Pancreas Transplantation: The Marginal Donor and Recipient

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Director, Pancreas and Islet Transplantation
Disclosures

• No commercial interests related to this topic
I am/will be looking for a job involving:

1. Kidney transplantation only
2. Liver transplantation only
3. Kidney & liver transplantation
4. Kidney, liver & pancreas transplantation
5. Kidney & pancreas transplantation
6. Nothing having to do with transplantation
7. Waiting tables at Applebee’s
I feel most confident transplanting and taking care of:

1. Kidney transplants
2. Liver transplants
3. Pancreas transplants
4. None of the above
The majority of programs perform few pancreas transplants

Distribution by center volume of the number of pancreas transplants performed (includes kidney-pancreas), 2009

Percent of centers

Percent of patients

Center volume (10=1-10, 20=11-20, etc.)

UNOS SRTR Report Am J Transplant 2011
Outline

- **Marginal Donor**
  - Pancreas Quality
  - Donor recovery errors
  - PDRI
  - Age and BMI
  - DCD
  - Pediatric
  - HTK

- **Marginal Recipient**
  - Age and BMI
  - Cardiac disease
  - Vascular disease
  - Type 2 DM
  - Re-transplant
Outline

Marginal Donor
- Pancreas Quality
- Donor recovery errors
- PDRI
- Age and BMI
- DCD
- Pediatric
- HTK

Marginal Recipient
- Age and BMI
- Cardiac disease
- Vascular disease
- Type 2 DM
- Re-transplant
Quality of the Pancreas
!!!!! Paramount importance !!!!!

Ideal

Fatty infiltration
BMI 43  Age 19
AmYLASE 321  Lipase 441
Closed Head trauma
DCD
Pancreas Graft Quality Assessment

- Fatty infiltration, marbling
- Firmness, fibrosis
- Evidence of hemorrhagic pancreatitis
- Atrophy, nodularity, calcifications, masses

Other issues:
- Length of PV
- Replaced RHA and potentially sacrificed inferior PDA
- Prior trauma splenectomy
- HbA1c
Replaced RHA: Is the Inferior PDA preserved after the liver is separated?

Cross-circulation SMA - Spl A

Margreiter et al. AJT 2010
Pancreas Procurement Errors

Pancreata recovered elsewhere and shipped to UW

- Ligated splenic vein at origin
- Short or non-existent portal vein
- Injury to PV (e.g. lacerated SMV-PV jcn)
- Sacrificed inferior PDA vessels
- Transected SMA at root of the mesentery proximal to the inferior PDA vessels
- Injury to the parenchyma
- Injury to the duodenal segment
- Staple line across the uncinate process
- Failure to ship/supply iliac Y graft
Pancreas Quality and Back Table Bench Preparation
### Pancreas Donor Risk Index (PDRI)

<table>
<thead>
<tr>
<th>Donor Characteristics</th>
<th>Reference Donor (DRI=1)</th>
<th>Change factor value to</th>
<th>DRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>male</td>
<td>female</td>
<td>0.87</td>
</tr>
<tr>
<td>Age</td>
<td>28</td>
<td>45</td>
<td>1.56</td>
</tr>
<tr>
<td>Black race</td>
<td>No</td>
<td>Yes</td>
<td>1.27</td>
</tr>
<tr>
<td>Asian race</td>
<td>No</td>
<td>Yes</td>
<td>1.17</td>
</tr>
<tr>
<td>BMI</td>
<td>24</td>
<td>30</td>
<td>1.17</td>
</tr>
<tr>
<td>Height</td>
<td>173</td>
<td>190</td>
<td>0.9</td>
</tr>
<tr>
<td>Cause of Death-CVA/Stroke</td>
<td>No</td>
<td>Yes</td>
<td>1.23</td>
</tr>
<tr>
<td>CIT (hrs)</td>
<td>12</td>
<td>20</td>
<td>1.13</td>
</tr>
<tr>
<td>DCD</td>
<td>No</td>
<td>Yes</td>
<td>1.39</td>
</tr>
<tr>
<td>SCr &gt;2.5 mg/dL</td>
<td>No</td>
<td>Yes</td>
<td>1.22</td>
</tr>
</tbody>
</table>
Pancreas Donor Risk Index (PDRI)

A. 1-year SPK Pancreas Graft Survival by DRI Among Median Recipient

B. 1-year PAK Pancreas Graft Survival by DRI Among Median Recipient

C. 1-year PTA Pancreas Graft Survival by DRI Among Median Recipient

- Axelrod et al. Am J Transplant 2010
Pancreas Donor Risk Index (PDRI)

• Increasing PDRI was associated with a significant graded risk of graft failure within 1 year

• PTA and PAK grafts from donors with elevated PDRI experienced a lower rate of 1 year graft survival (77%) compared with SPK recipients (88%)

• Pancreas allograft acceptance varied significantly by region particularly for PAK/PTA (p<0.0001)

- Axelrod et al. Am J Transplant 2010
Donor Cause of Death
Graft Thrombosis Rate

USA DD Primary Pancreas Transplants 1/1/2000 – 12/31/2005

P = 0.0001

Donor Cause of Death

- Trauma
- Non-Trauma

SPK, PAK, PTA
Technical Failure Rate

USA DD Primary Pancreas Transplants 1/1/2000 – 12/31/2005

P = 0.0001

Donor Cause of Death

- Trauma
- Non-Trauma

SPK

PAK

PTA
Old and heavy donors increase the risk of pancreas graft loss

- Krieger et al Transplantation 2003

Heavy = >200 lbs
Old = >45 yrs
### Results - Univariate Analysis

<table>
<thead>
<tr>
<th>Donor Characteristic</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.0001</td>
</tr>
<tr>
<td>BMI</td>
<td>0.0037</td>
</tr>
<tr>
<td>Weight</td>
<td>0.0365</td>
</tr>
<tr>
<td>Height</td>
<td>0.1824</td>
</tr>
<tr>
<td>Serum Glucose</td>
<td>0.6238</td>
</tr>
<tr>
<td>Serum Amylase</td>
<td>0.0844</td>
</tr>
<tr>
<td>Serum Lipase</td>
<td>0.1750</td>
</tr>
<tr>
<td>Abdominal Trauma vs other COD</td>
<td>0.6585</td>
</tr>
<tr>
<td>DCD</td>
<td>0.7736</td>
</tr>
<tr>
<td>Vasopressor use</td>
<td>0.9196</td>
</tr>
</tbody>
</table>

Multivariate analysis – only Age (p=0.0039) and BMI (p=0.021)
Factors Associated with Technical Failure

Composite Risk Model = donor age >50, donor BMI >30, donor Cr, >2.5 preservation time >20 hr and adjusted for surgical approach.
2 or more Donor Risk Factors Increases the Risk of Technical Failure and Graft Loss

Finger et al. AJT 2013
Rate of DCD-Donors
USA Pancreas Transplants 1/1/2000 – 12/31/2010
10-year Outcomes of Simultaneous Pancreas-Kidney Transplantation from Donation After Cardiac Death

SPK transplants from 1982 - 2007
DBD donors (n=914)
DCD donors (n=56)

No specific recipients or type of immunosuppression was used for DCD pancreata
Pancreas Graft Survival for SPK Donation after Brain Death vs. Cardiac Death

![Graph showing Pancreas Graft Survival](image)

- DBD
- DCD

$p = 0.8781$
## Long Term Pancreas Function

<table>
<thead>
<tr>
<th>Hb A1c%</th>
<th>DBD</th>
<th>DCD</th>
<th>p -Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 months</td>
<td>5.5 ± 0.95</td>
<td>5.42 ± 0.67</td>
<td>0.98</td>
</tr>
<tr>
<td>12 months</td>
<td>5.6 ± 1.0</td>
<td>5.58 ± 0.69</td>
<td>0.65</td>
</tr>
<tr>
<td>24 months</td>
<td>5.7 ± 0.89</td>
<td>5.66 ± 0.65</td>
<td>0.68</td>
</tr>
<tr>
<td>36 months</td>
<td>5.7 ± 0.93</td>
<td>5.54 ± 0.71</td>
<td>0.27</td>
</tr>
<tr>
<td>48 months</td>
<td>5.7 ± 0.94</td>
<td>5.35 ± 0.6</td>
<td>0.26</td>
</tr>
<tr>
<td>60 months</td>
<td>5.7 ± 1.1</td>
<td>5.53 ± 0.7</td>
<td>0.88</td>
</tr>
<tr>
<td>84 months</td>
<td>5.8 ± 1.2</td>
<td>5.5 ± 0.5</td>
<td>0.92</td>
</tr>
<tr>
<td>120 months</td>
<td>5.7 ± 1.0</td>
<td>5.5 ± 0.1</td>
<td>0.86</td>
</tr>
</tbody>
</table>
Kidney Graft Survival for SPK Donation after Brain Death vs. Cardiac Death

![Graph showing kidney graft survival over years for DBD and DCD donors with p = 0.8864]
Long Term Kidney Function

Greater DGF in DCD Kidneys compared to Kidneys from DBD donors in SPK recipients  \( P=0.001 \)

<table>
<thead>
<tr>
<th>Creatinine (mg/dl)</th>
<th>DBD</th>
<th>DCD</th>
<th>p -Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>POD #7</td>
<td>1.86 + 1.8</td>
<td>2.65 + 2.3</td>
<td>0.001</td>
</tr>
<tr>
<td>at time of D/C</td>
<td>1.42 + 0.5</td>
<td>1.60 + 0.5</td>
<td>0.03</td>
</tr>
<tr>
<td>6 months</td>
<td>1.51 + 0.8</td>
<td>1.35 + 0.4</td>
<td>0.23</td>
</tr>
<tr>
<td>12 months</td>
<td>1.54 +0.9</td>
<td>1.40 + 0.4</td>
<td>0.37</td>
</tr>
<tr>
<td>24 months</td>
<td>1.49 + 0.7</td>
<td>1.52 + 0.6</td>
<td>0.53</td>
</tr>
<tr>
<td>36 months</td>
<td>1.62 + 0.9</td>
<td>1.51 + 0.6</td>
<td>0.68</td>
</tr>
<tr>
<td>48 months</td>
<td>1.57 + 0.8</td>
<td>1.43 + 0.4</td>
<td>0.72</td>
</tr>
<tr>
<td>60 months</td>
<td>1.60 + 0.8</td>
<td>1.45 + 0.4</td>
<td>0.7</td>
</tr>
<tr>
<td>84 months</td>
<td>1.69 + 0.9</td>
<td>1.57 + 0.5</td>
<td>0.79</td>
</tr>
<tr>
<td>120 months</td>
<td>1.87 ± 1.3</td>
<td>1.64 ± 0.5</td>
<td>0.89</td>
</tr>
</tbody>
</table>
Delayed Kidney Graft Function in SPK Recipients is Associated with Poor Long Term Outcomes

733 consecutive primary SPK recipients 1994-2010

Follow-up Time (years)
What about the pediatric donor?
Are Pediatric Donors Suitable for Simultaneous Pancreas / Kidney Transplantation?

Luis A. Fernandez, M.D.; Jon S. Odorico, MD.; Glen Leverson, PhD.; L Thomas Chin, M.D.; Stuart J. Knechtle, M.D; Anthony D’Alessandro, MD; Yolanda Becker M.D.; Munci Kalayoglu, M.D.; and Hans W. Sollinger, M.D., PhD.

1986 -2001 680 SPK transplants
Pediatric < 18 yo (n=142)
Adult ≥ 18 yo (n=538)

Kidney Graft Survival
SPK Transplantation of Pediatrics vs Adult Donors

p = 0.0265
Kidney Graft Survival Rates
SPK Transplantation of Pediatric Donors at Different Ages

![Graph showing kidney graft survival rates over years with different donor ages and p-value]

$p = 0.1457$
Pancreas Graft Survival
SPK Transplantation of Pediatric vs Adult Donors

Pancreas Graft Thrombosis

<table>
<thead>
<tr>
<th>Donor</th>
<th>Cases</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peds</td>
<td>2/142</td>
<td>6.8%</td>
</tr>
<tr>
<td>Adult</td>
<td>13/538</td>
<td>8.4%</td>
</tr>
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</table>

p = 0.0533
## Comparison of Physiological Parameters

**SPK Transplantation of Pediatric vs Adult Donors**

### at 5 years

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Adults</th>
<th>Pediatrics</th>
<th>Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=237</td>
<td>n=63</td>
<td></td>
</tr>
<tr>
<td>GFR</td>
<td>58.3 ± 17</td>
<td>65.6 ± 16</td>
<td>0.002</td>
</tr>
<tr>
<td>GLYCEMIA-FBG</td>
<td>95.16 ± 29</td>
<td>85.3 ± 13</td>
<td>0.001</td>
</tr>
<tr>
<td>HbA1c</td>
<td>5.86 ± 3.5</td>
<td>5.47 ± 0.98</td>
<td>0.013</td>
</tr>
</tbody>
</table>

### at 10 years

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Adults</th>
<th>Pediatrics</th>
<th>Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td>GFR</td>
<td>n=66</td>
<td>n=24</td>
<td>0.015</td>
</tr>
<tr>
<td></td>
<td>54+ 17.7</td>
<td>65.9+ 18.8</td>
<td></td>
</tr>
</tbody>
</table>
Debate: HTK vs UW?
UW experience with HTK (shipped in organs)

- 2004-2010: 85 shipped in pancreata
- 9 flushed and preserved in HTK (all CIT >12h)
- Complications in 4/9 pts
  - Pseudocysts requiring intervention (n=2)
  - Pancreatitis/Graft Thrombosis (n=1)
  - Peripancreatic infection and enzyme leak req Lap (n=1)
Debate: HTK vs. UW?

- **Fridell et al. AJT 2010**
  Retrospective analysis of 308 pancreas transplants – 84% HTK, 16% UW
  Endpoints: 7day, 90 day and 1 yr Graft survival, peak and subsequent serum amylase and lipase, HbA1c and C-peptide
  Findings: No difference in any outcome variable
  Limitations – non-randomized, single center, more Sol. Panc transplants in UW group, longer CIT in UW group, both CIT under 10 hrs, more import organs and non-local OPO recovery in UW group

- **Schneeberger et al. Transplant Int 2009**
  Prospective randomized multicenter trial 68 pancreas transplants – 27 HTK, 41 UW
  Endpoints: Graft survival at 6 mos., post-operative amylase, lipase, Cpeptide, HbA1c and insulin req
  Findings: Sl.higher exogenous insulin use in UW arm resolved by 3mos.
  No difference in GS at 6 mos. or any lab values
  Limitations: Underpowered, mean CIT 10-11 hrs

- **Alonso et al. AJT 2008**
  Retrospective analysis of 97 pancreas transplants at 2 centers – 16 HTK, 81 UW; CIT-13-15 hrs
  Endpoints: Early complications-thrombosis, bleeding, abscess, pancreatitis, octreotide use, relaparotomy, LOS, amylase lipase levels, insulin independence at DC, graft survival
  Findings: 2yr graft survival – 70%HTK, 90% UW; Graft loss due to thrombosis: 19% HTK, 4% UW; Abscess: 38%HTK, 14%UW; Post-operative peak amylase, frequency of octreotide use and pancreatitis were significantly greater in the HTK group; Insulin independence at DC: 64% HTK, 97% UW
  "Resumption of UW use resulted in a series of 25 transplants without serious complications with 100% graft survival at 12 months."
  Limitations: mixed groups of transplants, relatively small sample size, bias in some outcome variables
HTK vs UW

UNOS 2004-2008 pancreas transplants
HTK (n=1081) and UW (n=3311)

• HTK was independently associated with an increased risk of graft loss (HR 1.30, p=0.014) especially with CIT >12 h (HR 1.42, p=0.017)
• Stratified for donors age > 40, the HRs were increased but not significant due to low power
• HTK was associated with a 1.54-fold higher risk of early, <30 days, graft loss (OR 1.54, p=0.008)

Stewart et al. AJT 2009
Conclusions

• PDRI can be used to predict outcomes but does not trump quality assessment

• Older age and high BMI are consistently risk factors for worse pancreas graft survival

• Donor risk factors primarily predict with short –term outcomes

• Two or more risk factors increase the risk of TF

• Young pediatric donors and selected controlled DCD donors are suitable for pancreas donation

• HTK solution provides suboptimal preservation in donors with long (>10-12 hrs) CIT and ? DCD donors
The single most important non-quantifiable donor factor predicting success in pancreas transplantation is:

1. Fibrosis
2. Pancreas quality assessment by an experienced transplant surgeon
3. Pancreas feel & size
4. Absence of atrophy
The 2 most important quantifiable donor factors correlating with pancreas graft survival are:

1. Presence of prior cardiac arrest and CIT
2. PDRI and % fat
3. Number of vasopressors are used and amylase level
4. Age & BMI
Outline

Marginal Donor

Pancreas Quality
Donor recovery errors
PDRI
Age and BMI
DCD
Pediatric
HTK

Marginal Recipient

Age and BMI
Cardiac disease
Vascular disease
Type 2 DM
Re-transplant
Age as Recipient Risk Factor

Cox regression patient survival post pancreas transplant by recipient age.

Cox regression pancreas graft survival by recipient age.

BMI as Recipient Risk Factor

Fridell et al. Clin Transplant 2011
Major Causes of Patient Death

USA Primary DD Pancreas Transplants 1/1/2005 – 12/31/2009

- CCV
- Infection
- Bleeding
- Malignancy

Months Posttransplant

SPK, PAK, PTA
Cardiac Disease – The Perfect Storm

• High prevalence of heart disease

• Often asymptomatic myocardial ischemia

• High false negative rate of cardiac stress tests
### Prevalence of Cardiovascular Disease

Table 2. PREVALENCE OF GENERAL VASCULAR DISEASE PRETRANSPLANT FOR STUDY PATIENTS IN ERAS 3 AND 4 COMBINED

<table>
<thead>
<tr>
<th></th>
<th>SPK (n = 187)</th>
<th>PAK (n = 198)</th>
<th>PTA (n = 74)</th>
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</thead>
<tbody>
<tr>
<td>Coronary artery disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pretransplant MI</td>
<td>37%</td>
<td>33%</td>
<td>14%</td>
</tr>
<tr>
<td>CAB</td>
<td>40%</td>
<td>22%</td>
<td>17%</td>
</tr>
<tr>
<td>CAA</td>
<td>12%</td>
<td>14%</td>
<td>11%</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Claudication</td>
<td>13%</td>
<td>18%</td>
<td>9%</td>
</tr>
<tr>
<td>Arterial bypass</td>
<td>8%</td>
<td>5%</td>
<td>0%</td>
</tr>
<tr>
<td>Major amputation</td>
<td>9%</td>
<td>6%</td>
<td>6%</td>
</tr>
<tr>
<td>Minor amputation</td>
<td>12%</td>
<td>22%</td>
<td>11%</td>
</tr>
<tr>
<td>≥1 manifestation</td>
<td>47%</td>
<td>42%</td>
<td>24%</td>
</tr>
</tbody>
</table>

MI, myocardial infarction; CAB, coronary artery bypass; CAA, coronary artery angioplasty; SPK, simultaneous pancreas-kidney; PAK, pancreas after kidney; PTA, pancreas transplant alone.

Sutherland et al Annals of Surgery 2000
The prevalence of CAD in Type I diabetic patients is 63%:
- 46% Non-Critical
- 17% Critical

Overall, stress testing has poor sensitivity and PPV for CAD:
- Sensitivity - 26.7%
- Specificity – 80%
- PPV – 22.2%
- NPV – 83.6%

Only disease duration and time of dialysis were MV risk factors for positive cardiac cath.

Patients who did not undergo coronary angiography 2 years prior to transplantation had a trend towards worse patient and graft survival.
Patients with Type 2 Diabetes

USA Primary DD Pancreas Transplants 1/1/1994 – 12/31/2010

PAK
PTA
SPK
SPKT Patient Survival by Diabetes Type

USA Primary DD Pancreas Transplants 1/1/2006 – 12/31/2010

<table>
<thead>
<tr>
<th>DM Type</th>
<th>n</th>
<th>1Yr Surv.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1</td>
<td>3,797</td>
<td>95.9%</td>
</tr>
<tr>
<td>Type 2</td>
<td>286</td>
<td>94.7%</td>
</tr>
</tbody>
</table>

P = 0.47

Months Posttransplant
SPKT Pancreas Graft Function by Diabetes Type

USA Primary DD Pancreas Transplants 1/1/2006 – 12/31/2010

<table>
<thead>
<tr>
<th>DM Type</th>
<th>n</th>
<th>1Yr Fxn.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1</td>
<td>3,797</td>
<td>85.6%</td>
</tr>
<tr>
<td>Type 2</td>
<td>286</td>
<td>85.3%</td>
</tr>
</tbody>
</table>

P=0.92
Optimal Type 2 DM Patient For Pancreas Transplant

- Insulin-dependent
- Fasting C-peptide >2 ng/ml and
- BMI ≤ 30 kg/m² or
- Low insulin requirement (no evidence for severe insulin resistance)
- Avoid obese recipients with high insulin requirements and metabolic syndrome
- Primarily SPK candidates – uremic T2DM
- Mild to moderate co-morbidities (minimal cardiovascular disease)
- Potential obstacles – ASCVD, PVD, reduced kidney survival

Courtesy of R. Stratta
Which T2DM are considered appropriate for pancreas transplantation?

1. Lean and no significant CVD
2. No insulin use and obese
3. Kidney disease and insulin requiring
4. All of the above
5. 1 & 3
6. None of the above
Re-Transplantation

*Immunological and Surgical Risks*

- Re-SPK vs. Kidney alone?
- Vascular /Cardiac disease?
- Sensitized?
- Risk of losing pancreas function after KASPK
Pancreas Retransplants

USA Pancreas Transplants 1/1/1988 – 12/31/2010
Repeat Transplant and Solitary Pancreas Transplant are Risk Factors for AMR

A Primary SPK vs. Primary Solitary Pancreas Transplants

B SPK and Solitary Pancreas Transplant

C SPK Transplant

<table>
<thead>
<tr>
<th></th>
<th>Primary SPK</th>
<th>Primary Sol Panc</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary SPK</td>
<td>10%</td>
<td></td>
</tr>
<tr>
<td>Primary Sol Panc</td>
<td>19%</td>
<td></td>
</tr>
<tr>
<td>Repeat Panc</td>
<td>26%</td>
<td></td>
</tr>
<tr>
<td>Repeat SPK</td>
<td>42%</td>
<td></td>
</tr>
</tbody>
</table>

Niederhaus et al. AJT, 2013
KASPK: Risk of Return to Insulin