

Hyperlipidemia and Transplantation: Etiologic Factors and Therapy

John D. Pirsch,¹ Anthony M. D'Alessandro, Hans W. Sollinger, Stuart J. Knechtle, Alan Reed, Munci Kalayoglu, and Folkert O. Belzer

J.D. Pirsch, Department of Medicine, University of Wisconsin School of Medicine, Madison, WI

J.D. Pirsch, A.M. D'Alessandro, H.W. Sollinger, S.J. Knechtle, A. Reed, M. Kalayoglu, F. O. Belzer, Department of Surgery, University of Wisconsin School of Medicine, Madison, WI

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ABSTRACT

Hyperlipidemia is a well-recognized complication of renal transplantation. In long-term survivors of renal transplantation, cardiovascular disease accounts for the majority of patient deaths. In the cyclosporine era, cardiovascular disease has surpassed infection as the number one cause of death. Risk factors in the transplant population for hyperlipidemia include age, male sex, diabetes, prednisone dose, graft impairment, obesity, and antihypertensive therapy. Recently, cyclosporine has been implicated as an aggravating factor in the development of hyperlipidemia after transplantation, although its role has been controversial. Because renal transplant recipients have other significant risk factors for the development of coronary artery disease, the amelioration of hyperlipidemia may improve long-term patient survival. Because most late deaths occur in patients with a functioning graft, long-term graft survival could also be improved. The role of corticosteroids in the development of hyperlipidemia is well established. Recent studies employing corticosteroid withdrawal after transplantation have shown a marked reduction in cholesterol despite the use of cyclosporine. Data on corticosteroid withdrawal in living related transplants at our center show a significant reduction in total cholesterol after steroid withdrawal. Data from heart transplant recipients under corticosteroid-free protocols show a similar reduction in total cholesterol. Other treatments for hyperlipidemia include diet and cholesterol-lowering agents, such as Mev-

acor® (lovastatin; Merck Sharp & Dohme, West Point, PA). The efficacy of lowering cholesterol in this high-risk population is unknown.

Key Words: Hyperlipidemia, renal transplantation, therapy, cyclosporine, corticosteroids

Hyperlipidemia is a well-recognized complication of therapy for end-stage renal disease. Abnormalities in serum lipids are common in dialysis patients and renal transplant recipients (1-6). With improvements in both modalities of therapy and longer life expectancy, it is not surprising to find that cardiovascular disease is the leading cause of death for both modalities of treatment (7). In transplant recipients under cyclosporine immunosuppression, cardiovascular mortality exceeds infection as the number one cause of death at our center (8). In long-term transplant survivors, death with a functioning graft is the second leading cause of graft failure after rejection (9). Decreasing mortality in long-term recipients would improve both patient and graft survival.

Recent studies, such as the Lipid Research Clinics Coronary Primary Prevention Trial (10,11) and the Helsinki Heart Study (12), have demonstrated significant reductions in the incidence of coronary heart disease events in patients who achieved a reduction in total cholesterol and low-density lipoprotein (LDL) cholesterol. These findings led to recommendations by the National Cholesterol Education Program and the development of guidelines for the treatment of hypercholesterolemia (13). Transplant recipients with risk factors for coronary artery disease have not been studied in sufficient detail to assess the efficacy of the treatment of hyperlipidemia. Despite the lack of evidence that treatment is beneficial, a large body of data exists regarding the risks for post transplant hyperlipidemia and recent evidence indicates that corticosteroids play a major role in its development.

CHARACTERIZATION OF HYPERLIPIDEMIA

Hyperlipidemia after transplantation was characterized in a number of studies during the 1970s (1-5,14-20). Lipid abnormalities in dialysis patients typically involve high triglyceride levels and normal cholesterol values (type IV hyperlipidemia) (1-3,6,20). Transplant recipients have different patterns of hyperlipidemia, with most studies demonstrating increased triglycerides and cholesterol

¹ Correspondence to Dr. J.D. Pirsch, Department of Surgery, University of Wisconsin Hospital and Clinics, 600 Highland Avenue, Madison, WI 53792.

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TABLE 1. Characterization of hyperlipidemia in transplant recipients

Triglycerides	↑→
Total cholesterol	↑
LDL cholesterol	↑
HDL cholesterol	↑→

(Table 1) (1–4,6,15–21). The predominant abnormality appears to be an increased total cholesterol with normal or slightly increased high-density lipoprotein (HDL) cholesterol values with the most common phenotypic patterns being type II, either a or b, and type IV. Ibels *et al.* (18) reported on 205 transplant recipients and found a 61% incidence of hyperlipidemia. Of those studied, 26% had type IV hyperlipoproteinemia, 23% had type IIb, and 11% had type IIa. Significant increases in serum cholesterol occurred in one third of the adult recipients and nearly half of the pediatric and diabetic recipients.

Levels of LDL and HDL are altered after transplantation (6,21–25). LDL levels are increased after transplantation (24,25). HDL levels are reported to be low in dialysis patients but rise to normal after successful transplantation (6,21–23). This increase in total HDL cholesterol from pretransplant levels is primarily due to an increase in the subclass HDL₂ levels because there is little change in subclass HDL₃ (26).

RISK FACTORS

Risk factors for the development of hyperlipidemia are well characterized (Table 2) (3,4,6,16–19,21,24,27–37). The majority of studies that analyzed risk factors for the development of hypertriglyceridemia found prednisone dosage, renal impairment, obesity, and antihypertensive therapy as cofactors for its development (4,18,27,34). The pathogenesis of hypertriglyceridemia is unclear. Earlier reports found that the posttransplant increase in triglycerides was related to hyperinsulinemia (15,38); however, others found no association (4,16). Lipolytic activity after transplantation is normal, making decreased triglyceride clearance unlikely (Table 3) (39,40). Calorie restriction normalizes triglyceride levels (19), and a number of studies have linked obesity and hypertriglyceridemia (4,16,18,27,31,34). Antihypertensive medications, particularly beta blockers and diuretics, have also been implicated in the development of hypertriglyceridemia after transplantation (27,34).

Risk factors for the development of hypercholesterolemia include prednisone dosage, poor renal function, pretransplant cholesterol, proteinuria, male sex, age, antihypertensive therapy, and increased body weight (3,16–18,21,24,27–34). Several investigators have reported a beneficial effect in pa-

TABLE 2. Risk factors for hyperlipidemia in transplant recipients (reference numbers)

Age (16, 30, 31, 32, 34)
Obesity (4, 16, 18, 27–32)
Prednisone Dosage (3, 4, 16, 18, 19, 21, 24, 27, 30, 32)
Renal Dysfunction (4, 6, 16, 18, 24, 27, 30)
Proteinuria (21, 24, 33, 34)
Antihypertensive Medication (17, 24, 27, 33, 34)
Pretransplant Hyperlipidemia (21, 32)
Male Sex (34)
Cyclosporine (35–37)
Diabetes (24, 30)

tients who are on alternate-day corticosteroid therapy (38,41,42), although others have not (16,18,27).

Altered lipid metabolism has also been noted in recipients of cyclosporine (35–37). Harris *et al.* (35) noted a marked improvement in serum cholesterol and triglyceride levels when patients were converted from cyclosporine to azathioprine. Versluis *et al.* (37) found a similar effect of cyclosporine on lipid values; however, other investigators have found no effect (30,31,34,43). Gonwa *et al.* (43) found no significant improvement in lipid values after conversion from cyclosporine to azathioprine. In addition, two recent studies in cyclosporine-treated renal transplant recipients found no significant association between levels of cyclosporine in blood and levels of serum lipids (30,34).

EFFECT OF STEROID WITHDRAWAL ON HYPERLIPIDEMIA

Both cumulative dose and maintenance doses of corticosteroids have been implicated in the development of posttransplant hyperlipidemia (3,4,16,18, 19,21,24,27,30,32). The effect of alternate-day steroids has proven beneficial in some studies (38,41, 42) but not in others (16,18,27). The introduction of cyclosporine has allowed several centers to conduct prospective steroid-withdrawal trials in heart (44, 45) and kidney transplantation (46,47).

Graft atherosclerosis is a significant complication in heart transplantation, resulting in patient loss and graft failure. Renlund *et al.* (44) studied the effect of corticosteroid-free immunosuppression in 117 heart recipients and found a significant decrease in their

TABLE 3. Pathogenesis of posttransplant hyperlipidemia

Steroid-Induced Hyperinsulinemia
Decreased Triglyceride Clearance (Decreased Lipoprotein-Lipase Activity)
Dietary Indiscretion
Concomitant Medications (Beta Blockers, Diuretics)

serum cholesterol levels when compared with those in patients receiving corticosteroids. Similar findings were reported by Taylor *et al.* (45) in a smaller study of heart transplant recipients under cyclosporine and azathioprine immunosuppression.

In a prospective trial of steroid withdrawal in cadaver kidney recipients, Hricik *et al.* (47) found a significant reduction in total serum cholesterol level despite higher trough cyclosporine levels in the patients not receiving corticosteroids. Patients in both groups had similar weight gain regardless of corticosteroid administration.

Data from our center support the observation that corticosteroid withdrawal lowers cholesterol levels (48). Since 1986, we have employed an aggressive steroid-withdrawal protocol in recipients of living related transplants. Corticosteroid withdrawal was attempted by day 12 in all recipients, and long-term immunosuppression consisted of azathioprine and cyclosporine. One hundred thirty-one living related recipients were entered (34 HLA-identical and 97 haplo-identical recipients). Fifty-two (39%) were insulin-dependent diabetics. Overall, 40% of the recipients were not receiving corticosteroids, with most patients reverting to steroids because of rejection.

Cholesterol levels were significantly lower in prednisone-free recipients compared with those in patients who returned to steroids because of rejection (Figure 1). An age- and disease-matched control group of azathioprine-prednisone recipients had intermediate cholesterol levels. Hypertension was also less frequent in recipients maintained off corticosteroids. Despite lower cholesterol values, weight gain was similar in all three groups.

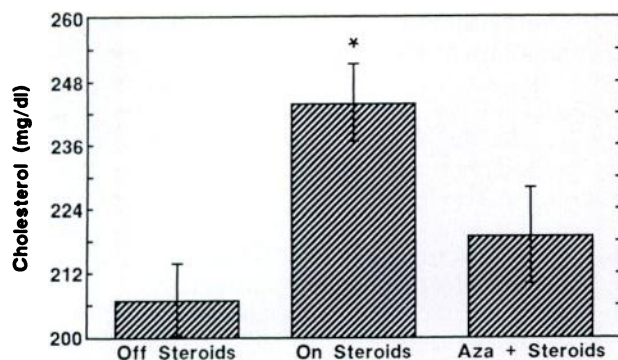


Figure 1. Total serum cholesterol in living related renal transplant recipients receiving cyclosporine and on or off steroids. Total serum cholesterol levels in cyclosporine-treated, living related renal transplant recipients on ($N = 52$) or off steroids ($N = 64$) and in a control group receiving azathioprine (Aza) and prednisone ($N = 40$). Total cholesterol is significantly higher in recipients receiving cyclosporine and prednisone than in the other two groups ($P < 0.01$).

TREATMENT

There are few studies that address the treatment of hyperlipidemia in transplant recipients. Dietary therapy has been successful in reducing lipids in transplant patients, but long-term efficacy has not been addressed (19,49). The role of pharmacologic therapy is even less clear, especially in view of possible drug interactions with the immunosuppressive medications. Severe rhabdomyolysis has occurred in cardiac transplant recipients who have received concomitant lovastatin and cyclosporine (50,51). The risk of rhabdomyolysis may be increased with the concomitant use of gemfibrozil and lovastatin (52).

A recent double-blind, placebo-controlled trial in renal transplant recipients demonstrated the efficacy of lovastatin when used in a dose of 20 mg/day (53). However, recipients receiving cyclosporine were excluded. Cholesterol values decreased 21% after the initiation of lovastatin with reductions of LDL cholesterol of 28%. Experience with the use of lovastatin at the University of Wisconsin has been favorable. To reduce the incidence of rhabdomyolysis, we initiate therapy at 10 mg/day and do not exceed 20 mg/day total dose. Only one patient has experienced significant side effects from lovastatin therapy, and this was associated with an increase of the lovastatin from 20 to 40 mg/day. Effective lowering of lipid levels has occurred in all patients with an absence of side effects. However, close monitoring of patients receiving lovastatin and cyclosporine is required.

CONCLUSION

Transplant recipients often have multiple risk factors for the development of coronary artery disease. In the cyclosporine era, death from cardiac disease is the number one cause of mortality. The high incidence of hyperlipidemia in transplant patients is a potential risk factor that could be modified in an attempt to lower this high risk of cardiac events. It appears from the data that immunosuppressive therapy with prednisone is one of the most significant risk factors for the development of posttransplant hyperlipidemia. The role of cyclosporine in the development of hyperlipidemia is less clear. Patients treated under steroid-withdrawal protocols after both heart and kidney transplant show a significant decrease in lipid values when compared with those treated with cyclosporine and prednisone.

The treatment of hyperlipidemia in transplant recipients is unclear. Dietary therapy remains the cornerstone of efforts to lower high total cholesterol and triglyceride levels. The recent introduction of lovastatin has been associated with a higher risk of rhabdomyolysis when used in higher doses and in conjunction with gemfibrozil. However, it has been shown to be effective in reducing lipid levels in trans-

plant recipients. Although efforts to reduce lipid values in transplant recipients is a worthy goal and may decrease the incidence of cardiac events, there are no published data that support this contention.

Clearly, efforts to decrease corticosteroid use after transplantation would help lower lipid levels. New investigational immunosuppressive agents, such as RS-61443 (Syntex Research, Palo Alto, CA) or FK-506 (Fujisawa, Deerfield, IL), may lessen the dependence on corticosteroids after transplantation. Until newer agents are available, dietary therapy combined with low- or no corticosteroid doses and the cautious use of 3-hydroxy-3-methylglutaryl-coenzyme A inhibitors, such as lovastatin, may lessen the effect of hyperlipidemia on cardiovascular mortality after transplantation.

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