Improving Outcomes In

DIABETIC KIDNEY DISEASE

A Clinical Update

Topics

- Adverse Outcomes Associated with DKD
- Management of DKD Overview
- SGLT2 Activity as a Therapeutic Target for DKD
- SGLT2 Inhibitors and Renal Outcomes in DKD

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Adverse Outcomes Associated with DKD

Diabetes is a common and complex disorder associated with multiple comorbid conditions and higher risk for mortality. The 2015 overall underlying-cause mortality rate attributable to diabetes was 24.7 per 100,000.[1] A collaborative meta-analysis suggested that a 50-year-old with diabetes died on average approximately 6 years earlier than an individual without diabetes.[2]

Multiple complications are associated with diabetes, including retinopathy and neuropathy. Diabetes is a major risk factor for cardiovascular disease (CVD) and diabetic kidney disease (DKD) or diabetic nephropathy.[3, 4, 5, 6] Diabetes is the leading cause of chronic kidney disease (CKD) and accounts for 44% of new cases of end stage kidney disease (ESKD).[1] All-cause mortality in patients with DKD is reportedly higher than in diabetes patients without kidney disease.[7,8]

Management of DKD Overview

Type 2 diabetes treatment generally involves multiple interventional strategies, including glycemic control and management of other CVD-related risk factors, many of which are also risk factors for CKD. Additional measures to help preserve kidney function can also include avoidance of nonsteroidal anti-inflammatory drugs (NSAIDs) and caution with the use of certain contrast dyes with imaging tests.

Drugs that interact with the renin–angiotensin–aldosterone system (RAAS), such as angiotensin-converting-enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs), can be applied to both blood pressure management and slowing kidney disease progression.[5,6,8] RAAS blockade agents have been shown to reduce blood pressure, decrease albuminuria, and help slow the progression of kidney disease in patients with DKD.[9, 10, 11, 12, 13, 14]

SGLT2 Activity as a Therapeutic Target for DKD

Research on various aspects of diabetes pathophysiology has led to new insights of the disease process, including the role of the kidney in glucose homeostasis and the discovery of additional therapeutic targets.[15, 16] One such example is sodium glucose co-transporter-2 (SGLT2), which is part of a class of membrane-bound proteins that reabsorb glucose back into the body from urine.[17, 18] Around 90% of glucose filtered form the kidneys is reabsorbed in the brush-border of cells in the proximal convoluted tubule by SGLT2 (Figure 1).[17, 18, 19]

With development of diabetes, there is an upregulation of SGLT2 transporters.[20] This activity leads to increased glucose reabsorption. Additional sodium and chloride are also reabsorbed; thus less sodium and chloride in the tubules is presented to the microcirculation regulator (macula densa) of the glomerulus (filtering device of the kidney). Decreased sodium presented to the macula densa results in a dilation of the incoming arterioles to the glomerulus and constriction of the outgoing arterioles of the glomerulus, which turn leads to increased pressure within the glomerulus and a condition called "hyperfiltration," causing further damage.[18,19,21,22,23]

Inhibition of the SGLT2 transporters is believed to reverse this process, resulting in less reabsorption of sodium and chloride. This activity leads to more sodium and chloride within the tubules, and in turn the macula densa. This action results in a reduction of blood flow into the glomerulus and a decrease in pressure within the glomerulus. This activity is considered one of the underlying benefits of SGLT2 inhibition.[7,19,24,25,26]

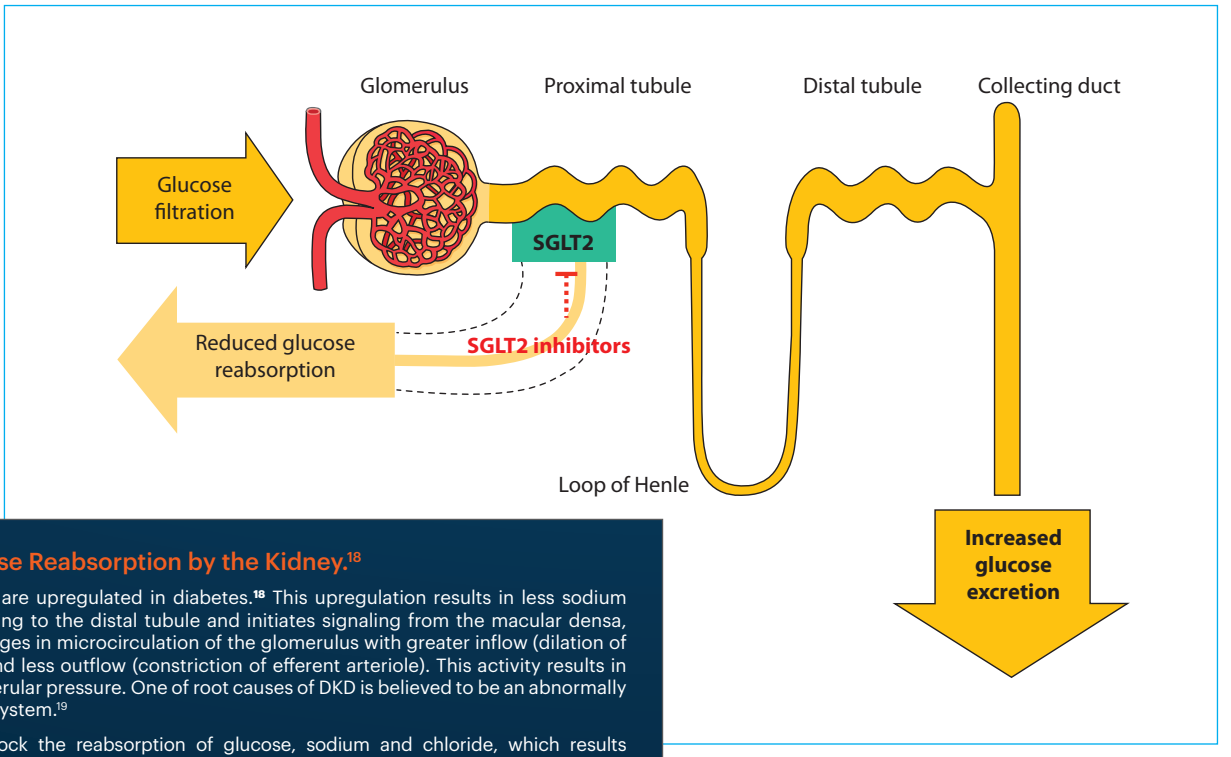

Figure 1: Glucose Reabsorption by the Kidney.[18]

SGLT2 transporters are upregulated in diabetes.[18] This upregulation results in less sodium and chloride travelling to the distal tubule and initiates signaling from the macular densa, which leads to changes in microcirculation of the glomerulus with greater inflow (dilation of afferent arteriole) and less outflow (constriction of efferent arteriole). This activity results in an increase in glomerular pressure. One of root causes of DKD is believed to be an abnormally functioning SGLT2 system.[19]

SGLT2 inhibitors block the reabsorption of glucose, sodium and chloride, which results in more sodium and chloride being presented to the macular densa. This activity results in microvascular changes including a constriction of the afferent arteriole and leads to a decrease in glomerular pressure. Glucose is then excreted into the urine. A decrease in glomerular pressure by changing microcirculation (afferent constriction or efferent dilation) may lead to a small decrease in eGFR, however the chronic effect may help preserve kidney function.[19]

Table 1:

Proposed Renal Effects of SGLT2 Inhibition[7,19,26]

- Tubuloglomerular feedback
- Oxidative stress ↓
- Tubular fibrosis ↓
- ↓ Intrarenal angiotensin

SGLT2 Inhibitors and Renal Outcomes in DKD

Current SGLT2 inhibitors approved by the U.S. Food and Drug Administration (FDA) for lowering blood glucose levels in patients with type 2 diabetes include canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin. They are available as single-ingredient products and in combination with other diabetes medicines such as metformin. Studies have also shown possible benefits in addition to glucose lowering. Reductions in CV events with the use of SGLT2 inhibitors have been shown in the trials EMPA-REG OUTCOME (Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients) and CANVAS (Canagliflozin Cardiovascular Assessment Study).[27, 28] All drugs in the SGLT2 inhibitor class have been shown to reduce of hospitalization for heart failure, and canagliflozin and dapagliflozin have indications.[29,30,31,32] Overall, these studies have supported the use of SGLT2 inhibitors in patients with type 2 diabetes to improve glycemic levels and reduce CV risk.

SGLT2 inhibitor cardiovascular outcome trials (CVOTs) have shown a secondary, exploratory or ad hoc analysis reduction in renal composites (EMPA-REG OUTCOME, CANVAS Program, DECLARE TIMI 58) in patients with mild renal impairment (mean eGFR ~80 mL/min/1.73 m^2 and median UACR of <30 mg/g).[7, 33, 34, 35, 36, 37, 38, 39] Some uncertainty in the long-term, glucose-independent effect of SGLT2 inhibition on kidney disease progression in DKD has persisted, since in many cases relatively few patients reached ESKD and trial patients were at lower risk for ESKD.[40]

The first completed, dedicated renal outcomes clinical trial, CREDENCE (Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation), represents a significant development in role of SGLT2 inhibitors for patients with type 2 diabetes and established DKD.

Researchers randomized 4,401 patients with type 2 diabetes and CKD to either placebo or 100 mg of canagliflozin.[40] All the patients had an estimated glomerular filtration rate (eGFR) of 30 to <90 mL/min/1.73 m^2 and albuminuria (urinary albumin-to-creatinine ratio (UACR) >300 to 5000 mg/g) and were treated with a maximally tolerated RAAS blockade agent. Participants entering the trial had a mean eGFR of 56 mL/min/1.73m^2 and the median UACR was 927 mg/g. The primary outcome of the study was a composite endpoint of ESKD, doubling of serum creatinine, CV death or renal death. The trial was stopped nearly two years early by the independent committee due to efficacy and safety.

Primary composite outcomes are shown in Figure 2. Highlights of the trial include the following:[40]

- Canagliflozin reduced the risk of the primary outcome of ESKD, doubling of serum creatinine, or renal or CV mortality by 30% (HR 0.70, CI 95%, 0.59-0.82, P<0.00001).
- The relative risk of ESKD was lower by 32% (HR 0.68, CI 95%, 0.54-0.86 P=0.002).
- Canagliflozin also attenuated the slope of chronic eGFR decline by 2.7 mL/min/1.73 m^2 per year compared to the control group.

The CREDENCE trial showed that canagliflozin safely reduced the risk of ESKD and prevented CV events in patients with type 2 diabetes and CKD at a median follow-up of 2.62 years.

Relative decreases in RRT (renal replacement therapy; dialysis and transplant) were also observed. Patients randomized to canagliflozin also showed a lower risk of several secondary outcomes, including CV mortality, myocardial infarction, or stroke and hospitalization for heart failure. All cause hospitalization, adverse events and serious adverse events were also lower. No significant difference was observed in the risk of lower-limb amputation or fractures in the CREDENCE trial. An increased risk of lower limb amputation was observed in another trial of canagliflozin (CANVAS).[28,36] Whether the increased risk of lower limb amputation in the CANVAS program was due to differing trial populations or protocols, or to chance remains unclear.[40]

Definitive clinical trials (DAPA-CKD and EMPA-KIDNEY) are underway to study the use of SGLT2 inhibitors in CKD patients with or without type 2 diabetes.[25, 41, 42] In summary, SGLT2 inhibitors represent a novel class of antidiabetic agents with several possible mechanisms of action independent of glucose lowering, which may offer potential renal- and cardio- applications beyond glycemic control in type 2 diabetes and DKD.

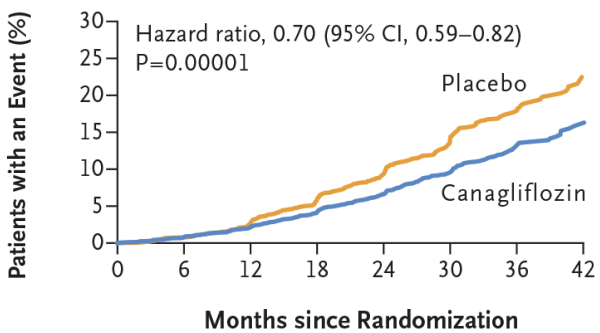

Figure 2:

CREDENCE Trial: Primary Composite Outcome.[40]

The primary composite outcome of end-stage kidney disease, doubling of serum creatinine level, or renal or CV death is shown.

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