failure. It is possible to make a strong argument for such therapeutic intervention in these individuals because hyperlipidaemia might also contribute to the high incidence of cardiovascular disease observed in this population.

A number of investigators have confirmed the safety and efficacy of lipid-lowering diets and drugs in patients with renal failure and the nephrotic syndrome but have not been able to convincingly demonstrate a beneficial effect on renal function [5,6]. Whilst this could mean that correction of hyperlipidaemia has no impact on progression of renal failure in man, most studies have been of relatively short duration, have achieved only modest reductions in plasma lipid levels and have not adequately assessed renal or indeed cardiovascular endpoints. In one uncontrolled trial that did achieve pharmacological normalization of cholesterol concentrations in a small group of LDL nephrotic patients, there was an increase in glomerular filtration rate as measured by $^{51}$Cr-EDTA clearance, although this was confined to a subgroup of patients with relatively well-preserved renal function [9]. Removal of LDL by apheresis would seem to be the optimal treatment to correct hyperlipidaemia associated with the nephrotic syndrome, and in another uncontrolled study led to a 60% reduction in plasma cholesterol in a group of eight patients with steroid resistant glomerular lesions [10]. This was accompanied by a reduction in proteinuria of more than 50% in five patients during six nephrotic episodes. Although the overall reduction in proteinuria for the whole group was not significant, the increase in plasma albumin concentration was. In addition, comparison of renal biopsies taken before and after treatment demonstrated a reduction in the intensity of staining for mesangial apoprotein B and in the number of intraglomerular macrophages. These findings would suggest that it might be possible to mobilize lipids deposited in the kidney by intensive lipid-lowering therapy. Whether such deposits disappear with resolution of proteinuria in patients with remitting nephrotic syndrome is not known.

Whilst such results are encouraging, further studies are required to confirm the benefits of lipid-lowering intervention in patients with chronic renal failure and the nephrotic syndrome. Such studies need to be large, prospective, and randomized with long-term follow-up and should be controlled for all risk factors other than hyperlipidaemia. Both cardiovascular and renal endpoints need to be adequately assessed. Unfortunately, as an increasing number of nephrologists are treating hyperlipidaemia in their patients because of the perceived cardiovascular risk, it will become increasingly difficult to conduct studies designed to investigate the true benefits of such intervention.

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References


Low molecular weight heparin — does it favourably affect lipid levels?

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The introduction of heparin for anticoagulation was an important step in the development of haemodialysis, and heparin has over the years proved to be a reliable anticoagulant in the extracorporeal circuit of haemodialysis. Although more than 75 years have passed since the discovery of heparin, the anticoagulant action of heparin is not yet fully understood. Unfortunately, the widespread use of standard heparin therapy has
Heparin has effects on fat metabolism mediated by its capacity to release lipoprotein lipase (LPL) and hepatic lipase from the vascular endothelium into the blood stream. Lipoprotein lipase, anchored to the vascular endothelium through heparan-sulphate, is an extracellular enzyme (or group of enzymes) responsible for the intravascular lipolysis process of chylomicrons and very low density lipoproteins. Heparin produces its lipolytic effect via strong electrochemical binding to heparan-sulphate, a process that releases LPL from the endothelium within minutes. One consequence of the heparin-induced increase in intravascular lipolytic activity is an elevation of plasma free fatty acids (FFA) which are produced and taken up by the cell for immediate energy utilization by oxidation or energy storage by re-esterification. In the clinical situation, the increase in plasma FFA levels after the injection of heparin could, on theoretical grounds, be considered disadvantageous or even harmful. It has been reported that high levels of FFA may have undesirable side-effects, such as the displacement of drugs from their albumin binding and substantial evidence has also been presented that elevated FFA levels induce cardiac arrhythmias during myocardial ischaemia. However, whether this is a real clinical problem remains to be determined.

Recent surveys on the mortality and morbidity of patients with end-stage renal diseases have shown that cardiovascular diseases are the main causes of death in patients treated with dialysis. Many factors such as hypertension, volume overload, hyperparathyroidism, insulin resistance and smoking, which frequently occur in haemodialysis patients, may increase the death rate due to atherosclerotic complications. Hyperlipidaemia, which accelerates atherosclerosis, may also be a risk factor for cardiovascular deaths in a haemodialysis population, as also is the case in those with normal renal function. Raised serum lipid concentrations, in particular hypertriglyceridaemia, is a problem in many patients on maintenance haemodialysis. The genesis of elevated triglycerides in haemodialysis patients is multifactorial and both impaired catabolism and increased synthesis have been implicated. The reason(s) for decreased catabolism are not known, although it has been suggested that this may be due to the inhibition of lipases through a uraemic factor or an excess of FFA. Patients on haemodialysis are subjected to heparinization three times a week. A diminution in lipolytic activity, due to the repeated heparin treatment, may also contribute greatly to impaired catabolism of triglycerides [1]. Indeed, the long-term use of heparin has been shown to be associated with a decreased plasma triglyceride clearance rate [1] and an increased severity of hyperlipidaemia in haemodialysis patients [2,3]. However, it is important to recognize that an increase in serum triglyceride values is not always seen with long-term conventional heparin treatment in haemodialysis patients.

The standard heparin preparations in clinical use today are heterogeneous with regard to molecular size (molecular weight 2000–25 000 daltons). In recent years considerable interest has focused on low-molecular-weight fragments (LMWH; molecular weight 4000–6000 daltons) of the heparin molecule. It has been concluded that LMWH fractions possess antithrombotic properties (anti-Xa activity), but do not significantly prolong clotting times (APTT). Extensive research has confirmed that LMWH has the same antithrombotic effect as standard heparin and that it can be used as a safe and convenient treatment for deep venous thrombosis and also to prevent thromboembolic complications. It has also been demonstrated that LMWH is a suitable alternative to standard heparin for anticoagulation in haemodialysis therapy [3,4]. In this context it is of particular interest that in-vitro and in-vivo studies have indicated a beneficial effect of LMWH on lipid metabolism. The lipolytic activity effect of LMWH is only half as strong as that of heparin when these two heparin compounds are given in doses with equipotent anticoagulation [5]. Accordingly, the weaker plasma lipolytic effect following injection with LMWH results in a significantly smaller elevation of plasma FFA levels, which could have some clinical advantages. The present results thus suggest that LMWH could be better than standard heparin for lipid metabolism. However, although conventional heparin has been reported to aggravate hyperlipidaemia in haemodialysis patients, there seems to be no strong evidence that this effect is due to the depletion of endothelial LPL [2,3]. In fact in the study by Schrader et al. [3] 12 months of standard heparin treatment was associated with a small increase in LPL and hepatic lipase activity. Lipoprotein lipase is normally cleared from the circulating blood by the liver. Recently, Liu et al. [6] demonstrated a lower affinity for LMWH to LPL, which did not result in a lower potency to release LPL, from endothelial binding sites in peripheral tissues, but rather in a substantially decreased effect on the hepatic clearance of the enzyme. On theoretical grounds it is therefore possible that a switch from conventional heparin treatment to LMWH will not reduce triglyceride levels, as pointed out by Schmitt and Schneider [7].

One may therefore ask if it is likely that LMWH will reduce lipid levels in haemodialysis patients. A number of studies have addressed this issue, but unfortunately the results are conflicting. Following LMWH treatment for periods ranging from 6 to 48 months, 24 and 55% decreases in triglycerides have been reported by some [2,4], whereas other studies have reported unchanged triglyceride levels following LMWH treatment for periods of 6–12 months [3,7]. In an individual-switch-over study, Deuber and Schulz [4] report data from five patients who received standard heparin, then LMWH for 12 months and again standard heparin. During the LMWH treatment period, significant reductions in both triglyceride and cholesterol blood concentrations were observed. In other studies, cholesterol values have been reported by some
authors to decrease by 8–20% following treatment with LMWH for 6 to 48 months [2,7], whereas no change in cholesterol levels following LMWH treatment were observed in the study by Schrader et al. [3]. There may be several reasons for the discrepancies in results reported in the literature. First, the length of the study period may be of importance, since some studies may have been too short for a recognition of the potential beneficial effect of the lower lipolytic activity of LMWH. Secondly, as the LMWH are heterogeneous preparations and various LMWH preparations have been used in the different studies, some of the observed discrepancies may be caused by the varying percentages of fractions with a high molecular weight. Finally, as pointed out by Schmitt and Schneider [7], apo E isoforms drastically influence the individual values of cholesterol and triglycerides which may have some impact on the effect of interventions. A criticism of some studies is that poor documentation of the initial conditions may have influenced the results.

In conclusion there is no doubt that safe and effective haemodialysis can be performed, using LMWH for anticoagulation. It is also established that long-term treatment with LMWH causes no progressive increase in serum triglyceride and cholesterol levels in haemodialysis patients, unlike the aggravated hyperlipidaemia seen during long-term treatment with conventional heparin in most haemodialysis patients. The reports concerning the lipid-lowering effects of LMWH are controversial, although most studies show a favourable effect on cholesterol and triglyceride levels. However, the important question of whether LMWH treatment reduces the risk of atherosclerotic complications in patients on maintenance haemodialysis is still open and needs to be examined in a long-term prospective trial. Until then it is important to recognize that LMWH is much more expensive than conventional heparin and LMWH may therefore be preferable to standard heparin, primarily in the clinical situation when severe hyperlipidaemia is present.

References


Should older patients receive renal transplants?

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In the treatment of chronic renal failure in the younger patient, transplantation has three potentially worthwhile advantages when compared with dialysis. Two of these are undisputed namely a better quality of life particularly as regards physical activity and secondly a release from the tedious and time-consuming process of dialysis. The third, namely longer survival, is less certain. While there is little difference between dialysis and transplantation in patient survival during the first few years, the impression exists, although not yet backed by conclusive evidence, that survival is better in the renal allograft recipient in the longer term i.e. in the period beyond 5 years. Do these three advantages apply to a sufficient degree for us to recommend renal transplantation in the older patient? If the answer is yes, are the arguments in favour of transplantation of sufficient strength to justify giving cadaver kidneys to older rather than younger patients in the setting of a widening gap between supply and demand? Before answering these questions we have to define the older patient and inevitably the division between younger and older must be arbitrary. I suggest 65 years as the dividing line as few would dispute the justification of renal transplantation below this age.

Outcome of transplantation in older patients

Although, as time passes, patients over 65 years account for an increasing percentage of those on renal