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Diabetic Kidney Disease: Chronic Kidney Disease and Diabetes

Preface

Jerry Yee, MD, Guest Editor

The traditional clinical hallmark of chronic kidney disease (CKD) in diabetic microvascular disease of the kidney has been overt proteinuria; once manifest, diabetic nephropathy was considered apparent. The term “nephropathy” classically was associated with foamy urine, hypertension, and renal edema formation attributable to sodium retention and fostered by impaired kidney function and hyperglycemia. In fact, the simultaneous diagnosis of the triad of proteinuria, high blood pressure, and edema actually indicated that “the horse was out of the barn”; diabetic kidney disease was already present and likely had been for years.

To emphasize the impact of diabetes on the renal parenchyma at much earlier stages of the disease, the National Kidney Foundation’s Kidney Dialysis Outcomes Quality Initiative Clinical Practice Guidelines and Clinical Practice Recommendations for Diabetes and Chronic Kidney Disease now promote the term “diabetic kidney disease” (DKD) as a nonproteinuric designation of CKD in type 1 or type 2 diabetes.¹ DKD will occur in 30–40% of people with diabetes, and one-third of these individuals may develop kidney failure. DKD occurs in patients with either type 1 or type 2 diabetes; however, patients with type 2 diabetes often present with a mixed picture of atherosclerotic renal changes coincident with diabetic histological findings. Judgment of whether hypertension or diabetes is the dominant lesion, in the absence of a kidney biopsy, is typically predicated on whether a renal ultrasonogram depicts small or normal-to-large kidneys. In the former instance, hypertensive angiosclerosis

is considered causative, whereas the latter circumstance coincides with DKD, irrespective of the level of proteinuria.

Importantly, when microalbuminuria, macroalbuminuria, or intermediate levels of protein excretion are detectable, the glomerular filtration rate (GFR) has usually passed through the stage of hyperfiltration. Thus, DKD is already present at a normal or slightly less-than-normal GFR.

Principally, kidney function is declining with the GFR. At this time, estimation of the GFR must be carried out, and although the clarion call for all patients with diabetes to have their urine tested for albuminuria has gone out, determination of the GFR from an estimating equation is indeed more important.² Hopefully, teamwork among governing bodies within primary care specialties, pathologists, and quality care consortia will demand serum creatinine standardization and mandatory laboratory reporting of the GFR.

Reliance on the Cockcroft-Gault equation, which estimates creatinine clearance as a surrogate for GFR, is passé and rife with misinterpretation in DKD for three reasons: 1) the equation was not validated in a patient population with a large proportion of diabetes; 2) the equation must be normalized to a body surface area of 1.73 m², which is almost never done and is especially important in obese individuals because of the weight term in the numerator; and 3) glycemic control must be evident at the time of creatinine clearance estimation because hyperglycemia can either promote hyperfiltration or induce extracellular fluid volume depletion, thereby nullifying the validity of the creatinine clearance.

Certain ethnic groups—especially Pima Indians and African Americans—are genetically predisposed to DKD. In fact, 3.2 million African Americans > 20 years of age have diabetes. This is 13.3% of this population and represents a nearly two-fold relative risk compared to non-Hispanic whites.³ Pima Indians, with a prevalence of diabetes in ~ 50% of adults, demonstrate > 20 times the rate of new cases of kidney failure than the general U.S. population, with 90% of cases resulting from DKD. Moreover, CKD is also the foremost cause of death from diabetes in these populations.

DKD has notable characteristics that distinguish it from other forms of CKD. Patients are often more anemic in DKD than in nondiabetic CKD. Inflammatory inhibitors of erythropoiesis and proteinuria, with losses of iron bound to iron-carrying proteins, have been variably implicated as causative.^{4,5} However, the less well appreciated interstitial compartmental lesion of DKD may be the more important factor. Progressive fibrosis of this region of the kidney precludes the adaptive increase of endogenous erythropoietin production in response to increasing levels of hypoxia sensed by the organ. When inflammation, proteinuria, or both are also present, DKD patients become highly susceptible to the anemia of CKD. This is a substantial risk multiplier for patients with diabetes, with high prevalence rates of left ventricular hypertrophy or heart failure.

Patients with diabetes are also predisposed to higher rates of kidney stone formation. Insulin resistance leads to more acidic urine, and, consequently, uric acid stone formation is higher in this population. This enhanced risk is also noted in people with the cardiometabolic syndrome and in those who are obese. In addition, kidney stones of other types, such as calcium-containing stones, are also more frequent in diabetes, but the relative risk for uric acid lithiasis is higher than in other stone types.

Endocrinologists have long espoused the confounding of glycemic control in the presence of renal impairment. Gluconeogenesis and glycolysis are impaired, yet there is insulin resistance.⁶ Consequently, patients with diabetes and kidney disease are prone to hypoglycemia because the kidney cortices can provide up to

half of gluconeogenesis in the post-absorptive state. Furthermore, these individuals will more easily incur hyperglycemia from insulin resistance, which promotes volume depletion that in turn strongly activates the sympathetic nervous system and begets subclinical diabetic ketoacidosis. Finally, persistent renin-angiotensin-aldosterone system (RAAS) activation from ongoing sympathetic nervous system stimulation encourages proteinuria and renal fibrosis.⁷

Another endocrinological manifestation that is more apparent in DKD is adynamic bone disease (ABD).⁸ This form of CKD mineral and bone disorder is characterized by a marked decrement in bone turnover in the absence of osteoid accumulation. ABD occurs more frequently in DKD and may be apparent before CKD Stage 5. This low-volume bone disorder is associated with lower parathyroid hormone levels, increased fracture risk, and cardiovascular calcification. The pathophysiology of ABD in DKD and other forms of CKD remains enigmatic. However, the adverse consequences that attend ABD are not. Principally, when calcium and phosphorus are not set in bone, they migrate to ectopic valvular and vascular sites, aggravating coronary artery disease and peripheral artery disease. The clinical manifestation of this example of Monckeberg's medial calcific sclerosis is demonstrated by the high pulse pressures that characterize CKD and DKD.

The alchemy of hypertension and diabetes for the kidney is particularly pernicious and is catalyzed by prolonged cigarette smoking, which has even been shown deleterious in nondiabetic CKD.⁹ In DKD in type 2 diabetes, the most common histological findings would be an admixture of diabetic glomerulosclerosis and hypertensive nephrosclerosis with tubulointerstitial involvement—not classical Kimmelstiel-Wilson lesions. The U.K. Prospective Diabetes Study forcefully instructed us that 1) patients with diabetes with seemingly trivial blood pressure elevations of 2 mmHg are fraught with significant risk for future renal impairment, and 2) blood pressure control, at least in the short term, is more important than glycemic control.¹⁰ Indeed, it has been difficult for the diabetologist in all of us to reconcile this notion in a

disorder defined by glucose. (“It’s the blood pressure, stupid!”)

The Appropriate Blood Pressure Control in Diabetes trial in type 2 diabetes was informative in terms of defining probabilities of adverse renal and cardiovascular outcomes.¹¹ Baseline overt albuminuria and autonomic neuropathy strongly predicted future cardiovascular events during 5 years of follow-up. In addition, overt albuminuria significantly predicted future heart failure, whereas autonomic neuropathy was a harbinger of stroke. Interestingly, CKD in general invokes adverse cardiovascular sequelae, and this occurs at ~ 40 ml/min/1.73 m², about midway between CKD Stages 3 and 4. Therefore, one must consider the addition of CKD to diabetes a risk multiplier for cardiovascular disease, all of which is aggravated by the anemia of CKD.

Fortunately, answers to the vexing problems of DKD remain, at least in part, before us. Many established treatments remain the same and hopefully will be complemented by new therapies on the horizon. Appropriate nutritional intervention reduces both hemoglobin A_{1c} levels and kidney stone frequency. Angiotensin-converting enzyme inhibitors and angiotensin-2 receptor blockers reduce blood pressure and offset the pathobiology of DKD, a significant portion of which is related to the RAAS. The recommendations of Gaede et al. promote the concept of multidimensional therapy to limit diabetic complications of all types.¹² This group is laudable in that it has followed the instructions of our diabetes educators far better than we have.

In this From Research to Practice section, four authors state their respective cases of how to diagnose, analyze, and treat DKD within their particular area of expertise. First, Neeta Bahal O’Mara, PharmD, BCPS, describes the problem of anemia of CKD and its aggravation by the diabetic state (p. 12). The author defines anemia and delineates its impact on patient health. She also provides a balanced treatment approach that uses iron and appropriate and safe amounts of erythropoiesis-stimulating agents (ESAs). The state of hyporesponsiveness to ESA therapy is also reviewed.

In our second article, Sarah Tomasello, PharmD, BCPS, underscores

the underappreciation of secondary hyperparathyroidism of renal origin and vitamin deficiency in CKD and the deleterious effects of derangements of bone and mineral metabolism in DKD (p. 19). She discusses the non-intuitive relationship between accelerated cardiovascular risk and bone and mineral metabolism in conjunction with a review of clinical practice recommendations that emphasizes directed pathophysiologically based drug therapy with strategies to optimize patient medication adherence.

Next, Patricia Weber, MS, RD, CDE, reinforces the role of diet in treatment of bone and mineral metabolism in CKD (p. 26). The controversy of protein restriction emerges once again, and the author reviews the concept of the protein-digestibility-corrected amino acid score. The application of this index provides support for dietary protein alteration to a soy-based approach in CKD. In addition, Weber emphasizes the importance of careful micronutrient assessment and explains how its appropriate application facilitates the achievement of other therapeutic targets such as hypertension.

With regard to the latter, Susan Steigerwalt, MD, FACP, critically

reviews our current state of knowledge in hypertensive kidney disease management and convincingly enumerates an approach that should reduce the blood pressure of diabetic patients (p. 30). She presents an invaluable guidebook to determining the primary reason(s) why patients do not obtain their blood pressure goals. Finally, she outlines a realistic vision of hypertension treatment in the not-so-distant future.

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