A Review Article

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CURRENT STATUS OF SODIUM GLUCOSE CO-TRANSPORTER 2 INHIBITORS IN MANAGEMENT OF DIABETES TYPE 2.

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ABSTRACT Diabetes is common worldwide, affecting millions of people, with significant systemic complications. Many pharmacological approaches are available to treat, including insulin and antihyperglycemic agents. Sodium glucose co-transporter 2 inhibitors are a novel approach in the management of type 2 diabetes and such agents have been approved by for clinical use since 2013. But SGLT 2 inhibitors use is associated with serious and significant adverse drug reactions. The US FDA warnings have been recommended on labels of canagliflozin and dapagliflozin. Long term clinical studies have been conducted to evaluate the safety and efficacy of SGLT 2 inhibitors. Purpose of this review is to elaborate usefulness of SGLT 2 inhibitors in management of type 2 diabetes mellitus with a focus on safety in different populations affected by the disease.

KEYWORDS : T2DM, Type 2 diabetes, SGLT 2, SGLT 2 inhibitors, canagliflozin, dapagliflozin, empagliflozin, US FDA, Diabetic ketoacidosis.

INTRODUCTION:

Prevalence of diabetes is increasing globally and approximately 425 million adults (20-79 years) are living with diabetes; by 2045 this number will rise to 629 million. In low- and middle-income countries 79% of adults were living with diabetes.[1] In the United States alone, more than 100 million adults are now living with diabetes or prediabetes, according to a new report released by the Centers for Disease Control and Prevention (CDC). An estimated 23.1 million people (7.2%) of the US population had diagnosed diabetes. Type 2 diabetes mellitus (T2DM) accounts for 90%–95% of cases of diabetes diagnosed in adults.[2]

DIAGNOSTIC CRITERIA FOR DIABETES:

American Diabetes Association (ADA) diagnostic criteria for T2DM is: a fasting plasma glucose (FPG) level 126 mg/dL (≥7.0 mmol/L), or a 2-hour plasma glucose level 200 mg/dL (≥11.1 mmol/L) during 75g anhydrous oral glucose tolerance test (OGTT), or a random venous plasma glucose of 200 mg/dL (11.1 mmol/L or higher in a patient with symptoms of hyperglycemia or hyperglycemic crisis. Glycosylated hemoglobin, A1C (HbA1c) level of 48 mmol /mol (≥6.5%) is a cut off point for the diagnosis of T2DM, but A1C <6.5% does not exclude diabetes diagnosed using glucose tests.[3] Prediabetes is defined as A1C levels ranging from 5.7% to 6.4%, are at risk of diabetes.[4]

DIABETES THERAPEUTIC GOALS:

Current recommendations for treatment of diabetes focus on improving diet and exercise, followed by monotherapy with an antihyperglycaemic agent (AHA). Adverse effects of oral hypoglycemic drugs i.e. hypoglycemia, weight gain and edema limit their use. A key therapeutic goal of treating metabolic syndrome and T2DM is improving glycaemic control. Hyperglycemia is strongly associated with increased risk of microvascular complications, including retinopathy and nephropathy. Every 1% decrease in A1C is associated with about 35 % reduction in microvascular complications.[4] The American College of Physicians (ACP) has updated guidance statements regarding HbA1C targets for non-pregnant adult patients with T2DM. The treatment goals should be based on the benefits and harms of pharmacotherapy, patient preferences, the patient's general health and life expectancy, treatment burden, and costs of care. The aim of hypoglycemic treatment in T2DM should be to achieve an HbA1c level between 7% and 8%. If a patient with T2DM achieves an HbA1c level <6.5%, clinicians should consider de-intensifying pharmacological therapy. In patients with T2DM aim should be to minimize symptoms related to hyperglycemia. Clinicians should avoid targeting a specific HbA1c level in patients with a life expectancy of <10 years due to advanced age (80 or older) because the harms outweigh the benefits in these patients.[5]

TREATMENT STRATEGIES FOR T2DM:

Multiple agents are available for the treatment of DM, but being a complex disease and intolerance, contraindications, or ineffectiveness of certain drugs for individual patients, still there is a requirement for novel antihyperglycemic agents (AHA). Currently, the American Association of Clinical Endocrinologists (AACE) includes the following oral agents for the treatment of T2DM in their glycemic control algorithm: metformin, sulfonylureas, meglitinides, thiazolidinediones (TZDs), dipeptidyl peptidase-IV (DPP-4) inhibitors, alpha-glucosidase inhibitors, colesevelam, bromocriptine, and the newest class of SGLT 2 inhibitors.[6]

ROLE OF SODIUM GLUCOSE COTRANSPORTER 2 INHIBITORS IN DIABETES:

SGLT 1 is primarily located in small intestine, but also in kidney, trachea, heart and colon. In kidney SGLT 2 is expressed in S1 and S2 segments of the proximal convoluted tubule (PCT).[7,8] In normoglycemic adults, 180 mg of glucose is filtered per day in glomerulus and 80-90% is reabsorbed by SGLT 2 in the PCT; and in people with diabetes reabsorption of glucose is enhanced by increased expression of SGLT 2. This reabsorptive activity of SGLT 2 is also independent of action of insulin. This suggests that kidney plays an important role in maintenance and progression of hyperglycemia in the diabetic patients; and the low-capacity sodium glucose co-transporter (SGLT1) reabsorbs the remaining 10%–20%.[9] Patients with diabetes have an upregulation of SGLT2 and absorb excess amounts of glucose that would be excreted normally by healthy individuals. Therefore, inhibition of SGLT2 provides a novel mechanism for control of hyperglycemia in patients with diabetes, enhancing urinary glucose excretion and promoting a natriuretic and diuretic action.[10] This unique mechanism of action results in decreased blood glucose levels and weight loss (via glucose excretion), and reduced blood pressure (via osmotic diuresis and decreased intravascular volume).[11]

Inhibition of renal glucose reuptake was confirmed to reduce blood glucose levels; therefore, several SGLT2 inhibitors, also called gliflozin drugs, have been developed as novel treatments for type 2 diabetes mellitus (T2DM), and canagliflozin was the first SGLT2 inhibitor to be approved for use in the United States in 2013.[12] Phlorizin, which is extracted from the root bark of apple trees in 1835, is the first nonselective SGLT inhibitor.[13] Currently 3 dugs of this class have been approved by the US Food and Drug Administration (FDA) and European Medicines Agency (EMA): canagliflozin, dapagliflozin and empagliflozin with several others in global or regional development e.g. ipragliflozin, ertugliflozin, remogliflozin, lusegliflozin, tofogliflozin and sotagliflozin.[14] SGLT2 inhibitors are expected to have various effects, including weight loss, blood pressure reduction, improvement in pancreatic and renal functions, and reduction in serum lipid levels, as well as hypoglycemia.[15] SGLT 2 inhibitors share a similar pharmacokinetic profile being prodrugs, with a rapid oral absorption, a long elimination half-life thus once daily dose, and extensive hepatic metabolism via glucoronidation to inactive metabolites; and a low renal elimination thus contraindicated in patients with severe chronic kidney disease (CKD).[16]

It is well known that T2DM is an important basis for the development of ischemic heart disease and CKD, and is simultaneously one of the factors in the progression of these diseases. There have been very few reports describing that treatment with conventional antidiabetic agents prevents the progression of these complications.[17] Ipragliflozin is an

orally bioavailable, next generation, SGLT2-selective inhibitor received first global approval in January 2014 for T2DM treatment. Ipragliflozin was associated with significant reductions in body weight and was well tolerated in clinical studies. Because of its mechanism of action and efficacy, safety of ipragliflozin might be compromised in patients with renal impairment (RI).[18]

EFFICACY OF SGLT 2 INHIBITORS:

Efficacy of SGLT 2 inhibitors as monotherapy, add on therapy to oral hypoglycemic drugs and in combination with insulin has been established in randomized controlled trials (RCTs). A1C reduction with SGLT inhibitors ranges from 0.5-1%, depending upon the dose, severity of diabetes and other patient-specific factors.[19,20] Because of their insulin independent action they may be useful at all stages of T2DM. Risk of hypoglycemia is rare, but may occur when SGLT2 I is used in combination with exogenous insulin or an insulin secretagogue.[21] SGLT 2inhibitors also cause a sustained reduction in systolic and diastolic BP because of their osmotic diuretic effect; and weight loss by their glycosuric effect especially in patients with higher baseline BMI.[22] Empagliflozin significantly reduced cardiovascular death in patients with T2DM and high cardiovascular risk (EMPA-REG OUTCOME).[23] Recently (Oct. 2018) US FDA has approved canagliflozin to reduce risk of heart attack, stroke or cardiovascular (CV) death in adults with T2DM and established CV disease. Based upon CANVAS Program, canagliflozin is the first AHA, having such a therapeutic indication. [24]

SAFETY OF SGLT 2 INHIBITORS:

AACE was the 1st professional organization to add SGLT 2i to their treatment algorithm for T2DM in 2013. They are placed as 5th line agent for monotherapy, 4th line agent for dual therapy in addition to metformin, and 3rd line in triple therapy.[25] They are generally well tolerated, but with some associated disadvantages i.e. an increase in urogenital infections (increased risk of genital mycotic infection).[26] FDA has warned regarding risk of urinary tract infections leading to urosepsis and pyelonephritis with SGLT2inhibitors,[27] and decrease in estimated glomerular filtration rate (eGFR) leading to decreased renal function.[28,29] FDA has warned on labels of canagliflozin and dapagliflozin regarding acute kidney injury, but this warning does not apply to empagliflozin which is associated with a slow progress of kidney disease (EMPA-REG OUTCOME).[30]

They can cause postural hypotension and dizziness especiaaly in the elderly and those taking loop diuretics. Canaflozin can increase rate of bone fracuters, FDA has issued a warning for decreased bone mineral density (BMD) and increased bone fracture risk.[31] SGLT 2 inhibitors increase serum phosphate levels increasing parathyroid hormone (PTH) and fibroblast growth factor (FGF) which promote phosphaturia and antagonize vitamin D metabolism decreasing 1,25 dihydrovitamin D levels.[32] Dapagliflozin and empagliflozin do not carry bone fracture risk warnings.[33]

CANagliflozin cardiovascular Assessment Study (CANVAS) and CANVAS-Renal (CANVAS-R), data analysis showed an increased risk of lower extremity amputation, mainly of the toe and middle of the foot, with canagliflozin. The amputation rates were 5.9 and 2.8 per 1000 person-years with canagliflozin and placebo, respectively, in CANVAS, and 7.5 and 4.2 per 1000 person-years with canagliflozin and placebo in CANVAS-R. Based on these findings, and the US prescribing information reflects an increased risk of amputation in patients with high risk of CV events or a history of CV events.[34] No imbalance in the risk of amputation in patients with high CV risk was reported in the completed EMPA-REG OUTCOME study of empagliflozin.[35]

Diabetic ketoacidosis (DKA) a life threatening triad of hyperglycemia (blood glucose > 250 mg/dL), metabolic acidosis & presence of ketones in urine or plasma, has been reported in T2DM patients who were being treated with dapagliflozin or ipragliflozin montherapy.[36] SGLT2 inhibitors lower serum glucose levels by increasing urinary glucose excretion, which in turn reduces insulin secretion from pancreatic β-cells. The decline in circulating insulin levels results in decreasing the anti-lipolytic activity of insulin and consequent stimulation of production of free fatty acids (FFA), which are converted to ketone bodies by β-oxidation in the liver.[36]

Empagliflozin is licensed as monotherapy when metformin is inappropriate and in combination with other glucose-lowering drugs, including insulin, for the treatment of adults with T2DM. The dose of insulin or a sulfonylurea may be lowered to reduce the risk of hypoglycaemia after adding empagliflozin. Treatment with empagliflozin should not be initiated in patients with impaired renal function (eGFR <60ml/min/ 1.73m2); measure renal function before and at least annually during treatment. No dose adjustment is recommended for people with hepatic impairment, though empagliflozin is not recommended when hepatic function is severely impaired. No dose adjustment for age is required but patients aged ≥75 are at increased risk of volume depletion and empagliflozin is not recommended for patients aged ≥85.[37]

Tofogliflozin, a highly selective SGLT2 inhibitor, has been approved in Japan for the treatment of T2DM.[38] Clinical trials have shown that tofogliflozin, when used as monotherapy or in combination with oral antidiabetic agents, significantly decreases A1C, fasting plasma glucose (FPG), body weight and systolic and diastolic blood pressure in patients with T2DM, while maintaining a low risk of hypoglycaemia.[39]

SGLT 2 INHIBITORS IN FIXED DOSE COMBINATION WITH DPP-4 INHIBITORS:

By inhibiting the degradation of glucagon-like peptide-1 (GLP-1), dipeptidyl peptidase-IV (DPP-4) inhibitors promote insulin secretion and suppress glucagon secretion. Because the mode of action is dependent on the glucose concentration, DPP-4 inhibitors have a low risk of causing hypoglycemia. SGLT2 inhibitors reduce urinary glucose reabsorption by inhibiting SGLT2, lower plasma glucose in an insulin-independent manner and help to alleviate glucose toxicity. They are also expected to improve insulin resistance by alleviating glucose toxicity and decreasing body weight. The independent mechanisms of action of these drugs and the low risk of hypoglycemia provide support for combination therapy as a therapeutic option.[40,41] Consequently, fixed-dose combinations of a DPP-4 inhibitor and an SGLT2 inhibitor were launched in the USA and Europe e.g. linagliptin/empagliflozin and saxagliptin/dapagliflozin.[42,43]

A randomized, placebo-controlled, double-blind, multicentre trial examined the efficacy and safety of teneligliptin or placebo added to canagliflozin therapy for 24 weeks in Japanese patients with inadequately controlled T2DM. Teneligliptin was associated with significant improvements in glycaemic control, including A1C, FPG and postprandial plasma glucose, compared with placebo. Moreover, greater proportions of patients in the canagliflozin + teneligliptin group achieved A1C <7.0% or <8.0%. These improvements were consistent with those observed in earlier clinical trials in which teneligliptin was added to AHA other than SGLT2 inhibitors.[44]

SGLT2INBITORS IN CLINICAL TRIALS:

In a study, treatment with ipragliflozin for 24weeks was associated with significantly greater improvements in glycaemic control and body weight in the ipragliflozin group than in the placebo group in the overall cohort, and in patients with mild RI. In patients with moderate RI, the improvements in glycaemic control were not significantly greater in the ipragliflozin group than in the placebo group. The improvements in glycaemic control in patients with mild RI and the reduction in body weight in patients with mild or moderate RI were apparent by week 4 of treatment and were maintained at week 52.[45] A randomized, double-blind, placebo-controlled study on long-term efficacy and safety of ipragliflozin treatment in patients with type 2 diabetes mellitus and renal impairment: showed that ipragliflozin significantly improved glycemic control and body weight in T2DM patients with mild RI, but not moderate RI.

PLACE OF SGLT2 INHIBITORS IN T2DM THERAPY:

SGLT 2 inhibitors are a new therapeutic option for patients with T2DM that will facilitate the recommended current management guidelines. The average A1C reduction that could be achieved with SGLT2 inhibitors would be expected to be in the range of 0.5–1.0%. However, other factors are also important in the management of T2DM, including weight reduction and the need for well-tolerated treatment with a low risk of hypoglycemia, in addition to the convenience of once-daily oral dosing. In addition, SGLT2 inhibitors offer other potential benefits, including BP reduction, CV risk reduction, and possible renal protective effects.[46]

SGLT2 inhibitors are generally well tolerated, but attention must be

paid to the possible risk of serious adverse events, including dehydration, development of DKA, serious UTIs, and bone fractures, as well as the risk of less serious but more common adverse events such as genital mycotic infection. These possible risks must be carefully weighed against the potential benefits for each patient. Patients should be encouraged to drink plenty of water and maintain good hygiene habits, and to contact a health care provider if symptoms of dehydration, genital mycotic infections, or UTIs occur. Patients should know the common symptoms of DKA i.e. nausea, vomiting, abdominal pain, tiredness, breathing difficulty, and patient should stop taking SGLT 2 inhibitors if such symptoms arise; and to manage in inpatient settings.[26,36]

SGLT2 inhibitors being a new class of AHA, with several questions remain about their place in clinical practice. With a strong evidence of a reduction in CV risk with empagliflozin in patients at high baseline risk of cardiovascular (CV) events in the EMPA-REG OUTCOME trial; could results of the study be applied to a larger population meeting the study inclusion criteria. There are serious adverse events associated with SGLT2 inhibitors, in magnitude and of clinical importance the T2DM patients, and FDA warnings regarding their prescription have been communicated. The ongoing research will further elucidate the future role of SGLT2 inhibitors in the management of patients with T2DM.[47]

CONCLUSION:

On the basis of the efficacy demonstrated in clinical trials, SGLT2 inhibitors are recommended as second- or third-line agents for the management of patients with type 2 diabetes. Beneficial effects on kidney disease progression, cardiovascular and all-cause mortality, and hospitalization for heart failure have also been demonstrated with SGLT2 inhibitors empagliflozin and canagliflozin. These medications have shown significant reductions in HbA1c (0.5%–1.0%) when used as monotherapy or in combination therapy. Improvements in weight, blood pressure, and lipid parameters, major cardiovascular events, in adults with T2DM, have been demonstrated. The primary safety concerns of increased genital mycotic infections and limitations based on renal function are expected based on the mechanism of the drug. These novel medications represent a new option for dual and triple therapy for T2DM or can be used as monotherapy in patients who cannot tolerate first-line options.

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