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# Pancreas-kidney transplantation: clinical, metabolic and immunological outcomes

## Transplante reno-pancreático: resultados clínicos, metabólicos e imunológicos

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The first pancreas transplant was performed in 1966[1] and since then much has evolved. Refinements in surgical technique, immunosuppressive protocols and post-operative care have led to progressively improved outcomes. These results have encouraged many transplant centres to implement pancreas transplant programmes. Simultaneous pancreas-kidney transplantation (SPKT) has better medium- and long-term results than pancreas after kidney or pancreas transplantation alone. Based on this, since 2000 the American Diabetes Association has recommended SPKT as the pancreas transplantation modality of choice for type-1 diabetes (DM1) patients with end-stage renal disease[2,3]. Pancreas after kidney transplantation is another option, especially for recipients having a living kidney donor. Pancreas transplantation alone remains restricted for those with minor renal disease and labile diabetes, with history of frequent ketoacidosis or hypoglycaemic coma episodes[3]. In recent years and mainly in the United States, some type-2 diabetes patients have also been considered for pancreas transplantation, following a very narrow selection process.

Successful SPKT frees the patient from dialysis, insulin and glucose monitoring, and from life-threatening hypoglycaemic episodes. Despite the initial increased morbidity and mortality, over time SPKT offers to selected DM1 patients not only a better quality of life but also some improvements – or, at least, stabilization – in long-term secondary diabetic complications compared to kidney transplantation alone.

This paper will deal with what pancreas-kidney recipients can expect from this type of transplant, the experience and research results obtained in several fields of SPKT at the Hospital Santo Antonio – Centro Hospitalar do Porto – pancreas transplant programme.

## GLOBAL OUTCOMES: SURVIVAL AND FUNCTION

In 2006 we reported our 5-year results, describing candidates' selection criteria, surgical technique, immunosuppressive protocol, and the main complications[4]. These encouraging initial data were a strong motivation to pursue this direction. By following the internationally accepted clinical guidelines, we could improve these data. At the 10-years mark[5], our results continued to align with the standards of other

world reference centres and the international pancreas transplantation registry (IPTR)[6]. Patient, kidney and pancreas graft survival rates reported by our group were 96%, 96% and 83%, respectively, for the 1st year and 94%, 91% and 75%, respectively, at 5 years. The annual number of SPTK has increased, reaching a plateau of 12 to 15 per year. As a result of this increment, time on the waiting list for such a transplant has substantially decreased. Acute rejection incidence improved to around 16% in a more recent analysis of 150 patients[7]. Ten-year patient, kidney and pancreas graft survival was then 91%, 79% and 69%, respectively. The contribution of the radiology department, which provides image-guided pancreatic biopsy, has enabled us to confirm or exclude pancreatic rejection more accurately in recent years.

A pancreas graft is considered to be functioning as long as it allows patients to remain free of the need for insulin injections. Of the first 150 SPKTs, 76% had a functioning pancreas graft and 87% a functioning renal graft[7]. Renal function expressed as mean serum creatinine and mean creatinine clearance was 1.2mg/dl and 76 ml/min, respectively.

## COMPLICATIONS AFTER SURGERY

Higher morbidity and even mortality after SPKT compared to kidney transplantation alone is quite well known. The candidates are recognized as high-risk patients and the procedure itself may lead to a higher rate of complications. In our experience, hospital stay in the first admission for SPKT is approximately twice that of kidney transplantation (median 22 days). Almost one-third of the recipients needed at least one surgical reintervention[8] with intra-abdominal bleeding or infection and graft thrombosis the majority of the causes. The readmission rate was also high (74.2%), mostly (57.4%) in the first year after the transplant[8]. The events occurring in the very early post-operative period, namely infection or graft thrombosis, may determine not only pancreas graft survival but also patient survival[7]. An uneventful early period usually indicates good mid-term results. Long-term pancreas failure was mainly due to rejection. Regarding kidney graft loss, chronic rejection was the cause of late losses[7], with one exceptional early loss due to thrombosis.

A multidisciplinary approach to these patients is mandatory and the key to the SPKT success. Our fruitful collaboration with Radiology has allowed not only suspected pancreas rejection to be excluded or confirmed through biopsy, but also the diagnosis and sometimes the treatment for several complications that may occur in these patients[9].

From our initial experience it seemed that peritoneal dialysis (PD) patients who underwent SPKT were more prone to developing intra-abdominal complications. We then conducted a study to analyse the differences between PD and haemodialysis (HD) patients and to clarify whether the two sets of patients had distinct outcomes[10]. Our study confirmed a higher intra-abdominal infection incidence and pancreas loss in PD patients. Microbial agents isolated from abdominal fluids after SPKT were distinct from the agents they evidenced in past peritonitis episodes. Additionally, PD patients tended to present a higher incidence of renal graft loss due to thrombosis, and also an increased mortality rate. We could not find the objective causes for this adverse outcome in the PD group. It is tempting to blame the peritoneum, previously damaged by PD and its complications. However, this direct relationship remains to be proven, as does which underlying peritoneal changes, or other changes, lead to those results. It is our aim to proceed with further studies in this field.

## METABOLIC OUTCOMES: CARDIOVASCULAR RISK FACTORS AND EVENTS

Cardiovascular (CV) and cerebrovascular diseases are the main cause of mortality in diabetic patients. Thus, controlling CV risk factors is crucial in reducing the incidence of stroke, myocardial infarction and peripheral artery disease. Steroids are usually part of the maintenance immunosuppressive protocols in solid organ transplantation, despite their known detrimental effects on hypertension, hyperlipidaemia, obesity, osteoporosis, and infection, among others. Steroid-free or steroid-limited protocols are sought, but acute rejection and graft failure are feared after steroids withdrawal. Some years ago we confirmed the feasibility of steroid withdrawal, normally after the 6th month post-SPKT[11]. With a cautious patient selection – only

patients who could maintain tacrolimus associated with an anti-proliferative drug were selected – we noticed that steroid tapering and discontinuation can be safe, with no subsequent acute rejection episodes or graft function deterioration. Within this sample of 54 SPKT with more than one year of follow-up, steroid suspension was achieved in 77.8% (42 patients). We were not able to demonstrate statistically significant differences regarding the lipid profile and hypertension rate between those who stopped steroids and those who didn't, but the limited sample may explain this lack of significance. Nevertheless, the results from this study, confirming the safety of the procedure, were important as they led us to implement our steroid withdrawal protocol.

More recently we analysed CV risk factors and CV events occurring in a wider sample of our SPKT patients, considering only those who maintained both grafts functioning[12]. Although these 103 SPKT were young (mean 35 years old), at the time of the transplant they had a mean time of diabetes evolution of 24 years and had been on dialysis for 30 months. The National Cholesterol Education Program Adult Treatment Panel3 (NCEP/ATP3) criteria were followed to characterize metabolic syndrome (MS) in our patients. Only 8.7% met the criteria (≥ 3) for MS. Hypertension was the most frequent single criteria (in 38.5%), followed by low HDL-c (in 19.4%) and hypertriglyceridemia (in 7.8%). Obesity and high fasting glucose levels (> 100 mg/dl) were rare. Among these patients, we compared the subgroup under steroids (n = 34) with the subgroup who stopped steroids (n = 69). Patients under steroids had higher triglycerides levels and more often tended to be hypertensive. Hypertension was associated with higher body mass index (BMI). BMI > 25kg/m$^2$ was associated with higher total cholesterol and LDL-c levels. These results allowed us to confirm the association between steroid maintenance and worse metabolic results and support our strategy to minimize steroid exposure, whenever possible.

Non-fatal CV events occurred in 6.8% (n = 7) of patients, mostly peripheral artery disease[12]. We also looked at the other 32 patients – among the global 135 SPKT at this time – who lost at least one graft (n = 26) or who died (n = 6). CV disease was the cause of death in two recipients. The incidence of CV events among those 26 alive but with one failed graft was substantially higher: 19.2%.

## PANCREAS-KIDNEY TRANSPLANTATION AND BONE MINERAL DISEASE

Bone mineral disease is a major concern in chronic renal patients and diabetes may contribute to additional bone mass loss. Several studies, mostly into kidney transplant recipients, have reported an initial bone mass worsening at least during the first 6 months, with possible recovery thereafter[13-15]. A retrospective evaluation was made in 54 patients, over 4 years after SPKT[16]. At the time of transplantation bone mineral density (BMD) – evaluated by dual-energy X-ray absorptiometry (DEXA) – evidenced osteoporosis in 28% of patients. One year after, 77.6% displayed improved lumbar T-score, with stable femoral neck T-score. BMD gradually improved through the 4 years' follow-up, more significantly at the lumbar level and less importantly at the femoral neck. At the end of the fourth year no cases of osteoporosis were observed, and 86.7% of patients were withdrawn from steroids.

Subsequently, we conducted a prospective study evaluating BMD (by DEXA) and serum levels of bone mineral metabolism markers at 3 different timepoints after SPKT[17]. BMD and blood samples were obtained from 48 recipients, firstly before the end of the 3$^{rd}$ month, the other two at least 2 years after the transplant and one year apart. At the first evaluation 35.4% were categorized as having lumbar osteoporosis and 39.6% as having femoral neck osteoporosis. Osteoporotic patients (lumbar/femoral) presented higher alkaline phosphatase levels. Patients with lumbar osteoporosis had significantly lower BMI. BMD significantly improved in subsequent evaluations, in both sites. Parathyroid hormone progressively decreased. At the end of follow-up 81.2% had been withdrawn from steroids. Multivariate analysis identified BMI increase as positively associated with BMD improvement and high values of alkaline phosphatase as increasing the risk of inferior BMD scores. The frequency of patients with osteoporosis at the last follow-up decreased to 4.2% at lumbar spine and 8.3% at femoral neck. Patients who remained osteoporotic presented the lowest BMI. This study provided additional evidence of bone density gain after SPKT and identified two factors, one with negative and another with positive correlation with BMD: alkaline phosphatase and BMI, respectively.

## AUTOIMMUNITY RELAPSE AFTER SPKT

At the time of DM1 diagnosis, most patients present circulating autoantibodies against pancreatic beta-cell antigens; additionally, an inflammatory infiltrate surrounding these cells has been documented. The autoimmune nature of the disease can be proved in nearly 95% of DM1 cases. After the onset and over the years, in the majority of patients these anti-islet antibodies tend to decrease and eventually to disappear, although in some patients they remain detectable.

When these patients are transplanted with a healthy pancreas, they express newly these islet antigens, corresponding to the new beta-cells. Immunosuppression applied to control alloimmunity in pancreas transplant recipients would be expected to also control autoimmune response. However, the first case of autoimmune diabetes recurrence after pancreas transplantation was described in 1984[18]. Thereafter several cases have been documented, despite maintained immunosuppression and with alloimmunity apparently controlled[19]. The study of the causes leading to graft dysfunction or failure excluded graft rejection and confirmed a lymphocytic infiltrate selectively targeting Langerhans islets beta-cells, sparing the other cell types and the pancreatic exocrine tissue[20]. In such cases, it is usual to observe a recurrence or an increase in pancreatic autoantibodies titles also. Some authors estimate that autoimmune diabetes recurrence may be responsible for half of the immunological pancreas graft losses, about 5%[21]. It is likely that this entity has been underdiagnosed and underevaluated.

In an initial prospective analysis of 65 SPKT with both grafts functioning performed in our unit, we noticed that one-third had positive pancreatic autoantibodies; some *de novo*, some with rising titres[22]. We could not correlate this positivity with acute rejection, HLA-mismatches, steroid withdrawal, or immunosuppressive drugs levels. Within the subgroup with positive pancreatic antibodies we found patients with the worst glycaemic profile, although this was not statistically significant. Our second study, into prospective determination of pancreatic autoantibodies in 135 SPKT[23], confirmed that these autoantibodies may remain positive or negative, or recur after transplantation. With such a larger sample we were able to demonstrate a negative impact of this positivity on pancreas graft function: higher fasting glucose levels, higher glycated haemoglobin (HbA1c) and lower C-peptide levels were registered in the subgroup with positive pancreatic autoantibodies. The odds of having these autoantibodies positive was 5.2 times higher among those with HbA1c > 5.6%, and 35% lower within those with higher C-peptide levels. Risk factors associated with the pancreatic autoimmune relapse did not emerge from this study, which encourages us to continue our search on this field. In a review article, we analysed the most interesting papers published on this theme[24]. Recent studies, namely regarding cellular immunity, have shown the role of the immune memory response and also the inability of immunosuppressive drugs currently used in organ transplantation to prevent this autoimmune process. Based on obtained data, several anti-T cell and anti-B cell therapies have been tried. To date, these attempts failed to prove sustained effectiveness in the treatment of this disease[25].

## ALLOIMMUNITY IN SPKT

Acute rejection incidence has decreased in several solid organ transplants and also in SPKT. The role of *de novo* donor-specific anti-HLA antibodies (DSA) emerging after kidney transplantation is quite well documented. However, there are scarce data about its relevance in SPKT[26,27]. Within a group of 136 SPKT we detected *de novo* DSA in 13.2%, after a median period of 3.3 years (from 0.4 to 8.7 years) post-transplantation[28]. Recipient younger age, pre-transplant (non donor-specific) HLA sensitization, mismatches in HLA-DR, and acute rejection were risk factors for DSA appearance. Acute rejection episodes of any graft, proven by kidney or pancreas biopsies, in particular vascular rejections, correlated with DSA emergence. Our data showed that DSA presence predicted the loss of each graft, independently, and loss of both grafts. The number of DSA detected, DSA against HLA class I+II, and their intensity, increased proportionally to the number of failed grafts. The median time between DSA appearance and graft loss was 10 months. Multivariate analysis revealed that DSA and acute rejection were independent predictors of graft loss: DSA-positive patients, but without evidence of

acute rejection, evolved more to graft failure than the DSA-negative. From these data we observed that *de novo* DSA screening, and the analysis of their characteristics, is helpful to identify patients at risk of graft failure also in SPKT. Nevertheless, the efficacy of the available therapeutic interventions is still unsatisfactory. At its date of publication, this was the study with the longest follow-up into DSA evaluation in SKPT, and the first reporting such results based also on pancreas biopsies.

## ADVANCED-GLYCATION ENDPRODUCTS (AGE) EVOLUTION AFTER SPKT

Increased AGE accumulation in diabetic patients is one of the most important pathways of microvascular injury[29]. AGE were also correlated with diabetic macrovascular disease[30]. After successful SPKT, patients restore normoglycaemia and renal function, two mechanisms that may decrease AGE production and deposition. However, this is an issue scarcely studied.

We conducted a prospective study to evaluate plasmatic and skin AGE evolution after SPKT[31]. Blood samples were collected on day 0, then at 3, 6 and 12 months after the transplant, in 20 patients. Carboxymethyllisine (CML), which is a well-known specific AGE, global AGE, and advanced oxidation protein products (AOPP) were analysed in plasma. Skin biopsies were collected on day 0 (during the surgery) and 12 months after SPKT. Immunochemistry with anti-AGE antibody was used to evaluate skin AGE deposits. There was an initial rise of CML, AGE and AOPP from 0 to 3 months, possibly associated to more intense inflammatory/infectious insults during this period. Thereafter, the markers progressively decreased. This decrease was statistically significant for CML and nearly significant for AOPP. Among several variables analysed, possibly interfering with AGE variation, only time on dialysis presented a nearly significant positive correlation with CML values.

The most common finding in skin biopsies regarding AGE immunostaining – comparing day 0 with 1 year post-transplant samples, for each patient – was a change from a cytoplasmic diffuse pattern to a peripheral pattern, saving the central cytoplasmic area[31]. A decrease on the AGE immunoreaction intensity was also observed in one-half of patients. Despite the short follow-up, we are able to report an AGE reduction in this early period (1 year after SPKT), at tissue and at plasma level. A subsequent study is planned to consubstantiate these data, in a larger sample with extended follow-up.

## CHANGES IN QUALITY OF LIFE (QOL) AFTER SPKT

Assessment of QoL in organ transplant programmes is often forgotten. If there is any transplant which can change QoL, it should be the pancreas-kidney transplant, which treats 2 severe diseases, diabetes and end-stage renal disease. Although the complex initial period after SPKT may hamper or delay the QoL gain, when patients overcome this period, the improvement tends to be very significant – more than that achieved with an isolated kidney transplant[32,33]. We have additionally addressed this issue in our SPKT population[34]. The QoL was assessed through two surveys: a generic one, the SF-36, and a more specific one, the GIQLI (gastrointestinal quality of life index), to evaluate gastrointestinal complaints, which are so frequently disabling for DM1 patients. Comparing pre-transplant status with last follow-up status, the results showed an impressive QoL gain at all levels: physical, social and psychological. The presence of two functioning grafts was predictor of greater QoL improvement. The health perception score rose from 40% at baseline to 80% after SPKT. Further, patients experienced a significant improvement in most gastrointestinal symptoms. Moreover, the rate of patients working or able to work increased considerably after the transplant.

Our experience, described above, leaves us with the firm conviction that SPKT is the best possible treatment for DM1 patients with end-stage renal disease, despite the initial morbidity and possible complications associated with the procedure. If these patients are able to be transplanted, we strongly recommend referring them to a pancreas-kidney transplant programme.

***Disclosure of Potential Conflicts of Interest:*** None declared.

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