

The Kidney as a Treatment Target for Type 2 Diabetes

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Abstract

Type 2 diabetes is a complex and progressive disease that affects 8.3% of the U.S. population. Despite the availability of numerous treatment options for type 2 diabetes, the proportion of patients achieving glycemic goals is unacceptably low; therefore, new pharmacotherapies are needed to promote glycemic control in these patients.

The kidney normally reabsorbs 99% of filtered glucose and returns it to the circulation. Glucose reabsorption by the kidney is mediated by sodium-glucose co-transporters (SGLTs), mainly SGLT2. SGLT2 inhibition presents an additional option to promote glycemic control in patients with type 2 diabetes. A number of SGLT2 inhibitors have been synthesized and are in various

stages of clinical development for the treatment of type 2 diabetes. Results from clinical trials show that these compounds decrease plasma glucose and body weight in treatment-naïve patients and in patients receiving metformin or insulin and insulin sensitizers. Overall, SGLT2 inhibitors appear to be generally well tolerated, but in some studies, signs, symptoms, and other reports of genital and urinary tract infections have been more frequent in drug-treated groups than in placebo groups.

Additional clinical trials will determine whether this class of compounds with a unique, insulin-independent mechanism of action becomes a treatment option for reducing hyperglycemia in type 2 diabetes.

Worldwide, more than 220 million people have diabetes.¹ In the United States, diabetes is present in 8.3% of the population.² Type 2 diabetes accounts for 90–95% of all diagnosed cases of adult diabetes.² The prevalence of type 2 diabetes is projected to increase further, in parallel with obesity,³ a major risk factor for its development.⁴

Hyperglycemia is the hallmark of diabetes and a key determinant of microvascular complications (e.g., retinopathy, neuropathy, and nephropathy).⁵ Type 2 diabetes is a major risk factor for the development of cardiovascular disease⁶ and chronic kidney disease.⁷ It is also the primary cause of end-stage renal disease, requiring either chronic dialysis or renal transplantation,⁸ and new cases of blindness among U.S. adults aged 20–74 years.³

Randomized, controlled clinical trials from the 1990s, including the Diabetes Control and Complications Trial (DCCT)⁹ and the U.K. Prospective Diabetes Study (UKPDS),^{10,11} found that intensive glycemic control (achieved A1C of ~7%) compared to conventional therapy (A1C of ~8–9%) can reduce the risk of microvascular complications in patients with type 1 diabetes and in patients with newly diagnosed type 2 diabetes. However, whether intensive glycemic control reduces cardiovascular events is less certain.¹² Long-term monitoring of patients from the DCCT¹³ and UKPDS¹⁴ trials found significant reductions in cardiovascular events in patients originally randomized to receive intensive therapy compared to patients who received standard therapy.

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However, recent clinical trials such as the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, and the Veterans Affairs Diabetes Trial (VADT) found no benefit,¹⁵⁻¹⁷ and possibly some harm, from intensive control.¹⁶ These trials were designed to test the effects of intensive glycemic control (achieved A1C of 6.4–6.9%) compared to standard therapy (A1C of 7.3–8.4%) on cardiovascular events (death from cardiovascular causes, nonfatal myocardial infarction, and nonfatal stroke) in relatively high-risk patients with established type 2 diabetes. Recent treatment guidelines stress the importance of individualized treatment goals in patients with diabetes.^{4,18}

Lifestyle changes that include a healthy diet, weight loss, and increased physical activity have many benefits in improving glycemic control and cardiovascular risk factors in patients with type 2 diabetes.¹⁹ However, weight loss and physical activity and their favorable effects are difficult to maintain over the long term, and most patients will require pharmacotherapy to achieve and maintain their glycemic goals.²⁰

Despite the availability of numerous treatment options for type 2 diabetes (e.g., insulin, sulfonylureas, meglitinides, biguanides, α -glycosidase inhibitors, thiazolidinediones, dipeptidyl peptidase-4 inhibitors, glucagon-like peptide-1 agonists, amylin analogs, a dopamine agonist, and a bile acid sequestrant)²¹⁻²⁴ with a variety of mechanisms of action, the proportion of patients achieving glycemic goals is unacceptably low. A recent analysis of diabetic patients from the National Health and Nutrition Examination Survey from 1999 to 2006²⁵ found that only 57% of patients with diagnosed diabetes achieved an A1C of < 7%.

Lack of treatment initiation and intensification, patient nonadherence, the risk of hypoglycemia with some commonly used antidiabetic drugs, and progressive decline in

β -cell function can all contribute to failure in the achievement of glycemic goals.^{26,27} Therefore, new pharmacological therapies with novel mechanisms of action that are independent of insulin secretion or action and have a low propensity to cause hypoglycemia may enhance patients' ability to achieve glycemic control.

The deleterious effects of diabetes on the kidney are well established. Less appreciated is the role the kidney plays in glucose homeostasis and the potential of the kidney as a therapeutic target in type 2 diabetes. This article reviews the role of the kidney in glucose regulation and the potential of inhibiting renal glucose reabsorption as a new treatment option in type 2 diabetes.

Role of the Kidney in Glucose Homeostasis

For most people, the major source of glucose is the diet. After a meal or glucose load, plasma glucose concentration peaks at ~ 90 minutes and thereafter declines over the course of the ~ 4.5-hour postprandial period.²⁸ During this time, ingested carbohydrate accounts for ~ 75% of circulating glucose. After a meal,

~ 45% of ingested glucose is taken up by the liver, and 30% is taken up by skeletal muscle and converted to glycogen.²⁹ During an overnight fast, glucose is released into the circulation, the majority (80%) of which comes from the liver as the result of glycogenolysis and gluconeogenesis. The breakdown of muscle glycogen leads to the formation of lactate, a gluconeogenic precursor.²⁹

However, it is now evident that the kidney also contributes to the maintenance of blood glucose levels by taking up glucose for energy needs, synthesizing glucose (through the process of gluconeogenesis), and reabsorbing glucose from the glomerular filtrate and returning it to the circulation. In humans, only the liver and kidney possess the necessary gluconeogenic enzymes to produce and release glucose.³⁰ Normally, the kidneys account for ~ 40% of total gluconeogenesis and ~ 20% of all glucose released into the circulation in humans.³¹ The kidney also takes up and metabolizes ~ 10% of all glucose utilized by the body.²⁸ Because of the distribution of glucose transporters and enzymes,^{32,33} the renal cortex is the primary site

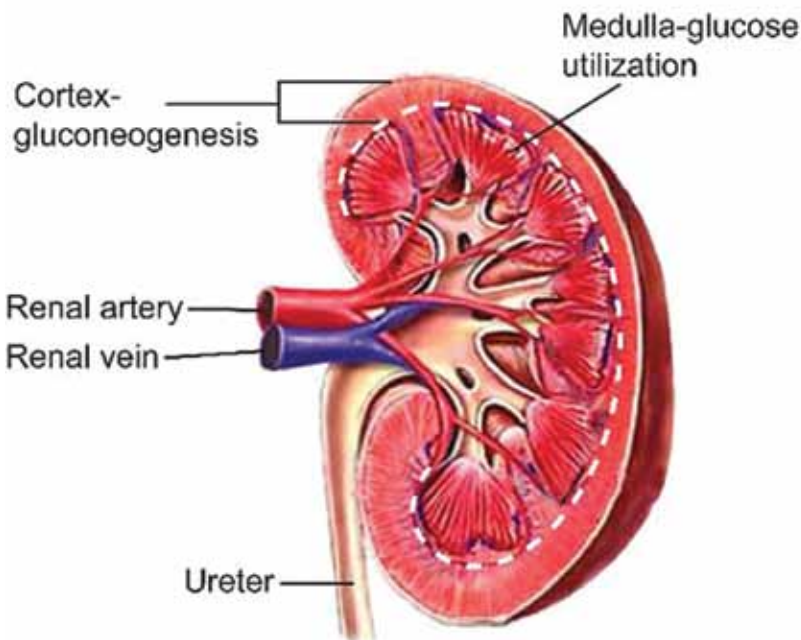


Figure 1. Site of gluconeogenesis and glucose utilization in the kidney. The kidney cortex is the primary site of renal gluconeogenesis, whereas the medulla is the primary site for glucose utilization. Dashed line indicates the boundary between the cortex and medulla.

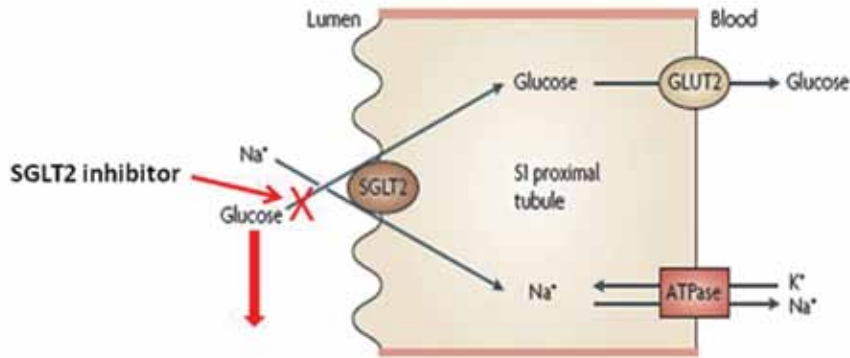


Figure 2. Glucose reabsorption by the proximal convoluted tubule. Gray arrows represent normal glucose transport. Red arrows represent the pharmacological effects of SGLT2 inhibition. Adapted with permission from Macmillan Publishers Ltd. From ref. 62.

of glucose synthesis and release, whereas the medulla is the primary site for glucose utilization in the kidney³³ (Figure 1).

Glucose Transport in the Kidney

Glucose is freely filtered by the glomerulus. Under normal conditions, ~ 180 g of glucose are filtered by the kidney each day.^{34,35} More than 99% of this glucose is reabsorbed by the proximal tubule,^{34,35} with < 0.5 g/day excreted in the urine of healthy adults.³⁵

The reabsorption and return of glucose from the glomerular filtrate to the circulation by the kidney is dependent on the function of specific transporters. Glucose reabsorption from the glomerular filtrate is mediated by sodium-glucose co-transporters (SGLTs). These transporters rely on the inwardly directed electrochemical sodium gradient established and maintained by the sodium-potassium adenosine triphosphatase (ATPase) located on the basolateral membrane as the driving force for glucose entry into the cell³⁶ (Figure 2). SGLT2 is a high-capacity, low-affinity SGLT located on the apical (luminal) membrane of the early proximal convoluted tubule.^{36,37} In animals, SGLT2 accounts for up to 90% of glucose reabsorption.^{38,39}

Another member of this family, SGLT1, is a low-capacity, high-affinity SGLT expressed mainly in the intestine but also present in the kidney. SGLT1, located in the late proximal tubule,^{36,37,40} accounts for the majority of the remainder of renal glucose reabsorption.^{35,38}

Once taken up into the proximal convoluted tubule cell via SGLT2, glucose exits the basolateral membrane into the interstitium by facilitative glucose transporters (GLUTs), primarily GLUT2 and, to a lesser extent, GLUT1^{36,41} (Figure 2). Glucose then re-enters the circulation via peritubular capillaries. In normal subjects, the kidneys can maximally reabsorb ~ 350–375 mg/minute of glucose.^{35,42} In hyperglycemic individuals, the transport maximum can be exceeded, and large amounts of glucose may be excreted into the urine.⁴³

Contribution of the Kidney to Hyperglycemia

The release of glucose into the circulation is a major cause of hyperglycemia in type 2 diabetes.⁴⁴ Until recently, this effect was attributed almost exclusively to the liver. However, the kidney is responsible for ~ 20% of total glucose release in normal postabsorptive (fasting) humans.³⁰ In fasting patients with type 2 diabetes, renal glucose release was increased by 300% compared to nondiabetic control patients.⁴⁴

The mechanisms of this effect are poorly understood. In addition to increased gluconeogenesis, the diabetic kidney may play a role in hyperglycemia by increased glucose reabsorption. Evidence from studies conducted in human renal tubular cells⁴⁵ and diabetic animals^{45–47} suggest that the expression of SGLT2 and GLUT2 is upregulated in diabetes, potentially allowing more glucose to cross the proximal

convoluted tubule and re-enter the circulation.^{43,48} Therefore, the kidney may contribute to hyperglycemia in type 2 diabetes by increasing gluconeogenesis^{30,44} and possibly by enhanced glucose reabsorption.⁴⁵

Rationale for SGLT2 Inhibition

In addition to controlling cardiovascular risk factors such as hypertension and hyperlipidemia, glycemic control is a primary goal of diabetes management.⁴ Because renal glucose reabsorption contributes to hyperglycemia, SGLT2 inhibition presents an additional option for glycemic control in patients with type 2 diabetes. Inhibition of reabsorption would be predicted to enhance glucose excretion and reduce hyperglycemia in type 2 diabetes independently of insulin secretion or action.

Moreover, SGLT2 inhibition appears to be relatively benign in humans. Evidence supporting the safety of SGLT2 inhibition as a possible therapeutic option can be found in studies of individuals with familial renal glucosuria. These patients have a number of identified inactivating mutations in the gene encoding SGLT2⁴⁹ and excrete large amounts of glucose (≥ 10 g/1.73 m²/day) without significant clinical consequences,^{49,50} except for polyuria and possibly subclinical extracellular volume depletion.^{51,52}

However, there may be other confounding or ameliorating physiological actions that may play a role in familial renal glucosuria, and direct pharmacological manipulation of SGLT2 may not have the same safety profile. The long-term safety of SGLT2 inhibition is under investigation.

SGLT2 Inhibitors

SGLT2 inhibitors exhibit several potential benefits over other therapeutic options for glycemic control. These agents directly and specifically target the kidney. Because their effects are independent of insulin secretion or action, they may be effective during the later stages of the disease when other therapies (e.g., insulin secretagogues and insulin sensitizers) have lost their efficacy because of the progressive decline

in β -cell function that is characteristic of type 2 diabetes. In addition, because the actions of SGLT2 inhibitors are independent of insulin, there is a decreased risk of major hypoglycemia events compared to some other agents.²⁹ Moreover, by increasing the excretion of glucose, SGLT2 inhibitors may promote weight loss,^{29,53} thus ameliorating one factor related to the pathophysiology of type 2 diabetes. Finally, because SGLT2 inhibitors specifically affect the kidney, there is a potential for combination therapy with agents targeting the variety of defects associated with type 2 diabetes to optimize treatment.⁵⁴

Phlorizin, a natural constituent of apple and other fruit trees, was the first agent discovered to inhibit SGLTs in the kidney.⁵⁵ This nonselective SGLT inhibitor has been an important tool for physiological and pharmacological research.⁵⁵ Studies in diabetic rat models demonstrated that phlorizin promotes glucose excretion, normalizes plasma glucose levels, and reverses insulin resistance.^{56,57}

However, because of its non-specificity, phlorizin inhibits SGLT1 as well as SGLT2. SGLT1 is highly expressed in the intestine. Subsequently, phlorizin causes diarrhea because it inhibits glucose absorption in the small intestine.⁴⁰ In addition, phlorizin is poorly

absorbed⁵⁸ and is metabolized to phloretin, which is an inhibitor of GLUT1.⁵⁹ GLUT1 is important for physiological glucose transport in a variety of tissues, including the brain.⁶⁰ Thus, phlorizin is a poor candidate for the treatment of type 2 diabetes in humans.

A number of selective SGLT2 inhibitors have been synthesized to address the shortcomings of phlorizin.⁶¹ Preclinical data are available for remogliflozin and sergliflozin, early compounds that were discontinued, and for dapagliflozin. These inhibitors cause dose-dependent increases in renal glucose excretion in a number of species. They also decrease plasma glucose without increasing insulin secretion in diabetic rat models.⁶²⁻⁶⁴

Clinical trials are underway to assess the efficacy and safety of investigational SGLT2 inhibitors (Table 1). Dapagliflozin (Bristol-Myers Squibb, New York, and AstraZeneca, Wilmington, Del.) is in the most advanced stage of clinical development and is the only SGLT2 inhibitor with fully published phase 3 trial data.

Dapagliflozin caused dose-dependent increases in renal glucose excretion in normal volunteers⁶⁵ and in patients with type 2 diabetes.^{66,67} In phase 3 trials (Table 2), dapagliflozin decreased plasma glucose and A1C in patients with type 2 dia-

betes when given as monotherapy to patients who were treatment-naïve⁶⁸ or as add-on therapy to metformin,^{69,70} glimepiride,⁷¹ pioglitazone,⁷² or insulin.^{73,74} In addition, dapagliflozin was associated with weight loss^{69,71,73,74} and a modest decrease in blood pressure.^{68,69,71,73,74}

Dapagliflozin was generally well tolerated (Table 3). The most common adverse events were headache, diarrhea, back pain, and nasopharyngitis, which occurred at similar frequencies in the placebo and dapagliflozin groups.⁶⁸⁻⁷¹ The incidence of hypoglycemia events was low in the trials of monotherapy⁶⁸ and add-on therapy to metformin⁶⁹ and was 10-fold lower when dapagliflozin was compared to glipizide.⁷⁰ Hypoglycemia events were more frequent in patients receiving dapagliflozin in the trials of add-on therapy to glimepiride or to insulin.^{71,73} However, there were no discontinuations due to hypoglycemia.^{71,73} The signs, symptoms, and other reports suggestive of urinary tract^{68,69,73,74} and genital^{68,69,71,73,74} infections have been more frequent in the dapagliflozin-treated groups than in placebo-treated groups (Table 3). All events were of mild to moderate intensity and responded to standard treatment.

In the dapagliflozin study of > 6,000 patients, malignancies were balanced between treatment groups,

Table 1. SGLT2 Inhibitors in Development

Compound	Phase	Clinical Results	Company	References
Dapagliflozin	Filed	Decreases A1C, FPG, body weight, and blood pressure as monotherapy or as add-on therapy to metformin, insulin, or glimepiride. Treatment duration up to 52 weeks.	Bristol-Myers Squibb/AstraZeneca	67-69,71,74,80
Canagliflozin	3	Decreases A1C, FPG, and body weight as monotherapy or as add-on therapy to insulin or metformin. Treatment duration up to 12 weeks.	Johnson & Johnson/Mitsubishi Tanabe	76,81,82
Empagliflozin (BI 10773)	3	Decreases A1C, FPG, and body weight as monotherapy. Treatment duration up to 12 weeks.	Boehringer Ingelheim/Eli Lilly	77
Ipragliflozin (ASP 1941)	3	Decreases A1C, FPG, and body weight as monotherapy. Treatment duration up to 12 weeks.	Astellas	78
LX4211*	2	Decreases A1C and FPG as monotherapy. Treatment duration of 4 weeks.	Lexicon Pharma	79

FPG, fasting plasma glucose.

*SGLT2/SGLT1 inhibitor.

Table 2. Effects of Dapagliflozin on Glycemic Parameters and Body Weight in Patients with Type 2 Diabetes: Published Phase 3 Trials

	Mean Change from Baseline [†]							
	<i>n</i>	A1C (%)		FPG (mg/dl)		Body Weight (kg)		Reference
		Placebo	Dapa [‡]	Placebo	Dapa [‡]	Placebo	Dapa [‡]	
Monotherapy	274	-0.23	-0.58 to -0.89	-4.1	-15.2 to -28.8	-2.2	-2.8 to -3.3	68
Add-on therapy to metformin	546	-0.30	-0.67 to -0.84	-6.0	-17.8 to -23.5	-0.9	-2.2 to -3.0	69
Add-on therapy to glimepiride	597	-0.13	-0.58 to -0.82	-2.0	-16.8 to -28.5	-0.7	-1.2 to -2.3	71
		Glip	Dapa	Glip	Dapa	Glip	Dapa	
Compared to glipizide	814	-0.52	-0.52	-18.7	-22.3	+1.4	-3.2	70

Dapa, dapagliflozin; *FPG*, fasting plasma glucose; *Glip*, glipizide.

[†]Adjusted for baseline value.

[‡]Data for *dapa* are ranges except for glipizide study.

Table 3. Summary of Adverse Events With Dapagliflozin: Published Phase 3 Trials

	Adverse Events (%)							
	Monotherapy		Add-on Therapy to Metformin		Add-on Therapy to Glimepiride		Compared to Glipizide	
	Placebo	Dapa [†]	Placebo	Dapa [†]	Placebo	Dapa [†]	Glip	Dapa
One or more adverse events	60	58–69	64	65–73	47	48–52	78	78
One or more serious adverse events	4	0–2	4	3	5	6–7	11	9
Hypoglycemia	3	0–3	3	2–4	5	7–8	40	3
Events suggestive of genital infections	1	8–13	5	8–3	1	4–7	3	12
Events suggestive of urinary tract infections	4	5–13	8	4–8	6	4–7	6	11
Reference	69		70		72		71	

Dapa, dapagliflozin; *glip*, glipizide.

[†]Data for *dapa* are ranges.

with a small numerical increase for breast and bladder cancers in patients on dapagliflozin.⁷⁵ This was unexpected because there were no preclinical signals that dapagliflozin was genotoxic or carcinogenic, and dapagliflozin has no known off-target pharmacology. The small number of events limits the ability to assess causality, and continued monitoring is warranted.

In preliminary reports, canagliflozin (Johnson & Johnson, New Brunswick, N.J.), a different SGLT2 inhibitor, increased renal glucose excretion and decreased A1C (placebo-corrected change from baseline of -0.73%), fasting plasma glucose (FPG) (-30.6 mg/dl), and body weight (-2.3 kg) in patients with type 2 diabetes after 12 weeks of treatment.⁷⁶ As with dapagliflozin,

an increase in genital and urinary tract infections was found in canagliflozin-treated patients.⁷⁶

The SGLT2 inhibitor empagliflozin (BI 10773, Boehringer Ingelheim, Ingelheim, Germany, and Eli Lilly, Indianapolis, Ind.) increased renal glucose excretion and decreased FPG (placebo-corrected, -31.1 mg/dl) and A1C (-0.72%) after 12 weeks of treatment in patients

with type 2 diabetes.⁷⁷ Decreases in body weight (−2.0 kg) have also been reported.⁷⁷ A small increased risk of genital infections was reported with empagliflozin.⁷⁷

Other inhibitors in early clinical trials include the SGLT2 inhibitor ipragliflozin (ASP1941, Astellas, Tokyo, Japan) and the SGLT2/SGLT1 inhibitor LX4211 (Lexicon Pharmaceuticals, The Woodlands, Tex.). Ipragliflozin treatment for 12 weeks lowered A1C by 0.8% compared to an increase of 0.5% in the placebo group.⁷⁸ Four weeks of treatment with LX4211 reduced A1C by 1.25% compared to a reduction of 0.53% with placebo.⁷⁹

Summary

Hyperglycemia is a major risk factor for the development of microvascular complications in type 2 diabetes. Control rates of hyperglycemia in type 2 diabetes are poor, and more treatment options are needed. Under normal conditions, the kidney plays an important role in glucose homeostasis by reabsorbing virtually all of the glucose that is filtered and by synthesizing glucose. In patients with type 2 diabetes, renal glucose reabsorption and gluconeogenesis are increased and contribute to the hyperglycemia associated with the disease.

SGLT2 is responsible for up to 90% of glucose reabsorption. Inhibition of SGLT2 is, therefore, an attractive target to increase glucose excretion and potentially reduce hyperglycemia. A number of selective SGLT2 inhibitors are being developed. Results from animal studies show that these compounds increase glucose excretion without inducing insulin secretion or hypoglycemia.

Initial results from clinical trials in patients with type 2 diabetes show that SGLT2 inhibitors decrease plasma glucose and body weight in treatment-naïve patients and in those receiving metformin or insulin and insulin sensitizers. SGLT2 inhibitors are generally well tolerated, but an increased incidence of urinary tract and genital infections has been observed in some clinical trials with some SGLT2 inhibitors. Long-term safety data are required to determine the impact of these observations.

Further clinical trials will provide needed data to assist regulatory agencies in determining whether this class of compounds with a unique, insulin-independent mechanism of action becomes an available treatment option for reducing hyperglycemia in type 2 diabetes.

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