Learning Objectives:

1. Discuss the pathophysiology and clinical impact of post-transplant diabetes mellitus in kidney transplant recipients
2. Evaluate differences in diabetes management between the general population and post-kidney transplantation
3. Review the pharmacology, safety, and efficacy of oral anti-glycemic agents in post-kidney transplant diabetes mellitus
Assessment Questions

1. **What is the pathogenesis of post-kidney transplant diabetes mellitus?**
   
   A. Insulin resistance  
   B. Impaired pancreatic beta cell function  
   C. Increased insulin elimination  
   D. All of the above

2. **What does the 2014 PTDM guidelines recommend for initial treatment of hyperglycemia in the first 45 days post-transplantation?**
   
   A. Metformin + lifestyle modifications  
   B. Insulin + lifestyle modifications  
   C. Pioglitazone + lifestyle modifications  
   D. None of the above

3. **Which oral anti-glycemic agent class has the most evidence of its use in solid organ transplantation?**
   
   A. Biguanide  
   B. TZD  
   C. DPP-4 Inhibitor  
   D. SGLT-2 Inhibitor
Post-Transplant Diabetes Mellitus (PTDM)

I. Background
   a. Greater than 7% of the United States general population are estimated to have diabetes\(^1\)
   b. DM prevalence in kidney transplant candidates is approximately 20% to 30%
   c. Post-transplant Diabetes Mellitus (PTDM) has been reported in up to 25% of kidney transplant recipients\(^2\)

II. Definition of PTDM
   a. Newly diagnosed diabetes mellitus in the post-transplant setting irrespective of timing or whether it was present but undiagnosed prior to transplant\(^3\)
   b. Historically known as NODAT, “New Onset Diabetes After Transplantation”\(^3,4\)
   c. Most recent recommendation from an international consensus meeting replaced NODAT with PTDM\(^3\)
      i. Change occurred due to high prevalence of undiagnosed pre-transplant diabetes mellitus

III. Risk Factors\(^5\)

<table>
<thead>
<tr>
<th>PTDM Risk Factors</th>
<th>General</th>
<th>Transplant-Specific</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-Modifiable</td>
<td>Age &gt; 45 years</td>
<td>HLA mismatch</td>
</tr>
<tr>
<td></td>
<td>Ethnicity (African American, Hispanic)</td>
<td>Deceased donor</td>
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<td></td>
<td>Family history of DM</td>
<td>Male donor</td>
</tr>
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<td></td>
<td>Genetic polymorphisms</td>
<td></td>
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<tr>
<td></td>
<td>Male</td>
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<tr>
<td></td>
<td>Polycystic kidney disease</td>
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<tr>
<td>Modifiable/Potentially Modifiable</td>
<td>Hepatitis C virus infection</td>
<td>Cytomegalovirus infection</td>
</tr>
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<td></td>
<td>Obesity</td>
<td>Immunosuppressive agent</td>
</tr>
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<td></td>
<td>Impaired glucose tolerance</td>
<td>Glucocorticoid treatment</td>
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<tr>
<td></td>
<td>Elevated LDL cholesterol</td>
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</tr>
</tbody>
</table>

Table 1: Risk factors of PTDM

   a. Montori et al.\(^6\)
      i. Meta-analysis showing 74% of the variability in incidence rates of PTDM can be attributed to the variation between immunosuppressive regimens, with high-dose steroids being associated with the highest incidence rates

IV. Differences in Pathogenesis of DM
   a. Pathogenesis of PTDM in KTR
      i. Many contributing factors exist contributing to development of PTDM
      ii. Insulin resistance, pancreatic beta cell dysfunction, increased insulin elimination\(^4\) (Figure 1)
iii. Hecking, et. al. compared stable renal transplanted patients with OGTT-derived data from a large general population cohort.

V. Glycemic Effects of Immunosuppression (Table 2)

<table>
<thead>
<tr>
<th>Immunosuppressive Agent</th>
<th>Pathogenic Mechanism</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corticosteroids</td>
<td>↓ insulin sensitivity Inhibits pancreatic insulin production and secretion ↑ Hepatic gluconeogenesis</td>
<td>Dose-dependent Potential ↓ risk of PTDM in steroid-free regimens</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>↓ insulin secretion</td>
<td>Dose-dependent ↑ Diabetogenicity with ↑ steroid dose</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>↓ insulin secretion (TAC &gt; CsA)</td>
<td>Dose-dependent ↑ Diabetogenicity with ↑ steroid dose</td>
</tr>
<tr>
<td>Sirolimus</td>
<td>↑ peripheral resistance Impairs pancreatic beta cell response</td>
<td>↑ Diabetogenicity when used in combination with CNI’s</td>
</tr>
</tbody>
</table>

Table 2: Summary of immunosuppression pathogenic mechanisms of hyperglycemia

a. Calcineurin Inhibitors (CNI’s)
   i. Evidence of diabetogenicity of tacrolimus (TAC) and cyclosporine (CsA) after renal transplantation, with greater incidence with tacrolimus use.
   ii. Proposed mechanism of hyperglycemia
      1. Impaired insulin secretion, direct pancreatic beta cell damage, decreased glucokinase activity and reduced insulin gene expression.

b. mTOR Inhibitors
   i. Impaired pancreatic beta cell proliferation, increased peripheral resistance

c. Steroids
   i. Steroid minimization is a common strategy to reduce risk of PTDM
   ii. Dose-dependent effect with potential to decrease the risk of PTDM in steroid-free regimens

d. Adjustments to immunosuppression for glycemic benefit must be weighed against the risk of long term graft survival.
VI. **Diagnosis of PTDM**
   a. A formal diagnosis should be made only once patients are stable on maintenance immunosuppression with stable kidney allograft function⁴
   b. **Screening Tests⁴**
      i. Oral glucose tolerance test (OGTT) is the gold standard diagnosing PTDM
      ii. OGTT’s can be time consuming and impractical and are not widely used
      iii. Hemoglobin A1c (HbA1c) can be used to recognize PTDM
         1. HbA1c levels in the first year post-transplant can underestimate PTDM
   c. **Diagnosis Requirements⁴**
      i. Symptoms of diabetes plus random plasma glucose ≥200 mg/dL
         1. Polyuria, polydipsia, and unexplained weight loss.
      ii. On 2 separate occasions
         1. Fasting plasma glucose ≥126 mg/dL
         2. Two-hour plasma glucose ≥200 mg/dL during an OGTT

VII. **Clinical Impact of PTDM**
   a. Development of PTDM increases risk of cardiac events¹¹,¹²
      i. Percentage of cardiac events higher in patients with PTDM than in patients without PTDM
   b. Kasiske, et al.: United States Renal Data System analysis of >11,000 KTRs¹²
      i. PTDM was associated with mortality, graft failure, and death-censored graft failure
   c. PTDM has shown to impact mortality, therefore contributing to graft loss; however, data is contradictory when adjusted for the increased risk of death¹³,¹⁴
   d. **Infections**
      i. Literature has shown increased infection risk in KTRs with PTDM¹⁴
   e. **Diabetic complications**
      i. KTRs with PTDM may develop complications associated with diabetes similar to the complications associated with general population including ketoacidosis, renal complications, ophthalmic complications, neurologic complications¹⁵

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**DM can impact both short and long term outcomes after kidney transplantation**

VIII. **Guideline Recommendations on Management of PTDM**
   a. Proposed post-transplant algorithm for PTDM⁷ (Figure 2)
   b. 2014 consensus guidelines recommendations⁴
      i. **Immediate Post-Transplant Hyperglycemia**
         1. Insulin therapy immediately post-transplant may benefit beta cell function, and decrease the risk of PTDM over time⁷
         2. Early post-transplant hyperglycemia: the reverse might be the most appropriate


Figure 2: The 2014 International consensus guidelines on the screening, diagnosis, and management of early posttransplant hyperglycemia and PTDM

ii. Late-PTDM
   1. Late-PTDM stepwise approach: lifestyle modification → oral anti-diabetic therapy → insulin
   2. Patient-specific factors and the pathophysiology underlying PTDM should help with deciding which oral anti-glycemic agent
   3. According to the consensus group, there is inadequate data to recommend a hierarchy of oral anti-glycemic agents is most beneficial

c. 2019 American Diabetes Association (ADA) guidelines on management of diabetes\textsuperscript{16}
   i. Management of PTDM
      1. Preferred diagnosis using OGTT
      2. Insulin therapy for initial post-transplant hyperglycemia
      3. No recommendation on oral anti-glycemic agent of choice in patients with PTDM

Clinical Question

What is the oral anti-glycemic agent of choice in KTR's with PTDM?
Oral Anti-Glycemic Agent Review

I. Guideline recommendations for the treatment of Type 2 DM
   a. American Academy of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE) 2017 clinical practice guidelines
      i. Lifestyle Modification
      ii. Medication management – 1st line agents
         1. Metformin
         2. Glucagon-like peptide-1 receptor agonists (GLP1 RA)
         3. SGLT-2 inhibitor (SGLT-2i)
         4. Thiazolidinedione (TZD)
         5. Dipeptidyl peptidase-4 inhibitors (DPP-4i)
         6. Alpha-glucosidase inhibitor (AGi)
   b. American Diabetes Association (ADA) 2019 Treatment Guidelines
      i. Lifestyle therapy, medical evaluation, management of comorbidities, and management of obesity for all patients
      ii. Medication management
         1. 1st line: Metformin first line if tolerated and not contraindicated
         2. 2nd line or add-on: other oral agent, GLP1 RA, basal insulin
      iii. Manage cardiovascular disease (CVD), CVD risk, blood pressure (BP) management, lipid management
   c. Summary or oral anti-glycemic agents in Appendix A

Sulfonylurea (Glipizide, Glyburide, Glimepiride)

I. Mechanism of Action
   a. Binds to pancreatic beta cell receptors to stimulate insulin secretion

II. Pharmacokinetics/Pharmacodynamics
    a. Glyburide
       i. DDI with CNI’s resulting in increased exposure of glyburide

III. Renal Adjustments (Appendix A)
    a. Glipizide: dose adjustment required at eGFR<50
    b. Glyburide: not recommended in CKD
    c. Glimeperide: consider alternative therapy at eGFR<15

IV. Pre-transplant Safety & Efficacy
    a. Efficacy: 1-2%
b. Safety: hypoglycemia, moderate gastrointestinal effects

c. Cardiovascular Effects: neutral, potentially harm

d. Weight Effects: weight gain

**Biguanide (Metformin)**

I. ADA recommends metformin as the initial pharmacological agent for treatment of type 2 DM in the general population if not contraindicated

II. Mechanism of Action\textsuperscript{19,20}

a. ↓ Hepatic glucose production

b. ↑ Insulin sensitivity

c. ↓ Glucose intestinal absorption

III. Pharmacokinetics & Pharmacodynamics\textsuperscript{19-21}

a. No concerns with DDI’s with CNI

II. Renal Adjustments\textsuperscript{19,20} (Appendix A)

a. eGFR 30-45: Use not recommended, maximum 1g/day

b. eGFR<30: Use contraindicated

III. Pre-transplant Safety & Efficacy\textsuperscript{16}

a. Efficacy: 1-2%

b. Safety: gastrointestinal effects, vitamin B12 deficiency, lactic acidosis

c. Cardiovascular Effects:

i. ↓ risk of MI

ii. ↓ overall mortality

iii. ↓ risk of diabetes-related death

d. Weight Effects: some weight loss

**Thiazolidinedione (Pioglitazone, Rosiglitazone)**

I. Mechanism of Action\textsuperscript{19,20}

a. Increases expression of genes responsible for glucose metabolism, resulting in improved insulin sensitivity

II. Pharmacokinetics & Pharmacodynamics\textsuperscript{19-21}

a. Substrate of 2C9 and 2C8

b. No significant DDI’s with immunosuppression

III. Renal Adjustments\textsuperscript{19,20} (Appendix A)

a. No dose adjustments necessary

IV. Pre-transplant Safety & Efficacy\textsuperscript{16}

a. Efficacy: 0.5-1.5%

b. Safety: fluid retention, bone fractures

c. Cardiovascular Effects: ↑ congestive heart failure (CHF) risk

d. Weight Effects: weight gain
DPP-4 Inhibitor (Sitagliptin, Saxagliptin, Alogliptin, Linagliptin)

I. Mechanism of Action
   a. Inhibit the breakdown of GLP-1 secreted during meals, increasing pancreatic insulin secretion, limiting glucagon secretion, slowing gastric emptying, and promoting satiety

II. Pharmacokinetics & Pharmacodynamics
   a. Substrate of CYP 3A4 and P-gp synthesis
   b. DDI with CsA resulting in increased exposure to DPP-4 inhibitor

III. Renal Adjustments (Appendix A)
   a. Linagliptin: no dosage adjustment
   b. Sitagliptin: eGFR 30-44: 50mg once daily; eGFR <30 or on dialysis, 25mg daily
   c. Saxagliptin: eGFR <45: 2.5mg daily

IV. Pre-transplant Safety & Efficacy
   a. Efficacy: 0.5-0.8%
   b. Safety: headache, severe joint pain
   c. Cardiovascular Effects: Possible ↑ CV risk (alogliptin, saxagliptin)
   d. Weight Effects: weight neutral

SGLT-2 Inhibitors (Empagliflozin, Canagliflozin, Dapagliflozin)

I. Mechanism of Action
   a. Increases urinary glucose excretion by blocking normal reabsorption in the proximal convoluted tubule
   b. Some effect on delaying GI glucose absorption

II. Pharmacokinetics & Pharmacodynamics
   a. DDI with CNI resulting in increased exposure of SGLT-2 inhibitor

III. Renal Adjustments (Appendix A)
   a. Canagliflozin: use contraindicated eGFR <30
   b. Dapagliflozin: use contraindicated eGFR <30
   c. Empagliflozin: use contraindicated eGFR<30

IV. Pre-transplant Safety & Efficacy
   a. Efficacy: 0.3-1%
   b. Safety: dehydration, hyperkalemia, increased urinary tract infections (UTI’s), euglycemic diabetic ketoacidosis
   c. Cardiovascular Effects: potential benefit with empagliflozin and canagliflozin
   d. Weight Effects: weight loss
I. Sulfonylurea (SU)
   a. Only one study regarding use of sulfonylureas in KTRs utilizes glijidone, a drug not approved in US\textsuperscript{22}
   b. Greatest concern with mechanism of action of SU in setting of pancreatic beta cell toxicity
   c. Potential concern for concomitant use with CNI’s, resulting in increased exposure to SU\textsuperscript{19–21}
      i. Potential DDI exists with CNI’s, however a small PK study found that glipizide treatment did not interfere with CsA in KTRs with PTDM\textsuperscript{23}

II. Biguanide
   a. One retrospective cohort study evaluating patient and allograft survival with metformin use compared with other anti-glycemic agents\textsuperscript{24} (Table 3)
   b. Majority of data on metformin in KTRs is limited to small retrospective studies\textsuperscript{25} (Table 4)
   c. Consensus guidelines state further clinical trials are warranted to assess safety and efficacy of metformin prior to recommending it as the anti-glycemic agent of choice\textsuperscript{4}

<table>
<thead>
<tr>
<th>Table 3. Stephen, et al. 2015\textsuperscript{24}</th>
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<tbody>
<tr>
<td><strong>Purpose</strong></td>
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<tr>
<td><strong>METHODS</strong></td>
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<tr>
<td><strong>Study Design</strong></td>
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<td><strong>Patient Population</strong></td>
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<tr>
<td><strong>Primary &amp; Secondary Endpoints</strong></td>
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<td><strong>RESULTS</strong></td>
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Outcomes

- Allograft and patient survival were found to be not worsened for both 1 and 3-year outcomes for KTRs who filled metformin claims compared to those who filled non-metformin claims.

<table>
<thead>
<tr>
<th>Adjusted Allograft and Patient Death</th>
<th>Adjusted HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allograft survival, living donor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-year</td>
<td>0.23 (0.06-0.91)</td>
<td>0.04</td>
</tr>
<tr>
<td>3-year</td>
<td>0.55 (0.038-0.80)</td>
<td>0.002</td>
</tr>
<tr>
<td>Allograft survival, deceased donor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-year</td>
<td>0.53 (0.032-0.89)</td>
<td>0.02</td>
</tr>
<tr>
<td>3-year</td>
<td>0.55 (0.44-0.70)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Patient survival, living donor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-year</td>
<td>0.17 (0.02-1.2)</td>
<td>0.08</td>
</tr>
<tr>
<td>3-year</td>
<td>0.40 (0.23-0.69)</td>
<td>0.001</td>
</tr>
<tr>
<td>Patient survival, deceased donor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-year</td>
<td>0.55 (0.29-1.02)</td>
<td>0.06</td>
</tr>
<tr>
<td>3-year</td>
<td>0.60 (0.46-0.79)</td>
<td>0.0003</td>
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</table>

**AUTHOR DISCUSSION & CONCLUSION**

**Author Conclusions**
- Metformin in KTRs is not associated with worse patient or allograft survival.

**Critique**

**Strengths:**
- Large sample size, especially compared to other KTR studies
- Comparator group were patients on other anti-glycemic agents

**Limitations:**
- No assessment of maintenance IMS therapy
- Baseline HbA1c’s reflected less severe diabetes
- Only first fill of metformin reported without assessing continued prescription fills and adherence
- Dose of metformin not provided, as well as change in eGFR over time
- Safety was not assessed

**Reviewer’s Conclusions**
- Metformin has potential benefit on patient and allograft survival
- Safety was not fully established by this study

**III. TZD’s**

a. Two studies have evaluated efficacy and safety of TZD’s in KTRs\textsuperscript{25,26}
b. Summary of TZD safety and effectiveness in KTRs provided in Table 4
c. Safety and efficacy of pioglitazone specifically provided in Table 5

**Table 4. Kurian, et al. 2008\textsuperscript{25}**

<table>
<thead>
<tr>
<th>Purpose</th>
<th>To investigate the long-term safety and effectiveness of TZDs and metformin in KTRs with PTDM</th>
</tr>
</thead>
<tbody>
<tr>
<td>METHODS</td>
<td>Retrospective chart review from 2000-2006 at an urban hospital transplant center</td>
</tr>
</tbody>
</table>

**Inclusion Criteria**
- Renal transplant recipients with PTDM or pre-existing DM
- Initiated on metformin or TZD therapy during 2000-2006

**Exclusion Criteria**
- Lack of recorded HbA1c at time of initiation of study medications
- Patients excluded from effectiveness group if taking an additional oral hypoglycemic agent (still included in safety group since other agents wouldn’t affect creatinine or GFR values)
### Primary & Secondary Endpoints
- **Efficacy:** mean difference in HbA1c from study beginning to end
- **Safety:**
  - Metformin group: presence or absence of lactic acidosis, mean change in eGFR and Scr
  - TZD group: presence of LFT abnormalities, development of edema or CHF (defined as a diagnosis of CHF requiring admission to the hospital or chest x-ray showing CHF

### Interventions
- Study group 1 (n=32): mean metformin daily dose of 1250mg initially and 1750 by study end
- Study group 2 (n=46): Mean pioglitazone daily dose initially 30mg and 45mg at study end or mean rosiglitazone daily dose initially 4mg and 6mg at study end

### RESULTS

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
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<tbody>
<tr>
<td>Baseline immunosuppression: tacrolimus, mycophenolate mofetil, and prednisone with an average dosage of 10mg/day on the center specific steroid taper</td>
</tr>
<tr>
<td>Mean age in both groups: 60 years</td>
</tr>
<tr>
<td>TZD group: 33/46 PTDM 13/46 pre-existing DM, 29/46 Males, 27 White</td>
</tr>
<tr>
<td>Metformin group: 21/32 PTDM 11/32 pre-existing DM, 11/32 Male, 24/32 White</td>
</tr>
</tbody>
</table>

### Outcomes

#### Metformin Group:
- **Effectiveness measure**
  - PTDM (n=16)
  - Pre-existing DM (n=8)
  - All Patients

<table>
<thead>
<tr>
<th>Measure</th>
<th>PTDM (n=16)</th>
<th>Pre-existing DM (n=8)</th>
<th>All Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean HbA1c study beginning (SD), %</td>
<td>6.8 (1.66)</td>
<td>7.5 (1.19)</td>
<td>7.0 (1.54)</td>
</tr>
<tr>
<td>Mean HbA1c study end (SD), %</td>
<td>6.7 (0.99)</td>
<td>7.0 (1.08)</td>
<td>6.8 (1.01)</td>
</tr>
<tr>
<td>p-value</td>
<td>0.811</td>
<td>0.232</td>
<td>0.429</td>
</tr>
</tbody>
</table>

#### TZD Group:
- **Effectiveness measure**
  - PTDM (n=19)
  - Pre-existing DM (n=12)
  - All Patients

<table>
<thead>
<tr>
<th>Measure</th>
<th>PTDM (n=19)</th>
<th>Pre-existing DM (n=12)</th>
<th>All Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean HbA1c study beginning (SD), %</td>
<td>7.4 (1.32)</td>
<td>7.5 (1.11)</td>
<td>7.47 (1.23)</td>
</tr>
<tr>
<td>Mean HbA1c study end (SD), %</td>
<td>7.1 (1.30)</td>
<td>7.67 (0.99)</td>
<td>7.38 (1.2)</td>
</tr>
<tr>
<td>p-value</td>
<td>0.469</td>
<td>0.414</td>
<td>0.624</td>
</tr>
</tbody>
</table>

#### Safety:
- **TZD:**
  - Mean duration of TZD use: 37.1 months (range 6-72 months)
  - 1/46 patients discontinued due to edema
  - No development of CHF or LFT abnormalities noted
- **Metformin:**
  - Mean duration of metformin use: 16.4 months (range 1-55 months)
  - No cases of lactic acidosis
  - Mean eGFR: slight decrease 74 to 67 (p =0.003), however, only statistically significant in patient patients with pre-existing DM (p<0.001)
  - Mean serum creatinine: statistically significant increase in patients with PTDM with an increase of 0.96 to 1.0 (p=0.03)
  - 8/32 patients discontinued metformin due to adverse effects
    - 5 discontinued due to increase in serum creatinine greater than 1.6 mg/dL
    - 3 discontinued due to gastrointestinal side effects

### Author Conclusions
- Metformin appears to be safe in renal transplant population for a mean duration of 16 months. TZDs appear to be safe for a mean duration of 37 months after renal transplantation

### REVEWER CRITIQUE & CONCLUSIONS

#### Critique
- **Strengths:**
  - Outcomes assessed within-group differences for both metformin and TZDs
  - Differentiated between PTDM and pre-existing diabetes alone
- **Limitations:**
  - Baseline characteristics regarding time of transplant and duration of steroid taper not provided
  - Patients received monotherapy with no other anti-glycemic agents
  - Decline in eGFR is expected with KTRs, and the decline in Scr is not clinically significant

#### Reviewer’s Conclusions
- Metformin and TZDs were not successful in significantly lowering HbA1c in post-kidney transplant patients, with increases in HbA1c occurring in patients with pre-existing DM on a TZD
- Both agents appeared to be safe with proper renal adjustments needed for metformin
IV. DPP-4i

a. Majority of studies in KTRs have focused on safety and efficacy of vildagliptin with limited but more recent evidence on linagliptin
   i. Vildagliptin
      1. Haidinger et al. conducted a double blind RCT and found significant reductions in 2HPG and HbA1c with vildagliptin vs. placebo in KTRs
      2. Adverse effects were mild and similar in both groups
      3. Vildagliptin has yet to be approved in US
b. Only 1 randomized controlled trial (RCT) evaluated efficacy of DPP-4i and TZDs with placebo
   i. Werwoza et al. compared the difference in change in 2-hour plasma glucose (2HPG) levels in patients receiving vildagliptin, pioglitazone, or placebo (Table 5)

Table 5. Werwoza, et al. 2013

<table>
<thead>
<tr>
<th>Purpose</th>
<th>To determine if vildagliptin or pioglitazone provides superior anti-glycemic control compared with lifestyle interventions alone in stable KTRs 6 months post-transplant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study Design</td>
<td>Randomized, placebo-controlled clinical trial between December 2009 to June 2011</td>
</tr>
<tr>
<td>Patient Population</td>
<td>Inclusion Criteria</td>
</tr>
<tr>
<td></td>
<td>• 6-months post kidney transplant</td>
</tr>
<tr>
<td></td>
<td>• Impaired glucose tolerance (IGT)</td>
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<tr>
<td></td>
<td>Exclusion Criteria</td>
</tr>
<tr>
<td></td>
<td>• 2HPG &lt; 140mg/dL</td>
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<tr>
<td></td>
<td>• 2HPG &gt; 200mg/dL</td>
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<tr>
<td></td>
<td>• History of Type 1 or 2 DM</td>
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<tr>
<td></td>
<td>• Pregnancy</td>
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<td></td>
<td>• Severe renal impairment with eGFR&lt;15 or on dialysis</td>
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<td></td>
<td>• Severe liver impairment</td>
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<tr>
<td>Primary &amp; Secondary Endpoints</td>
<td>Primary:</td>
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<tr>
<td></td>
<td>• Difference in change in 2HPG during an OGTT, fasting plasma glucose (FPG), HbA1c</td>
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<td></td>
<td>Secondary:</td>
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<td></td>
<td>• Change in kidney function, liver parameters</td>
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<td></td>
<td>• Rate of side effects</td>
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<tr>
<td>Intervention</td>
<td>• 52 patients were randomized 1:1:1 to receive vildagliptin (VG), pioglitazone (PG), or placebo</td>
</tr>
<tr>
<td></td>
<td>• Patients were instructed to continue their lifestyle modifications</td>
</tr>
<tr>
<td>RESULTS</td>
<td>Baseline characteristics</td>
</tr>
<tr>
<td></td>
<td>• Number of patients: 18 VG, 17 PG, 17 placebo</td>
</tr>
<tr>
<td></td>
<td>• No significant differences in age, sex, body mass index, kidney function including levels of proteinuria, time after transplantation, lipid metabolism, liver function, hemoglobin levels, and corticosteroid dose among the three groups at baseline</td>
</tr>
<tr>
<td></td>
<td>• Tacrolimus levels highest in VG group and lowest in placebo group (p=0.06)</td>
</tr>
<tr>
<td></td>
<td>• HbA1c highest in PG group and lowest in VG group (p=0.01)</td>
</tr>
</tbody>
</table>
Outcomes

• Baseline to 3 month changes in 2HPG, FPG and HbA1c

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>3 months</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vildagliptin</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2HPG</td>
<td>160±13</td>
<td>140±29</td>
<td>0.002</td>
</tr>
<tr>
<td>FPG</td>
<td>104±14</td>
<td>102±15</td>
<td>0.2</td>
</tr>
<tr>
<td>HbA1c</td>
<td>5.7±0.3</td>
<td>5.6±0.3</td>
<td>0.046</td>
</tr>
<tr>
<td><strong>Pioglitazone</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2HPG</td>
<td>174±14</td>
<td>151±33</td>
<td>0.004</td>
</tr>
<tr>
<td>FPG</td>
<td>109±16</td>
<td>98±13</td>
<td>0.003</td>
</tr>
<tr>
<td>HbA1c</td>
<td>6.2±0.5</td>
<td>6.0±0.4</td>
<td>0.03</td>
</tr>
<tr>
<td><strong>Placebo</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2HPG</td>
<td>162±14</td>
<td>162±45</td>
<td>0.49</td>
</tr>
<tr>
<td>FPG</td>
<td>106±11</td>
<td>102±13</td>
<td>0.06</td>
</tr>
<tr>
<td>HbA1c</td>
<td>5.9±0.4</td>
<td>6.0±0.4</td>
<td>0.23</td>
</tr>
</tbody>
</table>

• PG significantly improved 2HPG, FPG, and HbA1c
• VG significantly improved 2HPG and HbA1c
• No statistically significant difference between groups in change in eGFR, lipids, blood pressure, or hepatic parameters (exception glutamic pyruvic transaminase)

**AUTHOR DISCUSSION AND CONCLUSION**

**Author Conclusions**

• Both VG and PG are of potential benefit in patients with IGT after renal transplantation in addition to lifestyle modification.

**REVIEWER CRITIQUE & CONCLUSIONS**

**Critique**

**Strengths:**
- Provided definitions and cutoffs of impaired fasting glucose and impaired glucose tolerance
- Provided within group and between group comparisons in outcomes
- Included many risk factors for PTDM in baseline characteristics (i.e. CNI’s)

**Limitations:**
- Tacrolimus trough levels higher in VG group, potentially impacting metabolic function and results
- Excluded patients with high 2-hr glucose (>200mg/dL) which questions external validity to KTRs with uncontrolled PTDM
- VG has yet to be approved in the US

**Reviewer’s Conclusions**

• Although within-group differences in 2HPG and HbA1c were observed in each intervention arm, further evidence is required to compare the efficacy between VG, PG, and placebo
• VG did not significantly improve FPG with minimal clinical significance on HbA1c
• VG has yet to be approved in US and is not an option for KTRs at this time

V. **SGLT-2i**

a. Utilization of SGLT-2 inhibitors has demonstrated improved glycemic control, promoted weight loss, and reduced the risk of CV events in in non-transplant patients with type 2 DM and established cardiovascular disease16,18

b. Given these potential benefits, SGLT-2i may seem to be an attractive option in KTRs

c. Prior to 2018, only one small observational cohort study of 10 KTRs and simultaneous pancreas-kidney transplant recipients demonstrated overall improvements in glycemic control, weight, and blood pressure with canagliflozin28

d. Schwaiger, et. al. released the first prospective interventional trial assessing the use of empagliflozin in KTRs29 (Table 6)
**Table 6. Schwaiger, et al. 2018**

<table>
<thead>
<tr>
<th>Purpose</th>
<th>To evaluate the safety and efficacy of empagliflozin 10mg daily as replacement to insulin therapy in KTRs</th>
</tr>
</thead>
</table>

**METHODS**

**Study Design**
Prospective, interventional, non-inferiority pilot study at outpatient kidney transplant clinic from December 2016 to June 2017

**Patient Population**

**Inclusion Criteria**
- Stable kidney transplant recipients (KTRs) with PTDM, on long-term exogenous insulin therapy.
- KTR ≥18 years, transplanted for ≥6 months with estimated GFR ≥ 30 and treated PTDM for ≥6 months
- All patients had to received exogenous insulin therapy (TDD < 40 IU/day)
- HbA1c < 8.5%

**Exclusion Criteria**
- TDD insulin > 40 IU/day and HbA1c > 8.5%

**Primary & Secondary Endpoints**

**Primary:**
- Intra-individual difference in 2-hour glucose level between the first OGTT and second OGTT (average change of 30mg/dL considered clinically meaningful)

**Secondary:**
- Laboratory parameters, anthropometric measurements, blood pressure readings, and medications
- Influence on fluid volume status by assessing bioimpedance spectroscopy derived markers of fluid volume and body composition

**Safety:**
- Reinstitution of insulin therapy (reinstitution was mandatory if BG level exceeded 300 mg/dL or if 2-hr glucose obtained during second OGTT exceeded an increase of 100 mg/dL)
- Side effects (infections, ketoacidosis, etc.)

**RESULTS**

**Baseline characteristics**
- 19 patients included, 14 completed the trial to week 4
- Male: 7/14, Mean recipient age: 56.5 (SD±7.9)
- Mean time after transplant: 69.4 months
- 11/14 patients on tacrolimus, all on glucocorticoid treatment with mean prednisone dose of 4mg (SD±1)
- Mean TDD insulin: 27.2 units (SD±10.5)

**Outcomes**

**Primary & Secondary:**
- Fasting ad 2-hr glucose levels increased from baseline to 4 weeks to 144±45mg/dL (p=0.005) and 273±116 mg/dL (p=0.06)
- HbA1c increased from 6.5±0.8% to 7.1±0.8 at 12 months (p=0.03)

<table>
<thead>
<tr>
<th>Variable (SD)</th>
<th>Baseline</th>
<th>4 weeks</th>
<th>12 months</th>
<th>p-value (baseline to 4 weeks)</th>
<th>p-value (baseline to 12 weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean SCR, mg/dL</td>
<td>1.4 (0.3)</td>
<td>1.5 (0.4)</td>
<td>1.4 (0.3)</td>
<td>0.06</td>
<td>0.99</td>
</tr>
<tr>
<td>Mean eGFR, ml/min 1.73m²</td>
<td>54.0 (23.8)</td>
<td>45.6 (19.7)</td>
<td>53.5 (13.3)</td>
<td><strong>0.01</strong></td>
<td>0.93</td>
</tr>
<tr>
<td>HbA1c, %</td>
<td>6.7 (0.7)</td>
<td>6.8 (0.6)</td>
<td>7.1 (0.8)</td>
<td>0.89</td>
<td>0.03</td>
</tr>
<tr>
<td>Mean urinary ketones, mg/dL</td>
<td>0 (0)</td>
<td>0.3 (0.7)</td>
<td>0 (0)</td>
<td>0.35</td>
<td>-</td>
</tr>
<tr>
<td>Mean weight (kg)</td>
<td>83.7 (7.6)</td>
<td>81.6 (7.4)</td>
<td>78.7 (7.7)</td>
<td><strong>0.03</strong></td>
<td><strong>0.02</strong></td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>150 (26)</td>
<td>149 (16)</td>
<td>145 (20)</td>
<td>0.75</td>
<td>0.36</td>
</tr>
</tbody>
</table>

**Safety:**
- 2 patients dropped out due to insufficient glycemic control, 2 for recurrent urinary tract infections, and 2 for worsening renal function
- 7/14 patients required reinstitution of insulin therapy at 4 weeks, 4 of which dropped out of the study
- No cases of ketoacidosis
- 3 patients experienced urinary tract infections, but when compared to an independent PTDM reference population, similar incidence rates were found
<table>
<thead>
<tr>
<th>Authored Discussion &amp; Conclusion</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Author Conclusions</strong></td>
<td><strong>Empagliflozin can safely be used as add-on therapy in KTRs for PTDM with close monitoring</strong></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>REVIEWER CRITIQUE &amp; CONCLUSIONS</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Critique</strong></td>
<td><strong>Strengths:</strong></td>
</tr>
</tbody>
</table>
|  | • Only study to date to evaluate SGLT-2 inhibitors in KTRs  
|  | • Evaluated many safety variables including fluid volume overload  
|  | • Utilized a reference population for concerns of UTIs |
|  | **Limitations:** |
|  | • Measured HbA1c at 4 weeks which is not adequate enough time to observe a difference  
|  | • Only 8 patients continued on to 12 month follow-up, 3 of which were receiving dual insulin and SGLT-2 therapy |
|  |  |
| **Reviewer’s Conclusions** | **Glucose control with empagliflozin monotherapy did not improve FPG, 2HPG, and HbA1c**  
|  | • Despite similar incidence findings of KTRs on empagliflozin to a reference population, incidence of UTIs remains a concern |
Clinical Recommendations

**Oral Anti-Glycemic Therapy Algorithm**

**POST-TRANSPLANT HYPERGLYCEMIA**
- Insulin

**FIRST-LINE**
- Metformin

**SECOND-LINE**
- TZD

**ADD-ON THERAPY**
- DPP-4i

**AGENTS TO AVOID**
- SU
- SGLT-2i

**Anti-glycemic Agent Renal Dosing Adjustments**

**Biguanides**
- Metformin
  - Renal Adjustments:
    - eGFR 30-45: max dosing 1g/day
    - eGFR<30: use contraindicated
  - Contraindications:
    - Hypersensitivity
    - Severe renal impairment (eGFR<30)

**TZDs**
- Rosiglitazone
- Pioglitazone
  - Renal Adjustments:
    - No dose adjustment necessary
  - Contraindications:
    - Hypersensitivity
    - Class III/IV heart failure

**DPP4-Inhibitors**
- Sitagliptin
- Saxagliptan
- Linagliptin
  - Renal Adjustments:
    - Sitagliptin: eGFR 30-44: 50mg once daily, eGFR<30 or HD/PD: 25mg once daily
    - Saxagliptin: eGFR<45, HD/PD: 2.5mg once daily
    - Linagliptin: No dose adjustment necessary
  - Contraindications:
    - Hypersensitivity
References


### Appendix A. Summary of oral anti-glycemic agents

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>HbA1c Reduction</th>
<th>Mechanism of Action</th>
<th>Dosing</th>
<th>Adverse Effects</th>
<th>Contraindications/Precautions</th>
</tr>
</thead>
</table>
| **Biguanide** | 1-2% | • Reduces hepatic gluconeogenesis  
• Favorably affects insulin sensitivity and, to a lesser extent, intestinal absorption of glucose | • Initial: 500 mg once or twice daily (once daily with extended-release formulation)  
• Maximal daily dose: 2550 mg (more commonly, 2000 mg/day)  
• Can increase at weekly intervals as necessary  
• Small initial dosage and slow titration secondary to GI disturbances | Common:  
• Nausea, vomiting, diarrhea, epigastric pain  
Less common:  
• Decrease in vitamin B12 concentrations, lactic acidosis (rare) | Renal impairment: Discontinue if eGFR is < 30. Initiation not recommended if eGFR is 30–45  
Use caution in > 80 years old  
High risk of CV event or hypoxic state  
Hepatic impairment  
Congestive heart failure |
| **Sulfonylurea** | 1-2% | • Bind to receptors on pancreatic β cells, leading to membrane depolarization, with subsequent stimulation of insulin secretion | | Common:  
• Hypoglycemia, weight gain  
Less common:  
• Rash, headache, nausea, vomiting, photosensitivity | Hypersensitivity to sulfonamides  
Patients with hypoglycemic unawareness  
Poor renal function |
| **TZD** | 0.5-1.4% | • Increases expression of genes responsible for glucose metabolism, resulting in improved insulin sensitivity | • Pioglitazone: Initial: 15 mg once daily (max 45 mg); Slow dose titration with maximal effect not likely to be seen until 8-12 weeks  
• Rosiglitazone: 4 mg/day as a single dose or in 2 divided doses; may increase to 8 mg/day | • Weight gain, fluid retention, bone fractures  
• Possible risk of bladder cancer with pioglitazone (data contradictory)  
• Boxed warning: ↑ risk of HF | Hepatic impairment  
Class III/IV heart failure (symptomatic heart failure)  
Existing fluid retention |
| **DPP-4 Inhibitor** | 0.5-0.8% | • Inhibit the breakdown of GLP-1 secreted during meals, increasing pancreatic insulin secretion | • Sitagliptin: 100 mg once daily; renal adjustment required  
• Saxagliptin: 5 mg once daily; renal adjustment required, reduce dosage when co-administered with strong CYP34A/5 inhibitor (e.g., ketoconazole) to 2.5 mg once daily.  
• Linagliptin: 5 mg once daily (no dosage adjustment for renal impairment) | • Upper respiratory and urinary tract infections, headache, severe joint pain  
• Sitagliptin: some reports of acute pancreatitis, angioedema, SJS, and anaphylaxis  
• Increased risk of heart failure hospitalization (saxagliptin, alogliptan) | Previous hypersensitivity  
History of pancreatitis |
| **SGLT-2 Inhibitor** | 0.3-1% | • Increases urinary glucose excretion by blocking normal reabsorption in the proximal convoluted tubule  
• Some effect on delaying GI glucose absorption | • Canagliflozin: 100 mg once daily before the first meal of the day; renal adjustment required (max 300 mg)  
• Dapagliflozin: 5 mg once daily in the morning; renal adjustment required (max 10 mg)  
• Empagliflozin: 10 mg once daily in the morning; renal adjustment required (max 25 mg) | • Increased urination, UTI’s, genital mycotic infections, hypotension, euglycemic DKA.  
• Possible increased bone fracture risk/decreased BMD with canagliflozin | Empagliflozin: Discontinue or do not initiate if eGFR is less than 45 mL/minute/1.73 m²  
Dapagliflozin: Discontinue or do not initiate if eGFR is less than 60