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Acute Kidney Injury and Progression of Diabetic Kidney Disease

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Abstract

Diabetic kidney disease, commonly termed diabetic nephropathy (DN) is the most common cause of end-stage renal disease (ESRD) worldwide. The characteristic histopathology of DN includes glomerular basement membrane (GBM) thickening, mesangial expansion, nodular glomerular sclerosis, and tubulointerstitial fibrosis. Diabetes is associated with a number of metabolic derangements, such as reactive oxygen species (ROS) overproduction, hypoxic state, mitochondrial dysfunction, and inflammation. In the past few decades, our knowledge of DN has advanced considerably although much needs to be learned. The traditional paradigm of glomerulus-centered pathophysiology has expanded to the tubule-interstitium, the immune response and inflammation. Biomarkers of proximal tubule injury have been shown to correlate with DN progression, independent of traditional glomerular injury biomarkers such as albuminuria. In this review, we summarize mechanisms of increased susceptibility to acute kidney injury (AKI) in diabetes mellitus (DM) and the roles played by many kidney cell types, in facilitating maladaptive responses leading to chronic kidney disease (CKD) and end-stage kidney disease (ESKD).

Kidney Disease in Diabetes Mellitus

According to the National Diabetes Fact sheet data (www.cdc.gov), diabetes mellitus (DM) was the 7th leading cause of death in the United States in 2013, and more than 20% of health care was spent for patients with diabetes. Long-term complications derived from diabetes include both macrovascular and microvascular diseases. Diabetic nephropathy (DN) or diabetic kidney disease (DKD), is one of the main microvascular complications. After adjustment for age, sex, and race, diabetes remains the most common cause leading to end-stage renal disease (ESRD) in the United States.¹ Although the number of major complications from diabetes has substantially declined in the U.S., the smallest decline was in ESRD.² DN is characterized by glomerular basement membrane (GBM) thickening, mesangial expansion, nodular glomerular sclerosis, and tubulointerstitial fibrosis.³ While

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DN in individuals with diabetes is common it is important to recognize that not all patients with diabetes and impaired kidney function have DN with its characteristic pathological features as the cause of their kidney dysfunction and the renal pathology, if obtained, varies among patients.⁴⁻⁹ When we refer to DN in this manuscript we refer to patterns of injury that are consistent described as characteristic of nephropathy associated with diabetes without other contributors.

Acute Kidney Injury (AKI) in Diabetes Mellitus

Multiple studies have shown that diabetes alone is an independent risk for acute kidney injury (AKI).^{1,10,11} The incidence of AKI was found to be higher in diabetic patients undergoing surgery¹²⁻¹⁶, taking certain medications¹⁷, with sepsis/septic shock¹⁸, and even without precipitating events.^{19,20} Renal insults resulting in tissue injury, including acute tubular injury, may affect kidney function and the rate of chronic functional impairment in diabetic patients, due to the fact that the subsequent maladaptive recovery fails to fully reverse the insults.^{21,22} There is, in general, a strong association between AKI and development of chronic kidney disease (CKD) and ESRD²³⁻²⁶. Thakar et al. demonstrated, in a cohort of 4082 patients with diabetes, single or repetitive episodes of AKI significantly increases the risk of developing advanced CKD²⁷. Subsequently, a large prospective study further confirmed that AKI itself can also predict major adverse outcomes including doubling of serum creatinine or ESRD in patients with diabetes²⁸. In the past few decades, the knowledge of the impact of DN has expanded beyond the glomerulus (podocyte) to other cell types. In this review, we will discuss the pathophysiology of increased susceptibility to AKI in diabetes and the impact of AKI in diabetes on various kidney cell types, each of which can play a role in injury and maladaptive repair. Furthermore, we discuss how repair after injury might be particularly maladaptive given the diabetic milieu and underlying chronic diabetic changes in the kidney.

Endothelial Dysfunction in Diabetic Nephropathy

NO Production and Signaling in Endothelial Cells

Glomerular endothelial cells are highly-fenestrated cells, carrying a thick layer of negatively-charged glycocalyx as a component of the glomerular filtration barrier.²⁹ Dysfunction of endothelial cells is one of the key mechanisms in DN, and this dysfunction involves different parts of the kidneys including interstitial peritubular capillary vessels as well as the glomerular afferent and efferent arterioles.³⁰⁻³² Nitric oxide (NO), an endothelium-derived relaxation factor produced by endothelial nitric oxide synthase (eNOS), is known to be reduced in diabetic kidneys. In normal physiology, NO dilates both the afferent and efferent arterioles, regulates activity of sympathetic tone in the kidneys and modulates sodium homeostasis.³³ In advanced DN, although the expression of eNOS is upregulated, the production of NO is decreased due to the “uncoupling” of the synthase.³⁴ Insulin resistance can also inhibit insulin receptor signaling leading to reduction of NO synthesis.³⁵ Genetic polymorphisms causing reduced production of NO are reported to accelerate the progression of DN.³⁶⁻³⁸ Altogether, this disturbed NO metabolism in diabetes renders the renal vasculature more sensitive to stimuli leading to vasoconstriction.

Furthermore, the level of vasoactive hormone, endothelin-1 (ET-1), is significantly elevated in DN and makes the vascular resistance even worse.³⁹ Therefore, increased renal resistive indices and sensitivity to vasoconstrictors such as adenosine has been found in animal models,^{40,41} and also in patients with both metabolic syndrome and type 2 DM.⁴² These phenomena can explain why DN is a known risk factor for contrast-induced AKI, where vasoconstriction plays an important role, and ischemic-reperfusion injury (IRI), one of the most common causes of AKI often associated with shock, sepsis, surgery, or contrast administration. For example, the incidence of contrast-induced AKI (CIAKI) in DN is markedly higher than in the general population.⁴³ Several potential therapeutic agents against CIAKI were investigated in patients. These include vasodilators (calcium channel blockers^{44–46}, dopamine⁴⁷), sodium bicarbonate^{48–51}, N-acetylcysteine (NAC)^{52,53}, and statins^{54–56}. Unfortunately to date, none of these agents were found to be conclusively beneficial. One recent systemic review suggested that high-dose statin plus hydration with or without NAC might prevent CIAKI, but more trials targeted at specific populations such as DN are required to verify the result.⁵⁷

Vascular Rarefaction and Hypoxia

Besides endothelial cell dysfunction, persistent hyperglycemia can also lead to endothelial cells apoptosis via NF- κ B and c-Jun NH2-terminal pathways,^{58,59} and interstitial vascular rarefaction has been shown in human diabetic nephropathy.⁶⁰ Vascular rarefaction then leads to significant hypoxic state in the kidneys, and the endothelial cell itself responds to chronic hypoxia with apoptosis rather than proliferation.³² In addition, peritubular capillary changes can be also observed as a long-term consequence of AKI⁶¹, which means DN can potentially aggravate the loss of perfusion in kidneys during AKI. Since oxygen (O₂) supply is in high demand in kidneys, decreased O₂ supply secondary to vascular rarefaction can compromise the generation of ATP, which is very important for proximal tubule functions.⁶² Apart from impaired O₂ delivery, oxidative stress from overproduction of reactive oxygen species (ROS) in proximal tubules can damage the endothelial cells in the diabetic state. For example, Han et al. showed that, in the setting of persistent hyperglycemia, ROS such as H₂O₂ can be generated by proximal tubule cells via protein kinase C (PKC) and nicotinamide adenine dinucleotide phosphate (NAPDH) oxidase activity, and ROS can directly reduce the level of available NO.⁶³ Excessive oxidative stress has been well-validated as important pathway leading to CKD.^{64,65}

Sustained integrity between endothelial cells and pericytes is essential for blood vessels stabilization.^{66,67} During AKI, the transformation of pericytes to myofibroblasts leads to series of fibrotic response,⁶⁸ and pericytes detachment from endothelial cells can also trigger tubular injury and peritubular capillary rarefaction.⁶⁹ Given damaged endothelial cells due to DN, the loss of endothelial-pericyte interaction may also cause fibrosis and eventually CKD. Therapy targeted on pericyte differentiation has been discussed as a potential therapeutic option for DN, but more studies are required to confirm the role of pericytes in DN model.⁷⁰

Cross-talk Between Endothelial Cells and Podocytes

The cross-talk between glomerular endothelium and podocytes has been proposed to play an important role in DN. In the normal glomerulus, VEGF is mainly produced by podocytes

and binds to VEGFR-2 located at endothelium⁷¹, maintaining vascular formation and differentiation. This paracrine effect is shown to be renoprotective in many different kidney diseases.⁷² Specific deletion of VEGF in mice podocytes can lead to renal disease characterized by proteinuria and endotheliosis.⁷³ By contrast, increased levels of VEGF and VEGFR have been reported to aggravate DN^{71,74,75} due to the propagation of positive feedback loop from TGF- β /CTGF and overproduction of ROS.⁷⁶ Given this observation, multiple studies have attempted to reduce the VEGF signal and demonstrated a favorable outcome.^{77–79} A recent study by Oltean et al. evaluated the efficacy of anti-VEGF antibody (VEGF-A₁₆₅b) injection in both type 1&2 DN rodent models, and showed amelioration of renal function decline and pathological improvement.⁸⁰ However, Sivaskandarajah et al. used the Cre-Loxp system to specifically delete the *Vegfa* gene in glomerular podocytes, and showed that diabetic mice with *Vegfa* deletion paradoxically have greater proteinuria and glomerular scarring.⁸¹ These seemingly conflicting results suggested a stringent balance of VEGF signaling (such as different subtypes) at different stages of DN must be maintained to prevent progression in DN^{82,83}. It is unknown whether AKI on DN alters glomerular VEGF signaling.

Proximal Tubules Dysfunction in Diabetic Nephropathy

Pivotal Role of Proximal Tubules in DN

As DN is historically characterized by the development of albuminuria, glomerular change has been considered as primary with tubulointerstitial disease secondary. However, growing evidence argues that tubular damage occurs early in DN and may play a key role in progression of kidney disease.⁸⁴ The implications of proximal tubular injury for development of CKD has been well established in several cohort studies⁸⁵. There is a good reason to extrapolate to CKD secondary to tubular injuries in diabetes. Using biomarkers of tubular injury, we performed a cross-sectional comparison on samples from the second Joslin study, and concluded that lower urinary kidney injury molecule-1 (KIM-1) and N-acetyl- β -D-glucosaminidase (NAG) at baseline, which both indicate tubular damage, were associated with regression of microalbuminuria.⁸⁶ Another analysis of the same cohort revealed that elevated baseline plasma KIM-1 was significantly associated with the risk of early decline of renal function, independent of albuminuria.⁸⁷ Najafian et al. studied kidney biopsies obtained from type 1 DM patients, and found that, even with normal to only moderately impaired GFR, 17% of glomeruli were atubular, and 51% were attached to atrophic tubules.⁸⁸ These clinical and pathological data strongly suggested that tubular damage plays a critical role in the development of DN, and may precede and interact with functional glomerular changes.⁸⁹ As our previous laboratory work revealed that repetitive proximal tubular injury can lead to serial interstitial inflammation, fibrosis and eventually CKD, more attention to proximal tubules in DN is essential.^{22,90}

Hypoxia and Proximal Tubules

Anatomically, the proximal tubule can be divided into three different segments, S1, S2 and S3. The number of mitochondria decreases from S1 to S3, but S3 is more prone to ischemic changes due to baseline lower oxygenation, susceptibility to reduced blood flow and likely impairment in the ability of the S3 segment to switch from oxidative to glycolytic

metabolism.^{91–93} In diabetic animal studies outer medullary hypoxia has been documented using blood oxygen level-dependent (BOLD) MRI^{94,95}. Cortical and medullary hypoxia also have been reported in humans with DN.^{96,97} Since medullary hypoxia ensues in the early stages of diabetes before the presence of kidney disease measured by increased serum creatinine or albuminuria, hypoxia gets worse as kidney disease progresses. As mentioned above, capillary rarefaction with decreased O₂ delivery occurs in DN, the highly-demanded aerobic metabolic process of proximal tubules can be quickly disrupted during AKI. Meanwhile, the stress from mitochondrial dysfunction or increased O₂ utilization can further intensify the damage during hypoxia.⁹⁸ In this setting it is not surprising that patients with diabetes are more susceptible to insults that would further impair oxygen delivery to tubules which have increased oxygen utilization due to hyperfiltration associated with diabetes. Hypoxia-inducible factor (HIF)-1 α , a transcription factor activated during hypoxia which contributes to fibrogenesis, has been shown to be increased in expression and implicated in the progression of DN.^{99,100} Persistent HIF-1 signaling also plays an important role in development of CKD.¹⁰¹ Suppression of HIF-1 α both in vitro and vivo by using human renal proximal tubular epithelial cells (HRPTECs) and diabetic fatty rat ameliorated tubular injury¹⁰²; similarly, YC-1 (a HIF-1 inhibitor) decreased tubulointerstitial fibrosis in OVE 26 type 1 diabetic mice.¹⁰³ The preexistent HIF-1 upregulation in DN might explain more proximal tubular cells damage during AKI, since HIF-1 mediated pathways have been implicated in development of apoptosis after IRI.¹⁰⁴

Increasing O₂ utilization from upregulation of glucose transporters in diabetic proximal tubules may likewise worsen the hypoxia in DN. For instance, sodium-glucose cotransporter type 2 (SGLT-2), one of the proximal tubule glucose reabsorption transporters, is upregulated by four-fold to maximize the glucose reabsorption capacity¹⁰⁵. As such, O₂ consumption increases because the influx of glucose via luminal SGLT-2 requires a sodium gradient generated by Na⁺/K⁺-ATPase, an O₂-dependent process. Clinically, SGLT-2 inhibitor empagliflozin is associated with improvement in cardiovascular outcomes, reduction of GFR decline and incidence of AKI (EMPA-REG OUTCOME trial)^{106,107} The effects of SGLT-2 inhibitors to reduce O₂ usage has been compared with the “ β -blockers effect” to reduce workload on the heart.¹⁰⁸

Diabetic proximal tubules are also more susceptible to mitochondrial dysfunction during hypoxia due to heavy aerobic metabolism, and the delicate yet complicated dynamic of mitochondrial fusion and fission might be disorganized causing delayed recovery from kidney injuries.⁶⁸ Of note, the change of mitochondrial adaptation can occur at proximal tubules as early as 4 weeks of age in the diabetic rat model.¹⁰⁹ *Myo*-inositol oxygenase (MIOX), an enzyme specifically expressed in tubular cells, is found to be upregulated in the persistent hyperglycemic state. MIOX upregulation is accompanied with the accumulation of dysfunctional mitochondria, and therefore increased ROS production, apoptosis and eventually progression of DN.¹¹⁰ Sharma et al. reported that specificity protein (Sp)-1 epigenetically modulates the expression of MIOX. Using either a Sp-1 siRNA or inhibitor can significantly reduce ROS production.¹¹¹ The tubule-specific MIOX knockout mice are also protected from cisplatin-induced AKI.¹¹²

p53 and Proximal Tubules

The role of p53 in AKI has been extensively discussed in the past decade. In addition to our previous laboratory work reporting that activation of p53 during AKI leads to progressive renal fibrosis²², subsequent other studies have shown similar results both in vivo and in vitro.^{113–115} In 2015, Peng et al. demonstrated, in high glucose-conditioned renal proximal tubular cells (RPTCs) and Akita diabetic mice, that p53 is upregulated in azide-induced chemical anoxic injury and IRI respectively. In Akita diabetic mice pretreated with either Pifithrin- α (p53 inhibitor) or p53 siRNA, levels of blood urea nitrogen (BUN), serum creatinine, and tubular injury were reduced after IRI. The authors further tested proximal tubule-specific *p53*-knockout mice (PT-p53-KO) injected with streptozotocin (STZ), a commonly-used method to induce diabetes. After IRI, PT-p53-KO mice had lower BUN, serum creatinine, and apoptosis on histological analysis, supported by less cleaved/active caspase 3 and Bax in the mitochondrial fraction.¹¹⁶

Inflammation and Proximal Tubules

Inflammatory cytokines have been shown to play an important role in the development and progression of DN¹¹⁷. For example, tissue necrosis factor (TNF)- α , interleukin (IL)-1^{118,119}, IL-6^{118–121} have been reported to be upregulated and lead to serial cascades of inflammation. Hyperglycemia and advanced glycation endproducts (AGE) can induce the expression of adhesion molecules and chemokines in proximal tubular cells^{122,123}, and albuminuria itself is also a tubular stimulus to express IL-8 via the NF- κ B/PKC pathway and ROS production.¹²⁴ As acute tubular injury creates an inflammatory milieu attracting neutrophils, monocytes, and macrophages^{68,125–128}, the baseline inflammatory status in DN might predispose to an aggravated inflammatory state by the acute renal insult. Other studies have used tubule-specific genetic-modified mice and showed levels of tubular inflammation can affect the progression of DN. Gremlin, a bone morphogenetic proteins (BMPs) antagonist, is related to renal fibrosis and inflammation via activation of Smad/TGF- β and VEGFR2 respectively^{129,130}, and is found to be highly expressed in human DN biopsies predominantly in the areas of tubulointerstitial fibrosis.¹³¹ Marchant et al. used a diabetic model induced by STZ in transgenic mice overexpressing Gremlin in proximal tubular cells, and showed more interstitial fibrosis and inflammation after inducing diabetes.¹³² Overexpression of Netrin-1 (a regulator of leukocyte migration) in proximal tubules was shown to suppress inflammation and albuminuria in STZ-induced diabetic mice,¹³³ and the deletion of its receptor (UNC5B) aggravated albuminuria.¹³⁴ Recently, sphingosine kinase 2 global knockout in mice (*Sphk2*^{-/-}) was reported to attenuate kidney fibrosis after injury produced by folic acid (FA) injection or IRI.¹³⁵ Since increased sphingosine 1-phosphate has been reported to mediate inflammation and fibrosis in tubular injury in diabetic nephropathy.¹³⁶, deletion of *Sphk2* in proximal tubules will be informative to assess its role in enhancing susceptibility to AKI in DN.

Maladaptive proximal tubular injury with subsequent fibrosis is the key component in AKI to CKD transition¹³⁷, since tubulointerstitial fibrosis is the major determinant to ESRD.¹³⁸ In addition to different mechanism of injury to proximal tubules mentioned above, hyperglycemia or AGE can stimulate proximal tubules cells and lead to profibrogenic cytokine secretion. When proximal tubular epithelial cells (PTEC) are cultured in

hyperglycemia media, they can secrete extracellular matrix (ECM) via a TGF- β -dependent pathway.^{139,140} In vivo, TGF- β is found to be significantly elevated in both diabetic mouse model and human biopsy¹⁴¹, and considered as the key mediator of renal fibrosis. Blocking TGF- β signaling in DN has been investigated and shown decreasing fibrosis in animal models; however, it might remain a controversial therapeutic option due to increasing production of mineralocorticoids from adrenal glands.¹⁴² Platelet-derived growth factor (PDGF)^{143,144} and connecting tissue growth factor (CTGF)¹⁴⁵ are another two important profibrotic in DN.¹⁴⁶

Cross-talk between Proximal Tubules and Podocytes

In 2013, Hasegawa et al. published an important finding on the crosstalk between proximal tubular cells and podocytes in DN. The authors used the model of PT-specific *Sirt1* transgenic and *Sirt1* knockout mice, and demonstrated that Sirt1 can modulate the expression of Claudin-1 in podocytes by local nicotinamide mononucleotide (NMN) concentration in DN. The induction of Claudin-1 expression in podocytes leads to podocyte foot process effacement and albuminuria^{89,147}, possibly via destabilizing the slit diaphragm (SD), an essential cell-cell junction complex as filtration barrier.¹⁴⁸ A recent study showed that manipulation of SIRT1 by supplementation of NMN can protect mice from cisplatin-induced AKI¹⁴⁹, suggesting SIRT1 is another possible pathway to reduce AKI susceptibility in DN.

Podocyte Dysfunction in Diabetic Nephropathy

Apoptosis and Foot Process Effacement of Podocytes in DN

Podocytes are highly differentiated visceral epithelial cells within the glomerulus, and provide an important component of the glomerular filtration barrier (GFB) along with glomerular endothelium and glomerular basement membrane (GBM).¹⁵⁰ Podocytes are divided into three main components: cell body, major and foot process, and the processes are characterized by various types of cytoskeletons. Foot processes are enriched in actin filaments, and play an important role in cellular contracture features and forming slit-diaphragms (SD) with adjacent processes from the same cell body or adjacent podocytes. In the past decade, many proteins have been identified on the SD, and mutation of these proteins can lead to congenital nephrotic syndrome. Various genetic disease of podocytes have been summarized in a review.¹⁵¹ An important study describing the correlation between podocytes pathology and CKD progression in DN demonstrated the correlation of reduced podocytes (podocytopenia) with the progression of DN and the foot processes broadening on biopsies in type 2 DM patients.¹⁵² Such podocyte injury leads to the loss of integrity of GFB in the glomerulus, finally resulting in albuminuria in DN. As mentioned previously, albuminuria itself can damage tubular cells, and therefore uncontrolled albuminuria from podocyte injuries facilitates tubular epithelial cells injury leading to interstitial fibrosis which, in turn, impairs vascular supply to the glomerulus. Many clinical trials have sought to arrive at a treatment strategy to cease progression of DN. Therapeutic approaches have included angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs).¹⁵³ Currently, the Kidney Disease Outcomes Quality

Initiative (KDOQI) advises measuring albuminuria annually in patients with either type 1 or 2 diabetes after 5 years of diagnosis.¹⁵⁴

Podocytes Apoptosis in DN

Hyperglycemia can induce podocytes apoptosis via several mechanisms, such as excessive ROS, renin-angiotensin-system (RAS) activation, mammalian target of rapamycin (mTOR) pathway, tumor growth factor- β (TGF- β)/SMAD^{155–157}, or AGE.^{150,158,159} Apoptosis has been observed both in a diabetic mice model¹⁶⁰ as well as human renal biopsies in type 2 DM patients.¹⁶¹ Since podocytes have much lower capacity to regenerate when compared with tubular cells, podocytopenia in DN might be an irreversible process leading to permanent damage.¹⁶²

Susztak et al. used both an in vitro and in vivo model to demonstrate that in podocytes ROS are generated through NADPH oxidase (NOX) and consequently led to activation of mitogen-activated protein kinase (MAPK) and caspase 3.¹⁶⁰ Later, it was further suggested that NOX4 is the key NADPH oxidase, and pharmacological inhibition or genetic deletion of NOX4 ameliorates albuminuria.^{163,164} In addition to MAPK pathway, NOX4 can also be upregulated by mTOR pathway in hyperglycemia, and inhibiting mTOR by rapamycin reveals a similar phenotype as NADPH inhibition.¹⁶⁵ Since NOX4 is also highly expressed in other types of cells, Jha et al. used a podocyte-specific *Nox4* deletion mice, and established the deleterious effect of *Nox4* expression in STZ-induced DN, specifically in podocytes with resultant albuminuria and extracellular matrix accumulation.¹⁶⁶ Recently, the epigenetic regulation by histone methyltransferase enzyme enhancer of zeste homolog 2 (EZH2) further expands the role of oxidative stress in DN podocytes.¹⁶⁷

Using ACEIs or ARBs to reduce proteinuria has been widely used to control albuminuria in DN.^{168–171} Besides the concept of decreasing intra-glomerular pressure by ACEIs/ARBs, RAS blockade could also affect podocyte pathology in DN. Angiotensin II has been shown to cause podocyte apoptosis via TRPC6 (transient receptor potential canonical) calcium channel and resultant influx of Ca^{2+} .^{172,173} The authors of a recent study found that podocytes isolated from diabetic rats has increased response to Ang II, which could aggravate AII-induced damage to podocytes.¹⁷⁴ Since the RAS is activated in AKI^{175,176}, circulating angiotensin II levels during AKI could further enhance the apoptosis of diabetic podocytes and lead to progression of DN.

Insulin signaling deficiency, either from reduced insulin secretion (type 1 DM) or insulin resistance (type 2 DM), is characteristic of diabetes. Upon insulin stimulation, there is increased PI3K/MAPK signaling increases¹⁷⁷, as well as glucose uptake through nephrin-dependent translocation of GLUT4 in podocytes.^{178,179} In mice with podocyte-specific deletion of the insulin receptor albuminuria develops even under normoglycemic conditions. There is also impaired remodeling of the actin cytoskeleton which subsequently affects podocyte morphology.¹⁷⁷ Similarly, podocytes isolated from db/db mice also showed decreased response to insulin with reduced phosphorylation of AKT, and enhanced podocyte death after exposure to TNF- α treatment.¹⁸⁰ This result also provides a potential mechanism for increased podocyte death during AKI in diabetes, since TNF- α is an important mediator in AKI.¹⁸¹ Recently, Falkevall et al. demonstrated that inactivation of VEGF-B-mediated

lipid accumulation in podocytes can re-sensitize podocytes to insulin signaling and further improve podocyte survival. Therefore, anti-VEGF-B antibody might be another future treatment to halt DN progression especially in the context of episodes of AKI.^{182,183}

Foot Process Effacement in DN

In addition to occurrence of podocyte apoptosis, foot process effacement (FPE) is an anatomical feature associating with profound albuminuria in DN, and loss of nephrin expression on slit diaphragms is thought to be one of the main pathogenic features of FPE in podocytes.¹⁸⁴ Nephrin (a 180-kDa transmembrane protein) serves as an intracellular signaling scaffold^{185–187}, modulating podocyte cytoskeleton^{188–190}, and mediating insulin signaling. In DN, both increased levels of angiotensin and VEGF-A have been shown to decrease expression of nephrin.¹⁹¹ Recently, Teng et al. demonstrated that an increased expression of ubiquitous kinase/Cbl-interacting protein of 85 kDa (Ruk/CIN85), a binding partner of nephrin, mediated nephrin endocytosis via ubiquitination in DN.¹⁹² Of note, more glomerular insults by either unilateral nephrectomy or doxorubicin were observed in even short-term RNAi-mediated nephrin knockdown, which further suggests diabetic podocytes have higher susceptibility to AKI.¹⁹³

As foot processes contain a great deal of actin cytoskeleton, regulation of actin remodeling also has an essential role in FPE. Rho-family small GTPases can mediate actin cytoskeletal dynamics changes¹⁹⁴, and dysfunctions of RhoA, Rac1 and Cdc 42 have been related to podocyte diseases such as focal segmental glomerulosclerosis (FSGS)¹⁹⁵ and pediatric steroid-resistant nephrotic syndrome (SRNS)¹⁹⁶. In DN, down-regulation of PTEN (phosphatase and tensin homologue) can lead to unbalanced activation of the small GTPase Rac1/Cdc42 and RhoA,¹⁹⁷ and Rac1 activation in podocytes induces rapid FPE and proteinuria.¹⁹⁸ Blattner et al. used podocyte-specific *Rac1* knockout mice to assess the acute podocyte injury to protamine sulfate, and showed prevention of FPE in *Rac1* knockout mice. However, in chronic hypertensive glomerular damage, loss of Rac1 surprisingly leads to an exacerbation of albuminuria and glomerulosclerosis¹⁹⁹. Thus, whether Rac1 functional changes are beneficial or detrimental in chronic DN requires more research to clarify.

Other Mechanisms of Injury to Podocytes in Diabetes

Autophagy is an important intracellular catabolic process to degrade certain proteins or organelles via lysosomes under stress,²⁰⁰ and protects against acute kidney injury in several models.^{68,201} Our work recently demonstrated that KIM-1, which is upregulated with AKI, mediated phagocytosis, followed by autophagy, downregulates inflammatory response in proximal tubules.^{202,203} Autophagy has also gained more attention in the pathogenesis of DN in the past few years.^{204–206} Although initial hyperglycemia can induce autophagy in podocytes²⁰⁷, prolonged hyperglycemia eventually down-regulates autophagy via various pathways such as mTOR and β -arrestins.^{208–212} Recent work with podocyte-specific *Atg5* deletion (autophagy-deficient) mice showed additional acceleration of podocyte loss in both type 1²¹³ and 2 DM models.²¹⁴ Histone deacetylase 4²¹⁵ and inositol-requiring enzyme-1 α were also reported to regulate autophagy in podocytes.²¹⁶

As inflammation and mitochondrial dysfunction can occur during DN, several studies explored the specific role of podocytes in these processes. For example, Janus Kinase-Signal Transducer and Activator of Transcription (JAK-STAT) has been found to increase in early human DN,²¹⁷ and unsurprisingly acute injury to the kidney can also activate the JAK-STAT pathway.^{218,219} Overexpression JAK2 mRNA specifically in podocytes significantly increases albuminuria and reduces podocyte density in diabetic Akita mice, and a specific JAK1/2 inhibitor partly reversed the phenotype.²²⁰ Activation of Chemokine (C-C motif) receptor 2 (CCR2) occurs with AKI²²¹ and has been associated with altering podocyte integrity in DN, and podocyte-specific *CCR2* overexpression can mediate diabetic renal injury, independent of monocyte/macrophage recruitment.²²² A phase IIa clinical trial is currently under investigation evaluating CCL2 inhibition in diabetic patients.²²³ In podocyte-specific soluble epoxide hydrolase (sEH) knockout mice, serum levels of inflammatory cytokines and the degrees of proteinuria were significantly reduced, suggesting that expression of sEH in podocytes might mediate the inflammatory response to lipopolysaccharide (LPS)-induced AKI.²²⁴ In addition, mitochondrial dysfunction with ROS overproduction²²⁵ and the change of mitochondrial dynamics are related to hyperglycemia.²²⁶ Increasing glycolytic flux traditionally is thought to cause mitochondrial dysfunction. In this study by Qi et al., they found that through pyruvate kinase M2 (PKM2) activation, the authors can protect from progression of DN by increasing glucose metabolic flux. Worse albuminuria and glomerular pathology were observed in podocyte-specific *Pkm2*-KO mice with diabetes, as was more podocyte apoptosis apparent in *Pkm*-knockdown immortalized mouse podocytes.^{227,228}

Mitochondria play a key role in acute injury to the kidney. The dynamic of mitochondria consists of fission and fusion, and mitochondrial fission was shown to correlate with DN.²²⁶ The authors further identified the role of dynamin-related protein 1 (*Drp1*) in podocytes, showing that podocyte-specific deletion of *Drp1* ameliorated progression of DN and improved mitochondrial fitness.²²⁹ Taken together, these studies all point to a key role of mediators present in acute tubular injury which may affect podocytes and facilitate the progression of DN.

Cross-talk Between Podocytes and Endothelial Cells

Apart from the VEGF signaling between podocytes and endothelial cells mentioned above, other signaling such as angiopoietin-1/2^{230–232}, angiopoietin-like 4 (ANGPTL4)^{233,234}, and eNOS²³⁵ have been reported to be involved in cross-talk between these two cells (see review²³⁶). Another important cross talk occurs between podocytes and endothelial cells is endothelin-1 (ET-1) signaling. In AKI and DN, the expression of ET-1 by endothelial cells is increased²³⁷, and blockade of ET-1 signaling in podocytes by podocyte-specific deletion of both endothelin receptor type A (ETRA) and type B (ETRB) showed less podocyte loss and glomerulosclerosis.²³⁸ A subsequent study revealed that endothelin-1 can activate podocytes to secrete heparanase, an enzyme cleaving the heparin sulfate (HS) which is important for the integrity of glomerular filtration barrier. As endothelial glycocalyx fragmentation is shown to predict the development of AKI and mortality of critically-ill patients^{239,240}, ET-1 signaling in DN may also augment the severity of AKI. Treatment targeted at ET-1 receptors might be a future therapeutic option for DN.^{241–243}

Conclusion

As our understanding of pathophysiology of DN progresses in recent years, there are still few new therapeutic options approved to prevent from the incidence or renal function decline in DN. Although it is likely that AKI can facilitate progressive decline in diabetes, leading to CKD, the current definition of AKI may delay its timely diagnosis^{21,244}, and more precise understanding of the role that AKI plays in progression as well as the factors responsible for predisposition of the diabetic patient to AKI require better definition. The use of serum or urinary biomarkers in diagnosing and predicting outcome of DN is vigorously under investigation^{245,246}, and new transcriptomics-proteomics technology is increasingly being applied to dissect the kidney responses to AKI.²⁴⁷ Therapies targeted to different cell types (e.g. podocytes, tubular cells, endothelium) in DN will likely be of use to mitigate this common kidney disease with high levels of morbidity and mortality (table 1).

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Figure. Scheme of relationship between diabetic nephropathy (DN) and acute kidney injury (AKI)

Diabetic nephropathy ensues from chronic hyperglycemia via several mechanisms, such as worsening hypoxic status, chronic inflammation, mitochondrial dysfunction, increasing mTOR signaling, and exposure to advanced glycation endproduct (AGE). Diseased kidney cells are more susceptible to acute kidney injury (AKI), and vice versa these damaged cells from DN can hasten the damage during each AKI episode. As traditional paradigm of DN has been expanded from glomerulus (podocyte)-centered to other cell types, the crosstalk among different kidney cells are revealed to be crucial in DN development. After diabetic kidneys undergo repetitive AKI, maladaptive repair occurs from acute renal insults, and irreversible tubulointerstitial fibrosis accumulates and eventually lead to chronic kidney disease (CKD) and end-stage kidney disease (ESKD).

Table 1

Potential Treatments of Diabetic Kidney Diseases in Different Kidney Cells

	Mechanism of Injury	Potential Treatment
Endothelium	<ul style="list-style-type: none"> Decreased NO synthesis, increased susceptibility to vasoconstriction, hypoxia Increased VEGF/VEGFR, ET-1 ROS overproduction Endothelial-to-mesenchymal transition 	<ul style="list-style-type: none"> High-dose statin, hydration, with or without N-acetylcysteine in CIAKI⁵⁷ Anti-VEGF antibody (VEGF-A_{165b})⁸⁰, atrasentan (ET-1 antagonist)²⁴¹ Nrf2 activator^{248,249} DPP4-inhibitor²⁵⁰, ROCK-1 inhibitor²⁵¹
Tubule	<ul style="list-style-type: none"> Increased O₂ utilization Hypoxia, increased HIF-1α Mitochondrial dysfunction (MIOX upregulation) P53 activation Destabilizing podocyte slit-diaphragm Activation of fibrotic pathway Epithelial-to-mesenchymal transition Decreased autophagy 	<ul style="list-style-type: none"> SGLT-2 inhibitor^{106–108} YC-1 (HIF-1 inhibitor)¹⁰³, metformin¹⁰² Sp-1 (modulator of MIOX)¹¹¹, PGC1α activator²⁵², MitoQ²⁵³, SS-31²⁵⁴ Pifithrin-α¹¹⁶ Nicotinamide mononucleotide (NMN)¹⁴⁹ DPP-4 inhibitor²⁵⁵, Gremlin inhibitor^{132,256}, miR-21 silencing²⁵⁷ miR-130 inhibitor²⁵⁸ Metformin²⁵⁹
Podocyte	<ul style="list-style-type: none"> ROS overproduction Podocyte loss, FPE Inflammation Lipid accumulation Restoration of slit diaphragm protein Epithelial-to-mesenchymal transition Decreased autophagy 	<ul style="list-style-type: none"> NOX inhibitor^{260–262}, mTOR inhibitor¹⁶⁵, Nrf2 activator²⁴⁹, metformin^{263,264} RAAS inhibitor^{172,173}, PPARγ agonist²⁶⁵, miR-25 agomir²⁶⁶, miR-21 silencing²⁵⁷, ursodeoxycholic acid/4-phenylbutyrate²⁶⁷ CCR2 inhibitor²²², pentoxifylline (urinary NAG as surrogate marker)²⁶⁸ Anti-VEGF-B antibody¹⁸² ACEI²⁶⁹, SGLT2 inhibitor²⁷⁰ DPP-4 inhibitor²⁷¹ Resveratrol²⁷², PTP1B inhibition²⁷³, Astragaloside IV²⁷⁴, Berberine²⁷⁵, miR-217 inhibition²⁷⁶, spironolactone²⁷⁷, HDAC inhibition²¹⁵
Non Cell-type Specific	<ul style="list-style-type: none"> Unbalanced glomerular hemodynamics, hyperfiltration, albuminuria ROS overproduction ECM deposition Inflammation Activation of fibrotic pathway Mitochondrial dysfunction 	<ul style="list-style-type: none"> RAAS inhibitor^{168,278,279}, direct renin inhibitor²⁸⁰ Nrf activator²⁸¹ (BEACON trial, stopped due to cardiovascular events²⁸²), pentoxifylline^{283–286} (PREDIAN trial)²⁸⁷, H₂S donor (GYY4137)^{266,288} Nrf activator²⁸¹, CCR2 inhibitor²⁸⁹ (2 clinical trial^{223,290}), Pirfenidone (anti-TGFβ, in mesangial cells²⁹¹, clinical trial²⁹²), DPP-4 inhibitor²⁹³ miR-146a inhibition²⁹⁴ <i>Smad7</i> gene transfer²⁹⁵, miR-192 inhibitor (mesangial cells)²⁹⁶ MitoQ²⁹⁷

* Abbreviation Nitric oxide (NO); Vascular endothelial growth factor (VEGF); Vascular endothelial growth factor receptor (VEGF-R); Endothelin-1 (ET-1); Reactive oxygen species (ROS); Hypoxia-induced factor 1- α (HIF-1 α); *Myo*-inositol oxygenase (MIOX); Foot process effacement (FPE); Extracellular matrix (ECM); Contrast-induced acute kidney injury (CIAKI); Nuclear factor erythroid 2-like 2 (Nrf2); Dipeptidyl peptidase-4 (DPP-4); Rho-associated kinase 1 (ROCK1); Sodium-glucose cotransporter-2 (SGLT-2); Specificity protein-1 (Sp-1); Peroxisome proliferator-activated receptor gamma coactivator 1- α (PGC1 α); NADPH oxidase (NOX); mechanistic target of rapamycin (mTOR); Renin-angiotensin-aldosterone system (RAAS); Peroxisome proliferator-activated receptor gamma (PPAR γ); Chemokine (C-C motif) receptor 2 (CCR2); N-acetyl-beta-D-glucosaminidase (NAG); Angiotensin-converting-enzyme inhibitor (ACEI); protein-tyrosine phosphatase 1B (PTP1B); Histone deacetylase (HDAC); Transforming growth factor beta (TGF β); Mitochondria-targeted ubiquinone (MitoQ)