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Ameliorative impact of sodium–glucose cotransporter-2 inhibitors in diabetic kidney disease; a mini- review to current evidence

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ABSTRACT

The sodium–glucose cotransporter-2 inhibitors (SGLT2i) are a new class of antidiabetic agents. SGLT2i are able to inhibit SGLT2 transporter in renal tissue, increasing glycosuria and reducing blood sugar. These drugs act by inhibiting the SGLT2 in renal proximal epithelial tubular cells. SGLT2i are found to have beneficial effect on chronic renal failure caused by diabetic nephropathy.

Keywords: Sodium–glucose cotransporter-2 inhibitors, Chronic renal failure, Diabetic nephropathy, Type 2 diabetes, Sodium–glucose cotransporter-2, Nephroprotective effect, Acute kidney injury

Mini Review

Implication for health policy/practice/research/medical education:
A study of SGLT2 inhibitors in type 1 and 2 diabetes individuals showed a reduction in hyperfiltration in normotensive, normoalbuminuric type 1 diabetes patients and a significant reduction in albuminuria and hyperfiltration in type 2 diabetes individuals.

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Introduction

Chronic renal failure is prevalent in more than ten percent of the general population (1). Chronic kidney disease is considered as an irreversible loss of renal function. The loss of nephrons causes a compensatory circumstance of nephron hyperfiltration and renal tubular cells hypertrophy, which can eventually lead to glomerulosclerosis and the progression to end-stage kidney failure (2). Chronic renal disease affects nearly 35% of people with type 2 diabetes (T2D) and is associated with an increased mortality rate (3). Additionally, diabetic nephropathy is the utmost common cause of end-stage of kidney failure, despite the fact that its mechanisms are not yet fully understood (4). Recent studies show that nearly 40% of individuals with T2D have chronic renal failure as measured by glomerular filtration rate or by urine albumin execration (1). Various modalities have been used to reduce diabetic nephropathy, including strict blood control with anti-hyperglycemic agents, treatment of dyslipidemia and the use of renin-angiotensin-aldosterone blockers and inhibitors, but individuals with T2D are still at higher risk of mortality and morbidity from its complications (3). In various clinical and experimental studies, inhibition of the sodium–glucose cotransporter-2 (SGLT2) in kidneys has been found to reduce progression of diabetic kidney disease through combination therapy or alone (4). These agents are a novel approach to treating hyperglycemia. In patients with heart failure and a low left ventricular ejection fraction, sodium-glucose cotransporter-2 inhibitors (SGLT2i) are also a viable treatment option (5). This mini-review uses most recently published studies to explain the new concepts of SGLT2i kidney protective effects.

Search strategy

For this mini-review, we searched the Web of Science, Scopus, Embase, PubMed, and Google Scholar for sodium–glucose cotransporter-2 inhibitors, chronic renal

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failure, diabetic nephropathy, type 2 diabetes, SGLT2, nephroprotective effect and acute kidney injury.

Sodium-glucose cotransporter-2 inhibitors

The SGLT2i are a new class of anti-diabetic agents. They have the ability to inhibit the SGLT2 transporter in renal tissue, increasing glycosuria and reducing blood sugar (6). These drugs work by inhibiting the SGLT-2 in renal proximal epithelial tubular cells. In experimental studies, it is expected an increase in distal sodium delivery to the macula densa cells after reducing proximal tubular sodium reabsorption by sodium-glucose co-transporter-2, triggering tubule-glomerular feedback stimulation, then afferent arterial vasoconstriction, and finally hyperfiltration reduction (7). As a result, these agents reduce glucose reabsorption in the kidney and thereby increase glycosuria. As nephrons filter a large amount of sugar throughout the day, kidney proximal tubular cells must reabsorb all filtered sugar to keep it from excretion. This transport is carried out by sodium-glucose cotransporters SGLT1 and SGLT2, which are presented on the apical side of the membrane as well as glucose transporter type 4 (GLUT4) on the basolateral side of membrane (8). Surprisingly, sodium–glucose cotransporter-2 expression in the kidney proximal tubular cells is increased in T2D patients, resulting in increased sugar uptake and worsening hyperglycemia. As a result, blocking sodium-glucose co-transporter-2 can inhibit sugar and sodium reabsorption at the kidney proximal tubules (9). Additionally, the renal proximal tubular cells produce new glucose, primarily in the post-absorptive phase and to increase bicarbonate formation to maintain the acid-base balance. Finally, the reabsorbed or locally synthetized glucose is interred into the peritubular capillaries and returns back to the blood system or serves as an energy resource to other parts of nephrons, specifically the renal distal tubular segments, via basolateral facilitative glucose transporter type 1 (8).

It is important to note that the ability of SGLT2i to lower blood sugar levels is independent of insulin action. Moreover, because of their natriuretic and diuretic properties, these drugs may reduce sodium and volume overload, resulting in intravascular volume reduction. Furthermore, administration of this group of drugs has been linked to improved of hypertension and weight loss without causing reflex tachycardia (9). Many studies have also found that this group reduces glomerular pressure and improves glomerular hyperfiltration in individuals with diabetes. As a result, it may improve kidney outcomes, while some concerns have been raised that SGLT2 inhibitors may cause long-term kidney damage (3). These drugs also reduce serum uric acid levels. In addition, there was a decrease in systemic and intra-glomerular pressure after administration of this drug. It is possible that above ameliorative properties on renal disease were also tested in non-diabetic individuals (10). According to the numerous preclinical and clinical studies, these agents have a good safety profile and a suitable beneficial effect to lower blood sugar level and reduce the toxic effect of glucose in diabetes subjects, which is associated with improved glycemic control and weight loss (11). Administration of SGLT2 inhibitors in type 1 and 2 diabetes individuals showed a significant reduction of albuminuria and hyperfiltration in both type 1 and T2D individuals (7). However, there was an increase in the risk of urinary tract infection after administration of SGLT2i (12).

Cardiology aspects of SGLT2 inhibitors

In terms of cardiology, it was discovered that SGLT2 inhibitors reduce the risk of cardiac insufficiency and heart mortality in subjects with heart failure and reduced ejection fraction (13-15). The underlying mechanisms of these beneficial effects include a constructive influence of this agent on cardiac remodeling. Besides, the decrease in N-terminal pro-B-type natriuretic peptide during SGLT2i may be another beneficial action of this drug. Similarly, it has been reported that the SGLT2i are involved in reduction of left ventricular mass in individuals with T2D and coronary heart problems by weight reduction and blood pressure control (13-15). A recent clinical trial involving 76 people with T2D showed that the SGLT2i reduced blood pressure and the indicators of arterial stiffness, which was associated with improvements in arterial stiffness and vascular function (16). Other studies have found that SGLT2i decreases insulin resistance, visceral adiposity, volume overload, cardiac inflammation, hyperglycemia, dyslipidemia, hypertension and cardiac inflammation. Other studies recently found an improvement of low-nitric oxide (NO) production and oxidative stress reduction, as well as a decrease in heart inflammatory cytokine signaling. These studies also demonstrated Ca^{2+} overload inhibition and recovery in heart energy metabolism (17).

Administration of SGLT2 inhibitors in diabetic kidney disease

Diabetic nephropathy is the most common cause of morbidity and mortality worldwide, and it is a major health concern (18). This disease is associated with comorbid conditions such as atherosclerotic heart disease and cardiac failure (19). Because an increase in interstitial and luminal glucose levels are associated with an increase in matrix synthesis in the tubular extracellular area, this explains the progression of tubulointerstitial fibrosis in diabetic kidney disease. Numerous studies have detected that this drug has renoprotective properties (17-19). The potential mechanisms of kidney protection by SGLT2i may be directed toward various metabolic and hemodynamic pathways (18). A recent study found that these agents improved renal outcomes by inhibiting serum creatinine doubling, decreasing albuminuria and delaying the

initiation of kidney replacement therapy (20). Additional mechanisms for renoprotection impact of SGLT2i include kidney proximal tubular cells exposed to higher sugar levels, which results in a reduction in inflammatory and fibrotic biomarkers (21). Other possible mechanisms of renal protections by these drugs included changes in renin-aldosterone-angiotensin system (RAAS) activation at the systemic and local levels, and a shift towards higher ketone body consumption (22).

These drugs also stimulate erythrocytosis by influencing the hypoxia-inducible factors (HIFs), particularly HIF-1α and HIF-2α, which could be another mechanism for slowing the progression of kidney disease (23). T2D is defined in this context by kidney hypoxia, increased endoplasmic reticulum stress, oxidative process and also defective nutrient deficiency signaling, which predisposes to HIF-1α provocation and HIF-2α inhibition. This imbalance in HIF-1α/HIF-2α activity accelerates pro-fibrotic and pro-inflammatory pathways in renal tubular and glomerular cells. As a result SGLT2i ceases cellular stress and kidney hypoxia while increasing nutrient deprivation signaling, which explains suppression of HIF-1α and activation of HIF-2α, in conjunction with suppressing organellar dysfunction, decreasing inflammation and finally inhibiting the fibrosis. Thus, the nephroprotective benefits of SGLT2i could be attributed to their effect to induce oxygen deprivation signaling in the diabetic kidneys (23). Recent research has also discovered a role for sodium-glucose co-transporter-1 in acute renal injury (8). A recent meta-analysis of thirty randomized clinical trials found that inhibiting sodium-glucose co-transporter-2 reduced the risk of severe adverse effect due to acute kidney injury (24). Another meta-analysis found that SGLT2i such as empagliflozin, ipragliflozin, canagliflozin and dapagliflozin were significantly protective against acute renal failure when compared to placebo (25). According to other studies, SGLT2i reduced risk of both non-serious and serious acute kidney injury episodes by 25% (26).

Conclusion

In summary, the tubular and glomerular impact of SGLT2i explain the nephroprotective effect, in addition to their cardio-protective potency; however many aspects of this drug remain unknown.

Authors' contribution

Primary draft by DJ. Scientific edit by AN. Both authors read and signed then approved the final paper.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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