Are All Patients With Type 1 Diabetes Destined for Dialysis if They Live Long Enough? Probably Not

George L. Bakris[1] and Mark Molitch[2]

Over the past three decades there have been numerous innovations, supported by large outcome trials that have resulted in improved blood glucose and blood pressure control, ultimately reducing cardiovascular (CV) risk and progression to nephropathy in type 1 diabetes (T1D) (1,2). The epidemiological data also support the concept that 25–30% of people with T1D will progress to end-stage renal disease (ESRD). Thus, not everyone develops progressive nephropathy that ultimately requires dialysis or transplantation. This is a result of numerous factors, including the competing CV risk of death as well as blood glucose and pressure control. Good glycemic and blood pressure control have been documented in long-term trials to markedly slow nephropathy progression, with effects of blood pressure control seen as early as 2.5 years and of glucose control at 5–7 years (3,4). It is well documented that the presence of diabetic kidney disease increases the risk of CV events and death in persons with diabetes (5,6). Moreover, this is independent of hypertension.

Data from two recent studies reported in this issue of *Diabetes Care* examine the long-term incidence of chronic kidney disease (CKD) in T1D. Costacou and Orchard (7) examined a cohort of 932 people evaluated for 50-year cumulative kidney complication risk in the Pittsburgh Epidemiology of Diabetes Complications study. They used both albuminuria levels and ESRD/transplant data for assessment. By 30 years' duration of diabetes, ESRD affected 14.5% and by 40 years it affected 26.5% of the group with onset of T1D between 1965 and 1980. For those who developed diabetes between 1950 and 1964, the proportions developing ESRD were substantially higher at 34.6% at 30 years, 48.5% at 40 years, and 61.3% at 50 years. The authors called attention to the fact that ESRD decreased by 45% after 40 years' duration between these two cohorts, emphasizing the beneficial roles of improved glycemic control and blood pressure control. It should also be noted that at 40 years even in the later cohort (those diagnosed between 1965 and 1980), 57.3% developed >300 mg/day albuminuria (7).

Gagnum et al. (8), using data from a Norwegian registry, also examined the incidence of CKD development over a 42-year follow-up period in people with childhood-onset (<15 years of age) T1D (8). The data from the Norwegian registry noted that the cumulative incidence of ESRD was 0.7% after 20 years and 5.3% after 40 years of T1D. Moreover, the authors noted the risk of developing ESRD was lower in women than in men and did not identify any difference in risk of ESRD between those diagnosed with diabetes in 1973–1982 and those diagnosed in 1989–2012. They concluded that there is a very low incidence of ESRD among patients with childhood-onset T1D diabetes in Norway, with a lower risk in women than men and among those diagnosed at a younger age. In the Pittsburgh study (7), the rates of ESRD were only modestly lower in those with T1D onset <11 years of age and the authors did not notice any effect of gender.

Persons with T1D of 30 years' duration studied at the Joslin Diabetes Clinic in Boston had a cumulative risk for ESRD of 20%, similar to the Pittsburgh cohort, but these data were from prior to 1995, so many of the improvements in glycemic and blood pressure control and the use of agents blocking the renin-angiotensin-aldosterone system (RAAS) had only been available for a relatively short period of time (9).

The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications study (DCCT/EDIC) showed that by 30 years' duration of diabetes, only 2% of the conventional treatment group and 1% of the intensive treatment group developed ESRD (10). However, the selection criteria included normal blood pressure and lack of very high albuminuria for those entering the DCCT, so the long-term cumulative incidence could be lower on that basis. Analyses of population-based studies, similar to the Pittsburgh and Norway studies, showed that after 30 years of T1D the cumulative incidences of ESRD were only 10% for those diagnosed with T1D in

[1]Comprehensive Hypertension Center, Section of Endocrinology, Diabetes and Metabolism, Department of Medicine, University of Chicago Medicine, Chicago, IL
[2]Section of Endocrinology, Diabetes and Metabolism, Department of Medicine, Northwestern Medicine, Chicago, IL

Corresponding author: George L. Bakris, gbakris@medicine.bsd.uchicago.edu.

See accompanying articles, pp. 420, 426, and 434.

1961–1984 and 3% for those diagnosed in 1985–1999 in Japan (11), 3.3% for those diagnosed with T1D in 1977–2007 in Sweden (12), and 7.8% for those diagnosed with T1D in 1965–1999 in Finland (13) (Table 1).

The United States Renal Data System (USRDS) has grouped data from T1D and type 2 diabetes, so it is not possible to use the data to assess the incidence of only T1D ESRD. In the U.S. there has been a decline in the rate of kidney failure due to diabetes over the past decade. The rates varied widely by race and were markedly higher in blacks as compared with whites (391.6 versus 133.6 per million). However, it is notable that the rates in blacks have decreased by 21.1% since 2005, compared with nearly unchanged rates in whites. Males continued to have a higher rate of diabetic kidney failure than females (14). Conversely, the continued increase in diabetes incidence has culminated in an increasing total number of ESRD cases secondary to diabetes, albeit the increase is predominantly in patients with type 2 diabetes.

The USRDS report notes a 28.3% increase over 2014 in assessment of kidney function, microalbuminuria, and lipid levels in all people with diabetes; if eye evaluations are added it drops to 25.7%. Surveillance for ESRD risk has been increasing over the last 5 years (14). This suggests that more attention has been directed to assessment of risk factors for ESRD development over the past decade, which may account for a reduced incidence of ESRD in cohorts studied in more recent years.

The data from all these studies need to be put into context. First, there is a substantive difference between the numbers of people with stage 3 CKD (estimated glomerular filtration rate [eGFR] 30–59 mL/min/1.73 m^2) versus those with stages 4 and 5 CKD (eGFR <30 mL/min/1.73 m^2): 6.7% of the National Health and Nutrition Examination Survey (NHANES) population compared with 0.1–0.3%, respectively (14). This is primarily because of competing risks, such as death from CV disease that occurs in stage 3 CKD; hence, only the survivors are progressing into stages 4 and 5 CKD.

Overall, these studies are very encouraging. Since the 1980s, risk of ESRD has been greatly reduced, while risk of CKD progression persists but at a slower rate. This reduced ESRD rate and slowed CKD progression is largely due to improvements in glycemic and blood pressure control and probably also to the institution of RAAS blockers in more advanced CKD. These data portend even better future outcomes if treatment guidance is followed. Thus, clinicians need to continue to monitor kidney function with assessment of eGFR and albumin excretion and maintain guideline goals for glucose and blood pressure control. As emphasized by the recent American Diabetes Association hypertension position statement (15), many medications are effective in blood pressure control, but RAAS blockade should always be a part of any regimen when very high albuminuria is present.

References

1. Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) Study Research Group. Intensive diabetes treatment and cardiovascular outcomes in type 1 diabetes: the DCCT/EDIC Study 30-year follow-up. Diabetes Care 2016;39:686–693
2. Lewis EJ, Hunsicker LG, Bain RP, Rohde RD; Collaborative Study Group. The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. N Engl J Med 1993;329:1456–1462
3. Sternlicht H, Bakris GL. The kidney in hypertension. Med Clin North Am 2017;101:207–217
4. Zoungas S, Chalmers J, Neal B, et al.; ADVANCE-ON Collaborative Group. Follow-up of blood-pressure lowering and glucose control in type 2 diabetes. N Engl J Med 2014;371:1392–1406
5. Fox CS, Matsushita K, Woodward M, et al.; Chronic Kidney Disease Prognosis Consortium. 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
6. Tonelli M, Muntner P, Lloyd A, et al.; Alberta Kidney Disease Network. Risk of coronary events in people with chronic kidney disease compared with those with diabetes: a population-level cohort study. Lancet 2012;380:807–814
7. Costacou T, Orchard TJ. Cumulative kidney complication risk by 50 years of type 1 diabetes: the effects of sex, age, and calendar year at onset. Diabetes Care 2018;41:426–433
8. Gagnum V, Saeed M, Stene LC, Leivestad T, Joner G, Skrivarhaug T. Low incidence of end-stage renal disease in childhood-onset type 1 diabetes followed for up to 42 years. Diabetes Care 2018;41:420–425
9. Krolewski M, Eggers PW, Warram JH. Magnitude of end-stage renal disease in IDDM: a 35 year follow-up study. Kidney Int 1996;50:2041–2046
10. DCCT/EDIC research group. Effect of intensive diabetes treatment on albuminuria in type 1 diabetes: long-term follow-up of the Diabetes Control and Complications Trial and Epidemiology of Diabetes Interventions and Complications study. Lancet Diabetes Endocrinol 2014;2:793–800
11. Otani T, Yokoyama H, Ohashi Y, Uchigata Y. Improved incidence of end-stage renal disease of type 1 diabetes in Japan, from a hospital-based survey. BMJ Open Diabetes Res Care 2016;4:e000177
12. Möllsten A, Svensson M, Waernbaum I, et al.; Swedish Childhood Diabetes Study Group; Diabetes Incidence Study in Sweden; Swedish Renal Registry. Cumulative risk, age at onset, and sex-specific differences for developing end-stage renal disease in young patients with type 1 diabetes: a nationwide population-based cohort study. Diabetes 2010;59:1803–1808
13. Finne P, Reunanen A, Stenman S, Groop PH, Grönhagen-Riska C. Incidence of end-stage renal disease in patients with type 1 diabetes. JAMA 2005;294:1782–1787
14. United States Renal Data System. Chapter 2: Healthy People 2020 [Internet], 2017. Available from https://www.usrds.org/2016/view/v2_02.aspx?zoom_highlight=type%201. Accessed 12 November 2017
15. de Boer IH, Bangalore S, Benetos A, et al. Diabetes and hypertension: a position statement by the American Diabetes Association. Diabetes Care 2017;40:1273–1284

Table 1—Cumulative incidence of ESRD by 30 years' duration of type 1 diabetes

Authors, year (reference)	Country	Period*	No. of persons	Cumulative incidence*
Costacou and Orchard, 2018 (7)	U.S.	1950–1964	321	34.6%
		1965–1980	*435*	*14.5%*
Gagnum et al., 2018 (8)	Norway	*1973–2012*	*7,871*	*2.9%*
Krolewski et al., 1996 (9)	U.S.	1959–1994	142	20%
DCCT/EDIC research group, 2014 (10)	U.S.	*1968–1983*	*1,441*	*2%*
Otani et al., 2016 (11)	Japan	1961–1984	529	10%
		1985–1999	*485*	*3%*
Möllsten et al., 2010 (12)	Sweden	*1997–2007*	*6,495*	*3.3%*
Finne et al., 2005 (13)	Finland	1965–1999	20,005	7.8%

*Most recent dates and ESRD incidence rates are boldface and italicized compared with older dates and rates.