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Invited Review

Sodium glucose cotransporters inhibitors in type 1 diabetes

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ABSTRACT

Sodium glucose cotransporter inhibitors (SGLTi) are oral hypoglycemic drugs that reduce renal glucose re-uptake and induce glycosuria. SGLTi have been successfully tested in large randomized clinical trials for type 2 diabetes, and several molecules have been approved in this setting by the international pharmaceutical agencies. Additionally, recent evidence has shown that SGLTi may be useful also in type 1 diabetes (T1D). Indeed, these drugs can be used as an ancillary to insulin to improve glycemic control and reduce insulin dosage, and such regimens have been associated with a lower rate of hypoglycemic episodes. The pharmacological effects of SGLTi therapy are described herein, and we also discuss the future use of SGLTi in T1D.

1. Introduction

Since the discovery of insulin, the life expectancy of patients affected by type 1 diabetes (T1D) has increased from only a few years from diagnosis to currently just 10–12 years less than the general population [1,2]. However, despite the continuous improvement of insulin regimens, less than one-third of T1D patients reach optimal glycemic control, and some degree of insulin resistance is common after prolonged therapy [3,4]. Immunotherapy has been tested to avoid β-cell destruction but is often associated with poor outcomes, with the exception of hematopoietic stem cell therapy [5–9]. As a consequence, longstanding T1D patients are exposed to increasing doses of insulin and are more likely to develop insulin-related complications. Ideally, an insulin ancillary drug could improve glycemic control, thus enhancing insulin sensitivity and counteracting insulin adverse events with minimal additional risks. Moreover, as T1D patients are usually subjected to 4 daily injections and finger-stick capillary blood glucose monitoring, an oral drug may be a preferable option. In the last decade, several new therapies have been approved for type 2 diabetes (T2D). In particular, sodium glucose co-transport inhibitors (SGLTi or Gliflozins) have been successfully combined with different insulin regimens in large clinical trials, often with limited adverse events [10]. Following these encouraging results, the first T1D studies have been published and have demonstrated that SGLTi are endowed with most of the aforementioned characteristics of the ideal T1D ancillary therapy [3,11]. The aim of this review is to describe the clinical and pharmacological effects of SGLTi therapy and to discuss the potential future use of Gliflozins in T1D.

2. SGLT and SGLTi

Sodium glucose co-transporters (SGLT) are six proteins belonging to subgroup 5A of the solute carrier family (SCL5A). Unlike glucose transporters (GLUT), SGLT are active carriers due to the fact that they exploit the transmembrane sodium gradient; thus, they can take up glucose even at near-null concentrations. According to different nomenclatures, they are identified as SGLT1-6 or SCL5A1, 2, 4, 9 10 and 11, respectively [12]. These six transporters have distinctive affinities, capacities and specificities for glucose, and most can take up other molecules such as fructose, galactose, mannose, vitamins or inositol. It is believed that SGLT3 is not a transporter but rather a glucose sensor [12]. SGLT1 is a high affinity transporter expressed on the luminal surface of the small intestine and in the distal segments of the proximal kidney tubule; it is responsible for post-prandial glucose uptake and for a small amount of renal glucose handling [12]. SGLT2 is a high capacity transporter that is expressed almost exclusively by the proximal kidney tubular cells and that mediates 90% of renal glucose re-absorption [13]. Of interest, glycosuria is the primary inducer of renal SGLT1 and 2

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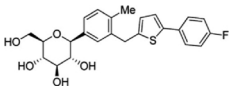
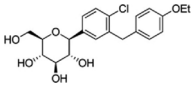
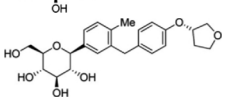
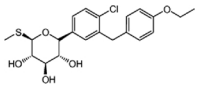
expression, as demonstrated by the high transporter concentration observed in kidneys from diabetic subjects [14]. Consequently, in diabetic patients, increased glucose uptake induces tubular protein glycation and oxidation, lipid accumulation and cell phenotypic alterations, with cytokine production and expression of leukocyte-recruiting adhesion molecules [15]. These findings are consistent with the increasing body of literature investigating the inflammatory basis of diabetic kidney disease (DKD) [16]. Indeed, recent publications demonstrate that glycemic stress in DKD induces overexpression of local (IL-8, IL-8 receptors, B7.1) and systemic (CRP, TNF, soluble TNF receptor-1) markers of inflammation [17–20]. Moreover, SGLT hyperexpression also subverts renal sodium handling; enhanced proximal sodium reabsorption directly increases volemia and causes low delivery to the distal tubule, thus triggering tubuloglomerular feedback and promoting glomerular hypertension.

Phlorizin, the first-discovered SGLTi, was isolated in 1835 from the root bark of the apple tree [21]. Since the late 19th century, this molecule has been known to induce glycosuria, and experimental evidence supported its positive effect on insulin sensitivity in the 1950s [22]. This drug is composed of a glucose molecule (which binds SGLT) connected to a bicyclic flavonoid (the inhibitory domain) through a C-glycosidic bond [23]. Phlorizin is highly effective as an SGLT1 and −2 inhibitor, and results in glycosuria and reduced intestinal glucose absorption. Oral bioavailability of the drug is compromised, however, due to cleavage of the C-glycosidic bond by intestinal bacteria. In the 1990s, synthesis of new polycyclic O-glycosidic molecules resulted in improved bioavailability and selectivity for SGLT2. Selective SGLT1 inhibitors also have been developed [24] but are not approved for human use; however, recent publications demonstrated that combined SGLT1/2 inhibition could be beneficial, primarily in T1D patients [11]. Currently, the Food and Drug Administration has approved 3 selective SGLT2 inhibitors for T2D therapy: Cangliflozin, Dapagliflozin and Empagliflozin; in parallel, the mixed SGLT1/2 inhibitor Sotagliflozin has been tested in two T1D trials (Table 1).

3. SGLTi effects

The primary consequence of Gliflozin therapy is the development of glycosuria, which is determined only by glycemia and glomerular filtration rate (GFR). In healthy subjects, the daily glomerular filtration of glucose is approximately 160 g (90 mg/dL of glycemia x 180L/day of GFR), and glycosuria is absent. In these conditions, high doses of SGLT2 inhibitors can cause 60–80 g/day of urinary glucose loss [25,26]. In diabetic patients, glucose excretion induced by SGLT2i is highly variable and can be over 100 g/day (i.e. 400 kCal/day) [27]. This relatively modest difference between healthy and diabetic subjects is due to the enhanced expression of both SGLT2 and −1 in diabetes and, possibly, to boosted para-cellular glucose transport [27]. Of note, this sole pharmacodynamical mechanism is responsible for a large number of indirect metabolic and non-metabolic systemic effects: (i) *Glycemic control*: As a consequence of SGLTi therapy, glucose disposal is continuous and proportional to glycemia [27]. Consequently, these drugs not only reduce mean glycemia and glycated hemoglobin but also glycemic variability with minimal risk of hypoglycemia. Of interest, in T2D, SGLT2i have been associated with better glycemic outcomes than most comparable drugs [28,29]. A possible exception is metformin, which was equal to SGLT2i in most trials and less effective in one study [30,31]. *(ii) Lipids*: The daily caloric wasting and lowered glycemia associated with SGLT inhibition significantly reduce triglyceride levels; the relevance of this improvement was queried by a recent meta-analysis that found an average decrease of 2 mg/dl [32]. Moreover, SGLTi have been associated with a slight but significant increase in both LDL and HDL. The clinical impact of LDL increase is unclear [33]. *(iii) Uric acid:* Several studies have demonstrated a reduction in uric acid levels in SGLTi-treated patients. This effect could be related to an overall improved metabolism. Moreover, by using the glycemic clamp technique, Lytvyn and colleagues demonstrated that glycosuria increases renal uric acid excretion and that this effect is magnified by SGLTi [34]. A post hoc analysis of four placebo-controlled phase III studies showed that the enhanced uric acid excretion was not associated with higher risk of nephrolithiasis [35]. *(iv) Weight loss*: All clinical trials on T1D, T2D and on non-diabetic subjects (e.g. obese patients) have demonstrated significant weight loss proportional to patient weight and pre-treatment average glycemia (range 1.5–5 kg). This variation is usually evident by the first 4–6 weeks of therapy and is maintained over time. Body composition studies demonstrated a reduction in both fluid retention and fat mass (mostly visceral fat) and a marginal reduction in lean mass [36]. *(v) Blood pressure:* Another effect observed in almost all published SGLT inhibition studies is the lowering of both systolic and diastolic blood pressure. Interestingly, some clinical trials have been specifically designed with blood pressure control as a primary outcome [37,38]. Average improvement is 4–6 mmHg for systolic and 2–3 mmHg for diastolic pressure in hypertensive patients [37,39], with significant effects also in patients being treated with other hypotensive drugs [40]. Finally, 24 h Holter studies demonstrated a higher daytime effect and a contained, but still significant, nighttime decrease [37]. *(vi) Insulin release and sensitivity*: Most studies examining the effect of SGLT inhibition on insulin sensitivity have been conducted on T2D patients; however, the observed effects may be relevant also for T1D patients with residual beta-cell function, for obese patients, and for longstanding T1D subjects with relative resistance to therapeutic insulin. As a consequence of the reduction in glycemia, Gliflozins improve both peripheral insulin resistance and beta cell function; in particular, Ferrarini et al. reported a 25% increase in beta cell glucose sensitivity in T2D

Table 1
Sodium Glucose coTransport (SGLT) inhibitors used in Type 1 Diabetes (T1D). RCT: randomized clinical trial, ** 2 weeks pharmacodynamical/safety study. $t_{1/2}$: half-life. Case reports have been excluded.

Molecule	Chemical structure	Transporter specificity	Tested dosages	$t_{1/2}$	Publications in T1D
Canagliflozin		SGLT2	100, 300 mg once/day	10–12 h	1 RCT 351 subjects [60]
Dapagliflozin		SGLT2	5, 10 mg once/day	13 h	1 RCT**, 1 case series, 82 subjects [58,59]
Empagliflozin		SGLT2	10, 25 mg once/day	10–12 h	1 cross over, 1 RCT; 115 subjects [55–57]
Sotagliflozin		SGLT1 SGLT2	400 mg once/day	24h	2 RCT, 1435 subjects [3,11]