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SGLT2 Inhibitors

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INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a chronic progressive disease characterized by hyperglycemia that results from insulin resistance, diminished or absent insulin secretion, or both. Morbidity and mortality associated with diabetes is high, resulting from a spectrum of complications, primarily cardiovascular disease and nephropathy.

Glucose-lowering therapies with insulin-dependent mechanisms of action, lose efficacy over time as both endogenous insulin secretion and insulin sensitivity decrease. Side effects such as hypoglycaemia and weight gain are significant issues in management, especially in the context of high prevalence of obesity and cardiovascular diseases in this patient population.

The sodium-glucose co-transporter 2 inhibitors (SGLT2i) are a new class of medications for the treatment of type 2 diabetes which improve glucose control by increasing urinary glucose excretion. These agents are efficacious as monotherapy and add-on therapy for patients with type 2 diabetes uncontrolled on metformin, sulfonylureas, insulin, and other antihyperglycemic combinations.

HISTORY AND DEVELOPMENT OF SGLT2I

Phlorizin is a bitter white glycoside which acts as a non-selective inhibitor of SGLT-1 and SGLT-2, and was isolated from the root bark of the apple tree by French chemists in 1835. In the late 19th century, phlorizin due to its bitter taste was used as an anti-malarial and other infectious diseases. During its use it was noted that high doses of phlorizin caused glycosuria. Since then, phlorizin has been shown to normalise blood glucose levels in pancreatectomised diabetic rat models. But it has not been developed as a glucose-lowering drug due to a combination of its poor bioavailability, poor side-effect profile, which is likely to be a result of its non-selective action (its metabolite, phloretin, inhibits SGLT-1 in the intestinal mucosa causing malabsorption of glucose and galactose). Hence, selective SGLT2 inhibitor was the need of the hour.

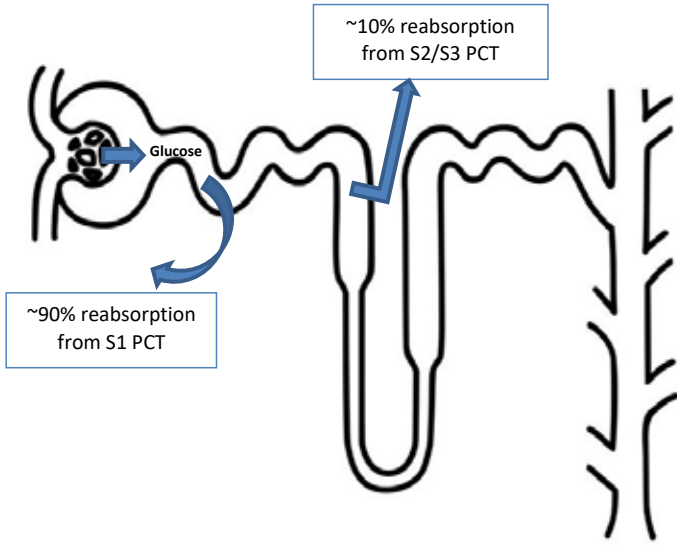

Fig. 1: Renal handling of glucose transport. PCT, proximal convoluted tubule

MECHANISM OF ACTION OF SGLT2I

The mechanism of action of SGLT2i is based on the role of kidneys in glucose metabolism and homeostasis. The kidney plays a significant role in glucose homeostasis through gluconeogenesis and glomerular filtration and reabsorption of glucose in the proximal convoluted tubules. Nearly all of the glucose filtered by the glomeruli (>99%) is reabsorbed in a healthy adult and returned to the circulation (~90% reabsorption take place from S1 segment of proximal convoluted tubule while ~10% reabsorption take place from S2/S3 segment of proximal convoluted tubule) (Figure 1). At plasma glucose concentrations beyond the resorptive threshold (~180 g/d), glucose begins to appear in the urine.

Glucose reabsorption occurs primarily within the proximal renal tubule. This occurs through carrier proteins - sodium-glucose transporter 1 (SGLT1) and SGLT2 which catalyze the active transport of glucose across the luminal membrane.

The SGLT2 transporter is found primarily in the S1 segment of the proximal tubule and accounts for approximately 90% of reabsorbed glucose, with expression limited to within the kidney.

SGLT1 is a low-capacity transporter found more distal in the S2/S3 segment of the proximal tubule and is involved with reabsorption of the remaining glucose load. It is primarily involved with glucose absorption within the gastrointestinal tract.

SGLT2 couples glucose with the transport of sodium and actively pumps it against a concentration gradient across the luminal membrane. Glucose passively diffuses out of the cell via facilitative glucose transporters (GLUT) 1 and 2.

The filtered glucose load is the product of the plasma glucose concentration and the glomerular filtration rate (GFR). As the plasma glucose concentration increases, the

filtered glucose load also increases in a linear manner. When the reabsorption capacity of the proximal tubule is surpassed, as occurs during hyperglycemia, glucose appears in the urine. This maximum reabsorption capacity is called as 'the maximum transport rate (Tm)'.

In healthy individuals without diabetes, Tm for glucose is reached at blood glucose concentrations of approximately 200 mg/dL. On the other hand the mean Tm for glucose has been reported to be higher – approximately 20% or more compared with healthy individuals.

Consequently, suppressing renal glucose reabsorption and effectively increasing urinary glucose excretion via SGLT2 inhibition is a logical approach to glycemic control. Since SGLT2 is only expressed in the kidney, the effects of SGLT2 i are limited to glycosuria and associated salt and water losses.

Several SGLT2i including canagliflozin, dapagliflozin, ipragliflozin, empagliflozin, and ertugliflozin have been developed or are currently undergoing clinical trials. Dapagliflozin, canagliflozin and empagliflozin have now been approved for clinical use in patients with T2DM in several countries.

The available SGLT2 inhibitors share similar pharmacokinetic characteristics, with a rapid oral absorption, a long elimination half-life allowing once-daily administration, an extensive hepatic metabolism mainly via glucuronidation to inactive metabolites, the absence of clinically relevant drug-drug interactions and a low renal elimination as parent drug. SGLT2 co-transporters are responsible for reabsorption of most (90 %) of the glucose filtered by the kidneys.

CLINICAL EFFICACY OF SGLT2 INHIBITORS

Glycemic benefits

Results of numerous placebo-controlled randomised clinical trials of 12-104 weeks duration have shown significant reductions in glycated haemoglobin (HbA1c), resulting in a significant increase in the proportion of patients reaching HbA1c targets. Significant lowering of fasting plasma glucose is observed when SGLT2i were administered as monotherapy or in addition to other glucose-lowering therapies including insulin in patients with T2DM. In head-to-head comparison trials of up to 2 years, SGLT2 inhibitors exerted similar glucose-lowering activity compared to metformin, sulphonylureas or sitagliptin. The durability of the glucose-lowering effect of SGLT2 inhibitors has been shown to be good in clinical trials.

The 52 week CANTATA-M study assessed the long-term efficacy and safety of canagliflozin monotherapy in patients with T2DM inadequately controlled with diet and exercise.

This study showed that canagliflozin monotherapy provided sustained improvement in glycemic control and body weight reduction, and was generally well tolerated in patients with T2DM over 52 weeks compared to sitagliptin.

As an add on to metformin, canagliflozin 100 and 300 mg was associated with significant glycemic improvements and body weight reductions and also found to be well tolerated compared with metformin alone in drug-naive patients with T2DM over 26 weeks. Combination therapy provided statistically significant greater reductions in HbA1c and body weight with a significantly higher proportion of patients achieving their glycemic goals.

Dapagliflozin 2.5 or 5 mg twice daily added to metformin was also effective in reducing glycaemic levels in patients with type 2 diabetes inadequately controlled with metformin alone as assessed through reduction in HbA_1c and FBG.

SGLT2i as an add on to dual or triple therapy regimens

The efficacy and safety of canagliflozin as an add-on to metformin plus sulphonylurea in patients with T2DM was evaluated in a randomised, double-blind, placebo-controlled, Phase 3 study.

HbA1c was significantly reduced with canagliflozin 100 and 300 mg vs. placebo at week 26 (-0.85%, -1.06%, and -0.13%; $p < 0.001$); these reductions were maintained at week 52 (-0.74%, -0.96%, and 0.01%). Both canagliflozin doses reduced FPG and body weight vs. placebo at week 26 ($p < 0.001$) and week 52.

The efficacy and safety of canagliflozin, has also been similarly evaluated in patients with T2DM inadequately controlled with metformin and pioglitazone and was found to improve glycaemic control, reduced body weight and systolic BP, and also found to be well tolerated.

Canagliflozin significantly improved health related quality of life, a benefit attributed to the additional weight loss benefits of the drug.

SGLT2i improves beta cell function

Canagliflozin has been shown to increase beta cell glucose sensitivity compared with placebo. Three separate phase 3 studies demonstrate that sustained treatment with canagiflozin for 6 to 12 months improved measures of beta cell function

Experience in Indian patients

Several Indian studies have shown canagliflozin to provide glycaemic control, body weight reduction, and good tolerability in Indian patients with T2DM similar to that seen in patient populations across the world.

Findings from this analysis support canagliflozin as an effective therapeutic option for patients with T2DM in India who may be on a range of background therapies.

EXTRA-GLYCEMIC BENEFITS

SGLT2i and blood pressure reduction

Emerging data suggests that the SGLT2 inhibitors provide a meaningful reduction in blood pressure (BP), although the precise mechanism of the blood pressure drop remains incompletely elucidated. It has been suggested that the blood pressure reduction is partially due to a combination of diuresis, nephron remodelling, reduction in arterial stiffness, and weight loss.

Since the main reason for reduction in BP has been attributed to decrease in intravascular volume associated with osmotic diuresis and natriuresis, the events of hypotension were, more common in patients particularly at risk of volume depletion, such as elderly patients, patients with renal impairment or those on loop diuretics.

Mean reductions (from baseline) in systolic BP of 3.6–6.7 mmHg with dapagliflozin were noted across studies up to 52 weeks, with no notable increases in the incidence of orthostatic hypotension. Sustained, although somewhat smaller, decreases in systolic BP were noted with dapagliflozin 10mg over 1–4 years.

Reductions in systolic BP of 3.3–5.4 and 4.3–6.9mmHg with canagliflozin 100 and 300mg, respectively, were noted across studies up to 52 weeks. Canagliflozin has shown to rapidly reduce 24 hour ABPM-assessed SBP both of which are important predictors of clinical CV risk and future events.

SGLT2i and weight loss

Increased renal glucose elimination also assists weight loss and these results have been very consistent across the trials and they represent additional advantages for SGLT2 inhibitors when compared with other oral glucose-lowering agents. In a 104 week study evaluating effect of canagliflozin on body weight and body composition, more patients on canagliflozin experienced ≥5% weight loss with canagliflozin with significant reduction in BMI and waist circumference. Moreover, it is also found that the weight loss occurring with SGLT2 inhibitors is majorly due to loss of fat mass.

SGLT2i and risk of hypoglycaemia

In various clinical trials, the lower risk of hypoglycemia is observed with the usage of SGLT2i compared to sulphonylureas and was similarly low as that reported with metformin, pioglitazone or sitagliptin.

Renoprotective effects of SGLT2i

Studies suggest that SGLT2i offer additional renoprotective effects. Canagliflozin 100 or 300 mg/d, compared with glimepiride, slowed the progression of renal disease over 2 years in patients with T2DM, and canagliflozin may confer renoprotective effects independently of its glycemic effects. In patients with T2DM at high cardiovascular risk, empagliflozin was associated with slower progression of kidney disease and lower rates of clinically relevant renal events than placebo when added to standard care.

SGLT2i in patients with renal impairment

SGLT2i is associated with an acute, dose-dependent reduction in glomerular filtration rate (eGFR) by ~5 ml/min/1.73m2 and ~30-40% reduction in albuminuria. These effects suggest that proximal tubular natriuresis activates renal tubuloglomerular feedback through increased macula densa sodium and chloride delivery, leading to afferent vasoconstriction. On the basis of reduced glomerular filtration, glycosuric and weight loss effects are attenuated in patients with chronic kidney disease (CKD, eGFR <60 ml/min/1.73m2). In contrast, BP lowering, eGFR and albuminuric effects are preserved, and perhaps exaggerated in CKD.

The pharmacodynamics response to SGLT2 inhibitors declines with increasing severity of renal impairment, and it is recommended that the prescribing information for each SGLT2i should be consulted regarding dosage adjustments or restrictions in moderate to severe renal dysfunction. Caution is also recommended in the elderly population because of a higher risk of renal impairment, orthostatic hypotension and dehydration, even if the absence of hypoglycaemia represents an obvious advantage in this population.

SGLT2i and diabetic ketoacidosis

Investigations into postmarketing reports of SGLT-2 inhibitor–associated diabetic ketoacidosis (DKA), which has been reported to occur in type 1 diabetes and T2DM patients with less than expected hyperglycemia (euglycemic DKA) , are on-going. However after a thorough review of the evidence during an October 2015 meeting, an American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE) Scientific and Clinical Review expert consensus group found that the incidence of DKA is infrequent and recommended no changes in SGLT-2 inhibitor labelling.

To minimize the risk of SGLT2i associated DKA, the AACE –ACE recommend to stop SGLT2i at least 24 hours prior to elective surgery, planned invasive procedures, or anticipated severe stressful physical activity such as running a marathon. In the event of an emergency surgery or any extreme stress event, the drug should be stopped immediately and appropriate clinical care should be provided. The recommendations also suggest that patients taking SGLT2 inhibitors should avoid excess alcohol intake and very-low-carbohydrate/ketogenic diets. However routine measurement of blood ketones is not recommended because urine ketone measurement can be misleading, and measurement of blood ketones is preferred for diagnosis of DKA in symptomatic patients.

Genital infections and urinary tract infections

High levels of glycosuria induced by SGLT2i raise the risk of developing genital infections (mostly candidiasis) and to a relatively lesser extent, urinary tract infections (UTIs) in treated patients. The most frequently reported adverse events are female genital mycotic infections, while urinary tract infections are less commonly observed and generally benign. Both infections respond to appropriate anti-infective agents.

Cardiovascular safety of SGLT2i

Although cardiovascular (CV) mortality is the principal cause of death in individuals with T2DM, reduction of plasma glucose concentration alone does not significantly lower CV disease (CVD) risk. SGLT2i exert multiple metabolic benefits, and the risk factors beyond glucose that can potentially be modulated positively with these agents include blood pressure, weight, visceral adiposity,

hyperinsulinemia, arterial stiffness, albuminuria, circulating uric acid levels and oxidative stress.

In a recent CV safety study on empagliflozin in T2DM patients with high CVD risk empagliflozin reduced the primary major adverse cardiac event end point (CV death, nonfatal myocardial infarction, nonfatal stroke) by 14%. This beneficial effect was driven by a 38% reduction in CV mortality with no significant decrease in nonfatal myocardial infarction or stroke. Empagliflozin also caused a 35% reduction in hospitalization for heart failure without affecting hospitalization for unstable angina.

A recently published meta-analysis substantiated this benefit as a class effect providing clear evidence that SGLT2 inhibition protects against major cardiovascular events, cardiovascular death, heart failure, and death from any cause.

The reasons for this benefit have been hypothesised in the "thrifty substrate hypothesis". It has been suggested that under conditions of mild, persistent hyperketonemia, such as those that prevail during treatment with SGLT2 i, b-hydroxybutyrate is freely taken up by the heart (among other organs) and oxidized in preference to fatty acids. This substrate selection improves the transduction of oxygen consumption into work efficiency in the endangered myocardium (and also improves metabolic status and function of other organs, mainly the kidney). These mechanisms in addition to enhanced diuresis and reduced blood pressure probably results in cardioprotection.

Possible factors contributing to CV effects of SGLT2i

- Glycemic control
- Decrease in body weight and visceral adiposity
- Decrease in blood pressure and arterial stiffness
- Decrease in oxidative stress
- Decrease in uric acid level
- Decrease in albuminuria

Effect of SGLT2i on bone

Inhibition of tubular glucose reabsorption has the potential to affect mineral metabolism and possibly bone health. On the other hand there is no data relating to the expression of SGLT2 in relevant bone-derived cell types relating to bone homeostasis, such as osteoblasts or osteoclasts suggesting that SGLT2 is unlikely to play a major functional role within bone tissue. Across clinical studies, canagliflozin did not meaningfully affect calcium homeostasis or hormones regulating calcium homeostasis.

A meta-analysis based on available randomised clinical trial data also does not support the harmful effect of SGLT2 inhibitors on fracture.

SGLT2i after metformin –comparisons with dipeptidyl peptidase-4 inhibitors (DPP- 4 inhibitors)

There are four head-to-head studies comparing DPP4i with SGLT2i either in treatment naive patient or on background metformin therapy or background SU plus metformin therapy. There was no significant difference among these agents in A1c reduction but SGLT2i were associated with consistent weight loss and BP reduction compared to DPP4i.

Place of SGLT2 inhibitors in therapy

The Update to the Position Statement of the American Diabetes Association and the European Association for the Study of Diabetes recommends the use of SGLT2 inhibitors as one of the second line therapy when monotherapy with metformin fails.

The AACE/ACE 2016 guidelines state that SGLT2 i as one of the acceptable alternatives to metformin as initial therapy.

The most recent guidance document from the National Institute of Health and Care Excellence (NICE), UK, on SGLT2i recommends canagliflozin, dapagliflozin or empagliflozin as a monotherapy options for treating T2DM in adults for whom metformin is contraindicated or not tolerated and when diet and exercise alone do not provide adequate glycaemic control, only if:

- a dipeptidyl peptidase-4 (DPP-4) inhibitor would otherwise be prescribed and
- a sulfonylurea or pioglitazone is not appropriate.

CONCLUSIONS

The kidney plays a key role in glucose homeostasis and the pathophysiology of T2DM. SGLT2 inhibitors, canagliflozin, dapagliflozin and empagliflozin are a new class of antihyperglycemic agents for the treatment of T2DM with a novel insulin-independent mechanism of action that targets the kidney. The SGLT2 inhibitors decrease renal glucose reabsorption, thereby increasing urinary glucose excretion and lowering plasma glucose levels in patients with hyperglycemia.

Modest reductions in body weight and blood pressure have also been observed following treatment with SGLT2 inhibitors. SGLT2 inhibitors appear to be generally well tolerated, and have been used safely when given as monotherapy or in combination with other oral anti-diabetes agents and insulin. The risk of hypoglycemia is low with SGLT2 inhibitors. Typical adverse events appear to be related to the presence of glucose in the urine, namely genital mycotic infection and lower urinary tract infection, and are more often observed in women than in men.

Data from long-term safety studies with SGLT2 inhibitors and from head-to-head SGLT2 inhibitor comparator studies are needed to fully determine their benefit-risk profile, and to identify any differences between individual agents. However, given current safety and efficacy data, SGLT2 inhibitors may present an attractive option for T2DM patients who are failing with metformin monotherapy, especially if weight is part of the underlying treatment consideration.

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