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Death Receptor in the First Year after Simultaneous Pancreas/Kidney Transplantation

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Abstract

Background: Simultaneous pancreas/kidney transplants require a long graft survival and recipient with to achieve more benefits than risks. In order to access the risk for this procedure, we evaluate the risk factors of death receptor with one year postoperatively in 292 simultaneous pancreas/kidney transplants evaluated 22 variables.

Materials and Methods: Twenty-two variables were selected for the study, nine from receivers, eight from donors and five variables related to the surgical procedure. To determine the survival of patients, we evaluated dates of transplants, the latest consultation and dates of deaths. All independent variables were compared with the dependent variable: patient lost in a year. Those with statistical significance through univariate analyzes, were also analyzed by multiple logistic regression technique in an attempt to develop a mathematical model capable of predicting 1-year patient loss.

Results: Relatively to the loss of patient in one year, the multivariate analysis identified body mass index receptor ($p \leq 0.008$) and induction therapy (negative factor $p \leq 0.008$) as independent risk factors.

Conclusion: Based on the results of this research can be concluded that the independent variables related to one year loss of receptor are: body mass index of the donor and induction therapy.

Keywords: Pancreas transplantation; Kidney transplantation; Graft rejection; Risk factors; Type 1 Diabetes Mellitus; Multivariate analysis

Introduction

Diabetes Mellitus is a clinical syndrome with multiple etiologies; stems from lack of insulin or the inability to execute properly its function. It is characterized by chronic hyperglycemia with disturbances in the metabolism of carbohydrates, lipids and proteins. Without proper treatment, 20 years after the establishment of diabetes mellitus, 50% of these patients may have vision loss, kidney failure, motor disturbances, sensory disturbances and severe circulatory changes in microvascular changes caused by inadequate glycemic control [1-4].

The discovery of insulin in 1922 by a former theology student named Dr. Frederick Banting, not meant to cure, but only poor control of the disease, especially in its acute complications. Thus, despite several regimens available, the secondary problems are just postponed, because the ineffective control of metabolic abnormalities responsible for chronic changes, even with a restricted diet [5-7].

Pancreas transplantation is the only therapy to restore normoglycemia potential, enhance quality of life and prevent, stabilize or even reverse certain chronic complications of insulin-dependent diabetes mellitus patients; simultaneous pancreas/kidney transplantation, enables the return to a stage of normoglycemic insulin independence, and completes normalization of glycated hemoglobin levels. It's well accepted by the American Diabetes Association as the treatment of choice for type 1 diabetic patients with ends renal disease [8,9].

It requires a long graft survival with transplanted pancreas in order to vest the lasting results of improved glycemic control in stabilization or regression secondary lesions of insulin dependent diabetes mellitus and to have more benefits than risks related to immunosuppression and complications of the surgical procedure [3,10,11].

The best approach to anticipate and increasing the care before possible variables linked to the loss of the patient, would be to identify a set of variables related to donors, recipients and the surgical technique that, when inter-related, could identify or refer to the risks of medical transplant patient's death. Knowing that the survival benefit for the double transplant is greater after one year, it's important identify those patients with more potential to overcome this most critical period for the success of the procedure [8,12,13].

Our idea is identify factors related to the patient's loss up to a year, even in the preoperative period, that associated with the potential donor recipients data, by the offer of an organ for transplantation, could help us to offer better chances of patient's survival.

Materials and Methods

We retrospectively studied 292 patients undergoing simultaneous

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pancreas/kidney transplantation at the Federal University of São Paulo, in the period between December 2000 and November 2010.

The study included patients with insulin dependent diabetes mellitus with chronic complications as a result of a long period of hyperglycemia, which presented with chronic renal failure on conservative treatment with creatinine clearance less than 20 ml/min/1,73 m^2 or already in replacement therapy and undergoing simultaneous pancreas/kidney transplantation.

The initial immunosuppression included Tacrolimus 0.15 mg/kg/dose whose target dose was adjusted according to the time post-transplant (serum level of 10-15 ng/ml during the first 30 days, 8-10 ng/ml between 31 and 90 days and 5-10 ng/ml thereafter); prednisone 0.5 mg/kg/day (maximum 30 mg/day and decrease of 5 mg every month until a maintenance dose of 5 mg/day from the sixth to eighth month of transplant); Mycophenolate Mofetil 2 g/day or mycophenolate sodium 1.44 g/day in all cases. The first 16 patients received cyclosporine to tacrolimus in place.

The intraoperative induction was performed with methylprednisolone (one gram intravenous) and Basiliximab 20 mg intravenous. For patients with PRA (Panel Reactive Antibody test) >30% or with delayed graft function in renal postoperatively, the option was the beginning of Thymoglobulin (1 mg/kg/day with programming five days), and adjusted to dose in the peripheral lymphocyte count from the previous day. The recommendation for anuric patients was Thymoglobulin induction with tacrolimus and early in the fourth postoperative day, using a reduced dose of Mycophenolate sodium (360 mg/dose twice daily) until the fourth postoperative day. On the fourth postoperative day, was administered a second dose of Basiliximab 20 mg intravenously (except for patients who received Thymoglobulin).

There wasn't patient excluded from the evaluation because of any exclusion criterion, because all gone through a rigorous protocol, thus, in the case of a fairly homogeneous group.

The variables related to the donor were: age, Body Mass Index (BMI), creatinine, sodium and serum amylase, norepinephrine, cause of death (cardiocerebrovascular source/other) [5] and gender. The variables related to the surgical procedure were: cold ischemia time of pancreas, cold ischemia time of renal, following the implantation of organs, the type of duodenal anastomosis (enteral/bladder) and the type of venous drainage (cava/iliac). For the evaluation of the receiver, the following variables were used: age, body mass index, duration of dialysis, duration of diabetes, need for dialysis, gender, cyclosporine, use of induction therapy and type of preservation fluid (only belzer/other combinations).

To determine the survival times of the patients were evaluated date of transplant, the latest consultation and date of deaths.

For all hypothesis tests performed, the significance level was set at 0.05. Initially, all the independent variables, as data donors, recipients, and surgical procedure are faced with the death receptor dependent variable with one year post-transplant [14].

Statistical analysis was performed using the SPSS 18.0 statistical package. The normality of continuous variables was checked by the Shapiro-Wilk. Univariate analysis was performed using the chi-square test and Student's t test for independent measures or Mann-Whitney test [15].

Interpretation of the test medium or ranks (Mann-Whitney and t test) was performed by comparing the mean or median between groups. In the table, T refers to the test result will Mann Whitney test - U refers to the results of Mann-Whitney. The interpretation of the chi-square is by comparing the frequency of each category of the variable of interest between groups. When any given frequency table presented below five, reported to the value of the Fisher Exact [15-19].

We consider this study a significance level of 0.20 ($p \leq 0.20$) for inclusion in the multivariate model. The odds ratios and corresponding confidence intervals of 95% were calculated, and evaluated significant in the final model at $p<0.05$.

Results

We studied 292 patients who underwent simultaneous pancreas/kidney transplants at the Federal University of São Paulo, from December 2000 to November 2010.

The mean age of patients was 36 years, ranging from 16 to 55 years. Regarding gender, 161 (55.1%) were males and 131 (44.9%) females.

There was no loss to follow-up in any case, the dates being considered for transplantation, graft loss, death and last contact.

Regarding donors, 179 (61.3%) were male and 113 (38.7%) females. There were 101 (34.6%) disease deaths cardio cerebrovascular and other 191 (65.4%) related to traumatic brain injury penetrating or blunt, anoxia or tumor, which were not considered together as cardio cerebrovascular. Norepinephrine in donors was necessary in 195 cases (66.8%) for hemodynamic stabilization and 80 (27.4%) were using dopamine in the last assessment before the capture of the organ.

Regarding the sequence of transplanted organs, the pancreas was initially implemented in 144 (49.3%) patients and the kidney in 148 (50.7%). In all access intraperitoneal transplantations was used for implantation into the extraperitoneal pancreas and kidney.

Regarding exocrine drainage during the first seven cases (2.4%), fashioned to one and the other branch duodenovesical 285 (97.6%) and a bypass duodenoileal lateral side [20].

In all cases, we used a graft "Y" iliac artery of the donor. Thus, in preparing the body (surgery table) were anastomosed the distal ends of the external and internal iliac arteries, respectively with the superior mesenteric artery and the splenic artery graft and surgery in the receiver, held an anastomosis Arterial with the right iliac artery of the recipient [20].

As the venous drainage, the donor's vein was anastomosed to the recipient vena cava in 106 (36.3%) transplants and 186 (63.7%) cases, this anastomosis was performed with the iliac vein of the recipient [20].

With regard to morbidity transplants were observed: 95 (32.5%) patients with delayed renal function, the total loss of the pancreas during follow-up was 88 (30.1%) cases, 57 (19.5%) deaths, the main factor was the intra-abdominal sepsis, 49 (16.8%) in these first year of transplantation simultaneous pancreas/kidney.

There were 56 (18.2%) cases of pancreatic graft loss in three months post-transplant and between three months and one year 10 (3.4%), totaling 66 (22,6%) losses in the first year of transplantation. There were 30 (10.3%) deaths with a functioning graft pancreatic until three months post-transplant and 9 (3.1%) in the three months to a year. There were 21 (7.2%) pancreatic losses one year after transplantation. Regarding the kidney, there were 75 (25.7%) graft losses throughout the whole study.

The graft pancreatectomy was performed in 33 (11.3%) patients, 25

(8.6%) in the first three months after surgery and the transplant was a case of pancreatic primary graft dysfunction.

The results of the univariate analyzes for the losses of patients with their respective frequencies and statistical analyzes are arranged in Tables 1 and 2.

Analyzing the variables in relation to the loss of the patient to a year, obtained a multivariate model based on body mass index receptor ($p \leq 0.008$), induction (negative factor $p \leq 0.008$) and a constant ($p \leq 0.000$). The data are shown in Table 3.

Discussion

To have more benefits than risks associated with immunosuppression and complications of surgery are needed a long graft survival in pancreatic and increased survival of the recipient in order to vest the lasting results of improved glycemic control in stabilizing or even regression of secondary lesions of insulin dependent diabetes mellitus [3-11].

An evaluation later (up to one year post-transplant), aims to get the factors of losses not related necessarily to the technical fault. Thus, once the most delicate moment of the first three months after transplantation, we could predict those factors that were not related to the surgical procedure itself.

We know that to achieve better results with simultaneous pancreas/kidney transplantation, we need to improve the survival of recipients, with survival for more than five years is that we have the real benefits of this modality [8,12]. According to the International Pancreas Transplant Registry-IPTR (2000-2004) survival in patients undergoing simultaneous pancreas/kidney transplantation was 95% in one year [13,21,22].

Through this analysis, we see the development of a mathematical model that enabled predict a greater or lesser chance of loss of patients since the preoperative period. Thus, we could optimize the characteristics of the donor, recipient and surgical techniques, to enable more selective and safer transplants, evaluating the most cost-effective, but no disrespect to ethical issues.

By using initially the univariate analyzes of the data donors, surgical and recipients simultaneous pancreas/kidney transplants, in comparison with the variable loss of patients at one year (Tables 1 and 2), we noted that transplants performed with higher body mass indexes receptor and induction immunosuppressive therapy are associated with a higher likelihood of late loss patient.

In multivariate analysis (Table 3), only variables: body mass index and receptor induction immunosuppressive therapy and remained in the final statistical model of multiple logistic regression as the loss of patients at one year. These two variables have statistical significance individually within this mathematical model.

Understanding the factors for early losses and hence reduction of technical failure, late complications related to chronic immunosuppression also gained importance in attempting maintenance of pancreatic function lasting. Currently, nearly all the transplants simultaneous pancreas/kidney described in the literatures are induced with depleting or non-depleting drugs, hence the incidence of graft loss due to immune pancreatic the first year post-transplant decreased to 2.6% [13,22,23].

Our goal in using induction therapy, this type of transplant, was to reduce the incidence of acute rejection. We use induction therapy in 38.4% of patients, respecting our protocol and availability of drugs in our service. We use Antithymocyte globulin (antibodies depleting - Thymoglobulin) or anti-IL2 (antibodies not depleting-Simulect®) has not been made comparisons between modalities. Organ Procurement and Transplantation Network - OPTN data (2008) show that 52.9% of patients were induced with these drugs, while 33% received no induction [22].

The literature recommends the use of these agents to allow a more effective immunosuppression and enable withdrawal or phasing of the corticosteroid, as well as the reduction of the dosages of calcineurin inhibitors.

This protocol was submitted to the Ethics Committee of the Federal University of São Paulo, reviewed and approved under number 1383\10.

The use of therapy with depleting drugs is associated with lower incidence of rejection but cause a higher incidence of cytomegalovirus infections, without impacting on patient survival or graft. But our study clearly showed the protective effect of induction therapy to the patient with loss of one year at the same time pancreas transplant/kidney [24].

A prospective, randomized, multicenter study compared the use of antibody therapy depleting not without induction therapy and outcome in the first year showed fewer episodes of rejection, however the three years, there was no difference in survival in acute rejection episodes and morbidity [25]. The use of daclizumab induction (non-depleting agent) also was not associated with change in graft survival or patient elsewhere [26].

Becker et al. compared the induction therapy using basiliximab

variables	Loss patient with a year												t ou U	P
	No						Yes							
	N	Med.	SD	Median	Min.	Max.	N	Med.	SD	Median	Min.	Max.		
Donor Age	244	26.3	9.3	23	10	46	48	27.9	9.7	25	10	45	5117.5	0,.67
BMI donor	244	23.6	2.8	23.79	11.57	32	48	23.9	3.0	24.11	12	29.2	5239	0.248
Donor creatinine	244	1.2	0.6	1.075	0.3	3.93	48	1.2	0.4	1.1	0.4	1.97	5726.5	0.808
Sodium do doador	244	154.8	16.5	154	114	200	48	157.1	14.7	157.5	126	189	-0.885	0.377
Amylase donor	244	163.4	231.0	89	10	1703	48	166.8	268.1	70	13	1345	5008	0.113
Pancreas Ischemia Time	244	14.8	3.7	15	6	26.4	48	15.4	3.3	16	7	22	-1.069	0.286
Renal Ischemia Time	244	15.0	4.5	14,5	6	28	48	15.2	4.4	15	6	25	5637	0.682
Recipient age	244	35.3	7.6	35	16	57	48	36.5	9.4	36	20	57	5398.5	0.392
BMI receiver	244	21.6	3.0	21.095	15.78	36.5	48	22.8	3.7	22.255	16	34.3	4702	0.031
Diálise (months)	244	32.6	19.6	31	0	108	48	33.6	25.5	31	0	120	5742	0.831
Diabetes (years)	244	21.2	7.2	21	0	47	48	21.4	7.0	22	1	34	5535.5	0.548

Table 1: Distribution of continuous variables simultaneously pancreas/kidney transplant according loss of the patient, one year, by univariate analysis.

Variables			Loss patient with a year		Total	χ2	p	Fisher p
			No	Yes				
Gender donor	**Male**	N	150	29	179	0.019	0.891	1.000
		%	83.8%	16.2%	100.0%			
	Female	N	94	19	113			
		%	83.2%	16.8%	100.0%			
	Total	**N**	**244**	**48**	**292**			
		%	**83.6%**	**16.4%**	**100.0%**			
Causa Mortis	Other	N	160	31	191	0.017	0.895	1.000
		%	83.8%	16.2%	100.0%			
	Cerebro-vascular	N	84	17	101			
		%	83.2%	16.8%	100.0%			
	Total	**N**	**244**	**48**	**292**			
		%	**83.6%**	**16.4%**	**100.0%**			
Use de Noradrenaline	No	N	80	17	97	0.125	0.724	0.739
		%	82.5%	17.5%	100.0%			
	yes	N	164	31	195			
		%	84.1%	15.9%	100.0%			
	Total	**N**	**244**	**48**	**292**			
		%	**83.6%**	**16.4%**	**100.0%**			
Following Implant	Rim	N	123	25	148	0.045	0.832	0.875
		%	83.1%	16.9%	100.0%			
	Pâncreas	N	121	23	144			
		%	84.0%	16.0%	100.0%			
	Total	**N**	**244**	**48**	**292**			
		%	**83.6%**	**16.4%**	**100.0%**			
type of anastomosis	Bladder	N	8	1	9	0.192	0.661	1.000
		%	88.9%	11.1%	100.0%			
	Enteral	N	236	47	283			
		%	83.4%	16.6%	100.0%			
	Total	**N**	**244**	**48**	**292**			
		%	**83.6%**	**16.4%**	**100.0%**			
Type Drainage	Cava	N	89	17	106	0.019	0.889	1.000
		%	84.0%	16.0%	100.0%			
	Iliac	N	155	31	186			
		%	83.3%	16.7%	100.0%			
	Total	**N**	**244**	**48**	**292**			
		%	**83.6%**	**16.4%**	**100.0%**			
Continuous Ambulatory Peritoneal Dialysis	No	N	187	34	221	0.735	0.391	0.461
		%	84.6%	15.4%	100.0%			
	yes	N	57	14	71			
		%	80.3%	19.7%	100.0%			
	Total	**N**	**244**	**48**	**292**			
		%	**83.6%**	**16.4%**	**100.0%**			
Sex receptor	Female	N	111	20	131	0.237	0.626	0.638
		%	84.7%	15.3%	100.0%			
	Male	N	133	28	161			
		%	82.6%	17.4%	100.0%			
	Total	**N**	**244**	**48**	**292**			
		%	**83.6%**	**16.4%**	**100.0%**	.		
Use of Cyclosporin	No	N	232	44	276	0.903	0.342	0.311
		%	84.1%	15.9%	100.0%			
	Yes	N	12	4	16			
		%	75.0%	25.0%	100.0%			
	Total	**N**	**244**	**48**	**292**			
		%	**83.6%**	**16.4%**	**100.0%**			
Induction	No	N	143	37	180	5.791	0.016	0.022
		%	79.4%	20.6%	100.0%			
	Yes	N	101	11	112			
		%	90.2%	9.8%	100.0%			

	Total	**N**	**244**	**48**	**292**			
		%	**83.6%**	**16.4%**	**100.0%**			
Perfusion	No-Belzer	N	92	17	109	0.090	0.764	0.871
		%	84.4%	15.6%	100.0%			
	Belzer	N	152	31	183			
		%	83.1%	16.9%	100.0%			
	Total	**N**	**244**	**48**	**292**			
		%	**83.6%**	**16.4%**	**100.0%**			

Table 2: Distribution of categorical variables simultaneously pancreas/kidney transplant according loss of the patient, one year, by univariate analysis.

Loss patient with a year	**B**	**S.E.**	**W**	**Sig.**	**(B)**	**95% C.I.**	
						Min.	**Max.**
BMI receptor	.128	.048	6.999	.008	1.137	1.034	1.250
Induction (Yes)	-1.014	.382	7.060	.008	.363	.172	.766
Constant	-4.150	1.085	14.624	.000	.016		

Table 3: Final result of the multiple logistic regression model for patients with loss of one year.

or daclizumab with immunosuppressive therapy without induction, combined modality pancreas/kidney. They observed no differences in patient survival or graft, but found higher mortality associated with sepsis in the group with induction, suggesting that transplantation without induction was safe and at lower cost [27].

Donors with body mass index greater than 30 kg/m^2 are associated with a greater number of surgical complications, especially infections and associated with thrombosis [28-30]. Other studies correlate with the loss pancreatic mass index greater than 30 kg/m^2 [1,13,21].

Conclusions

In assessing the risk factors of the patient's loss in the first year post simultaneous pancreas/kidney transplant, we conclude that the body mass index receptor and induction therapy are independent risk factors for these losses.

Acknowledgments

This research has no conflict of interest. This protocol was submitted to the Ethics Committee of the Universidade Federal de São Paulo, reviewed and approved under number 1383\10.

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