Individuals with type 2 diabetes suffer from increased morbidity and mortality secondary to both macrovascular (heart attack, stroke, and amputation) and microvascular (retinopathy, nephropathy, and neuropathy) complications. Hyperglycemia is the major risk factor for microvascular complications. Many studies, e.g. the Diabetes Control and Complications Trial (DCCT) and the UK Prospective Diabetes Study (UKPDS), have documented that correcting the hyperglycemia reduces the risk of microvascular complication. Every 1% decrease in glycated hemoglobin (HbA$\text{1c}$) is associated with ~35% reduction in microvascular complications.

Insulin resistance and progressive beta-cell failure represent the two core defects that characterize subjects with type 2 diabetes. Hyperglycemia plays an important role in the pathogenesis of insulin resistance and beta-cell failure, i.e. glucotoxicity. Thus, appropriate glycemic control in diabetic subjects would be anticipated to reduce the risk of microvascular complications and ameliorate the metabolic abnormalities that contribute to the progressive course of the disease. Thus, tight glycemic control has become the cornerstone of management in subjects with type 2 diabetes and all professional organizations recommend that HbA$\text{1c}$ should be maintained at ≤6.5–7%.

Progressive beta-cell failure, weight gain, and hypoglycemia represent major obstacles for the achievement of tight glycemic control and HbA$\text{1c}$ ≤6.5–7% in patients with type 2 diabetes. Therefore, the development of novel medications that effectively lower the plasma glucose level, produce durable glycemic control, and are not associated with hypoglycemia and weight gain are needed for the management of type 2 diabetes patients. Most recently, inhibitors of the renal sodium glucose co-transporter have been developed to produce glucosuria and reduce the plasma glucose concentration. Because the mechanism of action of these oral antidiabetic agents is independent of beta-cell and tissue sensitivity to insulin, they improve glycemic control while avoiding hypoglycemia and promoting weight loss. In this article, we will summarize the available data concerning the mechanism of action, efficacy, and safety of this novel antidiabetic therapeutic approach.

**Filtration and Reabsorption of Glucose by the Kidney**

Approximately 180 liters of plasma, which contain ~162g of glucose, are filtered by the glomeruli every day. In normal-glucose-tolerant subjects virtually all of this glucose is completely reabsorbed in the proximal tubule. The maximum glucose transport capacity (Tm) of the proximal tubule, on average, has a value of ~375mg/minute. In both the S1 and S3 segments of the proximal tubule, glucose transport is mediated by sodium–glucose co-transporters (SGLTs) and is coupled to sodium reabsorption. The sodium electrochemical gradient generated by active sodium transport provides the energy required for glucose reabsorption.
transport. SGLT1 mediates glucose transport in the S3 segment and SGLT2 mediates glucose transport in the S1 segment. As the filtered glucose load is less than 375mg/minute in non-diabetic subjects, all of the filtered glucose is reabsorbed and returned to the circulation (see Figure 1). If the filtered glucose load exceeds 375mg/minute, as often occurs in type 2 diabetes subjects, the Tm is exceeded and all of the glucose in excess of the Tm is excreted in the urine. The plasma glucose concentration at which the filtered glucose load reaches 375mg/minute is called the threshold. When the threshold is exceeded, the glucose excretion rate increases linearly and parallels the filtered load. The reabsorption and excretion curves display a non-linear transition as the Tm for glucose is approached. This ‘rounding’ of the curves is termed splay, and has been explained by heterogeneity in the Tm for individual nephrons and/or glomerulotubular imbalance.11

Normal-glucose-tolerant subjects have a Tm for glucose that is well above the filtered glucose load. This has major survival benefits, since it allows the kidneys to conserve this critical energy source for the brain, which (with the exception of prolonged fasting) can only utilize glucose to generate energy for neuronal function. However, in patients with diabetes this adaptive mechanism becomes maladaptive. In the presence of hyperglycemia, it would be desirable for the kidney to excrete the excess filtered glucose load to restore normoglycemia. In fact, the diabetic kidney has an increased Tm for glucose, thereby minimizing glucosuria and exacerbating the hyperglycemia. When viewed in these terms, it is evident that the kidney contributes to the development and maintenance of hyperglycemia in individuals with diabetes.

It also should be noted that increased glucose uptake in the proximal tubules in subjects with diabetes is accompanied by increased sodium reabsorption, which contributes to extracellular volume expansion and an increase in blood pressure.

Based on these pathophysiologic considerations, it follows that development of specific inhibitors of the renal SGLT2 transporter provides a rational and novel approach for the treatment of diabetic patients. The specificity for SGLT2 over SGLT1 transporters, which are present in both the gut and kidney, avoids impaired intestinal glucose absorption and diarrhea. Recent evidence also suggests the SGLT1 transporter in cells of the proximal small intestine may be responsible for generating the signal leading to the release of incretin hormones in response to nutrient ingestion.12

Pharmacological Inhibitors Of Renal Glucose Uptake

In 1886, von Mering demonstrated that ingestion of high doses of phlorizin (>1g), a natural product in the bark of apple trees, produced glucosuria in man.13 Studies in the 1950s and the 1960s demonstrated that the glucosuric action of phlorizin resulted from inhibition of active glucose transport in the apical membrane of the renal proximal tubule.14 Phlorizin competitively inhibits both SGLT1 and SGLT2 in the proximal tubule with a higher affinity (10-fold) for the SGLT2 versus SGLT1 transporter and, when given to normal subjects, produces glucosuria that resembles familial renal glucosuria.15 Despite the efficacy of phlorizin in inhibiting SGLT transporter activity and normalizing the plasma glucose concentration in diabetic animals, low bioavailability (~15%) following oral administration and inhibition of SGLT1 in the gastrointestinal tract negate its clinical usefulness in subjects with diabetes.16 As a result of these limitations of phlorizin, other compounds with greater bioavailability following oral administration and higher selectivity for SGLT2 compared with SGLT1 have been developed (see Table 1).

Since the SGLT2 gene primarily is expressed in kidney proximal tubules, downregulating SGLT2 gene expression with antisense oligonucleotides (ASOs) is another approach that has been used to inhibit renal glucose reabsorption.17 Studies in rats, dogs, and monkeys have demonstrated that ASOs decrease renal SGLT2 mRNA expression by ~80% with no significant change in SGLT1 expression and this is accompanied by pronounced glucosuria. Furthermore, a once-weekly injection of ASOs for four to five weeks caused a substantial reduction in plasma glucose concentration and HbA1c, without any appreciable side effects. As the ASOs work by reducing the SGLT2 protein content, rather than inhibiting the SGLT2 transporter, they have the potential to cause a much greater reduction in HbA1c.
Inhibition of Renal Glucose Transport Corrects Hyperglycemia—Proof of Concept

Studies performed with phlorizin in 90% pancreatectomized diabetic rats have provided proof of concept for the efficacy of SGLT2 inhibition in the treatment of type 2 diabetes. Chronic phlorizin administration in this insulinopenic type 2 diabetic model induced glucosuria and normalized both the fasting and fed plasma glucose levels with complete reversal of the insulin resistance. When phlorizin was withdrawn from phlorizin-treated animals, hyperglycemia and insulin resistance returned. Chronic phlorizin treatment also corrected the defects in both first- and second-phase insulin secretion in this diabetic rodent model.

Despite the large glucosuria, these subjects are asymptomatic with no signs of hypoglycemia. These observations provide proof of concept that pharmacological inhibition of SGLT2 is a safe and potentially effective strategy for reducing the plasma glucose concentration in subjects with diabetes.

Sodium–Glucose Co-transporter 2 Inhibitors in Type 2 Diabetes Subjects

Clinical trials with dapagliflozin are the most advanced of the SGLT2 inhibitors and two phase III trials have been completed. In a 14-day study, dapagliflozin (5, 25, and 100mg/day) caused glucosuria (20-200g per day). Despite the large glucosuria, these subjects are asymptomatic with no signs of hypoglycemia. These observations provide proof of concept that pharmacological inhibition of SGLT2 is a safe and potentially effective strategy for reducing the plasma glucose concentration in subjects with diabetes.

A number of other SGLT2 inhibitors have entered early trials for the treatment of type 2 diabetes. In a phase 1 study, a single dose of sotagliflozin (50–500mg) caused a dose-dependent increase in glucosuria in both normal and type 2 diabetes subjects. The 500mg dose reduced the mean plasma glucose concentration during the OGTT from 18.3mM to 11.2mM. More prolonged treatment (14 days) with sotagliflozin also induced dose-dependent glucosuria with modest weight loss. Interestingly, SGLT2 inhibition was accompanied by an increase in plasma glucagon-like peptide 1 (GLP-1) concentration and weight loss of 1.3–2.3kg.

In a double-blind, placebo-controlled, dose-ranging study in 451 metformin-treated type 2 diabetes subjects, canagliflozin in doses of 50, 100, 200, and 300mg/day for 12 weeks reduced HbA1c by 0.7–0.9% from baseline and by 0.5–0.7% versus placebo in association with weight loss of 1.3–2.3kg. The 300mg/day dose appeared to be slightly more
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effective then the lower doses. In a 16-day trial, canagliflozin was shown to improve beta-cell function in type 2 diabetes patients using a model-based method to calculate insulin secretion.\textsuperscript{61} In a small study involving 29 type 2 diabetic subjects sub-optimally controlled (HbA\textsubscript{1c} 8.4\%) with insulin, addition of canagliflozin at 100 and 300mg/day for 28 days reduced the HbA\textsubscript{1c} by 0.7% and 0.9%, respectively.\textsuperscript{62}

Similar results have been observed with other SGLT2 inhibitors. In a four-week study, BI 10773 at a dose 100mg/day increased urinary glucose excretion by 74.3g per day.\textsuperscript{63} In a 12-week double-blind study, 361 Japanese type 2 diabetes subjects treated with ASP1941 at doses ranging from 12.5 to 100mg/day experienced a 0.9% reduction in HbA\textsubscript{1c} at the highest doses (50 and 100mg/day).\textsuperscript{64} Bodyweight was also dose-dependently reduced by up to 2kg in the 100mg/day dose. In a phase 2A study, LX4211, which inhibits SGLT2 and to a lesser extent SGLT1, at doses of 150 and 300mg/day reduced HbA\textsubscript{1c} by 1.2% but starting HbA\textsubscript{1c} (8.2–8.5\%) was higher than in most other studies and the placebo decreased the HbA\textsubscript{1c} by 0.5%.\textsuperscript{65} Remogliflozin belongs to a different family of SGLT2 inhibitors and has a structural scaffold differing from that of pholizin.\textsuperscript{66} Remogliflozin caused a dose-dependent glucosuria and, in 35 patients with drug-naïve type 2 diabetes, 12 days of treatment with resulted in a decrease in fasting plasma glucose concentration (~30mg/dl), bodyweight (2.6kg), and blood pressure (~8mmHg).\textsuperscript{67}

It is noteworthy that the increase in urine glucose excretion (60–80g/day) observed with all SGLT2 an inhibitors currently in clinical trials, even with maximal doses, represents an inhibition of less than 50\% of the filtered glucose load. The failure to observe a greater inhibition of renal glucose absorption is unclear but could be explained by: inability of the SGLT2 inhibitor to reach the SGLT2 transporters because of their anatomical location; competitive inhibition that progressively raises the local concentration of glucose at the site of the SGLT2 transporter, thus reducing its effectiveness; insufficiently high drug concentrations in the tubular lumen to inhibit the SGLT2 transporter; glucose transporters other than SGLT2 in man are responsible for a much greater fraction of glucose reabsorption than previously appreciated; and upregulation of the SGLT1 or other glucose transporters offsets the glucosuric effect of SGLT2 inhibitors. The latter seems unlikely since the magnitude of glucosuria on days one to three versus day 14 after the start of dapagliflozin is similar.\textsuperscript{22}

No SGLT2 inhibitor has been studied in patients with diabetes and reduced glomerular filtration rate (GFR). Because of the reduction in GFR (reduced filtered glucose load) and/or tubular damage, it is likely that the efficacy of SGLT2 inhibitors will be reduced in individuals with reduced GFR. This needs to be examined before this class of drugs can be recommended in patients with diabetes and reduced GFR.

Finally, it remains to be determined whether oral SGLT2 inhibitors cause glucosuria by inhibiting the Tm for glucose and/or increasing the glucose splay. One study in rodents with sergliflozin indicates a reduction in Tm without change in the glucose splay.\textsuperscript{22} We believe that neither of these two explanations (reduced Tm or increased splay) can satisfactorily explain the marked glucosuria induced by the SGLT2 inhibitors in normal glucose-tolerant individuals with a fasting plasma glucose of 80–90mg/dl. Rather, we believe that the SGLT2 inhibitors inhibit a constant percentage of the filtered glucose load at all plasma glucose concentrations. At high plasma glucose concentrations, this would result in a greater amount of glucosuria than at low plasma glucose concentrations, although the fractional glucose inhibition would be similar. This does not exclude a concomitant reduction in the glucose Tm and is, in fact, most consistent with the effect of sergliflozin on renal glucose excretion.\textsuperscript{22}

Sodium–Glucose Co-transporter 2 Inhibitors and Diabetic Nephropathy

Hyperglycemia is the principal risk factor for diabetic microvascular complications (retinopathy, nephropathy, and neuropathy), and improved glycemic control—no matter how achieved—would be expected to reduce the risk of microvascular complications in subjects with type 2 diabetes.\textsuperscript{45} As a result of the important role of enhanced glucose reabsorption in the proximal tubule in altering renal hemodynamics and the development of diabetic nephropathy,\textsuperscript{42,43} inhibition of renal glucose absorption with an SGLT2 inhibitor might be expected to have an additional beneficial reno-protective action beyond its glucose-lowering effect. The increased filtered glucose load in diabetes results in increased glucose and sodium reabsorption by the SGLT2 transporter in the proximal tubule.\textsuperscript{44,45} Some investigators\textsuperscript{46} have postulated that the primary abnormality resides at the level of the proximal tubule and is characterized by an intrinsic increase in glucose/sodium reabsorption because of a generalized increase in kidney size and renal (both glomerular and tubular) hypertrophy. In either case, enhanced sodium reabsorption in the proximal tubule leads to a reduction in sodium delivery to the juxtaglomerular apparatus and activates the tubuloglomerular feedback reflex, resulting in vasodilation, elevated intraglomerular pressure and increased glomerular filtration rate until distal salt delivery returns to its normal set point.\textsuperscript{46} Renal hyperfiltration and increased kidney size are early characteristic changes of diabetic nephropathy\textsuperscript{47} and can be reversed by six weeks of intensive insulin therapy that normalizes plasma glucose concentration.\textsuperscript{47} Therefore, SGLT2 inhibitors could have a dual effect to prevent renal hyperfiltration: normalization of the plasma glucose concentration with reversal of renal hypertrophy, decreased intraglomerular pressure/renal hyperfiltration, and reduced filtered glucose load; increased sodium delivery to the distal tubule with inhibition of the tubuloglomerular feedback reflex. With regard to this, it is noteworthy that chronic T-1095 administration decreased HbA\textsubscript{1c} levels in mice with diabetes and stopped the progression of diabetic nephropathy with prevention of proteinuria and expansion of glomerular mesangial area.\textsuperscript{48}

Non-glycemic Benefits

In addition the beneficial effects related to improved glycemic control, SGLT2 inhibitors have a number of non-glycemic effects that make them desirable agents as monotherapy and for combination treatment with other antidiabetic agents. Weight gain is a major problem with currently available antidiabetes medications including sulfonylureas, thiazolidinediones, and insulin. The urinary loss of 60–80g of glucose per day equates to 240–320 calories/day or 2–3lbs/month if this caloric deficit is not offset by an increase in caloric intake. Consistent with this, 12–24 weeks of treatment with dapagliflozin has been associated with weight losses of 2–3kg.
A consistent finding in all dapagliflozin studies has been a reduction in blood pressure of 4–5/2–3 mmHg. Although this has been attributed to the mild fluid/sodium deficit that occurs during the first few days of dapagliflozin treatment, an equally plausible explanation is local inhibition of the renin–angiotensin system secondary to enhanced sodium delivery to the juxtaglomerular apparatus. Consistent with the inhibition of sodium-coupled uric acid reabsorption in the proximal tubule, a decrease in serum uric acid concentration has been observed in diabetic patients treated with dapagliflozin. The effect of dapagliflozin on plasma lipid levels has yet to be published.

Safety
The pharmacological properties of SGLT2 inhibitors suggest that they should have a good safety profile. As a result of their high selectivity for the SGLT2 transporter, no inhibition of the SGLT1 transporter in the intestinal mucosa is anticipated and gastrointestinal side effects have not been observed. Furthermore, because subjects homozygous for mutations in the SGLT2 gene generally are asymptomatic despite large amounts of glucosuria (>50–100 g per 24 hours), pharmacological inhibition of SGLT2 would not be expected to cause polyuria, nocturia, or volume contraction, and, in fact, these side effects have not been observed in clinical trials. When dapagliflozin has been administered to humans for up to 12–24 weeks, urine volume increased only modestly (200–400 ml/day) during the first two to three days after initiation of therapy and excessive urine losses of sodium, potassium, and other electrolytes was not observed. Consistent with mild volume contract, a small rise in hematocrit (1–2 volume %) and plasma creatinine to urea nitrogen ratio have been observed. Plasma electrolyte concentrations did not change following dapagliflozin. As stated previously, modest reductions in both systolic and diastolic blood pressure have been observed in type 2 diabetes patients. Lastly, because SGLT2 inhibitors have no effect on the glucose counter-regulatory mechanisms, hypoglycemia is not anticipated. In animals with and without diabetes and humans with diabetes, the administration of SGLT2 inhibitors was not associated with hypoglycemia. Although the SGLT2 inhibitors promote glucosuria and this could result in an increased incidence of urinary tract infections, patients with diabetes already have significant glucosuria and it remains to be determined whether the additional glucosuria will promote bacterial growth. Since chronic hyperglycemia inhibits phagocytic activity by white blood cells, it is possible that any increased risk of bacterial urinary tract infection would be offset by the improved phagocytic activity. The incidences of vulva-vaginitis and balanitis are increased approximately twofold. SGLT2 inhibitors have not been shown to have any deleterious effect on renal function as manifested by a rise in serum creatinine or development of albuminuria or tubular proteinuria in patients with diabetes and normal GFR. However, studies in individuals with a reduced GFR will be required to demonstrate the safety, as well as efficacy, in this group.

Summary and Conclusion
Current data in experimental animals and humans indicate that inhibition of the SGLT2 transporter is an effective and novel strategy to control the plasma glucose concentration in type 2 diabetes subjects. In type 2 diabetes patients, dapagliflozin—the most clinically advanced of the SGLT2 inhibitors—has demonstrated a good safety profile, modest weight loss, and HbA1C reduction of 0.7–0.8% with a starting HbA1C of 8.0%. As SGLT2 inhibitors have a distinct mechanism of action that is independent of insulin secretion or the presence of insulin resistance, the efficacy of this class of drugs is not anticipated to decline with progressive beta cell failure or in the presence of severe insulin resistance. Furthermore, this class of drugs can be used in combination with all other antidiabetic medications with anticipated additive efficacy on glycemic control. The SGLT2 inhibitors also are effective as monotherapy in newly diagnosed diabetic patients. To the extent that glucotoxicity contributes to the demise in beta cell function in subjects with impaired glucose tolerance (IGT) or impaired fasting glucose (IFG), these drugs may also prove useful in the treatment of ‘pre-diabetes’. Currently available data indicate that the SGLT2 inhibitors have a good safety profile. In addition, the asymptomatic clinical presentation of subjects with familial renal glucosuria, despite multiple generations of the disease, has documented the long-term safety of pharmacological inhibition of the SGLT2 transporter.

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