Section A -Research paper

Sodium-Glucose co-transporter 2 inhibitors: Review Article

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Abstract:

Although the benefits of sodium glucose cotransporter 2 inhibitors (SGLT2i) on cardiovascular events have been reported in patients with heart failure (HF), the impact of SGLT2i on cardiac remodelling remains to be established.

Keywords: Sodium-Glucose Cotransporter-2 Inhibitors, Left Atrial Function, heart failure.

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Introduction:

Sodium-glucose co-transporter-2 (SGLT-2) inhibitors are antihyperglycemic agents acting on the SGLT-2 proteins expressed in the proximal convoluted tubules. These drugs exert their effect by preventing the reabsorption of filtered glucose from the tubular lumen. There are four SGLT-2 inhibitors: canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin that are approved by Food Drug Administration (FDA) for their use in adults. All four agents are approved for use in adults with type 2 diabetes mellitus (DM) to improve blood sugar control adjunct to diet and exercise**.(1).**

Sodium–glucose co-transporter 2 (SGLT2) inhibitors have recently been recommended as a foundational therapy for patients with heart failure (HF) and reduced ejection fraction (HFrEF) because of their favourable effects on mortality, clinical events and quality of life**. (2)**

The SGLT2 inhibitor class of glucose-lowering agents has recently shown beneficial effects to reduce the onset and progression of renal complications in people with and without diabetes. **(3)**

Natural History:

The development of SGLT2 inhibitors can be traced from the nineteenth-century observations that the glucoside phlorizin caused glucosuria. **(4)**

Preclinical studies in the 1980s showed that phlorizin treatment could control hyperglycaemia in partially pancreatectomised rats, but clinical application awaited synthetic analogues that evaded intestinal glucosidase degradation and offered improved potency

and selectivity to inhibit SGLT2 rather than SGLT1**. (5).**

SGLT2 is found almost exclusively in the luminal membranes of epithelial cells lining the first and second segments of the proximal tubules, where it mediates reabsorption of most (typically ≥ 90%) of filtered glucose. SGLT1 in the luminal membranes of cells lining the third (straight) segment of the proximal tubules mediates reabsorption of low concentrations of glucose remaining in the tubule. SGLT1 is most abundant in the apical membranes of enterocytes where it mediates glucose uptake from the intestinal lumen. These sites are demonsterated in figure (1). **(6)**

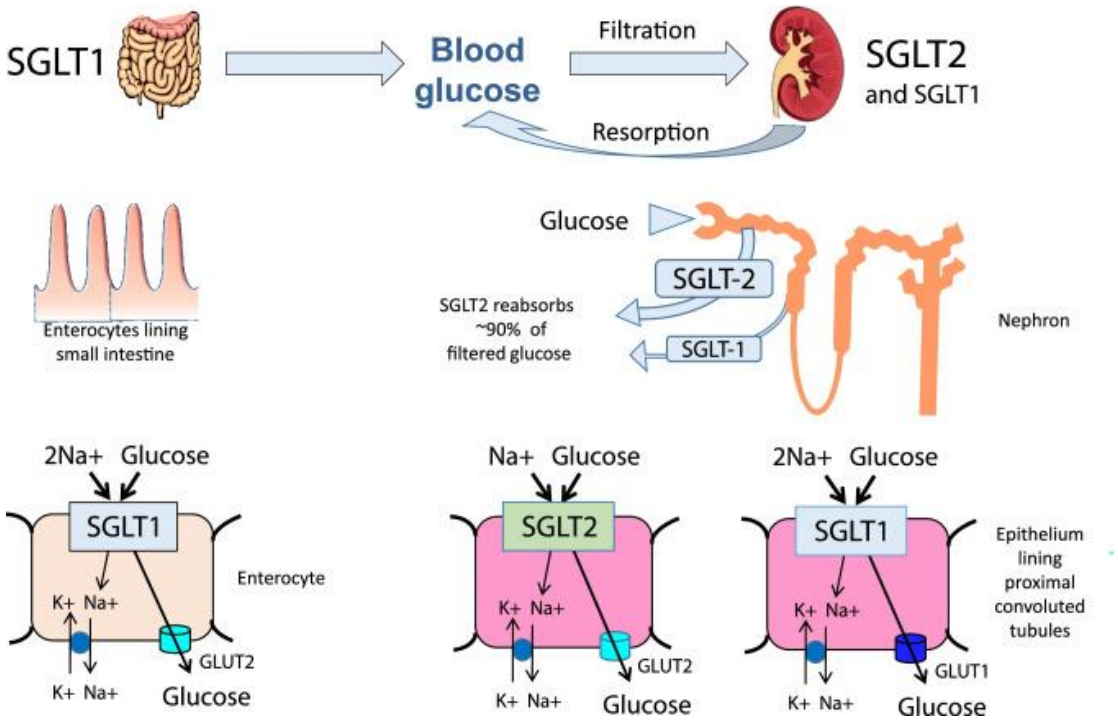

Fig (1): Key sites of action of sodium-glucose co-transporter (SGLT) inhibitors. **(6)**

The hyperglycaemia of diabetes means that greater than normal amounts of glucose are filtered from the glomeruli into the proximal tubules, and increased amounts are reabsorbed, associated with a compensatory upregulation of SGLT2 and SGLT1 expression **(7).**

Nevertheless, the renal threshold for glucose is often breached, and the glucosuria is enhanced by SGLT2 inhibitors which act by reversible competitive inhibition without being transported themselves **(8)**

They bind to the co-transporters at the luminal surface with greater affinity than glucose and with a residence time of several minutes. Thus, a trivial (therapeutic) concentration of an SGLT inhibitor in the filtrate can prevent the reabsorption of a large (up to about 100 g/day) amount of filtered glucose**.(3)**

Mechanism of action:

SGLT-2 are proteins expressed in the proximal convoluted tubules of the kidneys that exert their physiologic function by reabsorbing filtered glucose from the tubular lumen. All four SGLT-2 inhibitors reduce the reabsorption of filtered glucose, decrease the renal threshold for glucose (RTG), and promote urinary glucose excretion. SGLT2 inhibitors lower HbA1c by 0.7% **(9)**

By inhibiting the SGLT-2-dependent glucose and sodium reabsorption, there is an increase in distal tubular sodium load; the resultant inhibition of the renin-angiotensin-aldosterone system and reduction of afterload and preload is cardioprotective. **(10)**

Treatment with dapagliflozin improved endothelial function and arterial stiffness and had an overall favorable effect on the vasculature due to reduced oxidative stress**. (11)**

SGLT2 inhibitors reduce afterload by arterial vasodilation and preload by natriuresis and diuresis and decrease uric acid levels. SGLT2 inhibitors also alter cardiac fuel metabolism, shifting away from carbohydrate utilization to ketogenesis. Favorable hemodynamic effects and reduction in cardiac biomarkers may explain the beneficial effect of SGLT-2 inhibitors in patients with heart failure**.(12)**

The mechanism by which SGLT2 inhibitors may be nephroprotective is by increasing distal sodium delivery and inhibiting tubuloglomerular feedback leading to afferent vasoconstriction and a decrease in intraglomerular pressure. Interference with proximal glucose reabsorption and proximal sodium reabsorption results in natriuresis SGLT2 inhibitors decrease effective circulating volume, decrease blood pressure, and induce some weight loss. Additionally, SGLT2 inhibitors alter factors that promote inflammation and fibrosis, lowers kidney hypoxia, and alter mitochondrial metabolism in kidney tissue**.(13)**

Benefical effects:

1-SGLT2I as anti-diabetic:

Meta-analyses of the reduction in HbA1c with SGLT2 inhibitors in type 2 diabetes have consistently noted reductions of about 0.5 to 1% (6–11 mmol/mol) from a baseline of around 8% (64 mmol/mol). **(14).**

SGLT2 inhibitors have a different mechanism of action to other glucose-lowering agents, they can be used in combination with other agents including insulin and can often reduce the amount of insulin required in type 2 and type 1 diabetes. **(15)**

In type 2 diabetic patients, the weight reducing effect of SGLT2 inhibitors has typically been around 3 kg, levelling out by 6–12 months, although ‘real world’ observational studies have often noted reductions > 6 kg that continue beyond a year**.(16)**

2-Cardio-vascular effect:

SGLT2 inhibitors have consistently reduced blood pressure (systolic by 3–5 mmHg and diastolic by 2–3 mmHg)

during clinical trials without causing hypotension. (**17)**

SGLT2 inhibitors have also consistently reduced the risk of new heart failure and worsening of existing heart failure during clinical trials**. (18)**

Measures of atherosclerotic cardiovascular disease (cardiovascular deaths, non-fatal myocardial infarction and stroke) have also been reduced in some studies with SGLT2 inhibitors **(19)**

3-Effect on renal system;

All types of diabetes are associated with increased risk of impaired kidney function (referred to as diabetic nephropathy or diabetic kidney disease (DKD)). This is typically recognised by a progressive chronic kidney disease (CKD) with an estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73m2 that can be attributed to diabetes. (**20)**

SGLT2 inhibitors can protect against the onset of DKD and slow disease progression independently of and additively to blockade of the renin–angiotensin–aldosterone system **(21)**

SGLT2 inhibitor can provide renal protection through a decreased rate of decline in eGFR and reduced onset or progression of albuminuria. This has been seen in people with and without diabetes and appears to be independent of the stage of CKD, the extent of albuminuria, ethnicity, age, gender, reduction of body weight or presence of cardiovascular disease**.(22)**

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