

Sodium-Glucose Cotransporter 2 Inhibitors with Renoprotective Effects

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Keywords

Sodium-glucose cotransporter 2 inhibitors · Glycemic control · Diabetic nephropathy · Chronic kidney disease

Abstract

Background: Diabetes is the leading cause of end-stage renal disease (ESRD) and accounts for 40–50% of patients requiring renal replacement therapy. The main pathophysiology of diabetic nephropathy comprises glucose-dependent pathways, hemodynamic pathways, and genetic factors.

Summary: Glucose-dependent pathways, known as advanced glycation, polyols, and protein kinase C activation have been implicated in the pathogenesis of diabetic nephropathy. Current studies have indicated that intensified glycemic control retards the rate of development of albuminuria and impairs renal function in both patients with type 1 and 2 diabetes. However, therapeutic options have substantially increased over the last decade, but have not yet been translated to remarkably reduce the incidence of ESRD from diabetic nephropathy. Sodium-glucose cotransporter 2 (SGLT2) inhibitors are a novel class of glucose-lowering agents with potential renoprotective effects. **Key Message:** SGLT2 inhibitors represent a promising therapeutic approach to prevent and improve nephropathy among pa-

tients with type 2 diabetes. The current data strongly support that SGLT2 inhibitors have renoprotective properties not only by improving glycemic control but also through hemodynamic and nonhemodynamic renal effects. This review focuses on the latest published data dealing with hypoglycemic agents and SGLT2 inhibitors regarding the progression of kidney disease.

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Introduction

Typical diabetic nephropathy was first described as nodular glomerulosclerosis associated with proteinuria and hypertension by Kimmelstiel and Wilson. Diabetic nephropathy is the leading cause of end-stage renal disease (ESRD) in the world [1]. The prevalence of renal complications accounts for 30–50% of patients with type 1 and 2 diabetes. Nephropathy remains a major cause of morbidity and mortality for diabetic patients, mostly from cardiovascular complications [2]. Current treatments to prevent nephropathy and slow its progression, based on glycemic and hypertensive control with renin-angiotensin aldosterone system (RAAS) inhibition, are only partially effective, and a residual risk to develop

ESRD still remains. Thus, new therapeutic approaches including novel antiglycemic agents leading to additional risk reduction are needed.

Glucose-Dependent Pathways Leading to Nephropathy

The pathophysiology of diabetic nephropathy comprises glucose-dependent pathways, hemodynamic pathways, and various genetic factors that determine susceptibility and progression to ESRD [3, 4]. A major risk factor for the microvascular complications of diabetes is chronic high blood glucose levels. The facilitative glucose transporter GLUT1 mediates mesangial cell glucose flux, leading to the activation of signaling cascades, mesangial cell and matrix formation and an intrinsic pathway of proapoptotic signaling [5] favoring glomerulosclerosis [6]. Hyperglycemia-induced cell signaling, known as advanced glycation, polyols, and protein kinase C activation have been implicated in the pathogenesis and determine the progression of diabetic nephropathy. These pathways ultimately lead to increased renal albumin permeability and extracellular matrix accumulation, resulting in increasing proteinuria, glomerulosclerosis and ultimately renal fibrosis.

RAAS activation induces vasoconstriction and antinatriuresis, and promotes cell proliferation, apoptosis, and differentiation as main factors in developing kidney injury regarding type 2 diabetes [7]. Intrarenal RAAS activation by high glucose concentration leads to local angiotensin II overproduction in podocytes, mesangial cells and proximal tubular epithelial cells in type 2 diabetes producing inflammatory cytokines with progressive renal injury in the diabetic nephropathy [8, 9].

Chronic hyperglycemia inducing kidney injury occurs through the accumulation of advanced glycation end products (AGEs) in the kidney. The generation of AGEs in the kidney is linked to the development of diabetic nephropathy [10]. AGEs activate specific receptors, inducing cellular dysfunction and injury. An AGE-related functional defect in the permselective properties of the podocyte slit membrane may contribute to the development of albuminuria [11]. The activity of the enzyme, protein kinase C, has been reported to be increased in various diabetic tissues including the glomerulus. Finally, hyperglycemia-induced oxidative stress and inflammation are mediators of kidney injury in type 2 diabetes [12]. Restoration of the mitochondrial structure, function, and signaling may be novel ways to improve diabetic nephropathy and prevent the decline in organ function.

Genetic Factors

A family history of nephropathy and hypertension is associated with a higher incidence of diabetic nephropathy. Diabetic nephropathy is a classic complex trait, whose development in a given individual likely reflects contributions from multiple genes. Several studies have noted an association between susceptibility genes including angiotensin-converting enzyme, angiotensin II (Ang II) receptor, various aspects of glucose metabolism, lipid metabolism (apolipoprotein E gene polymorphism), extracellular matrix, and inflammatory cytokines with diabetic nephropathy based on the pathogenic role in the development of disease [13, 14]. Genome-wide linkage analysis has identified several novel risk loci including *SLC12A3* [15], *ELMO1* [16], and SAM and SH3 domain containing 1 (*SASH1*) gene [17]. Currently, researchers continue to seek replicable genetic polymorphisms that confer diabetic nephropathy risk.

Glycemic Control and Nephropathy

Blood glucose control reduces the risk of developing microvascular complications. It could partially reverse glomerular hyperfiltration and decrease the incidence of new-onset microalbuminuria in retrospective [18] and prospective studies of patients with diabetes [19]. The main studies in new-onset type 1 and 2 diabetic patients including the Diabetes Control and Complications Trial (DCCT) [20], the Kumamoto study [21], and UK Prospective Diabetes Study (UKPDS) [22] have also indicated that intensified glycemic control delays the onset and slows the progression of albuminuria and nephropathy. Recently, the Epidemiology of Diabetes Interventions and Complications (EDIC) study has reported that long-term intensive glucose control in type 1 diabetes for 12 years decreased the incidence of impaired glomerular filtration rate (GFR) by 50% compared with those treated with conventional therapy [23]. Similarly, the UKPDS study reported that long-term intensive glucose control in patients with type 2 diabetes for 10 years continued to provide risk reduction for myocardial infarction and death from any cause [24]. It indicated that early and long-term glycemic control significantly ameliorates all complications including diabetic nephropathy. Moreover, the diabetic renal pathology, especially nodular glomerulosclerosis lesions, can be reversed with long-term glycemic control following pancreas transplantation in patients with type 1 diabetes [25, 26].

Table 1. Hypoglycemic agents in diabetes patients with CKD

Class	Drugs	Glomerular filtration rate, mL/min/1.73 m ²				Disadvantages
		≥60	59–45	44–30	<30	
Biguanides	Metformin	++	++	+	–	Lactic acidosis Gastrointestinal side effects
Sulfonylureas	Glipizide	++	++	++	+	Hypoglycemia Weight gain
	Gliclazide	++	++	++	+	
	Glimepiride	++	+	+	–	
	Glyburide	++	–	–	–	
Meglitinides	Repaglinide	++	+	+	+	Hypoglycemia Weight gain
	Nateglinide	++	–	–	–	
Alpha-glucosidase inhibitors	Acarbose	++	++	–	–	Gastrointestinal side effects
Thiazolidinediones	Pioglitazone	++	++	++	++	Weight gain Fluid retention Bone fracture
Incretin mimetic	Exenatide	++	+	+	–	Gastrointestinal side effects Possible pancreatitis Possible medullary thyroid tumor
	Liraglutide	++	+	+	–	
	Albiglutide	++	+	+	–	
	Lixisenatide	++	+	+	–	
	Dulaglutide	++	+	+	–	
DPP-4 inhibitors	Sitagliptin	++	+	+	+	Heart failure hospitalization (saxagliptin, alogliptin)
	Vildagliptin	++	+	+	+	
	Saxagliptin	++	+	+	+	
	Alogliptin	++	+	+	+	
	Linagliptin	++	++	++	++	
SGLT2 inhibitors	Canagliflozin	++	++	–	–	Genital infections Polyuria Volume depletion Transient rising serum creatinine Diabetic ketoacidosis
	Empagliflozin	++	++	–	–	
	Dapagliflozin	++	–	–	–	

++, no dose adjustment; +, adjusted dose by 50%; –, avoid use.

Major studies of long duration of type 2 diabetes including ACCORD, ADVANCE, and the VADT found that targeting even lower hemoglobin A1C (HbA1C) goals (<6–6.5%) retarded the new onset of microalbuminuria, but failed to show cardiovascular disease risk reduction [27–29] and in the ACCORD trial, tight glycemic control was associated with a 22% increase in mortality from any cause [30]. A systematic review indicated that intensive glucose control reduced the risk for albumin-

uria, but evidence is lacking that intensive glycemic control reduces the risk for ESRD [31].

The Kidney Disease Outcomes Quality Initiative (KDOQI) updated 2012 guidelines recommended lowering HbA1C to below or around 7% for diabetes and chronic kidney disease (CKD) patients [32], and that this be implemented soon after the diagnosis of diabetes. Lowering HbA1C in these patients is associated with long-term reduction in macrovascular disease. However, these

recommendations are not strongly evidence based, because limited studies addressed the benefits and risks of intensive glycemic control in advanced stages of kidney disease [33, 34]. Less stringent HbA1C goals (such as <8%) are preferred among patients with a history of severe hypoglycemia, limited life expectancy, high comorbid conditions, longstanding diabetes, and advanced vascular complications, including advanced diabetic nephropathy. Glucose-lowering treatment and medications are based on the comfort of the patient and physician and must be individualized among patients with diabetic nephropathy. Patients with CKD are at increased risk of hypoglycemia due to decreased insulin clearance and hypoglycemic medications used to treat diabetes as well as reduce renal gluconeogenesis from CKD. Impaired renal function is associated with a prolonged insulin half-life and a decrease in insulin requirements and many hypoglycemic agents. The common hypoglycemic agents are excreted by the kidney, requiring dosage adjustment in CKD (Table 1).

Therapeutic options have increased substantially over the last decade, but the role of intensified glycemic control in patients with persistent microalbuminuria or overt nephropathy remains controversial. In addition, intensified glycemic control has not yet been translated into a remarkable reduction in the incidence of ESRD from diabetic nephropathy. Innovative strategies for glycemic control are needed to prevent renal complications. Promising clinical data suggest that sodium-glucose cotransporter 2 (SGLT2) inhibitors and glucagon-like-1 peptide agonists attenuate nephropathy independent of their glucose-lowering effects.

SGLT2 Inhibitors

The glucose filtered by the kidney is reabsorbed at a rate of approximately 180 g/day by the proximal tubules through SGLTs. The major glucose reabsorption is primarily handled by SGLT2 (up to 97%), and SGLT2-specific inhibitors reducing the maximum renal glucose-reabsorptive capacity and threshold used to treat patients with type 2 diabetes block approximately 50% of the total glucose reabsorption [35]. A maladaptive mechanism contributing to hyperglycemia in type 2 diabetes comprises an increased expression and activity of SGLT2 for glucose reabsorption [36, 37].

SGLT2 inhibitors are a newly developed class of oral antidiabetic agents with a unique mechanism of action that is indicated only for the treatment in patients with

type 2 diabetes. SGLT2 inhibitors improve glucose control by preventing reabsorption of glucose and increasing urinary glucose excretion. The mechanism of action of SGLT2 inhibitors also offers further glucose control by allowing increased insulin sensitivity and uptake of glucose in the muscle cells, decreased gluconeogenesis, and improved first-phase insulin release from the beta cells. These agents are efficacious as monotherapy and add-on therapy for patients with type 2 diabetes uncontrolled on metformin, sulfonylureas, pioglitazone, insulin, and other antihyperglycemic combinations.

Clinical studies with SGLT2 inhibitors have shown reduced HbA1C levels (0.7–0.9%) without stimulating insulin secretion, and therefore without increasing the risk of hypoglycemia [38, 39]. Several studies indicated that SGLT2 inhibitors are used particularly in place of an insulin-providing agent or lower insulin dose requirement. The efficacy of SGLT2 inhibitors depends on the GFR and on plasma glucose levels. Among patients with eGFR <60 mL/min/1.73 m² taking dapagliflozin, and patients with eGFR <45 mL/min/1.73 m² taking empagliflozin and canagliflozin, glycemic control was not improved compared with placebo [40–42]. In type 2 diabetes, these agents provide modest weight loss of up to 5 kg through urine glucose loss and systolic blood pressure reduction of up to 5 mm Hg, presumably through natriuretic effects. The SGLT2 inhibitor has been associated with a 10–15% reduction in plasma uric acid levels as a result of increased glycosuria, leading to the secretion of uric acid in exchange for glucose reabsorption through the GLUT9 transporter [39, 43], and serum uric acid-lowering effect of SGLT2 inhibition might improve endothelial dysfunction, hypertension, and microvascular injury in diabetes [44, 45].

SGLT2 Inhibitors and Nephropathy

SGLT2 inhibitors were effective in lowering albuminuria in patients with type 2 diabetes and hypertension using RAAS inhibition after adjusting for changes in HbA1C, blood pressure, body weight, and estimated GFR [46]. Overall, several clinical studies showed a significant reduction in albuminuria and a slow decline in GFR after SGLT2 inhibition initiation, and this lasted up to 2 years [46–48]. SGLT2 inhibition may lead to reduced long-term renal outcomes. A recent EMPA-REG OUTCOME study with a median follow-up of 3.1 years showed that in patients with high cardiovascular risk the SGLT2 inhibitor empagliflozin lowered the composite outcome of

Table 2. Potential mechanisms of renoprotection by SGLT2 inhibitors

Direct effects	Indirect effects
Renal hemodynamic effects	Lower plasma glucose and HA1C
Reduced intraglomerular pressure by restoring tubuloglomerular feedback	Lower serum uric acid
Reduced albuminuria	Lower blood pressure
Reduced tubular Na ⁺ reabsorption	Lower insulin level
Reduced ANP levels	Lower body weight
Renal nonhemodynamic effects	
Reduced tubular glucotoxicity	
Reduced AGE-mediated renal inflammation	
Reduced tubular apoptosis	
Reduced tubular excessive energy demands	
Reduced inflammatory mediators, and oxidative stress (MCP-1, ICAH-1, osteopontin, and TGF-beta)	

AGE, advanced glycation end product; ANP, atrial natriuretic peptides; ICAH-1, intracellular adhesion molecule-1; MCP-1, monocyte chemoattractant protein-1; RAAS, renin angiotensin aldosterone system; TGF-beta, transforming growth factor-beta.

myocardial infarction, stroke, and cardiovascular mortality by 14% (absolute rate 10.5 vs. 12.1% in the placebo group) and cardiovascular death by 38% (absolute rate 3.7 vs. 5.9%) [49]. Additional outcomes were reported from recent meta-analyses that included 57 published trials; SGLT2 inhibitors protected against the risk of major adverse cardiovascular events (relative risk 0.84 [95% CI 0.75–0.95]) and death from any cause (0.71 [0.61–0.83]) [50]. For renal outcomes, patients receiving empagliflozin showed a 39% reduction in the risk of new or worsening nephropathy including macroalbuminuria, doubling of serum creatinine with GFR <45 mL/min/1.73 m², and initiation of renal replacement therapy [51]. These data strongly support that SGLT2 inhibitors have renoprotective properties not only by improving glycemic control but also through some direct renal effects as described below (Table 2).

Renal Hemodynamic Effects

SGLT2 inhibitors have the potential to exert renoprotection through hemodynamic effects. Accumulating evidence supports that increased single-nephron hyperfiltration is the major factor for kidney disease progression. Glomerular hyperfiltration in diabetic rats was associated with a reduction in distal sodium delivery flow by increased proximal tubular sodium-glucose reabsorption [52]. The limited sodium delivery flow and transport in-

to the macula densa cells reduced ATP breakdown and adenosine generation in the juxtaglomerular apparatus. Decreased adenosine activation related to the lack tubuloglomerular feedback response causes vasodilation of the afferent arteriole and produces diabetic hyperfiltration and nephropathy [53]. Gene knockout of SGLT2 modestly lowered blood glucose in animal models of diabetes and prevented glomerular hyperfiltration [54]. SGLT2 inhibition treatment improves glomerular hyperfiltration with a reduction in GFR from 172 ± 23 to 139 ± 25 mL/min/1.73 m² in type 1 diabetes [55]. Such a natriuretic effect increases sodium delivery to the distal tubule, thereby stimulating tubuloglomerular feedback, ultimately causing increased afferent renal arteriolar tone, attenuating glomerular pressure and reducing albuminuria.

Treatment with SGLT2 inhibitors resulted in an initial decrease in estimated GFR during the first 4 weeks with a progressive recovery of GFR during the following weeks, consistent with the mechanism of action involving decreased intraglomerular pressure [46–48]. These renal hemodynamic effects are similar to the effect of RAAS blockers for slow renal progression. RAAS inhibitors reduce intraglomerular pressure through efferent arteriolar vasodilatation, leading to reduced renal hyperfiltration. However, reduced glomerular pressure observed with SGLT2 inhibitors is mediated by blood pressure-independent pathways using afferent arteriolar vasoconstriction.

Indeed, in a recent experimental study, the combination of SGLT2 and RAAS inhibition showed more benefits in protecting kidney injury from glomerular hyperfiltration and proteinuria in animal models of advanced diabetic nephropathy [56]. Moreover, most patients with type 2 diabetes in the EMPA-REG OUTCOMES study were using a RAAS inhibitor at baseline, and the renal beneficial effects of treatment were confirmed in the subgroup of patients using an RAAS inhibitor [51]. The combination of RAAS and SGLT2 inhibition was associated with additive renoprotective effects in diabetic nephropathy compared with either drug alone.

Finally, intrarenal actions of atrial natriuretic peptides (ANP) contribute significantly to glomerular hyperfiltration in animal models of diabetes [57]. A modest reduction in effective circulating fluid volume with SGLT2 inhibitors decreases blood pressure and suppresses plasma ANP level in newly diagnosed type 2 diabetes [58]. These findings support the ability of SGLT2 inhibitors to lower ANP levels and improve glycemic control, which may benefit intraglomerular pressure and albuminuria.

Renal Nonhemodynamic Effects

All the renal cellular elements including the glomerular endothelium, mesangial cells, podocytes, and tubular epithelium are affected in the setting of chronic hyperglycemia. Furthermore, renal tubular compartments have been increasingly reported to play an integral role in the pathogenesis of diabetic nephropathy, and they correlate well with progressive renal function decline and represent a final common pathway of CKD [59]. Type 2 diabetes patients with high levels of urinary tubular biomarkers presented a more rapid decline in renal function. High levels of urinary tubular biomarkers were independent predictors of rapid renal progression among these patients [60]. Interestingly, SGLT2 inhibitors also have inhibitory effects on the inflammatory and fibrotic responses of proximal tubular cells to hyperglycemia. An *in vitro* study using human proximal tubular cells indicated that SGLT2 inhibitors augmented AGE-induced apoptotic cell death of tubular cells through RAGE induction [61] and decreased the high glucose-induced inflammatory and fibrotic markers by reducing glucose transport to the proximal tubule cells [62]. In animal models of type 2 diabetes, SGLT2 inhibitors decreased renal hypertrophy, renal inflammation, inflammatory mediators, and oxidative stress including monocyte chemoattractant protein-1, intracellular adhesion molecule-1, osteopontin,

and transforming growth factor-beta, which are the main causes of diabetic nephropathy progression [63–65]. The benefits of SGLT2 inhibitors include attenuating renal glucose reabsorption in renal tubules and reducing proximal tubular glucotoxicity and glucose- and/or AGE-mediated renal inflammation.

High glucose and sodium reabsorption in the diabetic proximal tubules can increase oxygen consumption and glomerular hyperperfusion [66]. Recent evidence confirmed that chronic renal hypoxia initiated and promoted the microvascular injury and interstitial fibrosis that constituted the final common pathway to ESRD [67]. Thus, SGLT2 inhibitors reducing the excessive energy demands in the renal tubules might be a protective effect in diabetic nephropathy. In summary, in addition to glucose-lowering effects, SGLT2 inhibitors might be a promising therapeutic approach to prevent diabetic nephropathy by renal hemodynamic and nonhemodynamic effects.

The American Diabetes Association (ADA) indicated that metformin is recommended as the standard first-line treatment for type 2 diabetes. When second hypoglycemic agents are required to achieve HA1C targets, the benefits and risks of adding sulfonylurea, thiazolidinedione, dipeptidyl peptidase 4 inhibitor, glucagon-like-1 peptide receptor agonist, SGLT2 inhibitor, or basal insulin are weighed in the context of an individual patient's preferences, as well as various patient, disease, and drug characteristics, with the goal of reducing blood glucose levels while minimizing side effects, especially hypoglycemia. The ADA recently added a new indication for empagliflozin, to reduce the risk of cardiovascular death among patients with longstanding suboptimally controlled type 2 diabetes and established atherosclerotic cardiovascular disease [68].

Adverse Effects of SGLT2 Inhibitors

SGLT2 inhibitors are associated with a low risk of hypoglycemia, but they may lead to adverse effects like genital fungal and urinary tract infections. A recent meta-analysis of clinical reports showed consistent increased risks of genital infections by approximately 3.0- to 5.0-fold [50, 69]. Another adverse event related to SGLT2 inhibitors involves intravascular volume depletion arising from the osmotic diuresis of glucose, and from natriuresis, and although infrequent, is more common among older adults and is related to the use of loop diuretics and tubular dysfunction [70]. After surveillance in the US, a warning was released by the Food and Drug Administra-

tion stating that several patients on SGLT2 inhibitors developed diabetic ketoacidosis. These adverse events occurred in patients with type 1 diabetes receiving off-label therapy against indication and type 2 diabetes with decreased insulin treatment because of concomitant SGLT2 inhibition.

In conclusion, glycemic control is essential to delay the onset of vascular complications from diabetes. Even the most experienced physician would find it challenging, but diabetic nephropathy remains the main cause of ESRD. Thus, new therapeutic strategies are needed to reduce this burden. SGLT2 inhibitors are a novel class of glucose-lowering agents with potential cardio- and renoprotective effects. SGLT2 inhibitors reduce blood pressure, body weight, intraglomerular pressure, albuminuria, and renal inflammatory, oxidative and fibrotic markers through mechanisms that appear independent

of glycemia. According to an initial clinical study, this class of medications reduces renal events and dialysis in type 2 diabetes. Large long-term clinical trials are still needed to confirm the major renal benefits of SGLT2 inhibitors concerning the development and progression of diabetic nephropathy.

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Conflict of Interest Statement

The authors declare no conflicts of interest.

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