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EXPERT OPINION

1. Introduction
2. Background
3. SGLT2-inhibitors approved by regulatory agencies
4. Future directions

Sodium-glucose transporter 2 inhibitors in type 2 diabetes mellitus: navigating between Scylla and Charybdis

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Despite the extensive pharmacopeia for type 2 diabetes mellitus treatment, long-term glycemic control is far from being optimal, and morbimortality has increased. This demonstrates the importance of developing drugs with new mechanisms of actions, such as sodium-glucose transporter (SGLT) inhibitors (Charybdis). Since the beginning of 2000, numerous SGLT2-inhibitors have been developed and have started to be tested (Scylla) by the pharmaceutical companies that are engaged in this race. Although reductions in hemoglobin A1c have been shown in clinical trials, several issues related to the use of SGLT2 inhibitors deserve further investigation, rendering some aspects of their true safety still uncertain.

Keywords: glycemic control, glycosuria, SGLT1, SGLT2, sodium-glucose cotransporter

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1. Introduction

Scylla is a sea monster and Charybdis is a dangerous whirlpool of the mythology, noted by Greek poet Homer. They are located close enough to each other, offering a dangerous inescapable way to sailors, such as to the hero Odysseus (Ulysses in Latin) of the Homer's epic *Odyssey*. Avoiding Charybdis meant passing too close to Scylla and vice versa. Besides, sea storms made the navigation between Scylla and Charybdis more difficult.

Poor glycemic control in type 2 diabetes mellitus (T2DM) leads to increased morbimortality, imposing the development of new therapeutic approaches, such as sodium-glucose transporter inhibitors (Charybdis). However, the demand for new antidiabetic agents brought these drugs to clinical use before its true efficacy and safety had been completely established (Scylla).

2. Background

Since middle of twentieth century, it is known that glucose intestinal absorption and renal tubular reabsorption are sodium-dependent mechanisms; however, it was only by the end of the 1980s that sodium/glucose cotransporter (SGLT) proteins were molecularly characterized [1]. They are encoded by genes from the solute carrier 5A family; and SGLT1 and SGLT2 isoforms (*SLC5A1* and *SLC5A2* genes, respectively) play a fundamental role in intestinal and renal glucose handling. Other important transporters involved in these processes are the facilitative glucose transporters 1 and 2 (GLUT1 and GLUT2). In the small intestine, luminal glucose is cotransported into enterocytes by SGLT1, and then effluxes to interstitium through GLUT2. In proximal renal tubule, > 90% of filtrated glucose is reabsorbed in S1 segment, through coordinated action of SGLT2 and GLUT2; residual tubular

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glucose is reabsorbed up to the S3 segment, by the actions of SGLT1 and GLUT1 [1].

In a teleological point of view, when luminal glucose concentration increases, the glucose transporter system upregulates, increasing glucose intestinal absorption and/or renal reabsorption, aiming at improving energetic substrate disposal for the organism, as already described in diabetic patients [2]. Diabetes-induced increase of SGLT2 and GLUT2 expression in proximal tubule participates in the development of diabetic tubulopathy and glomerulopathy. We have investigated mechanisms involved in diabetes-induced renal regulation of SGLT2, SGLT1, GLUT2 and GLUT1, demonstrating hyperglycemia [3] and local angiotensin concentration [4] as powerful regulators.

Genetic disorders involving *SLC5A1* and *SLC5A2* genes also contributed to clarify the central role of SGLT1 and SGLT2 in glucose handling. Mutations in *SLC5A1* gene cause the glucose-galactose malabsorption syndrome, with minimal or no changes in renal glucose handling, but with varied degrees of osmotic diarrhea and dehydration [5]. Mutations in *SLC5A2* gene cause familial renal glycosuria, with various degrees of glycosuria and osmotic diuresis [6].

Phlorizin, a natural product found in some fruits, is a 2′-glucoside of phloretin which induces glycosuria and has been used in physiology research for over one-and-a-half centuries. After molecular characterization of SGLTs, phlorizin was recognized as an unspecific inhibitor of SGLT1 and SGLT2 [1].

Administered *per os* (p.o.), phlorizin inhibits SGLT1 in enterocytes, decreasing glucose/galactose absorption. Due to its low oral bioavailability, phlorizin glycosuric effect is small after p.o. administration, hampering its use as an antidiabetic agent. Thus, phlorizin has only been administrated experimentally, by routes other than p.o., to promote glycosuria. In diabetic rodents, subcutaneous phlorizin reduces glycemia as effectively as insulin, constituting a useful strategy to distinguish effects dependent on insulin from those determined by glycemic reduction [3,7]. Modifications of the phlorizin molecule, aiming at reducing its inhibitory effect on intestinal SGLT1 and enhancing its inhibitory effect on renal tubular SGLT2, were attempted as a way of promoting glycosuria without compromising intestinal absorption of glucose/galactose.

Since the beginning of 2000, synthetic analogs of phlorizin displaying high potency and selectivity for SGLT2 inhibition have been developed. Several pharmaceutical companies have engaged in this race, and numerous drugs have started to be tested. At that point, Scylla was born.

3. SGLT2-inhibitors approved by regulatory agencies

Dapagliflozin and canagliflozin were already approved by EMA (EU) and FDA (USA), respectively. In March 2013, empagliflozin was submitted to both agencies and ipragliflozin was submitted for approval in Japan. Two compounds (tofogliflozin and luseogliflozin) have reached Phase III, and two (LX4211 and ertugliflozin) have reached Phase II trials. A recently published manuscript reviews all SGLT2 inhibitors in clinical development [8].

The development program of dapagliflozin included 3 Phase IIb and 11 Phase III trials (4287 patients treated with this SGLT2 inhibitor vs 1941 in the control groups). Placebo-adjusted mean reductions in glycated hemoglobin A1c (HbA1c), in monotherapy and add-on therapy, were significant and ranged from -0.4 to -0.8% for doses of 5 and 10 mg; dapagliflozin 10 mg was noninferior to metformin XR and to glipizide. Reductions in blood pressure (BP) and body weight and a neutral effect on blood lipids were observed [9].

The development of canagliflozin included 9 Phase III trials where 4994 patients were treated with this SGLT2 inhibitor versus 2909 in the control groups. Placebo-adjusted mean reductions in HbA1c (monotherapy and add-on therapy) were significant, dose-dependent and ranged from -0.3 to -0.9% (100 mg) and -0.4 to -1.2% (300 mg). Canagliflozin was noninferior to glimepiride (both doses) and to sitagliptin (only 300 mg was evaluated). Reductions in BP and body weight were reported [10].

4. Future directions

4.1 The Charybdis's jeopardy

Despite the extensive pharmacopoeia for the treatment of T2DM patients, their long-term glycemic control is far from being optimal and T2DM-related morbimortality continues to increase (Charybdis), demonstrating the importance of developing drugs with new mechanisms of action to be used in combination with the preexisting ones.

4.2 The Scylla's jeopardy

The interest in developing new drugs for diabetes treatment is understandable but this must be done safely – to avoid future concerns (Scylla). That being said, several issues related to the use of SGLT2 inhibitors deserve further investigation, rendering some aspects of their true efficacy and safety still uncertain.

4.2.1 Preponderance of reviews over primary clinical trials

The most impressive fact related to the scientific development of SGLT2 inhibitors is the disproportional number of published trials and reviews. PubMed reveals 16 randomized placebo-controlled trials (RCTs) and 84 reviews published from 2007 up to September 2013. This suggests that opinions concerning these drugs have been consolidated mainly from reviews. Further, two excellent meta-analyses [11,12] pointed out as limitations of the available RCTS their small number, sample size and duration, which have not been highlighted in several reviews.

4.2.2 Drug metabolism

SGLTs inhibitor phlorizin was abandoned as an antihyperglycemic drug because, in addition to SGLT1 inhibition, it is highly susceptible to β-glycosidase-mediated conversion to phloretin, a potent inhibitor of GLUTs, such as GLUT1 and GLUT4. As phloretin generation increases, glucose metabolism impairs. Curiously, despite the well-known metabolism of phlorizin, nothing has been described concerning the metabolism of their analogs, and potential effects on GLUTs are unknown.

4.2.3 Weight loss

Weight loss has been emphasized as a benefit of SGLT2 inhibitors and described as around 1 – 3 kg in monotherapy or combination therapy after 12 weeks [12]. Further evaluation is probably necessary to clarify how much of this weight loss is due to glycosuria (energy loss) or secondary to osmotic diuresis (water loss). If the weight loss resulted only from energy loss, it should be proportional to the amount of urinary glucose excretion, which is not the case [13]. Therefore, it is probable that the diuretic effect of SGLT2 inhibitors contributes not only to BP reduction but also to some of the weight loss [13].

It is worth underlining that in animal studies, in which food intake was not restricted, weight loss induced by chronic dapagliflozin administration was attenuated by compensatory hyperphagia. Thus, in the clinical setting, maybe it is important that T2DM patients receive nutritional counseling, to avoid a compensatory increase in food intake [14].

4.2.4 Hypoglycemic efficacy in renal impairment

Dapagliflozin has shown reduced efficacy in patients with impaired renal function; the percentage of 24-h glucose excretion decreases 42, 80 and 90%, respectively with mild, moderate and severe renal impairment [12]. Efficacy of canagliflozin is also attenuated when estimated glomerular filtration rate (eGFR) is < 45 ml/min/1.73 m^2. Additionally, because patients with an eGFR 30 to < 60 ml/min/1.73 m^2 present a higher risk of volume depletion-related adverse reactions [10], the FDA recommended that the dose of canagliflozin is limited to 100 mg/day in patients with an eGFR 45 to < 60 ml/min/1.73 m^2, while it is contraindicated in those with an eGFR < 45 ml/min/1.73 m^2. Dapagliflozin, as approved by European Medicines Agency (EMEA), is contraindicated in patients with an eGFR < 60 ml/min/1.73 m^2.

4.2.5 Safety profile

Increased frequency of urinary and genital tract infections by bacteria and fungi has been reported [11,12], with glucosuria being the most probable explanation, since it has been shown to augment attachment of yeast and bacteria to uroepithelial and vaginal epithelial cells [15]. A meta-analysis of placebo-controlled (n = 45) and active-controlled (n = 13) studies with SGLT2 inhibitors confirmed the increased risk of i) urinary tract infections in comparison to placebo (odds ratio [OR] = 1.34 [CI: 1.03 – 1.74]) and other antidiabetic agents (OR = 1.42 [CI: 1.06 – 1.90]); and ii) genital tract infections in comparison to placebo (OR = 3.50 [CI: 2.46 – 4.99]) and active comparators (OR = 5.06 [CI: 3.44 – 7.45]) [16]. Pooled data from 12 RCT studies with dapagliflozin found that most infections were of mild or moderate intensity and resolved spontaneously or responded to standard antimicrobial therapy [17].

For dapagliflozin, safety issues that motivated the FDA to request additional data were: i) the imbalance in the frequency of bladder and breast cancers; and ii) one potentially serious case of drug-induced liver injury, which met Hy's law criteria (hepatotoxicity that affects global liver function and causes jaundice, likely to lead to patient's death if the drug is not withdrawal). The risks related to hypovolemia in elderly patients and in those on antihypertensive therapy were also mentioned [9].

For canagliflozin, although elevations of transaminases had been observed, cases did not meet criteria of Hy's law. The FDA mentions that long-term evaluations are required to clarify: i) effects on bone mineral density, because a significant increase in serum CTx (bone resorption marker) was observed in one trial; ii) renal consequences, because an early and persistent drop in eGFR was reported in a group of patients with median eGFR of 76 ml/min/1.73 m^2; and iii) cardiovascular risk, because canagliflozin increases low-density lipoprotein cholesterol concentrations, despite favorable changes in high-density lipoprotein cholesterol and BP [10].

A recent meta-analysis did not find a higher risk of a composite cardiovascular end point (cardiovascular death, myocardial infarction, stroke and hospitalization for unstable angina) for dapagliflozin (OR = 0.73 [CI: 0.46 – 1.16]) or canagliflozin (OR = 0.95 [CI: 0.71 – 1.26]), but authors considered data on cardiovascular safety of SGLT2 inhibitors still inconclusive because they are based on trials designed to evaluate short-term efficacy outcomes [16].

Yet, expectations of improving the benefits of SGLT2 inhibitors by increasing the inhibition rate of glucose renal reabsorption must be cautiously analyzed. Massive glycosuria is associated with i) aminoaciduria [5,6], because high tubular glucose concentration disturbs sodium-dependent amino acids reabsorption; and ii) natriuresis-related volume depletion with activation of renin-angiotensin-aldosterone system, as observed in some patients with mutations in *SLC5A2* gene. Finally, we must take lessons from transgenic mice carrying mutations of *SLC5A2* gene and rendered diabetic, which show improved glycemic control, but increased risks of infections, volume contraction, malnutrition and mortality [18].

4.3 The storm

If navigation between Scylla and Charybdis is a challenge, doing that during a storm is increasingly challenger. In this regard, the proposal of dual SGLT1 and SGLT2 inhibition

ravels the clear evaluation of these drugs. The observation that SGLT2 inhibitors only partially reduce renal glucose reabsorption has stimulated development of dual inhibitors. Some researchers have associated the limited inhibition of glucose reabsorption to the uninhibited SGLT1 [8,19], which is true, but they ignored an important finding: diabetes-induced GLUT2 translocation to the luminal membrane of the tubular cell [20]. Despite the proposal of inhibiting SGLT1 in the kidney, inhibition of SGLT1 in intestine seems to be the true additional benefit of the dual effect.

For canagliflozin, reductions in postprandial glycemia and insulin excursions were clearly demonstrated, indicating SGLT1 inhibition in intestine [21]. However, LX4211-induced inhibition of glucose intestinal absorption is not clear yet: i) area under the curve (AUC) of postprandial glycemia is unaltered after 2 days of treatment (inhibition of SGLT1 must be immediate); and ii) at 27 days of treatment, reduced glycemia AUC was not dose-related as expected [13]. Also, inhibition and/or delay on glucose reabsorption trigger GLP-1 and PYY secretions, which could additionally improve glycemic control, but it raises concerns regarding long-term safety.

It is worth mentioning that an inhibitory effect on renal SGLT1 was not clearly demonstrated yet. A suitable evaluation of this effect requires comparing a selective SGLT2 inhibitor with a dual inhibitor that presents a similar potency in inhibiting SGLT2. Still, concerning SGLT1 inhibition, additional aspects must be contemplated: i) inhibiting > 50% of glucose reabsorption might result in massive glycosuria with worse safety profile; and ii) SGLT1 is a powerful water transporter.

4.4 Final remarks

As Ulysses should have done, the best way to navigate between Scylla and Charybdis is to go ahead by the central area, avoiding both Scylla and Charybdis. By this way, a safe port of calm waters can be encountered.

We expect that SGLTs inhibitors continue to be carefully developed, focusing on their long-term safety. We underline the potential of these drugs being used across the whole spectrum of T2DM and even in type 1 DM, thanks to their unique mechanism of action targeting an organ not addressed by any other drug class and not depending on β-cell function. For those characteristics, SGLTs inhibitors are expected to be used as monotherapy, for instance, in newly diagnosed patients intolerant to metformin or combined with virtually any other antidiabetic agent, regardless of the degree of hyperglycemia.

Declaration of interest

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