

## Transplantation for type 1 diabetes mellitus. Whole organ or islets?

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### Abstract

Two types of transplants are offered to patients with complicated insulin dependent diabetes mellitus: a) whole pancreas transplantation, b) pancreatic islet transplantation. A total of 29000 whole pancreas transplantations and 1500 islet transplantations have been performed worldwide until today. Patient survival for whole pancreas recipients is 85% five years after transplantation, whereas very few islet studies focus on patient survival. Graft survival for whole pancreas recipients is 90%, 70% and 45%, at one, five and ten years after transplantation respectively. On the other hand, only 44% of islet recipients are still insulin free, one year after engraftment. If the definition of a successful islet transplantation is not insulin independence but production of C-peptide, then 80% of the same islet recipients have a functioning graft by the end of the first post-transplant year. It is a known fact that whole pancreas transplantation has significant complications. The most common complications after whole organ transplantation include technical failures, acute rejection and CMV infection, whereas islet transplantation is associated with portal vein thrombosis, bleeding, emergency exploratory laparotomy, liver steatosis and rapamune-induced mouth ulcers. The cumulative cost of a whole organ transplantation is about \$40,000. On the other hand, the cumulative cost of a pancreatic islet transplant is estimated to be higher than \$120,000. Whole organ transplantation halts the late complications of diabetes, namely vasculopathy, retinopathy, nephropathy and neuropathy. Although similar claims are made for islet transplantation, its impact on long-term diabetic complications is possible but not proven. Currently, in North America, lean young donors are utilized for whole organ transplants, whereas overweight or older donors are utilized for islet transplants. In conclusion, although islet transplantation is an extremely promising therapy and probably the way of the future, whole organ transplant is still the gold standard according to evidence-based medicine. Hippokratia 2009; 13 (1): 6-8

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The treatment of diabetes mellitus is greatly affected by the remarkable achievements in the area of transplantation the last 25 years.

The types of transplants offered to patients with complicated insulin dependent diabetes mellitus are: a) whole pancreas transplantation, and b) pancreatic islet transplantation. Naturally, these two therapeutic modalities are under constant comparison.

### Data Source

The International whole Pancreas Transplant Registry is located in Minneapolis, USA. The relevant website is: [www.iptr.umn.edu](http://www.iptr.umn.edu).

The International Islet Transplant Registry is located in Giessen, Germany. The relevant website is: [www.med.uni-giessen.de/itr](http://www.med.uni-giessen.de/itr). A medline search (including year 2007) has yielded 295 (90 randomized) and 63 (10 randomized) clinical studies for whole pancreas and islet transplantation respectively. Approximately 65% of those are dealing with immunological aspects of the transplant.

### Raw Data

A total of 29000 whole pancreas transplantations have been performed up to date. Twenty one thousand five hundred of those have been performed in North America. On the other hand, 1500 islet transplantations have been performed worldwide. More than half have been performed in Europe<sup>1,2</sup>. There are 131 centers performing whole pancreas transplantation in North America. Twenty of those perform more than 20 transplants per year. Half of the whole pancreas transplants are performed in 19 centers<sup>1</sup>. On the other hand, there are 47 centers that perform islet transplantations worldwide (18 of those perform islet auto-transplants too). Eleven of those (7 in Europe and 4 in North America) perform more than 20 transplants per year. More than half of the islet transplants have been performed by these 11 centers. The centers of Giessen and Edmonton have recently reached 100 islet transplantations each<sup>3</sup>.

Whole pancreas transplantation is sub-categorized as simultaneous pancreas-kidney transplantation (SPK), pancreas after kidney transplantation (PAK) and pancreas transplantation alone (PTA). It is also categorized, with

respect to exocrine drainage, as enteric drained (ED) or bladder drained (BD). Finally, it is categorized with respect to venous outflow as systemic (SV) or portal (PV). The most commonly performed whole pancreas transplantation is the SPK/ED (81%, n = 18300), 5 out of 6 of which are drained systemically<sup>4</sup>. Patient survival, initial graft survival<sup>5</sup> and complications<sup>4</sup> are comparable among the various whole pancreas transplantation sub-categories. So, to facilitate comparison with islet transplantation, the data that will be used derive from the most commonly performed sub-category of whole pancreas transplantation (i.e. SPK/ED).

Pancreatic islet transplantation is performed in the context of allo-transplantation and auto-transplantation<sup>2</sup>. Allotransplantation is sub-categorized into simultaneous islet-kidney transplantation (SIK), islet after kidney transplantation (IAK) and to islet transplantation alone (ITA). Allo-transplantations are the ones most commonly performed (73%, n=1200), 700 of which were performed after the introduction of the Edmonton protocol<sup>6</sup>. Therefore, in order to obtain an objective comparison with whole pancreas transplantation, the data that will be used derive from allo-transplantations that were performed under the Edmonton protocol.

#### Patient survival

Patient survival for whole pancreas recipients is 95% and 85% one and five years after transplantation respectively<sup>1</sup>. On the other hand, very few islet studies focus on patient survival. There is only one small retrospective study (n=11) in which recipient 2-year survival was 100%<sup>7</sup>. Even studies reviewed from relatively large centers failed to provide data on patient survival. In a recent publication<sup>8</sup> of 65 islet transplant recipients, only 44 were still followed after 5 years. Information on the outcome of the remaining 21 was not provided. Finally, patient survival with functioning islets is reported to be as high as 90%, more than five years after transplant<sup>9</sup>. However, the fact that most of the islet grafts failed, significantly reduced the overall (with an intention to treat) patient survival to 67%<sup>9,10</sup>.

#### Graft survival

Graft survival for whole pancreas recipients, as measured by insulin independence, is 90%, 70% and 45%, at one, five and ten years after transplantation respectively<sup>1</sup>. On the other hand, only 44% of islet recipients transplanted at the centers participating in the International Transplant Registry of Giessen are still insulin free, one year after engraftment<sup>2</sup>. If the definition of a successful islet transplantation is not insulin independence but production of C-peptide, then 80% of the same islet recipients have a functioning graft by the end of the first post-transplant year<sup>2</sup>. These results were recently reproduced by an international, multicenter study which incorporated the survival data of the 9 largest islet transplant centers in the world<sup>11</sup>. Furthermore, only 10% the Edmonton islet

recipients retained insulin independence five years after engraftment<sup>12</sup>. Finally, there is only one retrospective, single-center study comparing head-to-head whole organ versus islet transplantation. According to this study two year graft survival was 65%, 55% and 20% for whole pancreas (insulin independence), islet (C-peptide production) and islet (insulin independence) transplants respectively<sup>7</sup>.

#### Complications

It is a known fact that whole pancreas transplantation has significant complications. The most common include technical failures (thrombosis, bleeding, leak) with a rate of 6.5%, acute rejection in 12% of the cases and CMV infection with a rate of 10%<sup>4</sup>. However, despite the common perception to the contrary, islet transplantation is also associated with complications. The most common ones include portal vein thrombosis, bleeding, emergency exploratory laparotomy, liver steatosis and rapamune-induced mouth ulcers with rates of 5%, 14%, 8%, 23% and 77% respectively<sup>13</sup>.

#### Cost

The hospital cost for a whole organ pancreatic transplant is approximately \$20,000. The procurement cost of a pancreatic graft is approximately \$20,000. Therefore, the cumulative cost of a whole organ transplantation is about \$40,000. On the other hand, the hospital cost for an islet transplantation is approximately \$5,000. The procurement cost of a pancreatic graft is approximately \$20,000. Enzymatic graft treatment for islet isolation costs about \$20,000. One out of three attempts for islet isolation is not successful. Moreover, two or more processed grafts are required for a successful islet transplant<sup>6</sup>. Therefore, the cumulative cost of a pancreatic islet transplant is estimated to be higher than \$120,000, i.e. three times than that of the whole organ<sup>7</sup>.

#### Conflicting reports

According to Venstrom J et al<sup>14</sup> pancreas after kidney and pancreas alone transplant recipients were thought to have higher mortality than patients on the pancreas waiting list, with 1.57 relative risk of death (p < .001). However, a different analysis of the same patient cohort<sup>15</sup> revealed that first year survival of PAK and PAT recipients was higher than that of patients on the pancreas waiting list (90.5% vs 87.3%).

The high percentage (80%) of insulin independence initially reported one year after islet transplantation, has created great interest in the use of islet transplantation for the treatment of complicated type 1 diabetes and represents a significant improvement over earlier protocols. Subsequently, an intensive effort to generalize these results returned somewhat more modest data. Only three out of the nine largest islet transplantation centers achieved a 65% insulin independence rate one year after the engraftment, with many experienced centers reporting much lower success rates<sup>16</sup>.

There is a tendency to consider an islet transplantation successful if there is production of C-peptide, regardless of achievement of insulin independence. Although the presence of C-peptide reduces hypoglycemic unawareness episodes and normalizes glucose fluctuations, glucagon release is still blunted in insulin dependent islet recipients, a fact that still leads to some severe hypo/hyperglycemic episodes<sup>12</sup>.

Finally, it is well established that whole pancreas transplantation halts the late complications of diabetes, namely vasculopathy, retinopathy, nephropathy and neuropathy<sup>17-19</sup>. Although similar claims are made for islet transplantation<sup>20-22</sup> the truth of the matter is that its impact on long-term diabetic complications is possible but not proven<sup>10</sup>.

### The North America situation

Donors younger than 50 years of age and with a body mass index less than 30 are more suitable for whole pancreas donation<sup>1</sup> and use of these pancreata is associated with fewer technical complications (RR= 3.62, p = .007). On the contrary, overweight donors, or those older than 50 years are more suitable for islet donation, because their pancreata are easier to process<sup>4</sup>.

Since most of whole pancreas and almost half of islet transplants are performed in United States and Canada, the North America situation is quite indicative of the transplantation status for type 1 diabetes mellitus. Whole pancreas transplantation may be limited by availability of acceptable donors. Currently, in North America, lean young donors are utilized for whole organ transplants, whereas overweight or older donors are utilized for islet transplants<sup>7</sup>.

### Conclusion

Islet transplantation is an attractive alternative for restoring insulin secretion in patients with type 1 diabetes mellitus. However, although it is clearly less invasive, the success rate in terms of insulin independence or C-peptide secretion is still much lower than the ones achieved by whole pancreas transplantation. Therefore, even if islet transplantation is an extremely promising therapy and probably the way of the future, currently, whole organ transplant is still the gold standard according to evidence-based medicine.

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