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DYSLIPIDEMIA AFTER KIDNEY TRANSPLANTATION;A STUDY AT HIROSAKI UNIVERSITY HOSPITAL

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Abstract

Although graft survival rates in kidney transplant recipients have improved over the years. Cardiovascular disease remains the major cause of death after kidney transplantation. Therefore, relevant control of dyslipidemia is important for both the prevention of cardiovascular disease and protection of graft function.

We retrospectively analyzed 28 patients who underwent kidney transplantation from June 2006 to February 2011 at Hirosaki University Hospital, of which 6 were excluded because of insufficient data. We applied the following diagnostic criteria for dyslipidemia established by the Japan Atherosclerosis Society: (1) low-density lipoprotein cholesterol levels ≥ 140 mg/dl, (2) triglyceride levels ≥ 150 mg/dl, and (3) high-density lipoprotein cholesterol levels < 40 mg/dl. Serum samples were obtained after overnight fasting.

Five patients had dyslipidemia before kidney transplantation, and 4 patients developed new-onset dyslipidemia after kidney transplantation. Although 13 patients had normal lipid levels, 5 of them received prophylactic medication for dyslipidemia.

We analyzed the 3 groups of patients to determine risk factors for dyslipidemia related kidney transplantation. Our data suggested that high trough levels of tacrolimus (Tac) tended to correlate with new-onset dyslipidemia after kidney transplantation (P=0.06).

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Key words: Dyslipidemia; kidney transplantation; risk factor

Background

The graft survival rates in kidney transplant recipients have improved over the years. However, cardiovascular disease remains the major cause of death after kidney transplantation. Cardiovascular disease is more common among kidney transplant recipients than in the general population[1, 2)], and elevated levels of total cholesterol are associated with an increased risk of ischemic heart disease in kidney transplant patients[3, 4)]. A clinical trial showed that lowering cholesterol levels with fluvastatin significantly decreased the risk of major cardiac events[5)]. Another study showed fluvastatin reduced cardiac deaths or non-fatal myocardial infarction[6)]. The protective cardiovascular effect of fluvastatin was significant when the treatment was initiated at within 2 (compared with >6 years) years following kidney transplantation[7)].

Kidney transplant recipients typically have increased levels of cholesterol (low-density lipoprotein [LDL] and total cholesterol) and elevated levels of very low-density lipoprotein (VLDL), and triglycerides. Cholesterol has been shown to be an independent predictor of outcome

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after kidney transplantation[8]. Approximately 60–80% of adult kidney transplant recipients develop dyslipidemia, which occurs within 1 month of the initiation of immunosuppressive therapy and continues to persist unless it is treated. Dyslipidemia has been shown to contribute to chronic allograft dysfunction[9], and hypertriglyceridemia is an independent risk factor for graft loss[10, 11].

Consequently, control of dyslipidemia after kidney transplantation is very important. The aim of this study was to establish risk factors for dyslipidemia in kidney transplant recipients.

Methods

We retrospectively analyzed 22 patients who underwent kidney transplantation from June 2006 to February 2011 at Hirosaki University Hospital. Of these, 6 patients were excluded from the study owing to insufficient data. We applied the following diagnostic criteria for dyslipidemia established by the Japan Atherosclerosis Society: LDL cholesterol levels ≥ 140 mg/dl, triglyceride levels ≥ 150 mg/dl, and high-density lipoprotein (HDL) cholesterol levels < 40 mg/dl. Diagnosis of dyslipidemia was made when either type of lipid abnormalities was present. The serum was sampled after overnight fasting.

5 patients had dyslipidemia before kidney transplantation (Group A), and 4 patients developed new-onset dyslipidemia after kidney transplantation (Group B). 13 patients had normal lipid levels (Group C), and 5 patients from this group received prophylactic medication for dyslipidemia.

We compared the patients in these 3 groups to establish risk factors for dyslipidemia in kidney transplant patients.

Values are expressed as the means ± standard deviation. The quantitative levels of the aforementioned indications among 3 groups were evaluated by analysis of variance. A contingency table analysis was used to examine the qualitative variables.

Results

4 of 22 patients developed new-onset dyslipidemia after kidney transplantation. We analyzed 11 possible risk factors, and found that none of them correlated with new-onset dyslipidemia after kidney transplantation (See the Table 1).

Our data suggested that high trough levels of tacrolimus (Tac) correlated with new-onset dyslipidemia after kidney transplantation, although the results were not statistically significant (P = 0.06). The patients' ages at transplantation were 41.4 ± 16.5 (Group A), 38.5 ± 4.8 (Group B), and 41.6 ±14.5 (Group C) (P = 0.924). Factors such as gender (P = 0.884), dialysis period before transplantation (P = 0.623), primary disease, and diabetes mellitus (P = 0.184) did not significantly correlate with dyslipidemia (Table 1). The use of calcium channel blockers (P = 0.575), renin-angiotensin system inhibitors (P = 0.894), and induction immunosuppressants (Tac vs cyclosporine A) (P = 0.467) did not significantly affect the development of dyslipidemia. The levels of serum creatinine (P = 0.575) and dose of prednisone (P = 0.212) at analysis did not significantly differ between the groups.

Discussion

Hypertriglyceridemia, which was present in 53.8% of the pretransplant patients, was present in 41% of the patients 1 month following successful kidney transplantation and in 29% of patients at the 6-month follo-up[12]. In contrast, hypercholesterolemia, present in 34.6% of patients prior to transplantation, was found in 61.5% of patients 1 month after receiving a kidney allograft and in 38.4% of patients at the

Table 1 Clinical and demographic characteristics of the study groups

	Group A Dyslipidemia before kidney transplantation (n = 5)	**Group B** New-onset dyslipidemia after kidney transplantation (n = 4)	**Group C** Normal lipid levels (n = 13)	P
Age (y) at transplantation	41.4 ± 16.5	38.5 ± 4.8	41.6 ± 14.5	0.924
Gender male/female	3 /2	3/1	9/4	0.884
Dialysis period before Transplantation[1] (month)	35.8 ± 53.0 (preemptive 1case)	11.3 ± 11.9 (preemptive 1case)	20.6 ± 37.1 (preemptive 2cases)	0.623
Primary disease of renal failure	Glomerulonephritis, 3; Polycystic kidney disease,1; SLE, 1	Glomerulonephritis,1; Unknown, 3	Diabetic nephropathy, 4; Glomerulonephritis, 4; Unknown, 2; ANCA, 1; FGS, 1; Alport syndrome, 1	
Diabetes mellitus (n [%])	0 (0)	0 (0)	4 (30.8)	0.184
Calcium channel blocker (n [%])	2 (40)	3 (75)	7 (53.8)	0.575
Renin-angiotensin system inhibitor (n [%])	4 (80)	3 (75)	9 (69.2)	0.894
Serum creatinine (mg/dl)	1.38 ± 0.23	1.36 ± 0.40	1.65 ± 0.72	0.575
Induction immunosuppressant Tac (vs CsA) (n [%])	5 (100)	4 (100)	11 (85)	0.467
Tac trough levels[2] (ng/ml)	7.80 ± 1.55 (n = 4)	8.50 ± 2.20	6.48 ± 1.07 (n = 11)	0.06
Prednisone (mg)	4.3 ± 2.7	6.9 ± 2.4	4.6 ± 2.2	0.212

Values are expressed as means ± standard deviation
[1]Preemptive transplantation is regarded as 0 month
[2]Tac trough: 1 recipient of Group A and 2 recipients of Group C are excluded by administration of CsA instead of Tac.

6-month follow-up[12].

The risk of a major ischemic heart disease event occurring >1 year after transplantation in a group of 1124 kidney transplant patients was estimated in the Framingham Heart Study (FHS). The study showed that the risk associated with increased cholesterol levels was higher in transplant patients that in the FHS population, while the risks associated with HDL cholesterol levels and blood pressure were comparable[4]. A multicentre, randomized, double-blind, placebo-controlled trial of 2102 kidney transplant patients showed that fewer cardiac deaths or non-fatal myocardial infarction (70 vs 104, risk ratio 0.65; 95% confidence interval: 0.48 −0.88; P = 0.005) occurred in the fluvastatin-treated group than in the placebo group after a mean follow-up of 5.1 years[6]. The risk reduction for patients initiating therapy with fluvastatin at years 0−2 (compared with >6 years) following kidney transplantation was 59% (risk ratio: 0.41; 95% confidence interval: 0.18−0.92; P = 0.0328) [7].

It has been established that cyclosporine, but not Tac, significantly increases the incidence and prevalence of high total cholesterol[12, 13], triglycerides[13], and LDL cholesterol[12]. Several epidemiological and clinical factors such as corticosteroid, rapamycin, age, body mass index[14], pretransplant lipid levels, graft dysfunction, diabetes mellitus, and anti-hypertensive medication (beta-blockers and thiazide diuretics) have also been implicated in dyslipidemia. In a kidney transplant population, Tac-based immunosuppression and early statin use were not associated with significantly improved graft or patient survival[15].

In summary, we found that only a high trough level of Tac is correlated with new-onset

dyslipidemia after kidney transplantation (P = 0.06).

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