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Commentary

Therapeutic Strategies for Diabetic Kidney Disease

Keiichiro Matoba

Division of Diabetes, Metabolism and Endocrinology, Department of Internal Medicine, The Jikei University School of Medicine, Tokyo 105-8461, Japan; matoba@jikei.ac.jp

Abstract: Diabetic kidney disease (DKD) is a global epidemic leading to end-stage renal disease (ESRD) and susceptibility to cardiovascular disease, with few therapeutic interventions. A hallmark of DKD is the activation of the renin-angiotensin-aldosterone system and hemodynamic changes in glomerulus. Although intensive therapy with agents that targets those abnormalities lowers the risk of DKD progression, it does not completely abolish the risk of ESRD and cardiovascular events. Recent studies have illustrated the importance of renal inflammation, oxidative stress, and activated Rho-associated protein kinase (ROCK) signaling as essential pathogenesis for the development of DKD. In this commentary, these topics will be discussed.

Keywords: diabetes; diabetic kidney disease; mineralocorticoid receptor; inflammation; sodium–glucose cotransporter 2 (sglt2) inhibitors; chronic kidney disease

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Diabetes confers an increased risk of renal events. Despite the introduction of various approaches for the treatment of diabetes, diabetic kidney disease (DKD) is still a worldwide public health concern. In modern societies, DKD is the leading cause of end-stage renal disease (ESRD) and is strongly associated with a high cardiovascular death rate. Evidence is mounting to support that the presence of albuminuria increases the risk of coronary disease in patients with diabetes. The UK Prospective Diabetes Study (UKPDS) clearly demonstrated that the annual cardiovascular mortality rates increased to 3%, 4.6%, and 19.2% with progression to microalbuminuria, macroalbuminuria, and renal failure, respectively [1]. The detrimental interaction between DKD and cardiovascular disease (i.e., cardiovascular death, myocardial infarction, heart failure) is termed "cardio-renal syndrome". The mechanisms responsible for the link between the kidneys and heart involve metabolic imbalances, hemodynamic changes, signaling abnormalities, inflammation, and oxidative stress [2]. It would be of considerable interest to establish a novel therapeutic strategy for the treatment of DKD, as it would improve the prognosis of patients with diabetes and reduce the socioeconomic burden associated with the disease. Toward this end, a detailed understanding of the molecular basis is required.

The pathological significance of activation of the renin-angiotensin-aldosterone system (RAAS) and hemodynamic changes is becoming increasingly evident, and a large number of patients with diabetes are treated with RAAS inhibitors and/or sodium–glucose cotransporter 2 (SGLT2) inhibitors. SGLT2 inhibitors have emerged as a promising agent for the management of DKD following RAAS inhibitor treatment. The first encouraging demonstration came from the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME) trial [3]. In the trial, patients who received empagliflozin in addition to standard care had a significantly lower risk of renal events in comparison to those receiving a placebo. Empagliflozin attenuated the progression to macroalbuminuria, the doubling of the serum creatinine level, initiation of renal-replacement therapy, and death from renal disease, with a significant relative risk reduction of 38%, 44%, and 55%, respectively. Furthermore, in the primary outcome of the Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trial, the rate of renal events such as dialysis, transplantation or a sustained estimated glomerular filtration rate (eGFR) of <15 mL/min/1.73 m^2, the doubling

of the serum creatinine level, or death from renal or cardiovascular causes was 30% lower in the canagliflozin group than in the placebo group [4]. After a median follow-up period of 2.62 years, this trial was stopped early as canagliflozin significantly lowered risks for major cardiovascular events, including death. These observations are particularly intriguing because the cardiorenal protective effects of SGLT2 inhibitors are a class effect rather than the effect of a particular agent, and suggest that SGLT2 inhibitors have the potential to facilitate the management of DKD, providing clinical benefits and reducing the number of patients with cardiovascular disease. More recently, a Study to Evaluate the Effect of Dapagliflozin on Renal Outcomes and Cardiovascular Mortality in Patients With Chronic Kidney Disease (Dapa-CKD) trial demonstrated that kidney and cardiovascular risk was significantly lower in patients with chronic kidney disease treated with dapagliflozin, regardless of presence or absence of diabetes. The clinical impact of these trials led to a huge interest in the study of SGLT2 inhibitors. The mechanisms underlying the renal protection provided by SGLT2 inhibitors include increased natriuresis and a reduction of the single-nephron GFR by means of tubuloglomerular feedback [5,6]. Other effects, including modulation of the neurohormonal system, uric acid metabolism, and the inhibition of mechanistic target of rapamycin complex 1 are also reported [7].

While currently approved agents can retard the deterioration of the renal function, they cannot completely prevent progression to ESRD. There is a distinct possibility that combined nephroprotection can be achieved by novel drugs, and that this will further reduce the residual risk of GFR decline. Recently, mineralocorticoid receptor (MR) blockade has been demonstrated to reduce the urinary albumin-to-creatinine ratio (ACR) in patients with diabetes, and it has been suggested that these actions may translate into improved renal outcomes. Finerenone is a novel nonsteroidal MR antagonist with higher selectivity towards the MR than spironolactone, and a stronger MR binding affinity in comparison to eplerenone. The addition of finerenone to RAAS inhibitors resulted in a reduction in the ACR in patients with DKD. The Efficacy and Safety of Finerenone in Subjects with Type 2 Diabetes Mellitus and Diabetic Kidney Disease (FIDELIO-DKD) trial demonstrated the long-term effects of finerenone on kidney and cardiovascular outcomes in patients with diabetes [8]. During a median follow-up period of 2.6 years, patients treated with finerenone were at lower risk of DKD progression and cardiovascular disease than those treated with a placebo. While this finding supports the potential use of MR antagonists in combination with standard care in patients with DKD, the risk of hyperkalemia after an MR blockade could limit the clinical use of this class of drug.

Given the importance of the residual risk in patients treated with these agents, it is important to understand how renal and cardiovascular disease is involved. Recent advances in experimental studies have demonstrated the significant impact of inflammatory reactions, redox imbalances, and Rho-associated protein kinase (ROCK) signaling abnormalities on the progression of DKD [9].

1. Targeting Low-Grade Inflammation

Low-grade inflammation is clinically defined as an increase in circulating levels of pro-inflammatory mediators that induce immune system activation. Chronic low-grade inflammation is implicated in the pathogenesis of atherogenic changes and microvascular complications including DKD. As with diabetic retinopathy and neuropathy, immune cells infiltration is observed in the renal tissue of DKD, and this is closely correlated with the decline in the renal function, histological abnormalities, and a poor outcome in the context of diabetes [10]. Macrophage-derived products (e.g., reactive oxygen species, metalloproteinases) can damage renal tissue. Consistently, macrophage-depletion studies in rodent models, such as a macrophage scavenger receptor deletion model, have shown a causal role for macrophages in DKD [11]. The gene expression levels of pro-inflammatory factors were strongly suppressed in this diabetic mouse model.

Macrophages are classified into M1 and M2. Of note, macrophages in streptozotocin-induced DKD are predominantly of the M1 phenotype, which promotes inflammatory

reactions. Cell-based studies showed that macrophages switch to the M1 phenotype when cultured under high-glucose conditions. On the other hand, the deficiency of the toll-like receptor-2 induces a macrophage M1 to M2 polarization shift in DKD, which ultimately attenuates albuminuria, and protects podocytes from cell death [12]. The mechanisms by which M2 macrophages promote kidney repair and attenuate DKD progression are still under debate and merit further investigation. In the currently available anti-diabetic agents, SGLT2 inhibition by empagliflozin has been demonstrated to induce M2 macrophage polarization in diet-induced obese mice [13].

A variety of pathways orchestrate inflammatory transcriptional programs that affect the balance of inflammatory cytokines and adhesion molecules. Among these, nuclear factor κB (NF-κB) is a central factor in regulating inflammatory signals. NF-κB is activated by glucose-induced oxidative stress and advanced glycation end-products (AGEs). In addition, activating protein 1 (AP1) transcriptional factor is activated under high glucose conditions to mediate the expression of transforming growth factor β (TGF-β) in glomerulus [14]. Notably, ligands of peroxisome proliferator-activated receptor γ (PPARγ) are demonstrated to attenuate the induction of inflammatory mediators through the regulation of AP1, indicating a potential anti-inflammatory effect of thiazolidines.

2. Modulation of Cellular Redox Imbalances

Oxidative stress reflects an imbalance between the production of highly reactive molecules and antioxidative reactions. Reactive oxygen species, including superoxide anion (O_2^-), hydroxyl radical (OH), and hydrogen peroxide (H_2O_2), are produced in cells. In diabetic kidneys, nicotinamide adenine dinucleotide phosphate (NADPH) oxidase works as the most essential source of superoxide anion. Consequently, oxidative stress is induced in the kidney of diabetic animals and in glucose-stimulated renal cells. Excess free fatty acids, mainly derived from the obese state, are inducers of superoxide production in the setting of diabetes, which ultimately damage DNA, protein, and lipids, making them nonfunctional.

Antioxidants, such as superoxide dismutase, glutathione reductase, glutathione peroxidase, are important for maintaining redox balance. However, this protective system is impaired in the context of diabetes. It has been demonstrated that cAMP and protein kinase A (PKA) signaling play essential roles in the antioxidative system. Glucagon-like peptide 1 (GLP-1), a gut hormone secreted from intestinal L-cells after meal, induces elevation of cAMP and inhibits oxidative stress by attenuating AGE-receptor for AGE (RAGE) signaling [15]. Hence, GLP-1 receptor agonists are suggested to be protective against oxidative stress in DKD. Consistent with this data, the inhibition of the GLP-1 receptor in mice reads to the progression of DKD via the upregulation of NADPH and superoxide in the kidney. On the other hand, the GLP-1 receptor agonist attenuates these oxidative reactions through the actions on cAMP and PKA activity. These beneficial actions are observed without affecting blood glucose levels, further supporting the hypothesis of the direct renal effects of GLP-1 receptor agonists. Clinical trials demonstrated beneficial effects of GLP-1 receptor agonists on cardiovascular mortality and kidney outcomes in patients with diabetes. A research Study to See How Semaglutide Works Compared to Placebo in People with Type 2 Diabetes and Chronic Kidney Disease (FLOW) is ongoing to investigate if once weekly injection of semaglutide, a GLP-1 receptor agonist, delays progression of DKD and lowers the risk of death from kidney disease or cardiovascular disease in patients with diabetes.

The defense reaction is governed by nuclear factor erythroid 2-related factor 2 (Nrf2), which regulates the induction of antioxidants and detoxification enzymes. The cytosolic inhibitor Kelch-like ECH-associated protein 1 (Keap1) works as a "sensor" for cellular stress. Keap1 mediates the activity of Nrf2 by controlling its capacity to block Nrf2 nuclear translocation. The activation of Nrf2 has been demonstrated to improve glomerular damage of streptozotocin-induced diabetic animals via attenuation of oxidative stress [16].

3. Inhibition of ROCK Signaling

ROCK is a family of serine/threonine kinases that is involved in the regulation of various essential cellular functions. Glucose, angiotensin II, and inflammatory cytokines are known as ROCK activators. The elevation of ROCK signaling activity is described regardless of the diabetes type, which consequently induces glomerular fibrosis and podocyte loss. ROCK has also been demonstrated to increase oxidative stress, inflammatory reactions, and vascular spasm. The beneficial actions of ROCK inhibition have been reported in experimental models of DKD [17].

ROCK has two isoforms: ROCK1 (also referred to as Rho-kinase β/ROKβ) and ROCK2 (also known as Rho-kinase α/ROKα). These isoforms share 65% overall identity in amino acid sequence; however, ROCK1 and ROCK2 are activated by different mechanisms. ROCK1 functions after the caspase-3 cleavage, whereas ROCK2 can be activated by granzyme B or caspase-2. When considered alongside the fact that systemic knockout animals of ROCK1 and ROCK2 show distinct phenotypes, these isoforms seem to have divergent functions. While both isoforms are expressed in glomeruli and tubulointerstitium, the pathogenic roles of the ROCK isoforms are only beginning to be understood. Studies have elucidated the involvement of renal ROCK1 in mitochondrial morphology and endothelial-to-mesenchymal transition in glomeruli [18]. Meanwhile, ROCK2 activation results in mesangial inflammation, fibrosis, and cell death in podocytes. A loss-of-function analysis revealed that ROCK2, but not ROCK1, is responsible for the fibrogenic response in the diabetic kidney, concomitant with the regulation of mitogen-activated protein kinases, which in turn mediates the nuclear translocation of NF-κB [19]. In podocytes, ROCK2 deletion is protective against TGF-β-induced Notch activation. However, the activation of Notch signaling was not inhibited by ROCK1 deficiency. These findings highlight the importance of the isoform-specific role of ROCK in the mechanisms that facilitate DKD progression.

The ROCK activity can be ameliorated by Y27632 and fasudil; both of these agents inhibit ROCK1 and ROCK2 with equal potency. These chemicals greatly expanded the ROCK research field. Fasudil is already clinically approved in several countries for the treatment of vascular spasm after subarachnoid hemorrhage. Belumosudil (also known as KD-025 and SLx-2119) is recently developed as an orally available inhibitor of ROCK2. Belumosudil is used in clinical trials for patients with psoriasis, graft versus host disease, and systemic sclerosis. Since ROCK2 is a regulator of immunity, inflammation, and fibrosis, ROCK2 inhibition could potentially prevent the progression of renal dysfunction among patients with diabetes, thereby potentially improving their prognosis. The current momentum in this field continues to grow.

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