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Editorial

SGLT 2 inhibitors: Antidiabetic agents with promising effects beyond glucose control

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Type 2 diabetes mellitus is a growing public health problem worldwide. It has a close relation with metabolic problems like obesity, hypertension, dyslipidemia and atherosclerotic cardiovascular diseases. There are different antidiabetic agents being used in the treatment of diabetes mellitus with different mechanisms of action and a patient centered approach is required when choosing the appropriate treatment option. Sodium-glucose cotransporter (SGLT) 2 inhibitors also called glucoretics or gliflozins are members of a relatively new group of antidiabetic agents with promising cardioprotective and renoprotective effects beyond their glucose lowering efficacies.[1-3]

Kidneys are involved in glucose homeostasis via gluconeogenesis and glucose reabsorption. Under normoglycemic conditions kidneys of healthy individuals filter about 140-160 grams of glucose daily. This amount corresponds to about 30% of daily energy intake. More than 99% of filtered glucose is reabsorbed in the proximal tubules of kidneys by SGLT 1 and 2. Reabsorption of approximately 90% of the filtered glucose load is from SGLT 2 and remaining from SGLT 1.[4,5] SGLT 2 inhibitors act by inhibiting the reabsorption of glucose in the proximal renal tubule, resulting an increase in urinary glucose excretion and reduction in serum glucose levels. The glucosuric effects of SGLT 2 inhibitors are regulated by the filtered glucose load. Inhibition of SGLT 2 reveals the masked potential of glucose carrying capacity of SGLT 1 by increasing glucose load in the late proximal tubule. SGLT 1 starts to reabsorb more glucose. This property limits the further risk of glycosuria and hypoglycemia when the filtered glucose load reaches ≤80 g/day.[4,5] In addition to loss of calories by glucosuria, SGLT 2 inhibition alters substrate utilization from carbohydrates to lipids. Enhanced lipolysis and reductions in visceral and subcutaneous fat mass are reported. They are shown to decrease body weight, body mass index and waist circumference in different studies.[4-8]

SGLT 2 inhibitors are thought to reduce cardiovascular risk by several different mechanisms. They possibly reduce vascular tone by affecting the renin angiotensin aldosterone system, lower blood pressure via natriuresis without increasing heart rate, improve diastolic function by reducing left ventricular mass index and probably control the level of certain biomarkers (NT-pro BNP and hsTn1) increased in case of cardiovascular disease. Decrease in blood pressure and plasma volume reduce both cardiac pre and afterloads leading to rapid benefits in heart, especially in patients with cardiac failure. In heart failure, SGLT inhibitor induced glucosuria is thought to lead modulation of cardiac metabolism with reduced glucose oxidation and increased use of ketone bodies by heart muscle which probably

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improve left ventricular function.[9-11] SGLT 2 inhibitors decrease serum uric acid levels. In vitro studies indicated that glucose entering proximal tubule lumen may facilitate intracellular urate exchange via GLUT 9 isoform 2 and increase urinary urate excretion.[12]

SGLT 2 inhibitors also decrease microalbuminuria. In some type 2 diabetic patients, glomerular hyperfiltration occurs at the onset of the disease which can increase the risk of diabetic nephropathy. SGLT 2 inhibitors have a glomerular filtration rate (GFR) lowering effect independent of blood glucose lowering property. Following this decrease, GFR increases over the following weeks that is preserved after a few years of treatment duration. Lowering glomerular hyperfiltration reduces kidney's demand for oxygen, lessens urinary albumin /creatinine ratio and albuminuria.[13-15] By controlling blood glucose, body weight, blood pressure, uric acid levels and microalbuminuria and by some specific additive effects on kidneys and heart, SGLT 2 inhibitors are shown to have positive effects on renal and cardiovascular outcomes in type 2 diabetic patients. Besides they are shown to improve liver function tests probably due to improvements in fatty liver disease as a result of glycemic control and weight reduction.[4,16,17] It's known that patients with type 2 diabetes lose their beta cell reserve and endogenous insulin within years. SGLT 2 inhibitors act independently of insulin secretion or action and can be an option for all type 2 diabetics within indication even those with reduced beta cell function and/or insulin resistance. SGLT2 inhibitors act synergistically with other antidiabetic agents. Although SGLT 2 inhibitors do not usually cause hypoglycemia in monotherapy, attention for hypoglycemia should be given in patients taking insulin or insulin secretagogues.[1,5,18]

Until today, four different types of SGLT 2 inhibitors have been introduced into clinical use. These are dapagliflozin, empagliflozin, canagliflozin and ertugliflozin. Among them the first three are available both in Europe and the United States and ertugliflozin only in the United States.[1,17,19] It is important to individualize the choice of therapy according to patient characteristics in type 2 diabetes. The approach to initial therapy in type 2 diabetic patients includes lifestyle interventions by programming medical nutrition treatment, body weight control and exercise. Besides metformin is given as the first line antidiabetic agent if not contraindicated. SGLT 2 inhibitors are not considered as the first line treatment option. According to the results of cardiovascular outcome trials with SGLT 2 inhibitors, in type 2 diabetic patients who cannot reach glycemic goals with metformin and lifestyle interventions with overt atherosclerotic cardiovascular disease empagliflozin or canagliflozin and with heart failure empagliflozin, canagliflozin or dapagliflozin can be used as an add on treatment option to metformin. SGLT 2 inhibitors can also be added to metformin and lifestyle modifications as a second drug in patients in whom weight gain, risk of hypoglycemia and injection therapy lead to significant problems. They can also be added as the third line treatment option in case of inadequate glycemic control with 2 different antidiabetics.[1,2]

SGLT 2 inhibitors are shown to reduce mean hemoglobin A1c levels approximately 0.5 to 1.0 % compared to placebo depending on baseline level of hyperglycemia in meta-analysis of different clinical trials.[5,9,19-22] SGLT 2 inhibitors are available in tablets with different milligrams (mg) given once daily. They are started with their lowest dose initially and then increased in case of higher requirement. They require dose adjustments in renal insufficient patients according to GFR (Table 1). It is not recommended to use empagliflozin and canagliflozin in type 2 diabetic patients with GFR <45 mL/min and dapagliflozin and ertugliflozin

Table 1. SGLT 2 inhibitors and their administration

SGLT 2 inhibitor	Tablet dosages (milligrams)	Recommended daily dose (milligrams)	Route of administration	Frequency of administration	Renal dose adjustment
Dapagliflozin	5 and 10	5 to 10	Oral	Once daily	Required
Empagliflozin	10 and 25	10 to 25	Oral	Once daily	Required
Canagliflozin	100 and 300	100 to 300	Oral	Once daily	Required
Ertugliflozin	5 and 15	5 to 15 mg	Oral	Once daily	Required

GFR <60 mL/min due to their mechanisms of action.[1,2,4,17]

Common side effects include symptoms of polyuria, fluid loss, thirst, hypovolemia, hypotension, dizziness, urinary tract infections and mycotic genital infections. Less common side effects are hypoglycemia, dehydration, serum cholesterol and transient serum creatinine elevations. Dehydration is more frequent in the elderly and in patients with extracellular volume depletion like the ones using loop diuretics. Urosepsis, pyelonephritis and Fournier's gangrene are rare but serious side effects reported. Canagliflozin and ertugliflozin may be associated with an increased risk of lower limb amputations. Fractures have been reported with canagliflozin. Euglycemic, mildly or moderately hyperglycemic diabetic ketoacidosis can develop due to fluid loss in type 2 diabetic patients treated with SGLT 2 inhibitors. SGLT 2 inhibitors should be discontinued in patients with major surgery, severe disease and infection. They should not be used in pregnancy and lactation.[1,17,22,23]

In conclusion, SGLT 2 inhibitors are a newer group of antidiabetic agents with promising renoprotective and cardioprotective effects with a very rare incidence of hypoglycemia and without weight gain. Long-term studies should be conducted to clearly define their therapeutic values in type 2 diabetic patients especially with vascular complications.

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