

# Overview of Sodium-Glucose Co-Transport Inhibitors

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It has been almost 100 years since the discovery of a substance produced by the pancreas, which was named insulin. Now known to be the key regulator of blood glucose homeostasis, the impact this has had on diabetic patients has resulted in increased lifespan and decreased disease complications. Since the discovery of the role of the pancreas and insulin in the pathophysiology of diabetes, researchers have developed a number of drug classes aimed at increasing insulin secretion from the beta cells of the pancreas, increasing insulin sensitivity of target organs, and decreasing glucose production by the liver. With all of the treatment options for type 2 diabetic patients, it's curious as to why large portions of this disease population do not reach or maintain their goal blood glucose levels. Researchers continue to develop and test new medications with different pharmacologic activity in hopes of finding a solution to this problem. The newest addition to the oral anti-diabetic medications, sodium-glucose co-transport (SGLT2) inhibitors, acts independently of insulin to increase glucose excretion from the body [1]. These medications have shown a lot of promise in the treatment of diabetic patients by proven efficacy in reducing HbA1c and with a minimal side effect profile. With any new class of medications, safety profile is a concern and drug companies are required to do post-marketing studies to identify any possible adverse reactions. The FDA issued a warning in May 2015, indicating a possible association between SGLT2 inhibitors and ketoacidosis. These cases warrant further review of the pharmacologic relationship with this metabolic state.

The first SGLT2 inhibitor was approved by the FDA in March 2013 under the brand name Invokana (canagliflozin), with two more following in 2014, Farxiga (dapagliflozin) and Jardiance (empagliflozin), and a few others currently undergoing clinical trials. They are indicated for individuals with type 2 diabetes mellitus as an adjunct to diet and exercise. SGLT2 are the main transporters involved in glucose reabsorption in the kidneys and are present mainly on the S1 and S2 segment of the proximal tubule [2]. These transporters are responsible for roughly 90% of glucose reabsorption [3]. SGLT1 transporters play a minimal role in glucose reabsorption and are present mainly on the S3 segment of the proximal tubule, as well as on the intestinal wall [2]. These medications are predominantly selective for SGLT2 transporters. Canagliflozin also has some inhibition of SGLT1 transporters, which may result in small decreases in glucose absorption in the intestines, resulting in decreased postprandial blood glucose [1]. In a healthy individual without diabetes, an average of approximately 180 grams of glucose is filtered by the kidney and reabsorbed each day [4]. Individuals with diabetes have a greater amount of circulating glucose in the blood stream, which may result in an up-regulation of SGLT2 transporters in the kidney [2]. Inhibition of these transporters results in decreased glucose reabsorption, thereby increasing glucose excretion in the urine and subsequent decreases in blood glucose levels. SGLT2 inhibitors block reabsorption of 30-50% of filtered glucose, indicating other mechanistic actions of glucose reabsorption [3].

SGLT2 inhibitors are primarily metabolized by glucuronidation in the liver to inactive metabolites. Hepatic impairment results in a higher drug levels, requiring lower starting doses [1]. A small amount (<1%) is excreted unchanged in the urine. Individuals with renal impairment show a declining blood glucose-lowering response with the severity of dysfunction [1]. It is recommended not to use dapagliflozin with a creatinine clearance of <60 mL/min/1.73 m<sup>2</sup>, and not to use canagliflozin or empagliflozin with a creatinine clearance of <45 mL/min/1.73 m<sup>2</sup>[5,6,7]. A maximum dose of 100 mg is recommended for canagliflozin with a creatinine clearance between <60 mL/min/1.73 m<sup>2</sup> and ≥45 mL/min/1.73 m<sup>2</sup>[6]. Major drug interactions have not been seen with SGLT2 inhibitors[1]. Caution and monitoring should be advised with concomitant use of blood pressure lowering medications, other anti-diabetic medications, and digoxin, as digoxin levels may increase [6].

SGLT2 inhibitors have been studied as monotherapy in type 2 diabetics, as well as in combination with metformin, sulfonylureas, TZDs, DPP-4 inhibitors, and insulin. Monotherapy with canagliflozin has shown a decrease in HbA1c by -0.77 to -1.03% [4]. Similar results have been seen with other SGLT2 inhibitors [3]. A study conducted on treatment-naïve patients with type 2 diabetes showed non-inferiority with 10 mg/d of dapagliflozin compared to metformin in the reduction of HbA1c [1]. The efficacy of SGLT2 inhibitors is dependent on the amount of glucose in the blood and glomerular filtration rate (GFR)[3]. Increased glucosuria after administration of an SGLT2 inhibitor has demonstrated a paradoxical increase in glucagon concentrations, increasing endogenous glucose production [1]. This limits the HbA1c lowering capability of these medications. Many of the classes of medications currently on the market for type 2 diabetes have significant side effects, including hypoglycemia and weight gain. Since SGLT2 inhibitors act independent of insulin, there are few reports of hypoglycemia as compared to insulin and sulfonylureas [1]. If SGLT2 inhibitors are added to medications, risk of hypoglycemia increase, which increases the production and secretion of insulin [1]. SGLT2 inhibitors have also shown in clinical trials to modestly reduce weight by -2.5 to -3.2 kg [4]. This may be due to reduction of insulin production and secretion, following lower blood glucose levels. Slight reductions in blood pressure have also been consistently reported in patients treated with SGLT2 inhibitors. A reduction of systolic blood pressure by -4.4 mmHg and diastolic blood pressure by -2.1 mmHg has been reported [1]. SGLT2 inhibitors have osmotic diuretic effects which may account for the reduced blood pressure [1]. For this reason, the package inserts of these medications advice to be cautious when initiating therapy in patients with renal impairment, the elderly, patients with low systolic blood pressure, and patients on diuretics [5-7]. Few side effects have been reported with SGLT2 inhibitors. The most common side effects include genital mycotic infections and urinary tract infections. Females may experience vulvovaginitis and males may experience balanitis most

commonly due to *Candida albicans* growth [3]. It is important to advise patients to use good hygiene practices to prevent these infections.

On May 15, 2015, the FDA issued a warning regarding the potential risk of ketoacidosis in patients taking SGLT2 inhibitors. Twenty cases had been reported from March 2013 to June 2014, all which had resulted in hospitalization for this metabolic state [8]. Diabetic ketoacidosis (DKA) is a state characterized by inability to utilize glucose which results in the breakdown of fatty acids into ketone bodies in order to meet energy demands, resulting in acidic blood [9]. Insulin is required for proper uptake and storage of glucose into target organs; hence, insulin deficiency is the most common precipitating factor of DKA [9]. DKA has long been thought of as a condition which primarily affects type 1 diabetics, rarely identified in the type 2 population. In recent reports, as many as 20-50% of DKA cases have been recognized as type 2 diabetics who are considered to be ketosis-prone [9]. Ketosis-prone type 2 diabetics have inadequate insulin secretion which may be triggered by an increased need of insulin in times where blood glucose levels spike including: infections, certain medications (clozapine, corticosteroids, thiazide diuretics, etc.), and hypovolemia [9]. Symptoms of early acidosis include: weight loss, fatigue, dyspnea, vomiting, and abdominal pain. A fruity smell may be noted on the breath of individuals in this state. If left untreated, DKA can result in coma, cerebral edema, and death. Identification of DKA generally includes a blood glucose >250 mg/dL, pH <7.3, serum bicarbonate <18 mEq/L, elevated serum ketones, and dehydration [9]. The reported cases of DKA associated with the use of SGLT2 inhibitors showed a high anion gap metabolic acidosis and increased urine or serum ketones, but lacked the high blood glucose concentration [8]. The FDA safety announcement stated that the median time to onset of ketoacidosis was two weeks after initiation of an SGLT2 inhibitor. Potential triggers of ketoacidosis were identified in half of the cases and included hypoinsulinemia, due to acute illness, reduced caloric or fluid intake, and reduced insulin dose [8]. Other factors included hypovolemia, acute renal impairment, hypoxemia, reduced oral intake, and a history of alcohol use [8]. The correlation between SGLT2 inhibitors and ketoacidosis is currently under investigation. The down-regulation of insulin production from the beta cells due to decreased blood glucose may result in insufficient insulin levels in acute hyperglycemic episodes (injury, infection, etc.) and result in lipolysis. The osmotic diuretic effect of SGLT2 inhibitors may lead to dehydration and movement of electrolytes into extracellular spaces and cause electrolyte abnormalities.

SGLT2 inhibitors offer a novel and promising approach to the treatment of type 2 diabetes mellitus. They are effective in reducing HbA1c with the benefit of having minimal side effects. The long half-life of these medications allows for once daily dosing and the pharmacokinetics result in minimal drug-drug interactions. While the cardiovascular profile of these new medications is currently the subject of long-term studies, a large proportion of type 2 diabetics are overweight and may benefit from glucose lowering capability, in addition to reducing systolic blood pressure and body fat. With any new class of medication, caution should be used when prescribing due to lack of long-term data. Individuals taking SGLT2 inhibitors should be made aware of signs of acidosis and the importance of immediate medical attention, if they do occur. Further studies are needed to determine the correlation of SGLT2 inhibitors and the risk for ketoacidosis. Until then, SGLT2 inhibitors should be used cautiously in individuals after a thorough assessment of health status and past medical history.

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