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RESEARCH ARTICLE

SGLT2: A PERSPECTIVE ON PATHOPHYSIOLOGY AND IMPACT OF SGLT2 INHIBITION ON RENAL FUNCTION

Manish Hathial, Chandrakiran Hathial, Jayant Makwana, Anita George, Priyanka Bhat, Bhagyashree Yadav and Ganesh Nandgiri

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Abstract

In individuals with diabetes, kidney size and glomerular filtration rate (GFR) tend to increase, and elevated GFR is a risk factor for diabetic kidney disease. Hyperfiltration occurs when high glucose levels in the glomerular filtrate causes increased reabsorption of glucose and sodium by the sodium-glucose cotransporters SGLT2 and SGLT1 in the proximal tubule. This hyperfiltration puts additional stress on the filtration barrier and increases the oxygen demand for reabsorption. Tubular growth is associated with a molecular signature that leads to inflammation and fibrosis. SGLT2 inhibitors play a significant role in mitigating hyperfiltration by reducing sodium and glucose reabsorption, normalizing feedback signals, and alleviating the physical stress on the filtration barrier. This tubule-centered model of diabetic kidney physiology explains the positive effects of SGLT2 inhibitors on renal outcomes, as demonstrated in large-scale clinical trials. Although these medications primarily target glucose reabsorption , patients with type 2 diabetes mellitus benefit from reduced blood glucose levels along with various other physiological advantages. Data support their use for modifying risk of kidney disease progression and acute kidney injury, not only in patients with type 2 diabetes at high cardiovascular risk, but also in patients with chronic kidney disease or heart failure irrespective of diabetes status, primary kidney disease, or kidney function.

Introduction:-

The cell membrane consists of a hydrophobic lipid bilayer, which allows small molecules like oxygen and carbon dioxide to pass through via diffusion along their concentration gradient. However, larger molecules, cations (e.g., K+, Na+, and Ca2+), anions (e.g., Cl− and HCO3−), hydrophilic molecules, and macromolecules (e.g., proteins and RNA) cannot penetrate the lipid bilayer due to impermeability. Hence, these substances require specific transport systems. Monosaccharide's like glucose are hydrophilic and cannot pass through the lipid bilayer. They rely on carrier proteins to facilitate their diffusion across the bilayer. In humans, three gene families encode for glucose transporters: SLC2A, SLC5A, and SLC50A. [1]

Membrane transporters can be broadly classified into two categories: channels and carriers. Glucose transporters belong to the major facilitator superfamily (MFS), which includes more than 10,000 members across 74 families of membrane transporters that transport various molecules. [2]

Corresponding Author:- Manish Hathial

Glucose is transported across cell membranes and tissue barriers by different mechanisms, sodium-independent glucose transporters (facilitated transport), sodium-dependent glucose symporters (secondary active transport), and glucose uniporters through SWEET proteins.

These processes are facilitated by GLUT proteins (SLC2 genes), SGLT proteins (SLC5 genes), and SLC50 genes, respectively. [3]

Sodium Glucose linked Transporter

Sodium–glucose linked transporter-1 (SGLT1) was the first SGLT to be discovered and extensively studied. [4] The SGLT family of transporters consists of integral membrane proteins with 14 transmembrane helices, and both the COOH (C-terminus) and NH2 (N-terminus) terminals face the extracellular space. The SGLT family are relatively large proteins, ranging from 60 to 80 kilodaltons (kDa) in molecular weight. They are composed of approximately 580 to 718 amino acids, depending on the specific member of the family. The SLC family contains hundreds of members and has three main families involved in glucose transport: SLC2, SLC5, and SLC50. Specifically, the SGLT class of transporters are encoded by the SLC5 gene type. [4,5] There are twelve different transporter proteins encoded by the SLC5 genes, with six of them going under the alias of SGLT.

Table 1:- Nature, function and location of SGLT family [4,5,6]

Transporter Name	Nature	Function	Substrate	Location
SGLT1 (SLC5A1)	High Affinity in Intestinal cell High Affinity, Low Capacity in Proximal Tubutle	Involved in proximal tubule glucose reabsorption through transportation of glucose from the lumen into the cell. Expressed in wider variety of tissues.	Glucose, galactose, urea	Intestine, kidney, liver, heart, lungs
SGLT2 (SLC5A2)	Low Affinity High Capacity	Involved in proximal tubule glucose reabsorption like SGLT1. Commonly inhibited in T2DM treatment.	Glucose	Intestine, kidney
SGLT3 (SLC5A4)	Low affinity	May be involved in glucose sensing, does not transport glucose.	Sodium ions, hydrogen ions	Small intestine, skeletal muscle, kidney, uterus and testis
SGLT4 (SLC5A9)	Low Affinity	May be involved in mannose homeostasis along with transport of glucose.	Mannose, fructose, glucose	Kidney, small intestine, brain, kidney, liver, heart, uterus and lung
SGLT5 (SLC5A10)	High affinity to Mannose and Fructose	Involved in sodium dependent glucose transport along with its other substrates.	Mannose, fructose, glucose	Kidney cortex
SGLT6 (SLC5A11)	High Affinity for Myo-inositol, Low Affinity for Glucose	Does not transport glucose, expression is found throughout the body.	Myo-inositol, chiro-inositol	Thyroid, brain, heart, muscle, spleen, liver, lung.

SGLT, Sodium–glucose linked transported (sodium-dependent glucose transporter)

SGLT1 is essential for fast absorption of glucose and galactose in the intestine while the expression of SGLT2 is largely confined to the early part of the kidney proximal tubules, where it reabsorbs the bulk part of filtered glucose.

Physiologic effect of SGLT2

SGLT2 protein is expressed in the brush border membrane of the early proximal convoluted tubule. SGLT2 is a member of the SGLT (SLC5) family that contains six SGLT proteins, including SGLT3 which is a glucose sensor expressed in neurons.[7] SGLT2 is a specialized transporter with a high capacity but low affinity for glucose. It shows a strong preference for glucose while its affinity for galactose is significantly lower[8] and can be inhibited by phlorizin. The coupling stoichiometry of Na+ to glucose is 1:1. SGLT2 is responsible for the saturable Na+-dependent and phlorizin-sensitive transportation of D-glucose.

The daily amount of glucose filtered by the glomeruli in the healthy human kidney is (~ 100 mg/dL)160–180 gms of glucose per day gand almost all the filtered glucose (>99%) is reabsorbed along the tubular system by SGLT2 and SGLT1. Around 90% of the filtered glucose is reabsorbed in the early S1 segment of the proximal tubules, while a smaller fraction reaches the proximal straight tubule (comprising the later part of S2 segments and all of the S3 segments). The transportation of each glucose molecule is coupled either to the co-transport of one Na+ ion (SGLT2) or two Na+ ions (SGLT1). Once inside the cell, glucose can diffuse into the blood through GLUT2. To maintain the inwardly directed Na+ electrochemical gradient necessary for glucose transport across the brush border membrane, the Na+/K+-ATPase, located in the basolateral membrane, pumps Na+ out of the cell.[9] SGLT2, low affinity High capacity transporter is responsible for reabsorbing most of the filtered glucose load in the proximal tubule S1 segments. On the other hand, the high-affinity low-capacity glucose transporter, SGLT1, reabsorbs the remaining glucose molecules from the filtrate in the late proximal tubule, with predominantly GLUT1 in the basolateral membrane.

Upregulation of SGLT2 Expression in the Diabetic Kidney

Under diabetic conditions, there is an upregulation of SGLT2 expression in the proximal tubules. This increase has been observed in human tubular epithelial cells grown from the urine of patients with type 2 diabetes as compared to cells from control subjects without diabetes. The enhanced expression of SGLT2 in diabetic tubular cells has been associated with tubular growth stimulated by angiotensin (Ang) II and hepatocyte nuclear factor HNF1α. [10] Additionally, other potential regulators like NF-κB [11] and PKA signaling, the heterogeneous nuclear ribonucleoprotein F (Hnrnpf), [10] and nuclear factor erythroid 2-related factor 2 (NRF2) [12] may also play a role in this process. Furthermore, higher levels of SGLT2 protein and mRNA expression were detected in fresh kidney biopsies from individuals with type 2 diabetes and advanced nephropathy when compared to individuals with preserved kidney function and non-diabetic individuals. [13] This suggests a potential link between increased SGLT2 expression and the progression of diabetic kidney complications.

Hyperglycemia leads to an increased filtration of glucose, resulting in a higher load of glucose passing through the renal system. To preserve this valuable energy substrate, the capacity for tubular glucose transport is elevated in patients with both type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM) from approximately 400-500 g/day to about 500-600 g/day.

The growth and hypertrophy of the diabetic kidney may trigger a general increase in the transport machinery within the proximal tubule under diabetic conditions. This effect could be further exacerbated in cases of advanced nephropathy when nephrons are lost, and the remaining nephrons attempt to compensate.[14] The increase in SGLT2 expression at the apical membrane might be a consequence of the overall growth and hypertrophy of the diabetic proximal tubule. Studies in diabetic rats have shown that upregulation of SGLT2 protein expression is linked to the activation of angiotensin II (AngII) receptors in the basolateral membrane of the proximal tubule, along with the involvement of certain transcription factors.[15]

Insulin has also been suggested to play a role in this process by phosphorylating SGLT2 at Ser 624, thereby increasing its transport capacity. Consequently, postprandial insulin release may contribute to an increase in proximal tubular SGLT2 activity, enabling the retention of higher amounts of filtered glucose. [16]

The primary mechanisms and effects of SGLT2 inhibition

SGLT2 Inhibition on Glucose reabsorption

SGLT2 inhibitors are a class of medications that work by blocking this transporter, thereby reducing the reabsorption of glucose and increasing its excretion in the urine (glucosuria). Decreased Glucose Reabsorption: By inhibiting SGLT2, the renal glucose reabsorption capacity is reduced, bringing it down to the residual capacity of another glucose transporter called SGLT1. This leads to a sustained loss of glucose in the urine, resulting in a daily urinary glucose loss of approximately 40–80 grams.[17] Lowering Blood Glucose Levels: With the increased urinary excretion of glucose, blood glucose levels in patients with T2DM are lowered, resulting in improved glycemic control. This is reflected in a decrease in HbA1C levels (an indicator of long-term blood glucose control) by approximately 0.5–0.7%.[18]

Impact on Glomerular Hyperfiltration and Nephropathy

One of the most crucial reasons for inhibiting SGLT2 in the diabetic kidney is based on the tubular hypothesis of glomerular hyperfiltration and nephropathy. This hypothesis suggests that excessive glucose reabsorption in the

proximal tubules of the kidney contributes to glomerular hyperfiltration and may play a role in the development and progression of diabetic kidney disease. By inhibiting SGLT2 and reducing glucose reabsorption, this harmful process can potentially be mitigated.[19]

Weight Loss

SGLT2 inhibitors have a diuretic effect, which means they increase urine production and result in the loss of water and electrolytes, contributing to weight loss. Additionally, the excretion of glucose in the urine leads to calorie loss, shifting energy substrate utilization from carbohydrates to lipids, and reducing visceral and subcutaneous body fat. In patients with type 2 diabetes, including those in the EMPA-REG OUTCOME trial, the glucosuric effect of SGLT2 inhibition was consistently associated with a 2–3 kg lower body weight. [20]

Ketone Body Production

When SGLT2 inhibitors shift energy substrate utilization to lipids, adipose tissue releases free fatty acids that can be taken up by the liver to form ketone bodies. The oxidation of the ketone bodies is energetically more efficient than the oxidation of fatty acids because it results in a higher ATP/oxygen ratio than other substrates. According to the 'thrifty substrate' theory under conditions of mild, persistent hyperketonemia, such as during SGLT2 inhibitor therapy, β-hydroxybutyrate is freely taken up by the heart and oxidized instead of fatty acids and glucose . These ketone bodies can be utilized as an alternative energy source by various organs, including the kidneys, heart, brain, and muscles.[21]

Improved Pancreatic β-cell Function and Insulin Sensitivity

Lowering blood glucose levels and promoting weight loss with SGLT2 inhibitors can lead to improvements in pancreatic β-cell function and increased sensitivity to insulin, which are beneficial for individuals with T2DM. The SGLT2 inhibitors have been reported to ameliorate fatty liver, reduce visceral fat mass and increase insulin sensitivity. It was recently reported that the SGLT2 inhibitor luseogliflozin exerted protective effects on β-cell function and mass in obese T2D db/db mice. Pancreatic β-cell mass was larger in mice treated with luseogliflozin, which was due to increased β-cell proliferation and decreased β-cell apoptosis. Furthermore, expression levels of various β-cell-related factors, including insulin and insulin gene transcription factors, such as MafA and PDX1(pancreatic and duodenal homeobox 1), were significantly higher in mice treated with luseogliflozin.[22]

Inhibiting Potential Reduction of Glucotoxicity

SGLT2 inhibitors have the potential to reduce glucotoxicity, which refers to the damaging effects of prolonged exposure to high glucose levels, not only in the kidney but also in other organs outside of the kidney. 1 week treatment with empagliflozin, protective effects were seen on pancreatic β-cells in obese diabetic db/db mice.Expression levels of various β-cell-related factors, such as MafA and PDX1, insulin, the glucose transported Glut2, and GLP-1 receptor, were preserved in empagliflozin-treated mice.In addition, empagliflozin led to augmentation of β-cell proliferation. Combined, these findings suggest that SGLT2 can protect β-cells against glucose toxicity.[23]

Effects of SGLT2 inhibition on GFR

In diabetic kidney, it has been observed that the glomerular filtration rate (GFR) increases as a response to an elevated proximal reabsorption, aimed at restricting NaCl and fluid retention. An increase in glucose delivery to the Macula Densa indicates saturation of upstream SGLTs, leading to excessive reabsorption of sodium, glucose, and fluid. The increase in proximal reabsorption lowers Na^+-Cl^--K^+ concentrations at the macula densa (MD) and reduces tubular backpressure (hydrostatic pressure in the Bowman space), which, through the physiology of tubuloglomerular feedback (TGF) and an increase in glomerular hydrostatic filtration pressure, contributes to diabetic glomerular hyperfiltration.[24]

Inhibiting this compensatory rise in glomerular filtration rate (GFR) without offsetting the primary hyperreabsorption is expected to elevate blood pressure, as maintaining sodium homeostasis is a key mechanism in the body. Inhibition of SGLT2 has been found to mitigate hyper-reabsorption in the proximal tubule of the diabetic kidney, leading to a reduction in diabetes-associated glomerular hyperfiltration. This hyperfiltration is a consequence of the primary increase in proximal tubular reabsorption, which is reliant on the sodium-glucose cotransport mechanism.[25]

This short-term observable within a few minutes to hours/weeks of treatment initiation, GFR-lowering effect of SGLT2 inhibition has been confirmed in humans. T1DM patients with baseline hyperfiltration responded to treatment with SGLT2 for 8 weeks with a decrease in GFR, which was independent of lowering blood glucose levels. [26] Long-term studies (that is, with durations of months to years) that demonstrated a biphasic GFR response characterized by an initial reduction in GFR followed by preservation of GFR at the new, lower level.

Effect of Blood Glucose on the Response of the Macula Densa: Consequences at the Level of Tubule-Glomerular Feedback of SGLT2 Inhibitor

In diabetic renal pathophysiology, the presence of SGLT2-increased Na+/glucose reabsorption results in a lower urine NaCl concentration, leading to a decreased transit of NaCl across the dense macula (juxtaglomerular apparatus). The reduced NaCl concentration is perceived by the dense macula as a state of low volume and low perfusion. As a consequence, there is a decrease in Na+ delivery to the dense macula, which leads to a reduction in adenosine production. This, in turn, causes a vasodilating effect on the afferent glomerular arteriole, creating a relative disproportion with the efferent arteriole section. This imbalance results in intraglomerular hypertension and glomerular hyperfiltration. [27, 28]

Sodium-glucose cotransporter 2 (SGLT2) inhibition effectively counteracts the diabetes-induced excessive reabsorption of glucose and sodium in the early proximal tubule, leading to a decrease in hyperglycemia and an increased delivery of sodium chloride (NaCl) and fluid to the macula densa. As a result, the macula densa experiences higher concentrations of sodium, chloride, and potassium ([Na+/Cl−/K+]MD). [19] The elevation in [Na+/Cl−/K+]MD levels triggers a reduction in glomerular filtration rate (GFR) through tubuloglomerular feedback. This is achieved by inducing constriction in the afferent arteriole and, potentially, dilation in the efferent arteriole, both of which contribute to a decrease in glomerular capillary pressure (PGC). Furthermore, the increased delivery of fluid to the distal nephron causes a reduction in GFR by raising hydrostatic back pressure in the Bowman's space (PBOW).[19]

The reduction in GFR and PGC (and increasing PBow) helps to diminish the glomerular filtration of tubulo-toxic factors like albumin, growth hormones, and advanced glycation end products (AGEs). These factors, when filtered excessively, can exert harmful effects on the tubular system of the kidneys. Their interaction with the tubular cells requires energy, which can lead to cellular injury and promote conditions like hypoxia (lack of oxygen), impaired autophagy (the cellular recycling process), oxidative stress, inflammation, and fibrosis.

By inhibiting the excessive filtration of these tubulo-toxic factors and reducing the energy demand on the tubular cells, SGLT2 inhibitors can potentially mitigate the cascade of events that contribute to kidney damage and progression of diabetic kidney disease. Additionally, the increased excretion of glucose in the urine due to SGLT2 inhibition can lead to a reduction in the levels of other pro-inflammatory and pro-fibrotic substances, further protecting the kidneys from damage.[19]

Moreover, SGLT2 inhibition not only lowers blood glucose levels but also induces a shift in glucose reabsorption downstream, particularly to the S3 segment of the proximal tubule. This shift allows glucose uptake by SGLT1 to compensate for the inhibition of SGLT2, thereby reducing the risk of hypoglycemia.

Meta-analyses of clinical studies indicate that SGLT2 inhibition induces small increases in serum creatinine but reduces the incidence of acute kidney injury (AKI). SGLT2 Inhibition decreased urinary levels of markers of glomerular and tubular injury in T2DM patients . Along these lines, luseogliflozin reduced hypoxia and fibrosis and prevented renal capillary rarefaction in a murine model of renal ischemia-reperfusion (IR) [29,30]

Effects of sodium glucose co-transporter-2 inhibitors on kidney outcomes:

Large trials have shown that sodium glucose co-transporter-2 (SGLT2) inhibitors reduce the risk of adverse kidney and cardiovascular outcomes in patients with heart failure or chronic kidney disease, or with type 2 diabetes and high risk of atherosclerotic cardiovascular disease.

Systematic review and meta-analysis of SGLT2 inhibitor trials (13 trials involving 90413 participant) was anaylsed for 90409 participants (74804 [82·7%] participants with diabetes [>99% with type 2 diabetes] and 15605 [17·3%] without diabetes. Compared with placebo, allocation to an SGLT2 inhibitor reduced the risk of kidney disease

progression by 37% (relative risk [RR] 0·63, 95% CI 0·58–0·69) with similar RRs in patients with and without diabetes. [31]

Randomised data support their use for modifying risk of kidney disease progression and acute kidney injury, not only in patients with type 2 diabetes at high cardiovascular risk, but also in patients with chronic kidney disease or heart failure irrespective of diabetes status, primary kidney disease, or kidney function.

EMPA-KIDNEY and DAPA-CKD were large-scale clinical trials investigating the effects of SGLT2 inhibitors (empagliflozin and dapagliflozin, respectively) in patients with chronic kidney disease (CKD) to determine their impact on kidney disease progression and cardiovascular outcomes. The trials aimed to evaluate the efficacy and safety of SGLT2 inhibitors in patients with different levels of kidney function, of nearly 3000 patients with an eGFR of 20–30 mL/min per 1·73 m². A total of 489 kidney disease progression outcomes accrued in those with an eGFR less than 30 mL/min per 1·73 m² in those two trials.

The study DAPA-CKD showed that SGLT2 inhibition reduced the risk for kidney disease progression by 28%, regardless of diabetes, level of eGFR, and RAS inhibitors use.

The EMPA-KIDNEY trial adds substantially to the existing evidence by showing consistent benefits among 3569 patients (54.0%) without diabetes and, separately, among 2282 patients (34.5%) with an eGFR of less than 30 ml per minute per 1.73 m^2.

Data from patients with non-diabetic causes of chronic kidney disease DAPA-CKD and EMPA-KIDNEY trials, SGLT2 inhibitors reduced the risk of kidney disease progression by 30% (0·70, 0·50–1·00) in patients with ischaemic and hypertensive kidney disease, by 40% (0·60, 0·46–0·78) in patients with glomerular diseases, and by 26% (0·74, 0·51–1·08) in patients with other or unknown causes combined. Notably, these benefits extend across a diverse range of kidney function levels, despite a slight reduction in the effects of SGLT2 inhibitors on glycosuria in patients with lower kidney function.[32]

In the four chronic kidney disease trials (CREDENCE, SCORED, DAPA_CKD and EMPA-KIDNEY), the RRs for kidney disease progression were similar when analyses were separated by primary kidney diagnosis. SGLT2 inhibitors reduced the risk of kidney disease progression by 40% (0·60, 0·53–0·69). [31]

Interestingly, when analyzing the trials based on average baseline kidney function, the meta analysis did not indicate any attenuation of the kidney-related advantages offered by SGLT2 inhibitors. Furthermore, it is worth noting that SGLT2 inhibitors exhibit a high level of safety even at low levels of kidney function, with an eGFR of at least 20 mL/min per 1·73 m2 being considered safe for administration. Particularly in patients without diabetes, the risk of ketoacidosis or amputation remains notably low, regardless of whether they receive an SGLT2 inhibitor or not. Importantly, across all populations studied so far, the absolute benefits of SGLT2 inhibition far outweigh any serious hazards associated with its use.[31]

Based on the meta-analysis (90,000 patients) results, for every 1000 patients with CKD treated with an SGLT2 inhibitor for one year, the following outcomes were observed:

1. In patients with diabetes:
   - Approximately 11 cases of kidney disease progression could be prevented.
2. In patients without diabetes:
   - Approximately 15 cases of kidney disease progression could be prevented.

In addition to the prevention of kidney disease progression, the treatment with SGLT2 inhibitors was associated with the following benefits in both diabetic and non-diabetic patients:

- Around four to five fewer incidents of acute kidney injury.

These findings are significant as they suggest that SGLT2 inhibitors have a renoprotective effect, meaning they can protect the kidneys from disease progression and acute kidney injury in patients with CKD, regardless of whether they have diabetes or not.[31]

Early studies like **The EMPA-REG trial** found a 39% reduction compared with placebo for the renal composite outcome of progression to macro-albuminuria, a doubling of serum creatinine level accompanied by an eGFR of ≤ 45 mL/ min/1.73 m^2, initiation of renal replacement therapy, or death from renal disease.[34]

The DECLARE-TIMI 58 trial had a renal composite outcome consisting of sustained decrease in eGFR by at least 40% to less than 60 mL/min/1.73 m^2, end-stage renal disease, and renal death; there was a 47% reduction compared with placebo [35]

Guidelines and recommendation for SGLT2 in Diabetic/Non Diabetic Patients with/without Kidney disease
Some clinical practice guidelines have started recommending use of SGLT2 inhibitors in type 2 diabetes at eGFRs down to 20 mL/min per 1·73 m² (based on grade B levels of evidence)[33]many other recommendations limit initiation to those with eGFR greater than 25 mL/min per 1·73 m² or 30 mL/min per 1·73 m². [36] As patients with decreased eGFR are at the highest absolute risk of kidney disease progression,[37] clinical findings should encourage the initiation of SGLT2 inhibitors in patients with chronic kidney disease down to an eGFR of 20 mL/min per 1·73 m² with continued use below this level.

The Kidney Disease Improving Global Outcomes (KDIGO) working group 2020 guideline recommended SGLT2 inhibitors for patients with kidney disease and an estimated glomerular filtration rate (eGFR) of at least 30 mL/min/1.73 m2. Since the original guideline was published, seven large trials investigating the cardiovascular and kidney effects of various SGLT2 inhibitors have been conducted. These trials prompted a revision of the eGFR threshold for using SGLT2 inhibitors due to the positive results. Four of the new trials demonstrated cardiovascular and kidney benefits, including in patients with heart failure with reduced ejection fraction and those with preserved ejection fraction. The benefits were observed across all categories of eGFR.

The updated guideline now recommends the use of SGLT2 inhibitors among all patients with T2D and CKD (based on albuminuria or low eGFR without albuminuria) with an eGFR of at least 20 mL/min/1.73 m2 (Grade 1A).[38]

The United Kingdom Kidney Association (UKKA) guidelines have subsequently incorporated the findings from these studies, setting eGFR and UACR cutoffs for SGLT2 inhibitor use in both diabetic and non-diabetic kidney disease at ≥25 mL/min per 1.73 m2 and ≥25 mg/mmol, respectively. The UKKA guidelines recommend initiating SGLT2 inhibitors in patients with eGFR 25–60 mL/min per 1.73 m2 regardless of diabetes, and even in the presence of albuminuria when there is a need to modify cardiovascular risk, recognizing the potent cardioprotective effects of SGLT2 inhibition. [39]

The American Association of Clinical Endocrinologists have the following recommendations (AACE) regarding the use of SGLT-2 inhibitors and GLP-1 receptor agonists in the management of diabetes. These recommendations highlight the evolving role of these medications beyond glycemic control, particularly in patients with established atherosclerotic cardiovascular disease (ASCVD), high ASCVD risk, or chronic kidney disease.

1. In patients with established ASCVD, high ASCVD risk, or chronic kidney disease, SGLT-2 inhibitors and GLP-1 receptor agonists are recommended as first-line therapy independent of glycemic control.
2. If entry hemoglobin A_{1c} is less than 7.5%, monotherapy is recommended with metformin, a GLP-1 receptor agonist, or a SGLT-2 inhibitor (strength of the recommendation is equal).
3. If entry hemoglobin A_{1c} is 7.5% to 9.0% or higher or if uncontrolled on monotherapy, dual therapy is recommended with SGLT-2 inhibitor and GLP-1 receptor agonists as the top choices in the hierarchy along with metformin. The 2 drug classes are also the top choices for triple therapy.
4. For those with stage 3 chronic kidney disease, canagliflozin is recommended.

Six oral SGLT2 inhibitors are currently approved for the treatment of type 2 diabetes mellitus (T2DM) by the US Food and Drug Administration (FDA) together with the European Medicines Agency (EMA): canagliflozin (CANA), empagliflozin (EMPA), dapagliflozin (DAPA), ertugliflozin (ERTU), bexagliflozin, and sotagliflozin.[41]

Four combination drugs have also been approved by the FDA: canagliflozin/metformin (Invokamet®), dapagliflozin/metformin (Xigduo XR®), empagliflozin/metformin (Synjardy®) and empagliflozin/linagliptin (Glyxambi®. [41]

Table 2:- Selectivity of SGLT2 over SGLT1 of the approved SGLT2 inhibitors [42,43,44]

SGLT2 Inhibitors	Selectivity (SGLT2 over SGLT1)
Canagliflozin	250 fold
Dapagliflozin	1200 fold

Empagliflozin	2500 fold
Ertugliflozin	2000 fold
Sotagliflozin	36 fold
Bexagliflozin	2435 fold

Conclusions:-

Elevated blood glucose levels trigger an increase in glucose transportation to Bowman's space through glomerular filtration. This leads to heightened reabsorption of both glucose and sodium by the sodium-glucose cotransporters SGLT2 and SGLT1 in the proximal tubule. Diabetes mellitus induces growth in the proximal tubule, enhancing its transport capacity and further increasing glucose reabsorption, contributing to hyperglycemia. Additionally, this growth causes abnormally high reabsorption of filtered sodium chloride (NaCl).

The rise in proximal reabsorption leads to a decrease in the delivery of NaCl and fluid to the macula densa, triggering glomerular hyperfiltration through tubuloglomerular feedback and reducing tubular back pressure. This process aids in restoring renal NaCl and fluid excretion to normal levels.

The state of glomerular hyperfiltration places physical strain on the filtration barrier and elevates the demand for oxygen to reabsorb the filtered load. Additionally, hypertrophic tubular cells display a senescence-like phenotype, resulting in pro-inflammatory and pro-fibrotic effects that could potentially contribute to the development of diabetic kidney disease (DKD).

SGLT2 inhibitors exert protective mechanisms through both blood glucose-dependent and -independent pathways. These medications prevent both hyper- and hypoglycemia, leading to minimal impact on HbA1C levels. Metabolic changes occur due to increased urinary glucose loss, resulting in reduced fat mass and an increase in ketone bodies as an additional source of energy. By lowering glomerular capillary hypertension and hyperfiltration, SGLT2 inhibitors alleviate stress on the filtration barrier, decrease albuminuria, and reduce the oxygen demand for tubular reabsorption. This ultimately enhances cortical oxygenation, preserves tubular function, and may maintain the glomerular filtration rate over the long term. Importantly, they do not cause hypoglycemia when filtered glucose levels are below 80 g/day and can be used in diabetic patients with normal and preserved renal function. The pleiotropic and synergistic effects of SGLT2 inhibitors contribute to their reported cardio- and renoprotective benefits, even in patients with impaired renal function. SGLT2i are a cornerstone of clinical guidelines and recommendations for treatment of HF, DM and now, as is the focus of this review, DKD and non diabetic CKD as well. Several large scale studies and Meta analysis that have propelled them into wider usage.

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