



Sodium-Glucose Cotransporter 2 Inhibitors' Mechanism of Action and Use in Kidney Transplantation Recipients: Extended Review and Update

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Abstract

Five sodium-glucose cotransporters (SGLTs) protein family members are important for regulating blood glucose levels. The essential cotransporters for glucose reabsorption by proximal convoluted tubule are SGLT1 and 2. The newest recommendations advocate GLT2 inhibitors as first-line treatment for type 2 diabetes (T2D) with and without chronic kidney disease (CKD), improving CKD and cardiovascular outcomes. SGLT2 inhibitors enhance kidney transplant patients' life quality, delay CKD progression, have renoprotective effects, and reduce cardiovascular disease in CKD patients, despite minimal published evidence on the usage of SGLT2 inhibitors in kidney transplantation recipients (KTxRs) with T2D or new-onset T2D. They preserve and improve renal function and cardiovascular outcomes in KTxRs. SGLT2 inhibitors' safety issues have prevented KTxRs from participating in major randomized studies, leaving doctors and patients unsure whether these extraordinary drugs outweigh the risks. This extended review analyzes the established mechanisms through which SGLT2 inhibitors exert their positive effects, evaluate the potential advantages and drawbacks of these agents in KTx, and examine the current research findings on using SGLT2 inhibitors in KTxRs. Additionally, potential avenues for future research will be suggested. Different phrases were used to search for recent original and review articles published between January 2020 and November 2023 in PubMed, Google Scholar, Scopus, EMBASE, and Google to achieve the review objectives.

Keywords

- ▶ kidney transplantation
- ▶ SGLT2 physiology
- ▶ glucose kidney reabsorption
- ▶ SGLT2 inhibitor
- ▶ SGLT2i in kidney transplantation

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Introduction

Chronic kidney disease (CKD) and end-stage renal disease (ESRD) prevalence has consistently risen in recent decades, posing a significant burden on health care costs.¹ In the United States, type 2 diabetes (T2D) affected 14.3% of people in 2011 to 2012, with prediabetes affecting 38%. The disease burden has increased for 30 years, requiring more resources to combat it.^{2,3}

Kidney transplantation (KTx) is a recommended therapy for most individuals with ESRD. KTx recipients (KTxRs) had a superior life quality and enhanced long-term survival compared to CKD patients on hemodialysis waiting for KTx.^{4,5} Despite significant improvements in KTx care, patients nevertheless face a maintained death risk due to cardiovascular disease (CVD) and infection during the early and late stages after KTx.⁶ Transplant patients with T2D have a high risk of developing CVD, infection complications, death, and graft loss.^{7,8} The T2D load among KTxRs is multifaceted. T2D is the chief cause of native kidney ESRD. Furthermore, T2D accounted for 31% of patients waiting for KTx in 2019. Immunosuppressants required for successful transplantation also predispose KTxRs to beta-cell dysfunction and insulin resistance post-KTx.⁷ Posttransplant-diabetes mellitus (DM) is a term introduced in 2014 to refer to diabetes development after a transplant, which is seen in 10 to 40% of KTxRs.⁷ Effective care of T2D in KTxRs is crucial to avoid unfavorable outcomes.

Sodium-glucose transporters 2 (SGLT2) inhibitors have recently been identified as a novel treatment for conditions such as heart failure, CKD progression prevention, and T2D. SGLT2 inhibitors act via a novel mechanism of reducing proximal convoluted tubule (PCT) glucose reabsorption, reducing blood glucose without affecting insulin levels.² These inhibitors have shown positive effects on CVD and kidney survival in diabetic nephropathy patients, nondiabetic proteinuric-CKD, and heart failure. The effects of SGLT2 inhibitors were observed in both diabetic and nondiabetic native kidneys.^{3-5,9-12} A detailed investigation was conducted to explore the potential mechanisms of benefit, and it was determined that better glycemic control by SGLT2 inhibitors is unlikely to be the only factor.¹³ Upon examining these pathways, SGLT2 inhibitors may probably possess distinct advantages in KTxRs with T2D, heart failure, or proteinuria, leading to enhanced durability of the KTx and reduced CVD risk.

Nevertheless, administering SGLT2 inhibitor treatment in KTxRs is hindered by many circumstances that might reduce its effectiveness or subject patients to different complications. To address these issues, all major, randomized control studies (RCTs) that have been published and investigated the effectiveness and safety of SGLT2 inhibitors have yet to include KTxRs.^{11,14,15} As a result, there needs to be more data addressing the effectiveness of SGLT2 inhibitors in KTxRs despite the potential benefits these medications provide in treating this specific group of patients. Currently, there is a lack of evidence about the long-term effects of SGLT2 inhibitor treatment in KTxRs, specifically in terms of

overall and CV-related mortality, as well as the life of the transplanted organ. The little information in published research on KTxRs only investigates short-term results. The wide range of research design, demographic characteristics, period of follow-up, and evaluated outcomes greatly hampers the ability to derive significant conclusions from previous studies.¹⁶

Methods

In this review we examined the suggested mechanisms through which SGLT2 inhibitors exert their nephroprotective and CVD protection effects in KTxRs. We aimed to also explore the potential advantages and concerns of SGLT2 inhibitors used in KTxRs. Furthermore, we have addressed prospective research ideas about using SGLT2 inhibitors in KTxRs.

This is a narrative nonsystematic review. We searched Google, PubMed, Scopus, and Google Scholar for the most recent (January 2020 to November 2023) original and reviewed published articles. We used the following phrases and texts as search terms (SGL2 inhibitors, SGLT1 inhibitors mechanism of action, SGLT2 inhibitors in CKD, SGLT2 inhibitors in kidney transplantation, the effect of SGLT2 inhibitors effect on kidney graft, and SGLT2 inhibitors effect on life quality and kidney transplantation outcomes). No statistical analysis was performed on the original studies. The emerging themes resulting from the review are summarized in ►Table 1.

Results

Physiology of Glucose Reabsorption from the Filtrate

Although overall endogenous glucose release decreases substantially in the postprandial state, renal gluconeogenesis increases approximately twofold. Following a meal, glucose utilization by the kidney increases. Kidney glucose utilization after overnight fasting represents about 10% of glucose utilized by the body. Normally, the kidneys filter approximately 180 g of glucose daily; almost all of this is reabsorbed via sodium-glucose cotransporter 2 (SGLT2) and SGLT1-mediated mechanisms.¹⁷ The SGLT2s are expressed in

Table 1 The emerging themes resulting from the review of the literature

Physiology of glucose reabsorption from the filtrate
SGLT protein background
Mechanism of action of SGLT2 inhibitors: <ul style="list-style-type: none"> • Immediate SGLT2 inhibition physiological effects • SGLT2 inhibitors secondary effects • SGLT2 inhibitors mechanism to enhance oxygen transport and improve hemoglobin level • SGLT2 inhibitors additional potential mechanisms of action
Adverse effects of SGLT2 inhibitors
SGLT2 inhibitors in kidney transplantation

Abbreviation: SGLT2, sodium-glucose cotransporter 2.

the PCT cells.¹⁸ In contrast, SGLT1 cotransporters are primarily present in the small skeletal muscle, intestine, heart, and segment 3 of PCT.^{19,20} SGLT1 and SGLT2 are responsible for the 100% glucose reabsorption by the PCT. SGLT2 cotransporters are sited at the brush border cells of the first and second of PCT segments. These cotransporters have a high capacity for glucose transport. They are responsible for reabsorbing between 90 and 97% of filtered glucose.

Meanwhile, the third segment of the PCT efficiently reabsorbs the other $\leq 10\%$ of filtered glucose via the low-capacity SGLT1 cotransporters, which have a strong affinity for glucose. The facilitated diffusion glucose transporter 2 (GLUT2) and GLUT1 cells active transport system in the basolateral membrane transport the reabsorbed glucose into the bloodstream. The glucose and sodium transports are unidirectional and are linked to and sustained by the basolateral membrane $\text{Na}^+\text{-K}^+\text{-ATPase}$ pump.²¹ Glucose reabsorption in the PCT is achieved via cotransport diffusion (require carrier protein [GLUT] without energy consumption) and sodium active transport from inside the cell to peritubular kidney stroma by $\text{Na}^+\text{-K}^+$ ATP-dependent active transport mechanism (i.e., energy consumption).

PCT cells reabsorb more than two-thirds of the filtered elements and the total filtered glucose, contributing to renal pathogenesis-related glucotoxicity, such as T2D.²² Due to their kinetics, glucose facilitative and active transporters have different PCT distribution patterns. Hyperglycemia regulates renal SGLT via reactive oxygen species–nuclear factor- κB pathways. This shows that PCT transcellular glucose uptake causes diabetic-like nephropathy. Epidermal growth factor receptor (EGFR) transactivation by angiotensin II (ANG II) helps its development. Thus, hyperglycemia, EGFR, and ANG II regulate SGLT activity in diabetic-like nephropathy. Endogenously increased SGLTs protect nephron cells.²² Since renal PCT cells regulate plasma glucose levels,¹⁷ renal glucose transporters are of interest for treating different disorders, including T2D, CKD, and obesity. Furthermore, a new meta-analysis reported that SGLT2 inhibitors should be explored as an adjuvant medication for first-line antihypertensive treatment in individuals with T2D and hypertension who have a low risk of genital infection.²³

The glucose reabsorption into the PCTs is regulated in response to blood glucose level changes and is proportional to the quantity of the filtrate glucose content. The kidney has a tubular maximum renal glucose reabsorption threshold (TmaxG) for reabsorbing glucose, which occurs when the filtered glucose reaches about 19.4 mmol/L/min/1.73 m², which is comparable to a glycemia level of 10 to 11.1 mmol/L.²⁴

The collaborative function of the high-capacity/low-affinity and low-capacity/high-affinity SGLT1 cotransporters manages the amount of glucose that reaches segment 3 of the PCT. In a typical physiological context, the PCTs regulate glucose reabsorption according to changes in blood glucose concentrations. Moreover, glucose reabsorption is proportionate to the quantity of filtered glucose. The reabsorption capacity of glucose has a physiological limit, which is the TmaxG. Glucosuria occurs when the glucose level in the

blood surpasses the TmaxG threshold. In persistent hyperglycemia, the kidney adjusts the TmaxG to the highest glucose levels, about 13.3 mmol/L.²⁵ The PCTs upregulate the expression of SGLT2 cotransporters in response to the augmented luminal glucose flow.²⁶ The upregulation of SGLT2 cotransporters is accompanied by more energy consumption via the basolateral Na-K-ATPase and is believed to be a key factor in developing diabetic nephropathy.²⁷ The PCTs upregulate the expression of SGLT2 cotransporters in response to the elevated luminal glucose flow.²⁶ The upregulation of SGLT2 cotransporters is accompanied by energy consumption via the basolateral Na-K-ATPase , which is believed to be the crucial player in diabetic nephropathy development.²⁷ **Fig. 1** illustrates the physiology of glucose reabsorption mechanisms in the PCT.

SGLT Protein Background

According to messenger ribonucleic acid expression examinations, the human body has three additional SGLTs that interact for controlling, absorption, and reabsorption of glucose, which are SGLT1, 2, 3, 4, and 5.^{28,29} In SGLT3 presence, glucose depolarizes the plasma membrane saturability, Na^+ -dependability, and phlorizin sensitivity,³⁰ making SGLT3 a glucose level sensor via depolarization of SGLT-expressing cells.³¹ GLUT4 is an insulin-responsive glucose transporter. It is expressed in adipose tissue, skeletal muscle, the heart, and the brain.^{32,33} Insulin binding to insulin receptors triggers GLUT4 movement to the cell membrane, which, in turn, facilitates the transportation of glucose into cells. GLUT5, the transporter specifically designed for fructose, is mostly found in the small intestine, testes, and kidneys. GLUT5 facilitates the transportation of hexose from the villus epithelium in the gut in conjunction with SGLT1. The hexose molecule inside the cell exits the epithelium using GLUT2, which is situated in the basolateral membrane.³⁴ SGLT density and other channels' and transporters' contributions to membrane conductance determine native cell depolarization.³⁵

SGLTs are widely expressed in highly active metabolic organs, including the brain and kidneys. The widespread SGLT expression in various organs has two possible explanations. First, SGLTs protect cells by supplying enough glucose during anoxic ischemia. Second, SGLTs may control membrane potentials in response to extracellular glucose concentration variations. Human SGLT3 was detected initially as a glucose sensor.³⁶ This protein's function is not to transport glucose, but glucose depolarizes the membrane potential of SGLT3 protein-carrying cells in a phlorizin-sensitive manner, detecting the glucose level variation. SGLT3 had a considerable affinity for glucose; hence, modest changes in glucose levels caused a linear membrane potential shift.³⁵

Furthermore, In SGLT3 presence, glucose alters the plasma membrane saturability, Na^+ -dependability, deplorability, and phlorizin-sensitivity. SGLT3s act as sensors for glucose levels in neurons, small intestines, and stomach, reducing GLP1 formation and delaying gastric empty time,³⁵ although SGLT3 function and protein expression in the kidneys were unknown.²⁸ However, according to a study

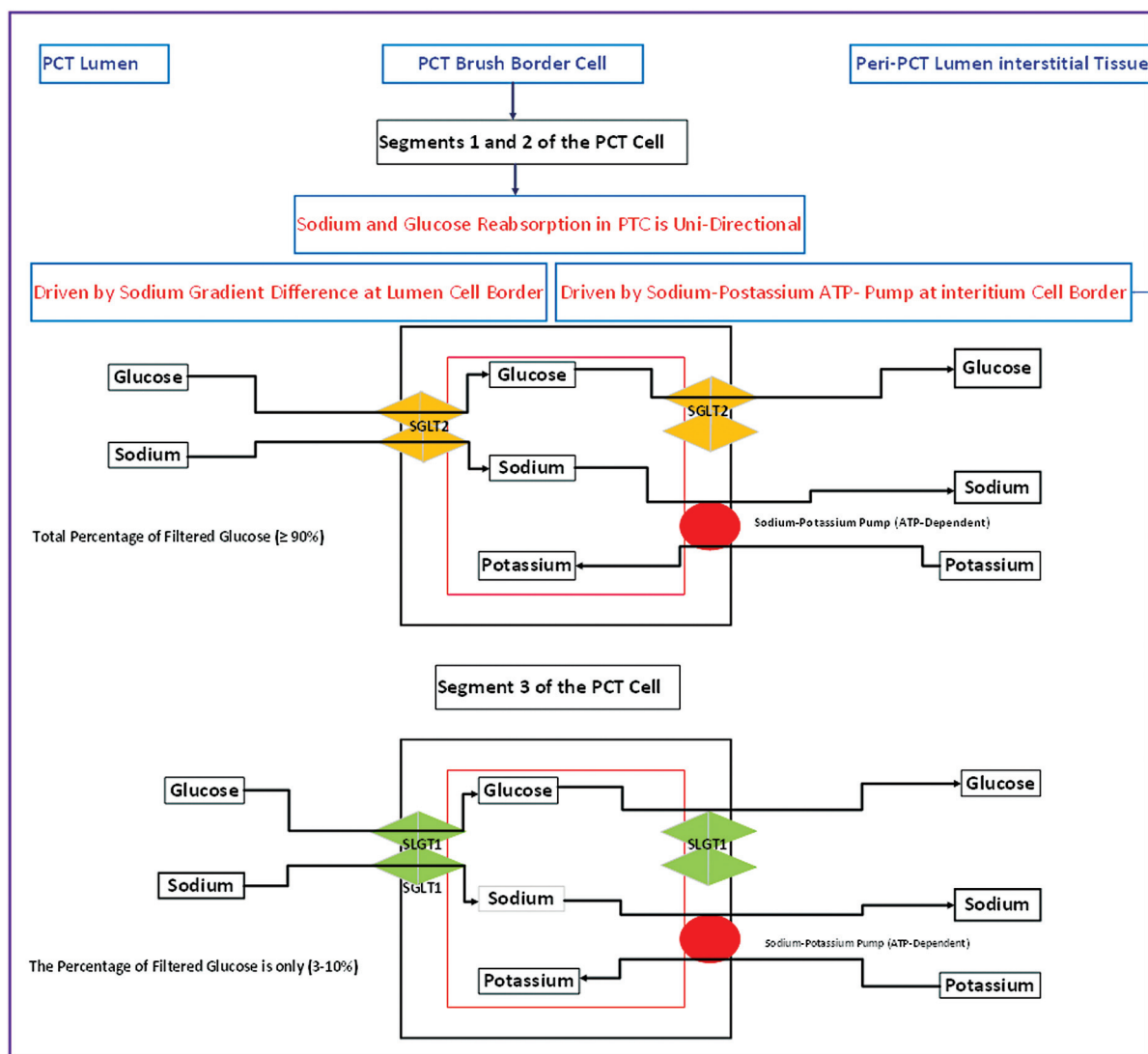


Fig. 1 Physiology of sodium-glucose cotransporters system and glucose reabsorption in the proximal convoluted tubule. Na⁺, sodium; K⁺, potassium; ATP, adenosine triphosphate; PCT, proximal convoluted tubule.

by Kothinti et al, SGLT3 is a recently discovered sodium transporter expressed in human PCT cells. In diabetics, the expression of SGLT3 in the PCT cells may increase, leading to a rise in sodium transport. This can potentially cause hyperfiltration and renal injury in this specific segment of the nephron in diabetics.³⁷ Furthermore, in humans, jejunal SGLT3 levels were reported to have a relationship with obesity,³⁸ possibly via increasing glucose reabsorption from the filtrate, increasing energy storage and rate of obesity. This proposal requires further studying.

Phlorizin is the earliest SGLT2 inhibitor derived from the apple tree's root bark, a naturally producing phenolic glycoside.^{39,40} It was first discovered and isolated during the 19th century. Phlorizin has antipyretic, antibacterial, organ-protective properties, and anticancer effects in vivo and in vitro.³⁹ In the 1960s, researchers characterized the glucose reabsorption process by the PCT. Successful SGLT2 cotransporter cloning was done in 1990.⁴¹ This led to a competent understanding of how

the kidneys handle glucose and phlorizin pharmacological action. As a result, researchers began studying nephron glucose reabsorption inhibition as a potential objective to control T2D. Preclinical investigations conducted in the 1980s showed that phlorizin enhanced insulin sensitivity in diabetic people without impacting insulin action in rats.⁴²

It was discovered that phlorizin lacks oral absorption, necessitating intravenous administration as the sole viable route. T-1095 is a synthetic agent obtained from phlorizin. T-1095 is a specific inhibitor of SGLTs. The first orally accessible SGLT2 inhibitor was formulated in the 1990s. The study has shown positive effects on hemoglobin A1c (HbA1c) levels, decreasing weight, and microalbuminuria in rats.⁴³ Regrettably, T-1095 exhibited nonspecificity toward SGLT2, and its influence on intestinal SGLT1 resulted in notable gastrointestinal side effects and intolerance.²¹ Since T-1095, a minimum of seven distinct SGLT2 inhibitors that may be taken orally have been created. Five of these—dapagliflozin, bexagliflozin,

canagliflozin, ertugliflozin, and empagliflozin—are currently approved for use.⁴⁴ Dapagliflozin, canagliflozin, and empagliflozin strongly prefer to inhibit SGLT2 rather than SGLT1.²¹

Several clinical studies have shown significant advantages of SGLT2 inhibitors in high-risk CVD populations. When they are incorporated into routine treatment for nondiabetic and diabetic nephropathy, they have shown a decrease in CV-related and other all-cause mortality, heart failure-related hospitalizations, adverse CV events, and albuminuria.⁴⁵ Notably, SGLT2 inhibitors improve diabetic nephropathy and heart failure in type 2 diabetics and even nephropathy in general in nondiabetic patients.²¹ Because of these beneficial effects of SGLT2 inhibitors, they are gaining more attention. Hence, a comprehensive understanding of the physiological processes and SGLT2 inhibition effects is essential to elucidate the reasons for their varied therapeutic advantages and prevent adverse effects.

Mechanism of Action of SGLT2 Inhibitors

Immediate SGLT2 Inhibition Physiological Effects

Gliflozins reduce PCT cells' ability to reabsorb glucose by the PCT's first and second segments (S1 and S2) by hindering the SGLT2 cotransporter. This results in T_{max}G decline to about 40 to 80 mg/dL,²⁵ and a drop in glucosuria's PCT threshold prevents substantial energy loss due to less glucose reabsorption and enhancing glucosuria. SGLT2 cotransporters achieve these effects by enhancing reabsorption by around 40%,⁴⁶ decreasing glucose reabsorption with minimal energy consumption reduction because of less glucose reabsorption. Moreover, one advantage of SGLT2 inhibitors use is that it does not correlate substantially with an increased likelihood of experiencing severe symptomatic hypoglycemia.⁴⁷

HbA1c levels noted blood glucose control decrease by about 0.5 to 1% in different reports.^{11,24,47} This effect of SGLT2 inhibitors is due to the heightened insulin sensitivity and improved beta-cell activity,^{48,49} leading to better safe HbA1c control. The primary clinical studies on SGLT2 inhibitors have consistently shown their positive effect on glucose regulation.^{10–12,14,50} This advantage is also seen even when included in conventional treatment.⁵¹

Natriuresis means an increased urine sodium content. Significant natriuresis was noted to affect blood pressure (BP) positively and may also reverse the stimulation of tubuloglomerular feedback. SGLT2 inhibition and glucosuria lead to natriuresis, linked to water and salt balance disturbances,⁵² reducing plasma volume and BP. The decrease in plasma volume is indicated by a decrease in systolic BP of 3 to 6 mm Hg and a drop in diastolic BP of 1 to 1.5 mm Hg.^{9,11} This is the possible mechanism through which SGLT2 inhibitor reduces BP in hypertensives; however, further studies are required to investigate this theory.

Physiological natriuresis and increased salt supply to the last section of the kidney are crucial for protecting the kidneys since they restore the proper tubuloglomerular feedback loop function. DM causes chronic hyperglycemia, increasing glucose reabsorption in the PCT by upregulating T_{max}G and SGLT2 cotransporter expression.²⁵ This upregulation enhances

glucose and sodium reabsorption, diminishing sodium delivery in the juxtaglomerular apparatus and triggering the tubuloglomerular feedback mechanism via increasing nitric oxide production.²⁷ Consequently, nitric oxide dilates the afferent arteriole to restore normal sodium load delivery to the distal convoluted tubules. Vasodilation of the afferent arteriole results in heightened intraglomerular pressure and leads to hyperfiltration, a defining feature of diabetic nephropathy. SGLT2 inhibition disrupts the feedback loop by enhancing the juxtaglomerular apparatus sodium supply, suppressing the tubuloglomerular feedback, and inducing afferent arteriole constriction.^{25,52,53} The outcome is a reduction of intraglomerular pressure and enhancement of hyperfiltration, shown as an initial glomerular filtration rate (GFR) decline.⁵⁴ The decrease in the GFR may be reversed by discontinuing SGLT2 inhibition and is a result of changes in blood flow dynamics. While the initial decrease in GFR initiated by SGLT2 inhibition seems usually substantial, it is often confined to a range of 2 to 4 mL/min in most clinical scenarios. Long-term studies indicate that the estimated GFR drop is noncontinuous and much lower than the decline found in placebo groups.

SGLT2 Inhibitors Secondary Effects

Enhanced reduction in albuminuria studies, including diabetic and nondiabetic individuals suffering from CKD, have shown that SGLT2 inhibitors effectively decrease albuminuria. This impact of SGLT2 inhibitors is autonomous and cumulative with the renin-angiotensin-aldosterone system (RAAS) effect inhibition by angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptor blocking (ARB) blockage effect.¹⁴ Over the last two decades, renin blockage by ARBs has been the exclusive therapeutic option for controlling proteinuria-induced renal disease in both those with native kidneys and those who have had KTx, besides the immunologically mediated graft rejection effect.⁵⁵ The albuminuria reduction is mediated by many factors, including afferent arteriole constriction, which leads to decreased pressure inside the glomerulus, excessive filtration, and systemic BP improvement.

Additionally, several studies have displayed that the podocytes, which possess SGLT2 cotransporters within the PCT brush border, have positive effects from SGLT2 inhibition. The administration of empagliflozin or dapagliflozin leads to podocyte effacement, causing their function improvement^{56,57} by restoring insulin sensitivity, mitigating the harmful effects of excessive filtrated glucose, and decreasing albuminuria.⁵⁸ The other possible effect of SGLT2 inhibitors is that they improve renal ability by increasing glycosuria, leading to relative blood glucose scarcity, causing a shift of energy substrate sources toward lipids instead of carbohydrates. This mitigates the harmful effects of excessive lipid accretion in cells and enhances the body's ability to manage oxidative stress. Moreover, this also promotes an increase in ketone synthesis, a more favorable energy source for renal and cardiac cells.

Furthermore, enhancing PCT function, oxygen utilization, and diabetes-induced hyperglycemia can lead to a surge in the PCT's atrium and glucose reabsorptive ability, triggering

tubuloglomerular feedback, which induces hyperfiltration. The positive feedback loop leads to an upsurge in cellular effort by enhancing the activity of Na-K-ATPase and causing hypertrophy in the PCT. In addition, elevated glucose levels inside the PCT cells are redirected toward metabolic pathways other than glycolysis, leading to an uprise in advanced glycation end-products. This, in turn, impacts mitochondrial function and results in heightened oxidative stress. Suppression of the tubuloglomerular feedback, excessive filtration, and heightened glucose reabsorption diminish energy use and oxygen utilization in PCT cells.⁴⁰ Lowering intracellular and blood glucose levels reduces cellular glucotoxicity, improving kidney function; however, this putative concept needs further investigation.

SGLT2 inhibitors lead to weight loss ranging from 2 to 4 kg after 6 to 12 months of therapy.^{24,47,59–61} The initial weight loss is caused by fluid volume reduction due to water diuresis, followed by the loss of calories via glucosuria. The Americans with Disabilities Act guidelines specifically endorse SGLT2 inhibitors as the primary choice for first antidiabetic medication when weight reduction is a desirable component of the treatment.⁶² According to different published reviews, it seems that SGLT1 has better safety and effectiveness in weight reduction.⁶³ Another study reported that SGLT2 inhibitors may cause more statistically significant weight reduction than GLP1 receptor agonists when combined with baseline diabetic treatments, all without impairing renal function.⁶⁴

SGLT2 Inhibitors' Mechanism to Enhance Oxygen Transport and Improve Hemoglobin Level

The enhancement in the functioning of PCT cells and the decrease in energy consumption decrease oxygen requirement and consumption, increasing oxygen availability in the kidney cortex.^{27,65} The SGLT1 cotransporters in the PCT in the latter segment are accountable for the completion of glucose reabsorption. Higher glucose load to the last PCT segment leads to increased oxygen consumption and energy expenditure in the outer medulla^{66–68} and local hypoxia, which can increase kidney damage.⁶⁹ Hypoxia triggers the activation of hypoxia-inducible factors HIF1 and HIF2,⁷⁰ increasing erythropoietin secretion⁷¹ and improving the hemoglobin level. Additionally, the moderate reduction in volume leads to a rise in hemoglobin concentration, which promotes the efficient transport of oxygen to various organs, preventing hypoxia. Clinical studies have shown that SGLT2 inhibitor-treated individuals have shown improved hemoglobin levels.⁷² Dapagliflozin seems to inhibit hepcidin and other proteins in iron metabolism, enhancing erythropoiesis.⁷³ Hemoglobin level improvement is an important effect of SGLT2 inhibitor therapy, which can improve patients' life quality.

SGLT2 Inhibitors Additional Potential Mechanisms of Action

Gliflozins decrease levels of inflammatory markers, including interleukin (IL)-6, tumor necrosis factor, nuclear factor-kappa B, interferon γ , transforming growth factor- β , and Toll-like

receptor-4.^{74,75} In addition, they seem to enhance mitochondrial activity,⁷⁶ decrease mesangial growth, and diminish the quantity of myofibroblasts in cardiac tissue.⁷⁷ Empagliflozin decreases the PCT cells' IL- β inflammatory pathway.⁷⁸ These actions would decrease oxidative stress, inflammatory processes, and kidney and heart tissue fibrosis. However, the effects of hemodynamic and metabolic SGLT2 inhibitors seem more important than all these other alterations. Further studies are required to investigate these effects and their role in preventing CVD and CKD progression.

Gérard et al reviewed the SGLT2 cotransporters' physiological function and SGLT2 inhibitor mechanisms of action.⁵³ In the early stage of type 1 diabetes (T1D), the intraglomerular BP increases, causing higher GFR. Concomitantly, PCT SGLT2 expression in the hyperplasia of PCT cells promotes sodium and glucose absorption to the maximum, reducing the sodium delivery to the S3 part of the PCT segment and leading to tubuloglomerular feedback inhibition. This inhibition enhances afferent vessels' dilation and glomerular hyperfiltration besides the primary SGLT2 inhibitor action, which reduces sodium reabsorption in PCT. They promote sodium export to circulation via the macula densa, reactivating tubuloglomerular feedback, promoting the reverse of the afferent vessels' vasodilation, and lowering intraglomerular pressure.

In contrast, in T2D with advanced CKD, tubuloglomerular feedback is unlikely to reactivate for various reasons.⁵³ First, SGLT2 inhibitors dramatically lowered GFR in people with T1D with hyperfiltration in euglycemic and hyperglycemic status. The lowered GFR in SGLT2 inhibitors therapy is mostly due to reduced plasma nitric oxide, effective kidney blood flow, and higher kidney vascular resistance, suggesting tubuloglomerular feedback reactivation. In congenital SGLT2 deletion with normal kidney parameters, diuretics may rapidly activate tubuloglomerular feedback.⁷⁹ Conversely, T1D with GFR < 135 mL/min/1.73 m² did not have this effect after 8 weeks of SGLT2 inhibitors treatment.⁸⁰ This shows that SGLT2 inhibitors only reactivate tubuloglomerular feedback during hyperfiltration. The severity of CKD in DM2 reduces the likelihood that SGLT2 inhibitors will reactivate tubuloglomerular feedback. Second, pathological investigations in hypertensive diabetic CKD patients demonstrate increasing intrarenal arterial stiffness with arteriosclerosis and afferent arteriole hyalinosis, which coincides with renal blood flow autoregulation loss.⁸¹ Third, like SGLT2 inhibitors, acetazolamide enhances salt delivery into tubule distal segments, which logically should activate the tubuloglomerular feedback like SGLT2 inhibitors. However, this mechanism is not proven to happen with acetazolamide therapy in DM2 with GFR < 60 mL/min/1.73 m². Fourth, nondiabetics cannot suppress tubuloglomerular feedback because PCT does not express more SGLT2 receptors. Hence, SGLT2 inhibitors' antiproteinuric impact should be higher in diabetic people than in nondiabetics if tubuloglomerular feedback is involved. The SGLT2 inhibitor's nephroprotective effect in nondiabetics is like that in diabetics. Lastly, one research examined SGLT2 inhibitors' renal hemodynamic effects in DM2. Measuring renal vascular resistance index

and filtration fraction by gold standard GFR and plasma flow, the SGLT2 inhibitors did not alter renal vascular resistance significantly during euglycemic or hyperglycemic episodes, indicating that efferent arteriole vasodilation caused the reduced filtration fraction.⁸²

RAAS blockade is the cornerstone of diabetic proteinuria control and renal preservation. Volume overload decreases renin release, which inhibits RAAS, downgrading RAAS blockers' effectiveness for hypertension control and proteinuric effect. When combined with salt restriction and RAAS blockers with diuretics, proteinuria improves, and the combination is more effective than dual RAAS blockade with angiotensin receptor blockers and ACEi or more dose titration.⁸³

SGLT2 inhibitors inhibit the PCT sodium-glucose cotransport system, leading to fast weight loss and BP reduction, resembling thiazide-induced volume depletion. In individuals with $GFR \leq 60 \text{ mL/min/1.73 m}^2$, SGLT2 inhibitors significantly impact glycosuria and have clinically substantial antihypertensive effects, showing that PCT salt reabsorption inhibition is still clinically meaningful. Furthermore, SGLT2 inhibitors might not act on afferent glomerular arterioles and tubuloglomerular feedback in DM2 and CKD progress. Still, SGLT2 inhibitors may synergistically act on efferent arterioles with RAAS blockers to control volume overload, as they do in heart failure. In addition to lowering intraglomerular pressure, SGLT2 inhibitors may improve vascular function, hypoxia, metabolism, and tubular workload. A study reported that combined ACEi's/ARBs and SGLT2 inhibitors improve albuminuria in CKD without DM and is suggested to increase kidney failure-free survival substantially.⁸⁴ Further work is needed to investigate this issue and to study the underlying mechanism. All the above effects and benefits are summarized in ►Fig. 2.

Adverse Effects of SGLT2 Inhibitors

SGLT2 inhibitor administration is linked to few and typically moderate unfavorable incidents; nonetheless, they should be counted. SGLT2 inhibitors cause osmotic diuresis, especially in older adults, which might be severe and harmful when used with diuretics.⁸⁵ Euglycemic diabetic ketoacidosis, albeit a significant but rare side event, was not seen in the CREDESCENCE¹¹ and DAPA-CKD⁵⁰ clinical studies. Patients utilizing SGLT2 inhibitors have a significantly higher genital mycotic infection occurrence rate, which may be up to fourfold.⁸⁶ Typically, they are minor and may be quickly remedied. Patients should be informed to carefully observe and track any indications or manifestations, as well as ensure proper cleanliness of the vaginal area. Bone fractures and limb amputations were linked to canagliflozin therapy without an increase in CV or stroke events in the CANVAS study.⁹ The Food and Drug Administration in 2018 released warning black box after reporting 12 cases of Fournier's gangrene (also called perineum necrotizing fasciitis) observed after dapagliflozin, canagliflozin, and empagliflozin use.⁸⁷ Still, these effects have yet to be duplicated in subsequent investigations. Hence, further research projects are required to investigate these SGLT2 side effects.

SGLT2 Inhibitors in Kidney Transplantation

Given the considerable issues of CVD and low allograft survival in KTxRs, the inhibition of SGLT2 provides an appealing therapeutic option. Nevertheless, the administration of SGLT2 inhibitors is intricate due to a single-functioning kidney and surgically modified genitourinary anatomy.¹⁶ Additionally, the simultaneous continuous immunosuppression use, increased viral infection risk, and the weakened immune system complicate the status. The possibility of infection is a major worry, and it is a substantial death cause, especially

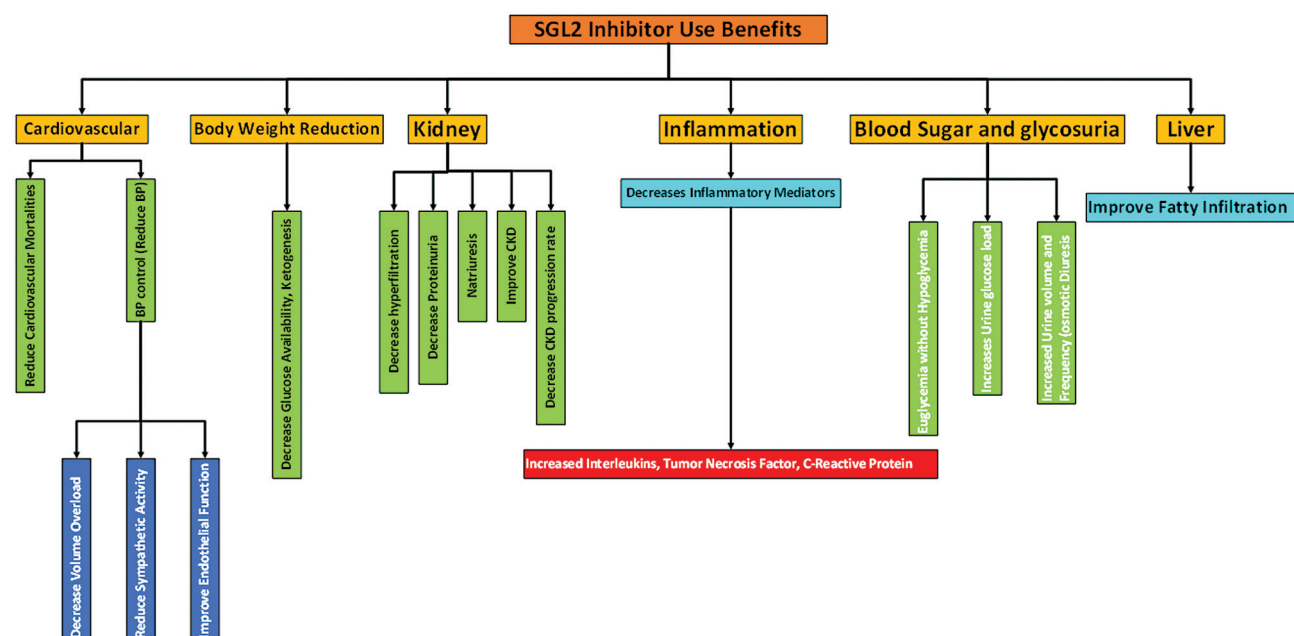


Fig. 2 Summary of sodium-glucose transporter 2 (SGLT2) inhibitor effects and benefits. BP, blood pressure.

during the early time after a transplant when the immune system is most suppressed.^{16,88,89} Moreover, KTxRs have atypical urogenital architecture, which increases their susceptibility to urinary tract infections (UTIs). UTIs are the most frequent infectious complication seen in KTxRs, with a prevalence of up to 41.6%, more common in the female gender. The same study reported that *Escherichia coli* (51.0%) was the most common, followed by *Klebsiella pneumoniae* (21.8%), during 6 years post-KTx.⁹⁰ Analysis of clinical trials conducted on individuals who did not undergo organ transplantation has revealed a heightened likelihood of developing fungal infections in the genital region when using SGLT2 inhibitors. Additional data gathered through postmarket monitoring has intensified concerns that SGLT2 inhibitors make patients more exposed to developing perineum necrotizing fasciitis (Fournier's gangrene).⁹¹ However, in another study in people with T2D, SGLT2 inhibitors did not increase Fournier's gangrene risk when compared to insulin or other antihyperglycemics.⁹² Although there is no evidence linking UTIs to SGLT2 inhibitor treatment in the general population, the increased glucosuria caused by SGLT2 inhibition raises concerns for KTxRs who are at a greater risk for Fournier's gangrene, severe UTIs, and urosepsis in different studies.¹⁶ However, these do not indicate the nonuse of SGLT2 inhibitors in KTxRs.⁹³

Aside from the potential for serious urogenital infection, evidence in nontransplant patients indicates that SGLT2 inhibitors could elevate euglycemic ketoacidosis risk, hypotension, acute renal damage, limb amputation, or bone fractures.^{16,92,94–96} The prevalence of these detrimental consequences is already heightened in the community of individuals who have had KTx. For instance, individuals with KTRs have a much higher susceptibility to hyperglycemic osmolar syndrome and diabetic ketoacidosis as compared to diabetics and the general population.⁹⁷ Although it is possible to avoid both illnesses, they nonetheless pose a significant risk of death if not treated effectively.⁹⁸ Furthermore, SGLT2 inhibitor treatment has been deliberately avoided in other situations where there is a higher likelihood of euglycemic ketoacidosis, such as T1D and instances of acute sickness, reinforcing the existing reluctance to use these medications in KTxRs.

Furthermore, KTxRs, especially those who receive cadaveric kidneys, are susceptible to different risk factors that might lead to hemodynamic ischemia damage in the early phases after transplantation. The high occurrence of CVD and the prolonged use of calcineurin inhibitor medication are significant factors that contribute to hemodynamic allograft damage, even many years after transplantation. As stated earlier, SGLT2 inhibitor usage causes afferent arterioles vasoconstriction, leading to decreased BP inside the glomerulus. This decrease in BP could cause ischemic damage in individuals who already have a diminished ability to regulate blood flow due to the use of calcineurin inhibitors.^{11,14} While most new studies proved that SGLT2 inhibitor usage has no link to acute kidney injury (AKI) for the native kidneys of type 2 diabetics, strict care must be applied in KTxRs because of their distinct risk profile.⁹⁹ In the early time after a transplant, excessive urination is quite common and often results

in reduced extra- and intravascular fluid volume, prerenal AKI, and low BP. SGLT2 inhibitors diuretic and natriuretic action might exacerbate this problem, making it advisable to avoid their use in the first few weeks after KTx. Additional considerations must be carefully considered while using SGLT2 inhibitors in KTxRs. These considerations include the possibility of the SGLT2 reduced effectiveness when used in a single denervated kidney, the potential for medication interactions, and their impact on immunosuppressive levels. Despite these conflicting reported data about the use of SGLT2 inhibitors in KTxRs, it was concluded in a 2018 review article that the index case demonstrated kidney transplant patients might safely utilize SGLT2 inhibitors for 2.5 years without formal trial data. Provided renal function is sufficient, physicians may employ SGLT2 inhibitors in this group on individual basis.¹⁰⁰ In a 2023 review, SGLT2 inhibitors may not be suitable for all solid organ transplants in T2D patients. When starting these agents, patients must be educated about diseases, such as sick day management, and monitored regularly for UTIs. Furthermore, short-term observations link lower HbA1c and more adverse outcomes. Hence, SGLT2 inhibitors' effects on solid organ transplant patients' death and other clinically relevant outcomes need more long-term RCTs.¹⁰¹

Conclusion

KTxRs using SGLT2 inhibitors have shown reasonable improvements in glycemia control and body weight, similar to nontransplant patients; however, evidence is limited. Although there is evidence of a tendency toward BP reduction with SGLT2 inhibitors therapy, it did not reveal a statistical significance by meta-analysis. The small sample size, diverse patient characteristics, and research design make insignificant meta-analysis results possible. There is reassuring evidence of a physiologic dip in estimated GFR consistent with an appropriate hemodynamic response and reduction in hyperfiltration that remains intact in KTxRs and may translate to long-term kidney survival and function benefit, improving patients' life quality. KTxRs had similar adverse effects to nontransplant patients and KTxRs without SGLT2 inhibitors therapy. Before SGLT2 inhibitors are claimed to be safe in KTxRs, extensive trial data are required due to inadequate evidence. Furthermore, SGLT2 inhibitor therapy's long-term cardiovascular and renal effects in KTxRs require larger RCTs with longer follow-ups.

Authors' Contributions

All the named authors contributed to the conception, data collection, critical review of the literature, and manuscript drafting and finalization. They all reviewed the final version of the manuscript before its submission and they all accept collective responsibility for its contents.

Compliance with Ethical Principles

No prior ethical approval is required for review article type of study.

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Conflict of Interest

None declared.

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