Post-Transplant Hyperlipidemia: Mechanisms and Management

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ABSTRACT

Hyperlipidemia is common after renal transplantation. In recent years, much progress has been made in understanding the causes and treatment of lipid abnormalities in renal transplant patients. Recently, short-term studies have shown that newer antilipemic agents appear to be safe and effective in treating hyperlipidemia in this population. Despite the absence of large, controlled clinical trials examining the effect of lipid-lowering strategies on cardiovascular disease and chronic transplant allograft rejection, therapy appears to be warranted in renal transplant patients with an atherogenic lipid profile and multiple risk factors.

Key Words: Kidney transplantation, cholesterol, triglycerides, coronary heart disease, graft rejection

Hyperlipidemia is common after renal transplantation (1–5). Recently, we examined post-transplant lipid abnormalities in a large cohort of renal transplant recipients with a long follow-up period (mean, 7 yr; range, 0.5 to 18 yr) (6,7). Hyperlipidemia was not only common, but was also persistent throughout the late post-transplant period (Figure 1). Others have also found that hyperlipidemia is present in the late post-transplant period, e.g., for more than 10 yr of follow-up (8). In this review, we will examine the mechanisms and management of lipoprotein abnormalities in renal transplant patients.

HYPERLIPIDEMIA AFTER KIDNEY TRANSPLANTATION

Reported changes of serum lipids include increases in both triglyceride and total cholesterol levels (2,5,8–14). Elevated serum low-density lipoprotein (LDL) cholesterol (9,11,13,15,16), and apolipoprotein (apo) B levels are common (8,17–19). Serum high-density lipoprotein (HDL) cholesterol levels have been reported to be low, normal, or even slightly elevated (3,8,10–13,15,19–23). Similarly, alterations in the HDL subfractions HDL2 and HDL3 (15,16,21,24), as well as changes in total apo A (including apo A-I and apo A-II) (10,18,25,26), have also been described. However, apo A-I levels were consistently normal or only slightly altered (3,17–19,27). In some studies, apo C-II, apo C-III, and apo E levels were normal or elevated (8,17–19,28). However, the calculated ratio of apo C-II/apo C-III, which is often inversely correlated with triglyceride metabolism, was diminished (8,17–19).

Most studies have reported normal lipoprotein(a) [Lp(a)] levels in patients who were not receiving cyclosporine (27,29–32), whereas renal transplant patients treated with cyclosporine alone have exhibited high levels (21,33). Discrepancies in Lp(a) levels among studies of patients treated with both corticosteroids and cyclosporine could be the result of many factors, including different cyclosporine and corticosteroid doses (27–32,34–41), and differences in apo(a) isoform frequency (42). Elevated lipid peroxidation products, increased LDL susceptibility to oxidation, and decreased antioxidant levels have been observed in renal transplant patients treated with cyclosporine (43–45). It has also been shown that LDL susceptibility to oxidation decreased upon conversion of cyclosporine to azathioprine (46). These are important observations, given recent data implicating oxidized LDL in the pathogenesis of systemic atherosclerosis.

It should be noted that post-transplant lipoprotein abnormalities are different from those that occur in patients before transplantation. Indeed, dialysis patients usually have normal levels of total cholesterol, LDL cholesterol, and apo B, as well as reduced levels of apo A-1 (47,48). It is also noteworthy that the pattern of lipoprotein abnormalities is similar among renal transplant patients treated with or without cyclosporine (21,27,49–51). Moreover, the lipoprotein alterations in renal transplant patients treated with cyclosporine are similar to those reported in non-transplant patients treated with cyclosporine (21, 49,52). Most agree that both corticosteroids and cyclosporine contribute to lipid abnormalities after transplantation.

MECHANISMS OF HYPERLIPIDEMIA AFTER KIDNEY TRANSPLANTATION

The pathogenesis of hyperlipidemia in renal transplant patients is poorly understood. Several possible
Renal Transplant and Hyperlipidemia

Figure 1. Percentage of renal transplant patients in whom serum lipid and lipoprotein concentrations exceeded the desirable range proposed by the National Cholesterol Education Council (97). The number of patients in whom serum lipid and lipoprotein levels were measured at each time after transplantation is shown above the curves. LDL, low-density lipoprotein; HDL, high-density lipoprotein.

causes include immunosuppressive therapy, genetic predisposition, age, gender, body-weight gain, renal function, proteinuria, diabetes, and antihypertensive drugs (9,50,53-55). However, the relative contribution of these factors in the genesis of post-transplant hyperlipidemia is unclear. Post-transplant hyperlipidemia is related to immunosuppressive therapy in a dose-dependent fashion (1,2,5). Moreover, the association between immunosuppressive therapy and hyperlipidemia has generally been observed early after transplantation, and it is probable that the persistent lipid abnormalities in the late post-transplant period are also the result of factors other than immunosuppressive therapy (5,9,53).

Post-Transplant Triglyceride-Rich Lipoprotein Metabolism

The altered metabolism of triglyceride-rich lipoproteins is probably the result of either increased hepatic secretion of very-low-density lipoproteins (VLDL), or decreased peripheral triglyceride-rich lipoprotein removal, or both (2,56-59). Catran et al. studied triglyceride turnover sequentially for up to 3 years post-transplantation and demonstrated that overproduction of triglycerides was the predominant defect (2). Hyperinsulinemia secondary to insulin-resistance might stimulate hepatic triglyceride-rich lipoprotein production. Indeed, hyperinsulinemia has been positively, but inconsistently, correlated to triglyceride concentrations in renal transplant patients (2,57). Corticosteroid treatment is probably the primary cause of insulin-resistance (60). Corticosteroids could increase the rate-limiting enzymes of lipogenesis, acetyl-CoA carboxylase, and free fatty acid synthetase (56). Increased serum free fatty acid concentrations have been demonstrated in corticosteroid-treated transplant patients (23). In addition, thiazide diuretics, renal failure, and weight gain may also participate in post-transplant insulin resistance and hyperinsulinemia. Whether cyclosporine affects peripheral insulin resistance and hyperinsulinemia is unclear (60,61).

A decrease in the catabolism of triglyceride-rich lipoproteins in renal transplant patients is evidenced by a decrease in VLDL turnover rate (58), a decrease in the fractional clearance rate of intralipid (57), and a decrease in the postprandial triglyceride clearance rate (59). Lipoprotein lipase (LPL) and hepatic triglyceride lipase (HTGL) are responsible for the catabolism of triglyceride-rich lipoproteins (Figure 2). The function of LPL and HTGL, measured by total post-heparin lipolytic activity, have been reported to be normal (3,58,59) or reduced (27,62). Thus, the role of LPL and HTGL in the decreased metabolism of triglyceride-rich lipoproteins in renal transplant patients is unclear. However, it should be noted that renal transplant patients have several factors (including insulin-resistance, renal failure, decreased apo C-II/C-III ratio, and β-blocker use) that could theoretically reduce the synthesis and/or the activity of these lipases. Moreover, the abnormal lipid and apoprotein content of triglyceride-rich lipoproteins could theoretically inhibit their catabolism, and triglyceride enrichment of VLDL has been documented in renal transplant patients (3,63,64). Finally, because the LDL receptor also recognizes VLDL, reduced hepatic LDL-receptor number and/or function could lead to the accumulation of triglyceride-rich lipoproteins. Corticosteroids have been shown to inhibit LDL-receptor activity in

Figure 2. Schematic representation of triglycerides and cholesterol metabolism. The movements of each particle are indicated by arrows. VLDL, very-low-density lipoprotein; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; R, LDL receptor; LPL, lipoprotein lipase; HTGL, hepatic triglyceride lipase; LCAT, lecithin-cholesterol acyltransferase; HDL, high-density lipoprotein; TG, triglycerides; C, cholesterol; CE, esterified cholesterol; CETP, cholesterol ester transfer protein; CM, chylomicron.
vitro (65). Cyclosporine could theoretically interfere with LDL receptors, leading to increased LDL levels (66). However, in at least one study, LDL-receptor function in peripheral blood mononuclear cells after renal transplantation was normal (67).

Post-Transplant Cholesterol-Rich Lipoprotein Metabolism

Few studies have examined cholesterol-rich lipoprotein metabolism. Increased synthesis of VLDL with normal conversion of VLDL to LDL could cause increased levels of LDL (2,56). However, whether the conversion of VLDL to LDL is normal in renal transplantation is unclear (3,27,58,59,62). Triglyceride enrichment of LDL has been documented in corticosteroid-treated patients, and triglyceride-enriched LDL may be less accessible for receptor uptake and degradation (3,63,64). As previously mentioned, corticosteroids and cyclosporine could theoretically interfere with LDL-receptor activity (65,66). Moreover, the decrease of bile-acid synthesis caused by cyclosporine, as demonstrated in vitro, could cause downregulation of hepatic LDL-receptor expression by feedback mechanisms (68,69). However, there are few studies that have measured post-transplant LDL-receptor number and/or function (67).

Post-transplant reverse cholesterol transport (Figure 2) appears to be comparable with that seen in healthy subjects (70,71). An increased triglyceride content of HDL has been reported, and could theoretically impair reverse cholesterol transport (10,63,64). In addition, the abnormal composition of triglyceride-rich lipoproteins may also decrease the transfer of esterified cholesterol, and disturb reverse cholesterol transport. However, normal transport of cholesterol between red blood cells and HDL has been reported (71). Also, plasma lecithin cholesterol acyltransferase (LCAT) activity, which converts unesterified cholesterol to cholesterol esters, has been reported to be normal or even elevated in renal transplant patients treated with corticosteroids (23,72-74). Moreover, newly synthesized cholesteryl ester transfer, an indicator of activity in the segment of reverse cholesterol transport involving LCAT and cholesterol ester transfer protein, was comparable in transplant and non-transplant subjects in the presence or absence of hyperlipidemia (70). Overall, post-transplant reverse cholesterol transport is probably linked to the turnover of triglyceride-rich lipoproteins as shown in non-transplant subjects (75).

Why Lp(a) appears to be normal in some renal transplant patients and increased in the others is unknown. It should be noted that in healthy subjects, the inverse association of plasma Lp(a) concentrations with apo(a) isoform size is not the result of differences in the catabolic rate of Lp(a), but rather to differences in Lp(a) production rates (76). Similar studies are needed to clarify this issue in renal transplant patients. The amelioration of renal function after renal transplantation may not be enough to explain the normalization of serum Lp(a) levels shown in some studies. Indeed, serum Lp(a) decreased quickly and markedly during the first week after renal transplant surgery, even though renal function had only partially recovered (39,42). Moreover, serum Lp(a) levels in four groups of renal transplant patients with different degrees of renal function, including marked renal failure (≤30 mL/min estimated GFR), were comparable with those of control subjects (29). These data suggest that, besides the normalization of renal function, other transplantation-related factors may play a role in the reduction of Lp(a) concentrations.

CONSEQUENCES OF HYPERLIPIDEMIA AFTER KIDNEY TRANSPLANTATION

Cardiovascular disease is one of the most common causes of morbidity and mortality among long-term survivors of kidney transplantation (6,77–79). There is increasing evidence that post-transplant lipoprotein abnormalities may contribute to the development of cardiovascular disease (6,53,80–82). HDL and triglyceride levels appear to be better predictors of post-transplant cardiovascular disease than cholesterol and LDL (6,53). However, the role of modified LDL in post-transplant cardiovascular disease has not been evaluated in renal transplant patients. Apo B, apo C-II, apo C-III, and apo E levels may also predict post-transplant cardiovascular disease (53). Moreover, post-transplant lipoprotein abnormalities were also predictors of asymptomatic carotid atherosclerosis (82).

There is indirect evidence that post-transplant lipoprotein abnormalities may influence the progression of chronic renal allograft rejection (7,83–88). Several clinical studies have reported an association between hyperlipidemia and chronic renal allograft rejection (7,83–88). Increased serum triglycerides appear to be the most consistent predictor of chronic renal allograft rejection (7,83–86). However, the association between chronic renal allograft rejection and hyperlipidemia may be a consequence rather than the cause of renal failure. Few studies have examined the effect of antilipemic therapies on the rate of decline in renal function in patients with chronic renal allograft rejection. However, in heart-transplant patients, pravastatin reduced the incidence of severe acute rejection, 1-year graft survival, and coronary vasculopathy (89). A similar study after kidney transplantation is still in progress, but the results appear to be promising (90). Whether this apparent reduction in acute rejection will reduce chronic renal allograft rejection remains to be determined.

MANAGEMENT OF HYPERLIPIDEMIA AFTER KIDNEY TRANSPLANTATION

There are no intervention trials examining whether antilipemic therapy is beneficial in the prevention of cardiovascular disease, or in slowing the progression
of chronic renal allograft rejection. However, because atherogenic changes in the levels and composition of lipoproteins occur in most renal transplant patients, it is reasonable to assume that the risks associated with hyperlipidemia and the benefits of correcting lipoprotein abnormalities in renal transplant patients are at least comparable with those found in the general population.

We recently used meta-analysis to compare and contrast the relative efficacy of different lipid-lowering strategies in various clinical settings of renal disease (91). Forty studies examined lipid-lowering strategies in renal transplant patients (91). Overall, these 40 studies were of short duration, included few patients, were generally uncontrolled, and most investigated one therapy (91). However, the results of the meta-analysis give some useful insights regarding the relative efficacies of different lipid-lowering strategies in renal transplant patients (Figure 3). Diet, 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase inhibitors, and fibric acid analogues consistently improved lipoprotein abnormalities (Figure 3). Because few studies in renal transplant patients examined the use of niacin or probucol, additional trials are needed before these agents can be recommended for routine use. Similarly, the safety of other lipid-lowering strategies in renal transplant patients needs further evaluation. The risk of rhabdomyolysis in renal transplant patients treated by HMG-CoA reductase inhibitors appears to be small when the doses are reduced and concomitant therapy with other drugs known to cause rhabdomyolysis is avoided (91). Interestingly, increased serum creatinine levels in cyclosporine-treated transplant patients has been reported with bezafibrate, fenofibrate, and ciprofibrate, but not gemfibrozil (92). The mechanism(s) and clinical implications of this increase in serum creatinine levels with fibric acid analogues need further studies. Bile acid sequestrants have not been adequately studied in renal transplant patients. Concerns about decreasing the bioavailability of cyclosporine with bile-acid sequestrants have not been thoroughly investigated (93).

In summary, we believe that antilipemic therapy is reasonable in high-risk renal transplant patients, e.g., patients who have multiple risk factors for cardiovascular disease, and particularly in renal transplant patients who have preexistent cardiovascular disease. Promotion of exercise and maintaining patients on the lowest possible doses of corticosteroids and cyclosporine compatible with prolonged allograft survival will help minimize hyperlipidemia (2,94–96). In the setting of persistently high concentrations of LDL cholesterol (LDL ≥ 160 mg/dL alone, or ≥ 130 mg/dL associated with either two or more risk factors or previous cardiovascular disease), a weight-reduction and low-fat diet should be prescribed (97). However, because diet alone is relatively ineffective in reducing LDL, a low dose of an HMG-CoA reductase inhibitor appears to be the best choice for therapy. It is reasonable to target LDL cholesterol < 130 mg/dL for primary prevention, and ≤ 100 mg/dL for secondary prevention (97). In patients with predominant hypertriglyceridemia (≥200 mg/dL), low calorie intake, low-fat diet, and, in some cases, fish oil may help to reduce triglyceride levels. A fibric acid analogue, e.g., gemfibrozil, may also effectively reduce triglycerides, but the dose must be reduced in patients with decreased renal function. Fibric acid analogues also reduce LDL cholesterol, but not as effectively as HMG-CoA reductase inhibitors. Whether combination therapy is safe and effective in

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**Figure 3.** Effects of antilipemic therapies on lipid and lipoprotein concentrations in renal transplant patients. Data shown are adjusted multiple linear regression coefficients ± confidence intervals. The number of study groups is shown in parentheses. For details see Reference 91. LDL, low-density lipoprotein; HDL, high-density lipoprotein.
reducing lipids in renal transplant recipients requires further studies.

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REFERENCES


