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Prevalence of Cardiovascular Risk Factors on Different Phases of Diabetic Nephropathy in Comparison to Type 1 Diabetes Recipients who had Undergone Simultaneous Pancreas Kidney Transplant

Maria Deolinda F Neves¹, Erika B Rangel^{2*}, João R Sá¹ and Sergio A Dib¹

¹Department of Medicine, Division of Endocrinology, São Paulo Federal University, Brazil ²Department of Medicine, Division of Nephrology, São Paulo Federal University, Brazil

Abstract

The aims of this study were to evaluate the relationship between different phases of diabetic nephropathy and the beneficial effect of successful simultaneous pancreas-kidney transplant (SPKT) on the prevalence of cardiovascular risk factors (CVRF). We analyzed 210 type 1 diabetic patients (age>18 years and diabetes duration \ge 10 years). Patients were divided into five groups: normo, micro, macroalbuminuric, end stage renal disease (ESRD), and SPKT. The following CVRF, besides diabetes, were analyzed: blood pressure, waist circumference, HDL cholesterol and triglycerides. The prevalence of \ge 2 CVRF increased from normoalbuminuric to end stage renal disease group: 20.7%, 43.4%, 53.6%, 71.4% (p<0.001), respectively. In the SPKT group, this prevalence was 18.5%. Two or more CVRF were positively associated with female gender (OR=2.5; p=0.008) and with diabetes duration over 15 years (OR=2.6; p=0.023). The SPKT was a protective factor (OR=0.3; p=0.047), and ESRD was a risk factor (OR=5.2, p=0.014) for the presence of CVRF. In conclusion, the severity of diabetic nephropathy was associated with a higher prevalence of two or more CVRF, that prevalence was similar to normoalbuminuric patients.

Keywords: Cardiovascular risk factors; Diabetic nephropathy; SPKT; Type 1 diabetes

Introduction

The relative mortality risk due to cardiovascular disease (CVD) in patients diagnosed with type 1 diabetes mellitus (type 1 DM) is estimated to be 10 times higher than age-matched individuals without diabetes [1]. Among the factors that contribute to this difference are those related to the development of renal disease. Notably, renal disease and younger age onset of diabetes can potentially result in longer exposure to cardiovascular risk factors (CVRF), such as hypertension, hyperlipidemia and poor glycemic control [2].

Diabetic patients with renal disease are at the greatest risk for presenting multiple CVRF, and the progression and severity of renal disease can increase all causes of mortality [3].

The correction of uremic and hyperglycemic environment, potential cardiovascular risk factors, is achieved with simultaneous pancreas-kidney transplant (SPKT). The SPKT is a treatment option for patients with type 1 diabetes and ESRD. The life expectancy of these patients is on average 15 years longer than patients who are waiting for a transplant [4]. Although cardiovascular disease is the leading cause of death after SPKT, most studies show an improvement in risk factors for atherosclerosis and a reduction in the number of cardiovascular events [5-8].

Therefore, it is important to understand from which stage of renal disease these CVRF become more prevalent. In the same way, it would be interesting to know which group of patients with diabetic nephropathy could be compared to patients who had undergone SPKT, regarding to CVRF.

Accordingly, this study evaluates the relationship between different phases of diabetic nephropathy and the prevalence of CVRF in patients with type 1 DM. Here we also show the beneficial effect of successful SPKT on decreasing CVRF.

Patients and Methods

Patients

This study involves a cross-sectional analysis in a randomized group of patients diagnosed with type 1 DM from an out-patient clinic of diabetes care at São Paulo Federal University Hospital, São Paulo, SP, Brazil. We defined T1DM as insulin-dependence within 6 months of diagnosis. Eligible patients were 18 years or older and had T1DM more than or equal to 10 years. Patients who have undergone simultaneous pancreas-kidney transplant (SPKT) less than 6 months prior to inclusion or who have lost renal and/or pancreatic graft function were excluded from the analysis. The study protocol was approved by the Institutional Review Board of São Paulo Federal University.

Clinical and laboratory parameters

A total of 210 patients with T1DM were studied. To aid the analysis, the total sample was divided into five groups according to the following criteria: Group NA (normal renal function without microalbuminuria), Group MI [microalbuminuria and/or use of ACE (angiotensin-converting-enzyme) inhibitors or angiotensin II receptor blockers, since introduced because of detection of microalbuminuria],

^{*}Corresponding author: Erika B Rangel, Department of Medicine, Division of Nephrology, São Paulo Federal University, Rua Botucatu, 740, Vila Clementino, SP 04023-900, Sao Paulo, Brazil, Tel: +55 11 59041699, +55 11 55739652; E-mail: erikabr@uol.com.br

Received January 19, 2013; Accepted March 20, 2013; Published March 24, 2013

Citation: Neves MDF, Rangel EB, Sá JR, Dib SA (2013) Prevalence of Cardiovascular Risk Factors on Different Phases of Diabetic Nephropathy in Comparison to Type 1 Diabetes Recipients who had Undergone Simultaneous Pancreas Kidney Transplant. J Diabetes Metab S9: 002. doi:10.4172/2155-6156. S9-002

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Group MA (macroalbuminuira and/or moderately or severely impaired renal function with estimated creatinine clearance between 15 and 60 mL /min/1.73 m²), Group ESRD (end stage renal disease, including hemodialysis or peritoneal dialysis), Group SPKT (simultaneous pancreas kidney transplant, with both grafts functioning). Enteric exocrine drainage was performed in all SPKT recipients, except for one that underwent bladder drainage. Systemic endocrine drainage was performed using the iliac venous or inferior cava vein anastomosis in all cases. The initial immunosuppressive regimen included tacrolimus 0.15 mg/kg/day, the dose was adjusted throughout the post-transplant period to maintain the serum levels of 10-15 ng/mL in the first 30 days, 8-10 ng/mL between 31 and 90 days followed by 5-10 ng/mL of the maintenance dose. Tacrolimus was prescribed in 92% of the recipients. The initial prednisone dose was 30 mg/day, reduced by 5 mg each month until the 8th month when the maintenance dose of 5 mg/day was obtained. Mycophenolate mofetil 2 g/day or mycophenolate sodium 1.44 g/day was administered in all cases. Induction with monoclonal or polyclonal antibodies was not routinely performed. However, the induction was carried out in cases of re-transplant, when the panel reactive antibody was greater than 20% or when the cold ischemia of the organ exceeded 24 hours.

At medical visits, the following anthropometric data were registered: weight (kg), height (m) and abdominal circumference (cm), which was taken halfway between the patient's 10th rib and the iliac crest. The body mass index (BMI) was calculated by the formula: weight (kg)/height² (m). Systolic and diastolic blood pressures were measured with the patient sitting down, after resting for at least 5 minutes, using a standard clinical sphygmomanometer. The average result from 3 measures taken during the same ambulatory visit was recorded.

Albuminuria was considered positive if detected in at least 2 to 3 samples within an interval of 3 months. Microalbuminuria and macroalbuminuria were defined as urinary albumin excretion rates between $20-200 \,\mu$ g/minute and over $200 \,\mu$ g/minute, respectively. Renal function was estimated using the Cockcroft-Gault formula.

The following cardiovascular risk factors (CVRF) were analyzed: arterial systolic pressure \geq 130 mmHg and/or diastolic \geq 85 mmHg and/or use of antihypertensives, abdominal circumference \geq 80 cm for females and \geq 90 cm for males, HDL-cholesterol <50 mg/dL for females and 40 mg/dL for males, triglycerides \geq 150 mg/dL, fasting glycemia \geq 100 mg/dL and or use of anti-hyperglycemic specific agent. This last criterion was fulfilled in all of the patients from groups NA, MI, MA and ESRD (diabetic patients).

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Laboratory parameters were analyzed according to the following methods: total cholesterol (colorimetric enzymatic method: reference <200 mg/dL), HDL-cholesterol (colorimetric method: reference >35 mg/dL), LDL-cholesterol (Friedewald formula), triglycerides (colorimetric enzymatic method: reference <150 mg/dL), glycemia (Hitachi 912 Roche enzymatic method: reference of 75 – 99 mg/L), glycated hemoglobin (high-performance liquid chromatography, reference range: 3.5–6.0%; Tosoh Bioscience, scenika@scenica.com. br), and albuminuria (imunoturbidimetric method: reference up to 20 μ g/min).

Statistical analysis

Because most quantitative variables had no adherence to the normal distribution (p<0.05 in the Kolmogorov-Smirnov test), a nonparametric test was chosen to evaluate them. The comparison between groups NA to ESRD, regarding quantitative variables, was performed by the Kruskall-Wallis test. In order to compare these groups to each other, the Tukey test of multiple comparisons was performed. To compare the quantitative variables among the SPKT variables and the other groups, the Mann-Whitney test was used. For the qualitative variables, the linear tendency and association were calculated by the chi-square test.

Additionally, to evaluate these factors in the total sample of patients, association was analyzed by the chi-square test (univariate analysis), selecting the factors with p<0.20. For this analysis, the patients' ages and age at diagnosis were split into tertiles: 18-23, 24-34, and 35-62 years old, and 1-6, 7-12, 13-35 years, respectively. Time on dialysis was also analyzed. After selecting factors by a univariate analysis, a multiple logistic regression analysis was performed. The Hosmer-Lemeshow test was used to verify model adjustment. In the statistical analyses, SPSS 11.0 software was used.

Results

General patient characteristics

Patients were classified in five groups (n=210): NA: 29 (13.8%), MI: 53 (25.2%), MA: 28 (13.3%), ESRD: 35 (16.7%), and SPKT: 65 (31%). Table 1 compares the demographic and clinical characteristics of the five groups.

Dro	NA	MI	MA	ESRD	SPKT	Multiple comparisons
Ν	29	53	28	35	65	
Gender M (%)	48.3	50.9	60.7	45.7	41.5	
Age (years)	21.9 (4.7)# *	26.4 (10.5)*	31.5 (8.1)*	32.6 (8.7)*	36.0 (7.3)	NA lower than MA and ESRD MI lower than ESRD All groups were lower than SPKT
Type 1 DM duration (years)	15.0 (4.6)*	17.2 (7.4)*	20.4 (5.6)	18.8 (4.5)	20.6 (5.2)	NA lower than MA, ESRD and SPKT MI lower than SPKT
Age at the diagnosis (years)	6.9 (3.5)*	9.1 (6.6)*	11.0 (7.9)	13.5 (7.5)	13.0 (6.9)	NA and MI lower than MA,ESRD and SPKT

NA: Normoalbuminuria; MI: Microalbuminuria; MA: Macroalbuminuria; ESRD: End Stage Renal Disease; SPKT: Simultaneous Pancreas Kidney Transplant # Data are shown as mean (S.D.) * p<0.05

Table 1: Demographic and clinical data.

The patients' cardiovascular risk factors were distributed as follows: high blood pressure 70%, high abdominal circumference 33.8%, low HDL-cholesterol 28.1% and high triglycerides 15.2%. Overall, two or more risk factors were diagnosed in 38.6% of all patients.

In ESRD patients, average time on dialysis (23.1 months) was similar to that reported for SPKT recipients (27.9 months). The majority (81%) of those patients were on hemodialysis.

In the SPKT group, the time elapsed after transplant averaged 28.6 months (range 6-75 months) by the time of the study.

Demographic data and cardiovascular risk factors prevalence on type 1 DM in different phases of renal disease

ESRD patients showed lower BMI compared to all other groups (p<0.05) and lower abdominal circumference than the MI group (p<0.05). Glycemic control (HbA1c) was similar in all four diabetic groups studied. The ESRD group also exhibited the highest levels of

systolic blood pressure (SBP) (p<0.05) and higher diastolic blood pressure (DBP) compared to the NA and MI groups (p<0.05).

Table 2 illustrates that in the MA, serum total cholesterol was higher (p<0.05) than in the NA groups, whereas serum LDL-cholesterol was higher than the ESRD group (p<0.05). Additionally, in the ESRD group, serum HDL-cholesterol was lower than the MI group (p<0.05) and serum triglycerides were higher when compared to the other groups (p<0.05). Antihypertensive drugs were reported in all groups: 3.4 % (NA), 54.7% (MI), 100% (MA), and 94.3% (ESDR). In addition, lipid lowering drugs were prescribed: 6.9% (NA), 15.1% (MI), 67.9% (MA), and 25.7% (ESRD).

The prevalence of two or more cardiovascular risk factors was described in 20.7% (NA), 43.4% (MI), 53.6% (MA), and 71.4% (ESRD). In light of these findings, we observed that after applying the chi-square for a trend test, there was a tendency toward increasing multiple risk factors prevalence according to the advance of diabetic nephropathy (p<0.001).

Dro	1 NA (N=29)	2 MI (N=53)	3 MA (N=28)	4 ESRD (N=35)	Multiple Comparisons	5 SPKT (N=65)	Group 5 vs
	M (SD)	M (SD)	M (SD)	M (SD)	(groups 1 to 4)	M(SD)	1,2,3,4
BMI (Kg/m²)	22.9 (2.7)	24.1 (3.4)	23.4 (3.4)	20.9 (2.4)	4<1,2 e 3	22.7 (3.4)	5<2 (p=0.023) 5>4 (p=0.008)
Abdominal circumference (cm)	78.7 (9.8)	83.6 (9.2)	80.5 (8.8)	78.6 (7.5)	2>4	84.3 (10.4)	5>1 (p=0.008) 5>4 (p=0.003)
SBP (mmHg)	116 (8.1)	123 (15.3)	132.3 (22.9)	150.5 (31.2)	1<3 4>1,2 e 3	128.7 (16.6)	5>1 (p=0.000) 5>2 (p=0.017) 5<4 (p<0.001)
DBP (mmHg)	76.2 (8.5)	79.3 (10.3)	86.6 (13.5)	91.1 (16.2)	1<3 4>1 e 2	81.3 (11.5)	5>1 (p=0.033) 5<4 (p=0.001)
Total cholesterol (mg/dL)	160.6 (25.8)	166.1 (30.4)	186.8 (46.4)	166 (45.4)	1<3	146 (24)	5<1 (p=0.009) 5<2 (p<0.001) 5<3 (p<0.001) 5<4 (p=0.032)
LDL cholesterol (mg/dL)	92.4 (21.5)	92.3 (24.1)	108.7 (38.6)	85.4 (43.8)	3>4	68.8 (20)	5<1 (p<0.001) 5<2 (p<0.001) 5<3 (p<0.001)
HDL-cholesterol (mg/dL)	49.6 (12.3)	55.5 (13.3)	53.6 (15.2)	47.6 (15.2)	2>4	58.6 (16.3)	5>1 (p=0.005) 5>4 (p=0.002)
Triglycerides (mg/dL)	89.9 (31.6)	96.3 (65.5)	101.7 (48.1)	160.1 (89.3)	4>1,2 e 3	92.8 (36.4)	5<4 (p<0.001)
A1C (%)	9.1 (2) ª;	8.7 (2) ^b ;	8.9 (1.6)°;	8.8 (2.3) ^d ;		5.3 (0.6)°;	5<1 (p<0.001) 5<2 (p<0.001) 5<3 (p<0.001) 5<4 (p<0.001)

SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure

a: N=26, b: N=49, c: N= 22, d: N=20, e: N=39

p=comparison of each one of the groups with SPKT (Mann- Whitney Test)

Table 2: Comparison of clinical and biochemical parameters in different phases of renal disease and SPKT.

Comparison between SPKT and the other groups studied

In the SPKT group, BMI (22.7 \pm 3.4 kg/m²) was lower than the BMI observed in the MI group (24.1 \pm 3.4 kg/m²; p=0.023), but higher than the ESRD group (20.9 \pm 2.4 kg/m²; p=0.008). Additionally, the abdominal circumference (84.3 \pm 10.4 cm) was higher in the SPKT group compared to the NA (78.7 \pm 9.8 cm; p=0.008) and MA (80.5 \pm 8.8; p=0.003) groups.

In the SPKT group, mean SBP (128.7 \pm 16.6 mmHg) was higher than the NA (116 \pm 8.1 mmHg; p=0.000) and MI (123 \pm 15.3 mmHg; p=0.017) groups, but lower when compared to the ESRD group (150 \pm 31.2 mmHg; p<0.001). .Furthermore, mean DBP was higher in the SPKT group (81.3 \pm 11.5 mmHg) in comparison to the NA group (76.2 \pm 8.5 mm Hg; p=0.033), but lower than the ESRD group (91.1 \pm 16.2 mmHg, p=0.001).

The HbA1c levels were lower in the SPKT group (5.3 \pm 0.6%) than the other groups (9.1 \pm 2; 8.7 \pm 2; 8.9 \pm 1.6; 8.8 \pm 2.3% respectively NA, MI, MA and ESRD; p<0.001).

Moreover, the SPKT group exhibited not only the lowest levels of total cholesterol (146 ± 24 mg/dL) when compared to the other groups (p ≤ 0.003), but also the lowest levels of LDL-cholesterol (68.8 ± 20 mg/dL) in comparison to the NA (92.4 ± 21.5 mg/dL; p<0.001), MI (92.3 ± 24.1 md/dL; p<0.001) and MA (108.7 ± 38.6 mg/dL; p<0.001) groups. However, HDL-cholesterol was higher in the SPKT group (58.6 ± 16.3 mg/dL) compared to the NA (49.6 ± 12.3 mg/dL; p=0.005) and ESRD (47.6 ± 15.2 mg/dL; p=0.002) groups. Notably, in the SPKT group triglycerides were lower (92.8 ± 36.4 mg/dL) when only compared to the ESRD group (160.1 ± 89.3 mg/dL; p<0.001).

Approximately half of the SPKT group were taking lipid-lowering medication (50.8%), more than in other groups (NA=6.9%, MI=15.1%, ESRD=25.7%), except for the MA group, in which 67, 9% of patients were taking lipid-lowering medication.

Two or more cardiovascular risk factors were observed in 18.5% of the SPKT group. This prevalence was similar to that found in NA group (20.7%), but lower than that observed in MI (43.4%), MA (53.6%), and ESRD (71.4%) groups. The most common CVRF detected in the SPKT group were, in decreasing order of prevalence, arterial hypertension (73.8%), increase of the abdominal circumference (44.6%), low HDL-cholesterol (20.0%), impaired fasting blood glucose (15.4%), and hypertriglyceridemia (9.2%). Among all these patients, 42% were using antihypertensive medication, and 50.8% were taking lipid lowering drugs.

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Factors associated with the presence of multiple cardiovascular risk factors

In the univariate regression analysis (Table 3), being part of group MI, MA, or ESRD was associated with the presence of two or more CVRF: MI (OR=2.9; CI: 1.02-8.39; p=0.044), MA (OR=4.4; CI: 1.37-14.19; p=0.012), and ESRD (OR=9.5; CI: 3.00-30.56; p<0.001). After adjusting for gender, age, and diabetes duration, being part of ESRD group remained a risk factor for the presence of multiple CVRF (OR=5.2 CI: 1.40-18.95; p=0.014), while SPKT was a protective factor (OR=0.3; CI: 0.06-0.98; p=0.047).

Adjustment by BMI was not conducted because of overfitting, suggesting that the excessive variables in the multiple model could compromise the model's accuracy and result in an increase of the OR and of the confidence interval.

In addition to being part of the ESRD group, there were other independent risk factors for the presence of two or more CVRF that included female gender (OR=2.5; p=0.008) and diabetes duration over 15 years. Age over 35 years exhibited marginal significance (OR=3.1; p=0.059).

Dialysis time in the ESRD and SPKT groups and the elapsed time after SPKT were not associated with the presence of multiple cardiovascular risk factors.

Discussion

In this sample of young adults with type 1 DM the prevalence

	Category	OR brute (p/ CI)	OR adjusted (p/ Cl)
Group	1	1.0 (referência)	1.0
	2	2.9 (0.044/ 1.02-8.39)	3.0 (0.061/ 0.95-9.22)
	3	4.4 (0.012/ 1.37-14.19)	2.4 (0.205/ 0.62-9.02)
	4	9.5 (<0.001/ 3.00-30.56)	5.2 (0.014/ 1.40-18.95)
	5	0.9 (0.800/ 0.29-2.59)	0.3 (0.047/ 0.06-0.98)
Gender	F	1.6 (0.092/ 0.92-2.84)	2.5 (0.008/ 1.27-5.02)
	Μ	1.0 (referência)	1.0
Age (vears)	18-23	1.0 (referência)	1.0
	24-34	1.9 (0.078/ 0.93-3.81)	2.0 (0.173/ 0.73-5.42)
	35-62	1.9 (0.084/ 0.92-3.72)	3.1 (0.059/ 0.95-9.75)
DM duration (Years)	10-15	10 (referência)	10
	16-19	2.1 (0.043/ 1.02-4.26)	2.6 (0.023/ 1.14-6.09)
	20-44	2.3 (0.019/ 1.14-4.66)	2.8 (0.049/ 1.00-7.74)
BMI	< 10	1.6 (0.385/ 0.56-4.42)	_
Divin	19-24 9	1.0 (referência)	_
	25-29.9	3 5 (0 001/ 1 69-7 01)	_
	>30	3.0 (0.161/ 0.64-14.02)	_

Hosmer and Lemeshow Test of the multiple model = 0.948

Table 3: Logistic regression analysis for the factors associated to the presence of multiple cardiovascular risk factors.

of two or more CVRF increase according to the advance of diabetic nephropathy (about 2 times from microalbuminuric to ESRD group). The female gender and duration of clinical diabetes above 15 years were also positively associated. Even after adjusting for gender, age, and diabetes duration, the ESRD state presented the greatest risk for increased prevalence of CVRF, while the SPKT group appeared as a protective factor.

Here, we showed that, after excluding patients of the SPKT group, multiple CVRF were present in 47.6% of 145 type 1 DM individuals on different phases of diabetic nephropathy with average age, time of diabetes history, and BMI of 28 years, 17.8 years, and 23 ± 3.3 kg/ m², respectively. This prevalence was superior to that described in the literature (8% to 40%) for type 1 diabetic patient with similar time of diabetes history [9-11]. Additionally, a recent study including type 1 diabetic individuals with comparable clinical characteristics reported a lower prevalence (12%) for two or more CVRF [10]. That difference may be explained by the fact that our type 1 diabetic population comprised a higher percentage of patients diagnosed with chronic renal failure.

Moreover, in our study we observed an increase in multiple CVRF prevalence in parallel to the worsening of diabetic nephropathy. This prevalence ranged from 20.7% in the normoalbuminuric group to 71.4% in those with ESRD. Thorn et al. analyzed 2415 patients with type 1 DM (average age and time of diabetes history of 37 years and 22 years, respectively) that were stratified according to their urinary albumin excretion rates in normal, micro, macroalbuminuria and ESRD [11]. Those authors confirmed an increase in the CVRF prevalence associated with the progression of diabetic nephropathy in normo (28%), micro (44%), macroalbuminuric (62%), and ESRD (68%) individuals.

Patients with ESRD, similarly to the patients who had undergone SPKT, were on average older at the time of diabetes diagnosis when compared to patients in the normo and microalbuminuric groups. The age at diabetes diagnosis is reported in some studies [12,13] as a risk factor for the development of microvascular complications in T1DM. Time of DM history seems to be more critical for the development of diabetic complications, such as diabetic nephropathy, when DM is diagnosed during the pre-puberal phase in comparison to the post-puberal diagnosis. However, there is no consensus in the literature regarding the relation between age at T1DM diagnosis and the risk of developing ESRD [14].

Data from the EURODIAB IDDM Complications Study Group showed that glycemic control is positively associated with total cholesterol, triglycerides and LDL-cholesterol and is negatively associated with HDL-cholesterol level [15]. Recently, we also have shown that in a group of T1DM individuals without ESRD, for each 1% of HbA1c increment, there is an increase by 22% in the probability of exhibiting two or more CVRF, even when data were adjusted for age, sex, and time from diagnosis [16]. In the present study, when we included patients with different phases of renal disease, but with similar glycemic control (HbA1c ranging from 8.8% to 9.1%), we observed that there was an increase in CVRF prevalence paralleling the progression of renal impairment. This finding suggests that other factors related to renal function might be implicated. One of these factors could be the insulin resistance, which is found mainly in stages 4 and 5 of chronic kidney disease. The mechanism of insulin resistance remains to be elucidated and appears to be post-receptor, and located in skeletal muscle. Other factors that may potentially be associated with insulin resistance are metabolic acidosis, the presence of uremic toxins, vitamin D deficiency, inhibition of nitric oxide production and an increase of homocysteine [17-20]. Some studies have shown a reduced sensibility to insulin in microalbuminuric compared to normoalbuminuric type 1 DM patients with the same age, diabetes duration, and BMI [21]. Analyzing diabetic nephropathy and glomerular filtration rate (GFR), Svensson et al. [22] identified a strong correlation between GFR and insulin sensibility and showed that even small reductions in GFR (average of 58 mL/min/1.73 m², ranging from 43 to 73 mL/min/1.73 m²) can lead to insulin resistance.

In the present study, we found a tendency of the renal impairment to increase the blood pressure and triglycerides levels and decrease abdominal circumference, but not affect HDL-cholesterol. The highest values of total and LDL-cholesterol were in the group with macroalbuminuria and/or clearance <60 mL/min. These data are in accordance with the conclusions of other studies that examined a greater number of patients and that correlated dyslipidemia to renal function [23].

In our ESRD group, the majority of patients (>80%) were on hemodyalisis treatment. Hemodialysis treated patients exhibit a paradoxical relationship of low levels of cholesterol and higher mortality risk, since these cholesterol levels become a marker of bad nutrition [24]. In patients submitted to peritoneal dialysis, hypertriglyceridemia is even more severe and hypercholesterolemia is more prevalent, since these patients are exposed to dialyzed glucose, which raises lipogenesis [25].

We choose to evaluate patients submitted to SPKT a minimum period of 6 months after the transplant, because from this period onwards, the immunosuppressive doses, mainly from corticosteroids and calcineurin inhibitors, were lower and had less impact on metabolic parameters and kidney function. That approach was in line with the findings that kidney function reestablishment and normalization of blood glucose levels achieved after SPKT, as reported by other studies, resulted in a reduction of cardiovascular risk factors [26].

However, our SPKT group still exhibited higher blood pressure levels when compared to the normo and microalbuminuric groups. Hypertension pathogenesis after transplant seems to be multifactorial and dependent on various factors such as immunosuppressive doses (calcineurin inhibitors and corticoids), chronic kidney allograft dysfunction, familial genetic factors, and the graft's renal artery stenosis [27].

It is well established that the type of immunosuppressive regimen affects body weight, cholesterol and glycemic levels, and renal function. Overall, we found a significantly smaller prevalence of multiple CVRF in the transplanted diabetic patients (18.5%) in comparison to the groups with diabetic nephropathy (43.4% to 71.4%). Similar results were also found by Rogers et al. in a prospective study involving 241 patients, from the wait list for SPKT and recipients 1 year following SPKT [28]. The authors observed a significant decrease in the prevalence of these factors following the transplant, ranging from 59% to 19%. In our study, the SPKT group showed a similar prevalence of multiple CVRF compared to the normoalbuminuric group (20.7%). To note, these 2 groups were different in relation to age, time of diabetes history (superior in the transplanted group), and glycemic control (HbA1c was lower in the transplanted group).

According to the univariate regression analysis in our study, HbA1c levels did not show association with multiple CVRF prevalence. On the other hand, the variables of time of diabetes history greater than 15 years and female gender were positively associated with the prevalence

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of those risk factors. When we adjusted the analysis by gender, age, and time of diabetes history, the SPKT group was a protective factor.

This study had three major limitations. 1) It was a cross-sectional study, not a prospective study. 2) Patients' familial hypertension and type 2 diabetes backgrounds were not available for analyses. In the DCCT (Diabetes Control and Complications Trial), the patients with positive familial history for type 2 diabetes showed greater weight gain and insulin-resistance characteristics in the lipid profile [29,30]. Furthermore, a recent study [31] from our group showed that a familial history of diabetes was related to higher values of insulin secretion and lower insulin sensitivity in patients submitted to SPKT. 3) The study lacked a group of patients with type 1 DM who have undergone isolated kidney transplant. This group could better elucidate the importance of normoglycemia and isolated renal function reestablishment and their relevance on the prevalence of other cardiovascular risk factors.

In conclusion, in a group of individuals with T1DM, the female gender, age, time of diabetes history, and the severity of renal disease, are important determinants for the presence of cardiovascular risk factors. Furthermore, pancreas and kidney function reestablishment following SPKT reduce the prevalence of cardiovascular risk factors to the same prevalence found in patients with T1DM and normoalbuminuria.

Acknowledgments

This study was supported by grants from Conselho Nacional de Pesquisa (CNPq) and Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES) of Brazilian Federal Government.

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