Simultaneous Pancreas Kidney Transplantation:

What is the added advantage, and for whom?

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Case

- 46 yo man with T1DM, prior poorly controlled diabetes with CKD/GFR 19, presents to transplant eval for KTX vs SPK. He has 2 brothers in good health interested in living donation.

- His HgbA1c is 7.6 using an insulin pump. His BMI is 29. He has not had ED/3rd party assistance for hypoglycemia. He has controlled retinopathy. No prior history of CAD

- What do you recommend?

- What if his age was >50, BMI > 30? Or HgbA1c 8.8, age 40?
The addition of pancreas to kidney transplant (SPK): Why?

Benefits of "euglycemia" vs.
risks of transplantation procedure
The effect of pancreas transplant on diabetic complications

In general, studies support a benefit of pancreas transplant but all studies not randomized, are small, not definitive.

Table 2. Impact of glycemic control on diabetic lesions [modified after (1)]

<table>
<thead>
<tr>
<th>Diabetic lesion/investigated parameter</th>
<th>Type of transplantation</th>
<th>Effect</th>
<th>Observation period</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetic nephropathy</td>
<td>PTA</td>
<td>No effect</td>
<td>5 yr</td>
<td>(8)</td>
</tr>
<tr>
<td>Diabetic nephropathy</td>
<td>PTA</td>
<td>Improved</td>
<td>10 yr</td>
<td>(7)</td>
</tr>
<tr>
<td>Diabetic nephropathy (of the renal allograft)</td>
<td>SPK</td>
<td>Inhibited</td>
<td>2-3 yr</td>
<td>(9)</td>
</tr>
<tr>
<td>Diabetic retinopathy</td>
<td>SPK</td>
<td>Stabilized/improved</td>
<td>6-60 months</td>
<td>(20)</td>
</tr>
<tr>
<td>Peripheral and autonomic diabetic neuropathy</td>
<td>SPK</td>
<td>Improved</td>
<td>6-48 months</td>
<td>(21)</td>
</tr>
<tr>
<td>Peripheral diabetic neuropathy (action potential)</td>
<td>SPK</td>
<td>Improved</td>
<td>Up to 8 yr</td>
<td>(22)</td>
</tr>
<tr>
<td>Autonomic diabetic neuropathy</td>
<td>SPK</td>
<td>Improved</td>
<td>12 months</td>
<td>(23)</td>
</tr>
<tr>
<td>Peripheral and autonomic diabetic neuropathy</td>
<td>SPK, PAK, PTA</td>
<td>Improved</td>
<td>1-10 yr</td>
<td>(24)</td>
</tr>
<tr>
<td>Blood pressure, pulse pressure, cholesterol</td>
<td>SPK</td>
<td>Reduced</td>
<td>1-12 yr</td>
<td>(25)</td>
</tr>
<tr>
<td>Progression of coronary artery disease</td>
<td>SPK</td>
<td>Decelerated</td>
<td>3.9 yr (mean)</td>
<td>(26)</td>
</tr>
<tr>
<td>Left ventricular ejection fraction</td>
<td>SPK</td>
<td>Improved</td>
<td>4 yr</td>
<td>(27)</td>
</tr>
</tbody>
</table>

SPK, simultaneous pancreas-kidney transplantation; PAK, pancreas after kidney transplantation; PTA, pancreas transplantation alone.

Transplantation of the type 1 diabetic patient: What option provides best patient survival?

• Collaborative Transplant Study of 15,118 T1DM transplant recipients (46 countries) from 1984-2007:

Morath C et al, CJASN 2010; 5: 549
“Living donor kidney vs. simultaneous pancreas-kidney transplant in type I diabetics: an analysis of the OPTN/UNOS database”

2000-2007: T1DM receiving first transplant were studied (SPK, LDKA, DDKA)

Unadjusted graft survival

Unadjusted patient survival

Conclusion: “LDKT utilization should be considered in all T1DM with an available donor”

Young et al. CJASN 2009; 4: 845-852
“Metabolic control improves long-term renal allograft and patient survival in type 1 diabetes”

In tx recipients with T1DM alive with kidney function at 10 years post-transplant, those with SPK had the greatest survival from years 10-18, dependent upon pancreas function.

Morath C et al, JASN 2008; 19: 1558
“12 Month Pancreas Graft Function Significantly Influences Survival Following SPK”

Weiss AS et al, CJASN 2009; 4: 988

9630
SPK Waitlisted
Patients Transplanted
1997-2005

7952
SPK

616
DD KA

1062
LD KA

12 month survivors with functioning kidney grafts*

6486
SPK, P+
Functioning Panc

371
SPK, P-
Failed Pancreas

520
DD KA

904
LD KA

*Excluded death, kidney graft loss, LTFU, <12mo FU
84 Month Patient Survival

**SPK, P+:** 88.6%
**LD KA:** 80.0%
**SPK, P-:** 73.9%
**DD KA:** 64.8%

P-value for Log-rank test of equality over strata < .0001

Weiss AS et al, CJASN 2009; 4: 988
SPK: Improved survival (2-5y after SPK) is related to pancreas function

<table>
<thead>
<tr>
<th>12 Mo survivors:</th>
<th>HR Death (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SPK, P+</td>
<td>1.0</td>
</tr>
<tr>
<td>SPK, P-</td>
<td>2.39 (1.81-3.15)**</td>
</tr>
<tr>
<td>DD KA</td>
<td>2.07 (1.54-2.78)**</td>
</tr>
<tr>
<td>LD KA</td>
<td>1.48 (1.49-2.49)**</td>
</tr>
</tbody>
</table>

**p<0.001 for all comparisons

Multivariate analysis, included significant variables in stepwise backwards regression: recipient age, recipient race, pretransplant dialysis, DGF, acute rejection

Weiss AS et al, CJASN 2009; 4: 988
Should Patients with T1DM and a Living Donor Wait for an SPK or Proceed with Living Donor Kidney Transplant?

Start Dialysis

1. Proceed with LDKT

2. Wait……… receive SPK

3. Wait…………………… receive SPK

4. Wait…………………………… proceed with LDKT

Is there an advantage, option 1 vs 2?

What is the penalty, options 3 or 4 vs 1?
Methods

• OPTN/UNOS database: 5664 patients with T1DM from 2000-2009 who received an SPK or LDK transplant either preemptively or within the first year after starting dialysis.
  – Limited to <1y of dialysis time since this may be what patients with living donors may consider a “maximum” waiting period for SPK

• Four groups:
  – Preemptive SPK
  – Preemptive LDK
  – SPK with 1-365 d of dialysis
  – LDK with 1-365 d of dialysis

Huang et al, Transplantation 2011 Sep 28
Wiseman et al, ATC 2011
Patient Survival

- Preemptive SPK
  - Huang et al, Transplantation 2011 Sep 28
  - Wiseman et al, ATC 2011

Proportion of Patients Survived

Years

- Preemptive SPKT
- Preemptive LDKT
- SPKT < 1 year
- LDKT < 1 year

P = 0.03

P = 0.44
Patient Survival For Pre-emptive LDKT vs SPK: Unadjusted and Multivariate analysis

- **Preemptive SPK:**
  - Non-proportional mortality risk over time compared to preemptive LDKT

<table>
<thead>
<tr>
<th></th>
<th>Preemptive LDKT (N=1353)</th>
<th>Preemptive SPKT (N=1429)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1 year mortality</td>
<td>1.4%</td>
<td>2.8%</td>
<td>0.02</td>
</tr>
<tr>
<td>1-7 year mortality</td>
<td>14.0%</td>
<td>8.0%</td>
<td>0.01</td>
</tr>
<tr>
<td>Overall (0-7y)</td>
<td>15.4%</td>
<td>10.8%</td>
<td>0.44</td>
</tr>
</tbody>
</table>

- Early (smaller) risk followed by later (larger) benefit of SPK vs. LDKT
  - **Preemptive SPK:** 2-fold higher early risk of death (year 1), 50% less risk of death after year 3 compared to preemptive LDKT

Huang et al, Transplantation 2011 Sep 28
Wiseman et al, ATC 2011
Conclusions:
The TIDM patient with CKD (no dialysis) and a living donor:

1. Proceed with LDKT
2. Wait……… receive SPK

SPK: better survival after 3 years (with small early mortality risk)
3. Wait…………………………… receive SPK

4. Wait………………………………proceed with LDKT

Neither option better than preemptive options

If waiting time and disease progression predict a need for dialysis prior to SPK, then LDKT should be encouraged
SPK vs LDKA: Summary
(“stocks vs bonds”)

• In “all comers”: Need to balance mortality in first 12 months (1-2% higher with SPK) vs. long-term benefits of SPK (after ~5 years)

• Pancreas graft function for a little as 12 months is associated with better survival than LDKA

• Early pancreas graft loss (~15% by recent UNOS/SRTR reports) results in outcomes ≈ DDKA

• Bottom line: With SPK, ~85% will have made the “right choice”, 15% will have made the “wrong choice”
SPK: mitigating the risks 
(avoiding the 15% “wrong decision”)

• **RECIPIENT FACTORS:**
  - Risk factor for pancreas graft loss: HR
  - Obese recipients: 1.41
  - Risk factors for death: HR
  - Prior Dialysis time 1.41
  - Recipient age >45 1.68

If TIDM with living donor:
take living donor if recipient BMI >30, age >45, or on dialysis
Make sure pancreas donor is “less risky” (low DRI) if proceeding with SPK

• **DONOR FACTORS:**
  - gender, age, race, BMI, cause of death, Cr, height, DCD status predictive of pancreas graft survival

• **Use of pancreas donor risk index (DRI):**

Gruessner AC et al, Cur Opin Organ Transplant 2010
Sampaio et al, Transplantation 2010
Axelrod et al, Am J Transplant. 2010
Waiting list survival of SPK candidates

40% mortality at 4 years while waiting for SPK

NEED TO MINIMIZE WAITING TIME

11,572 patients listed for pancreas transplant between 1995-2000

12,478 patients listed for pancreas transplant between 1995-2003

Venstrom et al. JAMA 2003;290:2817
Proposed algorithm for Type 1 diabetic patients requiring transplant

**Suitable Candidate for** Simultaneous Pancreas Kidney transplantation

- **yes**
  - Living kidney donor available?
    - **no**
      - Simultaneous Pancreas Kidney Transplant
      - **yes**
        - Patient on dialysis?
          - **yes**
            - Living Donor Kidney Transplant Alone*
          - **no**
            - List for Simultaneous Pancreas Kidney Transplant

- **no**
  - Evaluate for kidney transplant alone (living donor or deceased donor)

*Assess expected waiting time, consider continued waiting for SPK if waiting time less than 6-12 months

**Pre-emptive Simultaneous Pancreas Kidney Transplant**

**Progression to /nearing? dialysis**

Wiseman AC, ACKD 2009; 16(4): 278-87
Who benefits from SPK? Conclusions

• It is all about the WAIT:
  – SPK if it can be done preemptively or in a region with short waiting time (< 1 year?)
  – LDKA if in a region with long SPK waiting time
  – If LDKA: consider PAK (better if performed within 12 months, good GFR, no episodes of rejection or overt proteinuria)

• Ultimately, pancreas transplant should be considered on an individual basis with each patient in the context of the transplant center’s allocation policy and donor availability
Median waiting time to transplant (days) 2004

- SPK
  - A: 323
  - B: 520
  - O: 533
  - AB: 214

- Kidney
  - A: 815
  - B: 1655
  - O: 1568
  - AB: 602

INCENTIVE TO PUT PATIENTS ON SPK LIST (EVEN T2DM???)

SRTR Annual Report 2009
Organ Allocation:
“The kidney follows the pancreas”

Organ Donor: 2 kidneys, 1 pancreas

- **Pancreas list**
  - A (E on kidney list)
  - B
  - C (G on kidney list)
  - D

- **Kidney list**
  - A
  - B
  - C
  - D
  - E
  - F
  - G

If “Pancreas follows kidney”: Candidates A and B get kidneys, and B gets pancreas

If “Kidney follows pancreas”: Candidate A gets kidney, and E gets SPK

INCENTIVE TO PUT PATIENTS ON SPK LIST (EVEN T2DM???)
Simultaneous Pancreas Kidney Transplantation: For T2DM?
SPK for T2DM?

- OPTN/UNOS Data analysis of SPK recipients 2000-2007, by DM classification (n=582 T2DM recipients):

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>T1DM (n = 6141)</th>
<th>T2DM (n = 582)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diabetes onset, years</td>
<td>12 (8 to 18)</td>
<td>25 (18 to 31)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI, kg/m2</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&lt;18.5</td>
<td>2.8</td>
<td>2.8</td>
<td></td>
</tr>
<tr>
<td>18.5 to 25</td>
<td>54.2</td>
<td>43.9</td>
<td></td>
</tr>
<tr>
<td>25 to 30</td>
<td>32.3</td>
<td>36.2</td>
<td></td>
</tr>
<tr>
<td>&gt;30</td>
<td>10.7</td>
<td>17.1</td>
<td></td>
</tr>
<tr>
<td>Age at transplant, years</td>
<td>40</td>
<td>47</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age &gt;45 years %</td>
<td>27.5</td>
<td>54.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pretransplant dialysis, days</td>
<td>603</td>
<td>714</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pre-emptive transplant %</td>
<td>20.9</td>
<td>17.5</td>
<td>0.05</td>
</tr>
</tbody>
</table>

Sampiao M et al, CJASN 2011; 6: 1198
Pancreas transplant outcomes are equivalent in T1DM vs. selected T2DM

### Pancreas-related complications

<table>
<thead>
<tr>
<th></th>
<th>T1DM</th>
<th>T2DM</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>One-year kidney and/or pancreas rejection</td>
<td>15.8</td>
<td>14.7</td>
<td>0.89</td>
</tr>
<tr>
<td>Pancreas complications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>abscess/local infection</td>
<td>4.37</td>
<td>2.95</td>
<td>0.23</td>
</tr>
<tr>
<td>anastomosis leak</td>
<td>2.15</td>
<td>1.91</td>
<td>0.91</td>
</tr>
<tr>
<td>pancreatitis</td>
<td>2.43</td>
<td>1.56</td>
<td>0.42</td>
</tr>
<tr>
<td>primary nonfunction</td>
<td>0.86</td>
<td>0.86</td>
<td>0.75</td>
</tr>
<tr>
<td>surgery to convert bladder to enteric drainage</td>
<td>1.43</td>
<td>1.37</td>
<td>0.91</td>
</tr>
</tbody>
</table>

Sampiao M et al, CJASN 2011; 6: 1198
Should patients with T2DM also receive the same priority as those with T1DM?

• New allocation policies prioritize allocation of kidneys (with a pancreas) to patients listed for SPK transplant

• By “opening the window of opportunity”, more T2DM pts may be listed/receive SPK
  – Disadvantages T1DM access to SPK (scare resource)
  – Allow T2DM to be transplanted faster than other patients on the wait list (shorter waiting time for SPK)

• Unknown if the is a benefit of pancreas transplant over kidney alone in this group (NEED TO COMPARE SIMILAR T2DM WHO RECEIVE KIDNEY ALONE)
Does the added pancreas transplant lead to better outcomes for “young”, “thin” patients with T2DM?

- No increase in early graft loss or mortality, better patient survival with SPK
- Waiting time much shorter, donor age much less in SPK cohort

SRTR database analysis of patients with T2DM, age 18-59, with BMI 18-30 kg/m² receiving an SPK or DDKA during 2000-2008:

Patient Survival

Death-Censored Kidney Graft Survival

Wiseman AC and Gralla J, ATC 2011
Does the added pancreas explain the survival difference?

Multivariable analysis

<table>
<thead>
<tr>
<th></th>
<th>Odds Ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>DDKA vs. SPK</td>
<td>0.90 (0.66-1.23)</td>
<td>0.50</td>
</tr>
<tr>
<td>Recipient Age ≥50</td>
<td>1.39 (1.15-1.67)</td>
<td>0.0005</td>
</tr>
<tr>
<td>Wait time ≥24 months</td>
<td>1.11 (0.93-1.32)</td>
<td>0.27</td>
</tr>
<tr>
<td>Donor Age ≥35</td>
<td>1.24 (1.02-1.51)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

- The survival differences between SPK and DDKA were no longer significant.

- Outcomes were primarily related to donor age and recipient age.

- While this analysis generally favors SPK in selected T2DM, it does not support prioritization of T2DM candidates as SPK candidates due to the lack of evidence that the added pancreas improves survival.
Final Thoughts-
SPK as a Transplant Option

• Avoid dialysis…know the waiting time expectations for SPK and advise your patients accordingly

• Regarding pancreas organ selection, choose wisely if you have time

• Pancreas transplant can be life-changing both in the positive (now the vast majority of the time) and the negative