

# Diabetic Kidney Disease: Much Progress, But Still More to Do

Mark E. Molitch

When I was a medical student in the 1960s, about one-third of patients with type 1 diabetes developed end-stage renal disease (ESRD) by ~30 years' duration of diabetes (1), and there wasn't anything that could be done for them. Medicare only started paying for treatment of ESRD (dialysis/transplantation) in the United States in 1973. So, most of those patients died. Recently, the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) study showed that the cumulative incidences of ESRD were only 1% in the initial DCCT intensive therapy group and 2% in the initial conventional therapy group in subjects who had a mean diabetes duration of 28 years (2). Now, that's a difference!

Comparable numbers for type 2 diabetes are more difficult to interpret because of the very high competing risk of death from cardiovascular disease (CVD) in such patients and the various interventions that may differentially affect chronic kidney disease (CKD) versus CVD progression in this population. However, it is clear from analyses of the U.S. Renal Data System that the overall proportion of diabetic patients developing ESRD has decreased progressively and substantially since 1996 (3).

Nonetheless, the absolute number of diabetic patients developing ESRD and the percentage of patients whose ESRD is the result of diabetes continue to increase because of

the overall increase in the incidence of diabetes itself in the United States and worldwide. At present, 44% of all ESRD in the United States is caused by diabetes (4). This increase in the number of patients has costs, both to individuals and to society. In addition, the presence of CKD, even at its earliest stages, dramatically increases the risk of CVD (5,6). So, despite our clear progress, we have much more work to do, and there are still many unanswered questions.

Multiple studies have shown that even the slightest increases in albumin excretion and decreases in glomerular filtration rate (GFR) independently increase the risk of CVD (5). But we still have problems in accurately defining increased albuminuria and even in using consistent terminology. The diabetes community should be aware that the nephrology community is moving away from the terms we have become accustomed to; "microalbuminuria" is being replaced with "moderately increased albumin excretion," and "macroalbuminuria" is being replaced with "severely increased albumin excretion" (7). I'm not sure what will be gained by this substitution of four words for one. However, you will be running across these terms in the literature. Also, although indirect assessment of GFR using estimating equations (eGFR) has now become standard practice, the accuracy of various equations continues to be questioned, especially

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Division of Endocrinology, Metabolism, and Molecular Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL

Corresponding author: Mark E. Molitch, molitch@northwestern.edu

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in individuals with eGFRs in the normal or elevated range.

Although the risk for CVD is higher for people with diabetes than for those without it at all levels of albumin excretion and GFR, the incremental increases in CVD for increases in albuminuria or decreases in GFR are similar for people with and without diabetes (6). The increase in CVD mortality in type 1 diabetes is almost entirely accounted for by those with kidney disease (increased albumin excretion, decreased GFR, or both) (8,9). A recent analysis of data from the National Health and Nutrition Examination Survey shows that the presence of kidney disease (same definition) also accounts for the great majority of excess mortality in those with type 2 diabetes (10).

Although the epidemiological associations of albuminuria and decreased GFR with CVD are clear, the mechanisms underlying these associations remain to be determined. One early hypothesis generated at the Steno Hospital in Denmark is that, in susceptible individuals, there is a generalized inflammation and endothelial dysfunction that results in vascular disease and an increase in glomerular membrane permeability that results in increased albumin excretion (11). Known risk factors affecting both CVD and CKD include hyperglycemia, hypoglycemia, hypertension, and dyslipidemia (12). However, CKD itself may contribute to CVD through effects on blood volume, activation of the renin-angiotensin-aldosterone system (RAAS), changes in lipids, and anemia (12).

Treatment modalities available to clinicians include therapies for glycemic control, blood pressure control, and lipid control and the use of RAAS blockers. However, these interventions do not affect CKD and CVD equally. Although glycemic control has been shown to decrease the development and progression of kidney disease substantially in both type 1 and type 2 diabetes (13,14),

its effects on CVD and mortality are more modest, especially in type 2 diabetes (15–20). The downside of intensive glycemic control is hypoglycemia, and severe hypoglycemia (associated with seizure, coma, or the need for assistance from another person) has been associated with a slight increase in mortality in some, but not all, studies (16,21). However, as the DCCT/EDIC study has shown, on balance, the benefits of better glycemic control clearly outweigh the risks with respect to micro- and macrovascular disease and mortality. It must be remembered, however, that patients with CKD are at greater risk for hypoglycemia than those with a normal GFR, and special precautions—especially drug dose reductions—are needed to prevent hypoglycemia in such patients (22,23). Blood pressure control helps to slow the progression of both CKD and CVD. However, CVD mortality may actually increase when systolic blood pressure drops much below 120 mmHg, whereas the benefits on CKD progression do not show this J-curve effect (24). In diabetic patients, lipid control is clearly beneficial to prevent CVD (except when started in dialysis patients), but it has little effect on CKD progression (25). Secondary intervention with RAAS blockers is helpful for both CVD and CKD, but their use in primary prevention is less clear (26).

Diabetic kidney disease (DKD) thus remains a major management problem for patients and clinicians. Primary prevention and secondary interventions have reduced the proportion of patients developing ESRD, but the dramatic increase in the number of people with diabetes in recent years makes DKD a continuing and growing problem. In addition to the issues mentioned above, delivering appropriate medical care to this large number of patients in an efficient and effective way also creates major challenges to the health care system. The American Diabetes Association convened a consensus conference on

DKD in the spring of 2014 to address the subjects touched upon here and many more (27). Several of these issues are addressed in more depth in this issue of *Diabetes Spectrum* (p. 158-192 and p.214-224).

## Duality of Interest

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