The Importance of Reducing Hyperglycemia While Preserving Insulin Secretion—The Rationale for Sodium-coupled Glucose Co-transporter 2 Inhibition in Diabetes

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Abstract

The prevalence of type 2 diabetes continues to rise in a number of countries, presenting a need for additional effective therapeutic options to be developed. This condition has often been treated with medications that can lead to hypoglycemia (sulfonylureas), weight gain (thiazolidinediones), or other side effects, including the gastrointestinal side effects sometimes experienced with metformin. Sodium-coupled glucose co-transporter 2 (SGLT2) inhibitors are a novel class of drugs under investigation that target the kidney's ability to reabsorb glucose into the bloodstream, improving glycemic control and aiding weight loss without inducing hypoglycemia. These compounds have shown encouraging results in several studies without any serious adverse events. They could therefore potentially become an important addition to the currently available diabetes treatments.

Keywords

Sodium-coupled glucose co-transporter 2 (SGLT2) inhibitor, hyperglycemia, glucose reabsorption, type 2 diabetes, glucosuria, dapagliflozin, sergliflozin, remogliflozin, phlorizin, proximal tubule

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Type 2 diabetes affects an individual's ability to correctly regulate plasma glucose levels in the body, potentially leading to serious adverse events, including cardiovascular disease.[1,2] It is characterized by insulin resistance and beta-cell dysfunction with resultant hyperglycemia.[3] This condition affects more than 300 million people worldwide[4] and close to 24 million people in the US.[5] Obesity and weight gain have been reported to be leading risk factors for type 2 diabetes.[6,7] With obesity continuing to escalate in industrialized countries, the prevalence of diabetes is likely to increase substantially in the coming years. In fact, the incidence of type 2 diabetes in the US has been projected to reach 36.2 million people by 2025, an increase of 57% from 2003.[8]

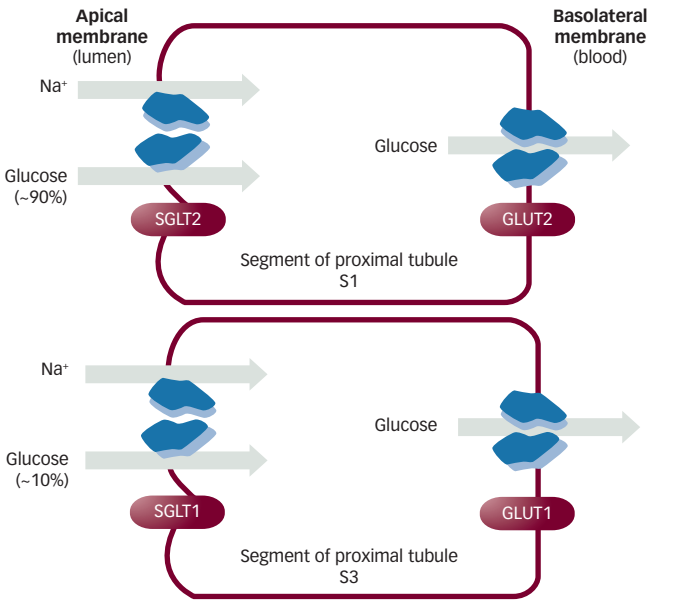
Various therapies have become established in the treatment of this potentially fatal disease, although finding optimal treatment options remains a challenge. Traditionally, strategies to counter hyperglycemia have involved developing medications that enhance insulin secretion and/or improve insulin sensitivity,[9] in particular metformin, sulfonylureas, and thiazolidinediones. Recently, dipeptidyl peptidase 4 (DPP-4) inhibitors and glucagon-like peptide 1 (GLP-1) mimetics have been added to this list. However, new drugs are constantly being developed and a novel class of agents currently under investigation focuses on a different strategy altogether, working to reduce hyperglycemia through the inhibition of glucose reabsorption in the kidneys.

Glucose and the Kidneys

The normal physiology of glucose regulation involves a delicate balance in the functions of different organ systems to maintain a plasma glucose level of 80–110mg/dl.[10] Despite large fluctuations that occur due to glucose intake in the form of meals and elimination from physical exertion, glucose concentrations in the blood are kept within this narrow range.[11] Mechanisms such as insulin production in the pancreas, glucose uptake by the brain and peripheral tissues, and gluconeogenesis in the liver and, to a lesser extent, the kidneys contribute to controlling glucose levels.

The kidney contains approximately 1.3 million nephrons, with each consisting of a glomerulus and a long tubule made up of three components: the proximal tubule, the loop of Henle, and the distal tubule.[12] In addition to gluconeogenesis, a major additional function of the kidneys is to reabsorb the approximately 180g of glucose that filters through the glomeruli every day (see *Figure 1*).[13] In individuals without diabetes and with normal renal function, virtually all of the glucose that passes through the kidneys is reabsorbed into the bloodstream; this is essential for energy conservation. This reabsorption is mediated by the sodium-coupled glucose co-transporters 1 and 2 (SGLT1 and SGLT2, respectively) located on the proximal tubule. SGLT2 is a high-capacity, low-affinity transporter expressed in the S1 segment of the proximal tubule and is responsible for 90% of renal glucose reabsorption.[14] The remaining 10% is reabsorbed

Figure 1: Normal Glucose Reabsorption in the Kidneys



GLUT = glucose transporter; SGLT = sodium-coupled glucose co-transporter.
Source: Lee and Han, 2007.[38]

through the high-affinity, low-capacity glucose/galactose transporter SGLT1 in the S3 segment of the proximal tubule (see *Figure 1*).[12,13] As a result, no glucose is found in the urine of healthy individuals.

However, individuals with diabetes are frequently hyperglycemic, with plasma glucose levels capable of saturating the SGLTs in the kidney and exceeding its maximal reabsorptive capacity. Once glucose concentrations surpass 180–200mg/dl, the kidneys are no longer able to reabsorb all of the glucose in the filtrate despite overexpression of the co-transporters in the proximal tubules of these individuals,[15,16] and any excess sugar is excreted in the urine, leading to glucosuria.[12,13,17] SGLTs have therefore become a potential target in diabetes research; by inhibiting these transporters, physicians can potentially further increase the amount of glucose excreted in the urine and lower plasma glucose levels in people with diabetes, thereby reducing hyperglycemia.

Intestinal Glucose–Galactose Malabsorption and Familial Renal Glucosuria

Before developing any drugs to inhibit SGLT function, it is useful to consider the possible clinical effects of such inhibition by looking at rare inherited disorders of SGLT dysfunction. SGLT1 is expressed in both the small intestine and the kidneys, where it filters glucose and galactose into the bloodstream. Individuals with mutations in the *SGLT1* gene develop the rare autosomal recessive disorder intestinal glucose–galactose malabsorption (GGM).[18,19] GGM causes severe and potentially fatal diarrhea after carbohydrate consumption, and can develop as early as the neonatal period.[18] Only mild glucosuria is observed with this condition, and symptoms can be treated by removing glucose, galactose, and lactose from the diet.

SGLT2s are found exclusively in the kidneys and, as a result, no gastrointestinal issues are observed when their function is disrupted. Instead, mutations in the *SGLT2* gene lead to the rare disorder familial renal glucosuria (FRG), where glucose reabsorption in the kidneys is severely impaired and large amounts of glucose are excreted in the urine.[20,21] Despite this severe glucosuria, FRG appears to be a benign condition, causing no serious adverse events or problems in kidney function. No negative complications have been reported with this disease and glucosuria does not appear to cause any particular harm. Research involving these inherited disorders therefore suggests that drugs inhibiting SGLT2 should be safe and are a superior choice to SGLT1 inhibition.

Early Animal Studies

Early studies in animals using the compound phlorizin found in apple trees showed the potential of SGLT inhibition in improving plasma glucose levels. This molecule is a natural competitive inhibitor of both SGLT1 and SGLT2[15] and provided proof-of-concept for SGLT inhibition. Phlorizin was shown in animal studies to reduce both fasting and post-prandial blood glucose levels without a risk for hypoglycemia.[22] It also provided positive outcomes in terms of decreasing insulin resistance at the peripheral tissue level.[16,22] Although phlorizin showed encouraging results, certain factors prevented it from proceeding beyond pre-clinical studies. Plorizin is poorly absorbed from the intestine and is easily hydrolyzed by lactase–phlorizin hydrolase.[23] Furthermore, phlorizin is non-specific, inhibiting both SGLT1 and SGLT2, thereby limiting its potential as a diabetes treatment since disruption of SGLT1 will necessarily result in gastrointestinal side effects. Instead, research has focused on finding a drug that safely and specifically blocks SGLT2. However, these early studies provided important insights into the concept of SGLT inhibition, and phlorizin is still the model on which many novel SGLT inhibitors are based.

Studies of Sodium-coupled Glucose Co-transporter 2 Inhibitors

T-1095

T-1095 is a prodrug analog of phlorizin taken orally that is readily absorbed from the intestine into the bloodstream, where it is converted into its active form.[24] Because T-1095 is inactive in the small intestine, it does not affect the SGLT1s in the gastrointestinal tract and will not cause the negative events associated with such inhibition. Active T-1095 is filtered by the kidneys, where it competitively inhibits both SGLT2 and SGLT1, increasing glucosuria and decreasing blood glucose levels.[25] Studies using diabetic rats showed that T-1095 treatment increased the amount of glucose excreted in the urine while decreasing plasma glucose levels and glycated hemoglobin (HbA_{1c}).[25,26] Despite these encouraging results, T-1095 was not developed past phase II trials, most likely due to its inability to specifically target SGLT2. Several other SGLT2 inhibitors have since been developed with slightly different structures from their predecessors, and are currently undergoing testing.

Sergliflozin

Unlike plorizin or T-1095, sergliflozin specifically inhibits SGLT2, exhibiting a 296-fold greater selectivity for SGLT2 over SGLT1.[27] Preliminary animal studies of this oral drug showed that when given to human subjects, the maximal resorptive capacity of the kidney for glucose was reduced by more than 60%, resulting in dose-dependent glucosuria after oral glucose loading.[27] Sergliflozin also decreased blood

glucose concentrations and improved insulin levels. Subsequent human studies were conducted to further evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of sergliflozin.[28,29]

Two small double-blind, randomized, placebo-controlled clinical studies were conducted using single oral doses of sergliflozin.[29] In the first study, sergliflozin doses ranging from 5 to 500mg were administered to 14 healthy males; in the second, eight subjects with type 2 diabetes were given 50–500mg of the drug. In both study groups, dose proportionality was observed, with a dose-dependent increase in urinary glucose excretion. The amount of glucose excreted in the urine reached a plateau at higher doses of sergliflozin, suggesting that the SGLT2 molecules were maximally inhibited.[29] Similarly, the higher the concentration of active drug in the system, the longer the duration of glucosuria. An oral glucose tolerance test in the subjects with diabetes showed a reduction of plasma glucose concentrations from 18.3 to 11.2mmol/h/l over four hours after receiving 500mg of sergliflozin. All doses of this SGLT2 inhibitor were well tolerated, with the most common adverse events being headache, sore throat, and dyspepsia. Sergliflozin therefore led to expected pharmacodynamic changes in the body based on lowered hyperglycemia effects, and had a favorable safety profile.[29]

Remogliflozin

Remogliflozin is currently under development. It has a 365-fold greater selectivity for SGLT2 versus SGLT1 than sergliflozin and is structurally unrelated to phlorizin.[30] In both non-diabetic and diabetic rats, remogliflozin reduced plasma glucose levels and decreased circulating insulin levels compared with placebo.[30] These antihyperglycemic effects were much more significant in the diabetic animals. Over six weeks, remogliflozin led to lower fasting plasma glucose and lower HbA_{1C} levels in obese diabetic rats. Furthermore, remogliflozin reduced circulating insulin levels and produced weight loss compared with the control group.[30] From these findings, it appears that this SGLT2 inhibitor is capable of reversing the many effects of hyperglycemia through the induction of urinary glucose excretion.

Dapagliflozin

Dapagliflozin is another SGLT2-specific inhibitor showing a 200–1,200-fold greater selectivity for SGLT2 compared with SGLT1 in *in vitro* studies with animal cells.[16,31] Unlike T-1095 or sergliflozin, dapagliflozin is active in its ingested form and, due to its c-glucoside structure, it has a half-life that is approximately 4.6 hours longer than the other two drugs.[16,31] This will enable dapagliflozin to be developed as a once-daily oral antidiabetic drug.

Preliminary animal and human studies illustrated the potential of dapagliflozin to lower plasma glucose levels and improve glycemic control in diabetics.[31,32] This justified dapagliflozin proceeding into larger-scale clinical studies, including two phase II trials.[33,34] In the first trial, 64 healthy subjects were recruited to determine the pharmacokinetic properties and safety of dapagliflozin.[33,34] This drug demonstrated dose-dependent glucosuria and SGLT2 inhibition for at least 24 hours. This encouraged its study as a once-daily treatment in patients with type 2 diabetes. A trial with 47 subjects with diabetes showed that the medication was effective both as a monotherapy and when administered in combination with metformin.[34] After 13 days of treatment, fasting serum glucose was reduced by 11.7% ($p<0.05$), 13.3% ($p<0.05$), and 21.8% ($p<0.0001$) for doses of 5, 25, and 100mg, respectively, compared with subjects receiving placebo, who showed no significant reductions. No serious adverse events were reported and negative effects were comparable between participants given dapagliflozin or placebo.

Results from a phase III trial were recently presented at the European Association for the Study of Diabetes Annual Meeting.[35] A total of 546 patients 18–77 years of age with type 2 diabetes inadequately controlled with metformin alone were enrolled in this double-blind, placebo-controlled, multicenter trial. After a two-week lead-in phase, subjects were randomized on a 1:1 basis to receive once-daily dapagliflozin 2.5, 5, or 10mg or placebo in addition to metformin. The primary end-point was change in HbA_{1C} after 24 weeks, with secondary end-points being fasting plasma glucose and change in total bodyweight.[35]

At week 24, mean HbA_{1C} levels were significantly reduced from baseline in all add-on dapagliflozin groups compared with the placebo group.[35] Fasting plasma glucose was also significantly lowered for all dapagliflozin groups versus placebo. More patients in the dapagliflozin groups reached an HbA_{1C} <7.0% than those on placebo, and the SGLT2 inhibitor was associated with continuous and progressive weight loss. Overall, adverse events were comparable between all groups, with rates of urinary tract infections being similar or lower with dapagliflozin (placebo 8.0%; dapagliflozin 2.5mg 4.4%; dapagliflozin 5mg 7.3%; dapagliflozin 10mg 8.1%). Conversely, genital infections were lower in the placebo group (placebo 5.1%; dapagliflozin 2.5mg 8.0%; dapagliflozin 5mg 13.1%; dapagliflozin 10mg 8.9%). Hypoglycemic events were similar across all groups and none resulted in discontinuation of the study medication. Therefore, patients with type 2 diabetes whose glycemic levels are not sufficiently controlled by metformin alone can benefit from the addition of the SGLT2 inhibitor dapagliflozin to their treatment regimen. A once-daily dose of this drug had a favorable safety profile and was associated with clinically meaningful weight loss over the 24 weeks relative to placebo.[35]

Currently, of the SGLT2 inhibitors, dapagliflozin is the closest to achieving marketing approval. If phase III trials continue to show positive results and favorable safety profiles, dapagliflozin could be approved as early as 2011.

Safety and Tolerability of Sodium-coupled Glucose Co-transporter 2 Inhibitors

There have been no human trials that have assessed the long-term safety of SGLT2 inhibitors. However, short-term trials have revealed no particular safety issues. In the 24-week phase III trial discussed above,[35] which is the longest study performed in patients with type 2 diabetes to date, no serious adverse events were reported. Contrary to logical expectations, no excessive loss of electrolytes was observed and urinary volume increase was minimal. Furthermore, because these inhibitors are specific for SGLT2, they should not affect SLGT1 in the small intestine, avoiding any gastrointestinal side effects such as diarrhea and abdominal cramps.[36]

A major concern regarding diabetes treatment is the possible occurrence of hypoglycemic events if glycemic levels decrease below

threshold. However, SGLT2 inhibitors act independently of pancreatic beta-cell insulin secretion and are dependent on plasma glucose levels; as glucose levels decrease, so does the amount of glucosuria. The risk for hypoglycemia is therefore low in patients receiving SLGT2 inhibitor treatment.

The use of an SGLT2 inhibitor will invariably result in glucosuria, making it necessary to ensure that this does not lead to any adverse events for the patient. Microbiological pathogens, particularly bacteria, proliferate at sites abundant in sugar, and it was hypothesized that glucosuria may lead to increased urinary tract infections. However, this was not observed, and the only negative effect reported in some studies was a slightly higher incidence of fungal infections of the vagina, which can easily be treated with antibiotics.[35] In addition, SGLT2 inhibitors do not appear to negatively affect kidney organ function despite altering the rate of glucose reabsorption.

Future Developments

Based on the studies conducted on the various SGLT2 inhibitors, it is reasonable to believe that these drugs can be added to any diabetes treatment regimen. Currently, the standard first-line therapy for type 2 diabetes is metformin, due to its low cost and favorable safety profile.[37] SGLT2 inhibitors could become second-line therapy, and could possibly replace metformin as the first-line therapy. In addition to acting as an effective monotherapy, SGLT2 inhibitors can also be safely given in combination with other established diabetes medications, including sulfonylureas and insulin. SGLT2 inhibitors are therefore believed to be appropriate for adding to the currently available treatment combinations.

As SGLT2 inhibitors proceed into the later stages of development, certain key issues remain that need to be addressed. In particular, the safety of these drugs needs to be verified. This class of medication has proved to be effective in reducing HbA_{1c} levels; however, overall drug safety is still a major concern for physicians and patients alike. More specifically, the safety of SGLT2 inhibitors used in combination with blood pressure medications is of particular concern. Finally, it would be of considerable interest to evaluate the efficacy of these drugs in type 1 diabetes to possibly expand the indications for which these inhibitors are applicable.

Summary and Conclusion

With the increasing prevalence of type 2 diabetes worldwide, it is becoming more important for researchers to develop new and more effective drugs for its treatment. SGLT2 inhibitors represent a novel class of agents under investigation that target the reabsorption of glucose by the kidney, in contrast to traditional approaches that involve increasing insulin secretion to reduce hyperglycemia and improve glycemic control. By selectively inhibiting SGLT2, these oral drugs can potentially reduce plasma glucose levels and glucose toxicity without causing any serious adverse events, with a low risk of hypoglycemia. SGLT2 inhibitors should therefore be a welcome addition to the currently available treatment options for type 2 diabetes. ■

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