Acute Kidney Injury and Progression of Diabetic Kidney Disease

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Diabetic kidney disease, commonly termed diabetic nephropathy (DN), is the most common cause of end-stage kidney disease (ESKD) worldwide. The characteristic histopathology of DN includes glomerular basement membrane thickening, mesangial expansion, nodular glomerular sclerosis, and tubulointerstitial fibrosis. Diabetes is associated with a number of metabolic derangements, such as reactive oxygen species 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 in diabetes mellitus and the roles played by many kidney cell types to facilitate maladaptive responses leading to chronic and end-stage kidney disease.

Key Words: Diabetic kidney disease, Acute kidney injury, End-stage kidney disease

KIDNEY DISEASE IN DIABETES MELLITUS

According to the National Diabetes Fact Sheet (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 expenses were spent on patients with diabetes. Long-term complications derived from diabetes include both macrovascular and microvascular diseases. Diabetic nephropathy (DN), or diabetic kidney disease, is one of the main microvascular complications. After adjustment for age, sex, and race, diabetes remains the most common cause leading to ESRD in the United States.[1] Although the number of major complications from diabetes has substantially declined in the United States, the smallest decline was in ESRD.[2]

DN is characterized by glomerular basement membrane thickening, mesangial expansion, nodular glomerular sclerosis, and tubulointerstitial fibrosis.[3] While 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 kidney pathology, if obtained, varies among patients.[4-9] When we refer to DN in this article, we refer to patterns of injury that are consistent with those described as characteristic of nephropathy associated with diabetes without other contributors.

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ACUTE KIDNEY INJURY IN DM

Multiple studies have shown that diabetes alone is an independent risk factor for acute kidney injury (AKI).[1,10,11] The incidence of AKI was found to be higher in diabetic patients undergoing surgery,[12-16] taking certain medications,[17] with sepsis/septic shock,[18] and even without precipitating events.[19,20] Kidney insults resulting in tissue injury, including acute tubular injury, may affect kidney function and the development of chronic functional impairment in diabetic patients, owing 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 ESRD.[23-26] 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 CKD.[27] 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 diabetes.[28] 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 (Fig 1). 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 DN

Nitric Oxide Production and Signaling in Endothelial Cells

Glomerular endothelial cells are highly fenestrated cells that carry a thick layer of negatively charged glycocalyx as a component of the glomerular filtration barrier (GFB).[29] Dysfunction of endothelial cells is one of the key mechanisms in DN, and this dysfunction involves different parts of the kidney including interstitial peritubular capillary vessels and 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 the 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 the reduction of NO synthesis.[35] Genetic polymorphisms causing reduced production of NO were reported to accelerate the progression of DN.[36-38] Altogether, this disturbed NO metabolism in diabetes renders the kidney 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] Increased kidney 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 (CIAKI), where vasoconstriction plays an important role leading to ischemic reperfusion injury (IRI), one of the most common causes of AKI.[43] Several potential therapeutic agents against CIAKI have been investigated in patients. These include vasodilators (calcium channel blockers,[44-46] dopamine[47]), sodium bicarbonate,[48-51] N-acetylcysteine,[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 N-acetylcysteine might prevent CIAKI, but more trials targeted at specific populations such as DN are required to verify the result.[57]

CLINICAL SUMMARY

- Multiple clinical studies have shown diabetes mellitus is an independent risk factor for the development of acute kidney injury.
- Sustained or uncontrolled hyperglycemia produces proximal tubule and podocyte damage via a host of metabolic stressors.
- The onset of albuminuria signifies a critical level of podocyte loss and disruption of the glomerular filtration barrier. Although many treatments have been targeted at improving renal outcomes in clinical trials, only the blockade of the renin-angiotensin-aldosterone system has proven utility.

Vascular Rarefaction and Hypoxia

Besides endothelial cell dysfunction, persistent hyperglycemia can also lead to apoptosis of endothelial cells via NF-κB and c-Jun NH2-terminal pathways,[58,59] and interstitial vascular rarefaction has been shown in human DN.[60] Vascular rarefaction then leads to significant hypoxia 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 a long-term consequence of AKI,[61] and DN can potentially aggravate this loss of perfusion in the kidneys following AKI. Because oxygen (O_2) supply is in high demand in kidneys, decreased O_2 supply secondary to vascular rarefaction can compromise the generation of adenosine triphosphate (ATP), which is very important for proximal tubule functions.[62] In addition to impaired O_2 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 H_2O_2 can be generated by proximal tubule cells via protein kinase C and nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, and ROS can directly reduce the level of available NO.[63] Excessive oxidative stress has been well validated as an important pathway leading to CKD.[64,65]

Sustained integrity between endothelial cells and pericytes is essential for the stabilization of blood vessels.[66,67] After AKI, the transformation of pericytes to myofibroblasts leads to a series of fibrotic responses,[68] and pericyte detachment from the 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 will facilitate fibrosis and eventually CKD. Therapy targeted to 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.[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, vascular endothelial growth factor (VEGF) is mainly produced by podocytes and binds to vascular endothelial growth factor receptor 2 (VEGFR2) located on the endothelium,[71] maintaining vascular formation and differentiation. This paracrine effect is shown to be renoprotective in many different kidney diseases.[72] Specific deletion of VEGF in non-diabetic mouse podocytes can lead to kidney 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 a positive feedback loop involving tumor growth factor-ß (TGF-ß), connective tissue growth factor 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-A_{165}b) injection in both type 1 and 2 DN rodent models and showed amelioration of kidney function decline and pathological improvement.[80] However, Sivaskandarajah et al. used the Cre-Loxp system to