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Dyslipidemia Can Be Controlled in Diabetic as well as Nondiabetic Recipients after Kidney Transplant

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Abstract

Background—Patients with diabetes have been reported to have greater dyslipidemia after kidney transplant (KTX). As post-KTX management of diabetes has changed dramatically since those reports, we hypothesized that lipids can be controlled as well in diabetic as nondiabetic recipients.

Methods—We compared lipids up to two years after KTX (n=192) between diabetic and nondiabetic recipients. The cohort was subdivided into non-diabetic (nonDM-K; n=123), type 2 (DM2-K; n=33), or type 1 diabetes after KTX (DM1-K; n=14), or type 1 after kidney-pancreas (DM1-KP; n=22).

Results—Mean age and BMI of DM2-K were greater than the others (p<0.01), and diabetes groups had a higher pre-transplant A1C than nonDM-K (p<0.001). After KTX, lipids were not greater in diabetic than nondiabetic recipients, and didn't increase in any group. Total and LDL-cholesterol decreased in DM1-K (p<0.001), HDL decreased in DM1-KP (p=0.02), and triglycerides were unchanged after KTX for all groups. A1C improved in DM1-K and DM1-KP (p<0.0001). There was less improvement in lipids with tacrolimus-sirolimus immunosuppression than other steroid-containing regimens (p<0.05).

Conclusions—Multiple mechanisms may contribute to better lipids in both groups as well as the lack of difference between diabetic and nondiabetic recipients compared to what has been reported previously: greater use of and more effective lipid lowering agents, no significant weight gain, no difference in renal function between groups, and better control of glucose in the diabetic group. Thus, overall, lipids can be controlled as well in diabetic as nondiabetic KTX recipients.

Keywords

Dyslipidemia; Diabetes; Kidney Transplant

INTRODUCTION

Cardiovascular risk is improved by KTX but remains the leading cause of mortality after kidney transplant and is 50-fold higher than the general population (1–4). Dyslipidemia, and hypercholesterolemia, in particular, are common after KTX in previous reports (2,5–8), and correlate with cardiovascular disease and chronic allograft nephropathy, decreasing long-term

graft function after KTX (9–11). Many factors contribute to dyslipidemia after KTX. Obesity (12), weight gain, diabetes (7,13–15), corticosteroids (16–18), calcineurin inhibitors and sirolimus (19) have all been reported to contribute to dyslipidemia. Greater dyslipidemia has been assumed to be one of the contributing factors to greater graft failure and mortality in diabetes patients after KTX (20). However, the effect of diabetes on lipids after KTX has not been assessed with more recent immunosuppressant medication regimens, and the effect of type of diabetes, type 1 vs type 2, on dyslipidemia after KTX has never been studied. For these reasons, we retrospectively analyzed a cohort of KTX recipients to compare lipid changes between diabetic and nondiabetic recipients.

MATERIALS AND METHODS

Patient population

We evaluated the records of all KTX recipients 21 y or greater performed between January 1, 2003 and December 31, 2004, at The Nebraska Medical Center (n=207) using the Organ Transplant Tracking Record (OTTR) *software* application of HKS Medical Information Systems, developed at University of Nebraska Medical Center for tracking organ transplant patients and their outcomes by Byers Shaw, MD, Hubert Hickman, and Paul Kenyon. Additional data was obtained as necessary from the computerized medical record to confirm findings. Of these, two were excluded because of death before 7 months follow-up, and 13 were excluded because they had previously received a liver, small bowel, lung, or heart transplant. Previous pancreas transplant recipients were included.

The characteristics of the 192 remaining recipients are shown in Table 1. Of these, 36 (19%) had type 1 diabetes (DM1), which were divided based on whether or not they also had a functioning pancreas graft: kidney transplant alone on insulin (DM1-K; n=14) including 7 with a previous failed pancreas graft; and pancreas-kidney with normal pancreas function (DM1-KP; n=22), including both simultaneous pancreas-kidney recipients (n=15) or kidney transplant after functioning pancreas graft (n=7). Thirty-three had type 2 diabetes (17%; DM2-K). All DM1-KP were off insulin or any other diabetes treatment and had an A1C<7% at all times.

The remaining 123 (64%) did not have diabetes (nonDM-K) but received a kidney transplant for diverse causes of renal failure: idiopathic causes of glomerular disease (n = 39), hypertensive kidney disease (n=22), chronic kidney disease (n = 20), polycystic kidney disease (n = 16), infection/obstructive kidney disease (n = 9), systemic causes of glomerular disease (n = 9), scleroderma (n = 2), acute renal failure with lesion of renal cortical necrosis (n = 1), sarcoidosis (n = 1), emphysema (n = 1), renal cell carcinoma (n = 1), unspecified viral infection (n = 1), and hemolytic uremic syndrome (n = 1).

Definition of post-transplant diabetes

The American Diabetes Association glucose threshold values for non-transplant patients were used to establish the International Guidelines for Post-Transplant Diabetes in 2003 (21): fasting glucose ≥ 126 mg/dl on more than one occasion, or random glucose ≥ 200 mg/dl with symptoms, or an abnormal oral glucose tolerance test. It is important to note that the guidelines for post-transplant diabetes do not specify the setting, so both inpatient and outpatient glucose values could be used to diagnose post-transplant diabetes, which is not the same as the same as ADA criteria. However, in a retrospective analysis, it can be difficult to determine if a sample is fasting or whether or not symptoms were present, which are also important to the criteria.

Among the nonDM-K group, 22 were recognized and treated for post-transplant diabetes (18%) with an oral agent, insulin, or both. However, assuming all first AM samples were fasting, as

is routinely requested for transplant clinic lab testing, and assuming all those with random glucose values >200 mg/dl had symptoms, an additional 40 subjects may potentially qualify as having post-transplant diabetes using the International Criteria. These subjects were never identified as having diabetes and no treatment was initiated, but the hemoglobin A1C of this group was normal post-transplant, $5.34 \pm 0.68\%$ (normal A1C <6%), and unchanged from their normal pre-transplant A1C ($5.30 \pm 0.65\%$; mean $\pm$ SD). Since, diagnosis of post-transplant diabetes cannot be assured in the glucose value only group, analysis of lipids for the post-transplant diabetes group was performed both ways: the clinically identified group only, and the clinically identified with the glucose value group.

Induction and Immunosuppression

All individuals receive thymoglobulin (rATG), accompanied by steroids, for induction. Most recipients subsequently received tacrolimus-sirolimus immunosuppression without corticosteroids (78%). The remainder were treated with a variety of other immunosuppression regimens (see Table 2). Corticosteroids were used chronically in 15% of the study population, including those prescribed for treatment of other conditions such as adrenal insufficiency or other autoimmune disease (e.g., lupus), unrelated to immunosuppression for transplant. Very few (n=5; 3%) received both corticosteroids and tacrolimus-sirolimus.

Biopsy-proven rejection was treated with a short burst of corticosteroids with OKT-3 reserved for severe or steroid-resistant rejection only, and a change in their underlying immunosuppression agent doses as indicated.

Demographic variables

Age, race and ethnicity, gender, weight, height and calculated body mass index (BMI), type of donor (living vs deceased donor), systolic blood pressure (SBP), and diastolic blood pressure (DBP) were all extracted from the medical record.

Laboratory tests

Fasting lipid profile, A1C (even in nondiabetic recipients), serum creatinine with estimated GFR by the MDRD equation (22), and immunosuppressant drug levels were evaluated over time. These tests are also ordered at each routine transplant visit (1, 3, 6, 9 and 12 mo and then annually). A1C, serum creatinine, fasting lipids, and immune suppressant medication levels were analyzed in the clinical laboratory of The Nebraska Medical Center. A direct LDL was also measured when triglycerides were high. A1C was performed by HPLC with normal range <6%. Immunosuppressant drug levels were evaluated by mass spectroscopy (23).

Management goals and definition of dyslipidemia

Lipid treatment goals in clinic during this interval were similar to those subsequently recommended in diabetic and nondiabetic recipients (2): total cholesterol <200 mg/dl, LDL <100 mg/dl, and triglycerides <150 mg/dl. In general, then as now, individuals whose lipid concentrations remain greater than these threshold values are considered to have dyslipidemia. Statins, fibric acid derivatives, ezetimibe, and fish oil were prescribed to improve lipids, although great care was exercised with combinations of hypolipidemic agents except when the second agent was fish oil because of the greater risk of side effects when used concomitantly with calcineurin inhibitors.

Type 1 diabetes patients were treated with insulin, except those that received a pancreas transplant, and only those with functional grafts off all insulin or other diabetic therapies were included in this group (DM1-KP). Type 2 diabetes patients were treated with a variety of oral hypoglycemic agents or insulin as needed to meet a minimum A1C goal of 7% or lower,

whenever it could be achieved safely. Treatment of diabetes was assumed to be beneficial not only for glucose but for lipid metabolism.

Statistical analysis

Pre-transplant characteristics were compared between four groups (DM1-KP, DM1-K, DM2-K, and nonDM-K) by Chi-squared test (gender), Fisher's Exact test (race, donor type), ANOVA (age, pre-transplant BMI, DBP and SBP) or Kruskal-Wallis test (to assess the sensitivity for ANOVA assumptions). Fasting lipids were compared between four groups (DM1-KP, DM1-K, DM2-K, and nonDM-K) pre-transplant and up to 2 y after KTX. Post-transplant values were grouped by time into 3–6 and >6 month intervals. Concentrations were summarized as mean $\pm$ SD. Lipids performed 0–3 months were excluded as this period of time often includes time of interrupted nutrition, hospitalizations, and rapidly changing immunosuppression and often not representative of later lipid concentrations, but lipid concentrations were not higher during this period of time for any group. Patient and graft survival analysis were performed using Kaplan-Meier curves and log-rank test.

We used multiple linear regression models to compare the change in LDL, HDL, and triglyceride concentrations from before to after transplant among the 4 groups. When it was identified that many individuals were not on statins before transplant, we chose to assess the impact of initiation of statins, in particular, as a contributing factor to changes in lipids between pre- and post-transplant and between groups. Thus, effect of statin initiation on lipids was evaluated by comparing those not on statins before or after transplant, to those who were not on statins before but were prescribed statins after, and those on statins before and after transplant. Diabetes status (group), statin usage pattern, and tacrolimus-sirolimus usage were forced into the model. Age, gender, race, pre-transplant BMI, A1c, SBP, DBP, donor type were included only when those variables have a p-value of 0.2 or less in univariate linear regression.

As most were prescribed tacrolimus-sirolimus, receiving tacrolimus-sirolimus treatment (Yes/No) was compared to all others in all multivariate models. Demographics (age, gender, White race, donor type) and prognostic factors (pre-transplant BMI, DBP, SBP and A1c) were included if they were at least potentially significantly associated ($p < 0.20$) with the outcome of change in LDL, triglyceride and HDL in univariate linear regression. For all pair-wise comparisons, we used Tukey's method to adjust for multiple comparisons (24).

All analyses are performed using SAS version 9.1 (Cary, NC).

RESULTS

Pre-transplant characteristics

Overall pre-transplant demographic and vascular disease risk variables for the four groups: type 1 diabetes following pancreas and kidney transplant (DM1-KP), type 1 diabetes after kidney transplant (DM1-K), type 2 diabetes (DM2-K), and non-diabetes (nonDM-K) are shown in Table 1. As expected, some characteristics were different between these groups before transplant. Mean age of DM2-K was higher than that of DM1-K ($p = 0.005$), DM1-KP ($p < 0.0001$) and nonDM-K ($p < 0.0001$). Pre-transplant BMI was significantly higher in DM2-K than DM1-K (mean $\pm$ SD: 30.3 ± 4.0 vs 24.2 ± 5.1 kg/m²; $p = 0.005$), DM1-KP (26.3 ± 3.6 kg/m²; $p = 0.02$) and nonDM-K (26.8 ± 5.2 kg/m²; $p = 0.001$). There was no significant difference in pre-transplant systolic (SBP) blood pressure among the groups, but pre-transplant diastolic blood pressure (DBP) was significantly lower in DM2-K than DM1-KP ($p = 0.03$) and nonDM-K ($p < 0.0001$). A1c was higher in DM1-K and DM1-KP ($7.8 \pm 2.1\%$ and $7.6 \pm 1.6\%$, respectively) compared to DM2-K and nonDM pre-transplant ($6.4 \pm 0.9\%$ and 5.4 ± 1.1 , respectively; $p < 0.005$).

Lipid changes after transplant

Lipids before and after transplant are shown in Figures 1–4. Pre-transplant total and LDL-cholesterol were higher in DM1-K compared to the other groups (Figures 1 and 2), but the differences were not statistically significant. HDL and triglycerides were not different between groups before transplant.

After KTX, there was no significant difference in total cholesterol, LDL, HDL or triglycerides between the groups. Total and LDL-cholesterol improved in DM1-K after KTX ($p=0.001$). Triglycerides remained unchanged in all groups after KTX (Figure 3). HDL decreased in DM1-KP after KTX ($p=0.02$; Figure 4).

After adjusting for multiple comparisons, DM1-K group had a significantly larger decrease in LDL after KTX than DM1-KP ($p=0.03$) or nonDM-K ($p=0.006$). Both DM1 groups, DM1-K and DM1-KP, also had a significantly greater decrease in HDL than DM2-K after KTX. In addition, female gender, non-white race and older age were significantly associated with a greater decrease in HDL. Other variables included in the multivariate model are the tacrolimus-sirolimus usage and statin usage status. Change in triglycerides after transplant was not different between the groups after adjusting for multiple comparisons.

Differences in co-variables that could affect lipid concentrations after transplant including rejection

Several potential factors that could affect lipids or lipid changes after transplant were analyzed. Incidence of rejection was not different between groups ($p=0.06$) with incidence by group as follows: 0 (0%) for DM1-K, 1 (4.6%) for DM-KP, 2 (6.1%) for DM2-K and 6 (4.9%) for nonDM-K. This suggests that neither rejection nor treatment of rejection had a significant impact on the other outcome measures identified below. There was also no significant difference in patient survival ($p=0.12$), or graft survival ($p=0.22$) between groups. However, the time interval for study was short, and the study was not designed to evaluate any of these outcomes. Thus, the lack of a difference does not preclude the possibility that graft or patient survival could be different between groups over time.

BMI did not significantly change after KTX in any group although BMI of DM2-K was still significantly higher than DM1-K ($p=0.006$), DM1-KP ($p=0.02$) and nonDM-K ($p=0.02$) as before KTX. As expected, A1C improved in DM1-KP after transplant ($7.58 \pm 1.57\%$ to $5.25 \pm 0.38\%$; $p<0.0001$), but A1c also improved in DM1-K after KTX ($7.84 \pm 2.11\%$ to $6.42 \pm 1.62\%$; $p<0.0001$). A1C did not change after KTX in nonDM-K ($5.35 \pm 1.14\%$ to $5.5 \pm 0.81\%$) and DM2-K ($6.35 \pm 0.92\%$ to $6.65 \pm 1.06\%$) groups ($p \geq 0.1$). After KTX, estimated GFR and serum creatinine were similar between groups, suggesting no significant differences in graft function between the groups that might affect lipid metabolism. Mean creatinine after KTX was 1.57 ± 0.72 mg/dl (mean $\pm$ SD) in DM1-K; 1.48 ± 0.67 mg/dl in DM1-KP; 1.79 ± 1.43 mg/dl in DM2-K; and 1.53 ± 0.60 mg/dl in nonDM-K. Of note, SBP and DBP were also unchanged after KTX. It is also important to note that serum creatinine of those treated with predominant immunosuppression regimen, tacrolimus-sirolimus, was not significantly different from serum creatinine of those treated with other combinations ($p=0.21$).

Use of hypolipidemic agents is a factor in lipid concentrations before and after transplant. A minority of the recipients was on statins at the time of transplant (14%), and use of statins at time of transplant was significantly different between the groups ($p=0.007$), with more diabetic than non-diabetic recipients likely to be prescribed statins before transplant (DM1-KP=36%; DM1-K=21%; DM2-K=15%; nonDM-K=9%). However, use of statins increased significantly in all groups after transplant to 69% overall, with no difference in utilization between groups ($p=0.84$). Other hypolipidemic agents were also prescribed after transplant in 29%, including

ezetimibe, fenofibrate, gemfibrozil, or fish oil, and most of these recipients (78%) were also taking statins.

The pattern of statin use was analyzed since initiation of statins could be a factor. Three statin usage patterns were compared: those starting statins after transplant, those treated with statins pre- and post-transplant, and those not treated with statins pre- or post-transplant. Statin usage pattern was potentially significant ($p<0.20$) in the univariate analysis of change in LDL and triglycerides after transplant. However, in multivariate analyses, initiation of statins was not significantly associated with change in LDL or triglycerides. Statin use was not a significant factor for change in HDL in either univariate or multivariate analysis.

Immunosuppression medications also affect lipids. Distribution of immunosuppressants used in each group post-transplant is shown in Table 2. There was no significant difference in use of tacrolimus or corticosteroids between the groups, but frequency of sirolimus and MMF did vary between groups as shown. Most KTX recipients were prescribed the combination of tacrolimus-sirolimus (78%) during this time period, so use of tacrolimus-sirolimus was compared to all other combinations as a factor for change in lipids after transplant in both univariate analysis, and with statin use in multivariate analysis.

Tacrolimus-sirolimus treatment, like statin use, was potentially significant ($p<0.20$) in the univariate analysis of change in LDL and triglycerides after transplant. Using multivariate analyses, those treated with tacrolimus-sirolimus treatment had less decrease, as in less improvement, in LDL ($p=0.002$) and triglycerides ($p=0.006$) after transplant, compared to other regimens. Tacrolimus-sirolimus treatment was not a significant factor for change in HDL after transplant in univariate or multivariate analyses.

Post-transplant diabetes and any associated differences in lipids

The incidence of new onset diabetes was 18%, based on cases identified clinically. If those identified with glucose testing only, using the new International criteria for post-transplant diabetes (21), were also included, with the limitations of not being able to establish whether the patient was fasting or had symptoms which is necessary to confirm the diagnosis, the incidence of post-transplant diabetes was potentially as high as 50% (62/123). Lipids and lipid changes were not different between those who developed post-transplant DM and those that did not using either criteria, clinical only or clinical plus those identified using the new International criteria. However, it should be noted that the subjects identified only by abnormal glucose value not only had a normal A1C post-transplant, $5.34 \pm 0.68\%$ (normal A1C $<6\%$), but had no change from their normal pre-transplant A1C ($5.30 \pm 0.65\%$; mean $\pm$ SD), suggesting these individuals did not have a significant change in mean glucose concentration, if they actually did meet criteria. Further, even if they were recognized as having diabetes, their treatment would not have changed, as their mean A1C was normal.

DISCUSSION

Dyslipidemia increases risk for ischemic heart disease and renal graft failure after KTX (25), and dyslipidemia is common after KTX in previous studies (5,9,26–31). Specifically, elevated cholesterol, defined as >200 mg/dl, has been reported in 83–90% of KTX recipients, and elevated LDL, as defined as >100 mg/dl, in 90–97%, in the past (28,32,33). More recently, 60% of KTX recipients have been reported to have an LDL greater than 130 mg/dl (34). Many factors, including obesity, diabetes, declining renal function and immunosuppressive drugs has been suggested to contribute to dyslipidemia after KTX (5,34–36).

Diabetes, particularly type 2 diabetes, can be associated with greater dyslipidemia in a variety of settings, particularly because of its association with obesity and insulin resistance. Insulin

is important to lipid metabolism so decreased insulin secretion or greater insulin resistance can also contribute to dyslipidemia. Hyperglycemia is generally assumed to be a contributing factor to the greater mortality and graft failure that is observed with diabetes (20), but greater obesity, hypertension, dyslipidemia, or a combination of the above could also contribute, particularly with type 2 diabetes. No previous report has compared lipids between type 1 vs type 2 diabetes after KTX.

In this report, neither type of diabetes was associated with greater dyslipidemia after KTX compared to nondiabetic recipients. In fact, lipid profile did not significantly worsen in any group. Availability of insulin and insulin action affects lipid metabolism, just as it affects glucose control. In this cohort, glucose control, as assessed by A1C, was either stable or improved, including after KTX alone in type 1 diabetes recipients. Thus, we cannot exclude the possibility that greater lipid changes might have been observed if the diabetes was not as well controlled. Finally, while differences in kidney function can affect lipid metabolism, kidney function was not significantly different between groups in this study.

Could the lack of a significant change in lipids be due to the predominant use of a steroid-free tacrolimus-sirolimus regimen? While corticosteroids can cause dyslipidemia, tacrolimus and sirolimus have also been linked to dyslipidemia (37). There was a difference in frequency of use of individual immunosuppression agents after KTX (see Table 2). Sirolimus was used more in type 1 diabetes recipients, and MMF was used less in DM1-K and nonDM groups. Since sirolimus is generally associated with more dyslipidemia, these differences in immunosuppression regimens do not explain the absence of greater dyslipidemia in diabetic recipients.

In fact, those treated with the tacrolimus-sirolimus regimen had less improvement in lipids than those treated with other, mostly steroid-containing regimens. There are few other reports evaluating the impact of tacrolimus-sirolimus on lipids after KTX. One study suggested lipid profile was better with MMF-tacrolimus-steroids than tacrolimus-sirolimus-steroids, although steroids were used in both groups (38). In another study, three immunosuppression regimens were compared: tacrolimus-sirolimus, MMF-tacrolimus, and sirolimus-cyclosporine. MMF-tacrolimus treatment resulted in a better lipid profile, than tacrolimus-sirolimus or sirolimus-cyclosporine (39). Thus, while corticosteroids can worsen lipids, at least some steroid-free regimens, such as tacrolimus-sirolimus, may not translate into improved lipids. Removing corticosteroids alone is not adequate to guarantee an improvement in cardiovascular risk. However, even though tacrolimus-sirolimus may not result in the best lipid profile, this study suggests that lipid goals can still be achieved in most.

In conclusion, dyslipidemia was not greater in diabetic than non-diabetic recipients after KTX, or significantly different between type 1 and type 2 diabetes recipients. Better monitoring and treatment of diabetes, greater use of lipid lowering agents that are far more effective than those available in the past, as well as adherence to specific lipid treatment guidelines, and absence of weight gain or difference in renal function between groups all likely contributed. Use of steroid-free immunosuppression was not a benefit to lipids in this cohort. These data show that with careful post-transplant monitoring, individuals with diabetes, type 1 or type 2, need not have worse lipids or glucose after KTX.

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LITERATURE CITED/REFERENCES

1. Kasiske B. Epidemiology of cardiovascular disease after renal transplantation. *Transplantation* 2001;72:S5. [PubMed: 11585242]
2. Kasiske B, Cosio FG, Beto J, et al. Clinical practice guidelines for managing dyslipidemias in kidney transplant patients: a report from the Managing Dyslipidemias in Chronic Kidney Disease Work Group of the National Kidney Foundation Kidney Disease Outcomes Quality Initiative. *Am J Transplant* 2004;4 (Suppl 7):13. [PubMed: 15027968]
3. de Mattos AM, Prather J, Olyaei AJ, et al. Cardiovascular events following renal transplantation: role of traditional and transplant-specific risk factors. *Kidney Int* 2006;70 (4):757. [PubMed: 16788687]
4. Ojo AO. Cardiovascular complications after renal transplantation and their prevention. *Transplantation* 2006;82 (5):603. [PubMed: 16969281]
5. Aakhus S, Dahl K, Wideroe TE. Hyperlipidaemia in renal transplant patients. *J Intern Med* 1996;239 (5):407. [PubMed: 8642233]
6. Brown JH, Murphy BG, Douglas AF, et al. Influence of immunosuppressive therapy on lipoprotein(a) and other lipoproteins following renal transplantation. *Nephron* 1997;75 (3):277. [PubMed: 9069448]
7. Shaheen FA, Souqiyyeh MZ, Shiek IA, et al. Hypercholesterolemia in renal transplantation. *Ann Transplant* 2001;6 (4):9. [PubMed: 12035461]
8. Kasiske BL. Clinical practice guidelines for managing dyslipidemias in kidney transplant patients. *Am J Transplant* 2005;5 (6):1576. [PubMed: 15888073]
9. K/DOQI clinical practice guidelines for management of dyslipidemias in patients with kidney disease. *Am J Kidney Dis* 2003;41(4 Suppl 3):I. [PubMed: 12671933]
10. Dimeny E, Wahlberg J, Lithell H, Fellstrom B. Hyperlipidaemia in renal transplantation--risk factor for long-term graft outcome. *Eur J Clin Invest* 1995;25 (8):574. [PubMed: 7589013]
11. Guijarro C, Massy ZA, Kasiske BL. Clinical correlation between renal allograft failure and hyperlipidemia. *Kidney Int Suppl* 1995;52:S56. [PubMed: 8587285]
12. Markell MS, Armenti V, Danovitch G, Sumrani N. Hyperlipidemia and glucose intolerance in the post-renal transplant patient. *J Am Soc Nephrol* 1994;4 (8 Suppl):S37. [PubMed: 8193294]
13. Pirsch JD, D'Alessandro AM, Sollinger HW, et al. Hyperlipidemia and transplantation: etiologic factors and therapy. *J Am Soc Nephrol* 1992;2 (12 Suppl):S238. [PubMed: 1498281]
14. Bastani B, Robinson S, Heisler T, et al. Post-transplant hyperlipidemia: risk factors and response to dietary modification and gemfibrozil therapy. *Clin Transplant* 1995;9 (4):340. [PubMed: 7579744]
15. Pannu HS, Singh D, Sandhu JS. Lipid profile before and after renal transplantation--a longitudinal study. *Ren Fail* 2003;25 (3):411. [PubMed: 12803504]
16. Curtis JJ, Galla JH, Woodford SY, Lucas BA, Luke RG. Effect of alternate-day prednisone on plasma lipids in renal transplant recipients. *Kidney Int* 1982;22 (1):42. [PubMed: 6750206]
17. Hollander AA, Hene RJ, Hermans J, van Es LA, van der Woude FJ. Late prednisone withdrawal in cyclosporine-treated kidney transplant patients: a randomized study. *J Am Soc Nephrol* 1997;8 (2):294. [PubMed: 9048349]
18. Vanrenterghem Y, Lebranchu Y, Hene R, Oppenheimer F, Ekberg H. Double-blind comparison of two corticosteroid regimens plus mycophenolate mofetil and cyclosporine for prevention of acute renal allograft rejection. *Transplantation* 2000;70 (9):1352. [PubMed: 11087152]
19. Miller LW. Cardiovascular toxicities of immunosuppressive agents. *Am J Transplant* 2002;2 (9):807. [PubMed: 12392286]
20. Cosio FG, Pesavento TE, Kim S, Osei K, Henry M, Ferguson RM. Patient survival after renal transplantation: IV. Impact of post-transplant diabetes. *Kidney Int* 2002;62 (4):1440. [PubMed: 12234317]
21. Davidson, J.; Wilkinson, A.; Dantal, J., et al. New-onset diabetes after transplantation: 2003 International consensus guidelines. Proceedings of an international expert panel meeting; Barcelona, Spain. 19 February 2003; p. SS3Transplantation 2003
22. Poge U, Gerhardt T, Palmedo H, Klehr HU, Sauerbruch T, Woitas RP. MDRD equations for estimation of GFR in renal transplant recipients. *Am J Transplant* 2005;5 (6):1306. [PubMed: 15888034]

23. Volosov A, Napoli KL, Soldin SJ. Simultaneous simple and fast quantification of three major immunosuppressants by liquid chromatography--tandem mass-spectrometry. *Clin Biochem* 2001;34 (4):285. [PubMed: 11440728]
24. Kleinbaum, D.; Kupper, L.; Muller, K.; Nizam, A. *Applied Regression Analysis and Other Multivariable Methods*. Vol. 3. Pacific Grove, CA: Brooks/Cole, Inc; 1998.
25. Isoniemi H, Nurminen M, Tikkanen MJ, et al. Risk factors predicting chronic rejection of renal allografts. *Transplantation* 1994;57 (1):68. [PubMed: 8291116]
26. Kasiske BL, Umen AJ. Persistent hyperlipidemia in renal transplant patients. *Medicine (Baltimore)* 1987;66 (4):309. [PubMed: 3298932]
27. Bittar AE, Ratcliffe PJ, Richardson AJ, et al. The prevalence of hyperlipidemia in renal transplant recipients. *Transplantation* 1990;50:987. [PubMed: 2256173]
28. Brown JH, Murphy BG, Douglas AF, et al. Influence of immunosuppressive therapy on lipoprotein (a) and other lipoproteins following renal transplantation. *Nephron* 1997;75:277. [PubMed: 9069448]
29. Kasiske BL. Cardiovascular disease after renal transplantation. *Semin Nephrol* 2000;20 (2):176. [PubMed: 10746859]
30. Kasiske BL, Chakkeria HA, Roel J. Explained and unexplained ischemic heart disease risk after renal transplantation. *J Am Soc Nephrol* 2000;11 (9):1735. [PubMed: 10966499]
31. Tse KC, Lam MF, Yip PS, Li FK, Lai KN, Chan TM. A long-term study on hyperlipidemia in stable renal transplant recipients. *Clin Transplant* 2004;18 (3):274. [PubMed: 15142048]
32. Gonyea JE, Anderson CF. Weight change and serum lipoproteins in recipients of renal allografts. *Mayo Clin Proc* 1992;67 (7):653. [PubMed: 1434899]
33. Moore R, Thomas D, Morgan E, et al. Abnormal lipid and lipoprotein profiles following renal transplantation. *Transplant Proc* 1993;25 (1 Pt 2):1060. [PubMed: 8442042]
34. Kasiske BL. Hyperlipidemia in patients with chronic renal disease. *Am J Kidney Dis* 1998;32 (5 Suppl 3):S142. [PubMed: 9820472]
35. Larsen JL, Larson CE, Hirst K, et al. Lipid status after combined pancreas-kidney transplantation and kidney transplantation alone in type I diabetes mellitus. *Transplantation* 1992;54 (6):992. [PubMed: 1465793]
36. Kisielnicka E, Zdrojewski Z, Wroblewska M, Kortas B, Rutkowski B. Lipid disturbances in a two-year follow-up after successful kidney transplantation. *Transplant Proc* 2000;32 (6):1358. [PubMed: 10995978]
37. Ichimaru N, Takahara S, Kokado Y, et al. Changes in lipid metabolism and effect of simvastatin in renal transplant recipients induced by cyclosporine or tacrolimus. *Atherosclerosis* 2001;158 (2):417. [PubMed: 11583721]
38. Wlodarczyk Z, Vitko S, Salmela K, Czajkowski Z, Margreiter R. Lipid metabolism in renal transplant patients receiving tacrolimus/sirolimus combination therapy. *Transplant Proc* 2005;37 (4):1871. [PubMed: 15919489]
39. Ciancio G, Burke GW, Gaynor JJ, et al. A randomized long-term trial of tacrolimus/sirolimus versus tacrolimus/mycophenolate versus cyclosporine/sirolimus in renal transplantation: three-year analysis. *Transplantation* 2006;81 (6):845. [PubMed: 16570006]

Figure 1. Total Cholesterol

Mean $\pm$ SD are shown. Values pre- and post-transplant (3–6 mo and > 6 mo after transplant) for all four groups, type 1 with kidney transplant alone (DM1-K), type 1 diabetes with pancreas and kidney grafts (DM1-KP), type 2 diabetes (DM2-K) and nondiabetic recipients (nonDM-K). * $p = 0.0008$ for compared to post-KTX DM1-K. Change after transplant also greater in DM1-K than nonDM-K ($p = 0.03$).

Figure 2. LDL

Mean $\pm$ SD are shown. Values pre- and post-transplant (3–6 mo and greater than 6 mo after transplant) for all four groups, type 1 with kidney transplant alone (DM1-K), type 1 diabetes with pancreas and kidney grafts (DM1-KP), type 2 diabetes (DM2-K) and nondiabetic recipients (nonDM-K). * $p = 0.001$ compared to post-KTX DM1-K. Change after transplant was also greater in DM1-K than nonDM-K ($p=0.02$).

Figure 3. Triglycerides

Mean $\pm$ SD are shown. Values pre- and post-KTX (3–6 mo and >6 mo after transplant) for all four groups, type 1 with kidney transplant alone (DM1-K), type 1 diabetes with pancreas and kidney grafts (DM1-KP), type 2 diabetes (DM2-K) and nondiabetic recipients (nonDM-K).

Figure 4. HDL

Mean $\pm$ SD are shown. Values pre- and post-KTX (3–6 mo and greater than 6 mo after transplant) for all four groups, type 1 with kidney transplant alone (DM1-K), type 1 diabetes with pancreas and kidney grafts (DM1-KP), type 2 diabetes (DM2-K) and nondiabetic recipients (nonDM-K). * $p = 0.02$ compared to Post-KTX DM1-KP.

Table 1
Pre-Transplant Demographic and Vascular Disease Risk Variables for all Groups

Mean $\pm$ SD shown. DM1-K: Type 1 diabetes with kidney only, DM1-KP: Type 1 diabetes with kidney and pancreas grafts, DM2-K: Type 2 diabetes with kidney only, nonDM-K: nondiabetic with kidney graft. P-value shown is for comparison of all four groups. Significant individual comparisons are shown below. Statins were the only hypolipidemic agents used prior to transplant in all groups.

	DM1-K	DM1-KP	DM2-K	nonDM-K	p-value
N	14	22	33	123	
Age at KTX (y)	47.3 $\pm$ 8.3	42.4 $\pm$ 7.4	60.4 $\pm$ 8.0*	47.6 $\pm$ 14	<0.0001
Gender: %F	14	50	36	46	0.11
Race: %Caucasian	93	95	73	76	0.07
Deceased donor (%)	64	77	64	50	0.06
BMI (kg/m ²)	24.2 $\pm$ 5.1	26.3 $\pm$ 3.6	30.3 $\pm$ 4.0 [^]	26.8 $\pm$ 5.2	0.0002
Systolic blood pressure (mm Hg)	136 $\pm$ 26	146 $\pm$ 23	143 $\pm$ 22	142 $\pm$ 24	0.71
Diastolic blood pressure (mm Hg)	76 $\pm$ 8.4	78 $\pm$ 9.9	68 $\pm$ 14**	81 $\pm$ 14	0.0001
A1c	7.8 $\pm$ 2.1 [#]	7.6 $\pm$ 1.6 [#]	6.4 $\pm$ 0.9	5.4 $\pm$ 1.1	<0.0001
TC (mg/dl)	203.8 $\pm$ 58.1	180.2 $\pm$ 42.8	179.0 $\pm$ 36.9	182.3 $\pm$ 46.0	0.35
LDL (mg/dl)	117.3 $\pm$ 38.2	101.4 $\pm$ 33.0	93.9 $\pm$ 32.5	99.7 $\pm$ 39.0	0.29
TG (mg/dl)	169.9 $\pm$ 81.9	167.4 $\pm$ 89.1	225.5 $\pm$ 188.8	186.5 $\pm$ 105.0	0.26
HDL (mg/dl)	54.8 $\pm$ 20.9	49.8 $\pm$ 17.8	44.5 $\pm$ 17.9	45.3 $\pm$ 16.0	0.16
Prescribed statins (%)	21	36	15	8.9	0.007

Using Tukey's method for multiple comparisons,

* p<0.01 compared to all groups;

[^] p<0.05 compared to all groups; and

** p<0.05 compared to DM1-KP and nonDM1-K;

[#] p<0.005 compared to DM2 and nonDM1-K;

Table 2

Immunosuppression medication use by group

% of those using each immunosuppressive drug at any time post-transplant for each group is shown below. In each case, both the number and % of each group treated with each medication is shown. P value shown compares the use of that medication among the groups shown. Thus, there was a significant difference in use of tacrolimus and MMF between the groups, as shown.

	DM1-K (%) N=14	DM1-KP (%) N=22	DM2-K (%) N=33	NonDM-K (%) N=123	p-value
Tacrolimus	14 (100%)	22 (100%)	31 (93.9%)	122 (99.2%)	0.22
Sirolimus	13 (93.9%)	21 (95.5%)	19 (57.6%)	98 (79.7%)	0.003
MMF	6 (42.9%)	18 (81.8%)	21 (63.6%)	60 (48.8%)	0.02
Corticosteroids	1 (7.1%)	5 (22.7%)	2 (6.1%)	21 (17.1%)	0.25
Cyclosporine	1 (7.1%)	2 (9.1%)	2 (6.1%)	4 (3.3%)	0.35