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...
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

The author has received research grants from Bayer, Eli Lilly and Company, Novartis, and Novo Nordisk and consultation honoraria from Bristol-Myers Squibb, Eli Lilly and Company, Janssen, Merck, Novartis, Novo Nordisk, and Pfizer. No other potential conflicts of interest relevant to this article were reported.

References

1. Krolewski AS, Warram JH, Christelieb AR, Busick EJ, Kahn CR. The changing natural history of nephropathy in type 1 diabetes. Am J Med 1985;78:785–794
2. DCCT/EDIC Research Group (Writing Group: DeBoer IH Sun W, Cleary PA, Lachin JM, Molitch MF, Steffes MW, Zimmerman BI. Intensive diabetes therapy and glomerular filtration rate in type 1 diabetes. N Engl J Med 2011;365:2366–2376
3. Burrows NR, Li Y, Geiss LS. Incidence of treatment for end-stage renal disease among individuals with diabetes in the U.S. continues to decline. Diabetes Care 2010;33;73–77
4. U.S. Renal Data System. USRDS 2014 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, Md., 2014
5. Bakris GL, Molitch M. Microalbuminuria as a risk predictor in diabetes: the continuing saga. Diabetes Care 2014; 37:867–875
6. Fox CS, Matsushita K, Woodward M, et al. Associations of kidney disease measures with mortality and end-stage renal disease in individuals with and without diabetes: a meta-analysis. Lancet 2012;380:1662–1673
7. Stevens PE, Levin A, for the Kidney Disease in the United States. National Institutes of Health, National Institute of Diabetes and End-Stage Renal Disease and Management of Chronic Kidney Disease Guideline Development Work Group. Evaluation and management of chronic kidney disease: synopsis of the Kidney Disease: Improving Global Outcomes 2012 Clinical Practice Guideline. Ann Intern Med 2013;158:825–830
8. Groop P-H, Thomas MC, Moral JL, et al., on behalf of the FinnDiane Study Group. The presence and severity of chronic kidney disease predicts all cause mortality in type 1 diabetes. Diabetes 2009;58:1651–1658
9. Orchard TJ, Secrest AM, Miller RG, Costacou T. In the absence of renal disease,
20 year mortality risk in type 1 diabetes is comparable to that of the general population: a report from the Pittsburgh Epidemiology of Diabetes Complications Study. Diabetologia 2010;53:2312–2319
10. Afkarian M, Sachs MC, Kestenbaum B, et al. Kidney disease and increased mortality risk in type 2 diabetes. J Am Soc Nephrol 2013;24:302–308
11. Jensen JS, Borch-Johnsen K, Jensen G, Feldt Rasmussen B. Microalbuminuria reflects a generalized transvascular albumin leakiness in clinically health subjects. Clin Sci 1995;88:629–633
12. De Ferranti SD, de Boer IH, Fonseca V, et al. Type 1 diabetes mellitus and cardiovascular disease: a scientific statement from the American Heart Association and American Diabetes Association. Diabetes Care 2014;37:2843–2863
13. DCCT/EDIC Research Group. Sustained effects of intensive treatment of type 1 diabetes mellitus on the development and progression of diabetic nephropathy. JAMA 2003;290:2159–2167
14. Perkovic V, Heerspink HL, Chalmers J, et al., for the ADVANCE Collaborative Group. Intensive glucose control improves kidney outcomes in patients with type 2 diabetes. Kidney Int 2013;83:517–524
15. DCCT/EDIC Research Group. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. N Engl J Med 2005;353:2643–2653
16. DCCT/EDIC Research Group. Association between 6 years of intensive treatment of type 1 diabetes and long-term mortality. JAMA 2013;313:45–53
17. Lind M, Svensson A-M, Kosiborod M, et al. Glycemic control and excess mortality in type 1 diabetes. N Engl J Med 2014;371:1972–1982
18. Gerstein HC, Miller ME, Byington RP, et al. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med 2008;358:2545–2559
19. Patel A, MacMahon S, Chalmers J, et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med 2008;358:2560–2572
20. Duckworth W, Abraira C, Moritz T, et al. Glucose control and vascular complications in veterans with type 2 diabetes. N Engl J Med 2009;360:129–139
21. Frier BM, Schernthaner G, Heller SR. Hypoglycemia and cardiovascular risks. Diabetes Care 2011;34(Suppl. 2):S132–S137
22. National Kidney Foundation. Kidney Disease Outcomes Quality Initiative clinical practice guidelines and clinical practice recommendations for diabetes and chronic kidney disease. Am J Kidney Dis 2007;49(Suppl. 2):S12–S154
23. Alsahli M, Gerich JE. Hypoglycemia, chronic kidney disease, and diabetes mellitus. Mayo Clin Proc 2014;89:1564–1571
24. Mancia G, Grassi G, Zanchetti A. Antihypertensive treatment and blood pressure in diabetic and nondiabetic patients. The lower, the better? Diabetes Care 2011;34(Suppl. 2):S304–S307
25. Molitch ME. Management of dyslipidemias in patients with diabetes and chronic kidney disease. Clin J Am Soc Nephrol 2006;1:1090–1099
26. Ruijope LM, Solini A. RAS blockade for every diabetic patient: pro and con. Diabetes Care 2011;34(Suppl. 2):S320–S324
27. Tuttle KR, Bakris GL, Bilous RW, et al. Diabetic kidney disease: a report from an ADA consensus conference. Diabetes Care 2014;37:2864–2883

Explore employment opportunities and career development tools for clinicians or scientists working in the field of diabetes.

professional.diabetes.org/careercenter