Sodium Glucose Cotransporter 2 Inhibitors as a New Treatment for Diabetes Mellitus

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Context: Sodium-glucose cotransporter 2 (SGLT2) expressed in the proximal renal tubules accounts for about 90% of the reabsorption of glucose from tubular fluid. Genetic defects of SGLT2 result in a benign familial renal glucosuria. Pharmacological agents that block SGLT2 are being tested as potential treatment for type 2 diabetes mellitus.

Evidence Acquisition: A Pubmed search was used to identify all relevant articles on the physiology of SGLTs as well as published preclinical and clinical experimental studies with SGLT2 inhibitors; a reference search of all retrieved articles was also undertaken.

Evidence Synthesis: SGLT2 is almost exclusively expressed in the proximal renal tubules. Preclinical studies with selective SGLT2 inhibitors show dose-dependent glucosuria and lowering of blood glucose in models of type 2 diabetes. Preliminary clinical studies of up to 3-month duration show dose-dependent lowering of glycated hemoglobin up to 0.9% along with modest weight loss. Side effects include an increase in genital fungal infection compared to placebo, increased urine volume (300–400 ml/24 h), and evidence of volume depletion consistent with mild diuretic effect.

Conclusion: SGLT2 inhibitors are showing promise as a useful addition to the current therapeutic options in type 2 diabetes mellitus. Results of ongoing phase III clinical trials are awaited and will determine whether the risk-benefit ratio will allow approval of this new class of drug for the management of type 2 diabetes mellitus. (J Clin Endocrinol Metab 95: 34–42, 2010)

Management of type 2 diabetes mellitus (T2DM) remains complex and challenging. Although a wide range of pharmacotherapy for T2DM is available, including metformin, insulin secretagogues (predominantly sulfonylureas), thiazolidinediones, α-glucosidase inhibitors, insulin, and more recently glucagon like peptide-1 agonists and dipeptidyl-peptidase-IV inhibitors, many patients do not achieve glycemic targets, partly due to limiting side effects of current therapies, including weight gain, hypoglycemia, fluid retention, and gastrointestinal side effects. Hence, the search for new treatment strategies is ongoing. Among the new therapies on the horizon, sodium-glucose cotransporter 2 (SGLT2) inhibitors seem promising, and there are a number of ongoing phase II and III clinical trials with a variety of these compounds. SGLT2 is almost exclusively expressed in the renal proximal tubules and accounts for 90% of the renal glucose reabsorption (1). SGLT2 inhibitors work independently of insulin and lead to negative energy balance by enhanced urinary glucose excretion. This makes it mechanistically possible for this class of drugs to reduce glucose levels without causing hypoglycemia and weight gain. However, the side effect profile remains to be further elucidated in ongoing phase III trials, and these compounds will need to be proven safe from a renal and cardiovascular perspective to meet current regulatory requirements for new diabetes treatment.

Glucose Transport across Biological Membranes

Glucose transporters

Glucose absorption at the enterocytes, reabsorption at the renal tubules, transport across the blood-brain barrier, and

Abbreviations: GLUT, Glucose transporter; HbA1c, glycated hemoglobin; MAD, multiple ascending dose; SAD, single ascending dose; SGLT, sodium-glucose cotransporter; SLC, solute carrier family; T2DM, type 2 diabetes mellitus; UTI, urinary tract infection.
uptake and release by all cells in the body are effected by two groups of transporters: glucose transporters (GLUTs) and sodium-glucose cotransporters (SGLTs).

GLUTs are facilitative or passive transporters that work along the glucose gradient. They belong to the SLC2 (solute carrier family 2) gene family, which has 13 members: GLUT 1-12 and the H+-myoinositol cotransporters. They are expressed in every cell of the body (2, 3).

SGLTs cotransport sodium and glucose into cells using the sodium gradient produced by sodium/potassium ATPase pumps at the basolateral cell membranes. They belong to the SLC5 gene family, which has nine members with known functions. Of these, six are plasma membrane sodium/substrate cotransporters for solutes such as glucose, myoinositol, and iodide (SGLT 1-6). SGLT1 is primarily expressed in the small intestine but is also found in the trachea, kidney, and heart, and its predominant substrates are glucose and galactose. SGLT2 is expressed in the S1 and S2 segments of the proximal convoluted tubules and is responsible for renal reabsorption of glucose (4). SGLT2 RNA is minimally expressed in the ileum, the level of which was insignificant by Northern blot analysis (5). Although one study using real-time PCR suggests widespread SGLT2 RNA expression in a variety of tissues (6), there is no published data to show that SGLT2 protein is found outside the kidney. There have been attempts to examine expression of SGLT proteins, but availability of antibodies that are specific enough seems to be the limiting factor. Therefore, the functional significance of mRNA expression in nonrenal tissues has not been established. However, there is some evidence for SGLT2 mRNA expression by real-time PCR as well as for SGLT2 protein expression in the placenta by Western blot analysis (7).

SGLT1 gene mutations lead to glucose-galactose malabsorption, which causes potentially fatal diarrhea. The oral rehydration therapy that saves millions of lives from infectious diarrhea works via SGLT1 transporters in the enterocytes (8, 9).

Much of the evidence for SGLT2 being a major pathway for renal glucose reabsorption comes from genetic studies of individuals with familial renal glucosuria (10, 11). Mutations in the SLC5A2 gene encoding SGLT2 lead to familial renal glucosuria, which is inherited as an autosomal recessive trait and is characterized by normal blood glucose levels, normal oral glucose tolerance test results, and isolated persistent glucosuria (10, 12, 13). A study analyzing 23 families with index cases of renal glucosuria found that each family had a unique mutation in the SGLT2 gene. Individuals who were found to be carriers of two mutated alleles showed severe glucosuria, defined by a urinary glucose of more than 10 g/1.73 m² per 24 h (55 mmol/1.73 m² per 24 h). The index patients who presented with mild glucosuria and the family members of cases of severe glucosuria were shown to be heterozygous carriers of SGLT2 mutations (11, 14). Another study found 20 different SLC5A2 mutations within 17 pedigrees. Glucosuria was mild in heterozygotes ranging from 2.7 to 10 g/1.73 m² per 24 h, whereas it was severe in homozygotes ranging from 15.2 to 86.5 g/1.73 m²/24 h. Two patients in the homozygous group had plasma renin and serum aldosterone concentration raised to an average of 4.6- and 3.1-fold, respectively, suggesting activation of compensatory mechanisms (15).

Renal glucose transport in health

Kidneys play a very important role in glucose homeostasis. Blood glucose is freely filtered by the glomeruli and is essentially completely reabsorbed from the proximal tubules via sodium-coupled transporters in the brush border membrane. The glomeruli filter about 144 g of glucose per 24 h, nearly 100% of which is reabsorbed in the renal tubules. When blood glucose levels reach the renal threshold for reabsorption, which is about 8 to 10 mmol/liter (180 mg/dl), glucosuria starts to develop (16). The proximal tubule has traditionally been divided into S1, S2, and S3 segments based on the cell morphologies, although more recent ultrastructural analyses of computer-assisted three-dimensional reconstruction of mouse proximal tubules revealed no obvious morphological segmentation of the proximal tubule (17). There is evidence, however, for heterogeneity of sodium-dependent glucose transport along the proximal tubule. The S1 and S2 segments of the proximal convoluted tubules show low affinity and high capacity for sodium-dependent glucose absorption, whereas the more distal parts show higher affinity and low capacity for the same (18). SGLT2 is located in the S1 and S2 segments where the majority of filtered glucose is absorbed, and SGLT1 is located in S3 segments responsible for reabsorbing the remaining glucose (4, 19). Combined in situ hybridization and immunocytochemistry with tubule segment-specific marker antibodies demonstrated an extremely high level of SGLT2 mRNA in proximal tubule S1 segments (1) (Fig. 1).

Renal glucose transport in diabetes

Renal tubular reabsorption is known to undergo adaptations in uncontrolled diabetes; particularly relevant in this context is the up-regulation of renal GLUTs. The increase in extracellular glucose concentration in diabetes lowers its outwardly directed gradient from the tubular cells into the interstitium. Hence, up-regulation of SGLT2 is an important adaptation in diabetes to maintain renal tubular glucose reabsorption. SGLT2 mRNA expression is up-regulated in diabetic rat kidneys and this up-regulation is reversed by lowering blood glucose levels (20). Hu-
Man exfoliated proximal tubular epithelial cells from fresh urine of diabetic patients express significantly more SGLT2 and GLUT2 than cells from healthy individuals (21). There is also evidence for up-regulation of GLUT2 gene expression in renal proximal tubules in diabetic rat models (22–24). Uncontrolled diabetes leading to increased expression of SGLT2 has practical significance in that the inhibitors are likely to produce greater degrees of glucosuria in the presence of higher prevailing plasma glucose levels. This has been shown in preclinical studies with the nonspecific SGLT inhibitor, T-1095 (25).

Interestingly, this up-regulation of SGLT2 receptors is also seen in renovascular hypertensive rat models. The authors speculated that angiotensin II-induced SGLT2 overexpression probably contributes to increased absorption of Na\(^+\) and thereby development or maintenance of hypertension. Rats treated with either ramipril or losartan showed significant reduction in the intensity of immunostaining and levels of SGLT2 protein and mRNA (26). This may have relevance in diabetes, given the high prevalence of hypertension in diabetes.

**Therapeutic Potential of Inducing Glucosuria**

Phlorizin is a glucoside consisting of a glucose moiety and two aromatic rings (aglycone moiety) joined by an alkyl spacer. In the 19th century, French chemists isolated it from the bark of apple tree to be used in treatment of fever and infectious diseases, particularly malaria. Von Mering observed in 1886 that phlorizin produces glucosuria. It has been used as a tool for physiological research for more than 150 yr (27). In 1975, DeFronzo et al. (28) showed that infusion of phlorizin in dogs increased fractional excretion of glucose by 60%, whereas glomerular filtration rate and renal plasma flow remained unchanged.

Phlorizin is a high-affinity competitive inhibitor of Na-dependent glucose transport in renal and intestinal epithelia (29). Hence, it causes malabsorption of glucose and galactose from the small intestines and of glucose from the renal tubules. Phlorizin caused heavy glucosuria and marked inhibition of glucose uptake in the small intestine during enteric perfusion in normal rats. It also significantly reduces blood glucose on oral glucose tolerance test in mice and lowers blood glucose in streptozotocin-induced diabetic rats (30). It improves counter-regulatory responses reducing the risk of hypoglycemia in animal models (31). In 1986, Unger’s group (32) reported that iv glucose failed to suppress the marked hyperglucagonemia found in insulin-deprived alloxan-induced diabetic dogs; however, when hyperglycemia was corrected by phlorizin, the hyperglucagonemia became readily suppressible. Phlorizin treatment of partially pancreatectomized rats completely normalized insulin sensitivity but had no effect on insulin action in controls (33, 34), suggesting that the effect on insulin sensitivity was by reversal of glucotoxicity, rather than by a direct effect on insulin sensitivity. Animal studies with phlorizin have shown that its effect of changing the ambient glucose independent of insulin levels can up-regulate the glucose transport response to insulin in adipose cells, which may be as a result of changes in GLUT functional activity (35).

These findings provided important proof of concept data, although phlorizin itself is unsuitable for development as a drug for the treatment of diabetes because of its nonselectivity and low oral bioavailability (25, 36).

T-1095 is a synthetic phlorizin derivative, which unlike phlorizin is absorbed into the circulation on oral administration and is metabolized to its active form T-1095A. It suppresses the activity of SGLT1 and -2 in the kidney and increases urinary glucose excretion in diabetic animals, thereby decreasing blood glucose levels. With long-term T-1095 treatment, both blood glucose and glycosylated hemoglobin (HbA1c) levels were reduced in streptozotocin-induced diabetic rats and the obese insulin resistant yellow KK rat models (25). Chronic administration of T-1095 lowered blood glucose and HbA1c levels, partially improved glucose intolerance and insulin resistance, and prevented the development of diabetic neuropathy in the diabetic insulin-resistant GK rat models. There were no adverse side effects reported at the end of the study (37). This drug, however, did not proceed to clinical development, presumably because it also inhibits SGLT1 (Fig. 2).

**Development of Selective SGLT2 Inhibitors**

Several specific and potent SGLT2 inhibitors have undergone preclinical testing. Most SGLT2 inhibitors are glu-
cosides, structurally related to phlorizin, which is an o-glucoside. The o-glucosides have to be administered as their prodrug esters to avoid degradation by $\beta$-glucosidase in the small intestine. Sergliflozin and remogliflozin etabonate, which are orally administered, are the ethyl carbonate prodrug esters of sergliflozin A and remogliflozin, respectively. Creating a carbon-carbon bond between the glucose and aglycone moiety converts o-glucosides to c-glucosides, which have a different pharmacokinetic profile, making them unsusceptible to $\beta$-glucosidase (38). Dapagliflozin is the first c-glucoside to be discovered that is currently in phase III trials. Several such structural alterations and new SGLT2 inhibitors have been reported (39–42) (Table 1).

**Antisense oligonucleotide therapy**

Preliminary findings of a novel method of SGLT2 inhibition have been presented in abstract form. ISIS 388626, an antisense oligonucleotide, reduces the expression of SGLT2 gene in the proximal renal tubules of rodents and dogs. Once-weekly administration of ISIS 388626 reduced renal SGLT2 mRNA expression by up to 80%. It did not affect the expression of SGLT1 or GLUT genes. Consistent with this, ISIS 388626 increased glucosuria and improved plasma glucose and HbA1c in Zucker diabetic fatty rats. There was no accumulation in liver, intestine, or cardiac tissues after 6 months of dosing in Zucker diabetic fatty rats, whereas kidney antisense oligonucleotide concentration was high, confirming its tissue specificity (43). A study examining the long-term effect of ISIS 388626 in nonhuman primates showed dose-dependent reduction in SGLT2 expression, with more than 75% reduction at the highest dose. This was accompanied by a

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**TABLE 1. SGLT2 inhibitors with published preclinical studies**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Chemical structure</th>
<th>Preclinical studies</th>
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<tbody>
<tr>
<td>T-1095</td>
<td>O-Glucoside</td>
<td>T-1095, an inhibitor of renal SGTLs, may provide a novel approach to treating diabetes (25) Long-term treatment with the SGLT inhibitor T-1095 causes sustained improvement in hyperglycemia and prevents diabetic neuropathy in Goto-Kakizaki rats (37)</td>
</tr>
<tr>
<td>AVE2268</td>
<td>Substituted glycopyranoside</td>
<td>Effects of AVE2268, a substituted glycopyranoside, on urinary glucose excretion and blood glucose in mice and rats (59)</td>
</tr>
<tr>
<td>Remogliflozin etabonate</td>
<td>O-glucoside</td>
<td>Remogliflozin etabonate, in a novel category of selective low-affinity SGLT2 inhibitors, exhibits antidiabetic efficacy in rodent models (41)</td>
</tr>
<tr>
<td>Sergliflozin</td>
<td>O-glucoside</td>
<td>Sergliflozin, a novel selective inhibitor of low-affinity SGLT2, validates the critical role of SGLT2 in renal glucose reabsorption and modulates plasma glucose level (36)</td>
</tr>
<tr>
<td>Dapagliflozin</td>
<td>C-aryl glucosides</td>
<td>Discovery of dapagliflozin: a potent, selective renal sodium-dependent glucose cotransporter 2 (SGLT2) inhibitor for the treatment of T2DM (46)</td>
</tr>
<tr>
<td>JNJ-28431754/TA-7284</td>
<td></td>
<td>JNJ-28431754/TA-7284, an SGLT inhibitor, lowers blood glucose and reduces body weight in obese and T2DM animal models (62)</td>
</tr>
<tr>
<td>BI 10773</td>
<td></td>
<td>In vitro properties and in vivo effect on urinary glucose excretion of BI 10773, a novel selective SGLT2 inhibitor (63)</td>
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</tbody>
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**FIG. 2.** Schematic representation of normal renal glucose reabsorption and the effect of SGLT2 inhibition. The amount of glucose filtered increases linearly with increasing plasma glucose concentration (gray dotted line). The threshold at which glucose appears in the urine is a plasma glucose concentration of around 8.3 mmol/liter, but some variability in reabsorption by individual nephrons is thought to account for the “splay” shown in the figure. Above the saturation threshold (13.3 mmol/liter), glucosuria increases in a linear fashion with plasma glucose. In diabetes due to up-regulation of SGLT2, the reabsorption curve is shifted to the right. SGLT2 inhibitors lower both the saturation threshold and the transport maximum (Tmax) for glucose. This results in increased glucosuria for a given plasma glucose level, represented here as a left shift of the glucosuria curve.
more than 1000-fold increase in glucosuria without any associated hypoglycemia, and the glucosuria persisted for several weeks after treatment cessation (44).

This novel approach is of potentially great interest, and ISIS Pharmaceuticals (San Diego, CA) recently announced that translation into human phase I studies is about to commence using a 12-nucleotide antisense oligonucleotide, ISIS-SGLT2RX although very careful safety evaluation will need to be undertaken given the novelty of this approach.

**SGLT2 inhibitors in clinical development**

**Dapagliflozin**

Dapagliflozin is a potent and highly selective SGLT2 inhibitor. The elimination half-life after intraarterial administration was 4.6, 7.4, and 3.0 h in rats, dogs, and monkeys, respectively (45). Single and multiple ascending dose (SAD and MAD) studies with dapagliflozin confirmed that it has a pharmacokinetic profile consistent with once-daily dosing and produces a dose-dependent increase in glucosuria in humans. Dapagliflozin was rapidly absorbed after oral administration, and maximum plasma concentrations (Cmax) were observed within 2 h of administration. The mean half-life after the last dose in the MAD study ranged from 11.2 to 16.6 h, and the data were similar for the SAD study with high dose. In the MAD study, a dose of 100 mg produced urine glucose of 58.3 g per 24 h and 55.4 g per 24 h on d 14. Dapagliflozin had no effect on urine and serum electrolytes, serum albumin, osmolality, or renal tubular markers such as N-acetyl-b-D-glucosaminidase and b2-microglobulin. Two events of mild asymptomatic hypoglycemia were reported in the SAD study. No treatment-related serious adverse events were reported in either study (46).

In a phase IIa study, 47 patients with T2DM were randomized to receive 5, 25, or 100 mg of dapagliflozin or placebo for 14 d. Those receiving 25 and 100 mg dapagliflozin had approximately 40% inhibition of renal glucose reabsorption as compared with baseline resulting in glucose excretion of up to 70 g per 24 h. Two of the 24 women who received dapagliflozin were diagnosed with mild vulvovaginal mycotic infections that resolved in 4 d with treatment. The most frequently reported treatment emergent adverse events were gastrointestinal, including constipation, nausea, and diarrhea. There were no drug discontinuations due to adverse events (47).

A phase IIb multiple-dose study to evaluate safety and efficacy of dapagliflozin-randomized T2DM patients to five dapagliflozin doses (2.5, 5, 10, 20, or 50 mg), metformin extended release, or placebo for 12 wk has recently been reported. Dapagliflozin improved hyperglycemia and caused weight loss by inducing controlled glucosuria with urinary loss of approximately 200–300 kcal/d. There was a weight loss of 2.5 to 3.4 kg in the dapagliflozin-treated patients, compared with 1.2 kg with placebo and 1.7 kg with metformin. Dapagliflozin treatment was not associated with clinically significant osmolarity, volume, or renal status changes. There was also no compensatory increase in hunger as assessed by visual analog scales. The rates of bacterial urinary tract infections (UTIs) were similar in the treatment and placebo arms, but there was higher incidence of genital infections in the dapagliflozin vs. placebo, especially at higher doses (48).

A double-blind, three-arm parallel group, placebo-controlled study randomized 71 patients 1:1:1 to placebo, 10 and 20 mg dapagliflozin, plus oral antidiabetic agents and 50% of their prestudy daily insulin dose. At wk 12, dapagliflozin 10- and 20-mg groups demonstrated −0.70% and −0.78% mean differences in HbA1C change from baseline vs. placebo. Mean changes from fasting plasma glucose were +17.8, +2.4, and −9.6 mg/dl, and mean changes in total body weight were −1.9, −4.5, and −4.3 kg (placebo, 10-, and 20-mg dapagliflozin groups, respectively). The baseline HbA1c in the three groups were 8.4 ± 0.9, 8.4 ± 0.7, and 8.5 ± 0.9, respectively. Overall, adverse events were balanced across all groups, but more genital infections occurred in the dapagliflozin 20-mg group than placebo. Also total hypoglycemic events were more frequently reported with dapagliflo-
zin than placebo, although none of them was major (49) (Fig. 3).

A number of phase III clinical trials with dapagliflozin, mostly as add-on therapies to existing antidiabetic drugs, are now under way.

Sergliflozin
A phase I study with 50–500 mg of sergliflozin in 14 healthy volunteers and a phase IIa study where the same dose range was given to eight subjects with T2DM showed a dose-dependent increase in urinary glucose excretion that plateaued at higher doses. It did not cause hypoglycemia in nondiabetic subjects, and there was a 1.5-kg weight loss from baseline to d 15 compared with placebo. There were no clinically significant effects on serum electrolytes or calculated creatinine clearance (50, S1). Development of sergliflozin has been discontinued in favor of remogliflozin.

Remogliflozin etabonate
Remogliflozin etabonate is metabolized to its active form remogliflozin, which is a benzylpyrazole glucoside. Its skeleton differs from that of phlorizin, T-1095, or sergliflozin, and hence is from a new category of SGLT2 inhibitors. Its inhibitory effect for human SGLT2 is approximately three times greater than that of phlorizin, but for SGLT1 it was only 1/20 that of phlorizin in in vitro studies. Animal studies have shown good linearity between urinary glucose excretion and the dose of remogliflozin etabonate. It did not significantly alter the plasma glucose level in 16-h fasted normal rats (41).

A study with 13 T2DM patients supported its coadministration with metformin in patients with T2DM with minimal risk of hypoglycemia. There was no drug interaction affecting the pharmacokinetics of either drug (52). In another study, remogliflozin etabonate administered to 10 healthy subjects (doses ranging from 20 to 1000 mg) and six subjects with T2DM (doses ranging from 50 to 500 mg) was rapidly absorbed and converted to remogliflozin, which had a plasma half-life of 120 min across doses and groups. It caused a dose-dependent increase in urinary glucose excretion in all subjects. There were no effects on plasma electrolytes and no serious adverse events (53).

AVE2268
A phase II study with AVE2268 recruited 300 patients with T2DM not adequately controlled by metformin to assess the effects of several doses of AVE2268 on glycemic control and to assess safety and tolerability. The results of this study are awaited.

Adverse effects
Increased urine volume (up to 400 ml) was observed in clinical studies with dapagliflozin, associated with increased hematocrit and urea, suggesting slight volume depletion. Electrolyte imbalance is also a consideration because physiological studies have shown increased sodium loss with phlorizin. A phase II trial reported one case of dehydration and prerenal azotemia, which resolved with oral rehydration and withholding angiotensin-converting enzyme inhibitor and diuretic therapy (49). Whether patients with diabetes mellitus who have neuropathy, hyporeninemic hypoaldosteronism, and nephropathy could be rendered more vulnerable to sodium wasting and hypovolemia will need to be assessed further. A statistically significant increase in magnesium (0.18 ± 0.16 mEq/liter; P < 0.001) and decrease in uric acid levels (−1.14 ± 1.15 mg/dl; P < 0.001) were reported in a phase II trial with dapagliflozin compared with placebo. In terms of bone metabolism, an increase in parathormone concentration (range, 0.6–7.0 pg/ml above baseline of 31.1–35.0 pg/ml) has been noted, which was greater than the 0.8 pg/ml increase for placebo. There was no change in serum 1,25-dihydroxyvitamin D and 25-hydroxyvitamin D values from baseline, and the mean changes in the 24-h urinary calcium-to-creatinine ratio were similar to those with placebo (48). The long-term effects on bone health will also need to be clarified by ongoing phase III trials.

The apparent presence of SGLT2 in the placenta does raise concern about its safety in women of child-bearing age.

Another important question is whether increased glucosuria would predispose to UTIs or genital fungal infections.

In vivo studies have not shown a higher prevalence of bacteriuria among diabetic patients with glucosuria compared with patients without glucosuria. Defects in the local urinary cytokine secretions and an increased adherence of the microorganisms to the uroepithelial cells have been proposed to increase the incidence of UTI in patients with diabetes (54, 55). This suggests that risk of UTI may not be increased in patients taking SGLT2 inhibitors, and this has been borne out by the available clinical data.

Symptomatic vulvovaginal candidiasis is more prevalent in patients with diabetes compared with the normal population (56, 57), and this increased prevalence is associated with poor glycemic control (58), but it is unknown whether circulating glucose concentrations or the presence of glucosuria is the critical factor. Both reported phase II studies with dapagliflozin suggest an increase in
SGLT2 inhibitors have a unique mechanism of action and have the potential to become a new treatment for T2DM. Several phase III trials with these compounds are ongoing and if their efficacy and safety profile are proven to be adequate, these agents may gain a place in the management of T2DM, particularly where weight gain is a concern. The potential for use as an insulin-sparing agent in patients on insulin has been highlighted in a recent trial (49) and a future role in the management of type 1 diabetes mellitus cannot be ruled out, although SGLT2 inhibitors have not yet been tested for this indication.

Acknowledgments

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Disclosure Summary: J.P.H.W. is a consultant to Bristol Myers Squibb/AstraZeneca (BMS/AZ), GlaxoSmithKline, and Johnson & Johnson in relation to SGLT2 inhibitors for diabetes treatment and is an investigator for ongoing trials with dapagliflozin (BMS/AZ). S.N. is a coinvestigator in an ongoing clinical trial of dapagliflozin (BMS/AZ).

References


