As we sit down to write this Editorial, the last issue of the Journal of the American Society of Nephrology stands in front of us. Its cover displays an add that publicizes canagliflozin, the first SGLT2i (Sodium GLucose Tранsporter 2 Inhibitor) approved, earlier this year, by the U.S. Food and Drug Administration (FDA) for the treatment of Type 2 Diabetes Mellitus (T2DM). This follows last year approval by the European Medicines Agency (EMA) of the first compound of its class, dapagliflozin. More than a century has elapsed since the original description of glucosuria induced by phlorizin, the parental compound from which all SGLT2i got their inspiration. During this period many insights on the homeostasis of sodium and glucose were unravelled. These two solutes are crucial for the survival of all organisms, higher vertebrates in particular, which have developed elaborate pathways to preserve them.

However, in face of the high caloric and salt content of western diets, these phylogenetically conserved pathways have now turned against us and we try desperately to overrun them. They have become “therapeutic targets”. The story behind SGLT2 inhibition is not only the story of sodium and glucose conservation by complex organisms, but also, and for the interested nephrologist, on how the proximal tubule supports and integrates the “functioning logic of the kidney”.

GLUCOSE TRANSPORT

Glucose is an apolar molecule that diffuses poorly across cellular membranes. Two distinct families of glucose transporters are in place to do the job: the ubiquitous GLUT (GLUcose Tранsporter) transporter family that ensures glucose transport according to its concentration gradient, and the SGLT co-transporter family. It is crucial whenever glucose needs to be reabsorbed by epithelial cells from the luminal side of the gastrointestinal tract and renal proximal tubule against its concentration gradient. The SGLTs are encoded by the SLC5 genes, a family that encompasses > 200 members, 13 alone in the human genome. The SGLT1 was cloned, back in 1987, by Ernest Wright’s group, at the UCLA1. In fact, most of the seminar work on SGLTs has been fostered by his team, including the recent solving of the crystal structure of SGLT2. We strongly recommend to our readers a recently published review on the subject by this author3 who, in addition, was the recipient of last year’s ASN Homer W. Smith award.

É um anti-hiperglicémico... É um diurético... É a inibição SGLT2!
MOLECULAR GENETICS OF SGLTS ASSOCIATED PHENOTYPES

Mutations in SLC5A1, encoding SGLT1, are responsible for the Glucose-Galactose Malabsorption syndrome, characterized by watery diarrhoea, upon the introduction of galactose, glucose or lactose in the diet of newborns, in accordance to SGLT1 major expression in the intestine. Although SGLT1 has a limited expression in the late (S3 – medullary) proximal tubule, it is SGLT2 that is predominantly expressed in the kidney and at the early proximal (S1) segment. Therefore, the SGLT2 coding gene, SLC5A2, has always been considered a natural candidate gene for Familial Renal Glucosuria (FRG), a renal phenotype displaying selective glucosuria in the absence of diabetes. Since the original description of SLC5A2 mutations in FRG, we and others have published and characterized several FRG cohorts (reviewed in 6). The distinct tubular sequential expression and transport kinetics of SGLT2 and SGLT1 act in concert to reabsorb all the glucose from the tubular lumen, so that no glucose will appear in the final urine. The bulk of the filtered glucose is reabsorbed in the early S1 segment by the high capacity but low-affinity SGLT2, while the remaining glucose that “escapes” SGLT2, will face SGLT1 in the later segments of the proximal tubule that, although having a lower capacity for glucose transport compared to SGLT2, displays a far more greater affinity for the ligand. Finally, the ubiquitous GLUT2 and GLUT1, ensure the efflux of glucose from the baso-lateral side of the epithelial cell into the systemic circulation.

TARGETING URINARY GLUCOSE EXCRETION IN T2DM

In diabetes, there is a paradoxical increase in the renal tubular reabsorption for glucose. Both the maximal transport and the renal threshold for glucose are found to be increased in diabetic individuals. In addition, T2DM is associated with an increase in renal neoglucogenesis, particularly in the post-prandial state. So, all of these pathways perpetuate hyperglycaemia in diabetes and account for the hypertrophy of the proximal tubule seen in the diabetic kidney. This increase in glucose reabsorption by the hypertrophic diabetic proximal tubule may also interfere with the tubuloglomerular feedback (TGFb) mechanism, by decreasing the amount of solutes (sodium in particular) that is being sensed by the macula densa, derepressing the TGFb and inducing glomerular hyperfiltration, a sine qua non condition for the development of the diabetic nephropathy.

Inducing urinary glucose excretion (UGE) is, therefore, an appealing and novel strategy for the treatment of T2DM.

SGLT2 INHIBITORS

Phlorizin, a natural product isolated from the root bark of the apple tree, and known since the 19th century to cause glucosuria, has been characterized as a β-D-glucoside (Fig. 1). It is comprised of a single glucose moiety and an aglycone in which two aromatic carbocycles are joined by an alky spacer. When phlorizin was subcutaneously administered to partially pancreatectomized rats, the hyperglycaemia was corrected without changing insulin levels, and both insulin sensitivity and insulin secretion were restored to normal. Despite demonstrating utility as an anti-hyperglycaemic agent in several rodent models of diabetes, phlorizin was discontinued. Being an O-glucoside, it was particularly susceptible to intestinal and liver β-glucosidases. In addition, it inhibited SGLT1 equally as well as SGLT2. Furthermore, its active metabolite, phloretin, inhibits non-specifically other glucose transporters.

Structure-activity relationship analysis allowed modification of the original compound, with the

![Figure 1](image-url)
development of new C-glucosides resistant to β-glucosidases (enabling oral administration) and subsequent modifications of the aglycone moiety (having higher affinity for SGLT2), leading to the discovery of dapagliflozin\textsuperscript{11}, emapagliflozin\textsuperscript{12} and canagliflozin\textsuperscript{13}, the first three SGLT2i expected to reach the market.

Finally, the finding that FRG, an essentially benign phenotype, could work as a safety model for the chronic pharmacological inhibition of SGLT2\textsubscript{z}, provided the adequate leverage for the final development of these compounds by the pharmaceutical industry.

\section*{CLINICAL TRIALS: BENEFITS AND PITFALLS OF SGLT2I}

Past the rationale of the pre-clinical development, there is now relevant published data on clinical efficacy and safety profiles for SGLT2 pharmacological inhibition. Being UGE an insulin independent mechanism, SGLT2i were found to be useful anti-hyperglycaemic drugs, either alone or in combination with other oral agents and insulin, not associated with hypoglycaemia. The level of haemoglobin A1c (A1c) reduction is dependent on dosing as well on the pre-treatment level. It ranged from -0.7\% to -0.9\% (absolute value) in naïve patients in monotherapy\textsuperscript{14} up to -2.6\% in T2DM individuals with inadequate glycaemic control having a pre-treatment level of A1c of 10-12\%\textsuperscript{15}. It is beyond the scope of this editorial to review the clinical research programme for the several SGLT2i available. Still, a few important features ought to be highlighted. These compounds are indeed true “calorieuretics”, in the sense that an UGE of ~70 g/day (the range usually observed in clinical trials) will lead to a caloric loss of 280 kcal. Weight loss is a unique and important characteristic of these compounds, and it can reach 3 kg by the end of the treatment period. An additional observation with SGLT2i, and one that we had already anticipated from our studies on FRG pedigrees, is the diuretic effect\textsuperscript{16}. Urinary osmol losses include both glucose and, most importantly, sodium. This certainly provides the basis for the anti-hypertensive effect observed with SGLT2i and is probably responsible for the good cardiovascular profile reported for this class.

The SGLT2i are generally well tolerated. Genital (mycotic) tract infections is one of the most common adverse event (AE) seen with these drugs, affecting ~13\% of treated individuals. Usually not severe and easily treated, they should not be a reason for treatment discontinuation.

The UGE is critically, and equally, dependent on both the plasma glucose concentration and the glomerular filtration rate (GFR). As expected, Chronic Kidney Disease (CKD) will lead to a decrease in SGLT2i efficacy. This was ascertained in several clinical trials involving CKD stage 3 (moderate renal impairment) patients, that also reported more AEs compared to placebo, including decreases in estimated GFR\textsuperscript{17-19}. Interestingly, even with CKD, blood pressure control with these compounds was still optimal, reinforcing the idea that they are indeed diuretics.

\section*{PENDING ISSUES AND UNSOLVED QUESTIONS}

In January 2012, the FDA voted against the approval of dapagliflozin until more data was provided, based on “imbalances in small numbers of 2 types of malignancies”... “breast and bladder cancers” between dapagliflozin treated and controls\textsuperscript{20}. The Advisory Committee also wrote that “Overall, the available data suggest that the likelihood of a causal association between dapagliflozin and bladder cancer is small.” This was a surprise for the diabetic community, in desperate need of novel strategies for the treatment of T2DM. Much has been written about the subject, and several reasons for this imbalance have been proposed – from recruitment bias to urine scrutiny (at least for bladder cancer). Some of us argued for the implausibility of the association – not only SGLT2 is exclusively expressed in the renal proximal tubule (no room for pleiotropy), but also the fact cancers were diagnosed too early in the treatment period (sometimes within the first month). Significantly, these “imbalances” seen with the first of its class, did not prevent the FDA from approving canagliflozin or EMA, dapagliflozin itself.

More appealing for the nephrologist with a special interest in renal physiology, is the finding of an almost dose dependency reduction in serum uric acid levels seen with SGLT2i, which is surprising in light of the associated diuretic effect of the compound. Also puzzling, are the reported increments in phosphate and parathyroid hormone serum levels,
even in non-CKD populations, and the risk of non-osteoporotic fractures in CKD stage 3. Let us not forget that urate (by means of URAT1 and GLUT9) and phosphate (via NaPi-IIa and NaPi-IIc) are reabsorbed from the luminal side at the proximal tubule, and that 1α-hydroxylation of the 25-OH-vitamin D3 also occurs in this nephron segment.

It is a misfortune that so many insights into the function of the proximal tubule are to be gained from a class of compounds nephrologists will seldom use; and then again, it may turn out that we, the nephrology community, may well find novel and ingenious uses for SGLT2 inhibition.

Conflict of interest: None declared.

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