Inflammatory Mechanisms as New Biomarkers and Therapeutic Targets for Diabetic Kidney Disease

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Diabetic kidney disease (DKD) is the leading cause of CKD and end-stage kidney disease (ESKD) worldwide. Approximately 30-40% of people with diabetes develop this microvascular complication, placing them at high risk of losing kidney function as well as of cardiovascular events, infections, and death. Current therapies are ineffective for arresting kidney disease progression and mitigating risks of comorbidities and death among patients with DKD. As the global count of people with diabetes will soon exceed 400 million, the need for effective and safe treatment options for complications such as DKD becomes ever more urgent. Recently, the understanding of DKD pathogenesis has evolved to recognize inflammation as a major underlying mechanism of kidney damage. In turn, inflammatory mediators have emerged as potential biomarkers and therapeutic targets for DKD. Phase 2 clinical trials testing inhibitors of monocyte-chemotactic protein-1 chemokine C-C motif-ligand 2 and the Janus kinase/signal transducer and activator of transcription pathway, in particular, have produced promising results.

Key Words: Inflammation, Chemokines, Cytokines, Diabetic kidney disease, Biomarkers

INTRODUCTION

Diabetic kidney disease (DKD) develops in 30-40% of patients with diabetes mellitus.[1,2] This is true of both type 1 and type 2 diabetes. As of the second decade of the 21st century, DKD is the leading cause of CKD and end-stage kidney disease (ESKD) worldwide.[3] Between 1980 and 2010, diabetes mellitus and CKD outpaced all reported chronic diseases in terms of the rate of increase in attributable age-standardized annual mortality rates.[4] Between 1990 and 2012, the number of deaths due to DKD increased by 94%.[5]

The dramatic rise in DKD prevalence and mortality over the last 3 decades mirrors the steady increase in global prevalence of diabetes and obesity.[6] In 2015, 1 in 11 adults worldwide, or 415 million people, had diabetes. By 2040, the prevalence of diabetes is projected to increase to 1 in 10 adults worldwide, or 642 million people.[6] The rising tide of diabetes has incurred a worldwide surge in diabetes-related complications. Compared to nondiabetic populations, individuals with diabetes have twice the risk of cardiovascular mortality, and this risk is further amplified by the presence of DKD.[7,8] Indeed, people with DKD are more likely to die from cardiovascular disease or infections than to progress to ESKD.[9] For patients that survive to ESKD, having diabetes is associated with worse outcomes and lower survival. Diabetic patients with ESKD exhibit an approximately 13% lower 3-year survival rate and a 1.4- to 1.8-fold excess risk of death compared to those without diabetes. Moreover, this risk disparity between diabetic and nondiabetic patients widens with increasing duration of ESKD.[10-14]

Current therapeutic options for DKD prevention and treatment are limited. Unfortunately, the extremely high economic cost of kidney replacement therapy precludes widespread accessibility for many patients in need, especially in low- and middle-income countries. Only a minority of patients across the globe who need kidney replacement therapy will receive it; thus, in many parts of the world, ESKD is a death sentence.[15] Therefore, novel therapies for preventing DKD onset and slowing progression are urgently needed to stem the economic and human catastrophe resulting from the diabetes pandemic.

A growing body of evidence points to major roles of the immune response and inflammation in the pathogenesis of DKD. Related proinflammatory signaling pathways and their downstream products are emerging as promising therapeutic targets.[16-18] The purpose of this review is to discuss recent findings about the interplay between inflammatory mechanisms and the onset and progression of DKD, with a focus on new biomarkers and candidate therapies that target these pathways.

INFLAMMATORY MECHANISMS IN DIABETIC KIDNEY DISEASE

At the end of the 20th century, the conventional paradigm of DKD pathogenesis held that the primary instigators were metabolic and hemodynamic factors resulting from the diabetic milieu.[19] Over the past decade, more precise insight into the taxonomy of human diseases has shifted the focus of DKD research toward disease-specific molecular pathways.[20,21] Recently, proteomic studies have detected molecular signatures for inflammatory mediators in urine from patients with early, uncomplicated diabetes.[22] The early appearance of these markers, which antedates development of DKD, suggests that inflammation plays a role in disease instigation and ongoing kidney injury. It is now believed that a chronic inflammatory insult to the kidney probably underlies many of the structural and functional changes in DKD (Fig 1).[22]

Innate Immune Response

The mononuclear phagocyte system in the healthy kidney consists of a resident network of cells coexpressing markers

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specific for macrophages and dendritic interstitial cells.[23,24] Metabolic and hemodynamic abnormalities induced by diabetes, including hyperglycemia and advanced glycation end products (AGEs), activate the mononuclear phagocyte system, precipitating a release of proinflammatory cytokines and paracrine signals.[24,25] A predominant cell type that infiltrates the kidney is macrophages[24,26,27] Additional monocytes and macrophages are recruited by cytokines released by resident macrophages and other kidney cells.[23,28] A cycle of cytokine release and monocyte and macrophage recruitment ultimately culminates in inflammatory-related structural changes associated with DKD (Figs 2 and 3).[23-25,28-30] The magnitude of macrophage infiltration in the diabetic kidney is associated with the extent of glomerulosclerosis, the degree of tubulointerstitial inflammation, and rate of loss of estimated glomerular filtration rate (eGFR).[26,27,31,32]

The mast cell is another type of innate immune cell that infiltrates the tubulointerstitium in DKD.[33,34] Mast cell degranulation releases inflammatory mediators and proteolytic enzymes, such as chymase, which may locally augment the conversion of angiotensin I to angiotensin II.[35,36] Progression of DKD and loss of eGFR also correlate with the number and extent of degranulation of mast cells (Fig 4).[34,37]

CLINICAL SUMMARY

- Mounting evidence indicates that a chronic inflammatory insult to the kidney underlies many structural and functional changes in DKD.
- Activated inflammatory molecules and pathways including cytokines, chemokines, innate immune cells, and adhesion molecules mediate the instigation and progression of DKD.
- Inflammatory mediators are under study as diagnostic and prognostic biomarkers and potential therapeutic targets.

Proinflammatory Cytokines

Involvement of proinflammatory cytokines in the pathogenesis of DKD is well recognized.[38] Cytokines are a group of polypeptide signaling molecules that promote autocrine, paracrine, and juxtacrine signaling as a part of the innate immune response. They are secreted from several cell lines including B and T lymphocytes; mast cells; macrophages; fibroblasts; stromal cells; and glomerular, endothelial, tubular, and mesangial cells of the kidney.[25,39-41] Production of cytokines is induced by numerous stimuli characteristic of diabetes, including hemodynamic and metabolic abnormalities (Table 1).

Among the most extensively studied mechanisms involved in the pathogenesis of DKD are the actions of interleukin 1 (IL-1), IL-6, IL-18, and tumor necrosis factor alpha (TNF-α). IL-1 stimulates production of prostaglandin E and the release of phospholipase A2 and has therefore been implicated in the development of intraglomerular hemodynamic abnormalities related to prostaglandins.[43] IL-1 activity is also linked to increased permeability of vascular endothelial cells.[75] IL-6 plays a critical role in facilitating the transition from innate to adaptive immune responses as well as in neutrophil infiltration of the tubulointerstitium.[76,77] Kidney biopsy studies have detected IL-6 mRNA in resident mesangial, interstitial, and tubular cells, as well as in infiltrating inflammatory cells.[78,79] In addition to its effects on immunity, IL-6 may influence extracellular matrix dynamics.[80] Indeed, increased IL-6 may promote overall kidney hypertrophy, thickening of the glomerular basement membrane, and podocyte hypertrophy and cell cycle arrest.[46,47,81] Overexpression of IL-6 is correlated with albuminuria, and recent studies show that urine and serum IL-6 levels are elevated even in patients before albumin excretion increases.[46] IL-18 induces release of interferon γ and other cytokines and increases expression of adhesion molecules and induction of endothelial apoptosis.[82,83] High serum levels of IL-18 have been noted in patients with macroalbuminuria, suggesting that IL-18 may play a specific role in the development of microvascular kidney complications in diabetes.[84,85]

Early in the course of diabetes, both glomerular and tubular cells increase expression of TNF-α mRNA.[86] Urine and serum concentrations of TNF-α are elevated in patients with DKD compared to both patients with uncomplicated diabetes and nondiabetic controls, independent of albuminuria.[52,87,88] TNF-α has multiple actions: induction and differentiation of inflammatory cells, cytotoxicity to various kidney cells including activation of apoptosis, altered glomerular hemodynamics, increased vascular endothelial permeability, and increased oxidative stress.[53,54,89-91] TNF-α exerts its biological actions via interaction with 2 cell surface receptors: TNF receptor 1 (TNFR1) and TNF receptor 2 (TNFR2) that show promise as new prognostic DKD biomarkers.[25,91]

Chemokines

Chemokines are a subgroup of cytokines that function as "chemoattractant" molecules. Together with their receptors, chemokines play a key role in inflammatory cell recruitment, migration, and interaction, as well as in cellular adhesion, differentiation, and tissue damage in the setting of DKD.[92-94]Current evidence supports the roles of several members of the inflammatory chemokine family in DKD pathogenesis, particularly monocyte-chemotactic protein-1 (MCP-1)/chemokine C-C motif-ligand 2 (CCL2), C-X3-C motif chemokine (CX3CL1), and C-C motif chemokine 5.[25,95] As for other cytokines, the chemokines exhibit upregulation in response to metabolic and hemodynamic features of the diabetic milieu, such as hyperglycemia; high levels of AGE, growth factors, protein kinase C, and reactive oxygen species; and mechanical stretching of the vasculature.[25]

Elevated levels of MCP-1/CCL2 have been reported in biopsied kidney tissue and urine from patients with DKD.[96] MCP-1/CCL2 is involved in the release of monocytes from the bone marrow and plays a role in macrophage infiltration of the tubulointerstitium in DKD.[57,97]