Treatment of Diabetic Kidney Disease With Hypertension Control and Renin Angiotensin System Inhibition

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The global incidence and prevalence of diabetes continues to expand due primarily to the influences of obesity and the contribution of obesity to the progression of type 2 diabetes mellitus. The rising prevalence of type 2 diabetes has driven an increase in rates of CKD in the past 3 decades in the United States. In turn, so have the rates for complications related to type 2 diabetes including CKD, eg, diabetic kidney disease (DKD). Although incident rates for DKD have stabilized in the recent years, diabetes continues to be the leading cause of ESRD in the United States. The United Kingdom Prospective Diabetes Study data and other population-level studies support that lowering blood pressure reduces kidney disease and cardiovascular disease in patients with type 2 diabetes. Furthermore, strategies targeting renin-angiotensin-aldosterone system interruption have shown to improve DKD outcomes to a greater extent than other classes of antihypertensive regimens.

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INTRODUCTION

Data fully support that the prevalence of diabetes mellitus is growing and is expected to increase the total number of affected patients from 415 million in 2015 to 642 million in 2040.[1] There is a general consensus that this global expansion of diabetes is being driven by an obesity epidemic, and further, the diabetes-related complications such as kidney disease are accentuated by the metabolic complications of obesity such as hypertension.[2] In this context, roughly a third of patients with diabetes will develop kidney disease (eg, diabetic kidney disease [DKD]), which is the leading cause of CKD and ESKD globally. Although rates of DKD in the United States have stabilized in the recent years, there are segments of the population still at risk for both development and progression of DKD and attributable complications such as hypertension and cardiovascular disease. This would include middle-aged African-Americans, Native Americans, and Hispanics.[3] In this context, the management of hypertension is one of the leading modifiable risk factors to reduce the burden of albuminuria in DKD, progression of DKD, and concomitant risk of cardiovascular disease.

There is an initial hyperfiltration phase in DKD that is characterized by an increase in glomerular filtration rate (GFR), followed by albuminuria, and then an eventually progressive reduction in GFR. Hypertension is a common feature of DKD, but importantly, the presence of DKD heightened the risk for other comorbidities such as dysglycemia and dyslipidemia, which collectively heightens the risk for fatal and nonfatal cardiovascular events.[4] In this regard, although combined blood pressure (BP), lipid and glycemic control, and smoking cessation have resulted in some stabilization of kidney end points in those with diabetes, the risk of cardiovascular complications and ESKD remains substantial.[5,6] There is a significantly higher prevalence of hypertension in those with DKD compared to the general population, and the prevalence increases in a graded fashion as the estimated glomerular filtrate rate (eGFR) declines.[7,8] Furthermore, BP control in this high-risk group, to a greater extent than other risk reduction strategies, contributes to cardiovascular disease risk reduction in DKD.[7,9] In this regard, there is a strong, continuous relationship between reductions in eGFR, an albumin:creatinine ratio ≥30 mg/gm, and subsequent cardiovascular event rates.[10] The increased morbidity, mortality, and high overall cost of health care in patients with DKD are in large part due to an increased risk for adverse cardiovascular outcomes such as heart failure, myocardial infarction, stroke, and ESKD and their many complications.[11,12]

Hypertension and Diabetic Kidney Disease

As mentioned previously, hypertension has a higher prevalence in those with diabetes and in those with DKD; the presence of hypertension increases with each progressing stage, approaching 90% for those with ESKD.[13] While many consider that albuminuria or overt kidney disease may precede the development of hypertension in type 1 diabetes,[14] hypertension mostly antedates the development of albuminuria or reduced eGFR in those with type 2 diabetes attributable to shared risk factors such as obesity, dyslipidemia, and the cardiorenal metabolic syndrome.[15] The majority of those with newly diagnosed type 2 diabetes (without proteinuria) already have hypertension, with the prevalence ranging from 58% to as high

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as 70%.[16] The prevalence of hypertension continues to increase in a graded, continuous manner in earlier stages (eg, stage 1) to roughly 80-90% in advanced CKD, eg, stages 4 and 5.[8] Data from the United Kingdom Prospective Diabetes Study, the STENO group, among other population-level studies further support the presence of hypertension that contributes to the progression of DKD and the increased incidence of cardiovascular disease events, management of which substantially reduces cardiovascular risk.[17-19]

There is a heightened awareness then to identify early for those at the highest risk for a cardiovascular event. In this regard, there is an increasing interest in the identification of various biomarkers and BP patterns in those with DKD. Compared to hypertensive patients with nocturnal dipping, a nocturnal "nondipping" BP pattern in type 1 diabetic individuals with no albuminuria predicts future microalbuminuria and onset of DKD.[20] Furthermore, a recent prospective study on hypertensive, CKD stage 2-4 patients, including those with diabetes, found greater rates of morning BP elevations and nondipping in diabetics, and the risk of nondipping was higher for stage 3-4 CKD for diabetics compared to nondiabetics.[21] The alterations in BP patterns and hemodynamics that prognosticate future cardiovascular events are a manifestation of a number of mechanisms that contribute to the development of DKD, including inappropriate activation of the sympathetic nervous system and the renin-angiotensin-aldosterone system (RAAS), increased sodium (Na^+) reabsorption, and volume retention as well as endothelin 1 release.[16] Each of these mechanisms induce activation of diverse signaling pathways in kidney endothelial, mesangial, epithelial, tubular cells, and podocytes that trigger various endocrine, inflammatory, and oxidative pathways that regulate nitric oxide, vascular tone, and volume retention.[22,23] Most of these pathogenetic factors are integral to the acceleration of DKD and cardiovascular disease risk. Thus, they serve as potential targets for the management of hypertension and DKD.

Despite ongoing study of novel therapies including inhibitors of oxidation, protein kinase C, fibrosis, xanthine oxidase, chemokine modulation, matrix mettaloproteinase, selective endothelin receptors, dipeptidyl peptidase-4 (DPP-4), sodium glucose cotransporter-2 (SGLT-2), and activators of vitamin D receptor, the inhibition of RAAS along with optimal control of glycemia and BP remains the cornerstone of managing DKD.[24-26] In addition, despite widespread understanding and adoption of RAAS inhibition in these patients, there remains a significant risk for the progression of DKD and cardiovascular disease. Therefore, continued exploration for alternative risk reduction strategies is imperative.

CLINICAL SUMMARY

- Hypertension is highly prevalent in patients with DKD.
- Treatment of hypertension in patients with DKD helps with reduction of cardiovascular risk and slows progression of renal disease.
- Inhibition of RAAS remains a cornerstone of therapy for managing DKD.
- Significant residual risk remains in these patients in spite of maximal RAAS inhibition and ongoing exploration for alternative risk reduction strategies is imperative.

The Renin-Angiotensin-Aldosterone System in Diabetic Kidney Disease

The diabetic milieu including insulin resistance and the compensatory hyperinsulinemia, hyperglycemia with advanced glycation end products, reactive oxygen species, and humoral and hormonal pathways (eg, Ang II, aldosterone, and endothelin 1) causes alterations in metabolic, hemodynamic, and inflammatory pathways that contribute to the development and progression of DKD.[22,23,27] The exploration of pathways that contribute to DKD has increased our understanding and has facilitated many therapeutic targets in the management of DKD.[25]

From an evolutionary perspective, the RAAS confers a survival advantage in the maintenance of BP via regulation of vascular tone and intravascular volume in situations of acute stress or injury.[28] In contrast to the survival advantage conferred in acute situations, chronic activation of the RAAS results in hemodynamic and nonhemodynamic changes that increase the risk and severity of kidney and cardiovascular disease. The traditional view of the RAAS as an endocrine system includes angiotensin production in the liver cleaved by renin produced from the juxtaglomerular apparatus (JGA) to form Ang I, which is then cleaved to Ang II by angiotensin-converting enzyme (ACE) produced mainly from the parenchyma of the lungs. Aldosterone is released in response to Ang II binding to the Ang II type 1 receptor in the adrenal cortex.[29]

Despite a state of salt and volume excess, DKD is associated with inappropriate chronic activation of the RAAS.[30] However, it is the dysregulation of paracrine/autocrine effects of locally produced "tissue" RAAS components[31,32] in the kidneys, heart, blood vessels, and other tissues that may contribute the most to the end-organ damage observed in DKD.[33]

The primary mechanism of RAAS activation in diabetes is not fully understood. The "tubular hypothesis" of diabetic hyperfiltration suggests that increased filtration and then proximal tubular absorption of glucose and sodium chloride decreases solute delivery to the macula densa and activates glomerular hyperfiltration and renin synthesis and release from the JGA.[34] Activation of the G-protein–coupled receptor (GPR91) in the kidney by high glucose and succinate produced via the citric acid cycle is another proposed link between hyperglycemia and renin release from the JGA.[35] An augmented glomerular hyperfiltration response due to increased sensitivity of the kidney to high levels of circulating amino acids in