Sodium–glucose transporter-2 inhibition as an antidiabetic therapy

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Sodium–glucose transporters (SGLT) are a family of transmembrane proteins—coded by the SLC5 gene—specialized in the cotransport of sodium and glucose across different cell types. Of the six isoforms so far identified, SGLT-2 is preferentially, though not exclusively, expressed in the brush-border membrane of proximal renal tubular cells in the S1 segment, while SGLT-1 is highly expressed in enterocytes and is also present in the S2/S3 segment of the proximal renal tubule. Unlike SGLT-1, which has high affinity for glucose ($K_m = 0.4$ mM), SGLT-2 is a low-affinity ($K_m = 2$ mM), high-capacity transporter, which transfers glucose and sodium (in a 1:2 molar ratio) from the lumen into the cytoplasm of tubular cells. At the basolateral membrane, a glucose transporter of a different family, GLUT-2, effects transfer of intracellular glucose to the interstitium by a facilitated transport process (via a Na/K ATPase) [1].

Tubular glucose reabsorption is a very efficient process. For a glomerular filtration rate of 180 L/day and at an average, around-the-clock plasma glucose concentration of 5.6 mmol/L, the filtered glucose load is 180 g/day, of which only little is eventually excreted (i.e. a renal glucose clearance in the order of 70–350 $\mu$L/min) [2]. As the transport maximum for glucose ($T_m_G$) is exceeded, progressively greater fractions of the filtered load spill over into the urine. This occurs with quasi-threshold kinetics due to a significant splay of the plasma glucose concentrations at which $T_m_G$ is surpassed; heterogeneity of nephrons is thought to be the basis for this phenomenon [3].

Glycosuria is at the same time a classical manifestation of diabetic hyperglycaemia and a mechanism of disposal of excess circulating glucose, a defence that is lost as renal insufficiency ensues. Early clinical studies in patients with type 2 diabetes showed that the $T_m_G$ is increased by 20–40% (from 350 up to 450 mg/min) in comparison with non-diabetic subjects [4]. The same finding has been reported in patients with type 1 diabetes [5]. More recent studies in cultured human renal tubular cells harvested from the urine of diabetic patients have shown that the expression of SGLT-2, its protein concentration and its $\alpha$-methyl-glucose transport capacity all increased markedly in comparison to non-diabetic subjects [6]. Thus, whether an intrinsic defect of diabetes or a result of chronic hyperglycaemia, renal glucose reabsorption is increased in diabetes. In contrast, familial renal glycosuria is a rare disorder caused by private missense or nonsense mutations and deletions in the SLC5 gene. Affected patients excrete between 1 and 170 g/day of glucose in the urine according to whether they are homozygous, heterozygous or compound heterozygous [7]. The condition is surprisingly benign, as these patients do not develop renal disease even in the long term and are not reported to be prone to, and may in fact be protected against, diabetes and obesity.

This experiment of nature has given rise to the postulate that lowering hyperglycaemia through enhanced renal glucose excretion may correct the pathophysiological abnormalities of diabetes, namely the insulin resistance of target tissues and the inability of the $\beta$-cell to cope with rising glucose levels with a robust and timely release of insulin. A series of elegant in vivo experiments in 90% pancreatectomized rats [8] showed that the peripheral and hepatic insulin resistance and the $\beta$-cell defect that these animals develop could be fully reversed by the administration of phlorizin, a non-specific inhibitor of SGLT-2; the effects of the drug were abolished upon its withdrawal. Since then, the concept of glucotoxicity, i.e. a specific role of high plasma glucose levels per se, not just in end-organ damage but also in glucose homeostasis, has gained both evidence and favour. In the liver, glucose toxicity manifests itself as an upregulation of gluconeogenic glucose synthesis by activation of key enzymes, such as phosphoenolpyruvate-carboxykinase and glucose-6-phosphatase [9]; in muscle and fat, chronically elevated glucose downregulates insulin signalling and GLUT-4 translocation [10]; in $\beta$-cells, even short-term, mild hyperglycaemia can impair glucose sensitivity [11]. The expectation, therefore, has been that lowering glycaemia by an insulin-independent mechanism—such as increased glycosuria—may reverse all manifestations of glucose toxicity.

As phlorizin is not absorbed by the gut, is non-specific and of undetermined toxicity, orally active small mole-
circumstances, turn out to be maladaptive rather than just compensatory. Nevertheless, the lack of hypoglycaemia is an important attribute for an antidiabetic drug. In addition, the nature of the signal(s) that inform the liver of the renal glucose leak represents a challenging physiological research theme. Finally, the loss of 30–80 g of glucose through the urine translates into the loss of 120–320 kcal (500–1300 kJ) over 24 h. If sustained, this caloric deficit would result in the loss of 6–16 kg in a year. Though weight loss is the therapeutic holy grail in the predominantly obese diabetic population (and, \textit{a fortiori}, in non-diabetic obese people), glycosuria—hence calorie loss—is expected to decrease as hyperglycaemia is corrected. Moreover, reactive enhancement of appetite and calorie intake may curtail actual weight loss.

Initial trial experience in patients with type 2 diabetes—as add-on to metformin or insulin [13,14] or in monotherapy [15]—has confirmed that SGLT-2 inhibition is associated with dose-proportional decrements in Hba1C and modest weight loss (1–3 kg over 24 weeks). In patients with poorly controlled diabetes (Hba1C > 10%), active treatment potently lowers Hba1C (by 2.5–3.5%) [15], while in the range of habitual Hba1C levels the efficacy of SGLT-2 inhibition appears to be similar to that of dipeptidylpeptidase-IV inhibitors or average doses of metformin. While neutral on the serum lipid profile, SGLT-2 inhibition consistently decreases both systolic and diastolic blood pressure (2–5/2–3 mmHg being the placebo-corrected average across different doses). This effect is welcome in the diabetic population in which hypertension is the most frequent comorbidity and often has a volume-dependent quality [16]. In addition to the weight loss, the inhibition of proximal sodium reabsorption may itself be a mechanism of blood pressure lowering. In fact, the inhibition of sodium-coupled uric acid reabsorption in the proximal renal tubule may be responsible for the consistent decrease in serum uric acid concentrations observed in the clinical trials [13–15]. Interestingly, these consequences of SGLT-2 inhibition directly oppose the antinatriuretic and anti-uricosuric effect of insulin [17] as well as its action to acutely raise pulse pressure [18]. Like insulin, however, SGLT-2 inhibitors do not cause significant changes in serum electrolytes. Also of interest, and somewhat unexpected, is the finding that following SGLT-2 inhibition urinary volume is increased by only 200–400 mL/day and haematocrit by 1–3%. Thus, the notion that glucose-induced diuresis should lead to dehydration, haemoconcentration and electrolyte waste is not borne out by the clinical experience so far reported with SGLT-2 inhibitors (and is not a feature of familial renal glycosuria [7]). Furthermore, no evidence of systematic changes in blood urea nitrogen or serum creatinine and cystatin C concentrations has emerged. All in all, the picture emerging from the renal effects of SGLT-2 inhibitors is compatible with that of a proximal tubule diuretic.

The prolonged excretion of urine with high sugar concentrations is classically reputed to be a risk factor for the development of genito-urinary infections. So far, an approximate doubling of episodes of vulvo-vaginitis and balanitis has been reported [13–15], while it is less clear whether urinary tract infections are also increased in frequency or severity. Close monitoring and management of

![Scheme of normal renal glucose handling, with reabsorption (in green) being complete, and excretion nil (in blue), up to a splayed threshold of plasma glucose concentration. The dotted red line and the underlying shaded area represent the hypothetical displacement of the excretion function when glucose reabsorption is reduced by SGLT-2 inhibition.](https://academic.oup.com/ndt/article-abstract/25/7/2041/1873953)
these adverse events is mandatory if this class of drugs is ever to make it to the marketplace. Clinical development will have to include testing SGLT2 inhibitors in diabetic patients with impaired renal function and/or microalbuminuria, who are at enhanced risk of cardiovascular disease [19]. In these patients, SGLT2 inhibition-induced glycosuria is expected to be reduced in some proportion to the reduction in glomerular filtration rate; improved weight and blood pressure control, however, may still offer a favourable therapeutical balance. In any event, the progression of renal dysfunction will have to be carefully monitored to rule out renal toxicity with chronic SGLT2 inhibition.

Conflict of interest statement. None declared.

References


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