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

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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

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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.

Duality of Interest. G.L.B. is the co-Principal Investigator for the outcome trial Efficacy and Safety of Finerenone in Subjects with Type 2 Diabetes Mellitus and Diabetic Kidney Disease (FIDELIO-DKD), sponsored by Bayer. He is also a member of the Steering Committee for the Evaluation of the Effects of Canagliflozin on Renal and Cardiovascular Outcomes in Participants with Diabetic Nephropathy (CREDENCE), sponsored by Janssen, and the Study of Diabetic Nephropathy with Atrasentan (SONAR), sponsored by AbbVie. He has also consulted for Merck, Relypsa, and Vascular Dynamics. M.M. has been Principal Investigator on research grants received by Northwestern University from Bayer and Novartis and has been a consultant for Novartis, Merck, Pfizer, and Janssen.

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.

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