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ROLE OF SGLT2 INHIBITORS IN TYPE 2 DIABETES MELLITUS

[1]*Dr. Deeksha Sharma and [2]Dr. Akshay Sharma

[1]MD Pharmacology, Dr RPGMC Kangra At Tanda, HP.
[2]Senior Resident, Department of Radiology, DR. RPGMC TANDA H.P.

***Corresponding Author: Dr. Deeksha Sharma**
MD Pharmacology, Dr RPGMC Kangra At Tanda, HP.
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INTRODUCTION

Diabetes mellitus (DM) is a common metabolic disease characterized by chronic hyperglycaemia that globally affects approximately 10% of the population, and its prevalence is expected to increase in the following years.[1] The leading cause of morbidity and mortality in the diabetic population remains cardiovascular (CV) disease, which is estimated to be 2-4 times more common in patients with DM when compared with people without DM.[2]

Drug therapy is aimed at preventing micro vascular complications, comprising end-stage kidney disease (ESKD) and blindness.[3]

The initial approach recommended by the American Association of Clinical Endocrinologists (AACE)/American College of Endocrinology and the American Diabetes Association (ADA) includes lifestyle changes and monotherapy, preferably metformin. Drugs currently commonly used to control blood glucose such as insulin, glucagon- like peptide 1 (GLP1) receptor agonists, sulfonylureas, thiazolidinediones, dipeptidyl peptidase-4 (DPP-4) inhibitors, SGLT2 inhibitors.[4]

The SGLT is a membrane protein capable of co-transporting sodium ions (Na+) and glucose into cells. In humans, we have 6 types of SGLT, those of type I and II are most responsible for the absorption of glucose. In particular, SGLT1 is located mainly at the level of the intestinal mucosa and also allows the absorption of galactose, while SGLT2 is mainly present in the proximal tubule of the renal nephron and it is responsible for the 90% of renal glucose reabsorption.

The class of SGLT2 inhibitors includes five oral drugs: canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, and sotagliflozin.[5]

Mechanism of action of SGLT2 inhibitors

SGLT2 are high-capacity, low-affinity transporters, present in the proximal convoluted renal tubule, and responsible for 90% reabsorption of filtered plasma glucose. SGLT2 inhibition simply inhibits the transporter and prevents the renal reabsorption of filtered glucose and sodium, reducing hyperglycaemia and facilitating glucose excretion in urine.[6]

Other potential effects of SGLT2 inhibition include reductions in albuminuria, weight loss and lipid metabolism shift, improvement in hemoglobin levels and reducing oxygen demand and cellular glucotoxicity. Moreover, SGLT2 inhibitors appear to reduce levels of inflammatory cytokines, such as IL-6, TNF, IFNg, NF-kb, TLR-4, and TGF-b, and improve mitochondrial function.[7]

Essential effects of SGLT2 inhibitors[8]

1) Effect on glycemic

A. The value of HbA1c level reduced approximately 0.7–1.0%
B. Lower fasting plasma glucose, about1.2 mmol/L
C. Improved beta cell function
D. Improve glucotoxicity
E. Improved insulin sensitivity
F. Increased endogenous glucose production
G. Reduced insulin resistance

2) Effects on lipids

A. Increased HDL, LDL and apolipoprotein
B. Does not alter the concentration of LDL-C, but decreases small, dense LDL-C and increases large buoyant LDL-C
C. Increased total cholesterol
D. Lower triglyceride levels
E. Lead to increased adiponectin

3) Weight

A. Decreased waist circumference, subcutaneous adipose tissue, and visceral adipose tissue
B. Increased glucagon secretion
C. Weight loss of about 2–4 kg

4) Cardiovascular effects

A. Reduced systolic blood pressure

B. Improve inflammation and oxidative stress
C. Improve vascular function
D. Reduce cardiac preload
E. Decreased left ventricular mass index
F. Decreased NT-proBNP concentration
G. Improve natriuresis
H. Reduces pathological cardiomyocyte stiffness
I. Lead to osmotic diuresis
J. Increase hematocrit
K. Lung fluid volume improved
L. Improves diastolic function
M. Improve cardiac remodeling
N. Reduce ischemia–reperfusion injury

5. Effects on fibrosis markers
A. Decreased Mac-2 binding protein
B. FIB-4 index decreased
C. Significantly lower NAFIC scores

6. Liver function improvement
A. Reduced fatty liver index
B. Decreased serum alanine aminotransferase, aspartate aminotransferase and gamma-glutamyltransferase levels.
C. Proton density fat fraction decreased

7. Effects on the kidneys
A. Reducing vascular volume
B. Reduce blood uric acid levels
C. Reduced proteinuria
D. Stabilize e GFR
E. Improve urinary albumin/creatinine ratio
F. Reduced kidney disease progression
G. Improve natriuresis

8. SGLT2 inhibitors may reduce bone density

9. Effects on inflammatory factors
A. Decreses soluble dipeptidyl peptidase levels
B. Decreases ICAM-1, VCAM-1, TNF-α and IL-6

10. Oxidative stress
A. Reduce H2O2,GSH, lipid peroxide
B. Prevent PKGIα oxidation

11. Effect on anemia
A. Decrease hepcidin levels
B. Improve erythropoiesis

Table 1: Pharmacological characteristic of SGLT2 inhibitors.

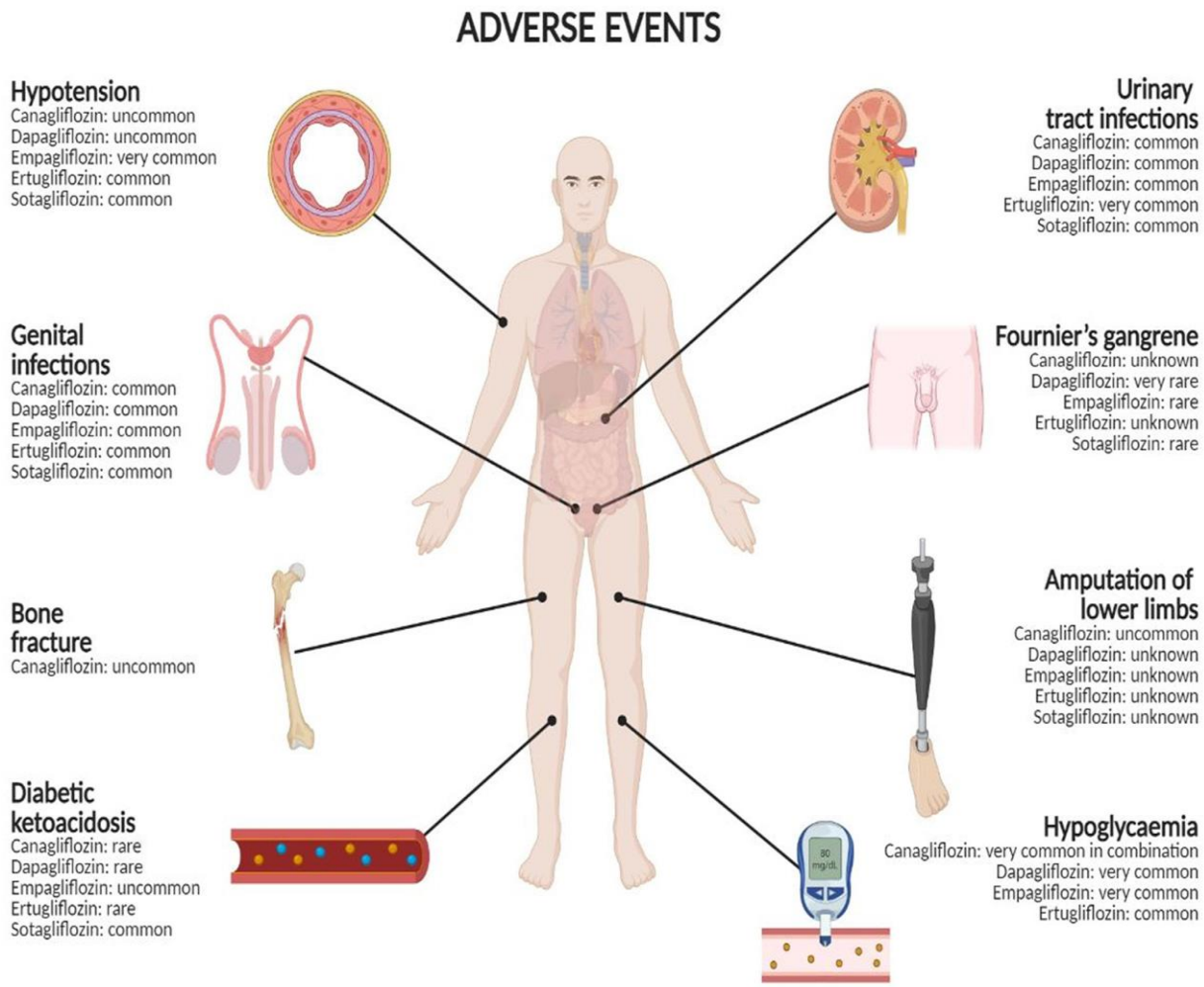
SGLT2 inhibitors	Therapeutic indication	Dosing	Age
Canagliflozin	Type 2diabetes mellitus	100mg once a day	Adult patients
Dapagliflozin	Type 2 diabetes mellitus Heart failure Chronic kidney disease	10mg once a day 10mg once a day 10 mg once a day	Adult patients
Empagliflozin	Type 2 diabetes mellitus Heart failure	10 mg once a day 10 mg once a day	Adult patients
Ertugliflozin	Type 2 diabetes mellitus	5mg or 10mg once a day	Adult patients
Sotagliflozin	Type 1 diabetes mellitus	200mg or 400mg once a day	Adult patients

Benefits of SGLT2 inhibitors in HF, HFrEF and HHF
SGLT2 inhibitors reduce left ventricular volume in T2DM or prediabetic patients with HFrEF. Favorable reverse left ventricular remodeling may be a mechanism by which SGLT2 reduces HHF and mortality in patients with HFrEF.[9]

Some randomized controlled trials have also confirmed the benefit of SGLT2 inhibitors in HF or HHF. In the CANVAS program, canagliflozin significantly reduced severe HF or HHF (P = 0.003) and HHF (P = 0.002) compared with placebo. Canagliflozin had a greater benefit of cardiovascular death or HHF in patients with a prior history of HF (HR 0.61 vs. 0.87; P = 0.021) compared patients without HF at baseline.[10] Empagliflozin was related to a 35 percent decrease in the relative risk of HHF compared with placebo in EMPA-REG OUTCOME.[11]

In DAPA-HF, the risk of HHF was lower in the dapagliflozin group for patients with (12.8% vs. 16.2%; P = 0.017) or without (7.2% vs. 11.2%; P < 0.001) T2DM.[12] SGLT2 inhibitors decreased the risk of cardiovascular death or HHF by 23% (P < 0.0001) and HHF by 31% (P < 0.0001), similar benefits were seen in patients with or without a history of HF or atherosclerotic cardiovascular disease.[13]

Safety and tolerability
Several clinical trials involving SGLT-2 inhibitors in T2DM patients have shown more adverse reactions such as genital infections, amputations, DKA, and fractures in SGLT-2 inhibitor compared with placebo.[14]



CONCLUSION

DM is associated with increased CV risk and SGLT2i were the first antidiabetic drugs that demonstrated impressive CV benefits apart from their glucose-lowering effect. In this review, we have outlined the main effect of four commercially available SGLT2i on glycemic control and on CV disease. SGLT2i reduce HbA1c by 0.5%–1.0% by inhibiting the absorption of glucose from the proximal tubule of the kidney, causing glycosuria. The predominant pathophysiological mechanisms that may explain the CV benefits of SGLT2i include plasma volume and diuresis, cardiac fibrosis, myocardial metabolism, as well as adipokine kinetics. Genital or urinary tract infections, amputations, fractures (canagliflozin), osmotic diuresis, ketoacidosis, sarcopenia and hypotension are common with SGLT2 inhibitors. SGLT2 inhibitors have a lower risk of hypoglycemia than glimepiride. The FDA has also issued a safety warning for canagliflozin and dapagliflozin, which may cause AKI or fractures. The balance of benefits and risks and risk mitigation strategies for SGLT2 inhibitors should be carefully considered.[15]

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