LIPOPROTEIN (A) LEVELS IN RENAL TRANSPLANT RECIPIENTS RECEIVING CYCLOSPORIN MONOTHERAPY

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SUMMARY

Elevated serum levels of lipoprotein (a) [Lp(a)] are a known risk factor for coronary heart disease in the general population. We measured the serum concentration of Lp(a) in 63 renal transplant recipients (41 male, 22 female) on cyclosporin monotherapy, and in 137 healthy controls. Serum Lp(a) levels were significantly elevated in the transplant patients with a median of 30.1 (range<0.8 – 140.3) mg/dl compared to 8.19 (rang <0.8 – 87.4) mg/dl in controls. This raised serum level of Lp(a) may contribute to the excessive cardiovascular morbidity that occurs following renal transplantation.

INTRODUCTION

There is an increased incidence of coronary heart disease (CHD) in patients with chronic renal failure (CRF), which persists following renal transplantation.[1] Perturbations in lipoprotein and apoliporotein metabolism are common in patients with CRF and renal allografts[2] and may explain, at least in part, the increased incidence of CHD. However hypertriglyceridaemia is the common abnormality in patients with CRF whereas hypercholesterolaemia is more frequent in transplanted patients. Thus a sharper perspective of which lipoproteins are directly involved in disease production is required and what concomitant variables may be associated.

Lipoprotein (a) [Lp(a)] is a serum lipoprotein which exists as a subspecies predominantly of low density lipoprotein (LDL) and uniquely contains apolipoprotein (a) [apo(a)].[3] Apo(a) has been shown to have close sequence homology with and to exist as a giant mutant form of plasminogen.[3] Furthermore it binds to plasminogen receptors but does not convert plasminogen to plasmin,[3] and so it has been proposed that Lp(a) may act as a competitive inhibitor of plasminogen activation and thus promote

thrombosis rather than fibrinolysis. A raised serum level of Lp(a) is a known risk factor for the development of CHD in the general population.[4] Serum concentrations of Lp(a) have been shown to be elevated in both dialysis patients[5] and patients with the nephrotic syndrome[6] Therefore we have determined the serum Lp(a) levels (and other lipid and lipoprotein values) in 63 patients with an established renal allograft receiving cyclosporin A monotherapy.

MATERIAL AND METHODS

a) Patients

Sixty-three non-diabetic Caucasian patients (41 male, 22 female) attending a transplant follow-up clinic were studied. The median age of the patients was 45 years, range 18-70 years. They had been transplanted at least 1 year earlier and had good graft function with median serum creatinine 135 umol/1, (range 80-265). All patients had received cyclosporin A as the sole immunosuppressive drug at a dose tailored to maintain a whole blood cyclosporin level of 80-150 ng/ml. All patients had a normal serum albumen level and no patient had a urinary protein excretion of greater than 2g/ 24 hours. Diet was unrestricted. Forty-seven patients (75%) were being treated for hypertension at the time of study with a variety of drugs including beta-blockers, calcium channel antagonists, ACE inhibitors and diuretics.

One hundred and thirty-seven europid adults (100 men, 37 women) with a median age of 50 years (range 20-74) and a similar social background working at a local factory acted as controls. None were known to have renal disease or CHD and none were taking drugs known to affect lipid metabolism.

b) Biochemical methods

Blood was taken after a 12 hour overnight fast and a concurrent 24 hour urine collection was made. Serum lipoproteins were isolated by ultracentrifugation and cholesterol and triglyceride in serum and lipoproteins determined enzymatically as reported previously., (7). Serum Lp(a) was determined by a two site immunoradiometric assay (Pharmacia, Uppsala, Sweden).

c) Statistical methods

Mean lipid and apolipoprotein levels for the 2 groups were compared using a one-way analysis of variance (Scheffe's test, 5% level of significance). Variables which were positively skewed (triglycerides and VLDL) were logarithmically transformed prior to analysis. The non-parametric Kruksal-Wallis one-way analysis was used for Lp(a), because both groups contained patients with values below the lower limit of detection (0.8mg/ dl). Pairwise comparisons were performed using the Mann Whitney U-test.

RESULTS

The lipid, lipoprotein and apolipoprotein values are shown in Table 1.

Mean serum cholesterol was significantly elevated in the transplant group with 34(54%) patients having a serum cholesterol greater than 6.5 mmol/1. The median serum triglycerides value was also significantly elevated at 1.82mmol/1 ($p < 0.001$) amongst the transplant group the serum Lp(a) values were significantly raised ($p < 0.001$) with 53% of the group having a Lp(a) level of >30mg/ dl, a level strongly associated with the development of premature vascular disease.

	Patients (n=63)	Controls (n=137)	
Sex (male:female)	41:22	100:37	
Age (years)	45(18-070)	50(20-74)	
Body mass index			
Total cholesterol (mmol/1	6.75 + 148	5.86 + 0.91	p< 0.001
Total triglycerides (mmol/1)	1.82(0.12-21.59)	1.16(0.22-4.44)	p<0.001
VLDL cholesterol (mmol/1)	0.59(0.10-3.48)	0.46(0.10-1.18)	p<0.05
LDL cholesterol (mmol/1)	4.50 + 1.17	3.87 + 0.95	p<0.001
HDL cholesterol (mmol/1)	1.26 + 0.37	1.39 + 0.32	p<0.05
HDL2 cholesterol (mmol/1)	0.65 + 0.15	0.67 + 0.31	NS
HDL 3 cholesterol (mmol/1)	0.59 + 0.15	0.73 + 0.23	p<0.001
Apob	108 + 28		
Lp(a) (g/dl)	30.1 (0.8 – 140.3)	8.19(<0.8-87.4)	p<0.001

TABLE – 1

DISCUSSION

The results of this study reveal that in a group of 63 transplant recipients, with stable and well maintained allograft function and receiving cyclosporin alone as the single immunosuppressive agent, the levels of Lp(a) are significantly elevated. All patients had received their transplant at least one year previously, and none had recently been treated with of high dose steroids as treatment for acute rejection. Factors known to affect serum Lp(a) levels such as diabetes mellitus, heavy proteinuria were excluded, and patients and controls were from the same ethnic group.

The reason for the raised level of Lp(a) is unclear. It is possible that uraemia disturbs the metabolism of Lp(a) either by increasing production or decreasing catabolism. If this hypothesis is correct it might be expected that a rise in Lp(a) levels would be seen as renal disease progresses with a reduction as renal function improves after transplantation. The values observed in this group of transplant recipients are similar to those reported in dialysis patients.[5] The only previous report, in abstract, of Lp(a) levels in a heterogeneous group of patients following renal transplantation merely documented an elevated level in hypercholesterolaemic recipients.[8] However increased Lp(a) levels are not generally associated with elevated cholesterol concentrations except in primary familial hypercholesterolaemia.[9]

Cyclosporin alone may increase serum Lp(a): raised levels are reported in cardiac transplant recipients.[10] Usually the only abnormality of renal function in these patients is as a consequence of cyclosporin nephrotoxicity. A comparative study of Lp(a) levels in renal allograft recipients not receiving cyclosporin may help answer this question, as would a study of Lp(a) levels in patients with psoriasis treated by cyclosporin.

This study has also confirmed the well known finding of hypercholesterolaemia associated with renal transplantation and also an increased LDL cholesterol concen-

tration, an abnormality associated with cyclosporin therapy.[2]

The findings of our study may implicate Lp(a) in the development of CHD in renal transplant recipients. Lp(a) binds to fibrin and there may be preferential retention of Lp(a) and thus the atherogenic apoB moeity of Lp(a), via fibrin binding, in developing atheromatous lesions rather non-Lp(a)- containing LDL.[3] Macrophage uptake of Lp(a) may be encouraged by its ability to bind to plasminogen receptors.[3]

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