Challenging Diabetes Cases

Anne Peters, MD
Director, USC Clinical Diabetes Programs
Professor of Medicine (Clinical Scholar)
USC Keck School of Medicine

Disclosure of Potential Conflicts of Interest

Advisory Boards
- Abbott Diabetes Care
- Boehringer Ingelheim
- Bigfoot Biomedical
- Lilly, Livongo
- NovoNordisk
- Sanofi

Research Funding
- Dexcom
- vTv Therapeutics

Stock Options
- Mellitus Health
- Pendulum Therapeutics
- Omada Health
- Stability Health
- Livongo

Objectives
- Consider how to treat an older patient with T1DM and CVD
- Explore the definition and clinical features of Monogenic Diabetes (MODY)
- Discuss the role of inhaled insulin in the treatment of diabetes
Questions

1. Use of SGLT-2 inhibitors are approved for use in T1D under if the following is present:
   - 1. Proteinuria
   - 2. Heart failure
   - 3. No indication (approved)
   - 4. Known CVD

2. Monogenic forms of diabetes represent how many cases of diabetes in the US?
   - 1. 1-2%
   - 2. 5%
   - 3. 10%
   - 4. 30%

3. Compared to rapid acting insulin, inhaled insulin has which of the following characteristics?
   - 1. Requires a lower dose
   - 2. Requires a higher dose
   - 3. Is more effective
   - 4. Causes more hypoglycemia

Case

Case History

- RD is a 68 yo male with a history of T1D x 35 years
- He was initially treated with NPH and regular, switched to MDI and is now on an insulin pump and a CGM.
- His A1C’s are generally 7.5 - 8.0%
- 15 years ago he developed ASCVD and required 5 cardiac stents over one year
- He was on a statin, an ARB, beta-blocker, diuretic and an anticoagulant
- Based on the Proactive Study I added pioglitazone 15 mg daily.
- His stents stopped occluding and until 1 year ago was stable
Case History

- Of note he served in Vietnam and was exposed to Agent Orange
- Currently his BMI = 37.6 kg/m², BP = 136/82, + mild peripheral neuropathy, 1+ pedal pulses
- eGFR = 48, A/C = 112, TG = 130, LDL = 70, A1C = 7.6%
- Anti-GAD antibody = 94  FPG = 186 mg/dl  C-peptide = 0.1 ng/ml
- One year ago he had another 2 stents placed after ischemia was found on a routine follow-up stress test.
- Would you start him on an SGLT-2 inhibitor?

DCCT: Proving the "Glucose Hypothesis" in T1DM

Study Purpose
Test the "glucose hypothesis" (ie, tight glucose control can prevent or delay micro/macrovascular complications)
- 1441 T1DM patients under age 39
- Half randomized to INT therapy
  - Goal: A1c close to normal glycemia as possible without causing AEs
  - Half to CONV therapy
  - Goal: asymptomatic glucose control
- After 6.5 years
  - INT cohort: A1c of ~7%
  - CONV cohort: A1c of ~9%

A1c, glycosylated hemoglobin; AEs, adverse events; CONV, conventional; INT, intensive.

DCCT Microvascular Benefits and EDIC Follow-Up

- INT proved superior to CONV¹
  - Microvascular: 78% less retinopathy; 50% less nephropathy; 60% less neuropathy
  - Macrovascular: CV and vascular events reduced by 41%
- 96% of patients enrolled in EDIC and were followed 20 more years²
  - Glycemic control converged for both groups to ~8%

Despite this, original INT group showed durable benefit for decades.

CV, cardiovascular; EDIC, Epidemiology of Diabetes Interventions and Complications.
SGLT-2 Inhibitors for Off-Label for T1D?
SGLT-1, 2 Inhibitor (Sotagliflozin) under FDA consideration

Clinical Effects
- Most patients will respond—action independent of beta-cell function
- A1C reduction ~0.4% with 2-3 kg weight loss
- Lower blood pressure
- Cardiovascular benefits
- Renal benefits

Possible Adverse Effects and Precautions
- Mycotic genital infections/UTI
- Findings due to volume depletion
- Do not use if eGFR <45%
- DKA (euglycemic and hyperglycemic)—biggest concern in T1D, but rare in T2D

SGLT Inhibitors Studied in Phase 3 Trials for T1DM

<table>
<thead>
<tr>
<th>Drug</th>
<th>Trial Name(s)</th>
<th>Doses Studied</th>
<th>Length of Trial</th>
<th>No. Pts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dapagliflozin</td>
<td>DEPICT-2&lt;sup&gt;1&lt;/sup&gt;, NCT02460978</td>
<td>5 mg, 10 mg, PBO, 24 weeks</td>
<td>N=813</td>
<td></td>
</tr>
<tr>
<td></td>
<td>DEPICT-3&lt;sup&gt;1&lt;/sup&gt;, NCT0268214</td>
<td>5 mg, 10 mg, PBO, 24 weeks</td>
<td>N=833</td>
<td></td>
</tr>
<tr>
<td>Empagliflozin</td>
<td>EASE-3&lt;sup&gt;1&lt;/sup&gt;, NCT02586591</td>
<td>2.5 mg, 10 mg, 25 mg, PBO, 26 weeks</td>
<td>N=975</td>
<td></td>
</tr>
<tr>
<td></td>
<td>EASE-2&lt;sup&gt;1&lt;/sup&gt;, NCT02414468</td>
<td>10 mg, 25 mg, PBO, 52 weeks</td>
<td>N=730</td>
<td></td>
</tr>
<tr>
<td>Sotagliflozin*</td>
<td>inTandem2&lt;sup&gt;3&lt;/sup&gt;, NCT0351035</td>
<td>400 mg, PBO, 24 weeks</td>
<td>N=1402</td>
<td></td>
</tr>
<tr>
<td></td>
<td>inTandem2&lt;sup&gt;3&lt;/sup&gt;, NCT02421616</td>
<td>200 mg, 400 mg, PBO, 24 weeks</td>
<td>N=782</td>
<td></td>
</tr>
<tr>
<td></td>
<td>inTandem3&lt;sup&gt;4&lt;/sup&gt;, NCT02384941</td>
<td>200 mg, 400 mg, PBO, 52 weeks</td>
<td>N=793</td>
<td></td>
</tr>
</tbody>
</table>

General Trends in SGLT Clinical Trials

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1c</td>
<td></td>
</tr>
<tr>
<td>Fasting Plasma Glucose</td>
<td></td>
</tr>
<tr>
<td>Postprandial Glucose</td>
<td></td>
</tr>
<tr>
<td>Body Weight</td>
<td></td>
</tr>
<tr>
<td>Blood Pressure</td>
<td></td>
</tr>
<tr>
<td>Genital Mycotic Infections</td>
<td></td>
</tr>
<tr>
<td>Urinary Tract Infections</td>
<td>or</td>
</tr>
<tr>
<td>Diabetic Ketoacidosis</td>
<td>with dose</td>
</tr>
<tr>
<td>Severe Hypoglycemia</td>
<td></td>
</tr>
</tbody>
</table>

Note: Not a meta-analysis, just a simplified illustration of general trends across the clinical trials.

Change in A1c: EASE Trials

<table>
<thead>
<tr>
<th>Time (Week)</th>
<th>Placebo</th>
<th>Empagliflozin 10 mg</th>
<th>Empagliflozin 25 mg</th>
<th>Empagliflozin 2.5 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>8.9</td>
<td>8.7</td>
<td>8.5</td>
<td>8.3</td>
</tr>
<tr>
<td>12</td>
<td>8.7</td>
<td>8.5</td>
<td>8.3</td>
<td>8.1</td>
</tr>
<tr>
<td>18</td>
<td>8.5</td>
<td>8.3</td>
<td>8.1</td>
<td>7.9</td>
</tr>
<tr>
<td>26</td>
<td>8.3</td>
<td>8.1</td>
<td>7.9</td>
<td>7.7</td>
</tr>
<tr>
<td>43</td>
<td>8.1</td>
<td>7.9</td>
<td>7.7</td>
<td>7.5</td>
</tr>
</tbody>
</table>

Representative CGM Profiles of Change in Mean Glucose in Individual Patients Over 3 Days

<table>
<thead>
<tr>
<th>Time (Minute)</th>
<th>0</th>
<th>5</th>
<th>15</th>
<th>30</th>
<th>60</th>
<th>120</th>
<th>180</th>
<th>240</th>
<th>300</th>
<th>360</th>
<th>420</th>
<th>480</th>
<th>540</th>
<th>600</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cana 100 mg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
DKA Incidence in the DEPICT-2, EASE-2/3, and inTandem3 Trials

- In general, DKA occurs in about 5% of T1DM patients, per year\(^1\)
- Although usually associated with hyperglycemia, DKA can occur in moderate or even low levels of blood glucose\(^2\)

<table>
<thead>
<tr>
<th>Trial</th>
<th>SGLT2 Agent</th>
<th>Doses</th>
<th>DKA Incidence %</th>
</tr>
</thead>
<tbody>
<tr>
<td>DEPICT-2*</td>
<td>Dapagliflozin (Farxiga)</td>
<td>5 mg</td>
<td>2.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10 mg</td>
<td>2.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PBO</td>
<td>0</td>
</tr>
<tr>
<td>EASE-2/3(^3)</td>
<td>Empagliflozin (Jardiance)</td>
<td>2.5</td>
<td>0.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10 mg</td>
<td>4.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>25 mg</td>
<td>3.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PBO</td>
<td>1.3</td>
</tr>
<tr>
<td>inTandem3(^4)</td>
<td>Sotagliflozin</td>
<td>400 mg</td>
<td>0.3</td>
</tr>
</tbody>
</table>

Note: Because these trials used different adjudication strategies to verify DKA, direct comparisons cannot be made.

How to Prevent/Treat DKA Due to SGLT-2 I

- Re-emphasize that patients with T1D know how to test for urine/serum ketones
- Establish baseline ketone levels prior to starting SGLT-2 I
- After starting, continue ketone testing for a few weeks to be sure ketones remain negative
- Then have patient hold SGLT-2 I for any illness, dehydration, sudden increase in exercise, surgery, etc and measure ketones, even if glucose level normal
- If ketones positive, have patient consume carbohydrates and fluids and give insulin
- Patient to go to ED if unable to keep down fluids

Case Conclusion

- The patient was taught to monitor his serum ketones and did baseline measurements
- Specific education was given around pump infusion set malfunction
- He has now been on empagliflozin 10 mg daily for 2 years
- His A1C fell slightly to ~7.4% with a reduction in variability; renal and cardiac function have remained stable.
Case Conclusion: Part 2

- One last thought: would you add a GLP-1 RA?

What is Monogenic Diabetes (MODY)?

- Rare type of diabetes caused by a single gene mutation.
- At least 11 different types of MODY; 1-2% diabetes
- Characteristics of both Type 1 and Type 2 DM, and is often misdiagnosed as one of those more common types.
- Important to identify because treatment differs.
- Common types:
  - HNF1-alpha gene—This type is common and can generally treated with sulfonylurea agents. (MODY 3)
  - HNF1-beta gene—this can cause kidney cysts, abnormalities of the uterus and gout. Insulin treatment is often needed. (MODY 5)
  - Glucokinase gene—very mild and usually requires no treatment. This type of MODY does not seem to cause the complications of diabetes. (MODY 2)

Joslin 50 Year Medalist Study

- Paper entitled: “Residual β cell function and monogenic variants in long-duration type 1 diabetes patients”
- 32.4% retained detectable C-peptide levels
- In 7.9% of medalists, the monogenic variants were discovered and classified as “likely pathogenic”.

JCI 2019;129:3252-3263. doi: 10.1172/JCI127397
MODY Genes: Who to Test

- Swedish National Cohort Study of patients aged 1-18 years
- GAD antibody, insulinoma antigen-2A, zinc transporter antibody, and IAA were negative
- Had family history of diabetes
- A1C <7.5%
- MODY positive in 78% of patients

Case of MODY at Roybal

- JC is a 48 year old Latino male
- He was diagnosed with type 1 diabetes at the age of 10.
- He was started on a multiple daily insulin regimen
- His blood glucose levels were difficult to control and he had frequent episodes of hypoglycemia
- He was referred to Diabetes Clinic with a BMI of 34 and Stage 4 CKD. He had a strong family history of T2DM.
- His A1C was 8.2% and insulin dose adjustments were made to improve his control.
- After a year he was lost to follow-up.

Case of MODY at Roybal

- He returned after a 6 month trip to Mexico; off insulin x several months
- His A1C was 7.6%, eGFR = 22
- Labs were measured: glucose = 148, C-peptide = 4.6, antiGAD antibodies negative
- Probable diagnosis = HNF1-beta gene defect (MODY 5)
New Form of MODY

- MC is a 23 yo female with "new onset" T1DM.
- She is lean (BMI = 21) with a FH of T1D in her younger sister, who was diagnosed at age 16 and is on an insulin pump. She is now 18 yo and is a freshman at Stanford.
- Six months previously she was found to have a FBG of 150 mg/dl and an A1C of 7.3%. She was started on insulin which resulted in frequent lows.
- She stopped the insulin after 2 weeks and went on a carbohydrate restricted diet and lost 6 pounds.
- Her blood sugars improved and her A1C fell to 6.7%.
- She was referred to me to determine what treatment she needed.

New Form of MODY

- A blinded CGM was placed but it did not record.
- An OGTT was done.

![OGTT Graph]

New Form of MODY

- Her blood was sent to the University of Chicago.
- She was found to be a compound heterozygote with a defect in a gene known as PCBD1 (phenylalanine metabolism) and a gene linked to a MODY3 type picture.
- Both her younger and older sister had the same genes. Her older sister has normal glucose tolerance.
- The younger sister was started on glyburide and weaned off her insulin pump and is now on glyburide alone.
- MC continues on lifestyle therapy alone.
Needs Premeal Insulin

Overbasalized: "I don't want premeal insulin"
After Adding Inhaled Insulin

Technosphere Insulin—2014
- Dry powder formulation of monomeric human insulin for oral inhalation
- Technosphere® particles consisting of fumaryl diketopiperazine (FDKP) onto which insulin is adsorbed

PK:PD Profile

FDKP, fumaryl diketopiperazine; IRB, glucose infusion rate; PD, pharmacodynamic; PK, pharmacokinetic; TEC, Technosphere Insulin. Adapted from Baughman et al. Poster presentation at American Diabetes Association 76th Scientific Sessions; June 10-14, 2016; New Orleans, LA. With permission.

33 ©2018 MannKind Corporation. All rights reserved. No copying or distribution of this material may be made without written consent of MannKind Corporation.
**Occurrences of cough**

- Reported in 26.9% of Afrezza patients vs. 3.2% of comparator treated patients.
- 99% of cough episodes were characterized as intermittent or single defined episodes.
- Cough was generally mild, dry, occurred within 10 minutes of inhalation, was transient and declined with continued use.
- Cough leading to discontinuation was uncommon (0.8%).

**Results**

Optimal mealtime dosing of TI is between 16 to 20 U per meal.

<table>
<thead>
<tr>
<th>Time of Meal</th>
<th>Initial Dose (U)</th>
<th>Final Dose (U)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breakfast</td>
<td>4</td>
<td>18</td>
</tr>
<tr>
<td>Lunch</td>
<td>4</td>
<td>16</td>
</tr>
<tr>
<td>Dinner</td>
<td>4</td>
<td>20</td>
</tr>
</tbody>
</table>

All patients began treatment with 4 U per meal of TI and followed the prespecified titration algorithm.
Conclusions

- There are many ways to treat diabetes
- There are also many different types of diabetes
- Be alert for “atypical” or challenging patients; working together can lead to solutions

THANK YOU