REVIEW ARTICLE

Why Are SGLT2 Inhibitors Nephroprotective? Mechanisms of Action And Possible Benefits A Review

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Abstract
Recent researches have demonstrated that SGLT2i (Sodium-Glucose Linked Transporter 2 inhibitors) play a role in preventing the development and progression of chronic kidney disease (CKD). However, these studies have not to look into the mechanisms that justify this progress. In this document, we will approach the physiologic causes of the kidney response to SGLT2i treatment.

SGLT2i were firstly designed as physiologic antidiabetic drugs due to its glucose anti-absorptive action in kidneys. Nevertheless, the effect on glucose levels has proved to be modest, so other different ways have to be involved in their renal benefits. After the commercialization of these drugs, their hypouricemic action, antihypertensive effects, and weight loss have been noticed. Although those actions are positive for the kidney, they are mild and hardly could induce a reduction of proteinuria and a kidney function stabilization effect.

Other actions such as anti-inflammatory and metabolic could have more importance in the role of SGLT2i. SGLT2i have been shown to reduce hypoxia and fibrosis in the kidney by changing energetic balance and by reducing inflammatory activity. These two mechanisms are closely related to the settlement and progression of CKD.

In addition, SGLT2i reduce proteinuria, which is probably the leading contribution of these drugs for renal function stabilization, due in part to its hemodynamic action by reducing intraglomerular pressure (tubule glomerular balance).

In conclusion, SGLT2i kidney benefits could hardly be explained by a single effect. In fact, SGLT2i trigger several effects, that taken together explain the kidney improvements that have been described.

Keywords: SGLT2i, diabetes type 2, Kidney, renal, proteinuria, albuminuria.
INTRODUCTION

Diabetic kidney disease is the leading cause of Chronic Kidney Disease (CKD) in the world (1). Despite the wide variety of treatments for diabetes management, many patients still suffer the consequences of this disease worldwide. Sodium-Glucose Linked Transporter 2 inhibitors (SGLT2i) are commonly used in type 2 diabetes treatment. Their mechanism of action consists of decreasing glycemia in a non-insulin-dependent manner by blocking the Sodium-Glucose Linked Transporter 2 (SGLT2), a molecular channel responsible for the reabsorption of 90% of the glucose filtered by the kidney (2). Besides, SGLT2i effect is exacerbated by the fact that SGLT2 channels are increased in patients with diabetes (3), leading to higher glucose reabsorption in the tubule and contributing to a worst glycaemic control.

Recent studies in diabetic patients treated with SGLT2i have shown great improvements in common comorbidities such as cardiovascular risk (4), heart failure (5), and myocardial infarction (6, 7). In addition, it has been reported that SGLT2i could decrease albuminuria and reduce the progression of CKD (6). All other diabetes treatments have reached their limited capability to reduce albuminuria and chronic kidney disease progression. In addition, SGLT2i do not have stronger glucose-lowering effects than other antidiabetic drugs, being, indeed, mild to moderate antidiabetic drugs. Taken together, this evidence leads to the conclusion that the renal benefits of SGLT2i may lay on different mechanisms rather than strictly their hypoglycemic power. However, these mechanisms have not been yet determined and are nowadays unclear. In this context, the purpose of this review is to assess the possible mechanisms underlying renal benefits caused by SGLT2i.

1.1 | Glycaemic control

Cardiovascular risk factors have been associated with deterioration of renal function (8), between those, diabetes has great importance (9). Diabetes is the main cause of CKD in developed countries representing more than 30% of all cases (10). Better glycaemic control could imply a reduction in the incidence of nephropathy and microalbuminuria (11). However, diabetes treatment shelve not been shown to improve renal prognosis, excepting some GLP-1 receptor agonists (12, 13) and SGLT2i (5, 7, 14). SGLT2i decrease blood glucose and average glycated hemoglobin 0.5% (15). In a meta-analysis of CKD type 2 diabetes patients, SGLT2i reduced the relative risk (RR) in glycated hemoglobin (HbA1C) by 71% (16), however, these results would depend on the basal glycated hemoglobin of each individual. SGLT2i efficacy and safety have been also demonstrated in renal transplant recipients, with stronger reductions in HbA1C in those higher at baseline, and in patients with higher Glomerular Filtration Rate (GFR) (17).

Moreover, it has been shown that SGLT2i increase the level of C peptide, a cleavage product of pro-insulin released from pancreatic beta cells that could be the consequence of higher pancreatic activity, and consequently results in higher insulin sensitivity. This effect could justify its renal and cardiovascular benefits. Additionally, a better glycaemic control favors less daily insulin requirements reducing up to 5 units per day (18). These lower daily requirements fall on a less anabolic insulin-mediated effect. In relation to this, researchers found diminution in glomerular diameter and stop in kidney growth in mice treated with SGLT2i (19).

These glycaemic benefits of SGLT2i are significant, but not stronger than those offered by other hypoglycaemic drugs. However, its hypoglycaemic action may be underestimated by the fact that in many studies, control groups could alter their treatment scheme to improve glycaemic control, this is the case of CANVAS (7), DECLARE (5), and EMPA-REG (14). It seems clear that other different factors are acting, since more powerful treatments have...
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failed to provide advantages at renal, cardiovascular, and mortality endpoints.

1.2 | Urate levels

High blood urate levels have been described as a risk factor for CKD in diabetic patients (20), contributing to the deterioration of renal function (21). SGLT2i have an impact at this point as they decrease plasma urate levels by increasing urate excretion (4, 15, 22, 23). Moreover, clinical trials have demonstrated those effects in renal transplant patients (17).

The molecular mechanism underlying SGLT2i effects in urate has been recently elucidated. Glucose Transporter 9 (GLUT9) and Urate Transporter 1 (URAT1) are in charge of the reabsorption of urate in the renal tubule (24). URAT1 reabsorbs urate in the apical membrane (25), while GLUT9 isoform 1 transports urate through the basolateral membrane to the blood (26). In addition, GLUT9 isoform 2 is expressed in the apical membrane exchanging intraluminal glucose with intracellular urate (24). SGLT2 does not play a direct role in urate transport. However, the increase of glucose in the proximal tubule lumen induced by SGLT2i may push on GLUT9 isoform 2 exchanging glucose and urate, thereby increasing both glucose reabsorption and urate excretion (27, 28).

Moreover, an animal model study demonstrated that both knock-out (KO) mice for SGLT1 and GLUT9 had lower urate plasma levels than the control group while they were treated with canagliflozin, a commercialized SGLT2i. In addition, GLUT9 KO mice had higher urate fractional excretion than the wild type group also under treatment with canagliflozin. The same study described that, in mice, SGLT2i treatment could increase the mRNA expression of GLUT9. Therefore, increased expression of GLUT9 could lessen the hypoglycaemic effect of SGLT2i by compensating mechanisms (29).

Finally, insulin has been described as a hyperuricemic agent (30), as it increases URAT1 expression in the kidney (31) enhancing urate reabsorption (22). So, SGLT2i may also modify urate levels by reducing insulin daily requirements.

1.3 | Albuminuria and proteinuria

It is well described that albuminuria is related to higher cardiovascular morbidity and mortality (32). Besides, the degree of proteinuria is a good marker of progression of CKD (33, 34) to the stent that controlling proteinuria levels favours to slow down CKD progression. (35)

In this context, renin-angiotensin system inhibitors are currently the main tool for treating proteinuria (36) and stabilize the glomerular filtration rate. However, this scenario might change because of the use of SGLT2i.

In diabetic patients, proteinuria is partially caused by hyperfiltration. It has been reported that diabetic patients have a higher capacity of glucose reabsorption in the tubule through a great number of SGLT2 channels (37, 38), which leads to hyperfiltration due to a lesser amount of sodium and chloride in the macula densa which promotes a vasodilatory response in the afferent arteriole. As a result, by blocking SGLT2 channel, intraglomerular pressure will decrease (39) and hyperfiltration would be ameliorated. This effect may be enhanced by a tubuloglomerular feedback response of vasoconstriction in the afferent arteriole (40) since macula densa would detect high levels of sodium and chloride. This effect is mediated by adenosine production, an important vasoconstrictor substance (41).

This new family of drugs has been shown to delay diabetes nephropathy, albuminuria, and cardiovascular events in multiple studies (5, 7, 14). Nevertheless, these studies have been carried out in a small population of patients with CKD, and renal function and albuminuria were not primary endpoints. In this context, the CREDENCE trial was designed as a study for canagliflozin in a population of 60% of patients with an estimated GFR of 30 to 60 ml/min per 1.73 m^2 and albuminuria >300 to <5000 mg (6). Additionally, the primarises endpoints of this study were focused on the kidney (doubling serum creatinine, end-stage renal disease, or death for renal or cardiovascular disease), with a reduction of 30% in the composite endpoint. Moreover, this impact in renal function was accompanied by a reduction of 31% in albuminuria. Taken together CREDENCE study
reinforces the role of SGLT2i in the progression of chronic kidney disease

In addition, obesity, a recognized risk factor for diabetes, increases renal pressure. SGLT2i could indirectly decrease renal pressure through their slimming effects.

1.4 | Blood pressure

Hypertension is not only a common cause of nephropathy, but also a progression factor (42). This relation has been well established, with a higher percentage of resistant hypertension in those who progressed of CKD stage (43). Moreover, the relationship between hypertension and albuminuria, another major risk factor of progression of CKD, is well documented (44, 45).

It has been demonstrated that SGLT2i has blood-pressure-lowering effects. In this line, patients treated with SGLT2i reduced systolic blood pressure (SBP) by 3 mmHg (6), and required less antihypertensive drugs (14). These effects on systolic pressure were stronger between those patients with more deficient pressure control, reaching differences of 7 mmHg with placebo (46). In another study SGLT2i, blood-pressure-lowering effects were evident since the first week of treatment, with reductions of 6.8 mmHg in SBP and 2.5 mmHg in diastolic blood pressure. Moreover, this benefit was kept along time (47).

Part of the anti-hypertensive effect may be due to its natriuretic and diuretic effect by a mechanism of osmotic diuresis (14, 48); however, this diuretic effect is finally compensated, disappearing after a certain time of treatment (49), so other properties of SGLT2i should justify their long-term benefits. SGLT2i also reduce body sodium content, the direct responsibility of hypertension, particularly at the skin (50). Herewith, the sodium-lowering effect also triggers a reduction in water retention, contributing to reduce blood pressure.

1.5 | Anti-inflammatory effects

Diabetes is associated with an inflammatory state that favours oxidative stress in blood vessels (51). Therefore, diabetic patients will have sicker blood vessels than the common population. Oxidative stress is in part due to glucotoxicity mediated by advanced glycated end products (52). In this sense, SGLT2i could reverse the characteristic inflammatory pattern of diabetic patients by reducing glucotoxicity and, thereby, oxidative stress (53).

Monocyte chemo attractant protein-1 (MCP-1) promotes monocyte infiltration and maturation. Infiltration of monocytes/macrophages into the kidney triggers tubular injury and boosts cyst appearance (54). A study carried out in mice demonstrated that pharmacological inhibition of MCP-1 restores glomerular glycocalyx and reduces albuminuria, underscoring the role of macrophages and MCP-1 in diabetic nephropathy (55). SGLT2i have been demonstrated to decrease MCP-1 levels (56) thus preventing macrophage infiltration and thereby kidney injury. This advantage is independent of hemodynamic improvement, which in turn shows a structural improvement of declining MCP-1 levels.

NADPH oxidase is also activated by hyperglycemia (57). Activated NADPH oxidase, generates super oxide which has roles in an immune response. These molecules have a widespread function, on the one hand, they suppress the action of nitric oxide diminishing vasodilation in the afferent arteriole, on the other hand, they generate ROS, and this flows to apoptosis of podocytes, enhanced epithelial-to-mesenchymal transition, proteinuria and basal membrane hypertrophy (58–61). Manifold studies have described that SGLT2i decreased aortic thickness and collagen content, NADPH oxidase contributing to, HO-1, monocyte chemoattractant protein-1 and 2 (MCP-1, and MCP-2) and eNOS over expression (56). These mechanisms intervene in better preservation of pancreatic function and improvements in renal function.

1.6 | Metabolic effects

Hypoxia is a determinant factor in the progression of chronic kidney disease (62). It is known to have a key role at the beginning of renal damage, but also continuous hypoxia contributes to the establishment of chronic kidney disease (63).
SGLT2i have a nephron protector role since they diminish oxygen consumption, thus avoiding hypoxia (64). It is well known that diabetes increases oxygen consumption as a consequence of higher amounts of sodium and glucose in the tubule which triggers an over activity of sodium and glucose transport channels, thereby increasing energy, and subsequently oxygen consumption (65, 66). Moreover, this effect would be magnified by the glomerular hyper filtration that occurs in the diabetic kidney at the beginning of the disease (67).

Conversely, it has been proposed that by blocking SGLT2, oxygen consumption would increase in the S3 segment of the glomerular tubule due to the higher arrival of sodium and glucose. Not with standing, there is also an increment in ketone bodies (68) that change the renal energy balance, which has been found to be duplicated (69). In this context, ketones would represent an energy contribution to the kidney (70), which constitute indeed, a more effective fuel than common energetic sources such as glucose (70). Thus, the increase in oxygen consumption in the S3 segment is compensated by enhanced ketone levels, thus avoiding or attenuating hypoxia. Furthermore, ketone bodies have been shown to trigger anti-inflammatory mechanisms, which could contribute to the benefits of SGLT2i in renal and cardiac function (71–73).

This change in renal metabolism keeps over time and set up early, explaining the advantages of this group of drugs even in short periods of time.

1.7 | Weight benefits

Obesity is a risk factor for development (74) and the progression of CKD and mortality (75). Obesity is also a risk factor for diabetes, hypertension (76), metabolic syndrome (77), excessive levels of urate, and development of some glomerulopathies (78), all of them well-established risk factors for suffering nephropathy.

Multifarious studies have demonstrated SGLT2i to decrease body weight. But, which is more important, these improvements are based on a lesser loss of lean body weight and a greater loss of visceral and subcutaneous fat (15). This effect has proven to be stable, keeping initial loss during the time (41). The total impact on body weight has been estimated at about 2-3 kg (79–82). However, weight reduction is lower than expected attending to the fact that SGLT2i provoke an increment in daily energy expenditure of 200–400 Kcal (83), which could be explained by an increment in appetite.

This effect on body fat deserves an especial mention in non-alcoholic fatty liver disease (NAFLD). NAFLD is a common disease between diabetic patients (84, 85) which has a role in the progression of diabetic nephropathy (86). Different SGLT2i have been proven to have a great impact on liver metabolism. Six months after initiating therapy with SGLT2i total liver fat was reduced on the order of 30% (87, 88). Likewise, a reduction of Gamma-glutamyl transferase (GGT), alanine aminotransferase (ALT), and aspartate amino transferase (AST) have been reported under SGLT2i treatment in a dose-dependent way (89). These results are significantly greater when compared with other antidiabetic drugs such as metformin, sitagliptin, and glimepiride (90–92). Additionally, a decline in liver fat could decrease the release of cytokines and other inflammatory agents which could damage the liver and other organs, including the kidney.

Finally, adipose tissue is a source of adipokines such as leptin, TNF-α, MCP-1, TGF-β, and angiotensin II (93, 94). Those adipokines, as previously mentioned, are related to inflammatory states that exert chronic damage. Moreover, this inflammation contributes to higher insulin resistance (95).

2 | DISCUSSION

SGLT2i represent a new strategy in diabetes treatment and confer a new option in incipient diabetic nephropathy. On the basis of the results is clear that other different mechanisms than exclusively hypoglycemic action are involved in setting back diabetic nephropathy. Other agents such as DPP4 inhibitors, metformin, and other hypoglycemic drugs had demonstrated better results in lowering glycemia (15, 96) but these results did not fall into the best prognosis of diabetic nephropathy.
in the way SGLT2i did (5, 7, 14). So other added actions must be involved in this improvement.

On the one hand, there are some measurable parameters that ameliorate the progression of kidney disease. It is well recognized the role of urate (5–7, 14) and glycemia in the development of chronic kidney disease. So by better control of these parameters, kidneys probably will keep healthier along time. The effects of SGLT2i on urate levels and blood pressure are mild, and cannot explain the whole effect of these drugs on kidney pathophysiology. However, SGLT2i exhibit a strong effect on albuminuria, in fact, they reduced basal albuminuria in a 31% (6), which in fact is a substantial effect; other drugs such as Angiotensin II Receptor Blockers (ARBs) and angiotensin-converting enzyme inhibitors (ACE-I) reduced 40% baseline levels of proteinuria (97). This is a notable decrease but could not justify, by itself, the role of SGLT2i on stabilizing renal function. Moreover, the mechanisms by which SGLT2i achieve this reduction also imply renal benefits. Similarly to ARBs and ACE-i, SGLT2i decrease proteinuria by decreasing intraglomerular pressure, thereby reducing hyperfiltration (39–41). It is known that the tone of the first effects generated by diabetes in the kidney is hyperfiltration, which elicits damage in the glomerulus; so probably by avoiding hyperfiltration, kidney ultrastructural changes could be prevented. This impact in intraglomerular pressure could be assisted by the weight benefits of SGLT2i (80–82). It is known that obesity is a factor associated with diabetes but also with hyperfiltration, so, SGLT2i could also lower intraglomerular pressure by reducing body weight.

On the other hand, there are other non- or hardly measurable factors that have an effect on the anatomy and physiology of the kidney. Firstly, SGLT2i, by their anti-inflammatory effect can prevent structural changes (55, 56); these changes include better preservation of podocytes which are essential for conserving the integrity of the glomerular membrane and forwarding off the adverse consequences of proteinuria and albuminuria in the subsequent parts of the nephron (58–61). Moreover, SGLT2i impede the formation of some other fibrotic and inflammatory molecules such as MCP1 and NADPH oxidase between others, that injure kidney structure. Secondly, SGLT2i change energetic balance in several ways, the first one consists of unbalancing the energetic equilibrium in favor of ketone bodies (68), which have proved to be more energetically efficient (69), thereby protecting the kidney from hypoxia. Hypoxia is essential in the initial but also in the subsequent phases of renal injury. Moreover, ketones had an anti-inflammatory effect that strengthens SGLT2i metabolic benefits and antifibrotic power (71–73). Canagliflozin, empagliflozin, and dapagliflozin have demonstrated solid cardiovascular and renal benefits (5–7, 14). Notwithstanding, VERTIS-CV (98) study suggests that ertugliflozin may not exert these cardio and renoprotective effects, demonstrating that this SGLT2i do not elicit a decrease in cardiovascular death nor adverse renal outcomes. This controversial new finding could be the result of diverse facts. Firstly, the dropout rate of this trial has not been published yet, since this study is based on an intention-to-treat analysis, a high dropout rate could drive to a lack of signification. Secondly, the study population displays an important difference when compared to other trials: VERTIS-CV (98) contained a higher proportion of the white population than CREDENCE, CANVAS, EMPA-REG, and DECLARE 88% vs 66%, 78%, 72%, and 79% respectively (5–7, 14). Furthermore, those populations’ differences affect the proportion of Asians being 6% in VERTIS CV(98) versus 19.9%, 12.7%, 22%, and 13% in CREDENCE, CANVAS, EMPA-REG and DECLARE respectively (5–7, 14).

Conversely, VERTIS-CV (98) demonstrates that ertugliflozin treatment could lead to a drop in heart failure hospitalization in line with previous trials. Finally, the lack of statistical differences between ertugliflozin and placebo treatment groups could lay on ertugliflozin molecular structure and architecture specifications as is the case of other families of drugs such as rosiglitazone (99) and certain GLP1s (100) among others.

In conclusion, SGLT2i provokes many physiological changes that individually could hardly justify their benefits, but that taken together could explain renal protective effects.
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3 | CONFLICTS OF INTEREST

All authors have no conflicts of interest to declare.

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5 | AUTHORS CONTRIBUTIONS

Carlos Santos-Alonso and Elena Díaz-García participated in the data collection and wrote the manuscript. Rafael Selgas and Olga Costero provided intellectual content of critical importance to the work and technical support. María Maldonado-Martín helped to draft the manuscript. Carlos Santos-Alonso, Elena Díaz-García, Olga Costero, María Maldonado-Martín and Rafael Selgas edited and revised manuscript. All authors read and approved the final manuscript.

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