Islet Transplantation in Type 1 Diabetes

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Objectives

- Describe the rationale for pancreatic islet transplantation
- Discuss the goals of islet transplantation
- Summarize the clinical outcomes in islet transplant recipients
- Review the patient selection for islet transplantation

Limitations of insulin for the treatment of type 1 diabetes

- Does not mimic physiologic insulin secretion
  - Variable absorption
  - Pronounced peaks
  - Less than 24-hour duration of action
- Can cause unpredictable hypoglycemia
  - Major factor limiting the achievement of euglycemia
  - Life-threatening consequence of insulin therapy

Physiologic insulin secretion 24-hour profile

**Diabetes Control and Complications Trial (DCCT)**

- Microvascular – risk reduction
  - Retinopathy – 63% \(p<0.002\)
  - Nephropathy – 54% \(p<0.04\)
  - Neuropathy – 60% \(p<0.002\)
- <5% of persons were able to achieve an A1C <6.1%
- Intensive insulin therapy group had 3-fold increased risk of hypoglycemia


**Alternatives to exogenous insulin therapy**

- The goal of treatment for type 1 diabetes is to provide physiologic insulin delivery
- Pancreas transplantation is invasive with significant risk of complications including death
- Transplantation of pancreatic islets can provide physiologic insulin replacement in a less invasive procedure

**The balance between prevention of complications and development of hypoglycemia: DCCT**

**Goals of islet transplantation**

- Insulin-independence *
- Sustained insulin secretion (positive C-peptide)
- Halt progression of diabetes complications
- Improvement in quality of life
  - Amelioration of severe hypoglycemia
  - Improvement in glycemic lability
- In renal transplant recipients, to protect the transplanted kidney from hyperglycemia

Edmonton protocol for islet transplantation

- First to achieve 100% insulin independence rates at one year
- Novel immunosuppression
  - Steroid-free
  - Reduced calcineurin inhibitor use
- Better isolation techniques
- Large number of islets: avg 11,547 IEQ/kg usually requiring 2-3 islet infusions

Shapiro JAM, NEJM 2000, 343:230-238

Islet transplant graft survival – 5 year follow-up

- At 5 years only ~10% remained insulin independent
- 80% have detectable C-peptide


C-peptide and diabetes control after islet transplantation

- Failed
  - Partial graft function
- Full graft function

* p = 0.025


Glycemic lability in C-peptide positive patients – CGMS®

Paty BW, et al., Diabetes Tech and Therapeutics 2006; 8:165-173
Hypoglycemia after islet transplant

Diabetes complications data after islet transplantation

Comparison of patients with type 1 diabetes receiving islet transplantation with those on intensive insulin therapy resulted in:

- Improved glycemic control: A1c 6.7% vs. 7.8% (p<0.001)
- Halted retinopathy progression: 0/51 vs. 10/82 eyes (p<0.01)
- Slower rate of decline in GFR
- Trend toward improved nerve conduction

Quality of life improvement – islet transplantation

- Hypoglycemia Fear Survey
- Change from baseline in hypoglycemia-related anxiety

Summary of outcomes for islet transplantation

- <10% insulin-independence long-term
- 80% remain C-peptide positive long-term
- Improved hemoglobin A1c
- Improvement in glycemic lability
- Fewer episodes of hypoglycemia and improved hypoglycemia awareness
- Stabilization of some diabetes complications
- Improvement in quality of life
Patient selection

- Risk-benefit ratio: identify those that will benefit from a transplant over traditional insulin therapy given the risks of the procedure and immunosuppression
- Patient selection is also limited due to lack of availability of pancreata for widespread application and the high cost of the procedure

Who should be considered for islet transplant referral?

- Patients with type 1 diabetes and a stable kidney transplant
- Patients with type 1 diabetes without a kidney transplant who have:
  - Poor quality of life related to hypoglycemic unawareness and/or glycemic lability
  - Failure of intensive insulin therapy to prevent progression of diabetes complications

![Hypoglycemia Score Table]

<table>
<thead>
<tr>
<th>Question</th>
<th>Always (A)</th>
<th>Sometimes (R)</th>
<th>Never (E)</th>
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</thead>
<tbody>
<tr>
<td>1) How often in the past month have you had readings &lt; 70 mg/dl?</td>
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<tr>
<td>2) How often in the past month have you had readings &lt; 50 mg/dl?</td>
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<td>3) How often in the past month have you had readings &lt; 40 mg/dl?</td>
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<td>4) How often in the past month have you had readings &lt; 30 mg/dl?</td>
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<tr>
<td>5a) How often in the past month have you had readings &lt; 70 mg/dl with symptoms?</td>
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<tr>
<td>5b) How often in the past month have you had readings &lt; 70 mg/dl without symptoms?</td>
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</tbody>
</table>

Additional patient considerations for islet transplantation

- Undetectable C-peptide
- Demonstrated efforts to control their diabetes through intensive insulin therapy
- Age 18-65 years old
- Low daily insulin requirements (<50u/day)
- No medical conditions that would make transplantation potentially unsafe or unsuccessful

Diabetes Care 18:517, 1995
What should my patients know?

- Islet transplantation can be beneficial in select patients with type 1 diabetes and severe glycemic lability, hypoglycemic unawareness, and recurrent hypoglycemia even in those who do not achieve full graft function.
- Benefits include improved glycemic control, reduced frequency of hypoglycemia, and halted progression of some vascular complications.
- Long-term insulin independence is only achieved in a small percentage of patients.

Objectives

- Describe the rationale for pancreatic islet transplantation.
- Discuss the goals of islet transplantation.
- Summarize the clinical outcomes in islet transplant recipients.
- Review the patient selection for islet transplantation.
- Describe the differences between pancreas and islet transplantation.
- Describe the procedure.

Islet Transplantation in Type 1 Diabetes

Amer Rajab, MD, PhD
Associate Professor of Surgery
Director, Pancreas & Islet Transplantation,
Comprehensive Transplant Center
Ohio State University Medical Center

Tissue replacement: whole pancreas or islet transplantation is currently the only way to restore physiologic glycemic control.
## Survival

- 10-year patient survival
- Non diabetic kidney recipient 72%
- Diabetic kidney recipient 37%
- K/P recipient 60%
- K/P recipient with pancreas loss 33%
  - Tyden et al.

## The Pancreas

- The pancreas is two organs
- The exocrine tissue = 80-90%
- The endocrine tissue = islets of Langerhans (2%)
- Diabetes: Dysfunction of the islets only
Statistics

- Number of transplant centers performing pancreas transplant: 107
- Total number of pancreas transplants: 17,888
- The total prevalence of diagnosed Insulin Dependent Diabetes Mellitus (IDDM) in the United States (all ages, 2005) is approximately 1,400,000-2,800,000 people


Statistics

- OSU (1988-2010): 856 total pancreas transplants
  - K/P: 756
  - Pancreas: 110
- Graft survival:
  - One year: 82% (5 year 71%)
- Patient survival
  - One year: 93% (5 year 90%)

Transplant center ranking by total number of pancreas transplants

National Data (OPTN)
**Anatomy of the Pancreas**

- 75-125 g
- 15-20 cm long
- 80-90% Exocrine: acinar cells and ductular network
- 2% Endocrine: islets of Langerhans
- Remaining: connective tissues: vascular, nervous, lymphatics

**Islet Sources**

- Only pancreata not used for whole organ transplantation are considered for islets:
  - Donors with significant atherosclerosis
  - Donors with prolonged down time, hypotension and hyperglycemia
  - Donors with extreme age
  - Fatty pancreas
  - Fibrotic pancreas
  - Pancreatitis
  - Pancreas with duodenal, parenchymal or splenic injury

**Islet Transplantation**

**Pancreas VS Islet**

**Pancreas**

- Maximally Invasive
- Recipient Selection
- Limited Supply
- Immunosuppression Required
- Preservation Time Limited
- Re-Transplant is difficult

**Islet**

- Minimally Invasive
- All Diabetics Qualify
- Potential for Unlimited Supply
- Manipulate Islets for Tolerance
- Longer Time Permitted
- Can be repeated multiple times
Essentials For Clinical Islet Transplantation Program

- Acquire the highly specialized islet isolation technology
- Establish an FDA approved islet isolation lab
- Apply and receive Investigational New Drug Approval (IND)
- Secure IRB approval
- Secure UNOS approval
- Resources

Human Islet Isolation

- Standard cadaveric pancreas procurement
- Pancreatic duct cannulation
- Enzyme digestion
- Islet purification
- Quality control

Islet Isolation Team

<table>
<thead>
<tr>
<th>Name</th>
<th>Title</th>
<th>Responsibilities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jill Buss, RN, MSN</td>
<td>Islet Research Assistant</td>
<td>Leads islet isolations/QC</td>
</tr>
<tr>
<td>Lynn O'Donnell, Ph.D.</td>
<td>Director, BMT Laboratory</td>
<td>Responsible for operational &amp; quality issues of BMT Lab</td>
</tr>
<tr>
<td>Amer Rajab, M.D., Ph.D.</td>
<td>Medical Director, BMT Laboratory</td>
<td>- Procurement, perfusion &amp; digestion phases of islet isolations</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Ensures islet products meet medical needs of patients</td>
</tr>
<tr>
<td>Dave Krouhl, MT(ASCP), SBB, CLS, CLCP(NCA)</td>
<td>BMT Program Quality Manager</td>
<td>Oversees Quality Program of BMT Lab, including islet QC/QA</td>
</tr>
<tr>
<td>Hillary Bradbury, MT (ASCP)</td>
<td>Supervisor, BMT Laboratory</td>
<td>- Manages BMT Lab</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Assists in islet isolations/QC</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Performs islet QC/QA</td>
</tr>
<tr>
<td>Elizabeth Diakoff, M.D.</td>
<td>Assistant Professor, Dept. of Endocrinology, Diabetes &amp; Metabolism</td>
<td>- Assists in islet isolation/teams</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Assists in islet isolations/QC</td>
</tr>
<tr>
<td>Residents &amp; Fellows</td>
<td></td>
<td>- Assist in islet isolations/QC</td>
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Human Islet Isolation

- Standard cadaveric pancreas procurement
- Pancreatic duct cannulation
- Enzyme digestion
- Islet purification
- Quality control
Quality Control
Product Release Criteria

- Islet Pellet Volume
- Viability Assay
  - Dithizone Staining
  - Fluorescent microscope using Calcein AM and ethidium homodimer-1.
- Islet Equivalents
- Islet Purity
- Endotoxin
- Functional Assay
  - Stimulation index: In-vitro Insulin Production in Low and High Glucose
- Sterility Testing
Islet Transplantation

- Minimally invasive (simple injection)
- All diabetics qualify
- Potential for unlimited supply
- Manipulate islets for tolerance