SODIUM-GLUCOSE TRANSPORTER 2 INHIBITION – A POTENTIAL OPTION FOR THE TREATMENT OF TYPE 2 DIABETES MELLITUS

Rucsandra Dănciulescu Miulescu [1], ***Liviu Șerb*** [2]

[1] Endocrinology Department, University of Medicine and Pharmacy, Bucharest
[2] Department of Endocrinology, Hospital of Mulhouse France

Abstract

Glucose homeostasis is maintained by the balanced actions of glucose absorption, gluconeogenesis, glycogenolysis, glucose consumption, glucose excretion and glucose reabsorption. The human kidney is involved in glucose regulation by three mechanisms: gluconeogenesis, uptake of glucose and reabsorption of glucose at the level of the proximal tubule. Transporters of two gene families are responsible for the absorption of glucose from the glomerular filtrate: glucose transporters (GLUT) and sodium-glucose transporters (SGLT). Approximately 90% of the glucose is reabsorbed in the first segment of the proximal tubule, where GLUT2 and SGLT2 are expressed, and approximately 10% is reabsorbed in the third segment of the proximal tubule, where GLUT1 and SGLT1 are expressed. In patients with diabetes, the kidney reabsorbs as much glucose as possible from the filtered fluid. An in vitro study of cultured human renal proximal tubular cells isolated from urine of patients with type 2 diabetes showed an increased expression of GLUT2 and SGLT2 and a higher threshold for glucose reabsorbtion by comparison with non-diabetics. Development of inhibitors with a high specificity for SGLT2 represents a potential option in the treatment of diabetes. In patients with type 2 diabetes, SGLT-2 inhibition is associated with dose-related decrements in glycosylated hemoglobin level and modest weight loss. SGLT-2 inhibition decreases systolic and diastolic blood pressure and serum uric acid concentration. The treatment with SGLT-2 inhibitors increases urinary volume and hematocrit. Prolonged glycosuria is a risk factor for development of genito-urinary infections and an approximate doubling of episodes of vulvo-vaginitis and balanitis has been reported. Monitoring of adverse effects is important for the patient safety in this class of drugs. Potential extrarenal effects need to be explored and potential progression of renal dysfunction will have to be monitored.

keywords*: glucose homeostasis, type 2 diabetes, sodium-glucose transporters inhibitors*

1. Introduction

Glucose homeostasis is maintained by the balanced actions of glucose absorption, gluconeogenesis, glycogenolysis, glucose consumption, glucose excretion and glucose reabsorption. The human kidney is involved in glucose regulation by three mechanisms: gluconeogenesis, uptake of glucose and reabsorption of glucose at the level of the

proximal tubule [1]. Renal glucose reabsorption is mediated by glucose transporters. Transporters in two gene families are responsible for the absorption of glucose across the glomerular filtrate: the glucose transporters (GLUT) or sodium-glucose transporters (SGLT) [1].

Glucose transporters (protein symbol GLUT, gene symbol SLC2 for Solute Carrier Family 2) mediate the passive transport of glucose across the membrane. Thirteen members of the GLUT/SLC2 have been identified and each isoform plays a specific role in glucose metabolism determined by its pattern of tissue expression, substrate specificity and transport kinetics [2]. Well-characterized glucose transporters were GLUT1-GLUT4. GLUT1 is expressed in the adult at highest levels in erythrocytes and in the endothelial cells of barrier tissues. GLUT2 is expressed by renal tubular cells and small intestinal epithelial cells, GLUT3 in neurons and in the placenta and GLUT4 in adipose tissues and striated muscle [3].

The transport of glucose through the membrane of intestinal and kidney epithelial cells depends on the presence of secondary active sodium–glucose transporters (SGLT). SGLT are a family of transmembrane proteins coded by the SLC5 gene specialized in the transport of sodium and glucose across different cell types. There are a total of seven members in the human protein family SLC5A [4]. SGLT1 and SGLT2 are members of the SLC5A gene family, SGLT1 is expressed in the third segment of the proximal tubule, intestine, brain, heart, trachea and SGLT2 is expressed predominately in the first and second segments of the proximal tubule, brain, liver, thyroid, muscle, heart [1]. Approximately 90% of the glucose is reabsorbed in the first segment where GLUT2 and SGLT2 are expressed and approximately 10% is reabsorbed in the third segment, where GLUT1 and SGLT1 are expressed [5]. In humans, mutations in SGLT2 are associated with familial renal glycosuria [6].

The human kidney contains approximately 1.3 million nephrons and each nephron is specialized to filter water and small solutes and then selectively reabsorb glucose, amino acids and electrolytes, primarily in the proximal tubule. Each day, approximately 180 g of glucose are filtered by the glomeruli and, in normal physiologic conditions, all glucose is reabsorbed by the proximal tubules. Glycosuria appears if the filtered glucose exceeds the renal glucose threshold of 180 mg/dl, the filtered glucose load exceeds 375 mg/min or the renal threshold for glucose is lowered [7]. In patients with diabetes the kidney reabsorbs as much glucose as possible from filtered fluid and in a study of cultured human renal proximal tubular cells, isolated from the urine of patients with type 2 diabetes, there was an increased expression of GLUT2 and SGLT2, as well as a higher threshold for glucose reabsorbtion than in subjects without diabetes [8].

2. Development of SGLT2 inhibitors

The development of inhibitors with a high specificity for SGLT2 represents a potential option in the treatment of diabetes.

The possibility of SGLT2 system modulation via inhibitor molecules is evaluated at the present. Several SGLT2 inhibitors have been developed. Clinical trials with sergliflozin and remogliflozin have been discontinued by GlaxoSmithKline and Kissei

Pharmaceuticals [9, 10]. Canagliflozin, another SGLT2 inhibitor, is being developed by Johnson & Johnson and is currently in phase III trials in the United States [11]. The prominent SGLT2 inhibitor at this time is dapagliflozin, a medication being co-developed by Bristol-Myers Squibb and AstraZeneca. Currently, 20 clinical studies have been completed or are in progress in the United States with this compound. Three other SGLT2 inhibitors are currently being evaluated in clinical trials. Two compounds (BI 10773 and BI 44847) are being developed by Boehringer Ingelheim in Germany and the compound YM-543 is being developed by the Japanese company Atstellas Additionally, the Isis Pharmaceuticals Company is developing anti-sense technology to reduce the expression of SGLT2 and one molecule ISIS-SGLT2Rx [12,13,14,15,16].

3. Potential of SGLT2 inhibitors in diabetes treatment

In healthy subjects, SGLT-2 inhibition induces dose-related glycosuria without causing hypoglycemia. The pharmacokinetic and pharmacodynamic profile of SGLT-2 inhibitors: the rapid onset of action, and efficacy results from repetition of single-dose effects with little cumulative effect. In non-diabetic subjects, plasma glucose concentrations are little affected by the induction of glycosuria meaning that the liver responds to the glucose loss by increasing endogenous gluconeogenesis. The loss of 30–80 g of glucose through urine generates the loss of 120–320 kcal over one day. The caloric deficit would result in the loss of approximately 6–16 kg in a year [17].

In patients with type 2 diabetes, SGLT-2 inhibition is associated with dose-related decrements in glycated hemoglobin level (HbA1c) and modest weight loss 1–3 kg over 24 weeks. In patients with HbA1c > 10%, treatment potently lowers HbA1c by 2.5–3.5%, while in the range of usual HbA1c levels, the efficacy of SGLT-2 inhibition appears to be similar to that of dipeptidyl peptidase-IV inhibitors or metformin [17,18].

Reduced hyperglycemia would be expected to improve insulin sensitivity and may have potentially significant benefit to the liver due, in part, to the effect of glucose itself on glucose-6-phosphatase gene expression. No significant enhancement of glucose uptake into skeletal muscle or adipose tissue was observed [19].

SGLT-2 inhibition decreases systolic and diastolic blood pressure with 2–5/2–3 mmHg (placebo-corrected average across different doses). Inhibition of proximal sodium reabsorption may be a mechanism of blood pressure lowering [17].

SGLT-2 inhibition decreases serum uric acid concentrations. The inhibition of sodium-coupled uric acid reabsorption in the proximal renal tubule may be responsible for the decrease in serum uric acid concentrations [18, 20, 21].

No evidence of systematic changes in blood urea or serum creatinine concentrations has been reported. SGLT-2 inhibition has neutral effect on the serum lipid profile [17].

SGLT-2 inhibitors do not cause significant changes in serum electrolytes [17].

The prominent SGLT2 inhibitor at this time is dapagliflozin and the drug is in phase III trials. A C-aryl glucoside bond confers resistance to degradation in the

gastrointestinal tract by beta glucosidase enzymes. Renal clearance of dapagliflozin is minimal less than 2.5% being excreted unchanged in the urine during a 24-hour period [22].

In experimental models on rodents, dapagliflozin administration resulted in an increase in glycosuria and decreased fasting and postprandral glucose levels, unaccompanied by hypoglycemia [22].

Komoroski et al. conducted the first clinical studies that evaluated the safety, tolerability, pharmacokinetics, and pharmacodynamics of dapagliflozin in healthy subjects. The drug was evaluated in single-ascending-dose (2.5-500 mg) and multiple-ascending-dose (2.5-100 mg) for 14 days. The authors concluded that: "Dapagliflozin exhibited dose-proportional plasma concentrations with a half-life of approximately 17 h. The amount of glycosuria was also dose-dependent. Cumulative amounts of glucose excreted on day 1, relating to doses from 2.5-100 mg" Dapagliflozin administration resulted in a dose-dependent glycosuria that is sustained over 24 h, which indicates that it is suitable for administration in once-daily doses [23].

The results of a 24-week international, randomized, double-blind, placebo-controlled study that evaluated the efficacy and safety of dapagliflozin therapy when added to the therapy of patients with type 2 diabetes with inadequate glycemic control on insulin were presented at the American Diabetes Association 70th Scientific Sessions (Orlando, June 2010) by dr. Wilding. Treatment with dapagliflozin achieved reductions in the primary endpoint, HbA1c, in inadequately controlled type 2 diabetes patients who were treated with insulin compared to placebo plus insulin. The study demonstrated that dapagliflozin generates reductions in the secondary endpoints that evaluated the change in total body weight from baseline, change from baseline in mean daily insulin dose and change from baseline in fasting plasma glucose. Signs and symptoms reports suggestive of urinary tract and genital infections were more frequently noted in the dapagliflozin treatment arms than in the placebo arm [24].

In June 2010 Bailey et al. published a study investigating the efficacy and safety of dapagliflozin in patients who have inadequate glycemic control with metformin. 546 adults with type 2 diabetes who were receiving daily metformin (1500 mg/day or more) and had inadequate glycemic control were randomly assigned to receive one of three doses of dapagliflozin (2.5 mg, 5 mg or 10 mg) or placebo orally once daily. Patients continued to receive their pre-study metformin dosages. The primary outcome was a change from baseline in HbA1c level. At week 24, mean HbA1c had decreased by 0.30% in the placebo group, compared with 0.67% in the dapagliflozin 2.5 mg group, 0.70% in the dapagliflozin 5 mg group and 0.84% in the dapagliflozin 10 mg group. Symptoms of hypoglycemia occurred in similar proportions in patients in the dapagliflozin and placebo groups. Signs and symptoms of genital infections were more frequently noted in the dapagliflozin groups than in the placebo group. The authors concluded that the addition of dapagliflozin to metformin provides a new therapeutic option for treatment of type 2 diabetes in patients who have inadequate glycemic control with metformin alone [25].

Canagliflozin is a new and promising addition to the drug class of SGLT2 inhibitors. The results from a first-in-humans study, testing the tolerability and pharmacodynamics of single doses of canagliflozin, were presented by dr. Sha on the second day of the American Diabetes Association 70th Scientific Sessions (Orlando, June 2010). Eight groups of six healthy men were given a dose of canagliflozin 10, 30, 100, 200, 400, 600 or 800 mg/day or 400 mg twice a day. For comparison, a further two men in each group were given placebo. They were then monitored for 5 days. Over a 5-day period, urinary glucose excretion was significantly increased by canagliflozin in a dose-dependent fashion [26].

In the same session, professor Rosenstock presented results from a phase IIB placebo-controlled, double-blind study in which 451 patients with type 2 diabetes under treatment with metformin (1500 mg/day or more) were given placebo, sitagliptin 100 mg/day, canagliflozin 50, 100, 200 or 300 mg/day or 300 mg twice daily for 12 weeks. The patients at baseline had a mean HbA1c level of 7.7% and a mean fasting plasma glucose level of 162 mg/dl. The mean change in HbA1c from baseline to 12 weeks was significant in all groups and increased with higher doses. In addition, 60-70% of the patients taking canagliflozin 300 mg/day or 300 mg twice/day achieved a target HbA1c level of below 7% by the time the study completed. Fasting plasma glucose and body weight were also significantly reduced in all canagliflozin groups. There was a small increase in the number of mild but symptomatic genital infections in patients taking canagliflozin in comparison to the placebo group [27].

BI 10773 and BI 44847 are selective SGLT2 inhibitors currently in phase II trials [22].

ISIS-SGLT2Rx is an antisense drug that inhibits the production of SGLT2 by decreasing the expression of the SGLT2 gene *in vivo*. The Phase 1 study of ISIS-SGLT2Rx is a double-blind, placebo-controlled study, conducted in healthy volunteers and is designed to assess the safety and pharmacokinetic profile of ISIS-SGLT2Rx as well as to measure ISIS-SGLT2Rxs activity by evaluating its effect on glucose excretion in urine [16].

4. Safety of SGLT2 inhibitors

The treatment with SGLT-2 inhibitors increases urinary volume with 200–400 ml/day and hematocrit by 1–3% [17].

The prolonged glycosuria is a risk factor for the development of genito-urinary infections and an approximate doubling of episodes of vulvo-vaginitis and balanitis has been reported [17, 24, 25, 27].

The monitoring of these adverse effects is important for the safety of this class of drugs. The potential extrarenal effects need to be explored and the progression of renal dysfunction will have to be monitored.

5. Conclusion

The development of inhibitors with a high specificity for SGLT2 represents a potential option in the treatment of type 2 diabetes.

The ability of SGLT2 inhibitors to reduce plasma glucose without inducing hypoglycemia or weight gain constitutes a major advance.

In patients with type 2 diabetes SGLT-2 inhibition is associated with dose-proportional decrements in HbA1c and modest weight loss.

SGLT-2 inhibition decreases systolic and diastolic blood pressure and serum uric acid concentration.

The treatment with SGLT-2 inhibitors increases urinary volume and hematocrit.

The prolonged glycosuria is a risk factor for the development of genito-urinary infections and an approximate doubling of episodes of vulvo-vaginitis and balanitis has been reported.

SGLT2 inhibitors have no gastrointestinal side effects, and the data suggest that they represent an attractive therapeutic candidate for the treatment of type 2 diabetes.

Monitoring of these adverse effects is important for the safety of this class of drugs. Potential extrarenal effects need to be explored and potential progression of renal dysfunction will have to be monitored.

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Correspondence Data:
Rucsandra Danciulescu Miulescu
rucsandra_m@yahoo.com
fax: 004021/2105575