NEFROLOGÍA. Volumen 25. Número 3. 2005

Short-term clinical course of cardiovascular risk factors in renal-pancreas transplantation

J. M. González-Posada*, L. Pérez Tamajón*, A. Caballero, I. Laynez***, D. Marrero*, C. Rodríguez*, A. Bravo****, M. Meneses****, A. Alarcó****, L. Morcillo** and D. Hernández***

*Nephrology Department. **Endocrinology Department. ***Cardiology Department. ****General and GI Surgery Department A.

IMPROVED SHORT-TERM CARDIOVASCULAR PROFILE AFTER SIMULTANEOUS PANCREAS-KIDNEY TRANSPLANTATION

ABSTRACT

The prognosis of type 1 diabetes mellitus (T1DM) patients with chronic renal failure (CRF) improves after simultaneous pancreas-kidney (SPK) transplantation. In order to evaluate the changes in cardio-vascular risk (CVR) factors after SKP, we studied nine recipients before and 6 months after SPK. There were five females and four males, with a mean age of 37 ± 8 years, duration of diabetes of 24 ± 5 years, three of them before starting dialysis, and six on dialysis (hemodialysis = 5; peritoneal dialysis = 1). Before SPK, all patients received anti-hypertensive therapy (1-4 drugs; mean 2.2 ± 0.9) and eight received statins. At 6 months after SPK, all patients were under triple immunosuppressive therapy (steroids + tacrolimus + MMF) without statins. They had normal renal function (Plasma Creatinine =1.2 ± 0.3 mg/dl) and pancreatic endocrine function (glycemia = 80 ± 8 mg/dl). HbA1c decreased significantly (8.4 ± 1.2 vs 4.7 ± 0.6 %; $p < 0.007$) with a value >7% in seven patients before SPK and in none 6 months after SKP transplantation ($p < 0.001$). Although Body Mass Index increased (23 ± 2 vs 25 ± 3 kg/m^2; $p < 0.05$), plasma triglycerides decreased (130 ± 51 vs 88 ± 33 mg/dl; $p < 0.05$), and total cholesterol, LDL-cholesterol and HDL-cholesterol were similar. Systolic and diastolic blood pressure (BP) decreased (156 ± 7 vs 133 ± 15 ; $p < 0.01$ and 96 ± 7 vs 79 ± 9; $p < 0.007$) with only two patients on anti-hypertensive therapy (1 drug). Likewise, before transplantation all patients were hypertensive (six grade 1 and three grade 2) while this was observed in only two at the end of follow-up (both grade 1) ($p < 0.001$). In conclusion, SPK transplantation with good renal and pancreatic function is associated with a short-term improvement in CVR profile.

Key words: Kidney pancreas transplant. Cardiovascular risk. Diabetes mellitus. Chronic renal failure.

Correspondence: Dr. J. M. González-Posada
Servicio de Nefrología
Hospital Universitario de Canarias
Ofra, s/n. La Laguna
38230 Sta. Cruz de Tenerife
E-mail: jmgposada@hotmail.com

EVOLUCIÓN A CORTO PLAZO DE LOS FACTORES DE RIESGO CARDIOVASCULAR TRAS EL TRASPLANTE RENO-PANCREÁTICO

RESUMEN

El pronóstico del paciente con diabetes mellitus tipo 1 (DMT1) e insuficiencia renal crónica (IRC) mejora tras el trasplante reno-pancreático (TRP). Con el fin de evaluar los cambios en los factores de riesgo cardio-vascular (RCV) se analizaron nueve pacientes que recibieron un TRP, antes (pre-TRP) y a los 6 meses de seguimiento (pos-TRP). Tres pacientes no habían iniciado diálisis, cinco estaban en hemodiálisis, y uno en diálisis peritoneal. Pre-TRP todos los pacientes recibían hipotensores (nº de fármacos = 2,2 ± 0,9; rango 1-4) y ocho de ellos estatinas. El tratamiento inmunosupresor consistió en Tacrolimus, Micofenolato Mofetil y esteroides. Pos-TRP todos mantenían función renal y pancreática normales (creatinina plasmática 1,2 ± 0,3 mg/dl; glucemia = 80 ± 8 mg/dl) sin necesidad de estatinas. La HbA1c descendió de forma significativa (8,4 ± 1,2 vs 4,7 ± 0,6%; $p < 0,007$), presentando un valor superior al 7 %, siete pacientes pre-TRP frente a ninguno pos-TRP ($p < 0,001$). Aunque el Índice de Masa Corporal aumentó (23 ± 2 vs 25 ± 3 kg/m^2; $p < 0,05$), los triglicéridos descendieron (130 _ 51 vs 88 ± 33 mg/dl; $p < 0,05$), y el colesterol total, HDL-colesterol, LDL-colesterol fueron similares. La tensión arterial sistólica (TAs) y diastólica (TAd) descendió de forma significativa (156 ± 7 vs 133 ± 15; $p < 0,01$ y 96 ± 7 vs 79 ± 9; $p < 0,007$ respectivamente) y sólo dos pacientes recibían hipotensores pos-TRP (1 fármaco). En conclusión, estos datos sugieren que a corto plazo el TRP mejora algunos de los factores de RCV lo que pudiera traducirse en una optimización del pronóstico a más largo plazo.

Palabras clave: Doble trasplante reno-pancreático. Riesgo cardio-vascular. Diabetes mellitus. Insuficiencia renal crónica.

INTRODUCTION

Survival of patients with type 1 diabetes mellitus (T1DM) and chronic renal failure (CRF) improves after renal-pancreas transplantation.[1,2] Glycemia and renal function normalization has been considered as the cause of this improvement, although modification of other classical cardiovascular (CV) risk factors (RF) such as dyslipemia and AHT may be implicated.

Coronary heart disease is one of the main morbimortality causes in patients with diabetes mellitus (DM). These patients are considered maximum risk, similar to patients con a history of ischemic heart disease, and it is recommended they should have a strict control on lipids (LDL-Cholesterol < 100 mg/dL) and blood pressure (BP < 130/80 mmHg).[3,4] Also, in these patients the risk for death of CV origin increases with HbA1c increase, the lowest mortality rate being with an HbA1c level < 5%.[5] In T1DM, dyslipemia is related to glycemic control, whereas the incidence of arterial hypertension (AHT) increases with disease duration and the presence of diabetic nephropathy. Glycemia and renal function normalization after renal-pancreas transplantation (RPT) improves endothelial function and blood pressure figures, as well as the lipid profile.[6,7] However, other factors inherent to transplantation, such as effects of immunosuppression and graft rejection, may negatively act since steroidal drugs produce endothelial dysfunction, AHT, hyperlipidemia, and glucose intolerance, and calcineurin inhibitors (Tacrolimus of Cyclosporin) produce nephrotoxicity, and toxicity to pancreatic B cells[8].

It has been clearly demonstrated that CV mortality in renal transplantation (RT), although lower than that in the dialysis population, is higher than that in the general population[9], being the main mortality cause with functioning graft[10,11]. DM, as a primary disease, importantly contributes to this fact.[11] Patients with T1DM and CRF show a clear benefit when they receive a RPT vs. isolated RT,[1,2,6] with a lower per-

centage of hypertensive patients and CV events.[6,13]

In order to know the changes in classical CV RF, we have analyzed the clinical course of 9 patients before (pre-RPT) and 6 months after (post-RPT) renal-pancreas transplantation.

MATERIAL AND METHODS

Between may 2002 and may 2003, 10 RPT were performed in our Center. One patient lost his pancreatic graft early in the clinical course and was excluded from the study. The clinical features of the remaining 9 patients and other transplantation-related data are shown in Table I.

In all the cases, the double RPT was done according to the usual surgical technique, with pancreas implantation intraperitoneally, enteric shunting and systemic venous drainage (iliac vessels) and extraperitoneal renal to the left iliac cavity. In all patients, the same immunosuppressor protocol was followed with Timoglobulin (7 doses of 1.5 mg/kg/day, varying according to lymphocytes count), receiving the first dose during surgery after methyl-prednisolone (MP) 500 mg, and followed by MP 20 mg, tacrolimus 0.1 mg/kg/day bid until reaching blood levels between 8-12 ng/mL, MMF 2 g/day and steroids (MP 500 mg the day of transplantation, 60 mg/day for 6 days, and thereafter, Prednisone 20 mg/day for the first two months, tapering by 5 mg/day within 6 months from transplantation). In all cases, antimicrobial prophylaxis was used with vancomicin 1 gr i.v. in the operating room (just one dose), plus cefotaxime 1 gr iv t.i.d., for 3 days: antifungal prophylaxis with fluconazole 100 mg/day for 3 weeks and nistatine p.o. from the beginning of oral tolerance until discharge; anti-cytomegalovirus with gancyclovir i.v. for one week, followed by gancyclovir p.o. for 6 weeks in high-risk patients (CMV+ donors, and CMV- recipient), and oral acyclovir in the remaining patients, and cotrimoxazol, 1 tablet p.o. for 6 months against Pneumocystis carinii.

Table I. General data of study patients

Recipient's age (years)	37 ± 8
Diabetes duration (years)	24 ± 5
Type of renal replacement therapy	3 predialysis/5 H/1 PD
Donor's age (years)	25 ± 5
HLA-A-B-DR mismatch	5 ± 0.7 (4-6)
Anti-HLA antibodies rate (%)	0
CIT pancreas (hours)	7.3 ± 0.9
CIT kidney (hours)	9.4 ± 0.8
Pre-RPT statins treatment yes/no	8/1
Pre-RPT hypotensive treatment yes/no	9/0
Number of anti-AHT drugs	2.2 ± 0.9
Immediate renal function post-RPT (%)	100
Patients with acute rejection	2/9

HD = hemodialysis; PD = peritoneal dialysis; CIF = cold ischemia time.

Parameters for glucose metabolism (baseline glycemia and HbA1c), lipid metabolism (Total cholesterol [TC], HDL-cholesterol [HDL-Ch], LDL-cholesterol [LDL-Ch], triglycerides [TG], Apo A and Apo B), weight, and systolic (SBP) and diastolic (DBP) arterial blood pressure, were determined pre-RPT and 6 moths after transplantation (post-RPT). Pre-RPT measurements were done during one of the follow-up visits scheduled in our Center for patient's inclusion in the double RPT waiting list, 1-4 months prior to performance of transplantation. As part of the assessment for inclusion in the waiting list, in all cases a cardiac stress-ultrasound was done to rule out ischemic heart disease, and lower limbs arteriography or angio-magnetic resonance imaging (angio-MRI) to rule out stenotic lesions within the iliac vessels. Other parameters such as weight and body mass index (BMI) and biochemical (plasma creatinine and creatinine clearance) were analyzed monthly during the follow-up.

The Wilcoxon's test was used for comparison of continuous variables and Fisher's test for comparison of dichotomous variables.

RESULTS

Within 6 months, the 9 patients presented normal renal function (plasma creatinine = 1.2 ± 0.3, creatinine clearance = 77 ± 21 mL/min), being free from insulin and without statins treatment.

Baseline glycemia and HbA1c significantly decreased within 6 months of study (Figures 1 and 2). The number of patients who presented a pre-RPT HbA1c level > 5% was 9 (100%) as compared to 3 (33%) post-RPT ($p < 0.004$), and with pre-RPT HbA1c level > 7% was 7 (78%) pre-RPT as compared to none (0%) post-RPT ($p < 0.001$) (Figure 2). Although BMI increased (23 ± 2 vs 25 ± 3 kg/m^2; $p < 0.05$), TG significantly decreased (130 ± 51 vs 88 ± 33 mg/dL; $p < 0.05$), whereas TC, HDL-Ch, LDL-Ch. Apo A and Apo B did not show significant differences (Table II). Pre-RPT, 2 patients (22%) had LDL-Ch > 100 mg/dL vs. 3 (33%) post-RPT (p = NS).

Blood pressure significantly decreased at the end of the follow-up period (Figure 3). Whereas pre-RPT all patients (100%) were hypertensive (6 stage I, and 3 stage II), post-RPT only 2 patients (22%) had stage I AHT ($p < 0.001$) that required treatment (one drug). In spite of antihypertensive drug treatment pre-RPT, in no case SBP and DBP reached figures < 130 and 80 mmHg, respectively, whereas post-RPT 5 patients (55.5%) kept BP below those levels ($p < 0.01$).

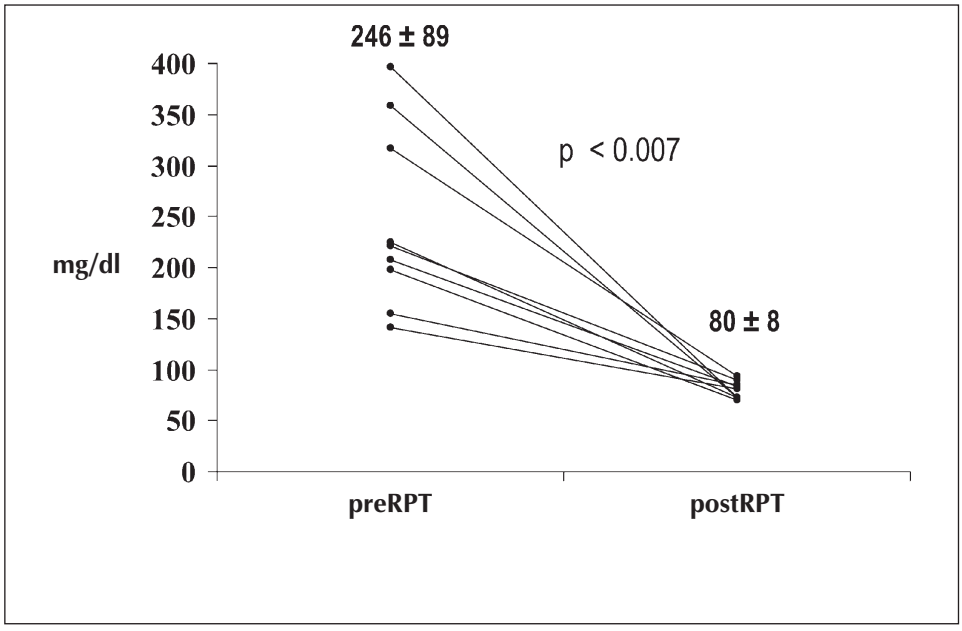

Fig. 1.—Course of fasting plasma glucose levels before (preRPT) and within 6 months follow-up (postRPT) renal-pancreas transplantation.

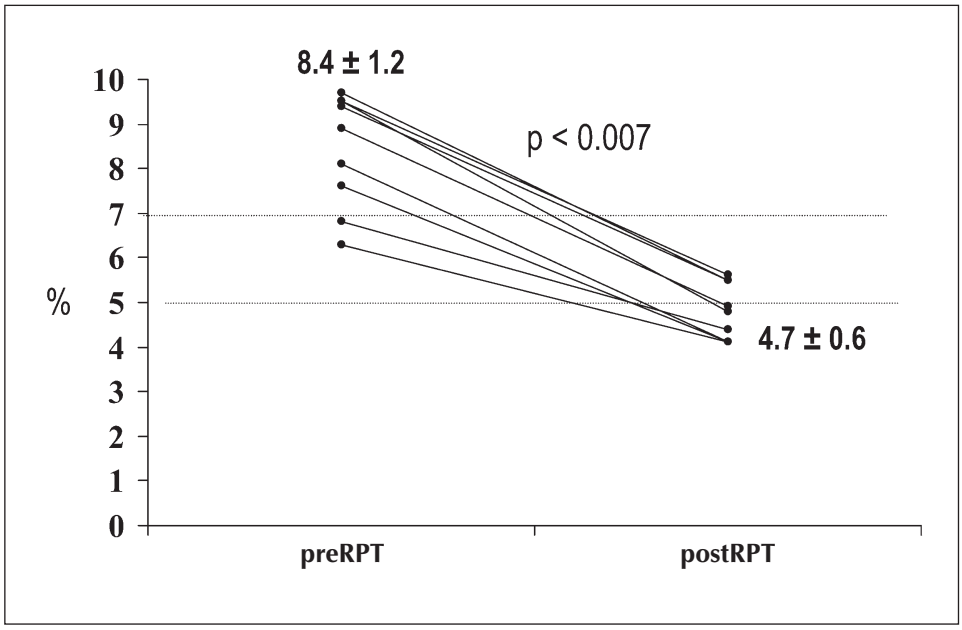

Fig. 2.—Course of HbA1c levels before (preRPT) and within 6 months follow-up (postRPT) renal-pancreas transplantation.

DISCUSSION

Patients with DM and CRF present a high CV mortality due to several factors such as the primary disease, the uremic milieu, volume overload, AHT, and dyslipemia.

In the present study, 9 out of 10 patients with T1DM and CRF that received double RPT presented, within 6 months of follow-up, a normal functioning of both grafts, including good renal function, and normal glucose and HbA1c levels. In addition, an appropriate lipid profile and a significant BP decent were achieved.

Chronic renal failure, defined as a renal glomerular filtration rate (GFR) lower than 60 mL/min, is and independent CV RF.[14] A GFR below 60 mL/min independently increases the risk for death from CV origin by 16%, reaching 30% when GFR is below 30

Table II. Lipids and BMI course in the study follow-up

	Pre RPT	PostRPT	p
Total cholesterol (mg/dL)	189 ± 63	175 ± 37	NS
HDL-Ch (mg/dL)	63 ± 16	59 ± 12	NS
LDL-Ch (mg/dL)	89 ± 47	99 ± 27	NS
Triglycerides (mg/dL)	130 ± 51	88 ± 33	< 0.05
ApoA (mg/dL)	150 ± 24	138 ± 39	NS
ApoB (mg/dL)	88 ± 37	85 ± 37	NS
BMI (kg/m^2)	23 ± 2	25 ± 3	< 0.05

Data expressed as mean ± standard deviation. NS = not significant.

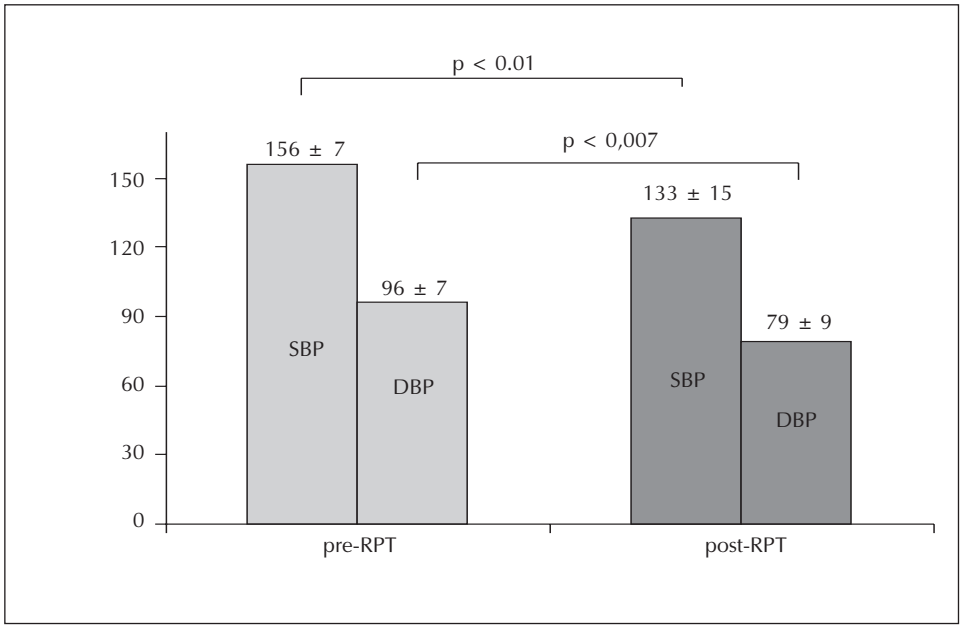

Fig. 3.—Course of systolic (SBP) and diastolic (DBP) blood pressure levels before (preRPT) and within 6 months follow-up (postRPT) renal-pancreas transplantation.

mL/min.[4,14] Although the transplanted renal patient presents an aged-adjusted CV mortality higher than that in the general population, this rate is lower than that of the dialysis patient.[9] Although follow-up time in the present study was only 6 months, 8 out of 9 patients presented a GFR > 60 mL/min. Considering that recipients received a renal graft from a young donor, and in all cases they had an immediately improved renal function and a low incidence rate of acute rejection, we do foresee a low incidence of chronic nephropathy in the grafted kidney, and a long renal graft survival I the long run.

Glycemia and HbA1c normalization is another factor that may have an effect on the better survival of patients with T1DM and CRF that receive a RPT, as compared to that of patients that receive only RT or remains on dialysis.[1,2] In this sense, several studies have shown a better control of classical CV RF, an improved endothelial and left ventricular function, in these patients with RPT as compared to RT.[6,7,13,15] The beneficial effect of glycemia control on several CV RF and myocardial function improvement has been similarly observed in patients with T1DM without renal impairment that received an isolated pancreas transplantation.[16]

Although the relationship between glycemic control and macrovascular disease in DM is controversial, in a large population of diabetic men older than 45 years, Knaw et al.[5] recently verified a 28% increase in CV mortality for each 1% increase in HbA1c, independently of other factors such as age, BP, total cholesterol, BMI, and cigarette smoking. The lowest mortality was found in those patients with an HbA1c < 5%. Besides, in young patients with T1DM,

it has been observed that patients submitted to intensive insulin therapy that achieved a better glycemic control and lower HbA1c levels had a tendency to a decrease in CV events. In that study, progression to retinopathy was minimal when HbA1c was kept < 7%.[17] More recently, in the continuation of that study, in patients with intensive insulin therapy, Nathan et al.[18] observed a lower progression of the carotid artery intimal-media layers thickening measured by ultrasound, as a marker of macrovascular involvement. This marker was correlated to HbA1c and other factors such as age, SBP, and LDL-Ch/HDL-Ch ratio. In the present study, in all cases an HbA1c level < 7% was achieved in all cases, and below 5% in 67% of the cases, which in association with a better control of other risk factors will likely reduce progression to retinopathy and macrovascular disease. However, the effect of CV RF on the transplanted patient requires larger studies with longer follow-up times.

In the present study, all patients kept and adequate lipid control, without needing statins. LDL-Ch recommended values in the DM patient (< 100 mg/dL)[3] were obtained in 6 out of 9 patients after RPT, and in all cases triglycerides significantly decreased. It is well accepted that hyperlipidemia increases CV disease in transplanted patients, although the precise relationship has not been fully determined in this population.[19] On the other hand, statins use after RT improves patients' survival independently of other risk factors. Cosio et al.[20], after controlling for several factors such as age and cholesterol level, observed a 24% decrease in mortality with the use of these drugs, not clearly determining whether the effect os statins on mortality is independent of lipid control. A longer follow-up period is required in RPT patients to assess the effect of statins and limit LDL-Ch levels in order to reduce the number of CV events.

The most remarkable effect on classical CV RF was observed in BP decrease after RPT. This finding has been described by La Roca et al.[7] who observed in 23 patients with T1DM and CRF a 100% prevalence of AHT pre-RPT as compared to 39% within four years of follow-up. It is difficult to assess whether the low AHT prevalence in our study is due to renal function normalization or to the effect of receiving grafts from young donors with short ischemia times, or whether other factors associated to glycemic control may involved. Anyhow, the better BP control may have an effect in optimizing the myocardial architecture and vascular remodeling, and in the long run, in a better survival in these patients after double RPT.

In summary, these data suggest that, in the short term, RPT improves some of the CV RF, which may translate into an optimization of long-term prognosis. Other emergent RF and an individualized assessment of CV RF must be used in the follow-up of this type of patients.

REFERENCES

1. Becker BN, Brazy PC, Becker YT, Odorico JS, Pintar TJ, Collins BH, Pirsch JD, Leverson GE, Heisey DM, Sollinger HW: Simultaneous pancreas-kidney transplantation reduces excess mortality in type 1 diabetic patients with end-stage renal disease. Kidney Int 57: 2129-2135, 2000
2. Ojo AO, Meier-Kriesche HU, Hanson JA, Leichtman A, Magee JC, Cibrik D, Wolfe RA, Port FK, Agodoa L, Kaufman DB, Kaplan B: The impact of simultaneous pancreas-kidney transplantation on long term patient survival. Transplantation 71: 82-90, 2001.
3. Executive Summary of the Third Report of the National Colesterol Educational Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholestero in Adults (Adult Treatment Panel III). JAMA 285: 2486-2496, 2001.
4. Chobanian AV, Bakris GL, Blak HR, Cushman WC, Green LA, Izzo JL, Jones DW, Materson BJ, Oparil S, Wright JT, Roccella EJ: National Heart, Lung, and Blodd Institute Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure Education Program Coordinating Committee. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure: The JNC 7 Report. JAMA 289: 2560-72, 2003.
5. Khaw KT, Wareham N, Luben R, Bingham S, Oakes S, Welch A, Day N: Glycated haemoglobin, diabetes, and mortality in men in Norfolk cohort of European Prospective Investigation of Cancer and Nutrition (EPIC-Norfolk). BMJ 322: 1-6, 2001.
6. Fiorina P, La Roca E, Venturini M, Minicucci F, Fermo I, Paroni R, D´Angelo A, Sblendido M, Di Carlo V, Cristallo M, Del Maschio A, Pozza G, Secchi A: Effects of Kidney-Pancreas Transplantation on Atherosclerotic Risk Factors and Endotelial Function in Patients with Uremia and Type 1 Diabetes. Diabetes 50: 496-501, 2001.
7. La Roca E, Fiorina P, Di Carlo V, Astorri E, Rossetti C, Lucignani G, Fazio F, Giudici D, Cristallo M, Bianchi G, Poza G, Sechi A: Cardiovascular outcomes after kidney-pancreas and kidney-alone transplantation Kidney Int 60: 1964-1971, 2001.
8. Boots JM, Christiaans MH, Van Hooff JP: Effect of immunosuppressive agents on long-term survival of transplants recipients: focus on the cardiovascular risk. Drugs 64: 2047-73, 2004.
9. Foley RN, Parfrey PS, Sarnak MJ: Cardiovascular disease in chronic renal diseae. Clinical Epidemiology of Cardiovascular Disease in Chronic Renal Disease. Am J Kidney Dis 32 (Supl. 3): S112-S119, 1998.
10. Dimeny EM: Cardiovascular disease after renal transplantation. Kidney Int 61: S78-S84, 2002.
11. Ojo AO, Hanson JA, Wolfe RA, Agodoa LY, Leavey SF, Leitchman A, Young EW, Port FK: Long-term survival in renal transplant recipients with graft function. Kidney Int 57: 307-313, 2000.
12. Gill JS, Pereira BJG: Death in the first year after transplantation: implications for patients on the transplant waiting list. Transplantation 75: 113-117, 2003.
13. La Roca E, Fiorina P, Astorri E, Rossetti C, Lucignani G, Fazio F, Castoldi R, Bianchi G, Di Carlo V, Pozza G, Sechi A: Pa-

tient survival and cardiovascular events after kidney-pancreas transplantation: comparison with kidney transplantation alone in uremic IDDM patients. Cell Transplant 9: 929-932, 2000.
14. 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: Kidney Disease as a Risk Factor for Development of Cardiovascular Disease: A Statement From the Americam Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. Circulation 108: 2154-2169, 2003.
15. Biesenbalch G, Margreiter R, Königsrainer A, Bösmüller C, Janko O, Brücke P, Gross C, Zazgornik J: Comparison of progression of macrovascular diseases after kidney or pancreas and kidney transplantation in diabetic patients with end-stage renal disease. Diabetología 42: 231-234, 2000.
16. Copelli A, Giannarelli R, Mariotti R, Rondinini L, Fossati N, Vistoli F, Aragona M, Rizzo G, Boggi U, Mosca F, Del Prato F, Marchetti P: Pancreas transplant alone determines early improvement of cardiovascular risk factors and cardiac function in Type 1 diabetic patients. Transplantation 76: 974-976, 2003.
17. The Diabetes Control and Complications Trial Research Group: The Effect of Intensive Treatment of Diabetes on the Development and Progression on Long-Term Complications in Insulin- Dependent Diabetes Mellitus. N Engl J Med 329: 977-986, 1993.
18. Nathan DM, Lachin J, Cleary P, Orchard T, Brillon DJ, Backlund JY, O´Leary DH, Genuth S: The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group. Intensive Diabetes Therapy and Carotid Intima-Media Thickness in Type 1 Diabetes Mellitus. N Engl J Med 348: 2294-1303, 2003.
19. Moore R, Hernandez D, Valantine H: Calcineurin Inhibitors and Post-Transplant Hyperlipaedemias. Drug safety 24: 755-766, 2001.
20. Cosio FG, Pesavento TE, Pelletier RP, Henry M, Ferguson RM, Kim S, Lemeshow S: Patient Survival After Kidney Transplantation III: The Effects of Statins. Am J Kidney Dis 40: 638-643, 2002.