Familial Renal Glucosuria and SGLT2: From a Mendelian Trait to a Therapeutic Target

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Four members of two glucose transporter families, SGLT1, SGLT2, GLUT1, and GLUT2, are differentially expressed in the kidney, and three of them have been shown to be necessary for normal glucose resorption from the glomerular filtrate. Mutations in SGLT1 are associated with glucose-galactose malabsorption, SGLT2 with familial renal glucosuria (FRG), and GLUT2 with Fanconi-Bickel syndrome. Patients with FRG have decreased renal tubular resorption of glucose from the urine in the absence of hyperglycemia and any other signs of tubular dysfunction. Glucosuria in these patients can range from <1 to >150 g/1.73 m² per d. The majority of patients do not seem to develop significant clinical problems over time, and further description of specific disease sequelae in these individuals is reviewed. SGLT2, a critical transporter in tubular glucose resorption, is located in the S1 segment of the proximal tubule, and, as such, recent attention has been given to SGLT2 inhibitors and their utility in patients with type 2 diabetes, who might benefit from the glucose-lowering effect of such compounds. A natural analogy is made of SGLT2 inhibition to observations with inactivating mutations of SGLT2 in patients with FRG, the hereditary condition that results in benign glucosuria. This review provides an overview of renal glucose transport physiology, FRG and its clinical course, and the potential of SGLT2 inhibition as a therapeutic target in type 2 diabetes.

Glucose is the primary energy source for brain, muscle, and other organs. Membrane lipid bilayers, however, are virtually impermeable to hydrophilic glucose molecules and rely on glucose transporters to facilitate their movement across cell membranes and their distribution to and within various tissues (1,2). The kidney contributes to glucose homeostasis by reabsorbing approximately 180 g from the glomerular filtrate each day. Because of the activity of glucose transporters in the renal proximal tubule, <0.5 g/d (range 0.03 to 0.3 g/d) is excreted in the urine of healthy adults (1,2).

There are two means of glucose transport, facilitative and secondary active transport, each of which involves different classes of transporters. Facilitative transport, which is driven by the concentration gradient across cellular membranes, occurs in essentially all cell types and is mediated by members of the GLUT transporter family. Secondary active transport is the first step in transcellular glucose transport in the intestine and kidney and is mediated by members of the SGLT transporter family. GLUTs are encoded by the SLC2 family, whereas SGLTs are encoded by the SLC5 family. It is possible that other transporters may account for additional glucose transport activity in the kidney. For instance, mutations in the monocarboxylate transporter MCT12, encoded by the SLC16A12 gene, were found to be responsible for an autosomal dominant inherited condition characterized by juvenile cataracts with microcornea and mild renal glucosuria (OMIM 612018), underlining the role of transporters other than the GLUTs and SGLTs in renal glucose handling (3).

There are >220 members in the SLC5 family, also known as the sodium substrate symporter gene family (SSSF); of these, 12 have been identified in the human genome (4,5). SGLT members are multifunctional membrane-bound proteins that display a vast array of functions from sodium-coupled co-transport for sugars, monocarboxylates, amino acids, vitamins, osmolytes, and ions to sodium uniporter activity, channels for urea and water, glucose sensing, and tumor suppression (4,5).

At least two sodium-coupled glucose transporters, SGLT1 and SGLT2, play an important role in the apical membrane of proximal tubular cells in the kidney (Figure 1). These transporters first bind Na⁺, before they bind glucose, and the electrochemical Na⁺ gradient generated by the Na⁺/K⁺-ATPase is the driving force for the symporter activity. SGLT1 is predominantly expressed in enterocytes (6). Its primary function here is to mediate active glucose and galactose transport across the apical membrane at low sugar concentration, but it also mediates expression of facilitative transporters at high glucose concentration. Although not involved in resorption of the bulk of glucose in the kidney, the kinetic characteristics of SGLT1 are favorable for transport of glucose when present at low concen-
trations. In addition to the intestine and kidney, SGLT1 is expressed in organs such as the brain and the heart. SGLT2 expression occurs predominantly in the luminal brush border of the proximal tubule of the renal cortex, where it is the principal transporter that mediates glucose resorption (7) (Table 1). It is also expressed to a much lower degree in other organs, including the liver. SGLT4, SGLT5, SGLT6, and SMIT1 are expressed in several tissues, including the kidney, and a putative role in glucose transport in the kidney is anticipated but has yet to be shown. SGLTs are multifunctional proteins, and for the remaining six products of SLC5 genes that are predicted to exist in the human genome, different functions have been reported. For instance, SGLT3, initially assigned to be a co-transporter on the basis of sequence homology, was later characterized as a glucose-gated ion channel expressed in cholinergic neurons and the neuromuscular junction (8) and might play a role in diet-triggered intestinal motility.

**Location and Relative Affinities of Renal SGLTs for Glucose**

SGLT2 and SGLT1 can be distinguished by their affinities for glucose and Na\(^+\) and their location in the kidney (9–12). SGLT2 is expressed exclusively near the early proximal convoluted tubule (termed S1) (13), whereas SGLT1 is expressed near the medullary proximal tubule (termed S3) (9–11). SGLT2 is a low-affinity, high-capacity glucose transporter, whereas SGLT1 is a high-affinity, low-capacity glucose transporter. SGLT1 transports glucose and galactose (10), has a K\(_{0.5}\) for glucose of approximately 0.4 mM, and carries two molecules of Na\(^+\)/H\(^+\) for every molecule of glucose. SGLT1 has a K\(_{0.5}\) of approximately 3 mM for Na\(^+\) for every molecule of glucose, and has a K\(_{0.5}\) for Na\(^+\) of 100 mM (14). SGLT2, unlike SGLT1, does not transport galactose. Thus, the bulk of glucose is reabsorbed at the S1 segment by the high-capacity SGLT2 transporter, whereas the remaining glucose that enters the S3 segment is reabsorbed by the high-affinity SGLT1 transporter; together they minimize glucose loss in the urine (14).

**SGLT Protein Structure and Transport Dynamics**

Human SLC5 genes code for proteins with a molecular mass of approximately 75 kD. They exhibit considerable functional similarity, despite that transported solutes are variable. The topology and secondary structure model of SGLT1, the most extensively studied member of the SSSF group, has been experimentally delineated by extensive analyses of its primary sequence, sequence comparison, computational prediction methods, and both functional and electron microscopic assays performed in heterologous expression systems (2,4,15,16). The

**Table 1. Substrates and distribution of human glucose transporters**

<table>
<thead>
<tr>
<th>Transporter (Gene)</th>
<th>Substrate</th>
<th>Size (Amino Acids)</th>
<th>Distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>SGLT1 (SLC5A1)</td>
<td>Glucose Galactose</td>
<td>664</td>
<td>Intestine, trachea, kidney, heart, brain, testis, and prostate</td>
</tr>
<tr>
<td>SGLT2 (SLC5A2)</td>
<td>Glucose</td>
<td>672</td>
<td>Kidney, brain, liver, thyroid, muscle, and heart</td>
</tr>
<tr>
<td>SGLT4 (SLC5A9)</td>
<td>Glucose Mannose</td>
<td>699</td>
<td>Intestine, trachea, kidney, liver, brain, lung, uterus, and pancreas</td>
</tr>
<tr>
<td>SGLT5 (SLC5A10)</td>
<td>Glucose (predicted)</td>
<td>596</td>
<td>Kidney</td>
</tr>
<tr>
<td>SGLT6/SMIT2 (SLC5A11)</td>
<td>Myoinositol</td>
<td>675</td>
<td>Brain, kidney, and intestine</td>
</tr>
<tr>
<td>SMIT1 (SLC5A3)</td>
<td>Myoinositol Glucose</td>
<td>718</td>
<td>Brain, heart, kidney, and lung</td>
</tr>
</tbody>
</table>

Adapted from reference (2).
membrane topology of other members of the SGLT family is anticipated to be similar on the basis of their common ancestry, function, and similar primary sequences. SGLT2, which is composed of 672 amino acids, bears 59% identity with the 664 amino acids that constitute SGLT1 (17). In general, cytoplasmic domains are better conserved than extracellular domains among SGLTs.

The members of the SGLT family share a common core of 13 transmembrane helices (TMH), although some members have one or two additional C-terminal helices. SGLT1 and SGLT2 both have 14 TMHs with both the hydrophobic N- and C-terminal domains lying extracellular (2). The SSSF consensus sequence $\text{[GSG]}-2(\text{H})-\text{L[LIY]}-\text{x}(\text{G})-\text{LIVMFYWSTAG}-7(\text{x})-\text{LIY}-\text{STAV}-8(\text{x})-\text{G}-\text{LMF}-\text{SAP}$ lies in TMH5. In addition, the smaller eukaryote SGLTs and SMIT subfamily members share an R-x-T-x(4)-F-L-A-G-x(4)-W-W-x(2)-G-A-S motif near the N-terminal domain, proximal in TMH2.

The crystal structure of vSGLT, a sodium-galactose symporter from Vibrio parahaemolyticus and a member of the SSSF, was reported recently (18). The protein assembles as a tightly packed parallel dimer, although previous work has shown that SGLT1 is fully functional as a monomer. The structural core is formed from inverted repeats of five TMHs (2 through 6 and 7 through 11; Figure 2A). Seven TMHs (2 through 4, 7 through 9, and 11) contribute to side-chain interaction for ligand selectivity. Extracellular and intracellular gates delineating the galactose pathway were identified, with residues M73, Y87, and F424 forming the extracellular and Y263, Y262, and W264 forming the intracellular ones. There is a plausible Na$^+$-binding site at the intersection of TMH2 and TMH9, approximately 10 Å away from the substrate-binding site. External Na$^+$ binds first, which facilitates TMH2 rearrangements to form the substrate-binding site. Galactose binding induces the formation of the extracellular gate and enlarges the intracellular cavity by conformational changes in TMH3, TMH4, TMH7 and 8, and TMH9 through 11. Finally, displacement of Y263 releases Na$^+$ and then galactose intracellularly (Figure 2B).

Other Functions of SGLTs

In addition to their role in sugar transport, SGLTs can function as uniporters. SGLT1, SGLT3, and SGLT5 transport Na$^+$ in the absence of sugar (19). SGLT3 functions as a glucose sensor in visceral neuronal cells (8). SGLT1 and other co-transporters have been shown to function as channels for water and other small hydrophilic solutes when expressed in oocytes (20,21) and are proposed to play an important role in fluid and urea transport across the intestine. SGLT1 has been shown to play a significant role in water transport across the intestinal brush border membrane by either co-transporting water along with Na$^+$ and glucose or by osmosis (20,22,23). SGLT1 does not simply mediate secondary active transport at the apical membrane of enterocytes itself but also regulates other glucose transport mechanisms, such as promoting insertion of GLUT2 into the apical membrane to provide a facilitative component of absorption up to three times greater than that of SGLT1 alone to match dietary intake of carbohydrates (24).

Regulation of SGLT2 Expression and Activity (in Diabetes)

It was previously shown that patients with type 1 diabetes had a significant increase in the renal transport maximum for glucose (25), and several rodent models of diabetes have shown upregulation of the GLUT2 protein in the renal proximal tubules of diabetic animals with long-term hyperglycemia, supporting the need for higher glucose efflux and glucose reabsorption (26,27). It is interesting that no changes in the SGLT1 protein expression were detected (27). Regarding SGLT2 ex-
pression, however, studies have been hampered by the lack of suitable antibodies.

Renal proximal cells isolated from the urine of patients with type 2 diabetes displayed an elevation of SGLT2 mRNA compared with healthy individuals (28), and in a rat model of diabetes, SGLT2 and hepatocyte nuclear factor 1α (HNF1α) mRNA expression was increased but reversed upon treatment with insulin or phlorizin, an inhibitor of SGLTs (29). Similar changes have been reported for GLUT2 in diabetic rats at day 6 of treatment with either insulin or phlorizin (30). HNF1α is a transcriptional activator encoded by the TCF1 gene, found to be mutated in maturity-onset diabetes of the young type 3 (MODY3), an autosomal dominant form of non–insulin-dependent diabetes (31). Defective renal glucose resorption in several families with MODY3, including in some euglycemic members, has been described (32,33). HNF1α−/− homozygous mice, compared with wild-type or heterozygous healthy littermates, displayed deficient insulin secretion and hyperglycemia (34); however, plasma glucose concentrations were lower than expected in light of the severity of the insulin secretory defect, probably secondary to the associated glucose resorption defect detected in these mice (33–35). SGLT2 expression has been shown in murine systems to be controlled by HNF1α, and HNF1α binding sites have been identified in the mouse SLC5A2 gene promoter (29,33); therefore, plasma glucose concentration seems to be an important modulator of SGLT2 activity, and this activity may be in part regulated by HNF1α expression.

Familial Renal Glucosuria

Glucosuria can occur in the setting of global dysfunction of the proximal tubule, known as the Fanconi-de Toni-Debré syndrome, or renal Fanconi syndrome. Glucosuria in this instance accompanies the excessive urinary excretion of amino acids, phosphate, bicarbonate, and other solutes that typically are reabsorbed in the proximal tubule. The occurrence of glucosuria in the absence of both generalized proximal tubular dys-function and hyperglycemia is known as renal glucosuria and recognized as an inherited disorder and hence the designation of familial renal glucosuria (FRG).

Diagnostic Criteria and Mode of Inheritance

Depending on the diagnostic criteria used, different prevalences and modes of inheritance were reported for FRG. Initial investigations used a nonquantitative assessment of glucosuria after an oral glucose tolerance test as a diagnostic technique (36). Under these circumstances, evidence emerged for an autosomal dominant inheritance. When later this technique was applied for screening purposes, an incidence of renal glucosuria in the general population of 0.29% was proposed (37). Marble in 1947 (38) defined more stringent diagnostic criteria, and the condition was reported to be autosomal recessive and uncommon. These revised criteria included a normal oral glucose tolerance test in regard to plasma glucose concentration, normal plasma levels of insulin, free fatty acids, glycosylated hemoglobin, and relatively stable urinary glucose levels (10 to 100 g/d; except during pregnancy, when it may increase) with glucose present in all urine samples. Urine should contain glucose as the only source of carbohydrate, and individuals should have normal carbohydrate storage and use (38). By the mid-1950s, renal titration studies delineated renal glucosurias into type A and type B (39). Patients with type A renal glucosuria are characterized by a low renal threshold for glucose and a low maximum tubular glucose reabsorption in contrast to individuals with FRG type B, who have a low threshold but still can reach a normal maximum tubular glucose reabsorption, causing an abnormal splay of their filtration-resorption curve (Figure 3). Later, the complete absence of renal glucose transport was found in very few individuals and designated as type O glucosuria (40). Glucose quantification in the collected urine 2 to 4 h after a glucose load of 50 g in three pedigrees gave the first insight that the mode of inheritance for FRG could be one of co-dominance: Individuals supposed to be homozygous for the condition had persistent heavy glucosuria and experienced “renal glucosuria,” whereas putative heterozygotes had mild (or no glucosuria) and had only the “renal glucosuria trait” (41). Elsas and Rosenberg (42) reported that both type A and type B renal glucosuria could be observed in the same family and that both parents could be completely normal or show an abnormality in renal tubular glucose transport. They postulated that this could be due to the variable expression of a dominant mutation or, alternatively, that two different genes could be involved: A mutant B gene that leads to decreased affinity of a glucose transporter for glucose and a mutant A gene that leads to reduced transport capacity.

Characterization of FRG into types A/B/O is presented here mainly for historical reasons. Current molecular findings have enabled appropriate genotype–phenotype correlations in the vast majority of cases and, consequently, a simpler and easier classification in FRG.

Molecular Genetics

Since SLC5A2 was cloned and the delineation of the major renal resorptive mechanism for glucose made apparent, this

![Figure 3. Correlation between glomerular glucose load and tubular glucose reabsorption (TG) in various renal glucosurias. TmG, maximum tubular glucose reabsorption; PG, plasma glucose concentration. The hatched area is the splay—the difference between actual and ideal reabsorption that is exhibited when the reabsorption curve shows a nonlinear transition as the TmG is reached. Redrawn from reference (72), with permission.](Image 314x150 to 554x287)
transporter was implicated as a major candidate gene for FRG (7). The first mutation in the SLC5A2 gene, positioned in 16p11.2, was reported by Santer et al. (43), and more case series have confirmed that mutations in SLC5A2 are indeed responsible for the large majority of cases of FRG (44–46). Additional support has come from several case reports (47–51).

Although the pattern of inheritance that best fits FRG is one of co-dominance, surprisingly, increased glucose excretion was not observed in all individuals with similar or identical mutations, heterozygosity for mutations in particular, suggesting a role of nongenetic factors or other genes in renal glucose transport. Furthermore, in only a few patients with FRG does the renal excretion approach the filtered load (e.g., in the original patient with familial renal glucosuria type O and homozygosity for a premature stop codon [347X]); however, other patients with truncating mutations (e.g., p.W440X) were found to excrete only approximately half the filtered load. This again suggests that other transporters under certain circumstances may reabsorb a significant amount of glucose in these patients. In particular, other SGLTs that are known to be expressed in the kidney and whose functions have not yet been clarified are candidates for modifier genes in FRG. At least three patients have been reported not to have any mutation identified after sequencing of the entire coding region of SLC5A2 (44,45), which also raises the possibility of genetic heterogeneity. Indeed, a locus on chromosome 6, in close genetic linkage with the HLA complex, has been positioned and named GLYS1 on the basis of segregation analysis in five unrelated affected pedigrees (52); however, this hypothetical gene remains to be cloned. Alternatively, mutations in the promoter region or heterozygosity for large deletions that are not detectable by PCR may also account for those findings.

Analysis of the genomic structure of human SGLT2 revealed a 14-exon gene that spans 8 kb with an intron-exon organization that is similar to SGLT1 (44). All of the introns display the donor and acceptor splice consensus sequences GT/AG, and a previously unreported CA repeat was identified in intron 1. The 2019-bp coding sequence accurately predicts the 672-residue SGLT2 protein previously reported after cloning of SGLT2 from a human kidney cDNA library (17). There are no reports of splice variants or isoforms.

**Genotype–Phenotype Correlations in FRG**

Establishing definite genotype-phenotype correlations in FRG is a difficult task because of the variable expressivity and because other genes may have an impact on overall renal glucose resorption. In general, patients with mild glucosuria (<10 g/1.73 m² per d) will usually be heterozygous for SGLT2 mutations, both nonsense and missense, although, as previously stated, this may not happen in all carriers of such mutations. Cases of severe glucosuria (≥10 g/1.73 m² per d) show the characteristics of autosomal recessive inheritance with homozygosity or compound heterozygosity for SGLT2 mutations (44–46).

Forty-four different mutations, scattered throughout the SLC5A2 gene, have been reported, with most being private (46) (Figure 4). Among them are missense and nonsense mutations, small deletions (in-frame and frame shift), and splicing mutations. IVS7 + 5G may be considered a mutational hot spot because of the recurrent finding of the IVS7 + 5G→A allele in several unrelated families who have FRG and are of different ethnic origin (44,46).

Molecular analysis may also be helpful in understanding the findings of earlier titration studies. Haploinsufficiency will result in a reduced number of normally functioning carriers in the renal tubule, thereby leading to type A glucosuria, whereas certain missense mutations might decrease SGLT2 affinity for glucose and patients will display type B glucosuria (44). Compound heterozygosity for SGLT2 mutations, however, is probably the reason that many past cases of severe glucosuria could

![Figure 4](image-url): Mutation analysis of the human Na⁺/glucose co-transporter gene SLC5A2 that encodes SGLT2. Transmembrane domains 1 through 14 are shown as dark gray boxes. Redrawn from reference (46), with permission.
not be clearly classified into type A or B and that a broad spectrum of impaired tubular glucose transport has been found in those patients. We therefore propose that individuals with FRG be characterized according to the amount of glucose excreted in a 24-h urine collection, normalized for body surface: Mild renal glucosuria for <$10 g/1.73 m² per d and severe renal glucosuria for $10 g/1.73 m² per d.

**Clinical Consequences of FRG**

Overall, patients with renal glucosuria have not been shown to be affected by severe clinical consequences, and this entity is considered a benign condition, more a phenotype than a disease. For example, polyuria and enuresis and later a mild growth and pubertal maturation delay were the only manifestations observed during a follow-up period of 30 yr (53). Several other manifestations have occasionally been reported in severe forms of FRG, such as episodic dehydration and ketosis during pregnancy and starvation (40), the presence of several autoantibodies without clinical evidence of autoimmune disease (54), or an increased incidence of urinary tract infections (54, 55). Activation of the renin-angiotensin-aldosterone system, secondary to natriuresis and possible extracellular volume depletion, has also been observed (45, 46).

Hypercalciuria was identified as an accompanying feature in five of seven male children with renal glucosuria in one study (56), and in one patient who displayed severe renal glucosuria, an elevated calcium/creatinine ratio on spot urine was also described (53). The reason for this finding remains unknown.

There are several case reports of selective aminoaciduria associated with renal glucosuria, involving aspartic acid in one; glutamic acid, citrulline, and alanine in another; and arginine, carnosine, and taurine in yet another patient (57, 58). Six children who had glucosuria, were from three pedigrees, and were homozygous for the novel SGLT2 p.K321R mutation were shown to have generalized aminoaciduria not accompanied by any other proximal tubular transport abnormalities (51). It was postulated that aminoaciduria could be secondary to glucosuria and not a primary effect of the SGLT2 mutation. Indeed, aminoaciduria has been found not only in MODY3 but also in types 1 and 2 diabetes, where it correlated positively with the amount of glucosuria (59). The proposed mechanism is that glucosuria is causing depolarization and dissipation of the electric gradient of sodium-dependent amino acid transporters in the proximal renal tubule.

**SGLT2 Inhibition: A New Option for the Treatment of Type 2 Diabetes**

Type 2 diabetes is characterized by hyperglycemia that results both from peripheral resistance to the action of insulin and from progressive failure of pancreatic β cell function (60). Chronic hyperglycemia of diabetes can lead to microvascular and macrovascular complications and also contributes, by means of glucotoxicity, to β cell dysfunction and insulin resistance, which aggravates the disease process (61). A novel strategy to reduce hyperglycemia is to target renal glucose excretion by inhibiting SGLT2. Evidence for such a beneficial effect comes not only from patients with FRG but also from studies of phlorizin, a natural product isolated from the root bark of the apple tree and known since the 19th century to cause glucosuria. When phlorizin was administered to partially pancreatectomized rats, the hyperglycemia was corrected without changing insulin levels, and both insulin sensitivity (62) and insulin secretion (63) were restored to normal. This provided the first evidence that hyperglycemia per se can lead to the development of insulin resistance. Despite demonstrating utility as an antihyperglycemic agent in several rodent models of diabetes, phlorizin was discontinued because it was readily hydrolyzed and poorly absorbed by the intestine, and it inhibited SGLT1 equally as well as SGLT2 (64). Furthermore, its active metabolite, phloretin, inhibits nonspecifically other glucose transporters.

Several selective inhibitors of SGLT2 have been developed to overcome the disadvantages of phlorizin. In a variety of animal models, they have been shown to induce glucosuria, lower blood glucose without altering insulin levels, improve insulin sensitivity, and reduce hepatic glucose output (65–69). Some are now under evaluation in clinical trials, and published data are available for dapagliflozin, which is 1200-fold more selective for SGLT2 than SGLT1. When administered for 14 d to drug-naïve or metformin-treated patients with type 2 diabetes, dapagliflozin induced a dosage-dependent increase in urinary glucose excretion, reaching a maximum of 70 g/d, and improved fasting blood glucose and glucose tolerance (70). In a more prolonged study, a total of 348 drug-naïve patients with type 2 diabetes were randomly assigned to receive 2.5, 5.0, 10.0, 20.0, or 50.0 mg of dapagliflozin; 1.5 g of metformin; or placebo (71). Significant reduction of glycosylated hemoglobin, fasting plasma glucose, and body weight had occurred by the end of the study. The compound was found to have a mild diuretic effect with a decrease in systolic BP. In the short-duration treatment trial with dapagliflozin previously reported, an increase in urinary sodium was initially observed, returning to baseline by day 13 (70). In the pilot study that enrolled 348 patients with type 2 diabetes, it was shown that dapagliflozin displayed a dosage-dependent mild diuretic effect as assessed by daily urine output (71). Unfortunately, urinary sodium was not reported, so we can only speculate whether this diuretic effect was a consequence of glucosuric osmosis or, alternatively, dependent of true natriuresis reflecting the failure of the distal nephron to compensate for the Na⁺ proximal losses. In any circumstance, no changes in serum sodium (namely hypernatremia) were reported, leading to the impression that the increase in free water clearance is clinically irrelevant.

In addition, treated patients experienced sustained weight loss. Hypoglycemic episodes were similar when compared with the metformin-treated group, but the incidence of genital infections was higher.

Of note, both studies with dapagliflozin reported incomplete inhibition of SGLT2 with lower levels of glucosuria than in the most severe forms of FRG. It is possible that the accumulating tubular glucose competes with dapagliflozin for SGLT2 binding, thereby limiting the degree of inhibition.

Inhibition of renal glucose absorption may provide several advantages in the treatment of patients with type 2 diabetes.
Unlike antidiabetic drugs that cause weight gain, the daily caloric loss of 100 to 300 kcal associated with SGLT2 inhibition may help patients actually to lose weight. They can also be expected to have a lower risk for developing hypoglycemia, an adverse effect often seen with insulin or insulin secretagogues. The mild diuretic effect observed may make SGLT2 inhibitors the preferred class of drugs to be used in conjunction with thiazolidinediones, which have been shown to cause fluid retention, especially in the presence of heart failure. Finally, the diuretic effect may contribute to BP control. Inhibition of SGLT2 is anticipated to be safe and free of undue consequences for patients, at least from chronic glucosuria. This can be deduced from the observation of patients who have FRG and in whom naturally occurring mutations of SGLT2 manifest as a mostly benign disorder.

Conclusions
Familial renal glucosuria is currently accepted to be a benign hereditary condition that, in the majority of cases, does not pose serious physical/clinical consequences to affected individuals. Mutations in SLC5A2 (the SGLT2-coding gene) underlie most, if not all, cases of FRG. Inherited as a co-dominant entity, there is, however, variable expressivity. Even in its infrequent severe forms, characterized by complete absence of tubular glucose resorption, clinical manifestations are rare. On the basis of these observations and ongoing clinical studies, inhibition of SGLT2 may be a feasible way to treat patients with type 2 diabetes.

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