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SGLT2 inhibitors in preventing progression of chronic kidney disease in patients with type 2 diabetes: a literature review

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Abstract

Introduction

Type 2 diabetes mellitus (T2DM) is an increasing health concern, and diabetic kidney disease (DKD) affects 30–40% of patients with diabetes. Sodium-glucose cotransporter 2 inhibitors (SGLT2i) are effective medications used in the treatment of T2DM, which not only improve glycemic control but also slow the progression of diabetic kidney disease (DKD), reducing the risk of renal and cardiovascular complications. They work by decreasing glomerular hyperfiltration and alleviating inflammation in the kidneys. Clinical studies have demonstrated significant therapeutic benefits, including a reduction in albuminuria and improvement in renal function. In the future, the development of new drug classes, such as Nrf2 activators and RAS inhibitors, which are currently under clinical investigation, may further advance the treatment of DKD, offering a more personalized approach to therapy. This article reviews the current knowledge on SGLT2i and their impact on the progression of DKD, the future prospects for therapies in managing diabetes and its complications.

Aim of the Study: The aim of this study was to gather and analyze available scientific publications regarding the effect of sodium-glucose cotransporter 2 inhibitors (SGLT2i) on slowing the progression of chronic kidney disease (CKD) in patients with T2DM and to determine the future of therapy based on new reports and research into emerging drug classes.

Materials and Methods: We conducted a review and analysis of the literature available in the PubMed database, using keywords such as SGLT2 inhibitors, gliflozins, chronic kidney disease, type 2 diabetes.

Results

Sodium-glucose cotransporter 2 inhibitors (SGLT2i) represent a promising class of drugs that reduce the progression of DKD and the risk of renal and cardiovascular complications. Studies have shown that SGLT2i, such as empagliflozin and canagliflozin, improve clinical outcomes by reducing albuminuria and mortality related to kidney disease. In the future, the development of new therapies, including Nrf2 activators and RAS inhibitors, may enhance the treatment of DKD, providing a more personalized approach to therapy.

Keywords: SGLT2 inhibitors, type 2 diabetes mellitus, chronic kidney disease, diabetic kidney disease

Introduction

Diabetes mellitus (DM) is one of the oldest known diseases, and its prevalence continues to rise. In 2013, it was estimated that approximately 382 million people worldwide were living with DM. The incidence of type 2 diabetes, which accounts for ~90% of all diabetes cases, is still increasing, and it is predicted that by 2035, the number of people diagnosed with this disease will exceed 590 million [1]. Especially in the last two decades, obesity, a significant risk factor for T2DM, has become a global public health issue, posing a threat to human health and life. It impacts nearly all systems and organs of the body, posing a major public health challenge as one of the most prevalent non-communicable diseases [2]. Type 2 diabetes mellitus is a disease with a complex etiology, characterized by hyperglycemia resulting from defects in insulin action, secretion, or both. This leads to disturbances in glucose transport to the liver, skeletal muscles, and adipose tissue, resulting in the onset of characteristic symptoms such as polyuria, polydipsia, weight loss, and chronic fatigue. Patients with T2DM are at risk of developing micro- and macrovascular complications, including accelerated atherosclerosis, retinopathy, neuropathy, and diabetic nephropathy, leading to the faster loss of health and life. Sodium-glucose cotransporter 2 inhibitors (SGLT2i) are a relatively new class of oral antidiabetic medications that target proteins in the proximal renal tubules, primarily in segments S1 and S2, as well as in the intestinal epithelium. Clinical guidelines recommend their use, especially in patients with T2DM who have vascular complications and/or heart failure, emphasizing the significance of SGLT2 inhibitors in the management of these patients [3].

Diabetic Kidney Disease

Diabetic kidney disease (DKD) is one of the leading causes of end-stage renal disease worldwide and affects 30–40% of patients with T2DM [4]. Although the incidence of diabetes-related kidney failure has decreased over the past 20 years, approximately 30% of patients with type 1 diabetes (T1DM) and 40% of patients with type 2 diabetes (T2DM) develop various forms of chronic kidney disease (CKD) [5], and about 20% of T2DM patients develop DKD even in the absence of albuminuria [6].

DKD begins with glucose metabolism disorders associated with hyperglycemia, which lead to microangiopathy and diabetic nephropathy, resulting from insulin dysfunction or insulin resistance. This causes glomerular hyperfiltration and hypertension—hemodynamic mechanisms long recognized as initiators and contributors to kidney damage in diabetes [7]. Glomerular hyperfiltration is exacerbated by high levels of amino acids, manifesting as albuminuria, proteinuria, nephrotic syndrome, and ultimately the progression to chronic kidney disease (CKD) [8]. DKD is diagnosed based on the presence of albuminuria (>300 mg/d) and/or a low estimated glomerular filtration rate (eGFR) (<60 ml/min/1.73 m^2) in patients with type 2 diabetes, after excluding other causes of CKD [9]. The only definitive diagnosis of CKD is the identification of characteristic morphological changes in a kidney biopsy.

Histopathology

The structural features of glomerular damage in diabetes include, among others, thickening of the glomerular basement membrane, diffuse and nodular expansion of the mesangium, podocyte damage and detachment, and glomerulosclerosis. Additionally, there is also arteriole hyalinosis, which is a characteristic vascular feature of diabetic kidney disease. The loss of the glycocalyx – a polysaccharide and proteoglycan gel covering the endothelium, which serves as a barrier against albumin loss – leads to albuminuria. Albuminuria precedes glomerular damage [10]. Inhibition of matrix metalloproteinase activity reduces proteinuria and helps rebuild the endothelial glycocalyx layer without affecting other glomerular structures. This suggests that this pathway may serve as a therapeutic target, particularly in the early stages of DKD [11].

Immunology

In patients with T2DM, glomerular changes are typically accompanied by significant inflammation in the renal tubules and fibrosis due to increased collagen synthesis [12]. Disrupted intracellular glucose metabolism leads to the formation of advanced glycation end products (AGEs), reactive oxygen species, and the activation of protein kinase pathways, inducing the expression and activation of interleukins, IL-1β and IL-18 [13,14]. Macrophages regulate tissue repair processes and fibrosis, though their role in renal tissue regeneration remains incompletely understood [15]. They produce tumor necrosis factor-α (TNF-α), which in the glomeruli and renal tubules induces the production of other cytokines and chemokines, leading to apoptosis and cytotoxic effects [16]. IL-1, IL-16, and IL-18 also play a significant role in the pathogenesis of diabetic kidney disease. IL-1 enhances endothelial permeability and glomerular hyperperfusion through the release of prostaglandin E and phospholipase A2, thereby contributing to worsening renal function. Elevated levels of IL-18, observed in the serum of patients with type 2 diabetes mellitus, induce apoptosis, increase the release of interferon-gamma (IFN-γ), and upregulate the expression of adhesion molecules, significantly exacerbating albuminuria. Elevated concentrations of chemokines released by damaged nephrons have been observed in kidney biopsies and urine of DKD patients. These chemokines may increase the production and transfer of inflammatory cells to the affected tissues, further amplifying the inflammatory process [17]. All of these mechanisms result in a continuous elevation of pro-inflammatory mediators, pro-thrombotic factors, and the recruitment of immune cells, leading to a chronic inflammatory state, which contributes to the structural remodeling of renal tissue and, ultimately, the progression of CKD [18].

SGLT2 Inhibitors in DKD

Sodium-glucose cotransporter 2 (SGLT2) is now recognized as an important modulator of glomerular hemodynamics, not only in the treatment of patients with cardiovascular diseases but also in those with diabetes mellitus. Under conditions of elevated blood glucose levels, the expression and activity of SGLT2 increase on the luminal surface of epithelial cells in the proximal convoluted tubule, as a compensatory response to reclaim more glucose from the urine [19,20]. Although the exact mechanisms through which SGLT2i provide clinical benefits are not fully understood, it is known that their

use in patients with T2DM reduces glomerular hyperfiltration, making them recommended as first-line treatment for patients with DKD, especially in combination with angiotensin-converting enzyme inhibitors (ACE inhibitors) or angiotensin receptor blockers (ARBs) [19].

It has been demonstrated that in patients with T2DM and eGFR ≥25 ml/min/1.73 m², SGLT2i reduce the progression of DKD and the risk of advancing to later stages of chronic kidney disease, thereby decreasing mortality associated with the disease, regardless of glycemic control [21,22].

In the 2016 EMPA-REG OUTCOME study, patients treated with empagliflozin showed a significant reduction in macroalbuminuria, decreased serum creatinine levels, and lower risk of initiating kidney replacement therapy or dying from CKD in the future [23].

Similarly, in the CREDENCE study, conducted with 4,401 patients with T2DM, CKD, and significantly elevated albuminuria (ranging from 300 to 5,000 mg/g), who were already being treated with ACE inhibitors or ARBs, canagliflozin was compared with a placebo. The study was prematurely terminated (the median follow-up was 2.62 years, compared to the planned 5.5 years) due to the clear benefits of canagliflozin [24]. These medications work by inhibiting SGLT2, located in the S1 and S2 segments of the proximal convoluted tubule of the kidneys, thereby increasing glucosuria and natriuresis [25]. This leads to a reduction in blood glucose levels, resulting in a lowering of glycated hemoglobin (HbA1c) by 0.6–0.8% (6–8 mmol/mol) without increasing the risk of hypoglycemia [19]. It has also been shown that a ~1% reduction in HbA1c is associated with a 33% reduction in the risk of developing albuminuria [26], and its control, maintaining levels below 6.5%, nearly completely prevents the onset of microangiopathic complications in the kidneys [27].

In T2DM complications related to increased inflammatory processes in the kidneys, the CANagliflozin Treatment And Trial Analysis-Sulfonylurea (CANTATA-SU) trial demonstrated that the use of canagliflozin reduced circulating levels of IL-6, TNF-1 receptor, matrix metalloproteinase-7, and fibronectin-1 [28], a finding also confirmed in the CANagliflozin cardioVascular Assessment Study (CANVAS) [29]. Additionally, the Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD) study showed that dapagliflozin also reduces circulating IL-6 levels, contributing to a reduction in kidney inflammatory response, improving renal function, and ultimately decreasing patient mortality [30,31].

Other Benefits of SGLT2 Inhibitors

Empagliflozin, approved by the FDA in 2014, significantly reduced cardiovascular mortality and hospitalizations due to heart failure. In subsequent years, other SGLT2 inhibitors, such as canagliflozin and dapagliflozin, have also demonstrated cardioprotective effects in patients with type 2 diabetes mellitus [32,33,34]. The DAPA-HF study, which included 4,744 participants with heart failure, with or without T2DM and a reduced ejection fraction (≤40%), found that patients receiving dapagliflozin had a lower risk of heart failure worsening or cardiovascular death compared to those receiving a placebo [35]. Similarly, in the EMPA-REG OUTCOME study, it was discovered that T2DM patients receiving empagliflozin who were at high risk for cardiovascular disease experienced early reductions in key risk factors for such events [32].

Another effect of SGLT2i therapy is the reduction in blood pressure through the inhibition of sodium reabsorption in the proximal renal tubules, leading to an increase in sodium excretion by 30–60% [36]. This results in enhanced natriuresis and osmotic diuresis, which lowers blood pressure: systolic by 1.0–2.6 mmHg and diastolic by 0.7–2.2 mmHg, without increasing heart rate. This reduction in blood pressure leads to a decrease in afterload, improvement in ejection fraction (EF), and ultimately better heart function [20]. The renal excretion of glucose due to enhanced glucosuria leads to the loss of this important energy substrate, without causing hypoglycemia. This contributes to weight reduction through increased ketogenesis and enhanced mobilization of fat stores in patients treated with SGLT2 inhibitors [37]. In a retrospective study involving 289 adult patients diagnosed with T2DM, who were newly treated with SGLT2i, either as monotherapy or in combination therapy, 45.6% experienced weight loss after initiating SGLT2i therapy [38]. Furthermore, it was noted that combining SGLT2 inhibitors with sulfonylurea derivatives, commonly used in diabetes therapy, was associated with an even greater degree of weight loss [39].

The use of SGLT2i also brings favorable changes in lipid profiles and uric acid metabolism. In patients treated with SGLT2 inhibitors, a reduction in serum triglyceride levels by approximately 1–9%, an increase in HDL cholesterol by 6–9%, and a decrease in uric acid levels by 0.3–0.9 mg/dL were observed, which may improve the overall health and survival of patients with T2DM [40].

The Future of Diabetic Kidney Disease Treatment

The future of diabetic kidney disease treatment using SGLT2 inhibitors appears promising, especially in the context of an increasing number of clinical trials and the development of new classes of drugs. In addition to SGLT2i, which have already demonstrated their effectiveness in slowing the progression of DKD, ongoing research is exploring other promising therapies, such as drugs targeting the glucose-fatty acid pathway and agents influencing inflammatory mechanisms. Potential therapeutic groups also include the development of activators of the NF-E2-related factor 2 (Nrf2) pathway and renin-angiotensin system (RAS) inhibitors, which may act synergistically with current therapies. As research progresses and a better understanding of the pathophysiology of DKD is gained, the introduction of new medications becomes feasible—therapies that not only slow disease progression but also improve patients' quality of life, offering a more individualized approach to treatment [41,42].

Conclusions

Sodium-glucose cotransporter 2 (SGLT2) inhibitors have proven to be an effective class of drugs that slow the progression of DKD and reduce the risk of renal and cardiovascular complications. By reducing glomerular hyperfiltration and alleviating renal inflammation, SGLT2i contribute to improved kidney function and a reduction in albuminuria, as confirmed by clinical studies. The future of DKD therapy appears promising with the development of new drug classes, such as Nrf2 activators and renin-angiotensin system (RAS) inhibitors, which are currently being investigated for their effectiveness in treating DKD. As research into the pathophysiology of DKD progresses, innovative therapeutic solutions are expected to emerge, which will be crucial in addressing the rising number of T2DM patients and the challenges faced by healthcare systems.

Disclosure

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Methodology: Michał Szczepański, Daniel Zapasek, Julia Słowik

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