Apple Trees to Sodium Glucose Co-Transporter Inhibitors: A Review of SGLT2 Inhibition

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For centuries, the kidney has been considered primarily an organ of elimination and a regulator of salt and ion balance. Although it was once erroneously thought to be the structural cause of diabetes and in later years was ignored as a regulator of glucose homeostasis, it is now recognized as an important player in the arena of glucose regulation. Today, we have a better understanding of the physiology of glucose transport via specific carriers such as the sodium glucose co-transporters (SGLTs). Parallel to these developments, a natural compound, phlorizin, was isolated in the early 1800s and for decades played an important role in diabetes and renal physiology research. Eventually, at the nexus of these aforementioned discoveries, it was recognized that the effect of a phlorizin-like compound on renal glucose transporters might offer a novel mechanism for the management of hyperglycemia. This has led to the development of several potentially effective therapeutic modalities for the management of hyperglycemia.

This article reviews the history of phlorizin, the role of the kidney in glucose regulation, and the modulation of that regulatory system via pharmacological means. It also offers a discussion of the results of clinical trials of the most salient SGLT inhibitor to date, dapagliflozin.

Phlorizin to SGLT2 Inhibitors

J.R.R. Tolkien once wrote that "few can foresee whither their road will lead them, till they come to its end." Certainly, this is the case in the story of sodium glucose co-transporter 2 (SGLT2) inhibitors.

In 1835, French chemists isolated a substance, phlorizin, from the bark of apple trees.[1] The compound was bitter in flavor and reminded them of similar extracts from the cinchona and willow tree and for a time was referred to as the "glycoside from the bark of apple trees."

Although the best thinking at the time concluded that phlorizin was a reasonable candidate for the treatment of fevers, infectious disease, and malaria, within 50 years, it was discovered that high doses of phlorizin caused glucosuria. Ultimately, it was determined that chronic administration of phlorizin in the canine model produced many of the same symptoms as observed in human diabetes (glucosuria, polyuria, and weight loss). Thus, the phlorizin-induced diabetes animal model was

IN BRIEF

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proposed and utilized in the early 1900s.[2]

During the next several decades, phlorizin continued to be used in trials evaluating renal physiology. By the early 1970s, research with phlorizin revealed the location (proximal tubule brush border) of the active-transport system responsible for glucose reabsorption and that phlorizin had a much higher affinity for these transporters than did glucose.[3]

There was a resurgence of interest in phlorizin in the late 1980s to early 1990s concurrent with the characterization of SGLTs and the realization of a potential novel mechanism for reducing hyperglycemia.[4,5] Animal studies carried out in 90% pancreatectomized diabetic rats demonstrated that phlorizin-induced glucosuria normalized fasting and postprandial glucose levels and reversed insulin resistance. Additionally, phlorizin administration was associated with reversal of first- and second-phase insulin secretory defects in this model.[5]

Phlorizin has not, however, been pursued as a medication for the treatment of diabetes in humans for several reasons. The compound is poorly absorbed from the gastrointestinal tract and inhibits both SGLT1 (primarily found in the gastrointestinal tract) and SGLT2. Analogs of phlorizin have been developed that circumvent these two problems. Currently, several of these analogs, including dapagliflozin and

canagliflozin, appear to be potentially pharmacologically viable.[5,6] Additionally, at least one company is developing anti-sense technology to reduce the expression of SGLT2 and one molecule, ISIS-SGLT2$_{Rx}$, is currently in phase 1 clinical trials.[7]

The Kidney and Glucose Homeostasis

As mentioned above, the kidney historically has not been thought of as one of the major organs responsible for glucose homeostasis. However, we now understand the kidney plays a major role in glucose homeostasis in two ways: *1*) gluconeogenesis and *2*) glomerular filtration and reabsorption of glucose in the proximal convoluted tubules. With today's greater understanding of the renal mechanisms responsible for glucose homeostasis and with modalities to manipulate that system, the kidney may one day play a key role in the management of hyperglycemia.

Filtration and Reabsorption of Glucose

The glomeruli of a normal healthy adult filter ~ 180 g of glucose daily.[8] Under normal circumstances, virtually all of this glucose is reabsorbed with < 1% being excreted in the urine.[9] The reabsorption of glucose from the tubules is a multistep process involving several transport mechanisms. The glucose, once filtered into the tubule, must be transported out of the tubule, through the tubular epithelial cells, and then across the basolateral membrane into the peritubular capillary. Under optimal conditions, when the tubular glucose load is ~ 120 mg/min or less, no glucose is lost in the urine. However, when the glucose load exceeds ~ 220 mg/min (the so-called "glucose threshold"), glucose begins to appear in the urine.

The blood glucose value required to provide such a tubular load is not a set value in humans, but rather is a range. One study evaluating this process reported that the required blood glucose concentration needed to exceed the tubular glucose threshold ranged between 130 and 300 mg/dl.[10] Additionally, the study reported a relationship between age and an increase in threshold levels.

This phenomenon raises an interesting question. Is blocking the reabsorption of glucose via SGLT2 inhibitors going to provide a greater effect in younger patients than in elderly patients?

It should be noted that the glucose threshold, at which some glucose is lost, is reached before reaching the transport maximum (T_m). The T_m is the concentration at which the transport system is saturated (analogous to V_{max} in metabolism). This is because some nephrons excrete glucose before others have reached their transport maximum.[8] The renal transport maximum is reached at the point where all nephrons have exceeded their maximum capacity to reabsorb glucose.

Clinically, the most common cause of glucosuria is diabetes. Therefore, average patients will not "spill" glucose into their urine until their blood glucose concentration exceeds 180 mg/dl, which does not normally occur in individuals without diabetes.

The first step in the reabsorption of glucose from the urine involves the transport of glucose from the tubule into the tubular epithelial cells. This is accomplished by SGLTs (Figure 1).

SGLTs include an extensive array of membrane proteins that transport glucose, amino acids, vitamins, ions, and osmolytes across the brush-border membrane of proximal renal tubules as well as the intestinal epithelium.[6] SGLT1 is a low-capacity, high-affinity SGLT. It is located principally in the gastrointestinal tract but can also be found in the S3 segment of the proximal tubule. Although SGLT1 is the key transporter for glucose absorption in the gastrointestinal tract, its impact in the kidney is less significant, accounting for only ~ 10% of glucose reabsorption in the nephrons.

The inhibition of this transporter has been of some interest pharmacologically because blocking the transporter theoretically attenuates gastrointestinal glucose absorption and might offer a method to induce weight loss or reduce postprandial hyperglycemia. In fact, at least one compound is being studied for this potential effect.

Conversely, SGLT2 is a high-capacity, low-affinity transporter found primarily in the kidney. A third member of this family, SGLT3, is found widely throughout the body in skeletal muscle and the nervous system. SGLT3 is not thought to be a glucose transporter, but instead acts as a glucose sensor.[11] Although other members of this family have been identified (SGLT4, -5, and -6), their function in humans is uncertain at this time.

The most prevalent and functionally important SGLT in the kidney is SGLT2. This transporter accounts for ~ 90% of glucose reabsorption in the kidney and because of this has become the focus of a great deal of interest in the field of diabetes. This transporter is found at a relatively high density on the brush-boarder membrane of the S1 segment (the early segment) of the proximal convoluted tubule.[6,12] SGLT2 binds with both sodium and glucose in the tubular filtrate. These compounds are then translocated across the apical cell membrane. This process is called secondary active-transport and is driven by the electrochemical sodium gradient between the tubular filtrate and the cell.[6]

The average maximal reabsorptive capacity (T_m) of the renal tubules is variable, but typically is ≈ 375 mg/
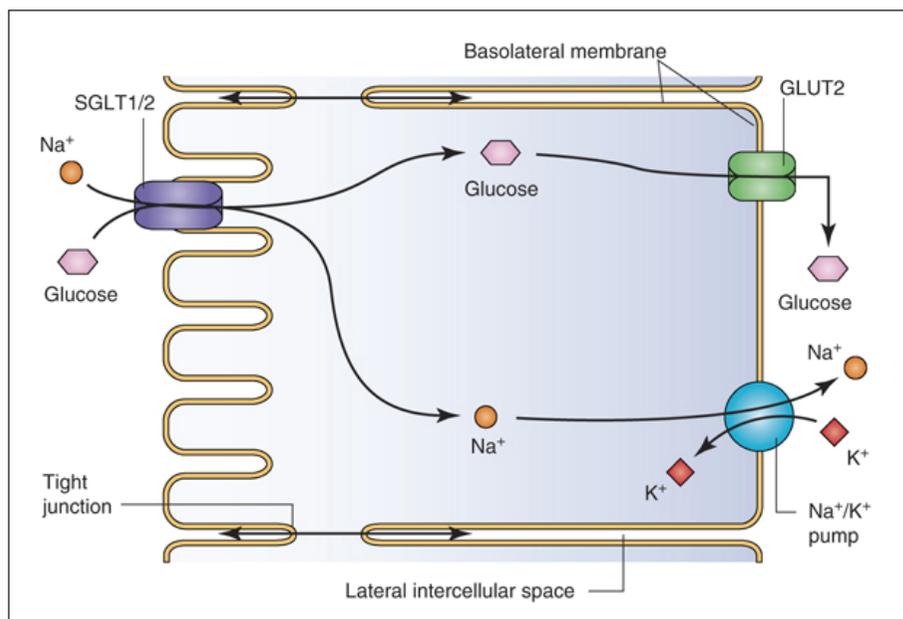
Figure 1. Glucose reabsorption from the glomerular filtrate through a proximal tubule epithelial cell into the blood. Reprinted with permission from Ref. 6.

min.[13] In nondiabetic individuals, the filtered glucose load does not, under normal circumstances, exceed 375 mg/min. In this situation, the filtered glucose is reabsorbed and returned to the systemic circulation. Conversely, hyperglycemic patients with diabetes routinely experience a filtered glucose load of > 375 mg/min. Under these conditions, the reabsorptive capacity of the SGLT2 transporters is exceeded, and the excess glucose is eliminated via the urine.

Inhibition of the activity of SGLT2 in the renal tubules has become an area of great pharmacological interest in the past few years. Pharmacological and even biological interventions to modulate this pathway by reducing the reabsorptive capacity of the renal tubules, with a resultant elimination of excess are being investigated. As mentioned above, at present, the two most likely effective methods are administration of chemical inhibitors of SGLT2 (thus reducing the activity of present SGLT2 transporters) or the use of SGLT2 anti-sense molecules

(thus reducing the expression of SGLT2 transporters). Although both methods offer promise, pharmacological inhibition of SGLT2 is at a more advanced stage of development (phase 3 trials).

The second step in the reabsorption of glucose is the transport of glucose through the basolateral membrane and back into the peritubular capillary. This facilitated diffusion of glucose is dependent on another well-recognized family of glucose transporter (GLUT) proteins.[14] This basolateral membrane-peritubular capillary transfer utilizes GLUT1 transporters in the late proximal tubule and GLUT2 transporters in the early proximal tubule.

Gluconeogenesis
The production and release of glucose into the systemic circulation can occur by gluconeogenesis or glycogenolysis. Currently, it is believed that gluconeogenesis is responsible for ~ 55% of glucose released during the non-fed period.[14] The liver and the kidney are the only two organs in the body that possess the gluconeogenic

enzyme and glucose-6-phosphate enzyme activity sufficient to drive gluconeogenesis. The kidney is important in this regard because renal glucose production accounts for ~ 20% of all overall endogenous glucose release and is responsible for ~ 40% of glucose released secondary to gluconeogenesis.[14]

The role of disproportionate gluconeogenesis as a factor worsening hyperglycemia in patients with either type 1 or type 2 diabetes is well documented.[14] Significant increases in renal gluconeogenesis have been demonstrated in animal diabetes models and in human studies. Renal glucose release was reported to be proportional to hepatic glucose release in one study in patients with type 2 diabetes.[15]

It seems probable that abnormalities in renal glucose production and release play a role in the progression of hyperglycemia in patients with diabetes. It is clearer, however, that the kidney plays a major role in glucose homeostasis and offers many junctures at which pharmacological intervention could be effective in the alteration of glucose balance in patients with diabetes and perhaps in obese patients as well.

SGLT2 Inhibitors and Diabetes
Although the possibility of modulation of the SGLT2 system via anti-sense molecules is being evaluated, the use of SGLT2 inhibitors is much further along in development. Several SGLT2 inhibitors have been developed, and some have already been discarded. Clinical trials with sergliflozin and remogliflozin (KGT-1611) have been discontinued by GlaxoSmithKline (GSK) and Kissei Pharmaceuticals. Cited reasons for this include "result of evaluating circumstances including the development status of SGLT2 inhibitors by competitors."[16] It is interesting to note, however, that Kissei/GSK are con-

tinuing work on an SGLT1 inhibitor (KGA-3235) for the management of hyperglycemia in diabetes.[17]

Another SGLT2 inhibitor, canagliflozin, is being developed by Johnson & Johnson and is currently in phase 3 trials in the United States. It is being studied as an add-on therapy to metformin versus glimepiride.[18]

The most prominent SGLT2 inhibitor at this time is dapagliflozin, a medication being co-developed in the United States by AstraZeneca and Bristol-Myers Squibb. Currently, 20 clinical studies have been completed or are in progress in the United States with this compound.[18]

At least three other SGLT2 inhibitors are currently being evaluated in clinical trials. Two compounds (BI 10773 and BI 44847) are being developed by Boehringer Ingelheim in Germany and another compound (YM-543) is being developed by the Japanese company Atstellas.[19]

Dapagliflozin

Dose and administration/pharmacokinetics

Dapagliflozin has been shown to have some anti-hyperglycemic efficacy at doses of 2.5, 5, 10, 20, and 50 mg daily in phase 2 trials.[20] The majority of phase 3 trials currently underway are evaluating the effects of 2.5-, 5-, or 10-mg tablets administered once daily.[18] One study assessing the potential for QT prolongation when dapagliflozin is administered concurrently with moxifloxacin is using single oral doses as high as 150 mg.[18] However, it is unlikely that this high provocative dose would ever be used clinically. One study in Japanese patients is using doses as low as 1 mg daily.

Dapagliflozin is rapidly absorbed after an oral dose in patients with type 2 diabetes with a median T_{max}

occurring at 1 hour (range 0.5–4 hours).[21] One small study in healthy volunteers suggested that the T_{max} occurs at a later time when the drug is administered in the fed state (median = 4 hours) but that there is very little difference in exposure to the drug when fed is compared to fasting (area under the curve [AUC] = 12,455 and 13,337 ng · hr/ml, respectively).[22] The half-life of dapgliflozin is reported to be ~ 16 hours.[21] Increases in C_{max} and AUC are roughly proportional to dose in the range of 5–100 mg (as is glucosuria effect).[21]

Renal clearance of dapagliflozin is minimal (~ 3–6 ml/minute) with < 2.5% being excreted unchanged in the urine during a 24-hour period. In vitro studies have suggested that dapagliflozin may be metabolized to an inactive metabolite via the glucuronosyltransferase enzyme coded for by UGT1A9.[20] A population kinetic analysis of 30 healthy subjects and 38 subjects with type 2 diabetes concluded that there were no substantive differences in the dapagliflozin pharmacokinetic parameters between the two groups.[23]

Clinical trials

A thorough review of all available phase 1 and phase 2 trials with dapagliflozin has been published.[20] Additionally, as mentioned above, a plethora of phase 3 trials are currently underway. Several published trials offer insight into how well dapagliflozin works and how well it is tolerated.

One study evaluated the effects of dapagliflozin in healthy subjects.[22] This trial assessed the safety, tolerability, pharmacokinetics, and pharmacodynamics of dapagliflozin in single-ascending-dose and multiple-ascending-dose fashion, with doses ranging from 2.5 to 100 mg daily. The authors reported

that the level of glucosuria was dose-dependent. The amount of glucose excreted via the urine ranged from 18 to 62 g of glucose daily with doses of 2.5–100 mg daily. The average amount of glucose lost daily remained stable during the 14-day dosing period of the study. No apparent change in glycemic indexes was observed in these patients during the study. No treatment-related serious adverse effects occurred during this trial. The authors concluded that dapagliflozin demonstrated pharmacokinetic and pharmacodynamic properties amenable to once-daily dosing.

Another trial carried out by the same group evaluated the effects of dapagliflozin in 47 subjects with type 2 diabetes.[21] Researchers randomized patients to placebo or 5, 25, or 100 mg dapagliflozin daily and assessed the effects of the drug during a 2-week period. The treatment groups were balanced in terms of demographics and baseline characteristics. The subjects were racially mixed, and 18 were being treated with, and continued, metformin therapy throughout the study.

Statistically significant, dose-dependent reductions in fasting serum glucose versus placebo were observed on day 14 (5 mg: 11.7%; 25 mg: 13.3%; 100 mg: 21.8%). Statistically significant reductions in oral glucose tolerance test results were also observed at all doses of active medication on days 2 and 13. Urine glucose loss on day 14 was ~ 37, 70, and 70 g daily for 5, 25, and 100 mg, respectively.

There were no reported serious adverse effects or discontinuations reported secondary to adverse effects in this trial. Reported adverse effects did not appear to be dose related. The most common adverse effects were gastrointestinal in nature and were more common in patients receiving metformin. There

were two reports of self-resolving hypoglycemia in this study in patients taking dapagliflozin plus metformin.

A larger trial was carried out in 389 diabetes drug–naive type 2 diabetic patients.[24] Researchers in this trial randomized patients at 98 clinical centers to either placebo; dapagliflozin in doses of 2.5, 5, 10, 20, and 50 mg daily; or extended–release metformin (titrated to 1,500 mg at week 2). The study was a prospective, 12–week, random-ized, parallel–group, double–blind, placebo–controlled trial and included a 2–week diet and exercise lead in. The primary objective of this trial was to evaluate mean A1C change from baseline after 12 weeks versus placebo. Secondary measures included fasting plasma glucose and percentage of patients achieving an A1C < 7%.

A total of 348 patients completed the 12-week study. At 12 weeks, all dapagliflozin patient groups had statistically significant reductions in mean A1C from baseline versus pla-cebo. Adjusted mean A1C reductions were −0.18% for placebo, −0.73% for metformin, and −0.55 to −0.9% for dapagliflozin. Adjusted mean fasting plasma glucose reductions were −6 mg/dl for placebo, −18 mg/dl for metformin, and −16 to −31 mg/dl for dapagliflozin. The fraction of patients achieving A1C < 7% at 12 weeks was 32% for placebo, 54% for metformin, and 40-59% for dapagliflozin. Also, reductions in total body weight were reported for all groups. Weight reduction at week 12 was 1.2% for placebo, 1.7% for metformin, and 2.5-3.4% for dapagliflozin.

No serious adverse effects were reported. Hypoglycemic events were reported in 4% of placebo-treated patients, 9% of metformin-treated patients, and 6–10% of dapa-gliflozin-treated patients with no

obvious dose relationship. There were no documented hypoglyce-mic events with fingerstick glucose concentrations ≤ 50 mg/dl. Urinary tract infections were reported in 6% of placebo-, 9% of metformin-, and 5–12% of dapagliflozin-taking patients. Also, genital infections were reported in 0% of placebo-, 2% of metformin-, and 2-7% of dapa-gliflozin-taking patients.

The impact of dapagliflozin on 546 patients inadequately con-trolled on metformin was evaluated in a recent 24-week, randomized, double-blind, placebo-controlled, multicenter trial.[25] The trial evalu-ated patients with type 2 diabetes between the ages of 18 and 77 years who, despite being treated with a dose of ≥ 1,500 mg of metformin daily continued to have A1C levels between 7 and 10%. After an initial 2-week lead-in phase, the patients were randomized to either placebo or dapagliflozin in doses of 2.5, 5, or 10 mg. All patients continued on metformin. The primary endpoint of this trial was A1C reduction at 24 weeks. Additional endpoints included fasting plasma glucose and percentage change in total body weight at 24 weeks.

Adjusted mean A1C reductions at 24 weeks were −0.3% for placebo and −0.67, −0.7%, and −0.84% for 2.5, 5, and 10 mg of dapagliflozin, respectively, compared to base-line. Adjusted mean fasting plasma glucose reductions were −6 mg/dl for placebo and −17.8, −21.5, and −23.5 mg/dl with 2.5, 5, and 10 mg of dapa-gliflozin, respectively, compared to baseline. The percentage change in baseline weight was −1.02% for placebo and −2.66, −3.66, and −3.43% for 2.5, 5, and 10 mg of dapa-gliflozin, respectively, at 24 weeks. Additionally, it was noted that ~ 25% of all dapagliflozin-taking patients

lost at least 5% of their baseline body weight at 24 weeks.

Urinary tract infections were reported in 8% of placebo- and 4.4-8.1% of dapagliflozin-taking patients. Also, genital infections were reported in 5.1% of placebo-, 2% of metformin-, and 8-13.1% of dapagliflozin-taking patients. Rates of hypoglycemia were similar in all groups in this study, and no patients discontinued the study because of hypoglycemia.

A very interesting trial evaluated the effectiveness of dapagliflozin in patients with diabetes poorly controlled with other oral anti-hyperglycemic agents and high-dose insulin.[26] Seventy-one patients in this trial were randomized to placebo or 10 or 20 mg of dapagliflozin. Patients were continued on their previous oral anti-hyperglycemic medications but continued insulin at half of their pre-study dose. After 12 weeks, A1C values were −0.7 and −0.7.8% for 10 and 20 mg of dapagliflozin, respec-tively, from baseline versus placebo. Mean reductions in body weight were −1.9, −4.5, and −4.3 kg for placebo, 10 mg, and 20 mg of dapa-gliflozin, respectively. There was a low incidence of adverse events in this trial. However, there were more genital infections reported for the group taking 20 mg of dapagliflozin than for placebo.

Conclusion
The kidney plays a key role in glucose homeostasis. The delineation of the role of SGLTs throughout the body has been a major advancement in our understanding of the kinetics of glucose in the body. Our better understanding of the physiology of renal glucose homeostasis and recent pharmacological advances have brought us to a point where pharmacological modulation of this system is possible. Although diabetes management is an obvious candidate

to benefit from these advances, other medical conditions such as obesity may also eventually be targeted via methods to modulate either SGLT1 or SGLT2.

Currently, a host of studies are underway evaluating the effects of the SGLT2 inhibitor dapagliflozin. Although the published studies offer a great deal of promise, there is still some concern regarding potential side effects, namely urinary tract and genital infections. As data from phase 3 trials develop, many of these unanswered questions will be resolved.

In addition to dapagliflozin, several other SGLT2 inhibitors, an SGLT anti-sense molecule, and SGLT1 inhibitors are being developed. Eventually, pharmacological or biological modulation of these transporters will almost certainly offer us a useful method of disease intervention.

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