Lipid Abnormalities in Chronic Kidney Disease

Patients with chronic kidney disease (CKD) are at higher risk of cardiovascular disease (CAD) than subjects in the general population. An increased prevalence of both CAD morbidity and mortality is evident at all ages among patients with CKD.1,2 Traditional risk factors (such as dyslipidaemia, diabetes and hypertension) as well as non-traditional risk factors (including oxidant stress, inflammation and malnutrition, and also disturbances of serum Ca²⁺ and PO₄³⁻ metabolism) associated with CKD, may further increase CAD risk in these patients.1,3 Dyslipidaemia is common in CKD patients and alterations in serum lipid profile vary widely depending on the level of kidney function and the degree of proteinuria.4,5 Prior to developing severe CKD, patients frequently have elevated serum total and low-density lipoprotein (LDL) cholesterol levels. As CKD advances to kidney failure, the prevalence of high LDL cholesterol levels decreases. The classic lipid profile of late-stage CKD includes increased triglyceride levels, moderately elevated or normal LDL cholesterol levels and low high-density lipoprotein (HDL) cholesterol levels.4,5

The reduction in serum levels of HDL cholesterol represents an important lipid protein abnormality in patients with decreased renal function.4 Low levels of HDL cholesterol have also been shown to be an independent risk factor for CAD and premature atherosclerosis regardless of serum LDL cholesterol and triglyceride levels.6 HDL is a potent antatherogenic lipoprotein and recent observational, biological and clinical evidence strongly suggests that HDL is a promising target of therapeutic intervention.7,8 The cardioprotective effects of HDL have been attributed to its role in reverse cholesterol transport, its beneficial effects on endothelium and its antioxidant and anti-inflammatory activities.5 Significant in the antatherogenic effects of HDL are two enzymes associated with it: platelet-activating factor (PAF)-acyethylhydrolase (PAF-AH) and paraoxonase-1 (PON1).9,10

In a prospective, randomised, multicentre study performed on pre-dialysis patients, it was shown that long-term epoetin administration increases HDL cholesterol levels only in patient groups treated with keto acids.17

Effect of Epoetin on Serum High-density Lipoprotein Cholesterol Levels

Recombinant human erythropoietin (epoetin) is widely used to correct anaemia associated with CKD.11 Previous studies clearly document the beneficial effects of epoetin on patients with CKD, not only in correcting anaemia: various other beneficial effects were also reported.12 Studies attempting to investigate whether long-term epoetin administration in CKD patients has an effect on lipid profiles of patients provided inconsistent results. These studies focused on haemodialysis patients and showed that epoetin treatment either does not affect serum lipid levels13 or significantly improves the lipid profile by decreasing the serum levels of triglycerides, total cholesterol and LDL cholesterol.14,15 Importantly, it was demonstrated that the beneficial effect on lipid profile may be balanced and overcome in some patients who show exaggerated increase in food intake.15 Studies on the effect of long-term epoetin administration on serum HDL cholesterol levels in CKD patients have mainly concentrated on dialysis patients15,16 and have also provided inconsistent results. Furthermore, in a prospective, randomised, multicentre study performed on pre-dialysis patients, it was shown that long-term epoetin administration increases HDL cholesterol levels only in patient groups treated with keto acids.17

In a randomised controlled trial we had previously demonstrated that early initiation of epoetin therapy in pre-dialysis patients with CKD stages 3 and 4 and non-severe anaemia significantly slows the progression of renal disease and delays the initiation of renal replacement therapy,18 while preserving erythrocyte defence mechanisms against oxidative stress.19 In a nested substudy performed on the same patients we observed a significant increase in HDL cholesterol levels in patients receiving epoetin (see Figure 1A), whereas there was no effect of epoetin on the other lipid parameters. Consequently, there was a significant
These phospholipids contain oxidatively fragmented residues at the position of the glycerol backbone. Such phospholipids are formed containing a polyunsaturated fatty acyl moiety esterified at the position and are produced during peroxidation of phospholipids during LDL oxidation and are thought to play key roles in inflammatory injury. Oxidised phospholipids are also substrates for PAF-AH.

According to our previously published results, baseline CETP activity in patients with CKD was not influenced by epoetin treatment. Consequently, CETP may not be involved in the increase in HDL cholesterol levels observed in patients treated with epoetin. In CKD patients, epoetin-induced improvement in tissue oxygenation could play a contributory role in increased HDL cholesterol levels. This suggestion is supported by the positive correlation between the increase in serum HDL cholesterol levels and the increase in haemoglobin values observed in epoetin-treated patients. Increased tissue oxygenation may lead to an increase in activity of several enzymes and transferring proteins involved in HDL physiogenesis as well as in HDL maturation, and lead to the increase in HDL cholesterol levels. Furthermore, the epoetin-induced improvement in tissue oxygenation could also increase the exercise capacity of our patients. Although the physical activity of our patients was not considered in our previous study, we cannot exclude the possibility that it may have contributed to the increase in serum HDL cholesterol levels. It is well-documented that an increase in physical activity leads to increased HDL cholesterol levels and it is currently considered to be one of the most important non-pharmacological strategies in increasing serum HDL cholesterol levels.

**Effect of Epoetin on High-density Lipoprotein-associated Antithromogenic Enzymes**

HDL contains a variety of proteins and enzymes that play important roles in its antithromogenic activities. Among them the enzymes PAF-AH and PON1 may significantly contribute to HDL’s antioxidant and anti-inflammatory activities. PAF-AH exhibits a Ca²⁺-independent phospholipase A₂ activity and degrades PAF and oxidised phospholipids by catalysing the hydrolysis of the ester bond at the sn-2 position. Experimental studies in humans and animals indicate that PAF may be an important mediator of renal damage, suggesting that its production and action in the kidney may be unregulated in a diseased state. In the kidney, PAF is synthesised by infiltrating cells as well as by mesangial cells, and plays an important role in renal haemodynamic changes and in the recruitment of inflammatory cells into glomeruli as observed in glomerular immune injury. Oxidised phospholipids are also substrates for PAF-AH. These phospholipids contain oxidatively fragmented residues at the sn-2 position and are produced during peroxidation of phospholipids containing a polyunsaturated fatty acyl moiety esterified at the sn-2 position of the glycerol backbone. Such phospholipids are formed during LDL oxidation and are thought to play key roles in inflammatory reactions, particularly in vascular inflammation and atherosclerosis. Although the role of these phospholipids in CKD remains to be established, it has been shown that oxidised LDL is localised in the glomeruli of patients with glomerulonephritis and exhibits pro-inflammatory activities. Thus, by degrading PAF and oxidised phospholipids, PAF-AH may not only play a role in atherogenesis, but may also be involved in renal pathology.

PAF-AH in plasma forms a complex with lipoproteins, thus it is referred to as lipoprotein-associated phospholipase A₂ (Lp-PLA₂). In human plasma, PAF-AH is mainly associated with apoB-containing lipoproteins and primarily with LDL, whereas a small proportion of circulating enzyme activity is associated with HDL. Data from large Caucasian population studies demonstrated an independent association between plasma PAF-AH (primarily the LDL-associated enzyme) with CAD risk.

In this regard, the role of the LDL-associated PAF-AH in atherogenesis is controversial. Thus, it is suggested that this enzyme may have an anti-inflammatory role as it degrades and inactivates pro-inflammatory PAF and oxidised phospholipids. Other studies showed that PAF-AH may have a pro-inflammatory and pro-atherogenic role since it generates lysophosphatidylcholine and bioactive oxidised fatty residues. In contrast to the LDL-associated enzyme, several lines of evidence suggest that HDL-associated PAF-AH (HDL-PAF-AH), although at low levels, contributes substantially to the antithromogenic effects of this lipoprotein.

Human plasma PON1 is an esterase exclusively present in plasma associated with HDL. In vivo substrates for this enzyme are phospholipid hydroperoxides and cholesteryl ester hydroperoxides (molecules that are formed during LDL oxidation). It has been shown that PON1 is able to retard LDL oxidation and to reduce the pro-inflammatory effects of oxidised LDL. Furthermore, PON1 may inhibit HDL oxidation, thereby preserving its antithromogenic functions.

In a recent study we examined whether epoetin has any influence on HDL anti-inflammatory and antioxidant potency (activities of PAF-AH
and PON1). The total plasma PAF-AH activity of CKD patients (stages 3 and 4) at baseline was higher compared with normolipidaemic controls, whereas no difference in the HDL-PAF-AH activity was observed among the studied groups. Thus, the ratio of HDL-PAF-AH to the plasma enzyme activity was significantly lower in both patient groups compared with controls. We have previously shown that this ratio may be used as a potential marker of atherogenicity. Long-term epoetin therapy induced a significant increase in the plasma PAF-AH and in HDL-PAF-AH activity—a phenomenon not observed in untreated CKD patients. Importantly, the percentage increase in HDL-PAF-AH activity was higher compared with that of total plasma enzyme, thus the ratio of HDL-PAF-AH to the plasma enzyme activity was significantly increased (improved) in epoetin-treated patients compared with the baseline values, a phenomenon not observed in patients not receiving epoetin. Since the main source of plasma PAF-AH is cells of haemato poetic origin, primarily monocytes/macrophages, we studied the effect of epoetin on PAF-AH secretion from peripheral blood mononocytes (PBMs) in culture. In vitro treatment with epoetin of peripheral blood mononocytes (PBMs) from CKD patients receiving epoetin resulted in a dose-dependent increase in total and secreted enzyme activity, a phenomenon not observed in patients who did not receive therapy with epoetin. This suggests that PBMs from CKD patients (stages 3–4) are defective in their ability to respond to epoetin stimulation for PAF-AH secretion in vitro, whereas long-term therapy with epoetin restores the responsiveness of PBMs to epoetin for PAF-AH secretion. Overall, the higher percentage increase in HDL-PAF-AH activity compared with that of total plasma enzyme activity and the improvement of the ratio HDL-PAF-AH to the plasma enzyme in vivo observed in epoetin-treated patients could be attributed to the increased secretion of PAF-AH from PBMs induced by epoetin therapy, as well as to epoetin-induced increase in the levels of serum HDL cholesterol. Since the PON1 activity, which is exclusively associated with HDL in plasma, is not affected by epoetin administration despite the increase in HDL cholesterol levels, we may represent an important antiatherogenic and cardioprotective effect of epoetin in these patients. However, the mechanisms at molecular level for these epoetin effects remain to be established. Furthermore, appropriately designed prospective randomised clinical trials are necessary to show whether the above epoetin effects have any clinical importance not only in the higher atherogenicity and prevalence of CAD exhibited by CKD patients, but also concerning the slowing in the progression of CKD and the retardation of renal replacement therapy.

Conclusions

In light of this review, recent data have provided evidence that long-term epoetin treatment for pre-dialysis patients with CKD significantly increases serum HDL cholesterol levels and improves the atherogenic ratio of LDL cholesterol to HDL cholesterol as well as the HDL antioxidant and anti-inflammatory potency (HDL-associated PAF-AH activity). This may represent an important antiatherogenic and cardioprotective effect of epoetin in these patients. However, the mechanisms at molecular level for these epoetin effects remain to be established. Furthermore, appropriately designed prospective randomised clinical trials are necessary to show whether the above epoetin effects have any clinical importance not only in the higher atherogenicity and prevalence of CAD exhibited by CKD patients, but also concerning the slowing in the progression of CKD and the retardation of renal replacement therapy.