Targeting the Kidneys to Improve Glycemic Control

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A 37-year-old woman with a history of papillary carcinoma (status post total thyroidectomy 12 years ago, with negative recurrence) presents for a check-up. She also has polycystic ovarian syndrome (PCOS) with obesity and is taking metformin XR (one 500-mg tablet bid). Her visit is uneventful, and she leaves the office with an order for labwork.

Results indicate normal thyroid function and negative thyroglobulin. However, her serum glucose level is 350 mg/dL, so the patient is called and informed of the result. She denies polyphagia, polydipsia, and polyuria. Repeat blood work confirms overt hyperglycemia (320 mg/dL) with an A1C of 13%, undetectable C-peptide, and negative glutamic acid decarboxylase 65 (GAD65) and islet cell antibodies.

She is advised to increase her metformin dose (to two 500-mg tablets bid) and is started on insulin detemir (20 U every evening), with instructions to increase the latter by three units every two to three days until a target fasting glucose level of 100 to 140 mg/dL is achieved. She is also advised to follow a low-carbohydrate diet and increase her exercise.

The patient returns in two weeks for follow-up. She remains asymptomatic and has now increased her insulin detemir to 34 U bid (she started splitting the dosage after it reached 50 U/d). However, her glucose is still in the low 200s in the morning and the high 200s during the day (after lunch and dinner).

Her overt hyperglycemia is most likely a result of her long-standing insulin resistance, essential lack of β-cell function, and PCOS-associated obesity. Once diabetes from autoimmunity is ruled out by laboratory findings (negative antibodies) and clinical assessment (classic metabolic syndrome features), we focus on her glycemic control.

Even with nearly 70 U/d of insulin, the patient's glycemic improvement is disappointing, suggesting significant insulin resistance and glucose toxicity. Living in an era with numerous classes of antidiabetic medications, we have lengthy discussions on treatment options. Canagliflozin, recently (at the time) approved, is included. The patient is interested in this new medication, and it is a reasonable choice to get her out of the glucotoxic phase.

After a discussion of benefits and potential adverse effects, she is placed on canagliflozin 100 mg/d. Her glucose log in one week shows fasting glucose values in the range of 140 to 160 mg/dL and postprandial glucose values in the 180s. As a result, she lowers her insulin to 25 U bid. Her renal panel shows a potassium level of 4.3 mEq/L (reference range, 3.5 to 5.3) and a glomerular filtration rate (GFR) of 103 mL/min/1.73 m^2. She is advised to further increase her canagliflozin to 300 mg and slowly titrate her insulin down as needed, with a target fasting glucose level of 80 to 110 mg/dL and a postprandial target of 100 to 140 mg/dL.

Q What are SGLT2 inhibitors, and how do they work?

Sodium-**GL**ucose co-**T**ransporter **2** (SGLT2) inhibitors are a new class of antihyperglycemic agent. The first, canagliflozin, was approved by the FDA in March 2013, followed by dapagliflozin (January 2014) and empagliflozin (August 2014).

As glucose is filtered through the nephrons of the kidney, about 90% is reabsorbed via SGLT2 in the proximal tubule (SGLT1 is responsible for the remaining 10%) so that glucose calories are not eliminated through urine.[1] In a healthy person, the renal glucose threshold is about 180 mg/dL.[1] When blood glucose exceeds this level, glucose is excreted into the urine. However, in diabetic patients, this threshold is higher due to the up-regulation of SGLT2s (and other glucose transporters), which worsens hyperglycemia.[1] SGLT2 inhibitors will reset the threshold, which in turn will increase glucosuria and thereby lower serum glucose.[1]

SGLT2 inhibitors lower A1C by about 0.7% to 0.8%.[2] Independent of other mechanisms such as the degree of β-cell function or insulin resistance, these agents can be used regardless of the duration of

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diabetes[3] if the GFR is intact (≥ 45 mL/min/1.73 m^2 for canagliflozin and empagliflozin, ≥ 60 mL/min/1.73 m^2 for dapagliflozin).[4,5]

Q What are the risks and benefits associated with these agents?

Modest weight loss is seen with the use of SGLT2 inhibitors. Initial weight loss is believed to be related to volume loss, but more sustained weight loss is thought to be from loss of fat mass.[6] This is not surprising, as excreting glucose means excreting calories through urine.

Risk for hypoglycemia is extremely low, which makes this therapeutic class an attractive option. However, caution should be exercised when SGLT2 inhibitors are combined with other agents known to cause hypoglycemia (sulfonylureas and insulin).[6]

The most common adverse effect is genital mycotic infection. Women with a history of recurrent genital mycotic infection and uncircumcised men are at the greatest risk.[6]

Due to increased glycosuria, which results in an osmotic diuresis, modest blood pressure improvement has been seen (3 to 4 mm Hg systolic and 1 to 2 mm Hg diastolic[7,8]) in patients taking SGLT2 inhibitors, which is an additional benefit for hypertensive diabetic patients.[6] On the other hand, use of SGLT2 inhibitors can also cause dehydration and volume depletion and can raise serum creatinine in patients who are already taking diuretics (particularly loop diuretics).[6] Drug tolerance and adherence can be improved by advising patients to expect transient increased urination (approximately 135 to 350 mL/d increase from baseline[5,9]) and emphasizing the importance of good hydration and maintaining good genital hygiene.

A slight increase in LDL cholesterol was seen in clinical trials of the SGLT2 inhibitors, although this phenomenon is poorly understood. However, HDL cholesterol increased as well, maintaining the LDL:HDL ratio.[6] No long-term cardiovascular outcome data are available at this time; as with any new antidiabetic medication, postmarketing studies, as required by the FDA, are currently ongoing.[6]

Q What are the options in this therapeutic category, and how are they distinct?

As mentioned previously, there are currently three SGLT2 inhibitors on the market: canagliflozin, dapagliflozin, and empagliflozin. There are subtle clinical differences among these three agents, which might direct the clinician's choice.

First, canagliflozin is available in dosages of 100 and 300 mg. The starting dosage is 100 mg, which can be titrated to 300 mg in patients with a GFR ≥ 60 mL/min/1.73 m^2 who require a greater glucose-lowering effect. Those with a GFR < 60 mL/min/1.73 m^2 but ≥ 45 mL/min/1.73 m^2 are limited to the 100-mg dosage. Dapagliflozin is available in 5-mg and 10-mg dosages, the former being the starting dosage. But dapagliflozin is not recommended in patients whose GFR is < 60 mL/min/1.73 m^2.[4]

Empagliflozin is available in dosages of 10 and 25 mg. The starting dosage of 10 mg can be increased to 25 mg if the patient has not achieved his/her target glucose level. Either can be used in patients with a GFR ≥ 45 mL/min/1.73 m^2.[5]

Second, hyperkalemia was seen in patients taking canagliflozin but not in those taking dapagliflozin or empagliflozin. Therefore, serum potassium should be monitored and caution used, especially when patients are being treated with potassium-sparing diuretics and/or ACE inhibitors or angiotensin II receptor blockers.[6]

Third, dapagliflozin carries a warning for bladder cancer, as higher rates of newly diagnosed bladder cancer were seen with this drug compared with placebo or comparator drugs (0.17% vs 0.03%, respectively).[4] However, this finding may have resulted from a randomization imbalance of patients in the study, and further research is needed to clarify this risk.[6] It is not recommended that dapagliflozin be used in patients with active or a history of bladder cancer at this time.

With these agents, there is a paradoxical rise in glucagon that increases endogenous glucose production from the liver.[10] The mechanism is poorly understood, but it might be due to the body's compensatory (survival) mechanism to "make up" the loss of glucose through urine by increasing hepatic gluconeogenesis.

Using an incretin agent, such as dipeptidyl peptidase 4 (DPP-4) inhibitors or glucagon-like peptide 1 (GLP-1) receptor agonists, in conjunction with an SGLT2 inhibitor, has been suggested as a way to potentiate the glucose-lowering effect, as it may attenuate the paradoxical rise in glucagon.[10] Since the incretin class is weight neutral (DPP-4 inhibitors) or associated with weight loss (GLP-1 agonists), using incretins

with SGLT2 inhibitors might produce more significant weight loss, which has numerous additional benefits for diabetic patients.

SGLT2 inhibitors are currently approved as an adjunct to diet and exercise for patients with type 2 diabetes. They are not approved for those with type 1 diabetes, although the mechanism of action of these drugs (which is independent of the β-cell function) might make them effective in this population. Active pilot studies of this patient population are in progress.[11]

CONCLUSION

In summary, SGLT2 inhibitors are an exciting new class of antidiabetic medication that offers a unique mechanism to lower serum glucose. It is the only medication that will actually remove glucose from the body; by contrast, all other existing antidiabetic medications move glucose within the body (to liver, fat, muscle, etc).

There is no curative medication for diabetes. But with an increasing diabetic population and an emphasis on individualizing antihyperglycemic regimens, we always welcome medications with novel mechanisms of action. Due to SLGT2 inhibitors' recent approval, however, short-term and long-term adverse effects are unknown, and ongoing postmarketing surveillance should be closely followed. **CR**

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