

# The Role of the Kidney and Sodium-Glucose Cotransporter-2 Inhibition in Diabetes Management

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**D**iabetes is a complex and chronic disease that affects an estimated 25.8 million people in the United States (8.3% of the population).<sup>1</sup> Type 2 diabetes accounts for >90% of all cases of diagnosed diabetes<sup>1</sup> and is expected to grow, owing to the high prevalence of obesity in the United States.<sup>2</sup>

Some symptoms of diabetes, such as excess urination and glycosuria, were described more than 3,500 years ago.<sup>3</sup> For many years, diabetes was thought to be a disease of the kidney and urinary bladder. However, with the observation in 1889 that pancreatectomized dogs developed diabetes<sup>3</sup> and the discovery and isolation of insulin in the early 1920s, diabetes was firmly established as an endocrine disease, and the potential role of the kidney in the pathogenesis of diabetes was largely ignored.

Interestingly, attention is once again focused on the kidney, not only as an organ that may be adversely affected by diabetes, but also as an important player in glucose homeostasis and a potential target for the treatment of hyperglycemia in type 2 diabetes.<sup>4</sup> The purpose of this article is to discuss the role of the kidney in normal glucose homeostasis and in type 2 diabetes and how inhibition of renal glucose reabsorption may become a novel treatment option in patients with type 2 diabetes from early diagnosis to long-term disease.

## Role of the Kidney in Glucose Homeostasis

The kidney contributes to the maintenance of blood glucose levels primarily by the reabsorption of glucose from the glomerular filtrate to the blood. Under normal conditions, almost all of the filtered glucose is reabsorbed and returned to the circulation in the proximal tubule of the nephron.<sup>4</sup> Glucose is reabsorbed by sodium-glucose cotransporters (SGLTs) in concert with facilitative glucose transporters (GLUTs).<sup>4</sup>

In animals, SGLT2 and GLUT2 are located in the early portion of the proximal convoluted tubule of the renal nephron and are responsible for the majority of glucose reabsorption.<sup>4,5</sup> Other glucose transporters such as SGLT1 and GLUT1 are present in the distal portion of the proximal tubule in animals and may account for additional glucose reabsorption (Figure 1).

The ability of the kidneys to reabsorb glucose is limited by the capacity of these transporters, and

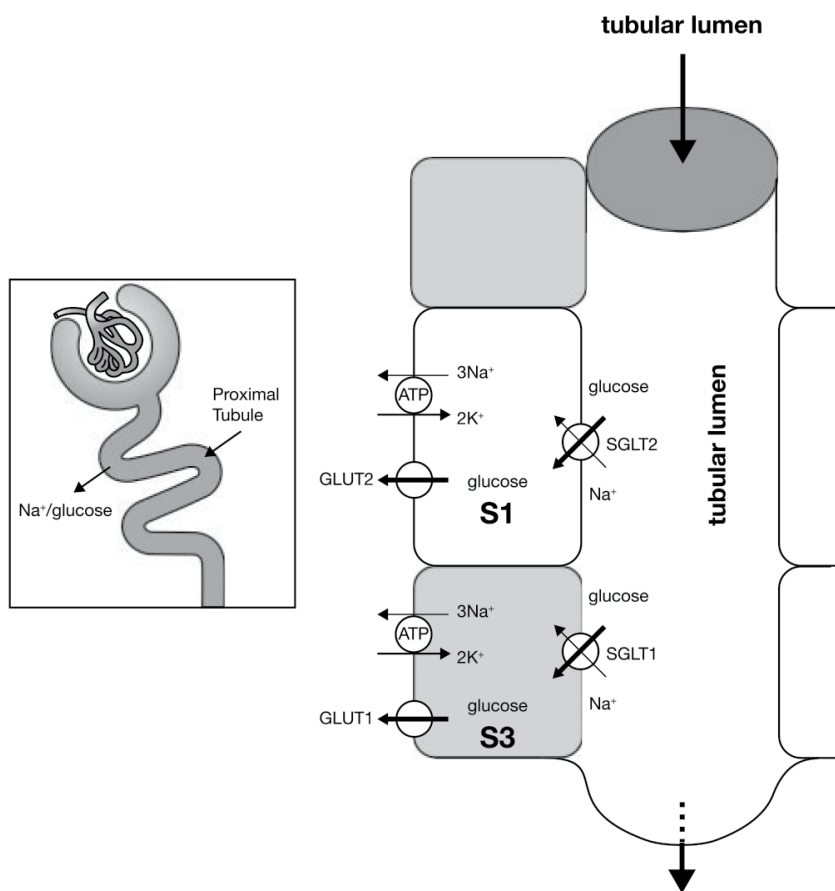
as plasma concentrations exceed ~180–200 mg/dl (the renal threshold),<sup>4</sup> glucose starts to appear in the urine. Nevertheless, the kidneys continue to reabsorb glucose even in the presence of abnormally high plasma glucose concentrations seen in type 2 diabetes and can contribute to the hyperglycemia characteristic of this disease.

## SGLT2 Inhibition

Increasing the excretion of glucose by inhibiting SGLT2 has a number of potential benefits. SGLT2 inhibitors, by increasing the excretion of glucose, decrease plasma glucose concentrations and have the additional benefit of reducing body weight.<sup>6</sup> Moreover, because the mechanism of action of SGLT2 inhibitors does not depend on the presence of insulin, the efficacy of SGLT2 inhibitors would not be primarily affected by the magnitude of insulin resistance or impairment of pancreatic  $\beta$ -cell function that accompanies type 2 diabetes progression. In addition, the risk of major hypoglycemic events is low with SGLT2 inhibitors because they do not impair normal endogenous glucose production in response to hypoglycemia<sup>7</sup> and do not stimulate insulin release,<sup>8,9</sup> suggesting that SGLT2 inhibitors may preserve the hypoglycemia counterregulatory response of glucagon-mediated glucose production. Finally, there is a potential for combination therapy with other diabetes agents, including insulin, to improve glycemic control.

### IN BRIEF

The kidney plays an important role in glucose homeostasis and has become a target for the treatment of hyperglycemia in type 2 diabetes. This review discusses the role of the kidney in glucose homeostasis and how inhibition of renal glucose reabsorption may become a novel treatment option for type 2 diabetes.



**Figure 1. Glucose reabsorption in the kidney.** Animal studies<sup>40</sup> have shown that SGLT2 is predominantly expressed in the early proximal tubule and is responsible for the majority of glucose reabsorption. SGLT1 is present in the late proximal tubule and may reabsorb additional glucose from the urine. GLUT, facilitative glucose transporter; SGLT, sodium-glucose co-transporter. Reproduced with permission from Santer R, Calado J: *Familial renal glucosuria and SGLT2: from a mendelian trait to a therapeutic target.* Clin J Am Soc Nephrol 5:133–141, 2010.

As discussed below, results from clinical trials have confirmed that SGLT2 inhibition improves glycemic control, reduces body weight, and is effective when used as monotherapy or as add-on therapy to commonly used diabetes medications in patients with type 2 diabetes, both in drug-naïve patients with a short duration of disease and in those with a long history of type 2 diabetes who are receiving insulin therapy. However, because SGLT2 inhibitors depend on the filtration and delivery of glucose to the proximal tubule, they are not effective in patients with moderate to severe renal impairment.<sup>10,11</sup>

Furthermore, continual excretion of urine with high glucose concentrations may predispose individuals to genital and urinary tract infections.

**SGLT2 Inhibitors**

A number of selective SGLT2 inhibitors are in various stages of clinical development for the treatment of type 2 diabetes (Table 1).

**Dapagliflozin**

Dapagliflozin is the SGLT2 inhibitor that is furthest along in clinical development. In phase 3 trials over the course of 24 weeks of treatment, dapagliflozin at doses of 2.5,

5, or 10 mg/day reduced A1C by 0.58–0.97%, compared to a reduction of 0.13–0.42% for placebo. It also reduced fasting plasma glucose (FPG) in patients with type 2 diabetes inadequately controlled with diet and exercise,<sup>12,13</sup> metformin,<sup>14</sup> glimepiride,<sup>15</sup> pioglitazone,<sup>16</sup> or insulin.<sup>13</sup> In addition, combining dapagliflozin (5 or 10 mg/day) with metformin as initial therapy was more effective than either drug alone in reducing A1C and FPG, and 10 mg/day dapagliflozin reduced A1C to a similar extent as metformin (up to 2,000 mg/day).<sup>17</sup> Finally, in a 52-week noninferiority trial, patients inadequately controlled with metformin monotherapy (1,500–2,500 mg/day) received add-on dapagliflozin (≤ 10 mg/day) or glipizide (≤ 20 mg/day). At the end of the study, the change from baseline in A1C was the same for dapagliflozin and glipizide (–0.52%).<sup>18</sup> Moreover, dapagliflozin produced significant mean weight loss (–3.2 kg) versus weight gain with glipizide (1.2 kg, *P* < 0.0001).

Dapagliflozin treatment was also associated with significant weight loss (up to –3.0 kg vs. up to –0.98 kg with placebo) when used as add-on therapy to metformin, insulin, or glimepiride<sup>13–15</sup> and with modest decreases in blood pressure.<sup>12–15</sup> Also, when added to pioglitazone therapy, dapagliflozin mitigated the weight gain associated with pioglitazone alone.<sup>16</sup> The changes in A1C, FPG, and body weight noted at 24 weeks were sustained for up to 2 years.<sup>19–21</sup>

Treatment with dapagliflozin was generally well tolerated with a low incidence of hypoglycemic events.<sup>12–14,16</sup> Genital infections<sup>22</sup> and, in some studies, urinary tract infections<sup>23</sup> were more frequent in the dapagliflozin groups than in the placebo groups. However, these infections were usually mild to moderate in severity, normally responded

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tract infections was similar across treatment groups.

### Potential Role of SGLT2 Inhibitors in Type 2 Diabetes Therapy

Type 2 diabetes is a progressive disease. As such, patients with type 2 diabetes can have various levels of hyperglycemia, and therapy should be individualized, taking into account the duration of disease, life expectancy, presence of complications and comorbidities, and risk for severe hypoglycemia.<sup>32</sup> For example, patients with an A1C  $\leq$  7.5% may be able to reach glycemic goals with monotherapy. In contrast, patients with an A1C of 7.6–9.0% will likely require two diabetes medications, and patients with an A1C  $>$  9% will probably require two diabetes medications and insulin.<sup>33</sup>

Because the mechanism of action of SGLT2 inhibitors is independent of insulin secretion or action, the efficacy of these compounds should not depend on the degree of insulin resistance or  $\beta$ -cell dysfunction. In support of this thesis, these compounds are effective in improving glycemic control in patients with both high and low baseline A1C levels<sup>12,34</sup> and in patients with type 2 diabetes of short ( $\leq$  0.5 year)<sup>12</sup> or long ( $\sim$  7 years) duration.<sup>15</sup> For example, in an analysis of early-stage patients not receiving pharmacotherapy (baseline A1C 7.60%) and late-stage patients being treated with a high dose of insulin plus insulin sensitizers (baseline A1C 8.35%), 12 weeks of therapy with dapagliflozin resulted in significant improvements in glycemic control and reductions in body weight in both groups of patients.<sup>34</sup>

Significant and sustained reductions in body weight of up to  $\sim$  5 kg have been observed in patients with type 2 diabetes treated with SGLT2 inhibitors for 12,<sup>25,27–29,31,35</sup> 24,<sup>13–15</sup> 48,<sup>13</sup> 52,<sup>18</sup> and 102–104 weeks.<sup>19,20</sup> Initial weight loss may be due to osmotic

**Table 1. SGLT2 Inhibitors in Development**

Compound	Company
Dapagliflozin	Bristol-Myers Squibb/AstraZeneca
Canagliflozin	Johnson & Johnson/Mitsubishi Tanabe
Empagliflozin	Boehringer Ingelheim/Eli Lilly
Ipragliflozin	Astellas
LX4211	Lexicon Pharmaceuticals
PF-04971729	Pfizer

to standard care, and rarely led to discontinuation from the studies.

In the overall clinical development program of more than 8,000 patients receiving dapagliflozin, placebo, or a comparator, malignancies were balanced across treatment groups, but a small numerical increase for breast and bladder cancers in patients receiving dapagliflozin was observed.<sup>24</sup> However, dapagliflozin has not been shown to be genotoxic or carcinogenic in preclinical studies. The small number of events limits the ability to assess causality, and this potential relationship should continue to be monitored during clinical trials and, if approved, clinical experience.

#### Canagliflozin

In phase 2 trials, canagliflozin (50–300 mg/day) increased glucose excretion and decreased A1C (placebo-corrected changes from baseline of  $-0.7$  to  $-1.0\%$ ), FPG, and body weight ( $-2.3$  to  $-2.4$  kg [placebo-corrected]) after 12 weeks of treatment in patients with type 2 diabetes as monotherapy<sup>25</sup> or as an add-on to metformin.<sup>26</sup> An increase in symptomatic genital infections has been reported with canagliflozin.<sup>25,26</sup>

#### Empagliflozin (BI 10773)

Empagliflozin (1–50 mg/day) increased glucose excretion and decreased FPG and A1C (placebo-corrected change up to  $-0.72\%$ ) after

12 weeks of treatment in phase 2 trials in patients with type 2 diabetes.<sup>27,28</sup> A reduction in body weight (up to  $-2.9$  kg vs.  $-1.2$  kg for placebo) was also reported. Rates of hypoglycemia were similar across treatment groups.<sup>28</sup> A slight increase in the risk of genital infections was reported with this compound.<sup>27,28</sup>

#### Ipragliflozin (ASP1941)

In a 12-week phase 2 trial in patients with type 2 diabetes, ipragliflozin (12.5–100 mg/day) decreased A1C ( $-0.8$  vs  $+0.5\%$  for placebo) and body weight ( $-2.0$  kg).<sup>29</sup> Adverse events were similar across treatment groups.

#### LX4211

LX4211 is an SGLT2 inhibitor that also inhibits SGLT1. LX4211 (150 or 300 mg/day) improved glycemic control (A1C  $-1.25$  vs  $-0.53\%$  with placebo) in patients with type 2 diabetes when administered in a 4-week, phase 2 study.<sup>30</sup>

#### PF-04971729

In a 12-week, phase 2 trial in patients whose type 2 diabetes was inadequately controlled on metformin, PF-04971729 (1–25 mg/day) reduced A1C by up to  $-0.83\%$  compared to a change of  $-0.11\%$  with placebo.<sup>31</sup> PF-04971729 also reduced body weight (maximum of  $-2.9$  vs.  $-0.8$  kg with placebo). The frequency of genital infections was higher with PF-04971729 (4%) than with placebo (2%), but the frequency of urinary

diuresis,<sup>14</sup> but the gradual reduction in body weight over time appears to be due predominantly to a reduction of fat mass.<sup>36,37</sup> This weight loss could serve to counteract the weight gain that commonly occurs with insulin, thiazolidinediones, and sulfonylureas.<sup>33</sup>

Decreases in systolic and diastolic blood pressure have been observed in patients treated with SGLT2 inhibitors.<sup>12–15,38</sup> These decreases in blood pressure may be related to SGLT2 inhibitor-induced diuresis and body weight changes.<sup>14</sup> Further study of the blood pressure effects is warranted in view of the high prevalence of hypertension (67%)<sup>1</sup> in patients with type 2 diabetes and the benefits associated with improved blood pressure control in this patient population.<sup>39</sup>

### Summary and Conclusions

Because of its role in glucose homeostasis, the kidney has become a target of drug therapy for the treatment of type 2 diabetes. Increasing the excretion of glucose by inhibition of SGLT2, the transporter responsible for the majority of glucose reabsorption, improves glycemic control in patients with type 2 diabetes.

Because the mechanism of action of SGLT2 inhibitors is independent of insulin secretion or action and complementary to existing diabetes medications, they may be effective across all stages of the disease when used as monotherapy or in combination with metformin, sulfonylureas, thiazolidinediones, or insulin. Additional effects that have been reported in some trials of SGLT2 inhibitors include weight loss and blood pressure reduction, both of which are beneficial in this patient population.

The long-term impact of an increased risk of genital and urinary tract infections will need to be evaluated to support the safe use of this

potential new class of compounds to improve glycemic control in patients with type 2 diabetes.

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