Beta cell replacement therapy in diabetes:
Islet cell transplants for type 1 diabetes and for children undergoing pancreatectomy

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Disclosures
• Consulting/Advisory Boards:
  – Current: ARIEL medicine
  – Historical: AbbVie, ViaCyte
• Research Support:
  – Current: Dompe pharmaceuticals
  – Historical: Medtronic, Merck
• Off label use: alloislet transplants (investigational product)

Objectives
• Discuss the reasons for islet transplant
  – Why and How
• Describe the rationale for and management of TPIAT for children
• Explain common islet transplant outcomes
  – Islet autotransplant
  – Islet allotransplant
From pancreas to liver: why transplant an islet?

• Allogenic islet transplant: To treat type 1 diabetes (complicated by hypoglycemia or microvascular disease)

• Autologous islet transplant: To prevent or minimize surgical diabetes resulting from pancreatectomy

From pancreas to liver: why transplant an islet?

• Allogenic islet transplant: To treat type 1 diabetes (complicated by hypoglycemia or microvascular disease) - research

• Autologous islet transplant: To prevent or minimize surgical diabetes resulting from pancreatectomy—clinical (children)

Islet Transplants for Pancreatic Disease

TYPE 1 DIABETES

PANCREATITIS

Elevated Blood Glucose

Severe PAIN
Differences Between Autoislet and Alloislet Transplant

ALLO
- Autoimmune destruction
- Alloimmune rejection
- Immunosuppressive drug toxicity (diabetogenic)
- Technical factors: cold ischemia, donor brain death
- # of islets >5000 IEQ/kg

AUTO
- Variable islet yield
- Procedural differences: fresh (non-cultured) islets, +/- purification

Moving an islet from the pancreas to the liver...
The process of islet isolation and intraportal infusion

An islet in the pancreas
Islet Cell Processing

What happens to an islet during isolation?

• Removed from surrounding exocrine pancreas
• Devascularized (later revascularizes)
• Deinnervated
• Beta cell apoptosis occurs

Intraportal infusion: An islet in the liver

• Initial infusion triggers inflammation, coagulation (IBMIR)
• Re-vascularizes, but early on…
  – Hypoxic environment
  – Beta cell apoptosis frequent
• Deinnervated (?)
• Exposed to portal “toxins”
• Glucose-responsive insulin secretion
• Deficient physiologic glucagon response to hypoglycemia
Islet revascularization occurs over 1-3 months post-transplant

<table>
<thead>
<tr>
<th>Hypoxia</th>
<th>Vascularization</th>
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</table>

Total pancreatectomy with islet autotransplantation (TPIAT)

Historical evolution of IAT

1977

TRANSPANTATION PROCEEDINGS

Human Islet Transplantation: A Preliminary Report

J. S. Najarian, D. R. Sutherland, A. J. Moore, M. W. Steffes, R. L. Swanson, and F. C. Cosimi

Pancreatic islet tissue can be successsfully transplanted in animals with minimal rejection. The recipient pancrease was autotransplanted when four islets were implanted.

Pancreatitis in children

Etiology of Disease:

**Hereditary/Genetic:**
- PRSS1 (cationic trypsinogen)
- SPINK1 (trypsin inhibitor)
- CFTR (Exocrine sufficient CF)

**Other:**
- Pancreatic divisum
- Autoimmune
- Medications
- Idiopathic
“Minnesota Paradigm”

→ Medical therapy
→ Endoscopic therapy/ESWL
   if fails
→ Surgical resection

TPIAT for diffuse disease (most common)

Drainage operations avoided
unless poor candidate for TPIAT

Traditional surgical options to treat chronic pancreatitis

- Drainage
- Resection

TPIAT for severe chronic pancreatitis

- Goal of pancreactomy = relieve pain, allow normal function
- Goal of islet autotransplant (IAT) = to prevent or minimize postsurgical diabetes
When consider TPIAT?

“The primary indication for TPIAT is to treat intractable pain with impaired quality of life due to chronic pancreatitis or recurrent acute pancreatitis, when medical, endoscopic, or prior surgical therapy have failed.”

PancreasFest 2012, consensus statement

Candidates for Pancreatectomy and IAT

- Chronic pancreatitis refractory to medical treatment and endoscopic interventions
- Narcotic dependence and/or significantly impaired quality of life
- Lack medical/psychosocial contraindications
- Non-diabetic, or C-peptide positive diabetes
- Willing to accept risk of diabetes for pain relief

A Life Altering Procedure

- 5 y/o male with cystic fibrosis from Ohio
- Acute pancreatitis, 1st episode at age 2y
- 20 hospitalizations; dependent on NJ tube feeds
- Withdrew from school
- TP-IAT performed
- Now 13 years post-transplant:
  - “J. celebrated ten years pain free and insulin free last week! Can you believe it has been ten years… We celebrated with dinner out. Jonah’s favorite thing… FOOD! † (mom, 6/14)
4 year old male with pancreatitis

- Onset of acute pancreatitis at age ~3 years (sx 1.5y)
- 10 hospitalizations for AP
- Frequent pain
- NJ feeds/ NPO; multiple ERCPs
- Much of ~6 mos prior to surgery spent in hospital
- Pain free, insulin free, no hospitalizations (2 yrs later)

Total pancreatectomy/ IAT procedure

- Total pancreatectomy, partial duodenectomy, duodenostomy or Roux-en-Y, choledochoduodenostomy, +/- splenectomy

TPIAT is major surgery, reserved for patients failing medical management. Risks include:

- Diabetes and diabetes-related complications
- Neuropathic pain (after years of pain/ opioids)
- Delayed gastric emptying/ motility/ constipation
- Ulcer/ GI bleeding
- Asplenia risks
- Micronutrient deficiencies
Post-Operative Management

- **Blood glucose / Diabetes**
  - Early hyperglycemia \( \rightarrow \) beta cell apoptosis
  - Tight glucose control early, wean after engraftment

- **Pain Control**
- **Nutrition**
  - Pancreatic Enzymes
  - Fat soluble vitamins/ micronutrients

- **Splenectomy precautions**

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Multi-Disciplinary Team

- **Surgeon**
- **Gastroenterologist**
- **Pain Specialist**
- **Endocrinologist**
- **Dietician**
- **Psychologist**
- **Nurse Coordinator**
- **Local PCP**

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HRQoL improves by SF-36 assessment

- Scores improve by 1 SDS on average
- 85% of patients self-report improved/resolved pain; improved health
- 15% similar to before surgery
The goal of TPIAT: relieve pain

- 90% of children have improvement in pain scores (p<0.001)
- SF-36 scores improve (+2 SDS)
  - Role-physical
  - Bodily pain
- Fewer days of limited activity (+5fold)

Impact on childhood activities

Hepatic islet success: established beta cell function & longevity
% Insulin independent by islet mass

<table>
<thead>
<tr>
<th>Islet Mass</th>
<th>6 MOS</th>
<th>1 YR</th>
<th>2 YR</th>
<th>3 YR</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;2,500 IEQ/kg</td>
<td>LOW MASS</td>
<td>13%</td>
<td>13%</td>
<td>13%</td>
</tr>
<tr>
<td>2,500 - 5,000 IEQ/kg</td>
<td>MODERATE MASS</td>
<td>29%</td>
<td>53%</td>
<td>53%</td>
</tr>
<tr>
<td>&gt;5,000 IEQ/kg</td>
<td>HIGH MASS</td>
<td>53%</td>
<td>76%</td>
<td>76%</td>
</tr>
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</table>

Which children become insulin independent?

<table>
<thead>
<tr>
<th></th>
<th>Odds Ratio</th>
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<tbody>
<tr>
<td>Prior Puestow</td>
<td>0.14 (0.03-0.72)</td>
</tr>
<tr>
<td>Age</td>
<td>0.85 (0.73-0.99)</td>
</tr>
<tr>
<td>Body Surface Area</td>
<td>0.25 (0.06-0.99)</td>
</tr>
<tr>
<td>Total IEQ (100,000)</td>
<td>1.81 (1.21-2.72)</td>
</tr>
<tr>
<td>IEQ/kg</td>
<td>1.05 (1.02-1.08)</td>
</tr>
</tbody>
</table>

Insulin use and HbA1c: age 3-8y

~80% ever off insulin
A1c <7% in ~90%
What about children who remain diabetic?

- Primary goal is pain relief
- 13 y/o Fm with hereditary pancreatitis, on insulin pump [from mother]:
  - Just wanted to take a moment today to thank the entire transplant staff for giving my daughter a chance at a new life. One year ago today her dad and I were sitting in the surgery waiting room. Today, 365 days after the scariest day of our lives, A is healthy, vibrant and completely without pain. She has gained thirty pounds and grew three inches, she has attended school regularly, she has played three sports this year and was the MVP in all three, she has gained victory over a disease that once ruled her life and livelihood.

Opportunities to improve diabetes outcomes

Prior surgical drainage procedure results in low islet mass isolated at the time of TPIAT
**Islet size: a potential risk for hypoxia?**

Marginal mass islet grafts (2,500-<5,000 IEQ/kg)

Islet size index and total daily insulin use (unit/day)

Islet use and islet size index

Suzyynski et al. 2014 in press

\[ ISI = \text{IEQ/islet number} \]

**Hepatic islet limitations:**

functional glucagon deficiency

Glucagon response to hypoglycemia clamp studies:

- Healthy control
- TP/IAT, liver only
- TP/IAT-Liver + Second Site

Restored glucagon response when partial islet mass is transplanted intraperitoneal

Robertson, 2013

**Challenges in diabetes remission**

- Isolation Stress
- Apoptosis
- Hypoxia
- Metabolic Stress
- BMI

Isolation and Transplantation ->
In vivo beta cell biomarkers

Unmethylated Insulin DNA Is Elevated After Total Pancreatectomy With Islet Autotransplantation: Assessment of a Novel Beta Cell Marker

Clinical trials: beta cell apoptosis/regeneration (GLP-1 therapies)

Clinical trials: Tighter glycemic control with new technology (CLP)
Clinical trials: Ongoing antiinflammatory trials

**Agents:**
- IL-8 inhibitor (reparixin)
- TNF-a blockade (etanercept) +/- IL-1 inhibitor
- Alpha-1 antitrypsin (Aralast NP)

Allogenic islet transplants for type 1 diabetes

The Problem: Type 1 Diabetes
- Autoimmune (T cell)-mediated destruction of the islets
- Affects 1 in ~400
- Results in complete insulin deficiency
Dealing with diabetes differently…

OLD | CURRENT | FUTURE
---|---|---

β-Cell Replacement | Technology | Prevention

Current therapy is suboptimal

- **Problem:** Goal HbA1c level is not achieved by most T1 diabetics in the U.S.
- **Problem:** Insulin therapy can result in dangerous:
  - hypoglycemia unawareness
  - Severe hypoglycemic episodes

Who Is Considered for an Islet Tx?

(Adult) Patients with **type 1 diabetes**
complicated by

hypoglycemia unawareness
&
severe hypoglycemic episodes

**OR**

Renal failure (Islet after Kidney)
Acute Complications of T1D: Hypoglycemia

- Limiting factor in diabetes management
- 25% of patients practicing intensive insulin therapy suffer ≥ 1 episode of severe hypoglycemia/year
- 4-9% of deaths in T1DM

Philip E. Cryer, *Diabetes* 2005

- Hypoglycemia unawareness develops in >12% of those with >20 year history of T1D

Pedersen-Bjegaard, *Diabetes Metab Res Rev* 2004

83 mg/dL (4.6 mmol/L): Insulin secretion stops

69 mg/dL (3.8 mmol/L): Glucagon secretion increases

68 mg/dL (3.8 mmol/L): Epinephrine secretion increases

> 54 mg/dL (3 mmol/L): Andrenergic “warning” sx (sweaty, hungry, shaky, tachycardia, nervous)

<49 mg/dL (2.7): *Cognitive dysfunction* (confused, tired, drowsy, faint, dizzy, unconscious, etc.)

What does an islet transplant involve?

- Detailed pre-transplant evaluation
- Eligible participants listed with UNOS (waitlist time ~1y)
- Hospitalized x 5 days
- Minor surgery: percutaneous or minilaparotomy
- Immunosuppression & infection prophylaxis
  - ATG, tacrolimus, and sirolimus/MMF
- Insulin weaned off gradually after transplant
Edmonton Protocol:

The New England Journal of Medicine

Daclizumab; 5 injections over 10 wks
Sirolimus + low-dose tacrolimus

Transplant #1
Transplant #2

10-12K IE/kg

7/7 recipients insulin-independent at ~1 year

Benefits of Islet Transplantation

• Eliminate severe hypoglycemia and glycemic lability
• Restore insulin independence
• Reduce progression of microvascular complications of diabetes

Long-Term Resolution of Hypoglycemia

Patients with graft function have significant and sustained reduction in hypoglycemia, regardless of insulin use, while maintaining goal HbA1c (<7%)

Ryan EA. Diabetes 54:2060-2069, 2005

HYPO score posttransplant

HbA1c posttransplant

Partial Fx

Full Fx

Time (Months)
Sustained insulin independence with current immunosuppression


Reduced Progression of Diabetic Microvascular Complications With Islet Cell Transplantation Compared With Intensive Medical Therapy

David M. Thompson,1,2 Mark Mehrotra,1 Dilling Xu,1 Bruce Peters,3 Paul Kocner,3 B. Jane Dougherty,1

TABLE 3: Progression of diabetic retinopathy in the medical and post-ICT groups

<table>
<thead>
<tr>
<th></th>
<th>Medical</th>
<th>ICT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild NPDR</td>
<td>16</td>
<td>6</td>
</tr>
<tr>
<td>Moderate NPDR</td>
<td>19</td>
<td>3</td>
</tr>
<tr>
<td>Severe NPDR</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>PDR</td>
<td>41</td>
<td>7</td>
</tr>
<tr>
<td>TOTAL</td>
<td>82</td>
<td>10</td>
</tr>
</tbody>
</table>

*The progression is significantly more in the medical than the post-ICT group (P<0.05).

ICT, islet cell transplantation; NPDR, non-proliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy.

Clinical Islet Transplantation Consortium

Phase III alloislet trials
Next steps…

What might the future hold for cellular therapy for (surgical and T1) diabetes?

Future Challenges: Increasing the applicability of islet transplant
Summary

• Islet transplantation is performed for labile T1D (allo) or surgical diabetes (auto)

• Allotransplants for type 1 diabetes require immunosuppression, high islet mass transplanted, but with high rates of insulin independence

• TPIAT (auto) transplants are non-immunogenic, restore insulin independence in 40%, with better function for the islet mass transplanted
  – TPIAT reduces pain, improves QoL/ function
  – Very young children with best diabetes outcomes

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Questions

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