Pancreatic Islet Cell Transplantation: A Not So Sweet Option

University of Colorado Department of Surgery Grand Rounds

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History

- 1966: First Pancreatic Tx performed at the University of Wisconsin
- 1980: International Pancreatic Tx Registry
  - 1-year graft survival rate of 21%
  - 1-year patient survival rate of 67%
- 1998: UW performed largest study showing long-term success of pancreas-kidney transplants
  - 10-year patient survival rate of 76.3%
  - 10-year maintained pancreatic function at 67.2%
History (Cont)

- Charles Pybus first attempted to graft pancreatic tissue
- In 1967, Paul Lacy discovered a collagenase-based method to isolate islet cells
- First human islet transplantation in 1974
- Human Islet transplantation trials in mid ’80s were unsuccessful
- First successful Islet transplantation occurred in 1990 at the University of Pittsburgh
- In 2000, Edmonton protocol was introduced and increased short term success
Islet Cell Transplant

Donor

Recipient with type 1 diabetes

2 – 4 Pancreata

5,000 - 11,000 Islet Equivalents/kg

Percutaneous Transhepatic Injection

Recipient

Islets in pancreas

Isolated Islets

Islet in portal vein

Once infused into the recipient’s liver, islet cells release the insulin
Criteria for Pancreas Alone and Islet Cell Transplantation

- Absence of indications for kidney transplantation
- A history of frequent, acute and severe metabolic complications requiring medical attention
- Clinical and emotional problems with exogenous insulin therapy that are so severe as to be incapacitating
- Consistent failure of insulin-based management to prevent acute complications

What’s in the News

- “Islet cell transplantation has greater than 80 – 90% success rate in achieving insulin independence.”
- “Results are closely approaching that of whole-pancreas transplantation.”
- “Insulin Independence from islet transplantation have long-lasting results.”
- “Islet transplantation can achieve near-normal glycemic control.”
Collaborative Islet Transplant Registry

CITR, Collaborative Islet Transplant Registry 2007 Scientific Summary.
Prevalence of Insulin Status and Detectable Fasting C-Peptide

Post Last Infusion
Islet Alone Recipients

Recient Status
- Insulin Independent
- Insulin Dependent with Detectable Fasting C-peptide
- No Detectable Fasting C-peptide
- Missing Data

CITR, Collaborative Islet Transplant Registry 2007 Scientific Summary.
CITR, Collaborative Islet Transplant Registry 2007 Scientific Summary. 
Post Last Infusion

- Pre Inf 1: N=292
- Month 6: N=277
- Year 1: N=250
- Year 2: N=192
- Year 3: N=140

Legend:
- No hypoglycemic episodes
- Having episodes and aware
- Partial awareness
- Hypoglycemia unawareness
- Missing data for recipient without islet graft function
- Missing data for recipient with islet graft function

CITR, Collaborative Islet Transplant Registry 2007 Scientific Summary.
Complications

- **Hypoglycemia**
  - Prior (76-87%)
  - Year 1 (5-20%)
  - Year 3 (9-43%)

- **Adverse Events**
  - 65% experienced adverse event in 1st year
    - 32.5% related to immunosuppression
    - 28.4% related to infusion procedure
  - 41% experienced one or more serious adverse events
    - 26.5% related to immunosuppression
    - 45.5% related to infusion procedure

CITR. Collaborative Islet Transplant Registry 2007 Scientific Summary.
Complications

- Adverse events recorded by Edmonton Group showed that they were higher than previously thought.

Table 1. Adverse events associated with clinical islet transplantation

<table>
<thead>
<tr>
<th>Procedure related (%)</th>
<th>Immunosuppressive related (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elevated liver enzymes (50)</td>
<td>Oral ulcers (95)</td>
</tr>
<tr>
<td>Abdominal pain (50)</td>
<td>Anemia (60)</td>
</tr>
<tr>
<td>Nausea/vomiting (50)</td>
<td>Diarrhea (50)</td>
</tr>
<tr>
<td>Fatty liver (long term) (20)</td>
<td>Weight loss (50)</td>
</tr>
<tr>
<td>Peritoneal hemorrhage (15)</td>
<td>Fatigue (50)</td>
</tr>
<tr>
<td>Portal vein thrombosis (4)</td>
<td>LDL elevation (50)</td>
</tr>
<tr>
<td>Gallbladder puncture (3)</td>
<td>Hypertension (50)</td>
</tr>
</tbody>
</table>

Note: Based upon findings published by the Edmonton group (36,41) and adapted from Paty (www.endotext.com).

aGFR = glomerular filtration rate.
International Trial of the Edmonton Protocol

- International trial to explore the feasibility and reproducibility of islet transplantation of a single common protocol

- 36 Type I Diabetic Subjects underwent Islet Transplantation 9 International Sites
  - 44% had insulin independence at 1 year
  - 28% had partial function
  - 28% had complete graft loss

International Trial of the Edmonton Protocol

- Success rates have been replicated inconsistently even with a standardized protocol
- Only 3 centers with the most experience had reasonable success rates in reaching the primary end point
Five-year Follow-up After Clinical Islet Transplantation

- 65 pts transplanted at the University of Alberta
- 52 of those had 2 transplants
- 11 of those had 3 transplants
- Pts were followed every 1-6 months for 5 years and glucose control and adverse events were reviewed

Five-year Follow-up After Clinical Islet Transplantation

Five-year Follow-up After Clinical Islet Transplantation

Five-year Follow-up After Clinical Islet Transplantation

- Post-Transplant Effects on Diabetic Complications
  - Rise in median serum creatinine (80 → 84)
  - Decrease in creatinine clearance (1.8 → 1.6)
  - Increase in albumin excretion rate
  - Increase in number of pts with macroproteinuria
  - More pts taking HTN meds (64% → 85%)
  - More pts taking more than one HTN meds (6% → 42%)
  - More pts taking lipid-lowering meds (23% → 83%)
  - Increase in triglyceride levels

University of Wisconsin’s Experience with SPK Transplants

- 500 SPK Transplants
  - World’s Largest Published Experience with SPK Transplantation
- Confirmed that SPK is a highly successful procedure for selected diabetic patients with renal failure

# Short and Long-Term Results of SPK Transplantation

<table>
<thead>
<tr>
<th></th>
<th>1 year</th>
<th>5 year</th>
<th>10 year</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient Survival</strong></td>
<td>96.4%</td>
<td>88.6%</td>
<td>76.3%</td>
</tr>
<tr>
<td><strong>Kidney Function</strong></td>
<td>88.6%</td>
<td>80.3%</td>
<td>66.6%</td>
</tr>
<tr>
<td><strong>Pancreas Function</strong></td>
<td>87.5%</td>
<td>78.1%</td>
<td>67.2%</td>
</tr>
</tbody>
</table>

Patient and Graft Survival of Pancreas Transplant Alone

<table>
<thead>
<tr>
<th></th>
<th>1 Year</th>
<th>3 Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient Survival</td>
<td>97.5%</td>
<td>90.8%</td>
</tr>
<tr>
<td>Graft Survival</td>
<td>78.3%</td>
<td>64.4%</td>
</tr>
</tbody>
</table>

Source: 2005 OPTN/SRTR annual report
Whole Pancreas vs. Islets

University of Pennsylvania Study

- Compared 30 Whole Organ Pancreas Transplants to 13 Isolated Islet Transplants

<table>
<thead>
<tr>
<th>TABLE 1. Characteristics of Pancreas and Islet Graft Recipients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Whole Organ Pancreas Recipients</strong></td>
</tr>
<tr>
<td>SPK</td>
</tr>
<tr>
<td>25</td>
</tr>
<tr>
<td>Mean age at transplant</td>
</tr>
<tr>
<td>39</td>
</tr>
<tr>
<td>Female gender</td>
</tr>
<tr>
<td>36%</td>
</tr>
<tr>
<td>White race</td>
</tr>
<tr>
<td>64%</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
</tr>
<tr>
<td>23.5</td>
</tr>
<tr>
<td>Duration of diabetes</td>
</tr>
<tr>
<td>26</td>
</tr>
<tr>
<td>History of dialysis</td>
</tr>
<tr>
<td>60%</td>
</tr>
<tr>
<td><strong>Isolated Islet Recipients</strong></td>
</tr>
<tr>
<td>ITA</td>
</tr>
<tr>
<td>9</td>
</tr>
<tr>
<td>Mean age at transplant</td>
</tr>
<tr>
<td>42</td>
</tr>
<tr>
<td>Female gender</td>
</tr>
<tr>
<td>44%</td>
</tr>
<tr>
<td>White race</td>
</tr>
<tr>
<td>100%</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
</tr>
<tr>
<td>24.2</td>
</tr>
<tr>
<td>Duration of diabetes</td>
</tr>
<tr>
<td>28</td>
</tr>
<tr>
<td>History of dialysis</td>
</tr>
<tr>
<td>0%</td>
</tr>
</tbody>
</table>

Whole Pancreas vs. Islets

**Whole Pancreas vs. Islets**

<table>
<thead>
<tr>
<th>Complication</th>
<th>SPK</th>
<th>PAK</th>
<th>Total (%)</th>
<th>ITA</th>
<th>IAK</th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>25</td>
<td>5</td>
<td>30</td>
<td>9</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Death</td>
<td>1</td>
<td>0</td>
<td>1 (3.3)</td>
<td>0</td>
<td>0</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Death</td>
<td>1</td>
<td>0</td>
<td>1 (3.3)</td>
<td>0</td>
<td>0</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Patients requiring post-transplant surgery</td>
<td>5</td>
<td>2</td>
<td>7 (23)</td>
<td>0</td>
<td>1</td>
<td>1 (7.7)</td>
</tr>
<tr>
<td>Transfusion</td>
<td>10</td>
<td>3</td>
<td>13 (43)</td>
<td>0</td>
<td>1</td>
<td>1 (7.7)</td>
</tr>
<tr>
<td>Transfusion</td>
<td>10</td>
<td>3</td>
<td>13 (43)</td>
<td>0</td>
<td>1</td>
<td>1 (7.7)</td>
</tr>
<tr>
<td>Abcess drainage</td>
<td>2</td>
<td>1</td>
<td>3 (10)</td>
<td>0</td>
<td>0</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Rejection</td>
<td>3</td>
<td>0</td>
<td>3 (10)</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Rejection</td>
<td>3</td>
<td>0</td>
<td>3 (10)</td>
<td>0</td>
<td>0</td>
<td>0 (0)</td>
</tr>
<tr>
<td>CMV infection</td>
<td>3</td>
<td>0</td>
<td>3 (10)</td>
<td>0</td>
<td>0</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Mouth ulceration</td>
<td>0</td>
<td>0</td>
<td>0 (0)</td>
<td>9</td>
<td>1</td>
<td>10 (77)</td>
</tr>
<tr>
<td>Hepatic steatosis on imaging</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>3</td>
<td>0</td>
<td>3 (23)</td>
</tr>
</tbody>
</table>

Whole Pancreas vs. Islets

Supported Benefits of Whole Pancreas Transplantation

- Prevents and Reverses Diabetic Nephropathy
  - Compared Kidney Bx’s at 4 years of SPK recipients and diabetic KTA recipients
    - All SPK recipients had normal GBM widths
    - Most KTA recipients had increased GBM widths
  

  - Comparison of Kidney Bx’s 5 and 10 years after PTA
    - At 5 years, there was no amelioration of diabetic nephropathy lesions
    - At 10 years, there was reversal of diabetic glomerular lesions in all who had functioning pancreatic grafts

Supported Benefits of Whole Pancreas Transplantation (Cont)

- Cardiovascular Benefits
  - SKP recipients were found to have decreased levels of von Willebrand’s factor, fibrinogen, TG, D-Dimers, and homocysteine when compared with KTA recipients 3 years after transplantation


  - Study comparing echocardiogram results in SPK recipients to KTA recipients before and 1 year post transplantation
    - SPK recipients had greater decrease in left ventricular mass and greater normalization of diastolic dysfunction

Supported Benefits of Whole Pancreas Transplantation (Cont)

Polyneuropathy
- 115 Pancreas Tx pt’s vs. 92 Diabetic controls
  - 60% Improvement in motor
  - 50% Improvement in sensory
  - 35 – 40% Improvement in autonomic
  - Neurologic evaluation demonstrated a general trend toward improvement in the motor and sensory nerve conduction studies a 1 year and autonomic function at 5 years

Supported Benefits of Whole Pancreas Transplantation (Cont)

- Overall Lifetime Gained for SPK patients is 23.4 years
  - 18 – 29 years old = 48.8 years
  - 40 – 49 years old = 18.7 years


- Improvement in Quality of Life After Pancreas Transplantation
  - Freedom from insulin
  - Avoidance of Hypo and Hyperglycemia
  - More positive health perceptions, improved social interaction and increased vitality/energy are significantly associated with successful pancreatic transplants

Shortcomings of Islet Transplantation

- May require up to 4 donor pancreata for one recipient
  - Only 50 -70% of all islet isolations lead to transplantable islet preparations
  - Most recipients require 2 or more islet infusions for insulin independence at 1 year
  - Leads to increased costs
- Reported success rates are not duplicated at other centers
- Graft Failure occurs earlier in islet transplantation than whole pancreas transplants
  - Inability to histologically diagnose and treat islet rejection
Shortcomings of Islet Transplantation

- Islet Transplant Alone is associated with worsening kidney function
- Insulin Independence does not last long enough to benefit in prevention and reversal of most diabetic complications
Conclusion

“Not much can be said about the principles of grafting, but it seems that until we are able to understand them (and I feel we do not understand them at present, especially the chemical factors), then we must continue to fail in such operations, although they may appear the most rational treatment for the diseases for which they were attempted”

- Pybus