Update on Diabetic Nephropathy: Core Curriculum 2018

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Diabetic kidney disease and diabetic nephropathy are the leading cause of end-stage kidney disease in the United States and most developed countries. Diabetes accounts for 30% to 50% of the incident cases of end-stage kidney disease in the United States. Although this represents a significant public health concern, it is important to note that only 30% to 40% of patients with diabetes develop diabetic nephropathy. Specific treatment of patients with diabetic nephropathy can be divided into 4 major arenas: cardiovascular risk reduction, glycemic control, blood pressure control, and inhibition of the renin-angiotensin system (RAS). Recommendations for therapy include targeting a hemoglobin A_{1c} concentration < 7% and blood pressure < 140/90 mm Hg with therapy anchored around the use of a RAS-blocking agent. The single best evidence-based therapy for diabetic nephropathy is therapy with a RAS-blocking medication. This Core Curriculum outlines and discusses in detail the epidemiology, pathophysiology, diagnosis, and management of diabetic nephropathy.

Complete author and article information provided before references.

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Epidemiology

Diabetic kidney disease occurs in patients with diabetes mellitus (DM) and reduced kidney function that can be from many diverse causes, including hypertensive nephrosclerosis and unresolved acute kidney failure. Diabetic nephropathy is a diagnosis that refers to specific pathologic structural and functional changes seen in the kidneys of patients with DM (both type 1 and type 2 [T1/T2DM]) that result from the effects of DM on the kidney. These changes result in a clinical presentation that is characterized by proteinuria, hypertension, and progressive reductions in kidney function.

The risk for the development of diabetic nephropathy has a genetic component that is likely polygenetic. The prevalence of diabetic nephropathy varies among racial and ethnic groups such that African Americans (potentially by *APOL1* gene variants), Native Americans, and Mexican Americans have increased risk as compared with European Americans. Although an argument can be made that barriers to care contribute to this discrepancy in prevalence, it is likely not the sole factor, such that genetic differences in these populations must also play a role. Familial studies have demonstrated clustering of diabetic nephropathy. Patients with DM with a first-degree relative with T1/T2DM and diabetic nephropathy have substantially more risk for developing diabetic nephropathy than those without an affected relative. This familial clustering has also been well documented in the Pima Indian population. Ongoing research is attempting to identify specific genetic factors and genes associated with the development of diabetic nephropathy. Although several candidate genes, including glucose transporter 2, transforming growth factor β, and endothelial nitric oxide synthase, have been identified, isolating a definitive causal pathway has proved to be elusive because there is no simple Mendelian inheritance and the interplay of several genes is likely involved and may differ between populations.

Additional Readings

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Pathophysiology

The pathophysiology leading to the development of diabetic nephropathy and resultant end-stage kidney disease follows from the diabetic milieu leading to the generation and circulation of advanced glycation end products, elaboration of growth factors, and hemodynamic and hormonal changes. These lead to the release of reactive oxygen species and inflammatory mediators. Collectively,

The Core Curriculum aims to give trainees in nephrology a strong knowledge base in core topics in the specialty by providing an overview of the topic and citing key references, including the foundational literature that led to current clinical approaches.

these changes result in glomerular hyperfiltration, glomerular hypertension, renal hypertrophy, and altered glomerular composition, which is manifested clinically as albuminuria and hypertension. Pathologically, the kidneys undergo several changes, including deposition (in primarily the mesangium) of extracellular matrix, glomerular basement membrane thickening, proliferative changes, and tubular atrophy, ultimately resulting in interstitial fibrosis and glomerulosclerosis (the final common pathway of many kidney diseases). A schema depicting this process is shown in Figure 1.

With the onset of DM, kidney size and weight increase by an average of 15%, and this size increase remains even after progressive reductions in kidney function occur. An examination of kidney tissue reveals thickening of the glomerular basement membrane and expansion of the mesangium. The classic pathologic lesion of diabetic nephropathy is nodular in nature and was first described by Kimmelstiel and Wilson in 1936. The nodules are typically acellular and positive by periodic acid–Schiff stain. Although these nodules are pathognomonic for diabetic nephropathy, they are reported in only 10% to 50% of biopsy specimens from patients with T1/T2DM. Far more common is the diffuse glomerular lesion that is characterized by diffuse mesangial matrix expansion. Arteriolar lesions involving both the afferent and efferent vessels are also prominent and common in DM. Over time, hyaline material replaces the entire vessel wall structure and this is highly specific for DM. Examples of these lesions are shown in Figure 2. It is important to note that lesions similar to both the nodular and diffuse varieties can be seen in other disease states, such as membranoproliferative glomerulonephritis, amyloidosis, and light-chain deposition disease. Specific stains, immunofluorescence staining, and electron microscopy, as well as the clinical history of the patient, will elucidate the specific diagnosis.

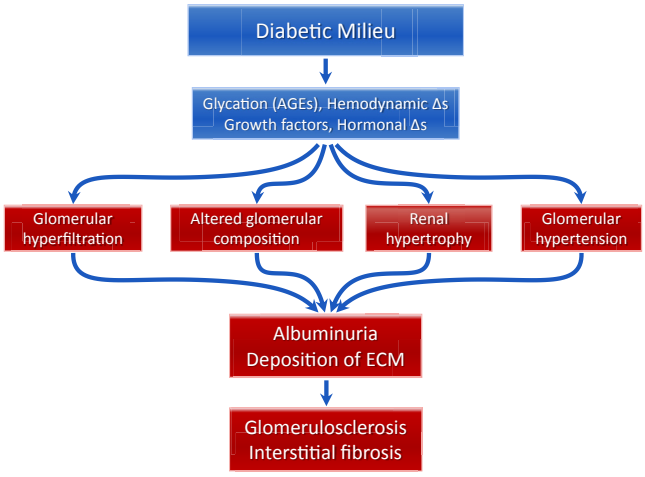

Figure 1. Pathophysiology of diabetic nephropathy. Abbreviations: AGE, advanced glycation end product; ECM, extracellular matrix.

Additional Readings

- Fioretto P, Mauer M, Brocco E, et al. Patterns of renal injury in NIDDM patients with microalbuminuria. *Diabetologia.* 1996;39:1569-1576.
- Fioretto P, Steffes MW, Sutherland DE, Mauer M. Sequential renal biopsies in insulin-dependent diabetic patients: structural factors associated with clinical progression. *Kidney Int.* 1995;48:1929-1935.
- Schwartz MM, Lewis EJ, Leonard-Martin T, Lewis JB, Batlle D. Renal pathology patterns in type II diabetes mellitus: relationship with retinopathy. The Collaborative Study Group. *Nephrol Dial Transplant.* 1998;13:2547-2552. ★ **ESSENTIAL READING**

Natural History

Case 1: *A 52-year-old woman with T2DM diagnosed 1 year ago is referred to you for evaluation of proteinuria noted first 3 months ago. Family history is positive for diabetic nephropathy. Physical examination shows blood pressure (BP) of 140/95 mm Hg and normal fundal examination findings and is otherwise unremarkable. Laboratory studies show serum creatinine concentration of 0.9 mg/dL, and urinalysis shows protein (3+) with unremarkable sediment.*

Question 1: Which of the following statements is correct?

a) The finding of proteinuria 6 months after the diagnosis of T2DM is strongly against the diagnosis of diabetic nephropathy.
b) Normal fundal examination findings should strongly suggest an alternative diagnosis.
c) The most likely diagnosis is diabetic nephropathy.
d) Increases in BP in the majority of patients with diabetic nephropathy are seen only after decline in kidney function.

For the answer to the question, see the following text.

The natural history of diabetic nephropathy in patients with T1DM was initially characterized in the late 1970s by Kussman et al by examining death records of patients with juvenile-onset DM who were classified as having died of kidney failure. This analysis resulted in an understanding of the true untreated natural history of diabetic nephropathy due to T1DM as it was before the advent of therapy for this complication of DM. Based on this study, proteinuria appears 11 to 23 years after the T1DM diagnosis, serum creatinine concentration begins to increase after 13 to 25 years, and end-stage kidney disease develops after 18 to 30 years. With the subsequent development of more sensitive assays to detect urinary albumin excretion, small amounts of albumin in the urine (microalbuminuria; 30-300 mg/g creatinine) were noted to precede the development of overt proteinuria (macroalbuminuria; >300 mg/g creatinine) in most patients, occurring 5 to 10 years after the diagnosis of DM. Presently, microalbuminuria and macroalbuminuria are referred to as