oxidation of polyunsaturated fatty acids within LDL is followed by fragmentation and the release of aldehydes and ketones, such as malondialdehyde and 4-hydroxynonenal, which can modify key lysine residues on apoproteinB (apoB).[13] The modified apoB is no longer recognised by the apoB receptor, but instead taken up by the macrophage scavenger receptor. This leads to unregulated uptake of LDL cholesterol, the formation of foam

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cells and eventually results in a fatty streak, the first phase of an atherosclerotic lesion.

Oxidised LDL has a number of other properties which increase its atherogenicity. It is chemotactic for circulating monocytes and inhibits their migration after they have entered the arterial wall and differentiated into macrophages. In addition, it is cytotoxic to endothelial cells, promotes the production of a range of cytokines and growth factors, increases platelet aggregation and interferes with the action of endothelial derived relaxing factor (EDRF).[6–8] Oxidised LDL is immunogenic, and can cause the formation of autoantibodies against antigenic epitopes.[14,15] The presence of oxidative stress in chronic renal failure is supported by the presence of increased concentrations of lipid and protein oxidation products in plasma and cell membranes.[16–18] In view of the key role of LDL oxidation in atherogenesis, the purpose of this paper is to review the evidence that in chronic renal failure there is increased free radical production, antioxidant depletion and changes in lipoprotein composition which will lead to increased LDL oxidation and hence cardiovascular disease.

INCREASED FREE RADICAL PRODUCTION IN CHRONIC RENAL FAILURE

Free radical production in human tissues and fluids may arise as a result of normal physiological mechanisms, pathological processes or as a consequence of environmental influences. There are several potential sources of increased free radical production in chronic renal failure. The accumulation of a low molecular weight (<3000 Daltons) oxidising species in plasma has been described, although the nature of this species remains poorly defined. The oxidant can be removed from plasma by dialysis, and its activity is not decreased by aqueous phase antioxidants such as ascorbate and glutathione.[19] Neutrophils and the complement pathway may be activated during haemodialysis, particularly when cuprophane dialysis membranes are used, with a subsequent increase in the neutrophil free radical production.[20–23] Cellulosic membranes cause increased intracellular production of reactive oxygen species in granulocytes during the first 30 minutes of dialysis,[24] which may lead to endothelial cell injury[25] and consequently cause vascular damage.[26]

There is substantial evidence that increased oxidative stress plays a role in the development of complications in diabetes mellitus. There are a number of similarities between diabetes and renal failure, and they share common mechanisms which may contribute to increased free radical production. The processes of glycation and oxidation are now known to be intimately linked in diabetes, with glycated proteins undergoing reactions leading to increased free radical production.[27,28] Advanced glycation endproducts (AGE) also accumulate in the plasma of renal failure patients and may participate in oxidative reactions.[29] Hypertriglyceridaemia has been shown to increase monocyte free radical production in patients with diabetes.[30,31] As hypertriglyceridaemia is a common feature of dyslipidaemia in chronic renal failure, this mechanism may also contribute to increased radical production.

A further source of increased oxidative stress in chronic renal failure is iron overload.[16] Iron supplementation (oral or intravenous) is often indicated in end-stage renal failure to treat anaemia, which is considered to be mainly caused by decreased endogenous production of erythropoietin. In patients who are hyporesponsive towards treatment with recombinant human erythropoietin, iron supplementation is frequent.[32,33] The oxidative metabolism of LDL has been found to be linked with intracellular iron metabolism[34] and increased lipid peroxidation occurs in red blood cells in patients on haemodialysis treated with iron.[35]

ANTIOXIDANT DEPLETION IN CHRONIC RENAL FAILURE

While the mechanisms outlined above will lead to increased free radical production, LDL would

probably undergo little oxidation if it were adequately protected by antioxidants. Such protection is normally provided by antioxidants within the LDL particle (ubiquinol, tocopherol, perhaps carotenoids and flavonoids) and in the extracellular fluid (ascorbate, urate, protein thiols, antioxidant enzymes).[36]

There is substantial epidemiological evidence supporting the hypothesis that a high intake of antioxidant vitamins, such as vitamin A, C, E and β-carotene, is associated with reduced CHD mortality.[37] Gey *et al.* have found a strong inverse correlation between CHD mortality and dietary vitamin E.[38] The relationship between vitamin C and CHD mortality is less strong, but there may be a synergistic effect between vitamin C and E.[38] This has been confirmed by the finding that ascorbate may play a role in recycling tocopherol at the aqueous lipid interface.[39] Renal failure, however, is associated with significant depletion of key antioxidants,[16,40–42] and the combination of antioxidant depletion and increased free radical production is likely to be particularly harmful. Total antioxidant capacity assessed with an enhanced chemiluminescent assay is increased in chronic renal failure,[41] but this is mainly attributable to an increase in urate which masks important changes in other antioxidants.[41] These changes include reduced levels of β-carotene, lipid corrected α-tocopherol, lycopene and ascorbate.[16,40–42] In the presence of very low levels of ascorbate, as found in advanced renal failure, the urate radical cannot be easily recycled and may cause oxidative damage to a variety of biomolecules, so the elevated urate levels which lead to an increase in total antioxidant capacity in renal failure may paradoxically promote oxidative damage.

Several mechanisms are likely to contribute to reduced availability of nutritional chain-breaking antioxidants in renal failure. The requirement to restrict potassium intake means that as a consequence little fruit can be eaten, and this will contribute to very low levels of ascorbate and carotenoids. In the case of ascorbate, deficiency is augmented by removal during haemodialysis,[43] and loss of ascorbate also affects patients on continuous ambulatory peritoneal dialysis (CAPD).[44] Depletion of ascorbate may contribute to increased turnover of tocopherol in an oxidising environment as a result of impaired tocopherol recycling. There is also evidence indicating that there is loss of tocopherol during haemodialysis, although to a lesser extent than for ascorbate. Peuchant *et al.* have shown that a very low protein diet supplemented with vitamins A, C and E reduces the malondialdehyde content of erythrocytes.[45]

A second major feature of the diet required in advanced renal failure is restriction of protein intake. This has also been shown to have adverse consequences on antioxidant status, particularly resulting in selenium deficiency, and could also reduce glutathione synthesis by limiting amino acid availability. Selenium is a cofactor for glutathione peroxidase, an enzyme which is important in detoxifying hydroperoxides, and a reduced intake of selenium may therefore lead to reduced activity of glutathione peroxidase.[46] It has been shown that both serum selenium and glutathione peroxidase activity are reduced in patients with chronic renal failure.[47,48] Other studies, however, have suggested that selenium levels in renal failure patients are within the normal range.[49] This is likely to be due to varying dietary selenium content, as selenium status is largely dependent on geographic factors like soil selenium content.[50] Plasma glutathione peroxidase activity, however, is significantly decreased in chronic renal failure, even when serum selenium concentrations are within the normal range. This may be caused by reduced expression of glutathione peroxidase mRNA by the human kidney as a consequence of renal dysfunction.[49]

The activity of antioxidant enzymes may also be reduced in renal failure by a number of other mechanisms. Carbamylation is a process by which thiol groups and amino groups are modified as a result of reactions with urea-derived cyanate, and protein carbamylation is known to be increased in renal failure.[51–53] The ferroxidase activity of caeruloplasmin is inhibited by carbamylation,[54]

and it is possible that other enzymes are also affected. In diabetes, superoxide dismutase activity is inhibited by glycation leading to reduced activity,[55] and carbamylation is likely to have very similar effects. Glycation of enzymes, leading to reduced enzyme activities, may also occur in renal failure, despite normal blood glucose concentrations. Concentrations of advanced glycation end-products are elevated in end-stage renal failure,[56] and hence may result in reduction of antioxidant enzyme activity due to posttranslational modification. Some enzymes are known to be susceptible to oxidative damage,[57] and the increased free radical production in renal failure may also contribute to reduced enzyme activity. This has recently been confirmed by the findings of Witko-Sarsat *et al.* who have shown that uraemia leads to enhanced protein damage reflected in an increase of advanced oxidation protein products due to increased oxidative stress. The increased protein damage may lead to a loss of enzymatic properties of various proteins.[18]

DYSLIPIDAEMIA AND LIPOPROTEIN OXIDATION IN CHRONIC RENAL FAILURE

Changes in LDL and LDL Oxidation

The most common plasma lipid abnormality in patients with chronic renal failure is hypertriglyceridaemia, mainly caused by decreased catabolism of apoB-containing lipoproteins.[58–62] In chronic renal failure LDL cholesterol levels are unchanged or marginally increased.[60] The susceptibility of LDL to copper oxidation *in vitro* is widely used as an indicator of susceptibility of LDL to oxidation *in vivo*.[36] Surprisingly, however, the majority of studies assessing the susceptibility of LDL to oxidation in renal failure have suggested that it is not increased.[63–66] Several factors influence the susceptibility of LDL to oxidation *ex vivo*. Renal failure is characterised by a shift in the LDL subfraction distribution towards smaller, denser LDL, which will tend to increase susceptibility to oxidation. In contrast, LDL in renal failure may contain a higher percentage of monounsaturated fatty acids, which will tend to make LDL more resistant to oxidation.[63,67] The balance between these and other factors, such as the antioxidant content of the LDL, will determine the inherent susceptibility of the particle to oxidation.

In vivo the extent to which LDL oxidation will occur is influenced by factors other than the susceptibility of the particle to oxidation. In particular, the extent to which LDL oxidation will occur in renal failure will be influenced by the amount of time for which LDL is exposed to the oxidising environment of the arterial wall. LDL can freely pass from the arterial lumen across the endothelium and into the arterial wall, where it is taken up via the apoB receptor by various cells in order to meet their cholesterol requirement. Any factor which inhibits uptake of LDL by the apoB receptor will result in LDL having a greater residence time in the extracellular space of the arterial wall and will therefore lead to increased LDL oxidation. In chronic renal failure LDL levels are normal or slightly raised.[61] However, a number of qualitative changes in LDL occur which inhibit binding to the apoB receptor. This is reflected by the observation that the clearance of LDL is impaired in patients on conservative management for chronic renal failure.[68] Qualitative changes in LDL which impair recognition by the apoB receptor include triglyceride enrichment[69] and relatively minor degrees of carbamylation of apoB.[70,71] The presence of elevated levels of antibodies against oxidised LDL in renal failure suggests that, overall, increased LDL oxidation does occur,[72] and may play a role in accelerated atherogenesis.

Lipoprotein(a)

Lp(a) is a lipoprotein particle similar to LDL, but with an additional glycosylated protein (apo(a)). Increased levels of Lp(a) have been shown to be an independent risk factor for myocardial

infarction in the general population.[73] Its atherogenicity may be related to its ability to bind apoB containing lipoproteins and to be taken up by macrophages.[74] As a consequence Lp(a) can accumulate within the atherosclerotic plaque and undergo further modification, including oxidation. Lp(a) levels have been reported to be 2–3-fold increased in patients with chronic renal failure compared to healthy control subjects,[75,76] possibly due to reduced renal catabolism. Cressman *et al.* have shown that Lp(a) is an independent risk factor for clinical events attributed to atherosclerotic cardiovascular disease in patients with chronic renal failure undergoing haemodialysis.[77]

Changes in VLDL and VLDL Oxidation

In contrast to LDL cholesterol levels, VLDL and IDL levels are generally increased in chronic renal failure,[59] and the presence of β-VLDL has also been reported.[78,79] β-VLDL has been shown to promote foam cell formation *in vitro*;[80] oxidation of β-VLDL potentiates an already high rate of degradation by macrophages and is therefore likely to produce a particularly atherogenic particle.[81] Furthermore, oxidation of β-VLDL occurs in the presence of endothelial cells[82] and uptake of oxidised β-VLDL by macrophages is increased.[81] McEneny *et al.* have recently shown that VLDL isolated from patients undergoing haemodialysis generates more peroxidation products during copper-mediated oxidation than control VLDL.[83] Increased VLDL oxidation may therefore contribute to the increased cardiovascular risk in patients with chronic renal failure.

Changes in HDL and Antioxidant Capacity of HDL

Decreased levels of HDL are a characteristic finding in chronic renal failure.[58–60] There is a shift towards a preponderance of small lipid poor HDL particles due to a relatively greater decrease of HDL_2. The main apolipoproteins associated with HDL (apoA-I and apoA-II) are also reduced, and the apoC-III/apoC-II ratio is increased.[60] The increased apoC-III/apoC-II ratio leads to decreased activity of lipoprotein lipase (LPL), which as a consequence contributes to defective catabolism of triglyceride-rich lipoproteins. Decreased concentrations of apoA-I may be linked to reduced activity of lecithin cholesterol acyltransferase (LCAT) in patients with chronic renal failure. LCAT, which is associated with the apoA-I containing subfraction of HDL, catalyses the esterification of cholesterol and plays an important role in reverse cholesterol transport. This may lead to impaired conversion of HDL_3 to HDL_2, which explains the relatively greater reduction of HDL_2 levels and reduced transfer of cholesterol esters from HDL to VLDL.[60]

Epidemiological evidence has demonstrated a strong inverse correlation between plasma concentration of HDL cholesterol and the risk of atherosclerosis,[84] and renal failure patients with decreased HDL cholesterol appear to be at a particularly high risk of developing cardiovascular disease.[85] In general, this inverse correlation has been attributed to the role of HDL in reverse cholesterol transport. However, HDL has also been found to protect LDL against oxidation by transition metals,[86–88] to prevent the production of mildly oxidised LDL by arterial wall cells and to inhibit monocyte transmigration.[89] Two enzymes associated with the HDL particle, paraoxonase and platelet-activating factor acetylhydrolase (PAF-AH), have both been shown to inhibit LDL oxidation *in vitro*.[90,91] Paraoxonase and PAF-AH have been suggested to work in concert to protect against the production and activity of minimally oxidised LDL by facilitating hydrolysis of active oxidised phospholipids. As a consequence, the biologically active lipids in minimally oxidised LDL are destroyed and hence LDL loses its ability to induce endothelial cells to bind monocytes.[92,93] Thus, the inverse relationship between HDL and cardiovascular risk may be partly due to the prevention of LDL oxidation by HDL associated paraoxonase and PAF-AH.

There are two common paraoxonase phenotypes attributable to amino acid substitutions at position 55 and position 192 of the enzyme.[94,95] The 55 polymorphism is related to paraoxonase mass,[96] whereas the 192 polymorphism is related to paraoxonase serum activity.[94,95] One genotype of each polymorphism has been found to be linked with a higher risk of atherosclerosis in diabetic populations.[96,97] In patients with chronic renal failure undergoing dialysis paraoxonase has been found to be decreased,[98,99] whereas PAF-AH activity is similar in patients with chronic renal failure compared to age and sex matched healthy control subjects.[99] The paraoxonase phenotype distribution for the 192 polymorphism, which distinguishes between high and low paraoxonase activity was not found to be different between renal failure patients and control subjects.[99] It has been postulated that paraoxonase activity is reduced in chronic renal failure due to decreased paraoxonase mass, as HDL cholesterol levels are reduced, or due to post-translational modification of paraoxonase as a result of reactions with advanced glycation endproducts or urea-derived cyanate. Reduced paraoxonase activity in patients with chronic renal failure may give rise to decreased HDL anti-oxidant capacity. LDL modification by lipid peroxidation might therefore be increased, hence contributing to the accelerated development of atherosclerosis.

OTHER PRO-OXIDANT MECHANISMS IN CHRONIC RENAL FAILURE

Homocysteine

Homocysteine is a sulphur-containing amino acid formed from the demethylation of methionine. It can either be remethylated to methionine (transmethylation) or converted into cystathionine (transsulfuration). Homocysteine metabolism is dependent on the cofactors vitamin B_6, vitamin B_{12} and folic acid.[100] Several studies have linked elevated homocysteine levels and cardiovascular disease.[101,102] In the Physicians' Health study, a total of 14,916 US male physicians aged 40 to 84 were followed up for 6 years. Men with elevated baseline homocysteine levels had a three-fold increased risk for myocardial infarction.[103]

The mechanisms underlying the relationship between hyperhomocysteinaemia and cardiovascular disease are not fully understood at present. Among a number of atherogenic properties, an increase in LDL oxidation in the presence of elevated homocysteine levels has been suggested.[104–106] Homocysteine accumulates in plasma of patients with chronic renal failure,[107,108] and the increase in homocysteine levels correlates positively with the degree of reduction of renal function assessed by plasma creatinine levels. Elevated plasma levels of the mixed disulphide homocysteine-cysteine have also been found in 27 renal transplant recipients with stable, but subnormal, renal function.[109] The reason for increased homocysteine levels in chronic renal failure are unknown at present. Possible explanations seem to be reduced renal excretion[110] or decreased catabolism of homocysteine.[111] Folate supplementation has been shown to lower elevated plasma levels of homocysteine in patients with chronic renal failure;[111,112] however, whether folic acid supplementation is effective in reducing the incidence of atherosclerosis remains to be proved.

Use of Cyclosporine in Renal Transplant Recipients

The use of cyclosporine has significantly improved graft survival after renal transplantation.[113] Cyclosporine, however, has also been linked with the development of hypertension and hyperlipidaemia after kidney transplantation,[114,115] which may contribute to increased cardiovascular risk.[116] Furthermore, Apanay *et al.* have shown that cyclosporine increases the susceptibility of LDL to oxidation in renal transplant recipients. This is reflected in a significantly

reduced lag phase during *in vitro* oxidation. They have also reported a negative correlation between cyclosporine concentrations in LDL and the susceptibility of LDL to oxidation.[117] It has also recently been shown that a conversion from cyclosporine to azathioprine treatment reduces the susceptibility of LDL to oxidation and results in a more favourable lipid profile.[118] The molecular mechanism, however, by which cyclosporine causes the increase in the susceptibility of LDL to oxidation remains unclear at present and further studies of the effects of cyclosporine on LDL oxidation and its implications on atherosclerosis are needed.

CONCLUSIONS

In conclusion therefore, we propose that a number of mechanisms combine to increased oxidative stress, and hence increased oxidation of LDL in patients with renal failure (Figure 1), despite the fact that the *in vitro* susceptibility of LDL to oxidation is not increased. These include increased production of free radical species, depletion of key chain-breaking and enzymatic antioxidants, increased residence time of LDL within the arterial wall, a reduction in the antioxidant capacity of HDL and the accumulation of homocysteine. The combined result of these changes will be to substantially increase the development of atherosclerosis in the presence of chronic renal failure. Given the evidence of antioxidant depletion and accelerated atherogenesis, patients with renal failure might receive particular benefit from increased antioxidant intake. In view of the restricted diet required in advanced renal failure, this can be best achieved by the use of antioxidant supplements. Consideration should therefore be given to a clinical trial of antioxidant vitamin supplementation in renal failure, probably combined with B group vitamins to reduce homocysteine.

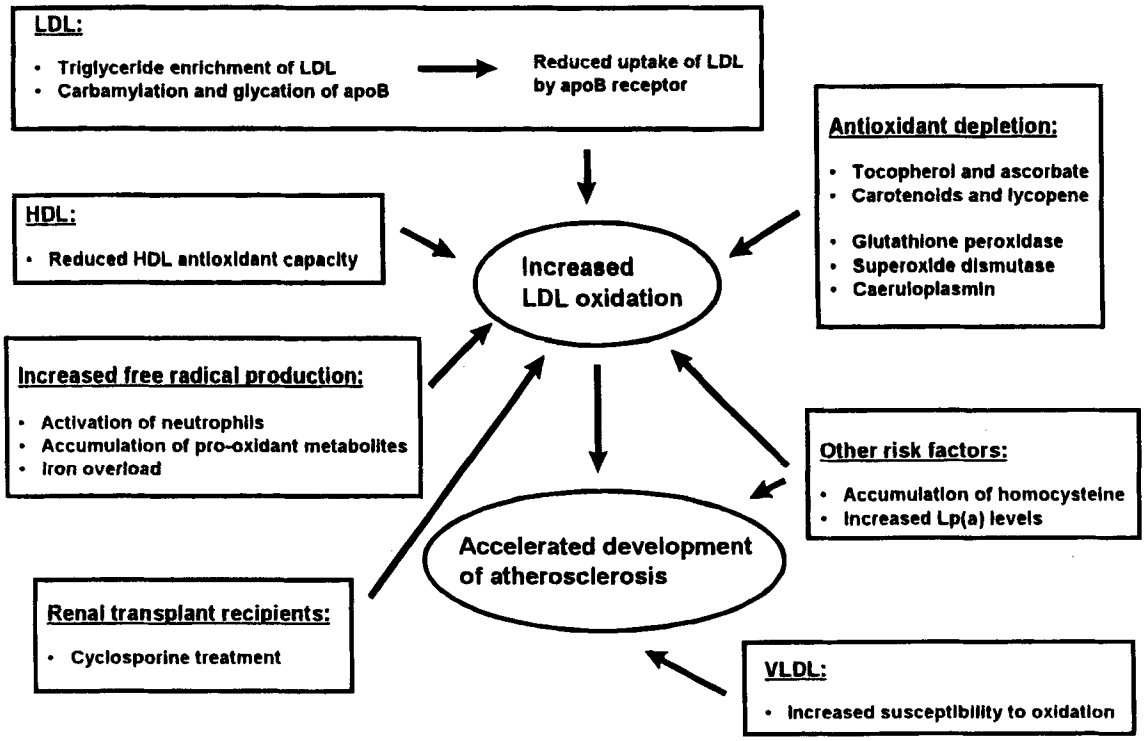

FIGURE 1 Mechanisms contributing to accelerated development of atherosclerosis in chronic renal failure.

Acknowledgements

We are grateful to the Northern Ireland Chest, Heart and Stroke Association and Deutscher Akademischer Austauschdienst for their support for our work in this area.

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