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


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

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

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

-param

Failed
○ Partial graft function
♦ Full graft function

* p = 0.025


Glycemic lability in C-peptide positive patients – CGMS®

-param

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

CITR Update: Transplantation 2008 86: 1783–1788

Quality of life improvement – islet transplantation

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

Barsches et al., Transplantation 2005: 6:1727-1730
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


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

---

### Hypoglycemia Score

1) Do you have symptoms when your blood sugar is low?  
   - Always (A)  
   - Sometimes (R)  
   - No longer (R)

2) Have you lost the ability to recognize symptoms that used to occur when your blood sugar was low?  
   - Yes (R)  
   - No (A)

3) In the last 6 months, how often have you had moderate hypoglycemic episodes?  
   - Never (A)  
   - Once or twice (R)  
   - Every other month (R)  
   - Once a month (R)  
   - More than once a month (R)

4) In the last year, how many times have you had severe hypoglycemic episodes?  
   - Never (A)  
   - 1 (R)  
   - 2 (R)  
   - 3 (R)  
   - 4 (R)  
   - 5 (R)  
   - 6 (R)  
   - 7 (R)  
   - 8 (R)  
   - 9 (R)  
   - 10 (R)  
   - 11 or more (R)

5a) How often in the last month have you had readings <70 mg/dl with symptoms?  
   - Never  
   - 1-3 times  
   - 1 time/week  
   - 2-3 times/week  
   - 4-5 times/week  
   - Almost daily

5b) How often in the last month have you had readings <70 mg/dl without any symptoms?  
   - Never  
   - 1-3 times  
   - 1 time/week  
   - 2-3 times/week  
   - 4-5 times/week  
   - Almost daily

6) How low does your blood sugar have to be before you experience symptoms?  
   - 66-69 mg/dl (A)  
   - 50-59 mg/dl (A)  
   - 40-49 mg/dl (R)  
   - <40 mg/dl (R)

7) To what extent can you tell by your symptoms that your blood sugar is low?  
   - Never (R)  
   - Rarely (R)  
   - Sometimes (R)  
   - Often (A)  
   - Always (A)

Total Number of “R” Responses:

Reduced awareness:  ≥4 R’s  
Aware: ≤2 R’s

Diabetes Care 18:517, 1995
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

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
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.

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
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

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


Transplant center ranking by total number of pancreas transplants
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%)

---

National Data (OPTN)

![Bar chart showing pancreas procurement and transplantation data from 2000 to 2008](chart.png)
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 Transplantation

[Diagram of islet transplantation process]

From Wikipedia, the free encyclopedia (islet transplantation PLoS Medicine.jpg)
### 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

### Pancreas VS Islet

<table>
<thead>
<tr>
<th>Pancreas</th>
<th>Islet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximally Invasive</td>
<td>Minimally Invasive</td>
</tr>
<tr>
<td>Recipient Selection</td>
<td>All Diabetics Qualify</td>
</tr>
<tr>
<td>Limited Supply</td>
<td>Potential for Unlimited Supply</td>
</tr>
<tr>
<td>Immunosuppression Required</td>
<td>Manipulate Islets for Tolerance</td>
</tr>
<tr>
<td>Preservation Time Limited</td>
<td>Longer Time Permitted</td>
</tr>
<tr>
<td>Re-Transplant is difficult</td>
<td>Can be repeated multiple times</td>
</tr>
</tbody>
</table>
# 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**

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## Islet Isolation Team

<table>
<thead>
<tr>
<th>Role/Position</th>
<th>Responsibilities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amer Rajab, M.D., Ph.D.</td>
<td>Medical Director, Islet and Pancreas Transplantation Medical Director, BMT Laboratory, Human Islet Isolations - Procurement, perfusion &amp; digestion phases of islet isolations - Ensures islet products meet medical needs of patients</td>
</tr>
<tr>
<td>Lynn O'Donnell, Ph.D.</td>
<td>Director, BMT Laboratory - Responsible for operational &amp; quality issues of BMT Lab - Assists in islet isolations/QC</td>
</tr>
<tr>
<td>Jan Sirilla, RN, MSN</td>
<td>Administrative Director, BMT Program - Administrative aspects of BMT Lab</td>
</tr>
<tr>
<td>Dave Krugh, MT(ASCP), SBB, CLS,CLCP(NCA)</td>
<td>BMT Program Quality Manager - Oversees Quality Program of BMT Lab, including islet QC/QA</td>
</tr>
<tr>
<td>Hillary Bradbury, MT (ASCP)</td>
<td>Supervisor, BMT Laboratory - Manages BMT Lab - Assists in islet isolations - Performs islet QC/QA</td>
</tr>
<tr>
<td>Cell Therapy Technologists, MT</td>
<td>- Assist in islet isolations - Perform islet QC/QA</td>
</tr>
<tr>
<td>Elizabeth Diakoff, M.D.</td>
<td>Assistant Professor, Dept. of Endocrinology, Diabetes &amp; Metabolism - Assists in islet isolations</td>
</tr>
<tr>
<td>Jill Buss, M.S.</td>
<td>Islet Research Assistant - Lead technologist for islet isolations - Performs islet QC testing</td>
</tr>
<tr>
<td>Residents &amp; Fellows</td>
<td>- Assist in islet isolations</td>
</tr>
</tbody>
</table>
Human Islet Isolation

- Standard cadaveric pancreas procurement
- Pancreatic duct cannulation
- Enzyme digestion
- Islet purification
- Quality control
OSU islet isolation protocol IND#13038
Quality Control
Product Release Criteria

- Islet Pellet Volume
- Viability Assay
  - Dithizone Staining
  - Fluroescent 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