

Renal Sodium Glucose Transport Inhibition for the Treatment of Type 2 Diabetes

BY LOREN D. GROSSMAN, MD, FRCPC, FACP

Despite a plethora of therapeutic options for the treatment of type 2 diabetes mellitus (T2DM), the ability to normalize glucose levels and reduce long-term complications of diabetes with treatment remains elusive. From the discovery of insulin in the early 1920s to the incretins of the last few years, as well as all the other developments in between, the ideal antidiabetes medication has not yet been revealed. Indeed, metformin, one of the original oral antihyperglycemic agents first described in 1957, remains first-line therapy in many clinical practice guidelines.^{1,2} As a result, newer medications continue to be the subject of intensive research. A number of new targets have indicated promise for the treatment of T2DM, including sodium glucose transport inhibition, glucokinase activation,³ glucagon receptor antagonism,⁴ fibroblast growth factor-21 receptor activation,⁵ 11 β -hydroxysteroid dehydrogenase type 1 inhibition,⁶ and others. This issue of *Endocrinology Rounds* reviews sodium glucose linked transporter-type 2 (SGLT2) inhibition as a potential new treatment for T2DM.

Renal sodium glucose transport

The kidney plays a major role in regulating glucose levels in nondiabetic individuals, since under normal physiological conditions, the kidney both filters and reabsorbs glucose. Filtration occurs in the glomerulus, and reabsorption occurs in the proximal tubule. Approximately 180 g of glucose is filtered on a daily basis, with 90% reabsorbed in the convoluted segment of the proximal tubule, and the remaining 10% in the distal straight segment of the proximal tubule.⁷ The proximal tubule has a maximal reabsorption rate of approximately 375 mg/mL.⁸ In nondiabetic individuals, the usual filtered glucose load remains well below this rate, such that all filtered glucose is reabsorbed. In patients with diabetes, however, hyperglycemia can lead to hyperfiltration, and the increased luminal glucose exceeds the maximal reabsorption rate, resulting in glycosuria. As well, maximal renal glucose reabsorption can further contribute to high plasma glucose levels. The inhibition of renal glucose reabsorption may result in decreased plasma glucose levels.

Transmembrane glucose transport is mediated by 2 types of transporters: sodium-glucose linked transporters (SGLTs) and facilitative glucose transporters (GLUTs).⁹ SGLTs are members of a large group of sodium substrate cotransporters, coded for by 12 human genes. Of these, 7 gene products are monosaccharide transporters that actively transport a sugar moiety coupled to sodium ion transport.¹⁰ Each has a different substrate affinity and a different tissue distribution (Table 1).^{7,10,11} SGLT1 is a high-affinity, low-capacity transporter, primarily found in the small intestine where it is responsible for dietary glucose absorption. SGLT1 is also found in the distal segment (S3 segment) of the proximal tubule of the kidney. Mutations in the SGLT1 gene result in glucose and galactose malabsorption with significant gastrointestinal dysfunction and only mild renal glycosuria.^{12,13} SGLT2 is a 672 amino acid, high-capacity, low-affinity transporter expressed in the convoluted segment (S1 segment) of the proximal tubule, where it is



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Table 1: Sodium glucose-linked transporter (SGLT) isoforms ^{7,10,11}			
Transporter isoform	Substrate	Primary tissue distribution	Other tissue locations
SGLT1	glucose, galactose	small intestine	kidney, heart, brain, trachea
SGLT2	glucose	kidney	
SGLT3 (SAAT1)	glucose	small intestine	thyroid, lung, muscle, pancreas
SMIT	myo-inositol	kidney	small intestine, brain, thyroid, lung, muscle, pancreas
SGLT4	glucose, fructose, mannose	small intestine	thyroid, lung, muscle, pancreas
SGLT5	glucose, galactose	kidney	
SGLT6	glucose, xylose, myo-inositol	kidney	brain, small intestine, thyroid, lung, muscle, pancreas

SAAT1 = sodium amino acid transporter 1; SMIT = sodium myo-inositol co-transporter

responsible for the majority of renal glucose reabsorption (Figure 1). Mutations in the SGLT2 gene result in renal glycosuria without hypoglycemia, and without significant clinical manifestations, although a few subjects with mutational variations may experience renal sodium wasting with or without mild volume depletion.¹⁴⁻¹⁷ Given its prominence in renal glucose reabsorption, inhibition of SGLT2 has been the subject of extensive research as a potential treatment for T2DM.

SGLT2 inhibitors

Phlorizin

Phlorizin is the prototype SGLT inhibitor; it was first isolated from the bark of the apple tree in the early 1800s.¹⁸ Since extracts from the willow and cinchona trees were known for their antipyretic properties, phlorizin was first investigated for this activity as well, but further study revealed the glycosuric effect of phlorizin.¹⁹ Phlorizin is known to specifically and competitively inhibit both SGLT1 and SGLT2, but with no effect on GLUT transporters. Although phlorizin was first used as a treatment for malaria,²⁰ its glycosuric

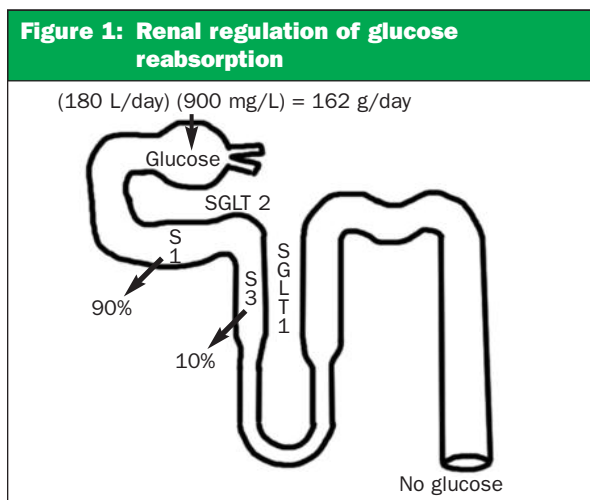
effect led to investigations for use in the treatment of diabetes. Phlorizin has been shown to lower glucose levels without increasing insulin secretion, and to normalize insulin sensitivity in animal models of diabetes.²¹⁻²³ Nevertheless, because it is poorly absorbed from the gastrointestinal (GI) tract and not specific for SGLT2, it has not been developed further as a medication for the treatment of diabetes.

Oral bioavailability was improved with the development of the phlorizin derivative, T-1095, a prodrug of the active SGLT inhibitor, T-1095A.²⁴ In streptozotocin-induced diabetic rats, T-1095 increases urinary glucose excretion, lowers plasma glucose levels, and lowers glycosylated hemoglobin (HbA_{1c}).^{24,25} These studies also revealed that T-1095A is a nonspecific inhibitor of both SGLT1 and SGLT2, which makes it unlikely to be suitable as a viable medication for chronic human use.

Dapagliflozin

Dapagliflozin is a highly selective SGLT2 inhibitor under clinical development by Bristol-Myers Squibb and AstraZeneca. In animal studies, dapagliflozin has been shown to acutely induce renal glucose excretion in normal and diabetic rats, improve glucose tolerance in normal rats, and reduce hyperglycemia in Zucker diabetic fatty (ZDF) rats after single oral doses ranging from 0.1 to 1.0 mg/kg. Once-daily dapagliflozin treatment at this dose range over 2 weeks significantly lowered fasting and fed glucose levels and resulted in a significant increase in the glucose-utilization rate and a reduction in glucose production.²⁶

In early clinical studies, dapagliflozin demonstrated promise as a glucose-lowering agent. Komoroski et al²⁷ reported both a single dose and a 14-day multiple dose study in 64 and 40 nondiabetic subjects, respectively. In the single-dose study, doses ranging from 2.5 to 500 mg resulted in a dose-dependent increase in cumulative urinary glucose excretion. Doses of 20-50 mg maintained a glucose excretion rate of close to the maximum of approximately 3 g/h for at least 24 h.



SGLT = sodium-glucose transporter

In the 14-day multiple-dose study, a close-to-maximum glucose excretion rate per day was achieved with doses of ≥ 20 mg. Serum glucose, insulin, and C-peptide concentrations remained unchanged and both the single and multiple doses of dapagliflozin appeared to be well tolerated. Adverse events were reported in 21% and 37% of subjects who received single and multiple doses of dapagliflozin, respectively, and in 35% of subjects who received placebo. Two mild, asymptomatic hypoglycemic events were reported in the single-dose study, one in a subject who received placebo. No clinically significant laboratory abnormalities were noted, and there was no evidence of increased sodium excretion in the multiple-dose study. These studies concluded that in nondiabetic subjects, dapagliflozin in doses of 20 mg/day and higher inhibited up to 50% of filtered glucose reabsorption, which resulted in glucose excretion of approximately 60 g/day and up to 3 g/h. Dapagliflozin induced a sustained dose-dependent glycosuria without reducing serum glucose in healthy subjects.

In a companion article, dapagliflozin treatment was studied in 47 patients with T2DM, who were randomized to receive 5, 25, or 100 mg daily, or placebo, for 14 days.²⁸ These T2DM patients were receiving treatment with either nonpharmacological therapy or metformin. Dapagliflozin resulted in a significant dose-dependent lowering of fasting serum glucose by -1.04, -1.60, and -2.15 mmol/L for the 5, 25, and 100 mg doses respectively, with no change in the placebo group. Dapagliflozin also resulted in a significant reduction in post-oral glucose tolerance test (OGTT) glucose excursions and an increase in 24-h cumulative glucose urinary excretion. Dapagliflozin had no effect on serum insulin, fructosamine, or C-peptide levels, or on body weight. Similar to the healthy subjects, dapagliflozin was reported to be well tolerated. The most frequent treatment-emergent adverse events were gastrointestinal and the frequency increased in those taking metformin as well. Two episodes of hypoglycemia were reported that resolved spontaneously.

Recently, List et al²⁹ reported a 12-week study of dapagliflozin in 389 drug-naïve patients with T2DM randomized to 5 different doses of dapagliflozin, 2.5, 5, 10, 20, or 50 mg, metformin, or placebo. The primary objective compared changes in the mean HbA_{1c} levels from baseline for each group versus placebo after 12 weeks. Secondary objectives compared dapagliflozin versus placebo for fasting plasma glucose change from baseline, dose-dependent trends in glycemic efficacy, proportion of patients achieving HbA_{1c} <7%, and change in 24-h urinary glucose-to-creatinine ratio. At 12 weeks, all dapagliflozin groups achieved significant reductions in mean HbA_{1c} change from baseline versus placebo, ranging in a non-dose-

Table 2: Adjusted mean change from baseline in hemoglobin HbA_{1c} at Week 12²⁹

Agent (dose)	HbA _{1c} (%)	P value (vs placebo)*
Dapagliflozin		
2.5 mg	-0.71	<0.001
5 mg	-0.72	<0.001
10 mg	-0.85	<0.001
20 mg	-0.55	0.007
50 mg	-0.90	<0.001
Metformin	-0.73	
Placebo	-0.18	

* Between-group comparisons significant at 0.012 (Dunnett's adjustment)

dependent fashion -0.55% to -0.90% for dapagliflozin, -0.18% for placebo, and -0.73% for metformin (Table 2). Fasting plasma glucose reductions ranged from -0.89 mmol/L to -1.72 mmol/L for dapagliflozin in a dose-dependent fashion, -0.33 mmol/L for placebo, and -1.0 mmol/L for metformin, with statistically significant reductions in the 5 mg to 50 mg dapagliflozin groups versus placebo (Table 3). Proportions of patients achieving an HbA_{1c} <7% at week 12 ranged from 40%-59% for dapagliflozin, 32% for placebo, and 54% for metformin. The comparison versus placebo was statistically significant only for the 50-mg group. Urinary glucose excretion increased in all dapagliflozin groups. Total body weight reductions occurred in all groups, ranging from -2.5% to -3.4% body weight for dapagliflozin, -1.2% for placebo, and -1.7% for metformin. Adverse events were reported at similar frequencies across all groups. No deaths or drug-related serious adverse events occurred. Hypoglycemic events were reported in 6%-10% of dapagliflozin-treated patients with no dose relationship, 4% for placebo, and 9% for metformin, but there were no symptomatic hypoglycemic events. Given the mechanism of action for this compound, there was a special interest in

Table 3: Adjusted mean change from baseline in fasting plasma glucose (FPG) at Week 12²⁹

Agent (dose)	FPG (mmol/L)	P value (vs placebo)*
Dapagliflozin		
2.5 mg	-0.88	0.03
5 mg	-1.04	0.005
10 mg	-1.16	0.002
20 mg	-1.33	<0.001
50 mg	-1.72	<0.001
Metformin	-1.00	
Placebo	-0.33	

* Between-group comparisons significant at 0.012 (Dunnett's adjustment)

urinary tract infections; infections were reported in 5%-12% of dapagliflozin-treated patients without a clear dose relationship, 6% for placebo, and 9% for metformin. Small dose-related increases in 24-h urine volumes were demonstrated at Week 12. There were small changes from baseline in serum blood urea nitrogen (BUN), but no change in serum creatinine at Week 12 at all dapagliflozin doses. No clinically meaningful change in the estimated glomerular filtration rate (eGFR) was found in any group, but all groups experienced a small decrease in 24-h creatinine clearance. The authors concluded that the study demonstrated clinical efficacy of dapagliflozin in the inhibition of renal glucose reabsorption in T2DM patients that warranted further investigation.

Sergliflozin

Sergliflozin is an SGLT2 inhibitor under development by Kissei Pharmaceutical Corporation. Sergliflozin is a prodrug of sergliflozin-A, an active, highly potent and selective inhibitor of SGLT2,³⁰ but it is structurally distinct from phlorizin and its derivatives. In normal rats, sergliflozin-A suppresses glucose reabsorption by inhibiting SGLT2 and lowering the threshold value for glycosuria. In normal mice, rats, and dogs, urinary glucose excretion was increased by the oral administration of sergliflozin in a dose-dependent manner. In streptozotocin-induced diabetic rats, sergliflozin significantly inhibited the expected increase in plasma glucose in a dose-dependent manner. In an OGTT from these diabetic rats, sergliflozin exhibited glucose-lowering effects independently of insulin secretion.

Clinical trials of single doses of sergliflozin, ranging from 5 mg to 500 mg, confirmed a dose-dependent increase in urinary glucose excretion in healthy subjects.³¹ The same article also reported 8 patients with T2DM, in whom 500 mg decreased plasma glucose concentrations during a 4-h OGTT from 18.3 mmol × h/L to 11.2 mmol × h/L. There were small transient increases in the urinary excretion of electrolytes, but not over a 24-h period. In healthy subjects, the most common adverse effects were headache and sore throat, with headache and dyspepsia reported most commonly in patients with diabetes. Another 14-day study in overweight and obese subjects revealed that doses of sergliflozin of 500 mg and 1000 mg 3 times daily did not result in any other clinically significant adverse events.³² Interestingly, although there are no known published clinical trial results on the long-term

efficacy of sergliflozin in patients with T2DM, a modeling exercise using virtual patient data suggests that in drug-naïve or metformin-treated patients with T2DM, with baseline levels of HbA_{1c} at approximately 0.085 and normal renal function, a daily excretion of 600 mM glucose, representing approximately 50% of the filtered glucose load, could potentially reduce the HbA_{1c} by -0.08.³³

Remogliflozin etabonate

A similar but chemically distinct compound to sergliflozin is remogliflozin etabonate, another specific SGLT2 inhibitor. Remogliflozin etabonate is a prodrug of the active form, remogliflozin, and is under development by Kissei Pharmaceutical Corporation and GlaxoSmithKline. Similar to other specific SGLT2 inhibitors, remogliflozin has been shown to increase urinary glucose excretion in a dose-dependent manner in both mice and rats.³⁴ As a result, it also inhibited the increase in plasma glucose after glucose loading without stimulating insulin secretion in normal rats. Remogliflozin etabonate also revealed antihyperglycemic effects in both streptozotocin-induced diabetic rats with OGTTs, and in *db/db* mice in the fed condition. Chronic treatment with remogliflozin etabonate reduced the levels of fasting plasma glucose and HbA_{1c}, as well, it ameliorated glycosuria in *db/db* mice. In high-fat-diet fed Goto-Kakizaki rats (an animal model for lean-T2DM), remogliflozin etabonate improved hyperglycemia, hyperinsulinemia, hypertriglyceridemia, and insulin resistance. In ZDF rats, when remogliflozin etabonate was administered at 3.3 mg/kg or 10 mg/kg, 1 to 3 times/day for 8 days, there was a dose-dependent reduction in plasma glucose and a reduction in HbA_{1c} at the higher doses.³⁵

Other SGLT2 inhibitors

A number of other SGLT2 inhibitors are under early-stage development, eg, sanofi-aventis is investigating AVE2268, an orally active and selective SGLT2 inhibitor.³⁶ Taisho Pharmaceutical Company recently announced the discontinuation of the development of their SGLT2 inhibitor, TS-033, although they have announced a backup compound that is in Phase 1 clinical trials.³⁷ As our knowledge of SGLT2 inhibition continues to grow, the clinical development of some of these compounds may be extended to become possible new medications for the treatment of T2DM.

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Abstracts of Interest

Sodium glucose co-transporter 2 inhibitors: blocking renal tubular reabsorption of glucose to improve glycaemic control in patients with diabetes

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BACKGROUND: The kidney plays a central role in the regulation of plasma glucose levels, although until recently this has not been widely appreciated or considered a target for therapeutic intervention. The sodium glucose co-transporter type 2 (SGLT2) located in the plasma membrane of cells lining the proximal tubule mediates the majority of renal glucose reabsorption from the tubular fluid, which normally prevents the loss of glucose in the urine. Competitive inhibitors of SGLT2 that provoke the renal excretion of glucose have been discovered, thereby providing a unique mechanism to potentially lower the elevated blood glucose levels in patients with diabetes.

OBJECTIVE: To explore the physiology of SGLT2 action and discuss several SGLT2 inhibitors that have entered early clinical development.

METHODS: All publicly available data were identified by searching the internet for 'SGLT2' and 'SGLT2 inhibitor' through 1 November 2007. Published articles, press releases and abstracts presented at national and international meetings were considered.

RESULTS/CONCLUSION: Sodium glucose co-transporter type 2 inhibition is a novel treatment option for diabetes, which has been studied in preclinical models and a few potent and selective SGLT2 inhibitors have been reported and are currently in clinical development. These agents appear to be safe and generally well tolerated, and will potentially be a beneficial addition to the growing battery of oral antihyperglycaemic agents.

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Sodium-Glucose Co-Transport Inhibition With Dapagliflozin in Type 2 Diabetes Mellitus.

LIST JF, WOO V, MORALES E, TANG W, FIEDOREK F

OBJECTIVE: Dapagliflozin, a novel inhibitor of renal sodium-glucose co-transporter 2, allows an insulin-independent approach to improve type 2 diabetes mellitus (T2DM) hyperglycemia. This multiple-dose study evaluated safety and efficacy of dapagliflozin in T2DM patients.

RESEARCH DESIGN AND METHODS: T2DM patients were randomized to one of five dapagliflozin doses, metformin XR, or placebo for 12 weeks. The primary objective compared mean change from baseline in glycated hemoglobin (A_{1c}). Other objectives included change in fasting plasma glucose (FPG), weight, adverse events, and laboratory measurements.

RESULTS: After 12 weeks, dapagliflozin induced moderate glucosuria (52–85 g urinary glucose/day) and demonstrated significant glycemic improvements versus placebo (Δ A_{1c}, -0.55 to -0.90%; Δ FPG, -16 to -31 mg/dl). Weight loss versus placebo was -1.3 to -2.0 kg. There was no change in renal function. Serum uric acid decreased, serum magnesium increased, serum phosphate increased at higher doses, and dose-related 24-h urine volume and hematocrit increased, all of small magnitude. Treatment-emergent adverse events were similar across all groups.

CONCLUSIONS: Dapagliflozin improves hyperglycemia and facilitates weight loss in T2DM patients by inducing controlled glucosuria with urinary loss of ~200–300 kcalories/day. Dapagliflozin treatment demonstrates no persistent, clinically significant osmolarity, volume, or renal status changes.

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