Clinical Manifestations and Natural History of Diabetic Kidney Disease

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KEYWORDS

• Diabetes • Kidney disease • Natural history • Clinical manifestations

KEY POINTS

- Diabetes mellitus, mostly type 2, has become the single most frequent cause of dialysis dependency.
- There are two key interventions to prevent, or at least retard, progression of diabetic kidney disease are blood pressure lowering and blockade of the renin-angiotensin-system.
- Beyond the classical presentation with nephromegaly and proteinuria, an increasing proportion of diabetic patients with CKD presents with minor (or no) proteinuria.

In order to be a competent nephrologist, one has to be a knowledgeable diabetologist.

—Eli Friedman (New York)

EPIDEMIOLOGY OF CHRONIC KIDNEY DISEASE AND END-STAGE KIDNEY DISEASE IN DIABETES

Renal failure in type 2 diabetes has been termed a medical catastrophe of worldwide dimension.[1] In 2001, at the author's unit in Heidelberg, it was found that 49% of incident patients requiring maintenance hemodialysis had diabetes (ie, 98 per million population [pmp] per year), 6% of whom had type 1 diabetes and most of the 94% had type 2 diabetes.[2] This frequency was much higher than the then reported frequency in Germany of approximately 35% of incident patients. The main cause for this underestimate was that the diagnosis of type 2 diabetes is often missed if an oral glucose tolerance test is not performed. Patients with diabetes with chronic kidney disease (CKD) tend to lose weight in the preterminal phase of renal failure.[3] This factor also explains why several reports stated that 10% to 15% of patients undergoing dialysis develop apparent de novo type 2 diabetes (presumably reappearance of type 2

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diabetes after hyperglycemia had disappeared in the preterminal stage of CKD). In patients with CKD, the prevalence of undiagnosed diabetes or prediabetes is high.[4] Importantly, presumed new-onset diabetes after the initiation of hemodialysis is associated with a similarly poor prognosis and survival rate as in patients with known preexisting type 2 diabetes.[5]

In the 1990s, a continuous increase of the incident rates of end-stage renal disease (ESRD) in patients with diabetes was noted both in Europe and in the United States.[6] In proteinuric patients with diabetes, it is only in relatively advanced stages of estimated glomerular filtration rate (eGFR) loss that the risk to develop ESRD exceeds the risk to die of cardiovascular causes. This point was recently confirmed by the Diabetes Mellitus Treatment for Renal Insufficiency Consortium in a meta-analysis of controlled intervention trials.[7] The progressive increase of ESRD in patients with diabetes in the past might have also been, at least in part, the result of improved cardiac care. Interestingly, the rate of patients with diabetes with ESRD per million population has recently stabilized in Europe as well as in the United States. According to the last report of the United States Renal Data System, the annual rate (per million population) of patients with diabetes reaching end-stage kidney disease was 160 pmp and the prevalence of patients with diabetes on dialysis is currently 650 pmp.

Patients with type 2 diabetes with CKD may have classic Kimmelstiel-Wilson disease or alternatively from a type of more nonspecific nephropathy.[8] In the author's clinical series,[2] 70% of the patients had the classic clinical features of Kimmelstiel-Wilson nephropathy (ie, renomegaly, heavy proteinuria with or without retinopathy); varying from year to year, up to 20% had small kidneys, little or no proteinuria, presumably ischemic nephropathy, and between 10% and 20% had primary kidney disease with superimposed type 2 diabetes.

One further mode of presentation of impaired renal function in patients with type 2 diabetes is acute kidney injury (AKI), usually in the form of AKI superimposed on CKD. Patients may or may not recover from AKI, and in the latter case remain dialysis dependent. If the patients recover, accelerated progression and increased risk of ESRD are common.[9,10] If patients with preexisting diabetic nephropathy survive an episode of AKI, the predictors of subsequent fast progression are high baseline serum creatinine, high blood pressure, and high proteinuria; any given level of serum creatinine proteinuria is a risk factor for more rapid development of end-stage kidney disease.[11]

In juvenile patients with type 1 diabetes, the diabetes control an complication trial/epidemiology of diabetes interventions and complications (DCCT/EDIC) trial showed that it takes decades until ESRD is reached.[12] In contrast, juvenile patients with type 2 diabetes have a substantially higher renal risk of early renal failure,[13] a point of considerable concern in view of the increasing frequency of obesity and type 2 diabetes in juveniles.

At what clinical stage can pathologic changes be documented in the kidney? Caramori and colleagues[14] found even advanced glomerular lesions in patients with type 1 diabetes who had normoalbuminuria but lower glomerular filtration rates. Numerous observational studies documented that patients with type 1 or 2 diabetes and advanced loss of GFR might have no proteinuria at all. This finding is presumably not, or at least not fully, explained as the result of the antiproteinuric effect of renin-angiotensin system (RAS) blockade.[15] The underlying renal histology in this subpopulation is not well known.

One specific form of nonproteinuric progressive renal failure has been identified in a prospective study in Japan.[16] In patients with type 2 diabetes with small vessel disease documented by cerebral magnetic resonance imaging, a high risk was found