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Studies on Post-Transplant Dyslipidemia in Kidney Transplant Patients

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ABSTRACT

This study was performed to retrospectively compare changes in the levels of total cholesterol, non-HDL cholesterol, triglycerides, and immunosuppressive drugs, cyclosporine A and steroids in patients with living-relation renal transplants with those from non-heart-beating donors. We experienced 11 cases of kidney transplants from non-heart-beating donors during the period from April 1995 to May 2003. We evaluated 13 cases of kidney transplants from living-relation donors during the same period. The immunosuppressants used included mainly cyclosporine A as well as mycophenolate mofetil or azathioprine, steroid and ALG, or basiliximab. Over-night fasting lipids (total cholesterol, triglycerides and HDL cholesterol) were studied before renal transplantation and repeated after renal transplantation at 1, 3, 6 and 12 months. The levels of total cholesterol and triglycerides remained in the normal range before transplantation. However, the levels of total cholesterol increased siginificantly 1 and 3 months after transplantation from non-heart-beating donors and remained at higher levels up to 12 months after transplantation. A similar pattern in the levels of triglycerides was observed. The levels of HDL cholesterol remained unchanged and stayed in the normal range before and 1, 3, 6, and 12 months after transplantation from non-heart-beating donors. On the other hand, significant increases in non-HDL cholesterol were observed 3 and 6 months after transplantation from non-heart-beating donors. After transplantation from living-relation donors, levels of total cholesterol, triglycerides, and non-HDL cholesterol remained unchanged and remained in the normal range up to 12 months after transplantation. Although there were no significant differences in the total dosage of cyclosporine A between the patients with living-relation donors and those with non-heart-beating donors, a significant increase in the total dosage of methylprednisolone was observed in patients with non-heart-beating donors compared with those in the patients with living-relation donors. Renal function recovery in patients with living-relation donors was better than in those with non-heart-beating donors. These results may suggest that significant increases in total cholesterol, especially non-HDL cholesterol and triglycerides, were probably partly due to an increased use of immunosuppressants, steroids. It is necessary to aggressively control post-transplant hyperlipidemia and important to reduce or withdraw steroids in the selected, low-risk recipients as early as possible from the viewpoint of preventing post-transplant hyperlipidemia.

Key words: *Renal transplantation, Dyslipidemia, Immunosuppressant, Cyclosporine A, Steroids*

Abnormal lipid and lipoprotein metabolism occurs in 20 to 70% of chronic renal failure cases[10)]. After renal transplantation, various types of metabolic dysfunctions associated with chronic renal failure reverse, but lipid abnormalities appear to progress in a large fraction of patients[3)]. Hyperlipidemia is linked closely to cardiovascular disease (CVD) and CVD is linked to renal transplant mortality[9)]. The incidence of CVD is very high in kidney transplant recipients. Indeed, available evidence in these patients suggests that the 10-year cumulative risk of coronary heart dis-

ease is at least 20%, or roughly equivalent to the risk seen in patients with a history of CVD[9].

In this study, we retrospectively compared changes in the levels of total cholesterol, non-HDL cholesterol, triglycerides and immunosuppressive drugs, cyclosporine A and steroids in patients with living-relation renal transplants with those from non-heart-beating donors.

SUBJECTS AND METHODS

From September 1971 to May 2003, we managed 178 cases of kidney transplantation. These cases included 145 cases of living-relation renal transplants and 33 cases of kidney transplants from non-heart-beating donors; 135 were male and 43 female. The median age at transplant was 33.0 years old. In kidney transplants from non-heart-beating donors, 11 cases (10 males and 1 female, aged 43 to 60 years) were performed in our hospital during the period from April 1995 to May 2003. These recipients were chosen by the Japan Organ Transplant Network according to the recipient selection criteria, as shown in our previous paper[11]. The underlying diseases in the patients included chronic glomerulonephritis in six patients, nephrotic syndrome in one patient, diabetes mellitus in one patient, and chronic renal failure in three patients (Table 1). As for HLA matching, one of the DR antigens was mismatched in 4 patients, but both DR antigens were matched in the other 7 patients. The immunosuppressants used included mainly cyclosporine A as well as mycophenolate mofetil, azathioprine or mizoribine, steroids and ALG. Tacrolimus was used in two patients. Rejection reactions occurred in seven cases, two of which were vascular rejections. Treatments with steroid pulse therapy and plasma exchange were performed. One patient died from interstitial pneumonia, and three patients had to be restarted on dialysis due to loss of function in the grafted kidney. The remaining seven patients made full recoveries. We evaluated 13 cases of kidney transplants from living-relation donors (8 males and 5 females, aged 22 to 59 years) during the same period (Table 2). The underlying diseases were chronic glomerulonephritis in four patients, systemic lupus erythematosus (SLE) in two patients, IgA nephropathy in two patients, membranoproliperative glomerulonephritis (MPGN) in one patient, rapidly progressive glomerulonephritis (RPGN) in one patient, and chronic renal failure in 3 patients. One of the DR antigens was mismatched in 12 patients, and both DR antigens were matched in one patient. The immunosuppressants used included mainly cyclosporine A as well as mycophenolate mofetil or azathioprine, steroid and antilymphocyte globulin (ALG), or basilix-

Table 1. Renal transplant recipients from non-heart-beating donors

Case	Age	Gender	Primary disease	Immunosuppressant	Rejection	Outcome	Complications
1	43	female	CRF	CY, MF, AZ, S, ALG	no	full recovery	no
2	46	male	CRF	CY, MZ, S, ALG	no	full recovery	no
3	60	male	CGN	CY, AZ, S, ALG	AR(1)	died of interstitial pneumonia 32M after TX	no
4	47	male	CRF	CY, MF, S, ALG	AR(1)	full recovery	no
5	46	male	nephrotic syndrome	CY, AZ, CP, S, ALG	VR(1)	graftectomy 1M after TX	no
6	53	male	CGN	CY, MZ, S, ALG	no	full recovery	no
7	58	male	DM	CY, MZ, AZ, S, ALG	AR(3)	hemodialysis begin due to chronic rejection 18M after TX	aortoiliac occlusive disease and IHD 15M after TX right thigh amputation 4Y after TX
8	42	male	CGN	CY (FK), AZ (MF), S, ALG	AR(4)	hemodialysis begin due to chronic rejection 22M after TX	no
9	59	male	CGN	CY, AZ, S, ALG	no	full recovery	no
10	45	male	CGN	CY, MF, S, ALG	AR(1)	full recovery	no
11	44	male	CGN	CY (FK), MF, S, ALG	VR(1)	full recovery	no

CRF; chronic renal failure, CGN; chronic glomerulonephritis
CY; cyclosporine A, MF; mycophenolate mofetil, AZ; azathioprine, ALG; antilymphocyte globulin, S; steroid, CP; cyclophosphamide, FK; FK506 (tacrolimus), MZ; mizoribine, AR; acute rejection, VR; vascular rejection, M; month (s), TX; transplantation, IHD; ischemic heart disease, Y; year (s)

Table 2. Renal transplant recipients from living-relation donors

Case	Age	Gender	Primary disease	Immunosuppressant	Rejection	Outcome	Complications
1	45	male	CRF	CY, AZ, MF, S	no	full recovery	anginal attack 3M after TX steroid-induced DM 6M after TX
2	22	male	CGN	CY, AZ, S, ALG	no	full recovery	no
3	41	female	SLE	CY, Br, S, ALG	no	full recovery	no
4	25	male	IgA nephropathy	CY, AZ, S	no	full recovery	CMV infection 6M after TX
5	24	female	IgA nephropathy	CY, MF, S	no	full recovery	no
6	39	male	CGN	CY, MF, S	no	full recovery	no
7	46	male	CGN	FK (CYA), AZ, S	mild AR(1)	full recovery	no
8	59	male	CGN	FK, AZ, S, ALG	mild AR(1)	full recovery	no
9	27	male	MPGN	FK (CYA), AZ, S, ALG	mild AR(1)	full recovery	no
10	25	female	SLE	FK, Br, S, ALG	mild AR(1)	full recovery	no
11	55	female	CRF	CY, MF, S, ALG	no	full recovery	generalized arteriosclerosis (pre-TX)
12	27	female	RPGN	CY, MF, S, BX	no	full recovery	no
13	31	male	CRF	CY, MF, S, BX	no	full recovery	no

SLE; systemic lupus erythematosus, MPGN; membranoproliferative glomerulonephritis, RPGN; rapidly progressive glomerulonephritis, BX; basiliximab, CMV; cytomegalovirus

imab. Tacrolimus was used in 4 patients. Mild acute rejections occurred in 4 patients. All cases recovered with steroid pulse therapy. Infectious disease complications included cytomegalovirus (CMV) in one patient. Over-night fasting lipids (total cholesterol, triglycerides and high density lipoprotein (HDL) cholesterol) were studied before renal transplantation and after renal transplantation at 1, 3, 6 and 12 months. Non-HDL cholesterol is defined as total cholesterol minus HDL cholesterol. The estimation of these lipids was done using kits from Kyowa Medics on a multichannel autoanalyzer JCA-BM 2250. For one patient with a transplant from a non-heart-beating donor (case 5), the lipid profile data was not obtained at 3, 6 and 12 months because of a graftectomy one month after transplantation: Therefore, data were analyzed for only 10 patients with non-heart-beating donors. Cyclosporine A administration was adjusted to maintain a whole-blood trough level between 150 and 250 ng/ml for 1 or 2 months after transplantation, and between 80 and 100 ng/ml thereafter. Oral administration of cyclosporine A was started 2 days before transplantation at a dose of 8 mg/kg per day, and drip infusion of cyclosporine A was administered on the day of transplantation at a dose of 3 mg/kg. Methylprednisolone administration was started on the day of transplantation at a dose of 250 to 500 mg/day and reduced to a maintenance dose of 8 mg/day by the second to third month. For treatment of acute rejection episodes, methylprednisolone at a dose of 250 to 500 mg was administered for 3 days. Total dosage of cyclosporine A and methylprednisolone was calculated according to the summation of the drug administered for the first one year. Results are expressed as the mean ± SE. Data were analyzed with the Wilcoxon signed rank test or Mann-Whitney U test with $p<0.05$ indicating a significant difference in all analyses. Analyses were performed with Stat View 5 software (Abacus Concepts, Inc., CA).

RESULTS

There were no significant differences in most of the baseline background profile between the patients with non-heart-beating donors and those with living-relation donors except for the greater percentage of males among those with non-heart-beating donors (Table 3). We examined changes in the levels of total cholesterol and triglycerides after transplantation from non-heart-beating donors (Fig. 1). The levels of total cholesterol and triglycerides remained in the normal range before transplantation. However, the levels of total cholesterol increased significantly 1 and 3 months after transplantation and remained at higher levels up to 12 months after transplantation. A similar pattern in the levels of triglycerides was observed, although significant changes were not seen 1 month after transplant. Levels of total cholesterol and triglycerides after transplantation from living-relation donors remained unchanged and remained in the normal range up to 12 months after transplantation (Fig. 2). We examined the levels of HDL cholesterol to determine whether the increase in total cholesterol after

Table 3. Background profile of patients with non-heart-beating donors and those with living-relation donors

	patients with non-heart-beating donors (n = 10)	patients with living-relation donors (n = 13)
recipient mean age	49.4 ± 6.82	36.3 ± 13.0
gender (%male)	90% (9/10)	61.5% (8/13)
serum creatinine (mg/dL)	11.7 ± 2.68	13.5 ± 3.62
systolic BP (mmHg)	151 ± 31.7	159 ± 88.8
diastolic BP (mmHg)	88.8 ± 8.01	83.0 ± 17.0
total cholesterol (mg/dL)	167 ± 33.5	185 ± 43.0
triglycerides (mg/dL)	121 ± 67.3	153 ± 105

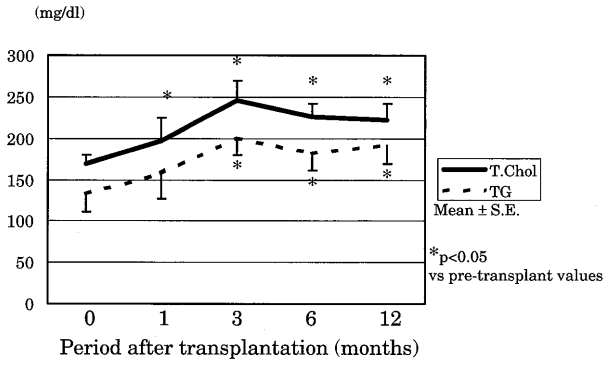

Fig. 1. Changes in the levels of total cholesterol and triglycerides after transplantation from non-heart-beating donors.
Straight line shows the level of total cholesterol after transplantation. Dotted line shows the level of triglycerides after transplantation. Values are the mean ± SE of 10 patients with non-heart-beating donors. *p<0.05 vs pre-transplant values.

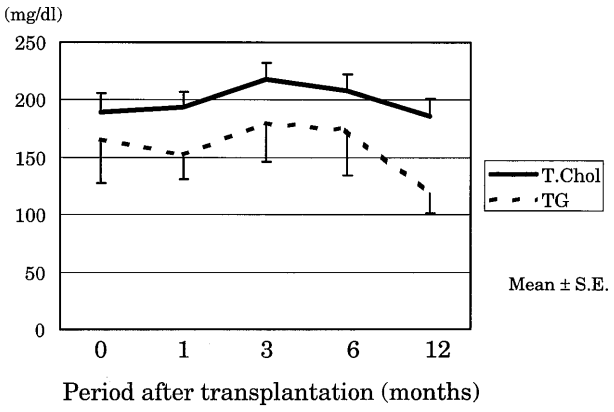

Fig. 2. Levels of total cholesterol and triglycerides after transplantation from living-relation donors.
Straight line shows the level of total cholesterol after transplantation. Dotted line shows the level of triglycerides after transplantation. Values are the mean ± SE of 13 patients with living-relation donors.

transplantation from non-heart-beating donors was due to increased non-HDL cholesterol. The levels of HDL cholesterol remained unchanged and stayed in the normal range before and 1, 3, 6, and 12 months after transplantation from non-

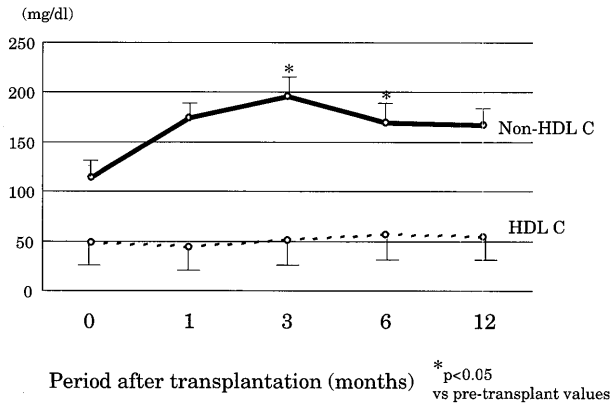

Fig. 3. The levels of HDL cholesterol and non-HDL cholesterol after transplantation from non-heart-beating donors.
Non-HDL cholesterol is defined as total cholesterol minus HDL cholesterol. Values are the mean ± SE of 10 patients with non-heart-beating donors. *p<0.05 vs pre-transplant values.

heart-beating donors (Fig. 3). On the other hand, significant increases in non-HDL cholesterol were observed 3 and 6 months after transplantation from non-heart-beating donors (Fig. 3). To study the influence of immunosuppressive drugs, cyclosporine A and steroids on post-transplant dyslipidemia, we compared the total dosage of cyclosporine A and steroids in patients with non-heart-beating donors with that in patients with living-relation renal transplants (Figs. 4 and 5). Although there were no significant differences in the total dosage of cyclosporine A between the patients with non-heart-beating donors and those from living-relation transplants (Fig. 4), a significant increase in the total dosage of methylprednisolone was observed in patients with non-heart-beating donors compared with the patients with living-relation transplants (Fig. 5). Fig. 6 shows the changes in the levels of serum creatinine after transplants in patients with non-heart-beating donors and in those from living-relation transplants. Significantly higher levels of creatinine were observed at 1, 3 and 12 months after transplants in patients from non-heart-beating donors compared with those from living-rela-

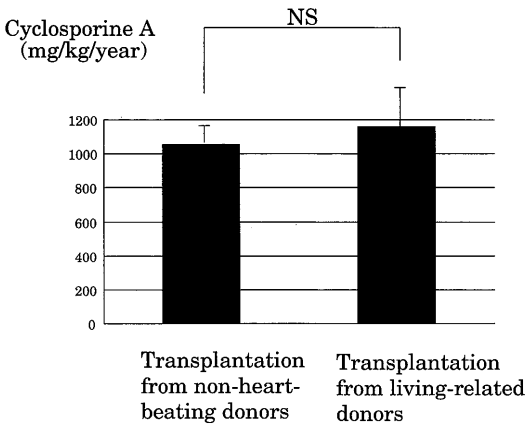

Fig. 4. Total dosage of cyclosporine A in patients with non-heart-beating donors and those with living-relation donors.
Total dosage of cyclosporine A is calculated according to the summation of the drug administered for the first one year. Values are the mean ± SE of 10 and 11 patients with non-heart-beating donors and living-relation donors, respectively.

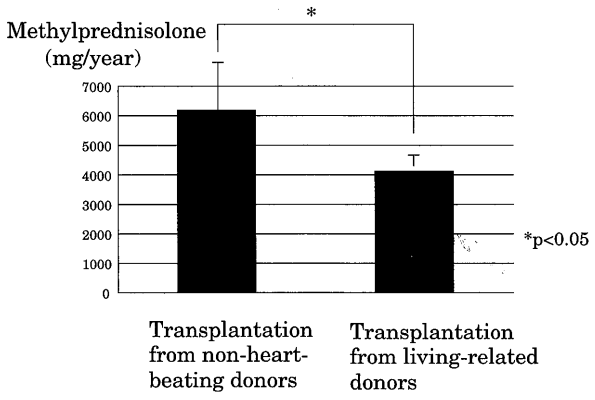

Fig. 5. Total dosage of methylprednisolone in patients with non-heart-beating donors and those with living-relation donors.
Total dosage of methylprednisolone is calculated according to the summation of the drug administered for the first one year. Values are the mean ± SE of 10 and 13 patients with non-heart-beating donors and living-relation donors, respectively.

tion donors. These results indicate that in patients with living-relation donors, renal function recovery was better than in those with non-heart-beating donors. There were similar blood pressure levels and lipid profiles at the beginning of the renal transplantation (Table 3). Although antihypertensive medications and HMG-CoA (3-hydroxy-3-methylglutaryl-CoA) reductase inhibitor were prescribed for one patient with a living-relation donor, these drugs were prescribed for three or four patients with non-heart-beating donors, respectively. Cardiovascular complications were observed in one patient with a non-heart-beating donor and two patients with living-relation donors

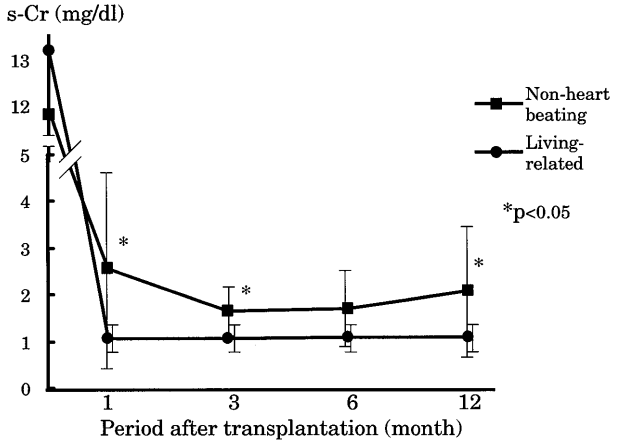

Fig. 6. Changes in the levels of serum creatinine after transplantation in patients with non-heart-beating donors and those with living-relation donors.
Values are the mean ± SE of 10 and 13 patients with non-heart-beating donors and living-relation donors, respectively. *p<0.05 vs values of patients with living-relation donors.

(Tables 1 and 2). In case 7, a patient with a non-heart-beating donor, aortoiliac occlusive disease and ischemic heart disease developed 15 months after the transplantation, and right thigh amputation was performed 4 years after the transplantation. PTCA (percutaneous transarterial coronary angioplasty) was performed twice. In a patient (case 1) with a living-relation donor, an anginal attack was observed three months after transplantation and steroid-induced diabetes mellitus developed six months after the transplantation. In case 11, a patient with a living-relation donor, preoperative examination for renal transplantation revealed generalized arteriosclerosis. In the procedure for renal artery reconstruction with the donor's renal artery to recipient's external iliac artery (end to side anastomosis), it was necessary to perform angioplasty of the external iliac artery.

DISCUSSION

The lipid abnormalities seen after renal transplantation are a complex mixture, attributable partly to drug treatment with steroids and cyclosporine, to impaired renal function, and to other factors such as persistent hyperparathyroidism[12]. The typical pattern includes marked hypercholesterolemia and moderate hypertriglyceridemia with increased apoprotein B. This study also showed significant increases in total cholesterol and triglycerides in the renal transplant recipients from non-heart-beating donors (Fig. 1). Previous studies have focused mainly on the elevation of serum cholesterol. However, our data demonstrates a significant increase in triglycerides after renal transplants from non-heart-beating donors. Hypertriglyceridemia is

considered an independent risk factor for CVD[4,9].

The most interesting point in this paper is the significant, progressive increase of total cholesterol, especially non-HDL cholesterol and triglycerides, observed in renal transplant recipients from non-heart-beating donors (Figs. 1 and 3). However, no significant increases in these parameters were found in the living-related renal transplant recipients after transplantation (Fig. 2). These dyslipidemias in the renal transplants in this study may probably be due to immunosuppressants. There is convincing evidence that corticosteroid therapy causes hypertriglyceridemia by causing insulin resistance resulting in impaired lipolysis, and by increasing hepatic triglyceride production[15]. Although numerous studies have found an association between steroid usage, particularly high-dosage regimens, and hypercholesterolemia, the mechanisms underlying this association remain unclear[12,15]. Our data also may support an association between steroid usage and dyslipidemias. A significant increase in steroid usage was observed in patients with renal transplantation from non-heart-beating donors (Fig. 5). One of the reasons for over-usage of steroids may be the poor renal function recovery of patients with non-heart-beating donors (Fig. 6), which may cause difficulty in steroid tapering. Another reason may be that these patients received many courses of steroid pulse therapy for acute rejection (Table 1). Recent clinical studies with early steroid withdrawal also showed reduced hyperlipidemia and antilipid agent use in renal transplant recipients[17,18]. Cyclosporine treatment contributes to increases in total cholesterol and LDL cholesterol after transplantation, as shown by cyclosporine withdrawal[14] and by prospective comparison of cyclosporine-based and cyclosporine-free treatment[8,13]. Kasiske et al[8] analyzed serum lipid changes in 573 patients 3 to 52 weeks after transplantation and observed a 15 to 20% increase in total cholesterol and LDL cholesterol concentrations in association with cyclosporine use. The mechanism underlying this change is uncertain. Cyclosporine is highly lipophillic, binds to cell membranes and lipoprotein particles, and may enter the cell through the LDL receptor[6]. It is possible that the binding of cyclosporine to LDL cholesterol may lead to impaired clearance of LDL from the circulation through cell surface LDL receptors. In our study, we could not find any significant difference in cyclosporine dosage between transplants from non-heart-beating donors and those from living-relation donors (Fig. 4). Tacrolimus appears to have less impact on cholesterol, LDL cholesterol, and triglyceride levels than cyclosporine, based on randomized trials[1,5].

The significance of these lipid abnormalities after transplants is not known, but patients who had a myocardial infarction during a follow-up period of 5 years had higher serum cholesterol levels than those who did not[7]. Hyperlipidemia may also contribute to chronic allograft nephropathy[2,8]. Additionally, recent studies have demonstrated that patients who had experienced a first year acute rejection episode and who had hypercholesterolemia had a significantly increased graft loss[16]. Therefore, aggressive treatment of post-transplant hyperlipidemia is indicated.

These results may suggest that significant increases in total cholesterol, especially non-HDL cholesterol and triglycerides, were probably partly due to an increased use of immunosuppressants, steroids. It is necessary to aggressively control post-transplant hyperlipidemia and important to reduce or withdraw steroids in selected, low-risk recipients as early as possible from the viewpoint of preventing post-transplant hyperlipidemia.

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