Management of Diabetes After Solid Organ Transplantation

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Upper NY-AACE Annual Meeting, October 14, 2017
OBJECTIVES

1. Understand importance of diabetes management after transplantation;

2. Recognize post-transplant risk factors that impair glucose metabolism;

3. Review therapeutic options and develop practical approach in management of hyperglycemia after transplantation.
## Transplantation in 2016

<table>
<thead>
<tr>
<th></th>
<th>Performed</th>
<th>Waiting list</th>
<th>NY State</th>
<th>Strong Memorial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidney</td>
<td>19,060</td>
<td>97,020</td>
<td>1,421</td>
<td>72</td>
</tr>
<tr>
<td>Liver</td>
<td>7,841</td>
<td>14,270</td>
<td>404</td>
<td>36</td>
</tr>
<tr>
<td>Heart</td>
<td>3,191</td>
<td>3,954</td>
<td>188</td>
<td>16</td>
</tr>
<tr>
<td>Lung</td>
<td>2,327</td>
<td>1,367</td>
<td>65</td>
<td></td>
</tr>
<tr>
<td>Kidney-Pancreas</td>
<td>798</td>
<td>1,710</td>
<td>36</td>
<td>2</td>
</tr>
</tbody>
</table>

*The U.S. Organ Procurement and Transplantation Network and the Scientific Registry of Transplant Recipients, assessed July 22, 2017*
Complications of Solid Organ Transplantation

- Cardiovascular morbidity (MI, stroke)
- Infections
- Allograft rejection
- Hyperglycemia
- Dyslipidemia
- Hypercalcemia
- Osteoporosis
- Cancer (skin, lymphoma, thyroid)

Adverse outcomes

Pretransplant milieu

Immunosuppression

Improved organ function
Terminology

• Pretransplant diabetes mellitus - diabetes diagnosed before the transplantation

• New onset diabetes after transplantation (NODAT) – diabetes that is diagnosed using conventional criteria after transplantation

• Posttransplant diabetes mellitus (PTDM) – diabetes diagnosed before and after transplantation

DM Prevalence in Pre-Transplant Population

• ~10% in general US population
• 32% in kidney wait list (OPTN/UNOS)
• 25% in lung wait list (Alfred hospital, Melbourne, Australia)
• 21% in liver wait list (OPTN/UNOS)
• 37% in heart wait list (Baylor Univ. MC)


OPTN/UNOS- the Organ Procurement and Transplant Network/United Network for Organ Sharing
Diabetes is Associated with Adverse Outcomes in Renal Transplant Recipients

- All cause mortality
  - CV mortality
- CV morbidity
- Graft dysfunction
  - Impaired long-term graft function
  - Graft loss

Gosmanova et al, *Endocrine Practice*, 2012
Kidney Tx - OPTN/UNOS Outcomes

• NODAT patients during the 1\textsuperscript{st} year – 50% higher rate of acute rejection compared with pre-Tx DM

• All cause mortality adjusted HR:
  – Pre-Tx DM – 1.70 (P<0.001)
  – NODAT – 1.17 (NS)

• CV mortality adjusted HR:
  – Pre-Tx DM – 2.08 (P<0.001)
  – NODAT– 1.20 (NS)

Kuo HT et al., AJKD, 2010
Graft Rejection Studies in NODAT

• Prospective 12-yr graft survival study in SUNY: RR of graft failure in NODAT patients compared with non-diabetic control is 3.72 (P=0.04) (Miles AM et al. Transplantation 1998; 65: 380–384)

• Longitudinal Taiwan study: 2-fold higher risk of reaching the primary outcome (doubling of serum Cr, graft failure, death) in NODAT patients compared with control (Tsai JP et al., World J Surg 2011; 35: 2818–25)

• Case-control study from the Cleveland Clinic: NODAT was associated with an increase in graft rejection (47 vs 23%, P=0.018) (Siraj ES, Transplant Proc 2010; 42: 1685–1689)
Post-transplant diabetes increases the risk of acute liver rejection and all-cause and CV mortality.
Increased mortality in patients with diabetes after lung transplantation

Hackman KL et al. Dia Care 2014;37:2919-2925
Conclusions

• NODAT is associated with inferior graft survival measures and higher mortality

• Pretransplant DM is associated with increased all-cause and CV mortality

PTDM can influence short- and long-term outcomes after transplantation
New Onset Diabetes After Kidney Transplantation – Diagnosis

<table>
<thead>
<tr>
<th>NORMAL</th>
<th>IFG or IGT</th>
<th>DIABETES</th>
</tr>
</thead>
<tbody>
<tr>
<td>FPG &lt; 100 mg/dl</td>
<td>IFG FPG ≥ 100 - 125 mg/dl</td>
<td>FPG ≥ 126 mg/dl</td>
</tr>
<tr>
<td>2-h PG &lt; 140 mg/dl</td>
<td>IGT 2-h PG ≥ 140 - 199 mg/dl</td>
<td>2-h PG ≥ 200 mg Random PG ≥ 200 + symptoms</td>
</tr>
</tbody>
</table>

Definition is similar to DM of ADA except that HbA1c is not recommended in early post-Tx period
## NODAT Risk Factors

<table>
<thead>
<tr>
<th>Risk Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt; 45 yrs</td>
</tr>
<tr>
<td>Nonwhite ethnicity</td>
</tr>
<tr>
<td>Overweight/obesity (BMI ≥25 kg/m²)</td>
</tr>
<tr>
<td>Weight gain after KT</td>
</tr>
<tr>
<td>Family history of DM</td>
</tr>
<tr>
<td>Impaired fasting glucose (blood glucose = 100-125 mg/dL)</td>
</tr>
<tr>
<td>Cytomegalovirus infection</td>
</tr>
<tr>
<td>Hepatitis C infection</td>
</tr>
<tr>
<td>Immunosuppression agents</td>
</tr>
</tbody>
</table>


Diabetic Medicine, 2012: 29(7): e1-e12
Incidence of new-onset diabetes mellitus after kidney transplant

Sixty-six percent of patients without diabetes before transplantation developed inpatient hyperglycemia and required insulin at hospital discharge.

Harini A. Chakker et al. Dia Care 2013;36:1406-1412
Immunosuppressive Medications and Glucose Metabolism
Glucocorticosteroids

- **Dose-dependent effect:**
  - Dose reduction to 5 mg affected least insulin sensitivity and was not different from withdrawal

- **Mechanisms:**
  - Peripheral insulin resistance
  - Suppression of endogenous insulin production

Gosmanova et al, *Endocrine Practice*, 2012
Calcineurin Inhibitors and NODAT after Kidney Tx

Woodward et al., *Am J Transplant*, 2003

<table>
<thead>
<tr>
<th>Type of Calcineurin Inhibitor</th>
<th>Sample Size</th>
<th>Days Before Transplant</th>
<th>Days After Transplant</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>-730</td>
<td>-365</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>1776</td>
<td>3954</td>
<td>5867</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>471</td>
<td>911</td>
<td>1260</td>
</tr>
</tbody>
</table>

*Note: The incremental incidence of diabetes for cyclosporine was 9.4% at 1 year and 8.4% at 2 years. The incremental incidence of diabetes for tacrolimus was 15.4% at 1 year and 17.7% at 2 years.*
Incidence of NODAT at 1 Year after Kidney and Liver Transplantation – Tacrolimus vs Cyclosporine

New-Onset Diabetes After Transplantation (NODAT): An Evaluation of Definitions in Clinical Trials

M. Roy First, Shobha Dhadda, Richard Croy, John Holman, and William E. Fitzsimmons

Background. New-onset diabetes after transplantation (NODAT) occurs commonly. Prior NODAT definitions have been inconsistent. Based on the American Diabetic Association criteria, we propose a new approach to defining NODAT.

Methods. Analysis of 1416 at-risk transplant recipients was performed. Data from three de novo Astellas registration transplant studies (two kidney and one liver) evaluated NODAT in 634 at-risk patients receiving tacrolimus, 630 at-risk patients receiving cyclosporine extended release, and 152 at-risk patients receiving cyclosporine. NODAT was defined as a composite endpoint consisting of first occurrence of one of four parameters: (i) two fasting plasma glucose levels ≥126 mg/dL (≥7.0 mmol/L) ≥30 days apart, (ii) oral hypoglycemic agent use for ≥30 consecutive days, (iii) insulin therapy for ≥30 consecutive days, and (iv) hemoglobin A1c ≥6.5%. We evaluated each of the above parameters, as well as the composite endpoint, in an attempt to establish an appropriate clinical approach to the diagnosis of NODAT.

Results. The composite definition results in a 1-year NODAT incidence of 30% to 37% in kidney and 44% to 45% in liver transplant recipients treated with tacrolimus. NODAT incidence was significantly higher with tacrolimus than cyclosporine; there was no difference between the two tacrolimus formulations.

Conclusions. Based on these analyses, the proposed composite definition for NODAT, incorporating broader criteria, is recommended for clinical trials. Appropriate definitions of NODAT allow for a better understanding of the incidence of this complication and may result in earlier initiation of therapy with improved long-term outcomes.

Keywords: New-Onset Diabetes After Transplantation (NODAT)

TABLE 5. NODAT incidence at 1 year in subjects with (baseline HbA1c 5.7% 6.5%) and without pre-diabetes by race/ethnicity and treatment

<table>
<thead>
<tr>
<th></th>
<th>African-American</th>
<th>Hispanic</th>
<th>Caucasian</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-diabetes, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>4/4 (100.0)</td>
<td>0/3 (0.0)</td>
<td>13/30 (43.3)</td>
<td>21/42 (50.0)</td>
</tr>
<tr>
<td>Tacrolimus BID</td>
<td>2/2 (100.0)</td>
<td>0/1 (0.0)</td>
<td>3/11 (27.3)</td>
<td>6/18 (33.3)</td>
</tr>
<tr>
<td>Tacrolimus QD</td>
<td>2/2 (100.0)</td>
<td>0/0 (0.0)</td>
<td>10/17 (58.8)</td>
<td>14/21 (66.7)</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>0/0 (0.0)</td>
<td>0/2 (0.0)</td>
<td>0/2 (0.0)</td>
<td>1/3 (33.3)</td>
</tr>
<tr>
<td>No pre-diabetes, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>38/117 (32.5)</td>
<td>36/87 (41.4)</td>
<td>401/1165 (34.4)</td>
<td>474/1375 (34.5)</td>
</tr>
<tr>
<td>Tacrolimus BID</td>
<td>20/48 (41.7)</td>
<td>11/30 (36.7)</td>
<td>183/524 (34.9)</td>
<td>219/616 (35.6)</td>
</tr>
<tr>
<td>Tacrolimus QD</td>
<td>16/45 (35.6)</td>
<td>18/38 (47.4)</td>
<td>196/523 (37.5)</td>
<td>229/609 (37.6)</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>2/24 (8.3)</td>
<td>7/9 (36.8)</td>
<td>22/118 (18.6)</td>
<td>26/149 (17.4)</td>
</tr>
</tbody>
</table>
Calcineurin Inhibitors and NODAT

- Dose-dependent effect of Tacrolimus
  - Hepatitis C positivity may result in a higher incidence of NODAT with Tacrolimus compared with Cyclosporine [Bloom et al, JASN, 2002]

- Mechanisms of diabetogenic action:
  - β-cell toxicity (reduce second-phase insulin secretion)
  - Reversible action
  - Cyclosporine inhibits metabolism of steroids by suppressing cytochrome P450 system
Other Immunosuppressants

• **Mycophenolate mofetil (Cellcept):**
  - Did not affect glucose metabolism in clinical trials.

• **Sirolimus (Rapamycin):**
  - Conflicting data from *in vitro*, *in vivo* and clinical trials;
  - May worsen peripheral insulin resistance

• **Everolimus (Afinitor):**
  - No glucose effects have been noticed

Pham et al., *Endocrinol Metab Clin N Am*, 2007
Chronic Viral Infection

• **Hepatitis C**
  - Increases 2-4 fold incidence of diabetes in non-transplant population,
  - HCV infection affects mostly peripheral insulin sensitivity

• **Cytomegalovirus**
  - Asymptomatic and symptomatic CMV infection is a risk factor;
  - CMV infection affects β–cell function via possibly cytokine mechanism
  - CMV infection increased 4-fold incidence of NODAT during first 3 months post-KT

Pham et al., *Endocrinol Metab Clin N Am*, 2007
Managing DM after Transplant

1. Pre-transplant work up
   - Identify and optimize pre-transplant DM

2. Monitor for hyperglycemia, d/c plans
   - Low threshold to use insulin

3. Monitor for hyperglycemia, graft function
   - Diet and medications optimization

4. HbA1c/OGTT to diagnose DM
   - Use safe anti-diabetes regimens

5. Consider broader hypoglycemic regimens
   - CV risk modification, full assessment
Why To Treat PTDM?

- Control of hyperglycemia symptoms
- Reduce post-op infections?
- Insulin provides anabolic action
- Diabetes is associated with increased mortality (long-term)
Pretransplant Diabetes Screening

• HbA1c – may not be a reliable marker
  – Anemia, acidosis, erythropoietin stimulating agents, Fe supplements, carbamylated hemoglobin.

• Fasting plasma glucose
  – low sensitivity

• 2-hour OGTT
  – Provides best sensitivity and specificity
  – Captures both fasting and postprandial glucose
  – Able to identify patients with DM and pre-DM

Bergrem et al, CJASN, 2010, 5: 616-622
Evidence Why ESRD Patients Should Be Screened for Dysglycemia

Undiagnosed Diabetes in Kidney Transplant Candidates: A Case-Finding Strategy

Henrik Andreas Bergrem,* Tone Greitland Valderhaug,*† Anders Hartmann,*
Jørjan Hjelmesæth,‡ Torbjørn Leivestad,§ Harald Bergrem,‖ and Trond Jenssen*†

Departments of *Medicine and †Thoracic Surgery and §Institute of Transplantation Immunology, Oslo University Hospital Rikshospitalet, Oslo, Norway; ‡Morbid Obesity Centre, Vestfold Hospital Trust, Tønsberg, Norway;
‖Department of Medicine, Stavanger University Hospital, Stavanger, Norway; and §Institute of Clinical Medicine, University of Tromsø, Tromsø, Norway.

Background and objectives: Guidelines recommend that candidates for kidney transplantation (KTx) who do not have diabetes perform a pretransplantation oral glucose tolerance test (OGTT) when fasting plasma glucose (FPG) is <110 mg/dl (<6.1 mmol/L); however, the OGTT is potentially costly and cumbersome. We studied the role of the OGTT for diagnosing diabetes and the accuracy of FPG and glycated hemoglobin (HbA1c) for predicting a diabetic OGTT before KTx.

Design, setting, participants, & measurements: In this cross-sectional study, 889 first single-kidney transplant candidates without diabetes, mainly white, performed an OGTT during the transplantation workup. Results were studied using receiver operating characteristic analysis.

Results: Of 72 (8.1%) patients with undiagnosed diabetes, only 16 (22%) had a diabetic FPG (≥126 mg/dl [≥7.0 mmol/L]). In patients with a nondiabetic FPG, diabetes (2-hour plasma glucose [2h-PG] ≥200 mg/dl [≥11.1 mmol/L]) was predicted by FPG but not by HbA1c. Performing the OGTT in patients with FPG 92 to 125 mg/dl (5.1 to 6.9 mmol/L) identified 65 (90%) patients with diabetes (16 by FPG, 49 by 2h-PG) and required seven OGTTs per patient identified. Subjecting all patients with FPG <110 mg/dl (<6.1 mmol/L) to the OGTT identified 60 (83%) patients with diabetes (16 by FPG, 44 by 2h-PG) but required 14 OGTTs per patient.

Conclusions: The OGTT was paramount in finding most cases of undiagnosed diabetes before KTx. FPG but not HbA1c predicted a diabetic OGTT. We suggest that white KTx candidates without diabetes perform a pretransplantation OGTT when FPG is 92 to 125 mg/dl (5.1 to 6.9 mmol/L).


26% had IGT and 11% had IFG = 37% had prediabetes
45% had dysglycemia!!!!
Assessment of Glucose Metabolism Before Tx

**Previous history of diabetes**
- Yes
  - Evaluate and optimize:
    - LSM
    - Glycemic control
    - Lipid control
    - Blood pressure control
  - Yes
  - DM diagnosed
  - No
  - Prediabetes diagnosed
- No
  - Evaluate:
    - Medical, family, and glucose history
    - If NODAT risk factors present (Table 1), assess:
      1. 2-hour OGGT and/or
      2. Fasting blood glucose
  - DM diagnosed
  - No
  - Prediabetes diagnosed
  - Yes
    - Initiate LSM and re-assess in 3-6 months
  - No
    - Reassess annually

**Additional Factors**
- Age > 45 yrs
- Nonwhite ethnicity
- Overweight/obesity (BMI ≥ 25 kg/m²)
- Weight gain after KT
- Family history of DM
- Impaired fasting glucose
- Cytomegalovirus infection
- Hepatitis C infection
- Immunosuppression agents

Gosmanova et al, *Endocrine Practice*, 2012
NODAT Case Detection

• No prospective trials to identify cost-effective approach to diagnose or prevent NODAT

• Early post-transplant evaluation:
  – Monitor glucose weekly for 4 weeks, then at 3, 6, 12 months and annually;
  – Patients with early transient hyperglycemia does not mean diabetes (not all early post-Tx patients with BG>200 will become diabetic)
  – Consider 2-hour OGTT at week 10-12 (lowest steroid dose, stable renal function)
  – HbA1c is not recommended first 3 months

  Kasiske at al, *Kidney Int*, 2010
  Pham et al., *Diabetes Metab Syndr Obes*, 2011
**Can Early Insulin Therapy Prevent NODAT?**

**Design:** Prospective RCT, 50 patients randomized on 2-3 day after KT to receive either NPH 6-10 units/d with titration for BG>140 vs standard of care (sliding scale insulin or SU) for BG>250mg/dL for 3 wks

**Immunosuppression:** Tacrolimus, MMF, steroids (Dexamethasone taper early followed by prednisone)

**Assessments:** HbA1c, OGTT, renal outcomes, diabetes status

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![Graph A: Glucose (mg/dL)](image)

**Graph A:**
- Glucose levels over time
- Mean ± SD bars
- p<0.001

![Graph C: Insulin (IU)](image)

**Graph C:**
- Insulin levels over time
- Mean ± SD bars
- p<0.001

**Table:**

<table>
<thead>
<tr>
<th>Time</th>
<th>Diabetic (n=5)</th>
<th>Non-diabetic (n=6)</th>
<th>Diabetic + Prediabetic (n=2)</th>
<th>Normal (n=1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 months</td>
<td>1.8 ± 0.5</td>
<td>1.6 ± 0.7</td>
<td>1.5 ± 0.3</td>
<td>1.8 ± 0.6</td>
</tr>
<tr>
<td>6 months</td>
<td>1.7 ± 0.5</td>
<td>1.5 ± 0.4</td>
<td>1.5 ± 0.4</td>
<td>1.6 ± 0.6</td>
</tr>
<tr>
<td>12 months</td>
<td>1.7 ± 0.5</td>
<td>1.5 ± 0.4</td>
<td>1.5 ± 0.4</td>
<td>1.6 ± 0.6</td>
</tr>
</tbody>
</table>

**Odds Ratios [95% CI]**

- Normal: <140 mg/dL
- Impaired glucose tolerance: 140-199 mg/dL
- Diabetic: ≥200 mg/dL

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Manfred Hecking et al. JASN 2012;23:739-749
## Analysis 1.7. Comparison of Any dosage belatacept versus calcineurin inhibitor (CNI), Outcome 7 Diabetes and use of blood pressure medicines.

**Review:** Belatacept for kidney transplant recipients

**Comparison:** Any dosage belatacept versus calcineurin inhibitor (CNI)

**Outcome:** 7 Diabetes and use of blood pressure medicines

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Belatacept</th>
<th>CNI</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>New-onset diabetes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ferguson 2010</td>
<td>2/41</td>
<td>1/17</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vincenti 2005 (1)</td>
<td>8/94</td>
<td>2/22</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BENEFIT-EXT 2009</td>
<td>14/270</td>
<td>12/119</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BENEFIT Study 2008</td>
<td>25/324</td>
<td>20/162</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>729</strong></td>
<td><strong>320</strong></td>
<td></td>
<td><strong>100.0 %</strong></td>
<td><strong>0.61 [0.40, 0.93]</strong></td>
</tr>
</tbody>
</table>

Total events: 49 (Belatacept), 35 (CNI)

Heterogeneity: Tau² = 0.0, Chi² = 0.60, df = 3 (P = 0.90); I² = 0.0%

Test for overall effect: Z = 2.30 (P = 0.022)

Masson P et al., Cochrane Database of Systematic Reviews 2014, Issue 11
Post-transplant DM Treatment

- **Pre-transplant Type 1 DM:**
  - Optimize insulin management

- **Pre-transplant Type 2 DM:**
  - Multiple daily insulin injections or
  - Long-acting insulin and oral medications

- **NODAT:**
  - Treat as Type 2 DM depending on degree of blood glucose elevation
  - Low threshold to start insulin therapy
List of the FDA-approved non-insulin agents for treatment of diabetes for mono- or combination therapy

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Name</th>
<th>Optimal dose</th>
<th>HbA1c reduction, %</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Biguanides</strong></td>
<td>Metformin IR†</td>
<td>1000 mg bid</td>
<td>1.0-2.0</td>
<td>↓ Hepatic glucose release</td>
</tr>
<tr>
<td></td>
<td>Metformin XR†</td>
<td>1000 mg bid</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Sulphonylureas</strong></td>
<td>Glyburide†</td>
<td>5 mg bid</td>
<td>1.0-2.0</td>
<td>↑ Endogenous insulin release</td>
</tr>
<tr>
<td></td>
<td>Glipizide†</td>
<td>5 mg bid</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Glipizide XR†</td>
<td>5-10 mg qd</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Glimepiride†</td>
<td>1-4 mg qd</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Glitiniades</strong></td>
<td>Nateglinide†</td>
<td>60-120 mg ac</td>
<td>0.5-1.5</td>
<td>↑ Endogenous insulin release</td>
</tr>
<tr>
<td></td>
<td>Repaglinide</td>
<td>0.5-1 mg ac</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Thiazolidinedione</strong></td>
<td>Pioglitazone</td>
<td>15-30 mg qd</td>
<td>0.5-1.5</td>
<td>↑ insulin sensitivity</td>
</tr>
<tr>
<td><strong>α-Glucosidase inhibitors</strong></td>
<td>Acarbose†</td>
<td>25-50-100 mg ac</td>
<td>0.5-0.8</td>
<td>↓ glucose absorption</td>
</tr>
<tr>
<td></td>
<td>Miglitol†</td>
<td>50-100 mg ac</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Bile acid sequestrant</strong></td>
<td>Colesevelam</td>
<td>1875 mg bid</td>
<td>0.5</td>
<td>? (↓ glucose absorption, liver)</td>
</tr>
<tr>
<td><strong>Dopamine agonist</strong></td>
<td>Bromocryptine XR</td>
<td>0.8-4.8 mg qd</td>
<td>0.4-0.5</td>
<td>? (CNS)</td>
</tr>
<tr>
<td><strong>DPP-4 inhibitors</strong></td>
<td>Sitagliptin†</td>
<td>100 mg qd</td>
<td>0.5-1.0</td>
<td>↑ insulin secretion, glucagon release, gastric emptying</td>
</tr>
<tr>
<td></td>
<td>Saxagliptin†</td>
<td>5 mg qd</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Linagliptin</td>
<td>5 mg qd</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Alogliptin†</td>
<td>25 mg qd</td>
<td></td>
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</tr>
<tr>
<td><strong>GLP-1 agonists</strong></td>
<td>Exenatide†</td>
<td>5-10 mcg bid sq</td>
<td>1.0-1.5</td>
<td>↑ insulin secretion, glucagon release, gastric emptying ↑ satiety</td>
</tr>
<tr>
<td></td>
<td>Liraglutide†</td>
<td>0.6-1.8 mg qd sq</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Exenatide QW†</td>
<td>2.0 mg qw sq</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lixisenatide</td>
<td>10-20 mcg</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Albilglutide</td>
<td>30-50 mg qw sq</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dilaglutide</td>
<td>0.75-1.5 mg qw sq</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>SGLT2 inhibitors</strong></td>
<td>Canagliflozin†</td>
<td>100-300 mg qd</td>
<td>0.5-1.0</td>
<td>glucosuria</td>
</tr>
<tr>
<td></td>
<td>Dapagliflozin†</td>
<td>2.5-5 mg qd</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Empagliflozin</td>
<td>10-25 mg qd</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

† - dose adjustment in renal dysfunction
# Anti-Diabetes Agents Early After Transplant

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Name</th>
<th>Optimal dose</th>
<th>Other considerations/contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Secretagogues</strong></td>
<td>Glipizide</td>
<td>2.5-5 mg qd</td>
<td>↑ Hypoglycemia, use lower doses, Glimepiride increases CsA level and renally cleared</td>
</tr>
<tr>
<td></td>
<td>Glimepiride</td>
<td>1-2 mg qd</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nateglinide</td>
<td>60-120 mg ac</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Repaglinide</td>
<td>0.5-1 mg ac</td>
<td></td>
</tr>
<tr>
<td><strong>Thiazolidinedione</strong></td>
<td>Pioglitazone</td>
<td>15-30 mg qd</td>
<td>↑ fractures, ↑ HF</td>
</tr>
<tr>
<td><strong>DPP-4 inhibitors</strong></td>
<td>Sitagliptin</td>
<td>25-50 mg qd</td>
<td>Only Vildagliptin was studied prospectively, ↑ pancreatitis, ↑ HF?</td>
</tr>
<tr>
<td></td>
<td>Saxagliptin</td>
<td>2.5 mg qd</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Linagliptin</td>
<td>5 mg qd</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vildagliptin</td>
<td>50 mg qd</td>
<td></td>
</tr>
<tr>
<td><strong>Insulin</strong></td>
<td>Basal</td>
<td>0.1-1.0 units/kg/day</td>
<td>Titration required</td>
</tr>
<tr>
<td></td>
<td>Rapid-acting</td>
<td></td>
<td>↑ Hypoglycemia</td>
</tr>
<tr>
<td></td>
<td>Premixed</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Can We Treat NODAT

Efficacy and Safety of Vildagliptin in New-Onset Diabetes After Kidney Transplantation—A Randomized, Double-Blind, Placebo-Controlled Trial

**Study Subjects:** >6 mos after KT newly diagnosed with DM, stable renal function, no prior DM

**Screened:** 509 with OGTT:
-30% had prediabetes
-12.5% had type 2 DM

**Intervention:** Life style modifications and Vildagliptin 50 mg or placebo for 16 weeks
Assessment of Glucose Metabolism After Tx

Previous history of diabetes

Yes

- Evaluate immune-suppression therapy
- Reinforce LSM
- Consider using insulin, secretagogues, and/or DPP-4 inhibitors as indicated

Target goals and screening:
- HbA1c < 7.0%
- LDL-C < 100 mg/dL
- Microalbuminuria
- Annual eye and foot examinations

No

Initiate testing:
- Fasting blood glucose weekly for 4 weeks and then at 3, 6, and 12 months and/or
- 2-hour OGTT

NODAT diagnosed

Yes

No

Continue to monitor for glucose metabolism and vascular risk factors

Gosmanova et al, Endocrine Practice, 2012
Does Early Intensive Insulin Therapy Improve Outcomes in Transplant Patients?
A Randomized Controlled Trial to Evaluate the Effect of Glycemic Control on Renal Transplantation Outcomes

**Design:** Prospective RCT, 104 kidney Tx patients randomized immediately post-op on intensive (IV insulin, BG goal 70-110) vs standard (sc insulin, BG 70-180) during first 3 days after Tx.

**Primary outcome:** delayed graft function.

**Secondary outcomes:** safety
Intensive Glycemic Control Group Was Associated with Inferior Graft Survival Rate

Conclusion:
Use common approaches in managing inpatient hyperglycemia after kidney transplantation

Hermayer KL et al., J Clin Endocrinol Metab. 2012;97(12):4399-4406
Does Glycemic Control Reduce Infections in Post–Liver Transplant Patients: Results of a Prospective, Randomized Study

**Design:** 164 liver Tx patients with any BG>180 (pre-Tx DM was only in 30%!)  
- All received IV and then sc insulin inpatient with BG target of 140-180  
- On discharge randomized to 140 vs 180mg/dL group using diet, OHAs, and/or insulin  

**Primary outcome:** infection rate within 1 year  

**Secondary outcomes:**  
- graft rejection, hypoglycemia

**Unknowns/Uncertainties:**  
- 70% of the patients did not have pre-Tx DM  
- anti-DM regimens and their complexities were not described  
- mean BGs throughout the study in both groups not reported  
- 3-fold risk of hypoglycemia in 140 mg/dL group

Initiating Basal Insulin Therapy in Transplant Patients with Mild-to-Moderate Hyperglycemia

Start with 10-12 U or 0.1-0.2 U/kg once daily if obese
- Administer in AM if nocturnal hypoglycemia is a concern
- If cost is an issue, use NPH (0.1 U/kg twice daily)

Monitor fasting PG to determine dosage adjustments

Increase dose by 2-3 U every 3-7 days until FPG is 80-130mg/dL

If hypoglycemia occurs or FPG < 70: reduce dose by 4 U or 10% TDD

A1C ≥ 7% after 3 months

YES

Intensify therapy

NO

Continue regimen; check A1C every 3 months
<table>
<thead>
<tr>
<th>Immunosuppressant</th>
<th>Glucose</th>
<th>Lipids</th>
<th>Blood pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucocorticoids</td>
<td>↑↑↑↑</td>
<td>↑↑</td>
<td>↑↑</td>
</tr>
<tr>
<td>Cyclosporine A</td>
<td>↑</td>
<td>↑↑</td>
<td>↑↑</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>↑↑</td>
<td>↔</td>
<td>↑</td>
</tr>
<tr>
<td>Mycophenolate mofetil</td>
<td>↔ ↔</td>
<td>↔ ↔</td>
<td>—</td>
</tr>
<tr>
<td>Sirolimus/Everolimus</td>
<td>↑ ↔</td>
<td>↑↑</td>
<td>—</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

Gosmanova et al, *Endocrine Practice*, 2012
Summary

• Diabetes mellitus is an independent predictor of inferior outcomes after solid organ transplantation

• There are no uniform guidelines on prevention, diagnosis, and therapy of diabetes mellitus

• Limited anti-hyperglycemic armamentarium in post-transplant care:
  – Follow safe and common sense therapeutic approaches

• Consider more proactive DM screening before and early after transplant

• Patients should be informed that newly diagnosed diabetes rates are high during first 1-2 yrs and existing DM patients will have worsening of glycemic control after Tx.
THANK YOU