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Review Article

Comprehensive approach to diabetic nephropathy

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Abstract

Diabetic nephropathy (DN) is a leading cause of mortality and morbidity in patients with diabetes. This complication reflects a complex pathophysiology, whereby various genetic and environmental factors determine susceptibility and progression to end-stage renal disease. DN should be considered in patients with type 1 diabetes for at least 10 years who have microalbuminuria and diabetic retinopathy, as well as in patients with type 1 or type 2 diabetes with macroalbuminuria in whom other causes for proteinuria are absent. DN may also present as a falling estimated glomerular filtration rate with albuminuria as a minor presenting feature, especially in patients taking renin–angiotensin–aldosterone system inhibitors (RAASi). The pathological characteristic features of disease are three major lesions: diffuse mesangial expansion, diffuse thickened glomerular basement membrane, and hyalinosis of arterioles. Functionally, however, the pathophysiology is reflected in dysfunction of the mesangium, the glomerular capillary wall, the tubulointerstitium, and the vasculature. For all diabetic patients, a comprehensive approach to management including glycemic and hypertensive control with RAASi combined with lipid control, dietary salt restriction, lowering of protein intake, increased physical activity, weight reduction, and smoking cessation can reduce the rate of progression of nephropathy and minimize the risk for cardiovascular events. This review focuses on the latest published data dealing with the mechanisms, diagnosis, and current treatment of DN.

Introduction

End-stage renal disease (ESRD) due to diabetes has been estimated to be 30–47% of all incident cases worldwide [1]. Disparities in the incidence of ESRD from diabetes among ethnic groups have existed for many years, but the magnitude has been increasing. Diabetic nephropathy (DN) develops along with generalized microvascular disease, most often concomitant with macrovascular disease including cardiovascular, cerebrovascular, and peripheral arterial diseases. Patients with DN have a higher risk of mortality, mostly from cardiovascular complications, than diabetic patients without nephropathy [2].

Risk factors

The epidemiology of DN has been best studied in patients with type 1 diabetes, because the time of clinical onset is usually known. The onset of overt nephropathy in type 1 diabetes is typically between 10 and 15 years after the onset of the

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disease. Both environmental and genetic factors have been postulated as DN risk factors. Poor glycemic control, long duration of diabetes, insulin resistance, high blood pressure (BP), advanced age, smoking, race, and genetic predisposition are the main risk factors for the development of DN. Many genes have been implicated as conferring DN risk [3].

DN is a classic complex trait, whose development in a given individual likely reflects contributions from multiple genes whose expression is modulated by environmental factors. Numerous genetic strategies have been used to identify common disease risk loci and genes, including candidate gene analyses, family-based linkage analysis and transmission disequilibrium testing, population-based admixture mapping, and genome-wide association studies (GWAS) [4]. Candidate gene-based association has been the most common approach used to identify susceptibility genes for DN. Genes encoding for angiotensin-converting enzyme, angiotensin II (Ang II) receptor, various aspects of glucose metabolism, lipid metabolism (apolipoprotein E gene polymorphism), extracellular matrix, and inflammatory cytokines have been selected to test for an association with DN based on the pathogenesis of disease [5,6]. Genome-wide linkage analysis facilitates the identification of previously unsuspected genes as risk factors. It is most powerful when the frequency of the polymorphism is low but the effect size is high. An early family-based genome-wide linkage analysis from the Family Investigation of Nephropathy and Diabetes (FIND) research group identified chromosomal loci for susceptibility genes, including 1q, 7q, and 18q linked to estimated glomerular filtration rate (GFR), in a multiethnic collection of families ascertained by a proband with type 2 diabetes and DN [7]. Using linkage analysis and the identification of positional candidate genes under the linkage peaks, others identified polymorphisms in the carnosinase 1 gene on chromosome 18q [8], the adiponectin gene on 3q [9], and the engulfment and cell motility (*ELMO1*) gene on 7p [10] as DN risk genes. GWAS have greater power than linkage analysis to identify polymorphisms when the gene effect size is low, but the frequency of the polymorphism in the population is high. GWAS identified several novel risk loci including—but not limited to—*SLC12A3* [11]; *ELMO1* [12]; 4.1 protein ezrin, radixin, moesin domain containing 3 (*FRMD3*) [13]; and SAM and SH3 domain containing 1 (*SASH1*) gene [14]. Collaboration among many genetic research groups around the world with thousands of samples and clinical databases continue to seek replicable genetic polymorphisms that confer DN risk.

Reflecting an appreciation for genetic–environmental interactions in DN development, an emerging science has evolved defining contributions of epigenetics to the development of DN. A growing number of pathogenetically important microRNAs (miRs) have been identified in DN [15], representing opportunities for risk assessment and therapeutic targeting.

Clinical staging

Renal disease in diabetic patients had been clinically characterized by increasing rates of urinary albumin excretion and decreasing renal function, with at-risk patients marching through the stages of normoalbuminuria, microalbuminuria, overt proteinuria, and finally ESRD. However, with treatment, not only can progression be slowed, but there is also some plasticity in this staging, and regression from a more severe to a less severe stage can sometimes be achieved. In the susceptible, normoalbuminuria progresses to microalbuminuria, macroalbuminuria, and eventually to ESRD. Persistent albumin excretion between 30 mg/d and 300 mg/d is defined as microalbuminuria. Regression from microalbuminuria to normoalbuminuria occurs spontaneously in a substantial proportion of diabetic patients [16]. Nevertheless, patients with persistent microalbuminuria are at high risk of progressing to overt nephropathy and developing cardiovascular disease [17]. Albuminuria in excess of 300 mg/d represents overt nephropathy. Once overt proteinuria occurs, there is concomitant loss of GFR in both type 1 and type 2 diabetes. Hypertension exacerbates GFR loss. Historically, studies dealing with the natural history of DN demonstrated a relentless, often linear but highly variable rate of decline in GFR ranging from 2 mL/min/y to 20 mL/min/y (mean 12 mL/min/y) [18]. However, the rate of decline may be substantially less with tight BP and blood glucose control. In a recent study, the rate of GFR decline ranged from 0 mL/min/y to 4 mL/min/y [19]. Thus, many patients who are well treated may achieve stable renal function for long periods.

Pathogenesis

Hyperglycemia-induced metabolic and hemodynamic stimuli are mediators of kidney injury [20,21]. These activate inflammatory, pro-oxidant, ischemic, and fibrotic pathways leading to mesangial matrix accumulation; podocyte effacement and loss; glomerular basement membrane (GBM) thickening; endothelial dysfunction; tubular atrophy, fibrosis, and dropout; tubulointerstitial inflammation, and renal arteriolar hyalinosis [20].

Hemodynamic factors

The hemodynamic factors contributing to DN involve increased systemic and intraglomerular pressure and activation of various vasoactive hormones, including the intrarenal renin–angiotensin–aldosterone system (RAAS), nitric oxide, vascular endothelial growth factor (VEGF), and endothelin. Hemodynamic changes play an important role, being present early in the disease, exacerbating albumin passage across glomerular capillaries, and contributing to mesangial matrix expansion, podocyte injury, and nephron loss [22].

Metabolic factors

Hyperglycemia accelerates the development of renal disease by increasing intracellular glucose availability. The facilitative glucose transporter, GLUT1 mediates mesangial cell glucose flux, which leads to the activation of signaling cascades favoring glomerulosclerosis, including pathways mediated by transforming growth factor β (TGF-β), advanced glycosylation end products (AGEs), protein kinase C, and various cytokines and growth factors [23]. In addition, decreased phosphorylated p38 (pp38) mitogen-activated protein kinase (MAPK) after chronic glycemic stress may contribute to podocyte cytoskeletal alterations and albuminuria [24].

In chronic hyperglycemia, glucose combines with free amino groups on circulating or tissue proteins. This nonenzymatic process initially forms reversible early glycosylation products and later irreversible AGEs. AGEs activate specific receptors, inducing cellular dysfunction and injury. AGEs contribute to the accumulation of glomerular extracellular