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Long-Term Complications After Renal Transplantation

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IN the past, every effort was directed at the prevention of acute rejection in renal transplant (RT) patients (pts). Ever since the introduction of the new immunosuppressive agents in the late 1990s, the short-term results of renal graft survival are considered satisfactory. In recent years, the prevention of long-term graft loss and the extension of life expectancy have gained new emphasis. The immunosuppressive agents though, namely calcineurin-inhibitors and steroids, may potentiate the development of several problems in RT pts: obesity, hyperglycemia, hyperlipidemia, and hypertension,[1] which are not only risk factors for cardiovascular disease but also for graft loss.[2,3]

We performed a retrospective analysis of all RTs performed at our unit that reached 10 years (y) with a functioning graft. The aim of the study was to evaluate long-term complications and, in view of the results, to seek a possible strategy that minimizes these problems.

PATIENTS AND METHODS

We analyzed 227 RTs performed between 8 July 1983 and 31 December 1989. The follow-up was truncated at 10 y; the last pt included completed follow-up on 31 December 1999. The study group consisted of 107 pts whose kidney grafts were functional at the end of follow-up.

RESULTS

The overall patient and graft survivals among the 227 pts was 93.4% and 74.1% at 1 y; 84.6% and 62.1% at 5 y; and 74.9% and 47.1% at 10 y, respectively. Among the 57 pts who died, 42.1% (24 pts) experienced a cardiovascular cause of death, including 33.3% (19 pts) with a functional kidney. The characteristics of the study population and the immunosuppressive protocol are presented in Table 1. The mean maintenance doses were: prednisone 10 mg/d; cyclosporine (CyA) 3.7 mg/kg/d; and azathioprine (Aza) 1 mg/kg/d (or 2 mg/kg/d for pts without CyA).

Table 1. Characteristics of the Study Population (n = 107 Patients)

Age on RT date (ys)	34.7 ± 10.3
Male gender	61.6%
First transplant	97.2%
Cadaveric graft	100%
Adults	100%
Immunosuppression (number of patients)	
Aza + Steroids	8
CyA + Steroids	71
CyA + Steroids + Aza	14
CyA + Steroids + ATG	5
CyA + Steroids + ATG + Aza	9

The prevalence of hypertension, (defined as the fraction of pts taking antihypertensive medications) at 1 y was 72.9%, including 4.7% who needed two or more drugs to control blood pressure. The 10-y frequency of hypertension was similar (77.6%), but 14.9% needed two or more medications.

Using the National Cholesterol Education Program Adult Treatment Panel III guidelines,[4] the prevalence of hypercholesterolemia (>200 mg/dL) was 63.5% at 1 y (mean level 219 ± 48 mg/dL); and slightly higher, 73.8%, at 10 y (mean level 230 ± 54 mg/dL). However, hypertriglyceridemia (>160 mg/dL) was slightly less prevalent at 10 y

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Table 2. Long-Term Complications in 107 RT Patients

	1 Year	10 Years
Hypertension	72.9%	77.6%
More than two drugs	4.7%	14.9%
Hypercholesterolemia	63.5%	73.8%
Hypertrigliceridemia	64.5%	61.6%
Low HDL-cholesterol	12.1%	5.6%
Gain of body weight (kg)	6.1 ± 2.8*	2.6 ± 1.2**
Diabetes (post-RT)	—	7.5%
Ischemic heart disease	—	14.9%
Peripheral vascular disease	—	4.7%
Cerebrovascular disease	—	3.7%
Chronic hepatitis (HBV, HCV)	—	26.1%

*Highly significant since RT day ($P < .001$).
**Significant since 1 y ($P = .006$).

(64.5% vs 61.6% at 1 y), but shared similar mean levels (1 y = 166 ± 76; 10 y = 170 + 99 mg/dL). A low HDL-cholesterol level (<40 mg/dL) was observed in 12.1% at 1 y and 5.6% at 10 y, with similar mean levels (55 ± 21 vs 57 ± 19 mg 7 dL). A total of 18.7% of patients received hypolipemic agents. The differences in the lipid profiles between 1 y and 10 y were not statistically significant.

The body weight increased significantly over the years, especially between RT and 1 y, namely a mean increment of 6.1 ± 2.8 kg (from 58.8 ± 11.1 to 64.6 ± 12.1 kg, $P < .001$). Also, between 1 and 10 y the body weights continued to increase by 2.6 ± 1.2 kg (mean body weight at 10 y was 67.0 ± 12.7 kg, $P = .006$).

After RT, 7.5% of pts became diabetic; 14.9% developed ischemic heart disease, with chronic heart failure in 5.6%. Clinically significant peripheral vascular disease occurred in 4.7%, with 3.7% displaying a stroke. Evolution of previous viral hepatitis resulted in chronic hepatitis in 26.1% (19.6% due to HCV, 6.5% due to HBV) (Table 2).

Malignancies other than skin localization were observed in 7.5% of pts. Important infections, excluding UTI, led to hospitalization in 14%. Bone complaints existed in 33.6%, including 6.5% who experienced a documented bone fracture. Hyperuricemia with gout occurred in 12.1%. Other problems (gum hyperplasia, cushingoid appearance, hypertrichosis) were noted by 42% of pt. At 10 y the mean serum creatinine was 1.59 ± 0.53 mg/dL, and the incidence of proteinuria equal to or greater than 0.5 g/d was 22.4%.

DISCUSSION AND CONCLUSIONS

Long-term complications represent important handicaps for the global success of RT. We observed a 23.3% incidence of serious cardiovascular problems, which is slightly higher than that found by Ponticelli et al.[5] Indeed, 42.1% of the RT pts died from a cardiovascular cause before completion of the 10-y follow-up, including 33.3% who has functioning grafts. This cause has become the major category of late graft loss.[6,7]

Obesity, which is often associated with the sedentary life style of these pts, is a known cardiovascular risk factor. We observed an extremely high weight gain of almost 14% in 10 y. This increment in body weight represented not only correction of a subnutritional status prior to RT, but an excessive body weight in most cases. In another study, after a nutritional evaluation, we found an obesity incidence of 11.4% (body mass index $\geq$30 kg/m^2) and an overweight incidence of 41.6% (body mass index $\geq$25 and <30 kg/m^2) in our RT pts.

In our unit the prevalence of hepatitis C virus (HCV) and hepatitis B virus (HBV) infection in RT pts has tended to decrease, accompanying the international tendency; at present it is 12.7% and 4.6%, respectively.

Although extremely high, the frequency of hypertension reported in this study is similar to that published by others.[5] Hyperlipidemia also affected almost 70% of pts. These two complications are still important problems. These complications associated with long-lasting immunosuppression may sometimes outweigh the short-term benefit of preventing acute rejection episodes. Some agents may potentiate individual cardiovascular risk factors,[1] and also represent a proclivity for graft dysfunction[8] and late loss. Especially after the first year, attention must focus on minimizing immunosuppressive side effects and controlling nonimmunologic risk factors.[1]

The judicious screening for pretransplant cardiovascular disease and the selection of more cardioprotective and renoprotective immunosuppressive protocols may alter these findings in the future. Meanwhile, encouraging both healthy life styles and early and strict control of risk factors like hypertension, hyperlipidemia, and obesity is mandatory to optimize transplant outcomes.

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