Sodium-Glucose Cotransporter 2 Inhibitors

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SGLT2 (sodium-glucose cotransporter 2) inhibitors are a new class of antihyperglycaemic drugs that act on the proximal tubules of the kidney. They have shown efficacy in the management of diabetes mellitus type 2 and their cardiovascular and renal safety have been extensively investigated and confirmed in clinical trials. However, inter-individual differences in response to treatment with SGLT2 inhibitors may present in everyday clinical practice, and good predictors of glycemic response and the risk for adverse events in an individual patient are lacking.

SGLT2 inhibitors | cardiovascular safety | renal safety | genetic polymorphisms

1. Introduction

Type 2 diabetes mellitus (T2DM) is a chronic, metabolic and progressive disease. The goal of treatment is good glycemic control, assessed by the hemoglobin A1C measurement, continuous glucose monitoring (CGM), and self-monitoring of blood glucose (SMBG). Evidence supports that in the long run, good glycemic control without large fluctuations in blood glucose levels prevents or delays microvascular complications such as diabetic nephropathy, neuropathy, and retinopathy. However, there are less data on the benefit of glycemic control in reducing macrovascular complications such as coronary artery disease, peripheral arterial occlusive disease (PAOD), and ischemic stroke [1].

The American Diabetes Association (ADA) provides comprehensive and evidence-based recommendations for the diagnosis and treatment of T2DM in their regularly revised and updated “Standards of Medical Care in Diabetes” [2]. These guidelines recommend metformin as the preferred initial pharmacologic agent in T2DM. Metformin has been in clinical use for more than 60 years and its mechanism of action is well known. It has pleiotropic effects, of which the inhibition of gluconeogenesis in the liver and the facilitation of glucose uptake into peripheral tissues contribute the most to glycemic control [3]. In recent years, several new agents, such as glucagon-like peptide 1 (GLP1) analogs, dipeptidyl peptidase-4 (DPP4) inhibitors, and selective sodium-glucose cotransporter 2 (SGLT2) inhibitors, were introduced for T2DM treatment, mostly as an add-on to first-line treatment.

SGLT2 (sodium-glucose cotransporter 2) inhibitors are a new class of insulin-independent anti-hyperglycemic drugs that inhibit glucose reabsorption in proximal tubules and, thus, affect glucose homeostasis via the kidneys [1]. In addition to other hormonal and signaling pathways that regulate glucose metabolism, the kidneys also play an important role in glucose homeostasis. SGLTs catalyze the active transport of glucose against concentration gradient across the apical (luminal) membrane by coupling it with the transport of sodium [4][5]. There are two SGLT isoforms; however, SGLT2 is the major isoform expressed in the first segment (S1) of the proximal tubules in the

kidney and has a high capacity, but a poor affinity, for glucose. SGLT2 is also expressed in human pancreatic α-cells and regulates glucagon release [6]. The other isoform, SGLT1, has a high affinity, but a low capacity, for glucose. Although SGLT1 may be expressed in the kidney, it is mainly expressed in the gastrointestinal tract where it participates in the absorption of dietary glucose, and also in the liver [4][7][8].

The maximum capacity of kidney glucose reabsorption is 375 mg/min. Around 180 g of glucose is pre-filtered through the kidneys daily in subjects with normal glucose tolerance, so most of the glucose that is filtered in the primary urine in the glomeruli is reabsorbed back into the blood in the proximal tubules via SGLT. In healthy subjects, glucose is excreted in the urine when the plasma glucose concentration exceeds 10 mmol/L. In patients with high plasma glucose levels due to poorly controlled T2DM, the filtered glucose load exceeds the maximum capacity for glucose reabsorption, resulting in glycosuria. Hyperglycemia may be reduced by a decrease in glucose reabsorption via SGLT2 in the proximal convoluted renal tubules of the kidney. In this way, SGLT2 inhibitors lower the renal threshold for glucose excretion and, consequently, cause glucosuria. In patients who receive SGLT2 inhibitors, the amount of glucose excreted depends on the level of hyperglycemia and the glomerular filtration rate (eGFR), and is approximately 80 g per day [9].

2. Pharmacokinetics and Pharmacodynamics of SGLT2 Inhibitors

Dapagliflozin (10 mg) was the first discovered highly potent SGLT2 inhibitor. The bioavailability of dapagliflozin is 78% and it is not altered by a high-fat diet, so the drug can be taken independently of food intake. It affects both fasting and postprandial plasma glucose levels. It is absorbed very rapidly, reaching peak plasma concentrations from one hour to one and a half hour after ingestion. The half-life (t ½)- is 13 h, so it can be prescribed once a day. UGT1A9 enzyme is responsible for metabolism of dapagliflozin in the kidneys and liver. It is known that the dapagliflozin dose should be reduced to 5 mg in patients with hepatic impairment. Dapagliflozin is not recommended in patients with moderate and severe renal impairment or dialysis, nor in older patients. Dapagliflozin is mainly excreted in the urine [10][11].

Empagliflozin is most selective for SGLT2. It is taken once a day, regardless of food intake; the maximum daily dose is 25 mg per day. In total, 40% is excreted in the feces and 55% in the urine. Similar to other SGLT2 inhibitors, empagliflozin prolonged hepatic metabolism, predominantly by glucuronidation into inactive metabolites [10].

Canagliflozin is usually recommended before the first meal at a starting dose of 100 mg (especially in the elderly), which can be titrated to 300 mg. Its bioavailability is 65%. It is 99% protein bound. It reaches peak plasma concentrations after one to two hours. At a dose of 300 mg, the t ½ is 13 h. Interactions with other drugs are not known. Use in patients with severe hepatic impairment is not recommended [10].

The most recent SGLT2 inhibitor on the market is ertugliflozin. In addition to empagliflozin, ertugliflozin has high selectivity for SGLT2. It is available as immediate-release tablets in doses of 5 and 15 mg. More than 85% of the

total drug load is dissolved in 15 min and its t ½ is 17 h. After one single dose, steady-state concentrations can be achieved by day 6. Its plasma protein binding is 93.6%. It is administered once daily as monotherapy or in combination with other antihyperglicemic drugs, regardless of meals. There is no need to adjust the dose in patients with renal impairment or mild-to-moderate hepatic impairment. Enzymes UGT1A9 and UGT2B are responsible for ertugliflozin metabolism [12].

3. Heart Failure and SGLT2 Inhibitors

It is known that patients with T2DM have an increased risk for HF with preserved ejection fraction (HFpEF) and HFrEF. Patients with T2DM have a significant prevalence of subclinical left ventricular (LV) diastolic dysfunction, which is an independent predictor of negative outcomes and a key cause of the development of HFpEF. Tissue hypoxia may further contribute to ventricular remodeling [13][14]. As heart failure progresses, renal failure also occurs, and this is associated with a poorer prognosis [15].

The DAPA-HF (Dapagliflozin And Prevention of Adverse-outcomes in Heart Failure) was a double-blind, placebo-controlled, event-driven study that included patients with HFrEF with and without type 2 diabetes on the optimal pharmacological therapy. No differences were found among different age groups, or between diuretic or, for example, sacubitril/valsartan users. In patients with HfrEF, one study found a minor impact on systolic blood pressure [16]. Regardless of baseline kidney function, dapagliflozin significantly reduced morbidity, mortality, and symptoms in patients with HFrEF when compared to placebo. The decline of kidney function was slower in the dapagliflozin group [17][18]. Dapagliflozin may thus present a new approach in the treatment of patients with HFrEF [19].

Ertugliflozin reduced the risk for first and total hospitalization due to outcomes in HF although SGLT2 inhibitors did not reduce hospitalizations due to atherosclerosis-related events [20]. The advantages of this class of drugs may be attributable to early beneficial hemodynamic effects on LV function rather than on atherosclerosis. The molecular mechanisms through which SGLT2 inhibitors lower hospitalizations due to HF are still unknown [13].

4. Genetic Variability of SGLT2 Transporter in T2DM and Treatment with SGLT2 Inhibitors

SGLT2 is encoded by the SGLT2 gene, also known as SLC5A2 (solute carrier family 5 member 2), located on chromosome 16. Several mutations in the SLC5A2 gene, affecting SGLT2 expression, membrane localization, or transporter function, were linked with familial renal glucosuria, characterized by abnormally high urinary glucose excretion in the presence of normal blood glucose levels [21][22][23]. In addition to these rare missense mutations, several common genetic variants were reported in the SLC5A2 gene that could play a role in glucose homeostasis and could potentially influence the risk for T2DM as well as the response to treatment with SGLT2 inhibitors [5]. However, the findings that common SLC5A2 genetic variants influence glucose homeostasis and metabolic traits in

nondiabetic individuals, or that they are associated with the risk of T2DM, are not consistent among studies, as detailed below and in **Table 1**.

Table 1. *SGLT2* genetic variability in T2DM and in treatment with SGLT2 inhibitors.

***SLC5A2* SNPs**	**Study Population**	**Outcome Studied**	**Main Findings**	
rs9934336 rs3813007 rs3813008 rs3116150	1013 subjects from German Sorb cohort: 106 with and 907 without T2DM; Validation: 2042 subjects from Metabolic Syndrome Berlin Potsdam Study: 359 with and 1683 without T2DM	T2DM risk, metabolic traits, glycemic control, and insulin levels after OGTT	No associations with T2DM risk; rs9934336 AA genotype associated with reduced glucose levels at 30 min and decreased insulin levels at 120 min of OGTT in nondiabetic subjects	
rs3116149 rs9934336 rs3813008 rs11646054 rs3116650 rs9924771	2229 subjects from Tübingen Family (TÜF) study: 1558 glucose tolerant and 671 prediabetic; 603 T2DM subjects on empagliflozin and 305 on placebo	T2DM risk, metabolic traits, response to empagliflozin	No association with metabolic traits; No association with response to empagliflozin	[24]
rs9924771 rs3116150 rs3813008 rs9934336	375 subjects at increased risk for T2DM	Plasma glucagon concentrations in the fasting state and during OGTT	No association with plasma glucagon levels	[6]
rs9934336, rs3813008, and rs3116150	1684 subjects undergoing coronary angiography including 400 patients with T2DM Meta-analysis of data from 3 studies	T2DM risk, risk for CAD (coronary artery disease), incidence of cardiovascular events	rs9934336 associated with decreased HbA1c and decreased T2DM risk; No association with CAD or incidence of cardiovascular events; rs9934336 association with T2DM risk confirmed in a meta-analysis	[25]
rs9934336	181 Slovenian T2DM patients	Glycemic control, risk for macro or microvascular complications	rs9934336 associated with increased fasting blood glucose levels and HbA1c; Higher risk for diabetic retinopathy in polymorphic rs9934336 A allele carriers compared to non-carriers; No association with other micro or macrovascular complications	[26]

SLC5A2 SNPs	Study Population	Outcome Studied	Main Findings	
SNPs with MAF > 0.01: rs9934336 and rs3116150 included in SGLT2 genetic score	Data on 416,737 UK Biobank subjects; Validation: 3316 subjects from LUdwigshafen RIsk and Cardiovascular Health study (LURIC)	Heart failure risk	Nominal association of SGLT2 genetic score with reduced T2DM risk; SGLT2 genetic score associated with lower risk of prevalent or incident heart failure; No association with atherosclerotic cardiovascular disease outcomes or markers	[27]

T2DM—type 2 diabetes mellitus; SNPs—single nucleotide polymorphisms; OGTT—oral glucose tolerance test; CAD—coronary artery disease.

Enigk et al. investigated four intronic single nucleotide polymorphisms (SNPs) encompassing genetic variability within the SGLT2 gene region and their association with the T2DM risk and related metabolic traits in two German cohorts. In the Sorb cohort that consisted of 1013 individuals, of which 106 had T2DM, 34 had impaired fasting glucose (IFG), 87 had impaired glucose tolerance (IGT), and 786 had normal glucose tolerance (NGT); none of the investigated SNPs showed any associations with the risk for T2DM. A lack of association of rs9934336 with the risk for T2DM was also observed in the validation cohort of 2042 individuals from the Metabolic Syndrome Berlin Potsdam Study that included 359 subjects with T2DM, 195 subjects with IFG, 329 subjects with IGT, and 1159 subjects with NGT. However, in 907 nondiabetic subjects from the Sorb cohort rs9934336, the AA genotype was associated with reduced glucose concentrations at 30 min and decreased insulin levels at 120 min during the oral glucose tolerance test (OGTT). In addition, rs3813008 was associated with insulin levels at 30 min, while rs3813007 was associated with glucose levels at 30 min during OGTT in the additive model. The combined analysis of both cohorts showed a nominal association of rs9934336 with insulin concentrations at 120 min during OGTT only in nondiabetic subjects [5].

These data suggested that some of the investigated variants could influence the proportion of glucose reabsorption by affecting baseline SGLT2 expression levels. Furthermore, it was proposed that such interindividual differences in SGLT2 expression levels might also influence the response to treatment with SGLT2 inhibitors, although SGLT2 inhibitors target this transporter directly. However, Zimdahl et al. performed a cross-sectional population study in a large cohort of 2600 metabolically well-phenotyped individuals at increased risk for T2DM and reported that, after correction for multiple testing, none of the five investigated common SNPs in the SLC5A2 gene locus influenced diabetes-related metabolic traits such as body fat, insulin sensitivity/resistance, insulin release, HbA1c, plasma glucose, or systolic blood pressure. This cohort also included patients from four phase III trials of empagliflozin, with a total of 603 T2DM subjects receiving empagliflozin and 305 subjects receiving placebo. The investigated SNPs did not interfere with the response to empagliflozin treatment in T2DM patients and were not associated with HbA1c levels, fasting glucose, body mass, or systolic blood pressure in empagliflozin-treated patients [24].

As SGLT2 is also expressed in human pancreatic α-cells and SGLT2 inhibitors may elevate circulating glucagon concentrations, it was suggested that SLC5A2 polymorphisms could modify circulating glucagon concentrations and hepatic glucose production. However, in a cohort of 375 healthy subjects at increased risk for T2DM, no associations were observed between these SNPs and plasma glucagon levels in the fasting state or upon glucose challenge with OGTT [6].

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