Novel Therapies for Diabetic Kidney Disease

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The number of people diagnosed with diabetes is rising throughout the world, which in turn drives upward the global frequency of diabetic kidney disease (DKD). Individuals with DKD are at an increased risk for premature death, cardiovascular disease, and other severe illnesses that result in frequent hospitalizations and increased health-care utilization. Current treatments concentrate on controlling hyperglycemia and hypertension with the specific use of renin-angiotensin system inhibitors. Although such measures reduce the risk of progressive kidney disease, DKD remains the leading cause of ESRD and the major risk amplifier for death in this population. Therefore, novel therapeutic approaches are urgently needed. Ideas for novel targets for therapy are founded on recent advances in understanding DKD mechanisms that are based on experimental models and human observations. The purpose of this review is to describe the epidemiology and present knowledge of DKD pathophysiology as the basis for novel therapies including inhibitors of Janus kinases (JAK), protein kinase C, fibrosis, advanced glycation end products treatments, and endothelin.

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Background

Epidemiology of Diabetic Kidney Disease: the Leading Cause of CKD and End-Stage Kidney Disease

One of the most important microvascular complications of diabetes is kidney disease; until recently it was referred to as diabetic nephropathy. The National Kidney Foundation's Kidney Disease and Outcomes Quality Initiative Clinical Practice Guidelines for diabetic and chronic kidney disease currently recommends replacing this term with the term diabetic kidney disease (DKD).[1] DKD is classified as kidney disease that develops as a result of the diabetic state, including several complex metabolic derangements. The association between diabetes and kidney damage has been recognized since the 2nd century.[2] It is a leading cause of ESRD throughout the world. Approximately 20% to 30% of people with type 1 diabetes and approximately 40% of people with type 2 diabetes will develop DKD. Approximately 12% of adults, or to put this number in perspective, more than 20 million of the adults in the United States, are estimated to have CKD. Most of these 20 million people (or >70%) have kidney disease attributable to diabetes and/or hypertension (HTN). Per the Centers of Disease Control, more than 35% of people with diabetes aged 20 years and older have CKD. It is important to note that kidney disease is now the 9th leading cause of death in the United States.[3,4]

The number of people diagnosed with diabetes is reaching stunning heights. In 2011, per the International Diabetes Federation, 366 million or 8.3% of adults worldwide had a diagnosis of diabetes, with an expected increase to 552 million people by 2030.[5] Unfortunately, changes in kidney structure characteristic of DKD, such as diffuse or nodular diabetic glomerulosclerosis, can be detected not only in people with diabetes but also in people with impaired glucose tolerance or metabolic syndrome.[6-8] This means that some additional 280 million adults worldwide, projected to reach 398 million by 2030, are at risk for kidney disease.[9] In the United States alone in 2010, 8.3% or 25.8 million people aged 20 years or older had diabetes: 18.8 million diagnosed and 7.0 million undiagnosed. The prevalence increased in older age groups and reached 26.9% (or 10.9 million people aged >65 years.).[6,9] Over the last few decades, much of the globe has experienced another epidemic that is considered a driving force behind the record numbers of people diagnosed with diabetes and impaired fasting glucose—obesity.[10,11]

In conjunction with the rising numbers of people with diabetes, the prevalence of CKD is escalating. According to an analysis of the 1988 to 1994, 1999 to 2004, and 2005 to 2008 Third National Health and Nutrition Examination Surveys, the prevalence of DKD in the U.S. population grew from 2.2%, to 2.8%, up to 3.3%. DKD was defined as diabetes with albuminuria (ratio of albumin to creatinine > 30 mg/g), impaired kidney function (estimated glomerular filtration rate [eGFR] < 60 mL/minute per 1.73 m^2), or both.[12] Similar trends are noticed elsewhere in the world. The "Prevalence and risk factors for microalbuminuria in a referred cohort of type 2 diabetic patients: a global.[13]

ESRD has traditionally been the most recognized outcome of CKD, only 2% of patients will progress to

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this stage.[14,15] The association of CKD with an increased risk for cardiovascular disease (CVD) has long been recognized. If kidney function is mildly or moderately decreased, then patients are 20 times more likely to die, most commonly of CVD, before needing kidney replacement therapy in the form of dialysis or transplantation. A recent analysis of 15,046 participants in the Third National Health and Nutrition Examination Surveys showed that kidney disease accounts for nearly all of the increased all-cause and CVD mortality risk observed in people with type 2 diabetes. The mortality rate in individuals with diabetes but without kidney disease was 11.5% (95% confidence interval [CI], 7.9-15.2%) whereas the rate in individuals with diabetes and kidney disease was 31.1% (95% CI, 24.7-37.5%), which represents an absolute risk difference of 23.4%.[16] In addition, hospitalization rates are relevant clinical outcomes because they are a proxy for severe illness as well as a measure of utilization of expensive health-care services. Data from the United States Renal Data System and from a broad payer-mix across the state of Washington show an advancing graded effect of CKD on risks of hospitalization and inpatient deaths.[17]

CLINICAL SUMMARY

- In 2011, 366 million people throughout the world have diabetes.
- About one-third of them will develop kidney disease in spite of optimal medical management.
- Pathogenesis of diabetic kidney disease is complex; involved local and systemic derangements are triggered by metabolic abnormalities associated with diabetes.
- New therapies for diabetic kidney disease are formulated to target different molecular mechanisms involved in pathogenesis.

Natural History and Clinical Manifestations of Diabetic Kidney Disease

The natural history of DKD has changed dramatically over the last 6 decades, probably because of improved glycemic and blood pressure control and better overall diabetes care. In the early 1980s, the risk of progression from microalbuminuria (urinary albumin excretion rate 20-200 μg/minute or albumin-to-creatinine ratio of 30-299 mg/g) to macroalbuminuria (albumin excretion rate > 200 μg/min or albumin-to-creatinine ratio > 300 mg/g) in type 1 diabetic patients was estimated to be 80% over 10 years.[18-21] More recent prospective studies estimated that only approximately 30% of patients with type 1 diabetes will progress from micro- to macroalbuminuria.[22-26] Classically, the natural history of DKD was one of clinical silence for years or decades, followed by the development of microalbuminuria, progression to macroalbuminuria, and eventually the loss of kidney function leading to ESRD. Despite clinical silence, underlying kidney damage develops, and once the stage of macroalbuminuria is reached, structural lesions in the kidney are advanced. It is important to note that many patients develop structural lesions and kidney failure without developing albuminuria.[27]

Diabetic patients who eventually develop clinically manifest DKD after prolonged periods of quiescence present in several ways. In a series reported by Ritz and colleagues, approximately 70% of patients had presented with classical features of DKD (large kidneys, albuminuria/proteinuria, with or without retinopathy). However, approximately 20% to 30% had small kidneys or other features suggesting another form of CKD superimposed on DKD. Further, the mode of presentation of impaired kidney function may be acute kidney injury (AKI) in patients with diabetes, either as abrupt worsening of CKD and/or conventional AKI (eg, ischemic, toxic, etc). If patients recover from AKI, then they are at an increased risk for accelerated DKD progression and ESRD.[28,29]

Pathology of DKD

Type 1 Diabetes

In 1959, Gellman and colleagues reported findings on kidney biopsies from living people with diabetes. Before this time, the kidney pathology of patients with diabetes was only described at autopsy.[30] The earliest changes that can be measured are the thickening of the glomerular basement membrane (GBM) and tubular basement membrane.[31] These changes are followed by the hyalinosis of the afferent and efferent arteriole along with glomerulopathy comprising mesangial expansion, which can be detected as early as 5-7 years after the onset of diabetes, followed by generalized and diffuse diabetic glomerulosclerosis and nodular glomerulosclerosis (Kimmelstiel-Wilson nodules).[32] The onset of albuminuria is associated with GBM thickening, endothelial disruption, and podocyte injury and loss. Mesangial expansion leading to the loss of the glomerular filtration surface area is closely associated with a reduced glomerular filtration rate.[33] Abnormalities of the junction of the proximal tubule with the glomerulus, which leads to the separation of the glomerulus from its tubule (atubular glomeruli), have been recently recognized as another hallmark of advancing kidney disease in diabetes.[34] Approximately 50% of patients with normoalbuminuria have various forms or degrees of glomerulopathy. It is interesting to note that in 1 series several patients with no increase in albuminuria had severe glomerulopathy consistent with that seen in the patients with high-grade albuminuria.[34]

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