Effects of Renal Replacement Therapy on Plasma Lipoprotein(a) Levels

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Abstract

Patients with end-stage renal disease (ESRD) have significantly higher levels of lipoprotein(a) [Lp(a)] when compared to control populations. Elevated levels of Lp(a) may play a role in the high incidence of cardiovascular disease in ESRD. We conducted a prospective study to test the hypothesis that plasma levels of Lp(a) decline rapidly after renal transplantation proportional to the improvement in renal function, but are not affected by hemodialysis. All adults that initiated hemodialysis or received a renal transplant from our institution during a 10-month period were invited to participate in the study. Lp(a) levels were obtained immediately prior to the initiation of renal replacement therapy. In transplant recipients, repeat Lp(a) measures were done at 3 days, 5 days, 1 week, 2 weeks, 3 weeks and 4 weeks post-transplant. In hemodialysis patients, repeat Lp(a) measures were done after 3 months. We used a mixed effects model to analyze the effect of time, race and creatinine on Lp(a) after transplant. Lp(a) levels decreased rapidly after renal transplantation. Mean Lp(a) levels at 2 weeks were 35.3% lower than prior to transplantation. Each reduction of 50% in creatinine was associated with a 10.6% reduction in Lp(a) (p < 0.001). In contrast, there was no significant change in Lp(a) after initiation of hemodialysis. The rapid decrease of Lp(a) levels after renal transplantation provides support for a metabolic role of the kidney in Lp(a) catabolism and suggests that the increase in Lp(a) seen in chronic kidney disease is due to loss of functioning renal tissue.

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Introduction

Lipoprotein(a) [Lp(a)] is similar in structure to LDL but is characterized by the presence of an additional protein called apolipoprotein(a) [apo(a)], which is linked by a single disulfide bond to ApoB [1]. Lp(a) levels are highly genetically determined and are determined primarily by the rate of production [2–4]. A large body of epidemiologial data supports an independent association between elevated plasma levels of Lp(a) and atherosclerotic vascular disease [5–7], but not all studies have confirmed this association [8, 9].

Recent studies have provided insight regarding the assembly and production of Lp(a) in the general population [10, 11]. However, the site(s) of clearance is still unknown. Patients with end-stage renal disease (ESRD) on dialysis have significantly higher levels of Lp(a) when compared to control populations [12–14]. Elevated levels of Lp(a) may play a role in the high incidence of cardiovascular disease in ESRD [5, 13, 15]. Lp(a) was shown to be an independent predictor of death attributable to cardiovascular events in hemodialysis patients [16]. The pathophysiologic mechanism underlying the increased levels of Lp(a) in ESRD is not known. One hypothesis is that the

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kidney plays a direct role in Lp(a) catabolism [15, 17, 18]. Renovascular arteriovenous differences of –9% in Lp(a) concentrations provide support for renal catabolism [19], but renal catabolism of Lp(a) has not been directly demonstrated. A second hypothesis is that ESRD causes a metabolic milieu that increases hepatic Lp(a) production or reduces Lp(a) catabolism at other (unknown) sites.

Renal transplantation is associated with reduced Lp(a) levels when measured 6–12 months post-transplantation in cross-sectional [12] and longitudinal studies [20]. However, the kinetics of the decline in Lp(a) post-transplantation have not been studied. If the kidney plays an active role in the catabolism of Lp(a), plasma levels of Lp(a) should decrease rapidly following renal transplant. Furthermore, if the kidney plays a key role in regulating Lp(a) levels, hemodialysis initiation should not reduce Lp(a) levels. We therefore conducted a prospective study in ESRD patients in a racially diverse population to test the hypothesis that plasma levels of Lp(a) decline rapidly after renal transplantation proportional to the improvement in renal function, but that initiation of dialysis therapy has no effect in lowering Lp(a) levels.

Methods

All adult consecutive renal transplant recipients from the Hospital of the University of Pennsylvania during a 10-month period were invited to participate in the study. Written consent was obtained. The University of Pennsylvania Institutional Review Board approved the research protocol. Patients with multi-organ transplants except those including the pancreas were excluded. Laboratory values (serum creatinine, glucose, albumin and immunosuppressant levels) that are obtained as part of routine clinical care were extracted from the medical records. The patient health characteristics at baseline (age, race, sex, and comorbidities) were recorded using standardized data forms. Important clinical events such as acute rejection and delayed graft function occurring within the first 6 months post-transplant were recorded. Delayed graft function was defined as need for dialysis within the first 7 days post-transplant. Blood was obtained into 0.1% EDTA tubes immediately prior to transplantation and at 3 days, 5 days, 1 week, 2 weeks, 3 weeks and 4 weeks post-transplant. Our standard immunosuppressive regimen comprised induction with rabbit antithymocyte globulin, followed by maintenance therapy with calcineurin inhibitor [tacrolimus (78.5%) or cyclosporine (21.5%)], mycophenolate mofetil capsules (MMF) and low-dose prednisone. Doses of cyclosporine are titrated to a level of 150–200 μg/l during the first year and doses of tacrolimus are titrated to levels of 8–10 ng/ml during the first year. All subjects were prescribed MMF dose along with prednisone that was tapered off. Usually by 3 months post-transplant, subjects were on 5–10 mg of prednisone daily. The dose of MMF varied by race with Caucasians traditionally receiving 500 mg twice daily and African-Americans 1,000 mg twice daily. MMF dose is reduced if side effects develop.

To examine the effect of initiation of dialysis therapy on Lp(a) in ESRD patients, we enrolled 31 incident hemodialysis patients from our institution during the same time recruitment period. Lp(a) and lipid parameters were measured on the day of and prior to the first dialysis treatment and at 1 and 3 months after the initiation of chronic dialysis.

All lipid assays were performed in the Lipid Research Laboratory, which participates in the CDC standardization program for lipids. All assays were run using commercially available reagents on a Cobas Fara II autoanalyzer. The cholesterol, HDL cholesterol, ApoA1 and ApoB and triglyceride assays are standard assays using reagents from Sigma Diagnostics. The Lp(a) assay uses reagents from Incstar Corp. Quantitative determination of Lp(a) is done by automated immunoprecipitin analysis. Following an incubation period lasting approximately 10 min, the absorbance of the solution is measured at 340 nm. A calibration curve is generated by assaying a series of standards with known concentrations of Lp(a) and using the instrument's data reduction capability or manually plotting the change in absorbance versus concentration. Concentrations of the controls and samples are interpolated from the calibration curve. This assay has a minimal detectable level of 1.5 mg/dl. The coefficient of variation was 7.5%.

Statistical Analysis

Categorical variables, nominal and ordinal, were summarized by frequencies. Mean, standard deviation, 95% CI, median, and range were used to summarize continuous variables. Where continuous variables were not normally distributed, such as Lp(a) and creatinine, log transformations to achieve a more normal distribution were used. Differences in means were analyzed by paired t-test. Comparison of medians was done by Wilcoxon rank-sum test. We used a mixed effects model to analyze the effect of time, race and creatinine on Lp(a) and appropriately deal with the repeated measures. All analyses were performed using STATA 7.0 (College Station, Tex., USA) and SAS Version 6.12 (SAS Institute, Cary, N.C., USA).

Results

Baseline Characteristics

66 renal transplant subjects consented to participate in the study. At the time of transplantation, the average (±SD) age of the subjects was 46.7 (±10.4) years. 71% of patients were Caucasians, 27% were African-Americans, and 1.5% were Asian. 58% were males and 34% had diabetes mellitus. The cause of ESRD was hypertension in 39%, diabetes in 27%, glomerulonephritis in 9%, polycystic kidney disease in 9%, and other or unknown in 16% of subjects. Coronary artery disease was present in 17% and hypercholesterolemia in 11% of subjects at the time of transplantation. Only 4.5% of subjects were on lipid-lowering medication at the time of transplantation. 87% of subjects had a history of hypertension with an average duration of 11.2 (±7.9) years.

Table 1. Lipid profile just prior to transplantation

Lipid parameter	Mean ± SD mg/dl	Range
Total cholesterol	183.4 ± 47.6	96–295
Triglycerides	202.5 ± 142.7	29–702
HDL	44.1 ± 17	21–88
ApoA1	123.8 ± 31.3	62–206
ApoB	92.8 ± 29.2	30–183

Table 2. Percent decrease post-transplant

	Creatinine mg/dl	Lp(a) mg/dl	Mean decrease Lp(a), %	p value
Pre-transplant	8.8	31.3		
After 3 days	4.0	30.9	1.3	0.88
After 5 days	4.1	28.4	9.2	0.29
After 1 week	2.3	27	13.7	0.25
After 2 weeks	1.8	20.2	35.3	<0.0001
After 3 weeks	1.6	21.2	32.1	0.0001
After 1 month	1.5	22.4	28.4	<0.0001

Table 3. Multivariate model predicting level of Lp(a) post-transplant

Variable	Estimate	Standard error	p value
Time	−0.0032	0.0048	0.50
Creatinine (log)	0.1613	0.0494	0.002
Caucasian	−0.5271	0.2399	0.03

Table 4. Lipid profile pre- and post-dialysis initiation

	Pre-hemodialysis mg/dl	Month 3 post-dialysis initiation, mg/dl	p value
Total cholesterol	159 ± 6.9	177 ± 8	0.12
Triglycerides	128 ± 11.7	155.9 ± 20.7	0.21
ApoA1	111.29 ± 6.6	111.4 ± 6.5	0.99
ApoB	86.8 ± 4	91.9 ± 5	0.44
HDL	40 ± 2.8	32.5 ± 2.3	0.04
Lp(a) mean	63.6 ± 11.5	67.2 ± 15.9	0.86
ln Lp(a)	3.7 ± 0.18	3.8 ± 0.26	0.76
Lp(a) median	40.5	44.1	

88% of subjects were on dialysis at the time of transplantation. 36% were transplants from living donor. 10% were kidney-pancreas recipients. 4 subjects with deceased donor renal transplant had delayed graft function requiring dialysis during the first week post-transplant. There were 4 treated rejection episodes in our cohort. The mean (±SD) creatinine 4 weeks post-transplant was 1.9 (±1.5). The median creatinine at 4 weeks was 1.5 mg/dl. 8% of subjects had a renal biopsy performed during the follow-up period. The median length of hospital stay was 7 days. Lp(a) levels were higher in African-American transplant recipients when compared to Caucasian transplant recipients (mean (±SD): 55.2 (±39.8) vs. 45.1 (±44.2)), but did not reach statistical significance. Lp(a) was also higher in patients with a history of cardiovascular disease (64.3 ± 54 vs. 44.2 ± 39.3) but did not reach statistical significance.

Changes in Lipids and Lp(a) Post-Transplant

There was a 20% increase in HDL cholesterol levels by week 2 compared to pre-transplant levels. ApoA1 decreased within days post-transplant but was significantly increased by week 3 post-transplant. There was no detectable difference in levels of cholesterol, triglycerides or ApoB in this cohort up to the first month post-transplant (table 1).

Lp(a) levels decreased rapidly after transplantation. In all patients, mean levels at 2 weeks were 35.3% lower than prior to transplantation (table 2). Using the mixed effects model in this transplant cohort, the effect of days post-transplant was significant on univariate analysis (p = 0.0001). Once controlled for creatinine level post-transplant, compared to African-Americans, Caucasians had a 60% lower Lp(a). The effect of days post-transplant became non-significant when the log of creatinine was added to the model (table 3). For every increase in log of creatinine, the ln Lp(a) increased by 0.16 (p = 0.0015). We were unable to detect any difference between Lp(a) according to type of transplant (cadaver vs. living). The median Lp(a) for patients that had delayed graft function was higher at week 1–2 than those without delayed graft function (23.6 vs. 54.8, p = 0.05).

Changes in Lipids and Lp(a) after Initiation of Dialysis

29 subjects were recruited. The majority of subjects were African-Americans (73%) and male (55%). 22% had diabetes mellitus. The mean age was 58 (±14.1) years. Mean and median Lp(a) levels were elevated at the initiation of dialysis and were unchanged after 3 months of hemodialysis. Natural log transformation of Lp(a) and evaluation by race yielded the same results. HDL cholesterol had decreased by 1 month and this decrease reached statistical significance by 3 months. There were no significant changes in cholesterol, triglycerides, ApoA1 or ApoB (table 4).

Discussion

Lp(a) is an atherogenic lipoprotein and despite enormous interest in this molecule the site of its catabolism has not been elucidated. We were interested in testing the hypothesis that plasma levels of Lp(a) decline rapidly after renal transplantation along with the improvement in renal function in a diverse population. We found that Lp(a) levels decrease rapidly after renal transplantation proportional to the decline in creatinine levels, but are unchanged after initiation of dialysis.

The inverse correlation between serum Lp(a) and creatinine in cross-sectional studies examining patients with mild to moderate renal failure and a frequency of distribution of apo(a) isoforms similar to controls suggest that the renal insufficiency itself is responsible for the increased Lp(a) levels [21–23]. Our data are consistent with other prospective studies that have shown decreases of Lp(a) after transplantation several months to years post-transplant [24–27]. Prevalence of Lp(a) >25 mg/dl was 31–37% after 2–10 months post-transplant [28, 29] and >12 mg/dl in approximately 60% of patients 1 year post-transplant [29]. There are several prospective studies looking at the changes in Lp(a) after transplantation. The Azrolan study is prospective and measured Lp(a) prior to transplantation and at 6 months to a year later [20]. A prospective study in 20 renal transplant recipients found a decrease in the median of apo(a) units/l from time of transplantation value of 403 U/l to 1 week (184 U/l, p < 0.001) that was sustained at 6 months (170 U/l, p < 0.001) in patients with successful transplants. There was no discussion of race and the etiological causes of ESRD differed significantly from the US population. For example, only 1 out of the 20 subjects had diabetic nephropathy. Our study is the first to demonstrate that changes in Lp(a) occur rapidly after renal transplantation (within days). Some studies have shown no correlation between creatinine and Lp(a) months to years post-transplant [28, 30]. We found that there was an association between the level of function of the transplanted kidney and Lp(a) level at 2 weeks post-transplant.

The influence of immunosuppressant therapy on Lp(a) levels remains controversial. Lp(a) levels decrease after renal transplantation [20, 27] but remain higher than normal [30] and are higher in recipients with proteinuria [26, 31]. Cyclosporin A (CSA) was shown to increase LDL [20] and lower HDL [29]. Patients on CSA in some studies have lower levels of Lp(a) at 1 year when compared to baseline when compared to patients on prednisolone alone [20]. The same result was not found in all studies [32, 33].

Brown et al. [29] found in a cross-sectional study that patients treated with CSA had higher levels when compared to individuals treated with azathioprine and prednisolone (median –32 vs. 18.3 mg/dl). HDL was also higher in the group not taking CSA (1.41 ± 0.4 vs. 1.24 ± 0.39 mmol). Kronenberg et al. [27] demonstrated that the significant Lp(a)-lowering effect of transplantation was only seen in patients who had large apo(a) isoforms and had no correlation with CSA therapy. All our subjects were on calcineurin inhibitors and therefore we were unable to explore the use of CSA or tacrolimus and the relationship with Lp(a). However, both CSA and tacrolimus have been associated with hypercholesterolemia and during long-term use no statistical significant difference in total or LDL cholesterol was found between them [34]. Therefore, it is reasonable to speculate that the effect on Lp(a) would be similar between these two calcineurin inhibitors.

One possible hypothesis is that ESRD creates a metabolic milieu that causes increased Lp(a) and that initiation of dialysis at least partially impacts on this, thus resulting in reduced Lp(a) levels. We investigated for the first time the effect of dialysis initiation on Lp(a) levels and found no effect. Lp(a) at 3 months after initiation of dialysis were just as high as immediately prior to initiation of dialysis. Thus not all forms of renal replacement therapy reduce Lp(a); only renal transplantation does so, presumably by providing functional renal tissue that in some way mediates reduction of Lp(a).

Frischmann et al. [35] demonstrated that hemodialysis patients have a decrease in Lp(a) clearance and not an increase in Lp(a) production. The ApoB-containing lipoproteins from which Lp(a) is assembled are almost exclusively a newly synthesized pool derived from the liver in both controls and hemodialysis patients whereas only a very small percentage of Lp(a) is assembled from circulating LDL. Use of a low-flux dialyzer has been associated with higher Lp(a) levels [36].

In conclusion, the rapid decrease of Lp(a) levels after renal transplantation provides support for a metabolic role of the kidney in Lp(a) catabolism. Hemodialysis itself has little effect on Lp(a) levels. Therefore, Lp(a) levels are elevated in chronic kidney disease secondary to loss of functioning renal tissue.

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