Kidney graft survival at a year, clinical evolution and associated factors in transplant patients with pre-existing diabetes

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Abstract

Kidney transplantation (KT) in patients with pre-existing diabetes is seldomly studied. The aim of the study was to show the 10-year experience of patients with diabetes mellitus before the surgical procedure and their clinical evolution after a year.

A retrospective cohort (2009-2018) was analyzed. The clinical and biochemical data were obtained from patient files after the transplant including a year of follow-up. For nominal variables, the data are shown in medians and interquartile ranges. The risk factor analysis was performed using logistic regression. p values of less than 0.05 were considered statistically significant. Data were analyzed with SPSSw version 25.

Patient survival was 95.34% for the total cohort *versus* 90.91 in diabetic patients, while graft survival was 90.25% *versus* 82.95%, respectively. The risk factor for lower patient survival was found related to the deceased donor (OR 8.55,95% CI 1.006-72.79, p 0.049). The risk factors for lower kidney graft survival were the deceased donor (OR 5.41,95% CI 1.40-20.85, p 0.014), delayed function (OR 19.05,95% CI 2.23-162.79, p 0.007) and acute dysfunction (OR 18.13,95% CI 2.07-158.15, p 0.009).

KT in patients with pre-existing diabetes has a good prognosis at a year. There was a lower survival rate for both the patient and the graft compared to non-diabetic recipients at our center.

Introduction

Peritoneal dialysis, hemodialysis, and kidney transplantation (KT) are the alternatives currently available for patients with end-stage chronic kidney disease (ESRD); among them, kidney transplantation is considered the best option [1]. Despite the above, until a few years ago KT was contraindicated in patients who had diabetic nephropathy as a cause of ESRD, today behaviors have changed and not only is the kidney transplanted, but the simultaneous pancreas/kidney transplant has increased the survival of these patients over other substitution therapies (peritoneal dialysis or hemodialysis) [2,3]. It has also been shown that patients with diabetes mellitus (DM) are less likely to receive a new kidney mainly due to the related cardiovascular comorbidity. However, the survival of patients is comparable to that of patients without DM [4].

DM is among the most frequent causes of kidney damage in Mexico and in the world, with figures ranging from 30% up to 40% in most populations [5-7]. Several studies have shown that mortality in transplanted diabetic patients is higher when compared to non-diabetic patients and may be more than double in some populations with the disadvantage greater in diabetic recipients under 40 years old [8]. The disadvantages are due to the association of DM with other diseases such as high blood pressure and obesity, which are on the rise [9]. Another important aspect is post-transplant metabolic control, for which effective measures have been established that include reducing immunosuppression and education programs aimed both at the recipient with pre-existing diabetes and at those who develop diabetes once transplanted [10-12].

Surveillance of the transplanted diabetic patient should include monitoring of fasting glucose, postprandial glucose, and glycosylated hemoglobin, and the use of ideal hypoglycemic agents for each case and insulin or both when considering treatment [13]; however, experience with the latter is still limited [13-15]. The aim of this study was to analyze the clinical outcomes in the first year after kidney transplantation in a cohort of diabetic patients accumulated over 10 years at a single center and to identify the factors associated with the survival of the recipient and the kidney graft.

Patients and methods/Material and methods

Design

A retrospective cohort of diabetic recipients of a kidney transplant at the 21st Century National Medical Center (Centro Médico Nacional (CMN) "Siglo XXI") of the Mexican Institute of Social Security in

Mexico City was studied over a period of 10 years and monitored for a year after transplantation.

Outcomes

The primary outcomes (endpoints) were patient and graft survival. Secondary outcomes included acute rejections, decreased kidney function, and hospital admissions.

Patients

Patients diagnosed with type 2 DM and receiving a transplant between January 1, 2009 and December 31, 2018 were considered eligible. Also included were patients with clinical and biochemical data necessary for a baseline analysis and during the one-year follow-up period. Patients with incomplete information or who lost social security medical insurance coverage were excluded.

Data collection

The clinical records were reviewed by trained personnel and the relevant information was retrieved. Demographic information and the evolution of diabetes prior to transplantation were included, as well as the dialysis modality and treatment times, biochemical and virology data (hepatitis B, C, HIV and cytomegalovirus), and evaluation by specialists related to the management of diabetes, particularly clinical, imaging, and cardiology functional tests. The compatibility with the donor was included (blood group, lymphocytotoxicity tests, HLA locus A, B, Cw, DR, DQ, DP), the type of induction of immunosuppression, the type of anticalcineurin, in addition to the time of the start of the function of the graft. Acute graft dysfunction and cause, as well as treatment were also recorded.

Statistics

Data are presented as means and standard deviations for continuous variables, or as frequencies or medians and interquartile ranges for nominal or non-normally distributed variables. The difference of means was established with chi square or Student's "t" test. The risk factor analysis was performed using bivariate logistic regression. p values of less than 0.05 were considered statistically significant. Data were analyzed with SPSSw version 25.

Results

During the study period (2009-2018), 1118 transplants were performed, including 89 in diabetic patients. One patient was excluded for not having information on the clinical outcomes under study. The pre-transplant data are shown in Table 1. Most of the patients had an acceptable nutritional and cardiovascular status according to the serum albumin level in normal ranges, as well as adequate values in the ejection fraction. The viral panel (hepatitis B and C, HIV) and VDRL were negative in all 88 cases. When the PPD was > 5 mm, prophylaxis with rifampicin 300 mg every 24 hours for 3-6 months was administered.

Men (67) (76.1%) predominated; blood group O + (59%), followed by group A + (26.1%), B + (12.5%) and a patient O– (1.1%) and another with AB + (1.1%). The dialysis modality was hemodialysis in 37 patients (42%), peritoneal dialysis in 41 (46.6%) and 10 underwent early transplantation (11.4%). Regarding the type of donor, 43 people received a graft from a deceased donor (48.9%) and the remaining 45 (51.1%) from living donors. Of these, 29 cases were related to donors and 16 cases were unrelated.

The findings in other studies were as follows: a) chest X-ray, normal in 62 cases (70.5%), cardiomegaly to some degree in 18 patients (22.4%)

Table 1. Baseline Characteristics. 88 transplanted diabetic patients

Variable	Mean	SD (±)	Median	IQR 25-75
Age (years)	47.89	10.39	49.5	41-55
Previous Transfusions	1.11	1.34	1.0	0-2
Weight (kilograms)	69.28	12.25	69.2	61-78
Height (meters)	1.64	0.09	1.6	1.58-1.70
Hemoglobin (gr/dl)	11.14	1.9	11.1	9.6-12.4
Hematocrit (%)	33.73	5.98	33.7	29.85-37.75
Leucocytes	7.14	1.99	7.1	5.8-8.5
Platelets	248.24	74.89	245.0	201-276
PT (prothrombin time, sec)	13.74	3.31	13.0	12.3-14.1
PTT (partial thromboplastin time, sec)	30.74	14.11	29.0	27-31
Albumin (gr/dl)	4.01	0.58	4.0	3.8-4.4
ALT (alanine aminotransferase, IU/l)	21.64	10.89	19.5	14.25-26.75
AST (aspartate aminotransferase, IU/l)	22.95	13.44	20.5	14-27
Uric Acid (mg/dl)	5.79	1.63	5.8	4.9-6.9
Sodium (mEq/l)	139.05	3.4	139.0	137-141
Potassium (mEq/l)	5.01	0.83	4.9	4.4-5.5
Calcium (mg/dl)	8.92	0.8	8.9	8.4-9.4
Glucose (mg/dl)	124.07	57.47	109.0	86-137.5
Cholesterol (mg/dl)	178.17	52.13	177.0	141-214
LVEF (%)	62.36	7.68	62.0	58-68

SD: standard deviation; IQR: interquartile range; LVEF: left ventricular ejection fraction

aortosclerosis in five cases (5.7%) pleural effusion in two patients (2.2%) and one case with an air bronchogram (1.1%); b) electrocardiogram, normal in 72 cases (81.8%), left ventricular hypertrophy in nine patients (10.2), other alterations in eight cases (9.1%); c) metabolic bone series, normal in 41 cases (46.6%), same for osteopenia (46.6%), six of them with some other changes (6.7%), d) endoscopy with normality in 38 patients (43.2%) with different findings in the rest of the patients from bulb-duodenitis, atrophic, erosive gastropathy, etc., e) voiding cystogram with normality in 69 cases (78.4%), residual urine in three cases (3.4%), and the other cases with increased and decreased bladder capacities, vesicourethral reflux in varying degrees, urethral stricture, proximal double ureter, among others, all these studies as part of the routine studies of the service.

The complementary studies considered in diabetic patients were the following: a) gastric emptying, 30 with delayed function (34.1%) and two with accelerated function (2%); b) ultrasound of iliac vessels with 60 patients with patency (68.2%), atheromatosis in seven patients (7.8%), one with vascular calcification (1.1%) and one with slow flow of the left common iliac (1.1%); the study was not carried out in 20 patients (22.8%), c) electromyography was normal in 11 patients (12.5%), the most common alteration was demyelinating axonal motor sensory polyneuropathy in 28 cases (31.8%), severe polyneuropathy in three cases (3.4%), 21 cases such as mild or moderate polyneuropathy (23.9%) and 25 patients did not undergo the study (28.4%), d) the cardiac scintigraphy with thallium was reserved for patients that the Cardiology Ward physicians considered necessary.

Surgical findings and immunosuppression are represented in Table 2, where the use of monoclonal agents for induction is included. In this case, 55 patients received basiliximab (62.5%), immunosuppression was entirely achieved with prednisone in 88 patients as a steroid, and mycophenolate mofetil as an anti-proliferative agent.

Complications and biochemical data at the end of a year of follow-up are shown in Table 3. Creatinine at one year equal to 1.64 mg/dl, glucose of 143 mg/dl and glycosylated hemoglobin of 8.97% (the latter was not taken in all the cases).

The results of the analysis of the factors related to the survival of the kidney graft and the patient are shown in Table 4. Eight patients (9.09%) died in the period analyzed, seven lost the graft (7.95%) and 73 of 88 (82.95 %) had a functional graft at the end of the first year. The factors analyzed were: sex (taking females as the reference group), deceased donor, induction with basiliximab, delayed graft function, reoperation, and acute graft dysfunction. When graft survival and patient survival were compared in the diabetic group with the total non-diabetic patients from the same center, a difference of 4.43% and 7.3% was found for patient and graft survival, respectively (Table 5 and Figure 1).

Discussion

Few studies have analyzed patient and kidney graft survival in diabetic patients whom were recipients of kidney transplantations. In this study, an integrated retrospective cohort was analyzed including 89 patients diagnosed with diabetes mellitus (DM) prior to transplantation, a cohort followed for 10 years and later undergoing transplantation. Patient survival was 90.91% (80 of 88) participants a year after transplantation, and graft survival was 82.95% (73 of 88) in the same period. Compared with a cohort of non-diabetic patients from the same center, lower patient and graft survival were found, 4.43% and 7.3%, respectively. The factors that influenced this decrease were receiving a kidney from a deceased donor, delayed graft function, and acute graft dysfunction. Creatinine at a year was higher than in non-diabetic patients with the same monitoring time and metabolic control outside the accepted range, glycated hemoglobin was 8.97% and fasting glucose was 143.28 mg/dl.

Table 2. Management related to the transplant and surgical maneuvers

Variable		Frequency	Percentage
Induction			
	Basiliximab	52	59.1
	Thymoglobulin	30	34.1
Steroid			
	Prednisone	88	100
Antiproliferative			
	Mycophenolate	88	100
Anticalcineuritc			
	Tacrolimus	68	77.2
	Cyclosporin	20	22.8
Kidney taken			
	Right	44	50
	Left	44	50
Number of arteries			
	1	53	60.2
	2	26	29.5
	4	1	1.1

Table 3. Clinical outcomes and biochemical parameters a year post-transplant

Variable			Frequency	Percentage
Retarded graft function			26	29.5
New surgery			12	13.6
Acute graft dysfunction			35	39.8
Graft survival			73	83
Patient survival			80	90.9
Variable	Mean	SD (±)	Median	IQR 25-75
Cr at a year (mg/dl)	1.64	1.4	1.29	0.96-1.75
Glucose at a year (mg/dl)	143.28	75.75	126	87-181
HbA1c (%)	8.97	1.84	8.55	7.8-10.15

SD: standard deviation; IQR: interquartile range; Cr: creatinine, HbA1c: glycosylated hemoglobin

Table 4. Regression Analysis Survival of the renal graft

Variable	p Value	OR	Confidence Interval	
			Inferior	Superior
Sex (Female)	0.780	0.830	0.230	2.960
Deceased Donor	0.014	5.419	1.408	20.854
Induction with basiliximab	0.761	0.837	0.260	2.630
Late function of the graft	0.007	19.050	2.230	162.790
Second surgery required	0.090	0.220	0.038	1.270
Acute graft dysfunction	0.009	18.130	2.070	158.150
		Survival of the kidney receptor		
Sex (Female)	0.351	0.480	0.100	2.220
Deceased Donor	0.049	8.550	1.006	72.790
Induction with basiliximab	0.955	0.957	0.210	4.350
Late function of the graft	0.102	6.540	0.680	62.380
Second surgery required	0.348	0.256	0.010	4.420
Acute graft dysfunction	1.000	1.000	0.000	0.000

OD: odds ratio; CMV: cytomegalovirus

Variable		Frequency	Percentage
Diabetic patients			
	Total	88	100
	Kidney graft survival	73	82.95
	Kidney recipient survival l	80	90.91
Transplant cohort 2013-2017			
	Total	1118	100
	Kidney graft survival	1009	90.25
	Kidney recipient survival	1066	95.34

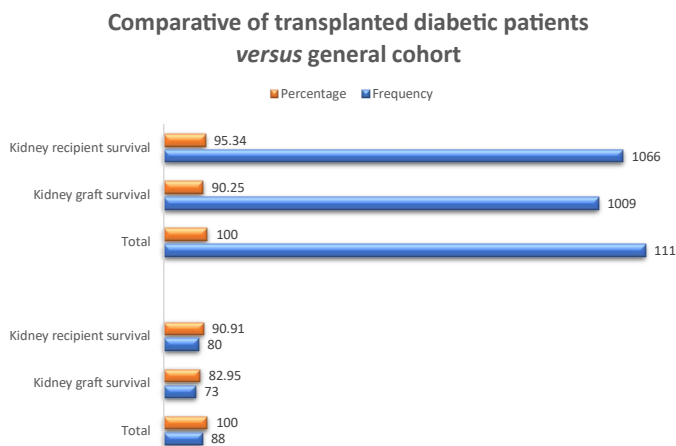Table 5. Diabetic patients and center cohort comparative

Figure 1. A comparative of transplanted diabetic patients versus general cohort of patients in relation to kidney graft and recipient survival at a year of follow-up

The increasing number of diabetic patients receiving a kidney transplant raises many questions and the comparison between diabetics and non-diabetics is required. In a study by Rocha A, et al. [16] in which 62 diabetics were compared to 62 non-diabetics, creatinine (Cr) values a year after transplantation were 1.3 mg/dl in both groups; however, in our study it was 1.64 mg/dl, similar to that of the non-diabetic cohort. In this study, 29.5% of the patients had delayed graft function, which was associated more with the deceased donor than with being diabetic. Acute graft dysfunction was found in 39.8% of the cases, the majority due to rejection, this percentage was less than 24.2% shown in that study. Survival at one year was not shown, so it cannot be compared with our study.

The study by Hee, et al. [17] is possibly the one most similar to ours. However, it does have some differences: among them: type of donor, in

that study all grafts were from living donors, while in ours 48.9% were from deceased donors. This difference is relevant since in the multiple logistic regression analysis it was found to be significant as a risk for graft survival (OR = 5.419, 95% CI 1.408-20.854, p = 0.014), as well as for recipient survival (OR = 8.55, 95% CI 1.006-72.790, p = 0.049). Our study does not have an adequate control group, we only have the graft and patient survival at a year to compare them with the rest of the cohort in the center; the two rates were higher in the cohort of non-diabetic patients. In the study by Hee, *et al.* survival at a year was 97.2% and 93.3% in non-diabetic and diabetic populations, respectively, and they concluded that these are favorable results and that diabetes, infections, and cardiovascular disease did not significantly influence kidney graft failure. In this study, the deceased donor, the delayed function of the graft (related to the type of donor) and the acute dysfunction due to any cause had an impact on graft survival, while only having a deceased donor was significant in patient survival.

For many years, the diabetic patient only had access to peritoneal dialysis or hemodialysis, as treatment options for ESRD. Since the first transplant attempts in diabetic patients, good results have been demonstrated, similar to those of non-diabetic patients, despite which accessibility to transplantation is still limited. Studies such as that by Keivinen M. *et al.* [18] in 2018, show that the probability of receiving a kidney transplant is lower in diabetics, which could not be fully explained by the characteristics and comorbidities of the patient; however, the 5-year survival was comparable to that of non-diabetic patients.

The monitoring of the metabolic control of the post-transplant patient is generally undemanding and the use of glycated hemoglobin (HbA1c) is rare, either to assess the current degree of control, or its ability to predict pre-diabetes and post-transplant diabetes mellitus (PTDM) associated or not with medications. In the study by Tillman F, *et al.* [19], it was found that the HbA1c level at 90 days after transplantation is able to predict an altered glucose metabolism at a year, and in the long term, it can serve as a predictor of diabetes and allow for early interventions to prevent PTDM if the level is over 6.2% (sensitivity = 0.97 and specificity = 1.00). In a study by Ussif, *et al.* [20], it was concluded that the combined use of fasting glucose and HbA1c values in patient follow-up are an applicable diagnostic strategy in patients at risk for PTDM without the need for a glucose tolerance curve after a year of follow-up (area under the ROC curve = 0.858). In our study, HbA1c was measured, but, although elevated levels were detected (median = 8.55%, IQR 7.8-10.15%), the number of measurements was insufficient for analysis.

The study had certain limitations. There was a multidisciplinary group in the control of the patients, there was no systematic nutritional surveillance, nor was guidance given to stimulate lifestyle changes, factors that have a decisive influence on the development of comorbidities in the diabetic patient.

Conclusion

Kidney transplantation in patients with pre-existing diabetes has a good prognosis at a year of follow-up, although it has a lower survival rate for both the patient and the graft compared to non-diabetic patients at our center. The deceased donor is also a good option; however, this is the most significant risk factor for patient survival. The significant risk factors for decreased kidney graft survival were the deceased donor, delayed graft function, and acute graft dysfunction. Studies are required that consider interventions in lifestyle, a healthy diet, and frequent monitoring of metabolic control to improve transplantation outcomes in diabetic patients.

Based on our findings, we thoroughly recommend searching for an insulin resistance syndrome. Another of the proposals, and supported by other studies is to carry out a strict control of glycated hemoglobin, fasting serum glucose, and postprandial serum glucose. We consider low doses of steroids, prevention of infectious processes, optimizing the control of arterial hypertension, hypertriglyceridemia, obesity and hyperuricemia within some other metabolic conditions important to follow in patients.

Conflict of interest

The authors have no conflicts of interest and have followed international ethical guidelines for the protection of patients' personal data.

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