Chapter 17 / Diabetic Nephropathy

Richard J. Solomon, MD and Bijan Roshan, MD

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INTRODUCTION

Diabetic nephropathy is the leading cause of end-stage renal disease (ESRD) in the United States, accounting for nearly 40% of incident ESRD (1). Diabetes mellitus (DM) is also an independent and strong risk factor for ESRD ascribed to causes other than diabetes (2), such as hypertension, pyelonephritis, and other forms of glomerulopathies that can lead to chronic renal disease. Here we focus mainly on diabetic nephropathy as a major microvascular complication of both type 1 and type 2 diabetes.

Between 35% and 57% of type 1 diabetics (3–5) and 25% and 46% of type 2 patients with long-lasting diabetes (4,6), develop clinically detectable nephropathy, indicated by proteinuria and/or renal insufficiency. In fact, the prevalence of proteinuria is the same in both types of diabetes, after adjustment for differences in diabetes duration (4,7). Cross-sectional studies indicate that 20% of type 2 DM have microalbuminuria, many at the time diabetes is diagnosed. The prevalence increases to nearly 50% in those with advanced retinopathy (8). Approximately 2–3% of patients with type 2 diabetes progress to overt proteinuria yearly (9).

PATHOGENESIS

Recent large-scale intervention trials have provided compelling evidence for the role of hyperglycemia in the development and progression of nephropathy in type 1 and type 2 diabetes (10,11). However the fact that only a proportion of individuals with diabetes develop nephropathy suggests that factors other than the hyperglycemic environment are involved in the pathogenesis of nephropathy. Genetic, ethnic, and familial factors may also play significant roles in the development of nephropathy. In the Diabetes Control and Complications Trial (DCCT) primary prevention cohort of type 1 patients without retinopathy, no familial concordance for development of diabetic retinopathy was found,
whereas for nephropathy significant correlation was found (12). On the other hand, analysis of the severity of nephropathy did not generally show familial correlation, although for the severity of retinopathy it was significant (12).

Recent investigations have identified a number of candidate gene polymorphism that may contribute to diabetic nephropathy. The angiotensin-converting enzyme (ACE) gene variant with a deletion (D) of a 287 base pair sequence is one such polymorphism. This gene-deletion polymorphism is associated with elevated circulating and tissue activity of ACE (13) and increased risk of left ventricular hypertrophy (14), ischemic heart disease (15), and lacunar cerebrovascular accident (16). A number of studies have found a positive association between the differential display phenotype and the prevalence and rate of progression of nephropathy (17–19). Kunz and his colleagues in their meta-analysis conclude that diabetic nephropathy is not associated with the presence of the ACE-D allele in Caucasians with type I and type II diabetes, whereas the risk for nephropathy seemed to increase by 50% to 70% in type II Asian diabetics (20). Additionally, the T allele of the AGT gene M235T polymorphism has been associated with increased risk of nephropathy (21) whereas the A14 allele of the NOS2 promoter has been associated with a decreased risk (22).

Another basis for genetic/familial clustering of diabetic nephropathy is an increase in vitro sodium-lithium (Na-Li) countertransport activity, a biochemical marker of increased sodium reabsorptive capacity of the kidneys. Increased Na-Li countertransport activity has been found in some groups of patients with essential hypertension (23). Abnormalities of this membrane countertransport system, which has an inheritable component (24), have been found to be associated with diabetic nephropathy (25,26) and to predict the development of microalbuminuria in type 1 diabetes (27). Recently, increased Na-Li countertransport has been identified with a splicing variant of the NHE1 exchanger that alters its affinity for lithium and eliminates its sensitivity to amiloride (28).

How hyperglycemia causes nephropathy is multifactorial and is related to the stages of nephropathy.

**Nephropathy Staging**

Mogensen and his colleagues have developed a staging classification for the evolution of diabetic nephropathy (29–32) (Table 1). This staging pattern is more heterogeneous and possibly the pathogenesis is more complex in type 2 (33), but overall similar patterns are seen in both type 1 and 2 patients (34).

Early after diagnosis of diabetes in both type 1 (35,36) and type 2 (37,38), glomerular filtration rate (GFR) increases. Nephromegaly and glomerular hypertrophy (36,39) accompany this glomerular hyperfiltration. More pronounced reduction in afferent compared to efferent arteriolar resistance may lead to elevated plasma flow in diabetics resulting in an increased GFR (36). Additionally, total capillary surface area increases in early diabetics (39) and both elevated renal plasma flow and increased capillary surface area (that in turn increases glomerular ultrafiltration coefficient) contribute to increased GFR.

Hyperglycemia may directly increase the production of vasodilatory prostaglandins that can contribute to renal hyperperfusion, intraglomerular hypertension, and hyperfiltration. In experimental models, such as the streptozotocin-induced diabetic rat, glomeruli show increased production of vasodilatory prostaglandins (40). Nitric oxide (NO) and atrial natriuretic peptide (ANP) are other vasodilator candidates for inducing hemodynamic changes leading to diabetic hyperfiltration. Elevated levels of ANP have been demonstrated in diabetic rats (41), and a specific ANP receptor antagonist is capable of reducing