



## Special article

## Pancreas transplant in Spain: Better late than...

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## A B S T R A C T

Pancreas transplant is the only method that enables diabetic patients to have a normal carbohydrate metabolism in the long-term. Its application in selected patients has shown to have patient survival rates, at 1 year of the graft, similar to those transplanted with other solid organs, such as kidney, heart, liver, etc. The indications are currently well established, with combined pancreas-kidney transplant being the most common, followed by pancreas transplant after a functioning kidney transplant and isolated pancreas transplant in pre-uraemic patients. In 2005, in Spain, under the auspices of the National Transplant Organisation (ONT), a consensus meeting was held with the scientific societies involved in this type of transplant, to standardise its indications and highlight its benefits in order to optimise the results of this transplant in our country. The most important conclusions of this consensus meeting are discussed in this short article.

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## Trasplante de páncreas en España, más vale tarde que...

## R E S U M E N

El trasplante de páncreas es el único método que permite normalizar a largo plazo el metabolismo hidrocarbonado en pacientes diabéticos. Su aplicación en enfermos seleccionados ofrece supervivencias del paciente y del injerto al año, similares a las del trasplante de otros órganos sólidos, como el riñón, el corazón, el hígado, etc. Las indicaciones están hoy bien establecidas, y el trasplante combinado páncreas-riñón es la más frecuente, seguida de trasplante de páncreas tras un trasplante renal funcionante, y del trasplante de páncreas aislado en pacientes preurémicos. En 2005 se celebró en España bajo los auspicios de la Organización Nacional de Trasplantes (ONT) una reunión de consenso con las sociedades científicas implicadas en este trasplante, para tratar de regular sus indicaciones, concienciar de su beneficio y, por tanto, optimizar en nuestro país los resultados de este trasplante. En este breve artículo se exponen las conclusiones más importantes de ese consenso.

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## Palabras clave:

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In 2001, in the editorial of the journal *Cirugía Española* entitled "Pancreatic transplantation in Spain: causes and solutions for a long-standing problem",<sup>1</sup> reference was made to the poor development of pancreas transplant in Spain compared to other countries in Europe. Spain is also prestigious in the field of solid organ transplants. The reasons behind limited activity in pancreas transplant were due to, among other causes, lack of coordination between the different groups of specialists involved. Amongst the possible solutions proposed, a consensus meeting was recommended between different scientific societies under the supervision of the Spanish Transplant Organisation (ONT).

Fortunately, in 2005 the ONT started a process of information and debate with all those involved in this issue: surgeons, endocrinologists, nephrologists, coordinators, administration agents, researchers, etc, represented by their respective societies. The final document dealt with criteria of indication, prioritisation, organ distribution, team movement, pancreas extraction for vascularised or islet transplant, and mechanisms for planning and approving centres in order to optimise treatment of diabetes in Spain.

The need for consensus was justified by the great advances in pancreas transplant, translated into better survival outcomes both for patient and graft. Furthermore, some important advances had occurred in research with pancreatic islets allowing their further clinical utilisation in control trials in selected groups.

So far the number of pancreas transplants performed worldwide in 2008 is 2797. Of these, more than half of them were performed in the United States; with a transplant rate of 4.2 per million inhabitants, against 2.3 in Spain for the same year, despite having almost 50% more donors by population rate.<sup>2</sup> Graft survival rate (insulin-free) is 85% the first year, according to the International Pancreas Transplant Registry, and about 70% to 5 years, overlapping rates from solid organs.<sup>3</sup> There are 11 hospitals approved for vascularised pancreas transplant in Spain at the moment. Seventy-four transplants were performed in 2003, 74 in 2004, 100 in 2005, 94 in 2006, 76 in 2007, and 104 in 2008.<sup>4</sup>

On the other hand, the approval of European guidelines (2001/20, 2003/63 EC, and 2004/23 EC) over quality and safety of cells and tissues, as well as over medicinal products and clinical trials, sets forth a new scenario in the European Community about issues involving utilisation of cells for therapeutic purposes.<sup>5,6</sup>

Although pancreatic islet transplant is still at a clinical trial stage, because of the new free-steroid immunosuppression protocols (Edmonton 2000), it began to be considered a real alternative in selected patients.<sup>7</sup> Despite technical and logistic difficulties of this type of transplant, pancreases continue to be processed for further research and clinical trials in at least 7 centres in Spain.

The conclusions arrived at in the consensus meeting held in Madrid were the following:

## 1. Type of donor

The recommended age for accepting a pancreas donor is between 10 to 50 years, a minimum weight of 30

kg and a body mass index (BMI) below 27.5 kg/m<sup>2</sup>. Of course, the donors required should have no infectious transmissible diseases, no malignant diseases, and no diabetic antecedents, alcoholism, acute arteriosclerosis, pancreatic traumatism, or pancreatic oedema at the moment of extraction, and they should not remit by administering albumin or mannitol. Moreover, prolonged stay in the ICU should be assessed individually, as well as prior hypotension episodes or cardiac arrest. Maximum ischaemia time should not exceed 16 h.

## 2. Extraction and preservation

There is general agreement on the convenience of having the same team extracting both liver and pancreas. The extraction technique is well documented with several possibilities for vascular reconstruction of pancreatic graft depending on whether the celiac artery will remain in the hepatic graft or not. When hesitant about some common vascular structure, the priority should be set on the hepatic graft, being this a vital organ. Extreme care should be taken with pancreas during multi-organ extraction, as pancreatic-duodenal graft is more sensitive than the liver to ischaemia, and, also, it should be remembered that during perfusion the pancreas may become injured by hyper-pressure. Preservation at 4°C using Wisconsin solution is of universal usage, although in case of using the pancreatic gland to isolate islets, the recommended preservation procedure is by double layer method.

## 3. Recipient selection

Pancreas transplant candidates are type 1 diabetic patients with over 20 years of evolution, with or without complications and fitting into 3 classic categories, although patients type 2 have been recently included.

*Diabetic patients type 1 with renal failure undergoing dialysis or pre-dialysis, indicated to be simultaneously transplanted for kidney and pancreas*

Although this is the most common type of transplant, the indication is not the same amongst different nephrology services due to different list inclusion criteria, not having a reference centre available nearby, and kidney competence from young donors with other special receptors (hyper-immunised, children), etc.

As there are no pancreas transplant reference centres in all the autonomous communities (CC. AA.) arrangements should be made by areas for this type of transplants, bringing those patients from communities lacking a pancreas transplant programme into other areas where such programmes exist, trying to integrate them as closely geographically as possible. Current indications are as follows:

a) patients with chronic renal failure for type 1 diabetes (peptide C <0.5 ng/mL);

- b) under 50 years of age; elderly patients should be individually assessed;
- c) absence of acute peripheral vasculopathy and coronary artery disease;
- d) absence of incapacitating motor or autonomic neuropathy;
- e) usual criteria for renal transplant;
- f) and absence of acute psychiatric or psychological disorders and of capacity to understand what a pancreas transplant implies with relation to post-surgery collaboration, complications that may occur, and treatment follow-up.

Amongst relative contraindications to be assessed individually are: patients younger than 18 and older than 50, recent retinal haemorrhage, active smoking, obesity with BMI  $>30 \text{ kg/m}^2$ , serology for HCV and HBV positive, and circulating cytotoxic antibodies  $>25\%$  (in these cases selecting a more suitable donor is required).

The method of choice for dialysis for these patients has to be haemodialysis, given the greater peritonitis incidence in pancreas transplant, although there is not contraindication in patients undergoing peritoneal dialysis treatment.

It is recommended to include candidates to simultaneous kidney-pancreas transplant in pre-dialysis situations in order to prevent organic and functional deterioration. Patients with renal failure not needing dialysis should be included in the waiting list on creatinine clearance  $<30 \text{ mL/min}$ .

#### **Diabetic patients with a previous functioning renal transplant**

The outcomes from previous functioning renal transplant (PAK, pancreas after kidney) have been gradually improving. In experienced centres, renal graft survival is higher with PAK than with isolated renal transplant. As a result, PAK should be offered to renal transplanted patients with diabetes type 1, who meet the same criteria as for simultaneous pancreas kidney transplant (SPK) and who, also, have their diabetes badly controlled.

The indications for this transplant would therefore involve diabetic patients meeting the following requirements:

- a) diabetes mellitus type 1 with previous renal transplant from living or cadaveric donor;
- b) unstable diabetes or poor metabolic control ( $\text{HbA}_{1c} > 8\%$ );
- c) deterioration of chronic lesions despite optimal treatment and after immunosuppression adjustments;
- d) tolerance to immunosuppression increase for PAK;
- e) pancreatic graft failure, after a pancreas-kidney transplant;
- f) and stable renal graft function in all the cases (creatinine clearance  $>40 \text{ mL/min}$ ).

#### **Diabetic patients with no renal failure and with evidence of progress of secondary complications PTA (pancreas transplant alone)**

An individualised indication is needed for patients with diabetes type 1 with no renal failure but with great lability to control blood glucose, as there is not as yet contrasted

evidence on transplant risk-benefit for this group. Indications for this type of patients are as follows:

- a) creatinine clearance  $>60 \text{ mL/min}$  and proteinuria  $<2 \text{ g/24h}$ ;
- b) frequent metabolic complications (hypoglycaemia, hyperglycaemia, ketoacidosis) requiring medical attention or threatening life;
- c) clinical or emotional problems with insulin therapy that turn out to be incapacitating;
- d) limitation of insulin therapy to prevent acute complications,
- e) and peptide C levels  $<0.48 \text{ ng/mL}$ .

#### **Patients with diabetes type 2 with great need of insulin**

At present, pancreas transplant in diabetes type 2 represents 6%–7% of the cases at the International Pancreas Transplant Registry. Survival both of patients and grafts overlap those of diabetes type 1, provided that the selection is made complying with the following criteria:

- a) five or more years of insulin treatment;
- b) insulin needs not higher than a unit/kg/day;
- c) peptide C  $<10 \text{ ng/mL}$ ;
- d) and BMI  $<30 \text{ kg/m}^2$ .

#### **Indications for islet transplant**

Indications for islet transplant are much more limited than for vascularised transplant. This transplant is basically recommended for those patients with very labile diabetes and with risk of acute hypoglycaemias. Given that it is a procedure staging clinic research, it should be set within a clinical trial. The requirements for receptor of pancreatic islet transplant are age  $>18$  and  $<65$ , peptide C  $<0.5 \text{ ng/mL}$ , creatinine clearance  $>70 \text{ mL/min}$ , BMI  $<28 \text{ kg/m}^2$ ,  $\text{HbA}_{1c} < 12\%$ , and insulin needs  $<0.7 \text{ U/kg/day}$ .

## **4. Organisation and planning: organ distribution and prioritisation criteria**

To optimise this type of transplant on the national level, one of the most important decisions approved by consensus is the prioritisation of all units of pancreas-kidney transplant over kidney alone transplant in adult patients. This is why every centre has to organise its own programme or set allocation of possible receptors from one community to another through management of an autonomic coordinator.

The ONT is the organisation identifying pancreas donors potentially valid and is in charge of offering the authorised transplant team nearest to the donor's place. The implanting team should perform the extraction, unless mediating exceptional circumstances, such as pancreas extraction from donor by an experienced transplant team at the donor's hospital, foreign to the transplanting centre. Whenever there is a potential pancreas-kidney donor, this should be considered for combined transplant,

be he or she the transplanting hospital donor or any other, in the same autonomous community as in the rest of the country (this would condition setting inter-change or return regulations between teams and autonomous communities<sup>8</sup>).

Each community with transplant teams should set their own mechanisms to prioritise possible receptors; the order of organs is: a) receptors to double transplant SPK; b) subsequent receptors of PAK and PTA, analysed individually; and c) lastly, when there are no organ receptors, the organ should be destined to islet receptors.

To avoid discrepancies at the moment of interpreting priorities in pancreas potential donors, some guiding criteria have been described between organ/islet depending on age and donor's cause of death, such as for example:

- Donor's age <45 years deceased by cerebrovascular accident CVA or craneoencephalic traumatism (CET) should have preference for organ transplant and be assessed for islet isolation if donor is not valid for organ transplant.
- Donor's age >45 years and <55 years deceased by CET, preference for organ transplant.
- Donor's age >45 years and <70 years deceased by CVA, for islet isolation.
- Donor's age >55 years and <70 years deceased by CET, for islet isolation.

When apart from the pancreas also the kidney has been donated, return criteria established are the following: no return applies within the referenced community; return applies if not within referenced community, and return applies within the transplanting community. Returns are done through the ONT, always with the kidney from the same group and with donors <45 years. Some groups have voiced ethical discrepancies for using kidneys from young donors for this type of diabetic patients to the detriment of other patient groups in a better biologic situation.

With respect to pancreatic islet transplant we should remember that when starting an islet transplant clinic programme, 2 to 3 pancreas need to be processed to obtain enough islets viable for a transplant. When assessing pancreas availability for islets (which would mean the rest of the pancreas not used for solid organ transplant and some others that, due to their age, are not accepted for solid organ transplant) together with the necessary experience that should be acquired for this difficult processing tasks, limiting the centres in Spain to isolate islets for clinical orientation would be reasonable. Doing otherwise would lead to inefficient use of resources that, in this case, have high costs, and besides, the minimum activity of islet processing would not be achieved to guarantee processing quality. As a result, in order to make the most of it, the proposal consists in processing centres every 8-10 inhabitants. This would mean 4 to 5 centres for Spain.

Other aspect would be the adequate number of centres for implant, which is less complicated than processing tasks. To begin with, 4 to 5 implant centres could be managed (where the processing banks are located) and once enough experienced has been achieved, then proceed to enhance

the number of centres and have the islets "travel" from the processing centre to the implant centre. The main objective is to achieve national consensus on the indications and start, as soon as regulations permit, the clinical trials to assess viability and develop training in the isolation and implantation centres.

In the end, to record both activity and results, the creation of Pancreas and Islet Transplant Spanish Registry was proposed.

## Conclusions

We believe that the application of this consensus in Spain between different scientific societies and working groups has been a great incentive to widespread development of pancreatic transplant. In only five years the transplant rate has gone from 1.2 to 2.3 per million people. As it was the case with hepatic transplant that entailed a change of mentality in hepatic-therapies and their therapeutic orientation, pancreas transplant has to consolidate itself as a procedure of choice in the diabetic patients selected along the particularities referred to in the section on indications. For this reason, we as surgeons and members of teams involved in the issue should congratulate ourselves on the ONT initiative and thank for their efforts to all those professionals that took part in this discussion.

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