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Effect of Renal Transplantation on the Cardiac Function of Patients With Hemodialysis

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Abstract

Objectives. This study investigated whether renal transplantation could improve cardiac function in patients who had undergone hemodialysis.

Methods. Cardiac function and coronary risk factors were compared between the renal transplantation group(RT group: $n=34$)and the maintenance hemodialysis group(HD group: $n=40$). The dialysis period was also evaluated.

Results. Anemia and electrolyte disorders significantly improved in the RT group compared to the HD group. However, both groups required therapy for coronary risk factors. Cardiac function in the RT group was better than in the HD group.

Conclusions. Disorders of cardiac function caused by chronic renal failure or the introduction of hemodialysis tended to improve after renal transplantation. Moreover, disorders of cardiac function seemed to improve more rapidly in patients in the RT group who had undergone hemodialysis for shorter periods prior to renal transplantation.

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Key Words

■Kidney(hemodialysis, renal transplantation) ■Renal function ■Heart failure ■Risk factors

INTRODUCTION

Maintenance hemodialysis and renal transplantation are the therapeutic options for chronic renal failure. The number of patients receiving hemodialysis increases yearly.[1] Moreover, more than 20% of such patients have been receiving hemodialysis for periods greater than 10 years, and the resultant complications have become a serious issue.[2] The most frequent cause of death in these patients is heart disease, which accounts for approximately 25% of deaths.[2] Cardiac function in long-term hemodialysis patients is affected by chronic cardiac strain such as electrolyte abnormalities, hypertension, and metabolic acidosis, resulting in the presentation of so-called uremic cardiomyopathy, which is a myocardial dysfunction unique to hemodialysis patients.[3] Ischemic heart disease is common among the heart diseases suffered by patients on maintenance hemodialysis.[1] Myocardial infarction commonly occurs in young hemodialysis patients.[4] Furthermore, in addition to the coronary risk factors found in non-hemodialysis patients, maintenance hemodialysis patients have factors that facilitate vascular injuries, including decreased elastase activity and epithelial cell

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injuries by angiotensin II [5] that promote the progression of coronary arteriosclerosis.

Renal transplantation is an effective treatment for terminal renal failure and provides an opportunity for social rehabilitation, but the hemodynamic course of the patients has not been fully investigated. However, one study indicated that more than half of renal transplant patients suffer from ischemic heart disease.[1] Most patients who underwent renal transplantation had a history of maintenance hemodialysis of varying durations prior to transplantation. Transplantation normally reduces the effects of hemodialysis on cardiac function, but postoperative medications including steroids and immunosuppressive drugs must be taken, which may lead to lipid disorders or hypertension, resulting in new coronary risk factors.[6,7] Therefore, like the artificial hemodialysis patients, renal transplant patients are prone to develop cardiovascular disorders. Consequently, the risk factors that renal transplant patients should be clarified to determine the therapeutic policies for terminal renal failure.

The present study investigated and compared the levels of dysfunction in the cardiovascular system and other indices to identify the effects of the therapeutic modality in patients with renal failure maintenance hemodialysis or who underwent renal transplantation followed by hemodialysis.

SUBJECTS AND METHODS

Patient selection

This study included 34 patients who had undergone maintenance hemodialysis (HD group; mean age 55.3 ± 7.3 years, female : male = 13 : 21, mean hemodialysis period 153 ± 3 months) and 40 patients who had undergone renal transplantation (RT group; mean age 48.3 ± 7.1 years, female : male = 9 : 31, mean preoperative hemodialysis period 55 ± 1 months, mean postoperative period 133 ± 2 months). This study was approved in advance by the ethical committee in our institution. In addition, consent for participation in this study was obtained from each patient after providing a full and detailed explanation.

Study design

Coronary risk factors and cardiac function in the HD group and RT group were investigated and compared. The presence of diabetes mellitus, hyperlipidemia, and hyperuricemia was determined and the levels of hemoglobin A_{1c}, low-density lipoprotein (LDL)-cholesterol, high-density lipoprotein (HDL)-cholesterol, and uric acid were evaluated as indices for risk factors. Presence or absence of hypertension and smoking habit were determined from the patients' medical records and interviews with their physicians. The plasma creatinine level, hematocrit, and albumin and electrolyte levels were measured to investigate the effects of the treatment on cardiac function. Types of prescribed medications were also recorded.

Circulatory dynamics were evaluated from the history of cardiac diseases via interviews with the patients' physicians. Left ventricular systolic function using left ventricular thickness (LVth), left ventricular end-diastolic diameter (LVDd) and fractional shortening (%FS) as indices were obtained from echocardiography. Left ventricular diastolic function using early diastolic waves and the atrial systolic wave as indices was obtained by the pulse Doppler method.

Cardiac function by echocardiography in the RT group was evaluated in two sub-groups: 23 patients with a relatively short preoperative hemodialysis period (S-RT group; mean age 49.2 ± 1.1 years, all males, mean preoperative hemodialysis period 33 ± 5 months, mean postoperative period 149 ± 11 months) and 17 patients with a relatively long preoperative hemodialysis period (L-RT group; 10 patients, mean age 50.0 ± 3.1 years, male : female = 8 : 9, mean preoperative hemodialysis period 111 ± 4 months, mean postoperative period 101 ± 2 months).

Analysis

Coronary risk factors and cardiac function by echocardiography are expressed as mean ± SD. The χ^2 test was used for statistical analysis. A value of $p < 0.05$ was considered statistically significant.

RESULTS

Coronary risk factors

The underlying renal diseases in the HD group were diabetic nephropathy in 9 patients, chronic glomerulonephritis in 12 patients, and renal tuberculosis in one patient. All patients in the RT group had chronic glomerulonephritis and all had received systemic steroids or cyclosporine.

Oral medications for hyperlipidemia were prescribed for 40% of patients in the HD group

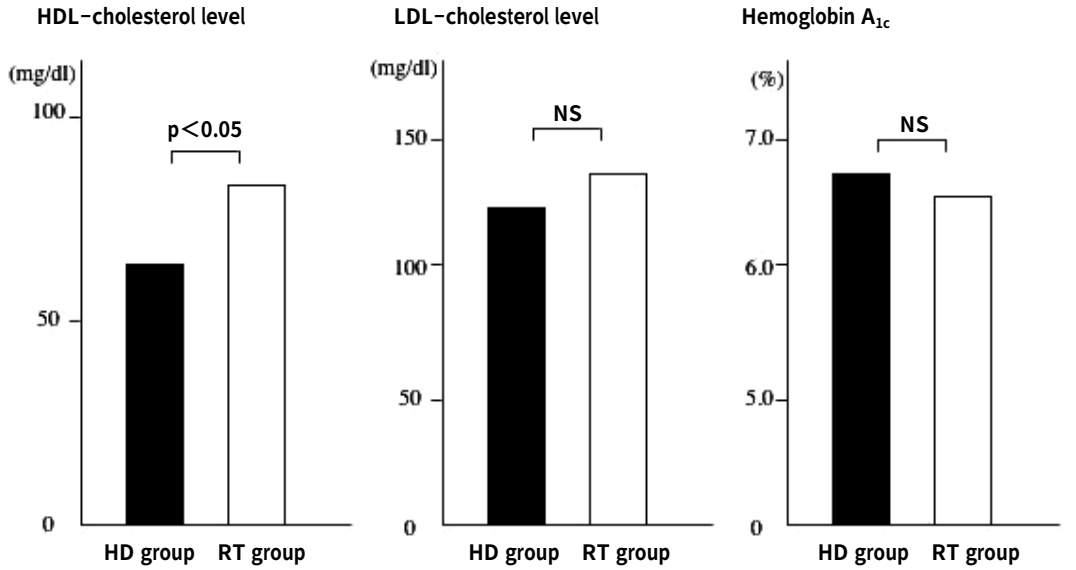

Fig. 1 Comparison of lipid levels and hemoglobin A_{1c} in the RT group and HD group
HDL-cholesterol level was significantly higher in the RT than in the HD group.
HD = hemodialysis; RT = renal transplantation; H(L)DL = high(low)-density lipoprotein.

and 100% of the patients in the RT group. Consequently, the HDL-cholesterol and the LDL-cholesterol levels were significantly high in the RT group. Ten patients in the HD group had received insulin treatment and two patients in the RT group received oral medications for diabetes mellitus. Although the hemoglobin A_{1c} level was slightly higher than the normal range in both groups, the hemoglobin A_{1c} level seemed to indicate relatively favorable control(**Fig. 1**). All patients in the HD and RT groups had received oral medications to correct the uric acid level, which was higher than the normal range but did not differ between the two groups. Creatinine and albumin levels, and indicators of anemia, factors that are believed to influence cardiac function, were significantly improved in the RT group. In addition, calcium and phosphorus levels were ameliorated after renal transplantation(not shown). Hypertension was treated effectively with oral medications in both groups. Smoking habit was found in 20% of the patients in the HD group and 60% of the patients in the RT group(**Table 1**).

Table 1 Coronary risk factors and past history

	HD group (n=21)	RT group (n=24)	p value
Hypertension	19(52)	18(75)	NS
Diabetes mellitus	10(48)	2(8)	<0.05
Hyperuricemia	21(100)	24(100)	NS
Hyperlipidemia	8(38)	24(100)	<0.05
Smoking	4(19)	13(54)	<0.05
Heart failure	11(52)	0	<0.05

( ): %.
Heart failure: Medical history of heart failure and ischemic heart disease.
Abbreviations as in Fig. 1.

Cardiac function

Oral questionnaires revealed histories of heart failure, angina pectoris, or cardiac valvular disorders only in the HD group. Cardiographic studies revealed calcified lesions in all patients in the HD group, but in none in the RT group. Moreover, the echocardiographic study demonstrated that the LVDd was significantly larger in the HD group than in the RT group. However, the LVDd in the RT group was also slightly larger than normal. Cardiac function studies demonstrated decreased left ventricular systolic function, but no significant difference between the groups. More specifically, decreased left ventricular diastolic function and increased LVth were observed in the HD group (**Table 2**).

Cardiac function in the RT group

Echocardiography revealed that the left ventricu-

Table 2 Echocardiographic findings (1)

	HD group (n=21)	RT group (n=24)	p value
LVDd (mm)	59.1±1.3	57.3±0.9	<0.05
LVth (mm)	12.0±0.6	10.2±0.8	<0.05
Fractional shortening (%)	22±0.2	23±1.8	NS
Diastolic dysfunction	18 (85.7)	5 (20.8)	<0.05
Calcification lesion	21 (100)	8 (33.3)	<0.05

Continuous values are mean±SD. ( ): %.
LVDd=left ventricular end-diastolic diameter; LVth=posterior left ventricular wall thickness in diastole. Other abbreviations as in Fig. 1.

Table 3 Echocardiographic findings (2)

	S-RT group (n=14)	L-RT group (n=10)	p value
LVDd (mm)	56.3±1.9	56.9±0.2	NS
LVth (mm)	9.6.0±0.3	10.5±0.4	NS
Fractional shortening (%)	23±1.2	24±1.9	NS
Diastolic dysfunction	0	5 (50)	
Calcification lesion	1 (7.1)	7 (70)	

Continuous values are mean±SD. ( ): %.
S=short preoperative; L=long preoperative. Other abbreviations as in Fig. 1, Table 2.

lar cavity was increased in both sub-groups, and that the LVDd was significantly increased in the L-RT group compared to the S-RT group. There were no differences in left ventricular systolic function and LVth between the two sub-groups. Decreased left ventricular diastolic function was observed only in the L-RT group (**Table 3**).

DISCUSSION

The present study of the changes in circulatory dynamics induced by the therapeutic modality for patients with terminal renal failure demonstrated that the degree of anemia and electrolyte disorders significantly improved in the RT group compared to the HD group. However, both groups required therapy for coronary risk factors. Cardiac function in the RT group was better than that in the HD group. In addition, hemodialysis was likely to influence cardiac function even if the period of hemodialysis was short.

Patients with chronic renal failure requiring hemodialysis frequently have abnormal levels of serum calcium and phosphorus caused by imbalance of the hormones that regulate blood calcium and phosphorus levels, such as parathyroid hormone, active vitamin D, and calcitonin.[1] In our study, blood levels of calcium and phosphorus in the HD group were out of the normal range. Although the serum calcium level is low in the classic type of renal failure, hypercalcemia is currently observed in many patients due to phosphorus modification resulting from medications for phosphorus excretion disorders.[8] This is a clinically serious problem, but the serum calcium level was high in our study as well. In contrast, the abnormal levels of serum calcium and phosphorus were improved over pre-transplant levels in the RT group. Therefore, there was no need for antacids and phosphorus-absorbing drugs due to cessation of hemodialysis, and natural renal function was recovered after renal transplantation. Renal function and the degree of anemia were also improved in the RT group due to erythropoietin production from the normally functioning kidney after transplantation.

Evaluation of the coronary risk factors must consider the effects of steroids and immunosuppressive drugs that were mandatory for all patients in the RT group. Hypertension[6] and increased LDL-cholesterol levels[7] are known to result from these drugs. In the present study, all patients in both groups received anti-hypertensive drugs, resulting in good blood pressure control. HMG-CoA reductase inhibitors for hyperlipidemia were given to 40% of patients in the HD group and all patients in the RT group. Thus, regardless of the prescription of immunosuppressive drugs, the LDL-cholesterol level in the RT group was almost equivalent to that in the HD group. In addition, the significantly higher HDL-cholesterol level in the RT group was caused by the administration of HMG-CoA reductase inhibitors.[9]

All patients with diabetes mellitus were under strict control, and there were no differences in the level of hemoglobin A_{1c} in diabetics between the groups. Diabetic nephropathy has become the major underlying disease to consider before the introduction of dialysis.[1] Therefore, effective dietary management of such patients may reduce the risk of developing diabetic nephropathy.[1] The incidence of post-renal transplantation diabetes mellitus ranges from 2.5% to 50% and steroid treatment is the major cause.[10] However, steroid therapy is essential for patients who undergo renal transplantation, so careful postoperative management is

required. There were no patients with diabetic nephropathy in the RT group of our study. We should think carefully about performing renal transplantation in patients with diabetic nephropathy because of the risk of aggravation of the diabetes by administration of steroids or immunosuppressive drugs.[11] Patients with diabetic nephropathy generally do not expect renal transplantation because hemodialysis is possible at higher ages than for other basal diseases.[12] However, the incidence of diabetes is expected to increase, so adaptation and education about renal transplantation will be important because more patients with diabetic nephropathy will undergo renal transplantation.

The serum uric acid level increases in patients with renal failure, as renal function diminishes consequent to excretion disorders. Sex may have had some effect on our results, as more males than females participated, but uric acid eliminator agents were administered to both groups. More patients smoked in the RT group than in the HD group. The postoperative questionnaire to the RT group indicated that the absence of limitations on diet and activities of daily living were major benefits of renal transplantion.[13] Although the issue of smoking should be left to the individual judgment of the patient, detailed postoperative education is expected to minimize such future risks.

Only patients in the HD group had a history of cardiac disease. Since patients in the HD group had received hemodialysis for more than 10 years on average, as high as 50% of the patients may have had a history of cardiac diseases. Echocardiography revealed a significant increase in LVth and a decrease in left ventricular diastolic function in the HD group compared to the RT group. Patients in the early phase of hemodialysis tend to develop tachycardia due to anemia and internal shunt, but chronic cardiac strain develops thereafter, mainly due to weight increase, and decrease and metabolic acidosis between the hemodialysis periods. Clinically, the so-called uremic cardiomyopathy can be classified into two groups similar to dilated cardiomyopathy and hypertrophic cardiomyopathy.[3] Uremic cardiomyopathy has no unique pathological features, but enlarged myocardial cells and interstitial fibrosis are frequently observed, as in other heart diseases.[14] The HD group combined a mixed population of patients with uremic cardiomyopathies similar to dilated and hypertrophic cardiomyopathies. In addition, many patients had a history of angina pectoris and calcified lesions of the heart valves.

None of the patients in the RT group had a history of cardiac diseases. However, although patients in the RT group had already stopped hemodialysis, their left ventricular systolic function was reduced, similar to that of the HD group. Treatment with immunosuppressive drugs is considered to affect cardiac function. In the present study, all patients in the RT group received cyclosporine, a type of calcineurine inhibitor[15] which may be associated with cardiac enlargement. However, we observed no case of left ventricular enlargement. Cyclosporine also seems to affect myocardial and cardiovascular functions, such as decreased NO production,[15] sympathetic neuropathy,[16] and the rennin-angiotensin system.[15] The reduced left ventricular systolic function and enlarged LVDd observed in the RT group were possibly associated with cyclosporine administration. However, it is also possible that the patients had not fully recovered from or adjusted to the cardiac strain induced by renal failure or that these effects were sequelae of dialysis prior to renal transplantation.

A correlation between the period of hemodialysis and the incidence of heart diseases has been suggested previously, and the percentage of patients who develop various cardiac complications increases as the hemodialysis period lengthens.[2] The present study focused on the hemodialysis period prior to renal transplantation in the RT group, which was divided into two sub-groups to further investigate the effects of renal transplantation on cardiac function. The results indicated that cardiac function in the group with a longer preoperative hemodialysis period had declined in comparison to those with a shorter preoperative hemodialysis period. More specifically, there were significant differences in left ventricular diastolic function between the two sub-groups. Cardiac function recovers after renal transplantation.[17] Our study results also showed better cardiac function in the RT group compared with the HD group. However, our results also suggested that recovery of cardiac function may be delayed in accordance with the length of the preoperative dialysis period, indicating the likelihood of better recovery of cardiac function after transplantation in patients with a shorter preoperative hemodialysis period. In addition, regardless of the administration of cyclosporine and steroids to all patients, none of our findings indicated negative

effects from these agents on cardiovascular dynamics.

Renal transplantation is the last treatment of choice for patients with terminal renal disease, because of the risk of other renal diseases such as proteinuria or hematuria depending on postoperative management. Therefore, this may lead to a vicious cycle affecting the once-recovered heart function. The major cause of death in renal transplant patients is heart disease,[1] so renal transplantation cannot be expected to dramatically improve life expectancy in renal failure patients. Moreover, many renal transplant patients already have some conditions indicating heart disease at the time of transplantation.[1] Careful postoperative management is required as new factors that could possibly exacerbate existing risk factors may arise after transplantation. However, postoperative management of renal transplant patients is usually performed by renal physicians and transplantation surgeons.[13] Therefore, cardiologists generally examine patients only after they develop heart diseases, and few cardiologists participate in the management of renal transplant patients in relation to possible cardiac disorders. Cardiac events were significantly reduced when fluvastatin was administered to renal transplant patients.[18] Moreover, administration of angiotensin Ⅱ receptor antagonist or angiotensin-converting enzyme inhibitors was reportedly effective against postoperative hypertension that developed after transplantation in addition to regulating any already existing hypertension and protecting the transplanted kidney.[19] These reports indicate that prevention of cardiac events is critical to improve the life expectancy of patients who undergo renal transplantation, and that cardiologists should be involved in the management of these patients, not only after transplantation but also as early as possible during the preoperative stage.

CONCLUSIONS

The present study investigated cardiovascular disorders in patients with terminal renal failure who underwent either maintenance hemodialysis or renal transplantion after hemodialysis. Medications that effect cardiovascular function such as steroids and immunosuppressive drugs are mandatory for renal transplant patients. Correct management of the medical therapeutic plan allows elimination of such effects on cardiac functions. This study did not compare cases before and after renal transplantation. However, renal transplantation is an important therapeutic method for patients with terminal renal failure which provides an opportunity for social rehabilitation. Life expectancy can be further improved by carefully taking effective measures

要　　約

維持透析患者での腎移植後の心機能の改善

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目　的: 維持透析患者における心機能低下が，腎移植により是正される可能性があるか否かを検討した．

方　法: 維持透析導入後，腎移植を受けた群（移植群，34例）と維持透析群（40例）において，心機能評価および冠危険因子の比較を行った．また，透析期間に着目した評価も行った．

結　果: 貧血と電解質異常は移植群のほうが是正されていた．両群で冠危険因子に対する治療が行われていた．また移植群の心機能は維持透析群より良好であった．また腎移植前の透析期間が短いほうが，心機能が良好であった．

結　論: 維持透析と関連する心機能障害は，腎移植後に改善される可能性がある．また腎移植前の透析期間が短いほうが，心機能の改善がより見込まれる可能性がある。

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References

1) Sarnak MJ, Levey AS, Schoolwerth AC, Coresh J, Culleton B, Hamm LL, McCullough PA, Kasiske BL, Kelepouris E, Klag MJ, Parfrey P, Pfeffer M, Raij L, Spinosa DJ, Wilson PW; American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention: Kidney disease as a risk factor for development of cardiovascular disease: A statement from the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. Circulation 2003; **108**: 2154−2169
2) Harnett JD, Foley RN, Kent GM, Barre PE, Murray D, Parfrey PS: Congestive heart failure in dialysis patients: Prevalence, incidence, prognosis and risk factors. Kidney Int 1995; **47**: 884−890
3) Parfrey PS, Foley RN, Harnett JD, Kent GM, Murray D, Barre PE: Outcome and risk factors of ischemic heart disease in chronic uremia. Kidney Int 1996; **49**: 1428−1434
4) Rostand SG, Brunzell JD, Cannon RO Ⅲ, Victor RG: Cardiovascular complications in renal failure J Am Soc Nephrol 1991; **2**: 1053−1062
5) Irish AB: Plasminogen activator inhibitor-1 activity in chronic renal disease and dialysis. Metabolism 1997; **46**: 36−40
6) Oflaz H, Pusuroglu H, Genchallac H, Demirel S, Bugra Z, Sever MS, Yildiz A: Endthelial function is more impaired in hemodialysis patients and renal transplant recipients. Clin Transplant 2003; **17**: 528−533
7) Kyriakides G, Miller J: Use of cyclosporine in renal transplantation. Transplant Proc 2004; **36**(2 Suppl): 167S-172S
8) Shepherd J, Cobbe SM, Ford I, Isles CG, Lorimer AR, MacFarlane PW, McKillop JH, Packard CJ; West Scotland Coronary Prevention Study Group: Prevention of coronary heart disease with prevastatin in men with hypercholesterolemia. N Engl J Med 1995; **333**: 1301−1307
9) Trenkwalder E, Gruber A, Konig P, Dieplinger H, Kronenberg F: Increased plasma concentrations of LDL-unbound apo(a)in patients with end-stage renal disease. Kidney Int 1997; **52**: 1685−1692
10) Kasiske BL, Chakkera HA, Roel J: Explained and unexplained ischemic heart disease risk after renal transplantation. J Am Soc Nephrol 2000; **11**: 1735−1743
11) Waki K: Impact of diabetes mellitus on transplantation. Clin Trasnpl 2004; **4**: 357−377
12) Goovaerts T, Jadoul M, Goffin E: Influence of a pre-dialysis education programme(PDEP)on the mode of renal replacement theraphy. Nephrol Dial Transplant 2005; **20**: 1842−1847
13) Holley JL, McCauley C, Doherty B, Stackiewicz L, Johnson JP: Patient s̀ views in the choice of renal transplant. Kidney Int 1996; **49**: 494−498
14) Rambausek M, Amann K, Mall G, Ritz E: Structural causes of cardiac dysfunction in uremia. Ren Fail 1993; **15**: 421−428
15) Ding B, Price RL, Borg TK, Weinberg EO, Halloran PF, Lorell BH: Pressure overload induces severe hypertrophy in mice treated with cyclosporine, an inhibitor of calcineurin. Circ Res 1999; **84**: 729−734
16) Lim HW, De Windt LJ, Steinberg L, Taigen T, Witt SA, Kimball TR, Molkentin JD: Calcineurin expression, activation, and function in cardiac pressure-overload hypertrophy. Circulation 2000; **101**: 2431−2437
17) Lindholm A, Albrechtsen D, Frodin L. Tufveson G, Persson NH, Lundgren G: Ischmic heart disease: Major cause of death graft loss after renal transplantation in Scandinavia. Transplantation 1995; **60**: 451−457
18) Holdaas H, Fellstrom B, Jardine AG, Holme L, Nyberg G, Fauchald P, Gronhagen-Riska C, Madsen S, Neumayer HH, Cole E, Maes B, Ambuhl P, Olsson AG, Hartmann A, Solbu DO, PedersenTR; Assessment of LEscol in Renal Traneplantation(ALERT)Study Investigators: Effect of fluvastatin on cardiac outcomes in renal transplant recipients: A multicentre, randomiesd, placebo-controlled trial. Lancet 2003: **361**: 2024−2031
19) Hernandez D, Lacalzada J, Rufino M, Torres A, Martin N, Barragan A, Barrios Y, Macia M, de Bonis E, Lorenzo V, Rodriguez A, Gonzalez-Posada JM, Salido E: Prediction of left ventricular mass changes after renal transplantation by polymorphism of the angiotensin-converting-enzyme gene. Kidney Int 1997; **51**: 1205−1211