Learning Objectives
After participating in this educational activity, participants should be better able to:
1. Increase awareness of renal mechanism in glucose regulation
2. Detail and clarify the multiple dimensions involved in glucose control in type 2 diabetes (T2DM)
3. Develop a treatment plan that promotes adherence and incorporates renal glucose excretion into an overall management plan for patients with T2DM

Introduction
The kidneys play a vital role in glucose homeostasis. Both the kidney and the liver ensure that the energy requirements of the body are maintained during the fasting state. In T2DM, the kidney’s filtration of glucose becomes defective which amplifies the patient’s insulin resistance. The renal sodium-glucose cotransporter (SGLT) system is responsible for the efficient reabsorption of glucose from the renal tubules into the plasma. 90% of all glucose filtered by the kidney is
reclaimed into the plasma via the proximally expressed SGLT2 cotransport mechanism, whereas the remaining 10% of the glucose is reabsorbed by the SGLT1 cotransporters located in the distal tubules. Pharmacologic blockade of the SGLT2 transport mechanism can result in a predictable reduction of one’s fasting and postprandial glucose levels (PPG). Because A1C is a reflection of one’s fasting and PPG levels, one would anticipate that SGLT2 blockade would reduce one’s A1C. Up to 400 kilogram calories (Kcal) of glucose is lost daily in the urine in patients using SGLT2 inhibitors. Thus, one would anticipate that weight loss would be the rule rather than the exception when these drugs are used. Side effects would also be anticipated including frequent urination, urinary tract infection, fungal infections, and alterations in blood pressure. This continuing medical education (CME) activity will address the rational use of SGLT2 inhibitors in patients with T2DM.
CASE 1

Gracie is a 48 year old female with T2DM for 7 years.

Patient History

- T2DM for 7 years, Stage 2 hypertension x 10 years, Type 2-B hyperlipidemia, and osteoporosis due to surgically induced menopause 4 years ago
- History of gestational diabetes age 24
- Both parents have T2DM and are obese
- Father is 72 years old with diabetic neuropathy and known coronary artery disease (2 stent placements in past year)
- Patient does not smoke, exercise, use caffeine, or use alcohol
- Has group health insurance with a $10 copay for generic and $25 co-pay for branded drugs
- Works for the Environmental Protection Agency as an administrative assistant
- Allergies: Metformin intolerant (diarrhea)
- Current medications: Glimepiride 4 mg at bed time, Aspirin 81 mg every day (QD), Vitamin D3 4000 IU QD, Losartan 100 mg QD, Lovastatin 40 mg QD, denosumab 60 mg twice yearly IM (for osteoporosis)

Physical Exam

- BP: 134/76 mm Hg, P: 74 BPM, BMI: 29 kg/m2
- Eye: No retinopathy or macular edema
- Cardiovascular exam: Normal
- Abdomen: Slightly obese, but no masses or tenderness
- Neurological exam: Loss of vibratory sense, ankle jerks, and hot/cold sensation in both feet suggestive of peripheral diabetic sensory neuropathy

Laboratory Studies

- A1C: 8.4% (up from 8.1% 6 months ago)
- GFR: 72 ml/min
- Creatinine: 0.9 mg/dL
- Spot urine for microalbuminuria: negative
- Lipids, thyroid, and basal metabolic profile all normal
Treatment Options

Clinicians should consider the patient’s individualized metabolic (A1C, lipids, blood pressure) targets when intensifying diabetes therapy. Additionally, medications should be prescribed which are likely to correct the known pathophysiologic disturbances of type 2 diabetes as shown in Table 1.

Table 1. Summary of Pathological Deficits Associated with T2DM[1,2]

<table>
<thead>
<tr>
<th>Target Organ/Tissue</th>
<th>Physiological Defects</th>
<th>Glycemic Effects</th>
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</table>
| Pancreatic β-cells  | • Loss of first-phase insulin secretion  
• Delayed second-phase insulin secretion  
• Loss of amylin secretion                     | • Glucose toxicity results in β-cell apoptosis                                      |
| Pancreatic α-cells  | • α-Cell hypertrophy  
• Loss of α- and β-cell signaling results in loss of appropriate and timely counter regulation; patients are more likely to develop hypoglycemia awareness autonomic failure over time.  
• Exaggerated, paradoxical, and untimely secretion of glucagon during both the fasting and postprandial states | • Hyperglucagonemia results in glucose toxicity, β-cell destruction, and excessive hepatic glucose production.  
• Patients experience an increase in fasting and postprandial glucose levels; this will increase their A1C.  
• Insulin resistance is exacerbated. |
| Hepatocytes         | • Excessive hepatic glucose production despite initial elevations in circulating plasma insulin levels  
• The liver excretes > 25 g/day of extra glucose into the plasma | • Increases insulin resistance  
• Increases gluconeogenesis and glycogenolysis                                      |
| Myocytes            | • Impaired uptake and intracellular utilization of glucose                             | • Increases peripheral insulin resistance  
• Increases fasting and post absorptive glucose levels  
• Marked deficiency in peripheral glucose utilization is the most significant defect observed in insulin resistance |
<table>
<thead>
<tr>
<th>Gut</th>
<th>Adipose tissue</th>
<th>Brain</th>
<th>Kidneys</th>
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<tbody>
<tr>
<td>Reduction in secretion of GLP-1 and GIP by the intestines in response to oral glucose stimulation</td>
<td>Increased lipolysis in response to a reduction in circulating endogenous insulin</td>
<td>Loss of neuroprotection</td>
<td>Increased expression of SGLT2 in the proximal glomerular tubules</td>
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<tr>
<td>When GLP-1 is secreted, approximately 80% of the gut hormone is immediately deactivated by DPP-4; reduced levels of GLP-1 result in proportionally lower amounts of GLP-1 being expressed at pancreatic β-cell receptors</td>
<td></td>
<td></td>
<td>Daily renal filtered glucose threshold increases from 180 g/day to 240 g/day.</td>
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<td>GLP-1 resistance at target tissue site</td>
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<tr>
<td>Amylin levels are reduced within pancreatic islets; amylin and insulin are co-secreted in a glucose-dependent manner.</td>
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<tr>
<td>Alters gastric emptying</td>
<td></td>
<td></td>
<td>Ninety percent of filtered glucose is absorbed via SGLT2 in the proximal tubules, and 10% is absorbed by SGLT1 in the distal tubules. SGLT1 is also expressed in the gut, where daily dietary glucose absorption of 180 g occurs. If the renal glucose threshold of the SGLT2 transport mechanism is surpassed, glycosuria occurs. In T2DM, the threshold is increased from 180 g/day to 240 g/day.</td>
</tr>
<tr>
<td>Causes weight gain</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Increases fasting and postprandial glucose levels</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Reduces sense of satiety</td>
<td></td>
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<td></td>
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<tr>
<td>Causes loss of neuroprotection against Alzheimer's disease and Parkinson's disease</td>
<td></td>
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<tr>
<td>Reduction in amylin accelerates gastric emptying and impairs satiety. The overall effect is a rise in postprandial glucose values.</td>
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which results in an increased renal absorption of glucose regardless of the patient's state of chronic hyperglycemia. Excessive reabsorption of glucose from the kidneys exacerbates insulin resistance.


Reducing the A1C remains the primary focus of therapy for patients with diabetes. Both microvascular and macrovascular complication risks are mitigated when patients are treated to lower glycemic targets.[3,4] Lifestyle intervention remains the foundation of care which is augmented by pharmacotherapy. The efficacy of weight loss and exercise in restoring normal glucose homeostasis is most beneficial when initiated within the first 1-2 years after one is diagnosed with diabetes.[5] As pancreatic beta cell function deteriorates and diabetes progresses, ambitious and timely pharmacotherapies are needed to minimize one’s “glycemic burden.” The glycemic lowering agents available in the US today are very effective at improving fasting, postprandial, and A1C targeted glucose targets. Although most patients with diabetes should be treated to an A1C of 6.5-7%, recently published randomized outcome studies have suggested that the glycemic targets be individualized.

In 2008, three studies [Action to Control Cardiovascular Risk in Diabetes (ACCORD),[6] Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified-Release Controlled Evaluation (ADVANCE),[7] and Veterans Affairs Diabetes Trial (VADT)[8]] reported the effects of two levels of glycemic control on cardiovascular end points in middle-aged and older individuals with well-established T2DM at high risk for cardiovascular events. ACCORD and VADT aimed for an HbA1C <6.0% using complex combinations of oral agents and insulin. ADVANCE aimed for an HbA1C ≤6.5% using a less intensive approach based on the sulfonylurea gliclazide. None of the trials demonstrated a statistically significant reduction in the primary combined cardiovascular end points. However, in ACCORD, a 22% increase in total mortality with intensive therapy was observed, mainly driven by cardiovascular mortality.
The patients at highest risk of mortality in ACCORD were those who were poorly controlled; that is those with the highest baseline A1Cs who failed to improve their glycemic control after intensification was initiated.[9] Patients who had an A1C <7% at baseline and thus considered well controlled, were NOT at increased risk of mortality.

One plausible explanation for higher mortality rates in poorly controlled patients with T2DM involves a phenomenon known as “hypoglycemia preconditioning.” Hypoglycemia results in the release of catecholamines (epinephrine). Patients with lower A1C levels tend to become hypoglycemic more frequently than individuals with elevated A1C values.[10] Repeated mild or moderate hypoglycemic events can suppress the usual response of catecholamines resulting in both a delay in reversal of low glucose levels and an increased risk of recurrences of subsequent hypoglycemia episodes. Although this may increase one’s risk of falls and motor vehicle accidents, blunting the catecholamine response may protect against the risk of developing potentially fatal arrhythmias during an episode of hypoglycemia.[11] Minor hypoglycemia was very common during intensive glycemic treatment in ACCORD. Patients with higher A1Cs (> 8%) who were exposed to severe hypoglycemia, may have succumbed to fatal arrhythmias induced by catecholamines secreted above a safe threshold in these patients with pre-existing coronary artery disease.

Therefore, when intensifying diabetes therapy, one must consider pharmacotherapeutic interventions which are not only effective at lowering A1C, but able to minimize the risk of hypoglycemia.

Figures 1-3 show the American Diabetes Association and the European Association for the Study of Diabetes recommendations for managing hyperglycemia in patients with T2DM.

In summary, a patient with a long-duration diabetes, who does not respond to pharmacologic intensification should be considered to have a higher risk of all-cause mortality.
Healthy Eating, Weight Control, Increased Physical Activity

**Legend:** Initial therapy for patients with T2DM include metformin. The drug is considered highly effective initially at lowering A1C. Patients who use metformin are at low risk for hypoglycemia and weight gain. The most common side effects would include nausea and diarrhea. If the A1C target is not achieved after 3 months, one should consider intensifying therapy using it with a sulfonylurea, TZD, DPP-4 inhibitor, GLP-1 RA, or insulin. Although efficacious, SUs and insulin are likely to cause weight gain and hypoglycemia.
Figure 2. ADA/EASD Recommendations: Managing Hyperglycemia in Patients with Type 2 Diabetes[12]

<table>
<thead>
<tr>
<th>Initial Drug Therapy</th>
<th>Healthy Eating, Weight Control, Increased Physical Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Efficacy (↓A1C)</strong></td>
<td>Metformin High</td>
</tr>
<tr>
<td><strong>Hypoglycemia</strong></td>
<td>Low Risk</td>
</tr>
<tr>
<td><strong>Weight</strong></td>
<td>Neutral/Loss</td>
</tr>
<tr>
<td><strong>Side effect(s)</strong></td>
<td>GI/Lactic acidosis Low</td>
</tr>
<tr>
<td><strong>Cost</strong></td>
<td>Low</td>
</tr>
</tbody>
</table>

If needed to reach individualized A1C target after 3 months, proceed to 2-drug combination.

<table>
<thead>
<tr>
<th>2- Drug Combination</th>
<th>+TZD</th>
<th>+DPP-4 Inhibitor</th>
<th>GLP-1 RA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Efficacy (↓A1C)</strong></td>
<td>High</td>
<td>Intermediate</td>
<td>High</td>
</tr>
<tr>
<td><strong>Hypoglycemia</strong></td>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
</tr>
<tr>
<td><strong>Weight</strong></td>
<td>Gain</td>
<td>Neutral</td>
<td>Loss</td>
</tr>
<tr>
<td><strong>Major side effect(s)</strong></td>
<td>Edema, HF, Fx</td>
<td>Rare</td>
<td>GI</td>
</tr>
<tr>
<td><strong>Cost</strong></td>
<td>High</td>
<td>High</td>
<td>High</td>
</tr>
</tbody>
</table>

The TZDs can result in long bone fractures, edema, and weight gain. Metformin can be used with a DPP-4 inhibitor or a GLP-1 RA.
SGLT2 inhibitors are also considered safe and effective drugs to use in combination with metformin as well as other agents for T2DM. Note that the drugs are effective at reducing A1C 0.5-1%, have a low risk of hypoglycemia, and favor weight loss.

Therefore, a patient, such as Gracie, may be an appropriate candidate for an SGLT2 inhibitor.

**Mechanism of Action of SGLT2 Inhibitors**

The kidneys play a vital role in maintaining glucose homeostasis during the fasting state. 180 liters of plasma and 162 grams of glucose are filtered through the kidneys per day.[2] This ensures that the fasting glucose levels are maintained at approximately 100 mg/dL. Glucose is efficiently reabsorbed from the kidneys via the sodium-glucose cotransporter system which includes SGLT2 (located in the proximal glomerulus) and SGLT1 expressed in the distal glomerulus. If the capacity to reabsorb glucose via the cotransport system is exceeded, glycosuria will occur. Patients with T2DM have an overexpression of SGLT2 in their proximal glomeruli. Thus, the “threshold” for glucose absorption is moved from approximately 180 grams per day to 240 grams per day. This excessive amount of glucose reabsorption contributes to hyperglycemia and exacerbates insulin resistance. Overexpression of SGLT2 cotransporters alters the homeostatic
balance from euglycemia towards the classic state of chronic hyperglycemia as observed in T2DM. (Figures 4-6)

**Figure 4. Renal Glucose Transport**

SGLT2 is a glucose transporter located in the 1st segment of the proximal glomerulus tubule and mediates 90% of the renal glucose plasma reabsorption. The remaining 10% of renal glucose reabsorption occurs through the SGLT1 found in the distal proximal tubule. In the intestine, dietary glucose and galactose are absorbed through the SGLT1 cotransporters. Blockade of SGLT1 glucose absorption is not a therapeutic option as this could result in osmotic diarrhea, abdominal pain, and malabsorption.
Euglycemic individuals have a renal glucose “threshold” of 180 g/d. Thus, the SGLT2 and SGLT1 transporters absorb all of the glucose which is filtered through the glomeruli until that threshold is surpassed. Above the threshold of 180 g/d, the glucose transport system becomes saturated and all the filtered glucose in excess of this threshold is excreted in the urine as glycosuria. The amount of glucose reabsorption may vary slightly between nephrons resulting in a splay. The glucose excretion rate may also vary between individuals, but has an average value of approximately 375 mg/min. In T2DM, the threshold of glucose absorption is INCREASED to approximately 240 g/d which worsens insulin resistance. Pharmacologic SGLT2 inhibition is designed to LOWER the renal threshold to 70 g/d. Blocking the SGLT2 absorption mechanism will inhibit the kidney’s ability to absorb glucose into the plasma. Glucose will pass into the urine resulting in glycosuria. (Figure 6)
Blockade of the SGLT2 cotransport mechanism, results in glycosuria leading to correction of hyperglycemia. Patients will experience lowered fasting blood glucose levels, lowered postprandial glucose, and lowered A1C. The 400 Kcal of glucose excreted in the urine daily should result in weight loss in most patients. Patients may experience weight gain if they consume in excess of 400 Kcal/day. Blood pressure would be expected to decline as well because water must be excreted to clear the glucose from the kidneys. Note that SGLT1 is NOT affected by blockade of the SGLT2 cotransporters. Thus, glucose is still absorbed from the kidneys via the SGLT1 cotransport mechanism.
SGLT2 Pharmacology

Drugs in the SGLT2 inhibitor class include: empagliflozin, canagliflozin, dapagliflozin, and ipragliflozin. Canagliflozin was approved by the FDA in March, 2013 as adjuvant therapy for the treatment of T2DM in patients 18 years of age and older and dapagliflozin was approved by the FDA on January 8, 2014. Canagliflozin (Invokana) and dagagliflozin (Forxiga) may be used as monotherapy or in combination with other antihyperglyemcic agents including insulin. Figures 7A and 7B compare dapagliflozin to the first approved SGLT2 inhibitor, canagliflozin.

Figure 7A. Metabolic Comparisons Between Dapagliflozin and Canagliflozin

**Dapagliflozin (FORXIGA®)**
- Once daily SGLT2 inhibitor indicated as add-on therapy
- Additional A1c reduction -0.32% vs. -0.14% SU add-on
- Weight loss ~3.7 kg after 24 months vs. +1.36 kg with SU add-on

**Canagliflozin (Invokana®)**
- Once daily SGLT2 inhibitor as add on
- A1c reduction -0.93% vs. -0.81% (glimepiride) as met add-on
- A1c reduction of 0.65%-0.73% as add-on to insulin
- A1c additional reduction -0.37% vs. sitagliptin as add-on to met/SU
Figure 7B. Metabolic Comparisons Between Dapagliflozin and Canagliflozin

<table>
<thead>
<tr>
<th>Drug</th>
<th>A1C Lowering Effect (%)</th>
<th>Reduction in Systolic BP</th>
<th>Wt. Loss</th>
<th>Adverse Effects</th>
</tr>
</thead>
</table>
| Canagliflozin (100 and 300 mg/d) | -.57 to -1.16 (placebo subtracted) | -1.6 to -7.9% change from baseline | -4 to -3.7% (placebo subtracted) | • Increased urination  
• Increased thirst  
• Nausea  
• UTI  
• Genital mycotic infections  
• Hypoglycemia 5.6%  
[Cana 100 mg + glimepiride]  
• Not recommended if eGFR <45 ml/min/1.73 m^2 |
| Dapagliflozin (10 mg/d)    | -0.8 to -0.89 (change from baseline) | -3.5 mm Hg (placebo subtracted) | -1.6 to -3.4 kg (change from baseline) | • UTI  
• Genital Infections  
• Back pain  
• Hypoglycemia *5.2%  
[Dapagliflozin 10 mg+ metformin]  
• Not recommended if eGFR <45 ml/min/1.73 m^2 |

Table 2. Practical Prescribing Points for SGLT2 Inhibitors

- SGLT2 inhibitors are approved for use with all other antihyperglycemic agents including insulin.
- Renal function should be assessed prior to initiating SGLT2 inhibitors. Because this drug class efficacy is based upon the number of glomeruli available for filtration, patients with an estimated glomerular filtration rate (eGFR < 45 ml/min/1.73 m^2) are unlikely to derive any benefit from this drug class.
- The initial dose of canagliflozin is 100 mg/d. The dose should be maintained at 100 mg/d if the patient’s eGFR is 45-60 ml/min/1.73 m^2. The dose can be increased to 300 mg/d if the eGFR is > 60 ml/min/1.73 m^2.
- The initial dose of dapagliflozin is 5 mg/d. In patients requiring additional glycemic control, the dose can be increased to 10 mg once daily.
- Monitor renal function periodically when using SGLT2 inhibitors. Initially the eGFR may decline, but will normalize over the course of 6-12 months.
- Elderly patients should be observed and warned about symptoms related to intravascular volume contraction, i.e. symptomatic hypotension, when using SGLT2.
inhibitors. Patients may notice that they become light headed after starting this class of medications. These side effects are usually short lived in clinical practice.

- Patients using ACE inhibitors or angiotensin II receptor blockers (ARBs) should have the potassium levels monitored. Infrequently, hyperkalemia has been reported when canagliflozin has been used with ACE inhibitors or ARBs.
- Hypoglycemia is rare when SGLT2 inhibitors are used. Insulin and insulin secretagogues are known to cause hypoglycemia. When used with an SGLT2 inhibitor, the dose of insulin or the sulfonylurea should be reduced to minimize the likelihood of treatment emergent hypoglycemia.
- As with all diabetes drugs, the efficacy of SGLT2 inhibitors are more pronounced in patients with shorter diabetes duration.
- The safety cohort population for canagliflozin includes over 10,000 patients. Of these 10,000 patients, 11 discontinued the use of study drug from the canagliflozin cohort compared with 4 patients who stopped the drug from the placebo group. 99.8% of patients continued to take the drug despite having a UTI.
- Male mycotic infections do NOT occur in circumcised men.
- Canagliflozin can result in a 4-8% rise in LDL cholesterol. However, the change in particle size is unclear.
- The long-term cardiovascular safety of SGLT2 inhibition is not known.
- A small 2-week randomized placebo-controlled phase 2a pilot study using dapagliflozin in patients with T1DM demonstrated improvement in glycemic control and a reduction in daily insulin doses.[13]

### Customizing Gracie's Glycemic Targets

Returning now to our patient, Gracie, who is 47 years old and has had T2DM for 7 years. Her A1C is 8.4 % and she has normal renal function. Gracie, who is overweight (BMI 29 kg/m2) is using glimepiride at bedtime. Glimepiride, a secretagogue, can cause weight gain and hypoglycemia. We are concerned that treatment emergent hypoglycemia can increase the risk of mortality in patients with known coronary artery disease (CAD) who have an elevated A1C. Although our patient has a family history of CAD, her ABI is considered to demonstrate a low risk for atherosclerosis. Therefore, targeting an A1C to 7% while minimizing the chance of severe hypoglycemia is reasonable. Table 3 compares the pharmacologic properties of agents which may be considered for Gracie at this time.
Gracie was asked to reduce her glimepiride to 2 mg at bedtime and was started on canagliflozin 100 mg in the AM before breakfast. She will have a basic metabolic panel and A1C repeated in 6 weeks to monitor her renal status, making certain she does not have hyperkalemia, and to ascertain whether her A1C is declining. Assuming her A1C is dropping and her eGFR is > 60 mL/min/1.73 m2, the dose of her canagliflozin will be increased to 300 mg/d. Gracie was encouraged to check her blood glucose levels fasting for the first 7 days of each month and contact her clinician if any of her levels are < 70 mg/dL. She was advised that she may urinate more frequently on the new agent and to be cautious about the effects of orthostatic hypotension. Gracie is excited about the kick boxing classes she will be taking 5 days a week in order to improve her endurance and improve her weight loss.

Summary
Diabetes pathogenesis involves multiple defects in a number of target organs including the pancreas, liver, adipose tissue, brain, skeletal muscle and the kidneys. No single antidiabetic medication can reverse or correct all of these metabolic disturbances. The SGLT2 inhibitors have a unique mechanism of action targeting the kidney and allowing patients to restore normal glucose homeostasis. Patients using SGLT2 inhibitors will likely notice improvement in fasting and postprandial glucose levels as well as their overall A1C. They will have a minimal risk of treatment emergent hypoglycemia. The most common side effects, UTI and mycotic infections rarely result in patients discontinuing drug therapy. Weight loss is commonly observed with this class of
therapy. Importantly, SGLT2 inhibitors can be co-prescribed with other antihyperglycemia agents currently marketed.

References


and the European Association for the Study of Diabetes (EASD), Diabetes Care. 2012. 35: 1364-1379.