Impact of delayed pancreatic graft function in simultaneous pancreas-kidney transplantation

Impacto da função retardada do enxerto pancreático no transplante simultâneo pâncreas-rim

ABSTRACT

Objective: Simultaneous pancreas-kidney transplantation is an effective treatment for patients with type 1 diabetes mellitus and end-stage chronic kidney disease. Delayed pancreatic graft function is a common and multifactor condition with significant impact in short-term outcome of simultaneous pancreas-kidney transplantations. The aim of this study was to analyze the impact of pancreatic delayed pancreatic graft function on simultaneous pancreas-kidney transplantation.

Methods: Donor and recipient’s demographic data, percentage of panel reactivity, acute rejection incidence, and patient and grafts survivals were retrospectively analyzed in 180 SPKT performed between 2002 and 2007.

Results: The incidence of pancreatic delayed pancreatic graft function was 11%. Donors older than 45 years had significant risk of pancreatic delayed pancreatic graft function (OR 2.26; p < 0.05). Patients with pancreatic delayed pancreatic graft function had higher rates of acute renal rejection (47 versus 24%; p < 0.05), altered fasting plasma glucose (25 versus 5%; p < 0.05) and mean glycated hemoglobin (5.8 versus 5.4%; p < 0.05), than patients without pancreatic delayed pancreatic graft function at the end of the first year of follow up. There were no significant differences between patients with and without pancreatic delayed pancreatic graft function regarding patient survival (95 versus 88.7%; p = 0.38), pancreatic graft survival (90 versus 85.6%; p = 0.59) and renal graft survival (90 versus 87.2%; p = 0.70), respectively at the sample period of time.

Conclusion: Pancreatic delayed pancreatic graft function had no significant impact in the short-term outcome of simultaneous pancreas-kidney transplantation.

RESUMO


Métodos: Análise retrospectiva de 180 receptores de transplante pâncreas-rim, incluindo dados demográficos dos doadores e dos receptores, a reatividade contra painel, a incidência de rejeição aguda e as sobrevidas do paciente e dos enxertos pancreático e renal.

Resultados: A incidência de função retardada do enxerto pancreático foi 11%. A idade do receptor superior a 45 anos apresentou associação com o risco de desenvolvimento de função retardada do enxerto pancreático (Razão de chances 2,26; p < 0,05). Os pacientes com função retardada do enxerto pancreático apresentaram maior incidência de rejeição aguda renal (47 versus 24%; p < 0,05), glicemia de jejum alterada (25 versus 5%; p < 0,05) e média de hemoglobina glicada (5,8 versus 5,4%; p < 0,05) ao final do primeiro ano de acompanhamento em relação aos pacientes sem função retardada do enxerto pancreático. Não houve diferenças estatisticamente significativas entre os grupos de pacientes com e sem função retardada do enxerto pancreático quanto à sobrevida do paciente (95 versus 88,7%; p = 0,38), do enxerto pancreático (90 versus 85,6%; p = 0,59) e do enxerto renal (90 versus 87,2%; p = 0,70), respectivamente, nesse mesmo período.

Conclusão: A função retardada do enxerto pancreático não exerceu impacto significativo nos resultados em curto prazo dos transplantes pâncreas-rim desta.
transplantations. Although delayed pancreatic graft function had no impact on 1-year pancreas graft survival, it contributed to early pancreas graft dysfunction, as assessed by enhanced insulin and oral anti-diabetic drugs requirements.

Keywords: Kidney transplantation. Pancreas transplantation. Graft rejection. Survival analysis. Logistic models.

**INTRODUCTION**

Simultaneous pancreas-kidney transplantation (SPKT) is a therapeutic modality accepted throughout the world for insulin-dependent patients with type 1 diabetes mellitus (DM) and end-stage chronic kidney disease, especially when they also present inappropriate glycemic control, asymptomatic hypoglycemia, and lesions in target organs. SPKT is not formally recommended for patients with type 2 diabetes.\(^1\)

In the United States, survival rates of patients submitted to SPKT after 1 and 5 years of follow-up are 95% and 87%, respectively. Survival rates of pancreatic graft after 1 and 5 years are 84% and 73%, respectively, and survival rates of renal graft after 1 and 5 years are 92% and 78%, respectively.\(^2\) In Brazil, according to the Brazilian Transplantation Registry, survival rates of patients submitted to SPKT after 1 and 5 years are 83% and 77.3%, respectively.\(^3\)

The benefits of SPKT are not limited to glycemic control and treatment of end-stage uremia; it also improves the disabling comorbidities related to long-lasting diabetes mellitus. In most patients, retinopathy related to DM stabilizes.\(^4\) In addition, a significant reduction in the occurrence of cardiovascular episodes in the long term follow-up is often observed, as well as improvement in markers of atherosclerosis of coronary circulation and of performance of the left ventricle.\(^5\)\(^-\)\(^7\)

Delayed pancreas graft function (DPGF) is a significant risk factor for the survival of renal and pancreatic grafts, and also for the patient. DPGF is the result of a combination of factors related to the recipient, the donor, and also to ones inherent to the transplant itself. Although the absence of standardized diagnostic criteria makes analysis and comparison of results more difficult among different centers, DPGF has been strongly associated with a poorer prognosis after SPKT.\(^8\)\(^-\)\(^10\)

This study aims at analyzing the results of the SPKT performed at Universidade Federal de São Paulo (Unifesp); the incidence and risk factors for the occurrence of DPGF; and the impact of DPGF on the short-term survival rates of patients and renal and pancreatic grafts.

**METHODS**

One hundred and eighty medical records of SPKT recipients who were subjected to surgery between December 2000 and September 2007 at Unifesp were analyzed. The research project was previously approved by the Research Ethics Committee of Unifesp (protocol No 162/08).

**INDICATIONS AND SURGICAL TECHNIQUES**

SPKT was indicated for insulin-dependent diabetic patients who were not obese [body mass index (BMI) \(<32\ \text{kg/m}^2\)\], aged no more than 55 years old, presenting instability in glycemic control and two or more complications related to DM, such as nephropathy, retinopathy, and neuropathy.

The first 41 transplantations were performed with grafts obtained from donors who had been exposed to 2 L of Belzer solution, for the perfusion of the aorta before organ removal. As to the remaining donors, different combinations of solutions were used: Belzer, Euro-collins, Celsior, and histidine-tryptophan-ketoglutarate. Renal graft was preferably placed into the left iliac fossa, by the standardized surgical technique of kidney transplant, with termino-lateral vascular anastomosis in the external iliac vessels and urethrovesical anastomosis, especially with the Gregoir technique. Pancreatic transplantation was performed after the kidney transplant, whenever the cold ischemia time of the pancreatic graft was less than 10 hours.\(^11\) Pancreatic graft was inserted in the right iliac fossa with termino-lateral anastomosis in the external iliac vessels. Surgical
techniques included exocrine bladder derivation in the first seven transplantations, and exocrine enteral derivation in the others. Bladder exocrine derivation was early renounced due to the high frequency of unfavorable evolution with dehydration, hemorrhagic cystitis, and pancreatic reflux.

**IMMUNOSUPPRESSION**

All patients received a combination of calcineurin inhibitor, prednisone, and mycophenolate. The calcineurin inhibitor used in the first 16 patients was cyclosporine, at a dosage of 5-6 mg/kg twice a day. The initial cyclosporine dose was adjusted in order to obtain blood concentration between 150 and 200 ng/ml (up to 30 days), 100 and 150 ng/ml (30 to 90 days), and 50 and 100 ng/ml (> 90 days). The calcineurin inhibitor used in the other patients was tacrolimus, at a dosage of 0.15 mg/kg twice a day. The dose of tacrolimus was adjusted in order to obtain blood concentration between 10 and 15 ng/ml (up to 30 days), 8 and 12 ng/ml (30 to 90 days), and 5 and 10 (> 90 days). Prednisone was used at an initial dosage of 0.5 mg/kg, with a maximum daily dose of 30 mg/day, and a progressive reduction every 3 weeks, until 5 mg/day 180 days after transplantation. Transplant recipients who were subjected to surgery before January 31, 2005 received mycophenolate mofetil at a dosage of 1.0 g twice a day. After this date, the recipients were given the formulation of mycophenolate sodium at a dosage of 720 mg twice a day. Therapy with mono- or polyclonal antilymphocyte antibodies was reserved for the recipients who presented elevated risk of delayed renal graft function, for patients who had previously been submitted to transplantations or for those who were hypersensitive (reaction against a panel of cells superior to 30%). Some of the recipients who did not meet the described criteria indicating treatment with antilymphocyte antibodies received anti-IL-2R antibodies after July 30, 2003.

**STUDY DESIGN AND DATA COLLECTION**

The selection of patients and the data collection were conducted retrospectively. At first, the analysis focused on demographic and clinical characteristics, incidence of acute renal and pancreatic rejection, short-term survival of patients and renal and pancreatic grafts. There was a suspicion of episodes of acute rejection, considering both renal and pancreatic grafts, based on clinical, laboratorial, ultrasonographic, and histological findings. The study considered as acute renal and pancreatic rejection all the episodes treated for at least three days, with or without histological confirmation. Increase in serum amylase and lipase, as well as sudden hyperglycemia, were considered as criteria for indication of pancreatic graft biopsy. The 180 patients were analyzed in two distinct subgroups, according to the presence of DPGF. DPGF was defined as the need for insulin at the time of hospital discharge. Delayed renal graft function was defined as the need for dialysis during the first week post-transplant. As secondary end-points, the incidence of post-transplant DM, alterations of fasting glucose (between 100 and 125 mg/dl), deep venous thrombosis, pancreatic fistulas, peripancreatic abscesses, pancreatitis and dyslipidemia were analyzed, as well as the levels of serum glycated hemoglobin, renal function estimated by the formula of MDRD, and BMI at the end of the first year of follow-up in both groups. Data collection was based on medical records. September 30, 2008, was the due date for the registration of events and for the calculation of follow-up time.

The analyzed variables were age, gender, pre-transplant BMI, time of DM diagnosis, type of renal replacement therapy, cold ischemia time of renal graft, cold ischemia time of pancreatic graft, reaction against a panel of cells, and post-transplant time of hospitalization. Donor’s age and BMI were also assessed.

**STATISTICAL ANALYSIS**

Data were presented by absolute frequency, as well as percentage, means, standard deviation, and maximum and minimum values whenever it was appropriate. The chi-square test was used to compare categorical variables. Student’s t-test was used to compare continuous variables. Kaplan-Meier was used for univariate analysis of both patient and graft survival. Log-Rank method was used to compare survival curves of patients who did or did not have DPGF. The contribution of the variables “recipient’s age”, “donor’s age”, “donor’s BMI”, “recipient’s BMI”, “time of diabetes diagnosis”, “percentage of reaction against a panel of cells”, “donor’s death due to cardiovascular problems”, and “cold ischemia time of pancreatic graft over the risk of DPGF” was analyzed through multiple logistic regression analysis. The results were presented according to odds ratio index. The value p <
0.05 was considered statistically significant. All statistical analysis was conducted with the *Statistical Package for the Social Sciences* (SPSS) program.

**RESULTS**

**PATIENTS**

Demographic characteristics of the 180 patients (recipients and donors) classified according to the presence of DPGF are shown in Table 1. There were no statistically significant differences as to age, gender, pre-transplant BMI, time of diabetes diagnosis, type of renal replacement therapy, cold ischemia time of pancreatic and renal grafts, reaction against a panel of cells, time of hospitalization, use of immunosuppressants with mono- or polyclonal antilymphocyte antibodies, and use of immunosuppressants with anti-IL-2R in the group of recipients that evolved with DPGF (*n* = 19) and the group without DPGF (*n* = 161). Also, there were no statistically significant differences in the groups as to age, donor’s BMI and use of different preservation solutions.

**RATES OF ACUTE REJECTION**

In the end of the first year of follow-up, 49 patients had rejected renal graft (27%) and 12 had rejected pancreatic graft (6%). Patients that developed DPGF had an incidence of renal acute rejection significantly higher than the ones who did not have DPGF (47% *versus* 24%, respectively, *p* <0.05). There was no significant difference in the incidence of DRGF between the groups (21 *versus* 24, *p*=0.71). However, no statistically significant

<table>
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<tr>
<th>Table 1. <strong>TRANSPANT RECIPIENT AND DONOR DEMOGRAPHIC DATA</strong></th>
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<td><strong>Variable</strong></td>
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<tr>
<td><strong>Recipient</strong></td>
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<td>Age (years)</td>
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<td>Female</td>
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<td>BMI (kg/m²)</td>
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<td>Time of DM (years)</td>
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<td>pancreatic CIT (hours)</td>
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<td>Reactivity against a panel of cells&gt; 30%</td>
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<td>Hospitalization (days)</td>
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<td>Induction with antilymphocytes antibodies</td>
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<td><strong>Donor</strong></td>
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<td>Age (years)</td>
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<td>BMI (kg/m²)</td>
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<td>Preservation Solutions</td>
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<td>Belzer 1L + Belzer 1L</td>
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<td>Others*</td>
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*Other solutions included different combination of Belzer, Euro-collins, Celsior, and Histidine-Tryptophan-Ketoglutarate solutions.*
differences were observed between the rates of pancreatic acute rejection in the group of patients with DPGF in comparison with the group without DPGF (15% versus 5%, p = 0.1) (Figure 1). According to the post-transplant time, ten were considered as early rejection (in the first 30 days of follow-up) and two were considered as late rejection (after 6 months of follow-up). Considering only the 10 patients who presented early rejection, 3 (30%) also had DPGF. Minimum time of hospital stay was 8 days, and maximum was 28 days (14 ± 6.5 days).

Complications

The proportion of patients with DPGF who had diabetes in the end of the first year of follow-up was not significantly different from the proportion of patients without DPGF who had diabetes (11% versus 2%, respectively, p = 0.08). However, when the patients who had diabetes (diagnosed after transplantation) were excluded from the sample, it was observed that the number of patients who presented altered fasting glycemia was perceptually higher in the group with DPGF (25% versus 5%, p = 0.02), as well as the glycated hemoglobin means (5.8% versus 5.4%, p < 0.05). Patients who developed DPGF also received insulin (26.3% versus 2%, p < 0.05) and oral hypoglycemic drugs (33% versus 6%, p < 0.05) more frequently than the group without DPGF. Considering the 180 patients, 158, 155, 159, and 171 did not need insulin until the end of 1, 3, 6, and 12 months of follow-up, respectively. Among the 19 patients who developed DPGF, 12, 11, 9, and 5 received insulin until the end of 1, 3, 6, and 12 months of follow-up, respectively.

The rates of deep venous thrombosis (5% versus 1%, p = 0.33), pancreatic fistulas (5% versus 10%, p = 0.69), peripancreatic abscesses (0% versus 8%, p = 0.36), pancreatitis (0% versus 3%, p = 1), dyslipidemia (60% versus 52%, p = 0.51), glomerular filtration rate estimated by the formula of MDRD (64 versus 69 mL/min/1.73m², p = 0.33) and BMI values evaluated in the end of the first year of follow-up (22 versus 21.9 kg/m², p = 0.96) were not statistically different, respectively, between patients with and without DPGF.

Survival Rates Analysis

Survival rates of patients 6 and 12 months after transplantation were 86.1% and 83.3%, respectively. Survival rates of pancreatic graft 6 and 12 months after transplantation, including all failures, were 80.3% and 77%, respectively.

Survival rates of patients who developed DPGF 6 and 12 months after transplantation were 100% and 95%, respectively, and those of patients who did not develop DPGF were 91.5% and 88.7%, respectively. Comparison between groups showed no statistically significant differences (p = 0.38) (Figure 2).

Renal graft survival rates 6 and 12 months after transplantation in the group of patients who developed DPGF, including all failures, were 95% and 90%, respectively, and in the group of patients who did not develop DPGF, 90.8% and 87.2%, respectively.

Figure 1. Incidence of renal and pancreatic grafts acute rejection according to the existence of delayed pancreatic graft function. *p < 0.05

Figure 2. Patients’ survival curve in recipients that evolved with or without delayed pancreatic graft function.
Comparison between groups showed no statistically significant differences (p = 0.70) (Figure 3).

Pancreatic graft survival rates 6 and 12 months after transplantation in the group of patients who developed DPGF, including all failures, were 95% and 90%, respectively, and in the group of patients without DPGF, 89.2% and 85.6%, respectively. Comparison between groups showed no statistically significant differences (p = 0.59) (Figure 4).

**Risk Factors for DPGF**

Multiple logistic regression analysis indicated that only the variable "recipient’s age over 45" (odds ratio of 2.26, p < 0.05) was identified as a risk factor for DPGF. Logistic regression analysis did not show significant correlations between the variables: recipient’s age over 40 (p = 0.7); donor’s age over 40 (p = 0.08); donor’s age over 45 (p = 1); recipient’s BMI higher than 30 (p = 0.34); donor’s BMI higher than 25 (p = 0.36); donor’s BMI higher than 30 (p = 0.9); recipient’s BMI higher than 30; and donor’s BMI higher than 25 (p = 1); time of diabetes diagnosis (p = 0.6); percentage of reactivity against a panel of HLA class I cells higher than 10% (p = 0.9); percentage of reactivity against a panel of HLA class I cells higher than 20% (p = 1); percentage of reactivity against a panel of HLA class II cells higher than 10% (p = 1); percentage of reactivity against a panel of HLA class II higher than 20% (p = 1); donor’s death due to cardiovascular causes (p = 0.7) and cold ischemia time of pancreatic graft (0.9) over the risk of DPGF development.

**Discussion**

The definition of DRGF that takes into account the need for dialysis during the first week of follow-up after kidney transplant is adopted by most centers. However, diagnosis criteria for DPGF are not widely accepted. A great variety of factors related to the clinical conditions of donor and recipient, as well as the transplantation itself, significantly influences DPGF and contributes to the non-existence of a universally accepted definition of DPGF. A proposal for diagnostic standardization included the need for cumulative doses of insulin, higher than 30 UI, from 5 to 10 days after a successful SPKT, or a higher than 15 UI, between the 11th and 15th days. Another proposal established that the need for insulin at hospital discharge after a successful pancreas-kidney transplantation should be used as an isolated criteria. More recently, DPGF has been defined as the need for insulin or oral hypoglycemic medication and/ or fasting glycemic level higher than or equal to 126 mg/dl in the first 30 days post-transplant. In the present study, DPGF has been defined as the need for insulin at hospital discharge after a successful SPKT according to the criteria proposed by Tan et al. in 2004.

It is important to mention that the DPGF diagnosis according to the criteria used in this study does not distinguish functional damage and tissue damage to the pancreatic graft. Some situations, such as recipient’s obesity and lipid disorders, are followed by a greater incidence of DPGF due to increased risk of resistance to insulin. Other factors, such as the use of steroids and calcineurin inhibitors, as well as...
infections, make the initial function of the pancreas more difficult, since they delay tissue regeneration, which is necessary after ischemia and reperfusion, and favor the development of ischemia and systemic inflammation. Therefore, glucose intolerance may be present without necessarily indicating DPGF secondary to structural damage. These conceptual differences represent additional challenges to establish the role of DPGF in the short- and long-term results of SPK.

Many variables are indicated as predisposing factors for DPGF, such as: donor’s and recipient’s age, donor’s and recipient’s BMI, cold ischemia time of pancreatic and renal grafts, as well as reactivity against a panel of class I and II cells higher than 30%. Donor’s age over 45 years is pointed out as the main risk factor for DPGF, probably due to the little amount of functional pancreatic mass and the presence of atherosclerotic lesions in the grafts obtained from these donors. In this study, only the recipient’s age over 45 years presented a statistically significant association with the development of DPGF.

Glucose tolerance decreases with aging, and it is often associated with resistance to insulin. Even though higher resistance to insulin may be a very probable hypothesis to support such observation, the impossibility to measure C-peptide during the follow-up of these patients did not allow us to establish definite conclusions. The cause of death of the donor has been investigated in some centers as an independent risk factor for DPGF. The main evidence lies on cardiovascular causes, condition in which the quality of the organ to be transplanted is much inferior. The cause of death of the donor was also analyzed in this study, and no direct relation between the cause of death and the incidence of DPGF was found. DM time showed no associations with DPGF in this study or preceding ones.

The adequate preservation of the pancreas is essential to prevent the development of DPGF. The search for more favorable cost-benefit alternatives in comparison to the very expensive Belzer solution, which is traditionally the best option for preserving the pancreas for transplantation, resulted in the use of different combinations of preservation solutions in the donors included in the present study. Although it may be valid to question the influence of such heterogeneity in the results presented in this study, percentage comparisons involving the use of different combinations of preservation solutions in these groups of patients had no statistically significant differences, suggesting that different methods of organ preservation did not have significant influence on the development of DPGF.

A higher incidence of renal acute rejection among the recipients who developed DPGF was observed. However, there was no significant difference between the groups as to the rate of pancreatic acute rejection. Although some methodological variations related to the confirmation of diagnosis in acute rejection – both for pancreatic and renal grafts – could explain such observations, it is very likely that intravenous steroids usually used for the treatment of renal acute rejection contributed to the post-transplant development of DPGF. However, the influence of such variable was not specifically investigated in the present study.

Patients with DPGF had severe post-transplant dislipidemia (in the first 6 months) more often than patients without DPGF. The cohort of patients presented here did not reproduce such observation. Severe dislipidemia before SPKT is also described as an independent risk factor for DPGF.

Pancreas with fat deposits and several atherosclerotic lesions, usually calcified, presents a higher risk of post-transplant technical and metabolic complications, which indicates that the organ should be discarded under such conditions.

Family history of DM in first-degree relatives was not identified as a significant risk factor for DPGF in this study, although some authors have observed that SPKT recipients who had first-degree relatives with diabetes presented higher levels of insulin secretion followed by reduced tissue sensitivity.

It is widely accepted that pancreatic acute rejection determines dysfunction and immediate pancreatic tissue damage, which is often irreversible and has a negative interference on pancreatic graft survival. In addition, there is a strong correlation between pancreatic acute rejection and DPGF. In the present study, pancreatic acute rejection had no statistically significant association with the occurrence of DPGF. Although this observation does not reproduce results of previous studies which included a large series of patients, it is possible that the improvement in the diagnosis of pancreatic rejection and the inclusion of more patients indicate the expected correlation between these variables in further analyses.

The main limitations of this study were related to the relatively small number of patients, retrospective design, and absence of diagnostic uniformity of pancreatic acute rejection. Monitoring of amylase and lipase serum levels was not systematically used for the follow-up of SPKT recipients and not all episodes of acute rejection were histologically confirmed. Such observations may justify the lower rates of renal (27%) and pancreatic (6%) acute rejection compared

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to multicenter registrations. When considering the 4,251 recipients of simultaneous pancreas-kidney transplantation notified in the North American registration UNOS, 36% presented at least one episode of renal acute rejection, 3% had at least one episode of pancreatic rejection, and 16% presented rejection in both grafts simultaneously.\textsuperscript{12}

DPGF is significantly associated with lower pancreatic survival rates,\textsuperscript{8} especially when there is an activation of the immune system, reduced pancreatic mass (in older donors), as well as ischemia and reperfusion lesions.\textsuperscript{5} Episodes of intra-abdominal infections, vascular thrombosis and renal acute rejection are also known as factors related to lower pancreatic survival rates in the short-term (1 year of follow-up).\textsuperscript{21} The presence of DPGF was not a significant risk factor for lower survival rates of patients and grafts in the present study.

The increase in the use of insulin and oral hypoglycemic medication at the end of the first year of follow-up after SPK in patients who developed DPGF in relation to the group without DPGF indicates partial functioning of the pancreatic graft. Higher glycated hemoglobin levels were observed after one year in patients with DPGF, which may indicate a higher incidence of pancreatic graft dysfunction.

Therefore, DPGF determined a greater need for oral hypoglycemic medication and insulin during the first year of follow-up after SPK, without compromising patient’s short-term survival, as well as renal and pancreatic rates.

**References**


