Cumulative Kidney Complication Risk by 50 Years of Type 1 Diabetes: The Effects of Sex, Age, and Calendar Year at Onset

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OBJECTIVE

A common belief is that only a minority of patients with type 1 diabetes (T1D) develop advanced kidney disease and that incidence is higher among men and lower in those diagnosed at a younger age. However, because few patients with T1D survived to older ages until recently, long-term risks have been unclear.

RESEARCH DESIGN AND METHODS

We examined the 50-year cumulative kidney complication risk in a childhood-onset T1D cohort diagnosed during 1950–80 (n = 932; mean baseline age 29 years, duration 19 years). Participants comprised 144 who died prior to baseline, 130 followed with periodic surveys, and 658 followed with biennial surveys and a maximum of nine examinations for 25 years. Micro- and macroalbuminuria were defined as an albumin excretion rate of 20–199 and ≥200 μg/min, respectively, and end-stage renal disease (ESRD) was defined as dialysis or kidney transplantation. Cumulative incidence was estimated at 10-year intervals between 20 and 50 years' duration and compared by calendar year of diabetes onset.

RESULTS

By 50 years' T1D duration, ESRD affected 60% of the cohort; macroalbuminuria, 72%; and microalbuminuria, 88%. Little evidence existed for declines in cumulative incidence in recent cohorts, except for ESRD (microalbuminuria 3% increase, macroalbuminuria no change; ESRD 45% decrease by 40 years of T1D duration). Onset before age 6 years was associated with the lowest risk; incidence generally did not differ by sex.

CONCLUSIONS

Some degree of kidney disease in T1D is virtually universal at long durations and not declining, which has major implications for formulating health care and research strategies. ESRD has declined, but continues to affect >25% of the population by 40 years' duration.

Nephropathy is commonly believed to eventually affect 30–40% of patients with type 1 diabetes (T1D) (1). Clinical trials have provided evidence for a protective effect of ACE inhibitors/angiotensin receptor blockers against the progression of kidney disease among individuals with diabetes and proteinuria (2–4). Since the 1980s, results from these trials have contributed to the wide adoption of medications that block the renin-angiotensin system with the hope of reducing the incidence and progression of kidney disease in diabetes. However, debate continues about whether the incidence of end-stage renal disease (ESRD) has declined despite these efforts, especially in the T1D population (5–8).

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Controversy also surrounds the hypothesis that onset of T1D before puberty (9–13) or, as others have suggested, before 5–6 years of age (14–18) delays the development of chronic diabetes complications, including kidney disease. Proponents of a protective effect of an earlier, prepubertal diabetes onset have proposed that hormonal and body composition changes during puberty, along with their associated dysglycemia and insulin resistance, may be factors contributing to an increased risk for diabetes complications (9,19,20). Thus, in a small Swedish study of pubertal girls with T1D, elevated androgen levels were observed with prevalent microalbuminuria, although significance was lost after adjustments (21). In the Oxford Regional Prospective Study, higher HbA_{1c}, lower IGF-I, and elevated androgen concentrations were associated with the development of microalbuminuria during puberty in adolescents with T1D (22). In the latter study, insulin doses were similar by microalbuminuria status despite higher HbA_{1c} among incident case subjects, suggesting either the presence of insulin resistance among case subjects or poor diabetes management. Nevertheless, not all investigations concur that prepubertal diabetes confers renoprotection or that a pubertal diabetes diagnosis comes with an increased risk for complications (23–26). A potential reason for discrepancies in research findings may relate to differences in the age ranges compared across studies, the variable length of follow-up, and the difficulty of disentangling the effects of age at diabetes onset from those of chronological age and/or duration of diabetes, especially in cohorts of childhood-onset T1D where these three factors are closely interrelated. This is because individuals diagnosed with T1D at a younger age will, by definition, be younger at any diabetes duration.

A somewhat related disagreement involves the risk associated with sex and whether the effect of sex is modified by the age at diabetes onset. Thus, although insulin sensitivity is reduced in children with T1D compared with control subjects regardless of pubertal status (27), girls are disproportionally affected by vascular risk factors during the pubertal period (e.g., adiposity, insulin resistance) (28). These findings suggest that if the diagnosis of T1D occurs in puberty, girls may be at a greater risk for subsequent vascular complications than boys. Indeed, the aforementioned increase in androgens with microalbuminuria during puberty was more striking among female than male adolescents with T1D (22). However, data on sex differences in kidney disease risk have been mixed. A greater likelihood of developing microalbuminuria among girls was previously suggested in four cohort studies (14,26,29,30). In Finland, no sex differences in the cumulative incidence of ESRD were reported within an overall cohort of individuals diagnosed with T1D at <30 years of age (17), yet a greater risk in men than women was noted among those diagnosed with T1D after 10 years of age (13). In a Swedish study, an increased ESRD risk in men was seen among those diagnosed between age 20 and 34 years (12). In previous analyses, we noted that the excess of kidney disease cases in males observed in the earlier diagnosis cohort (1950–64) was eliminated in the younger cohort (1965–80), although we did not evaluate the effects of age at diabetes onset (31). Having now accumulated >25 years of follow-up, representing up to 50 years of diabetes duration within the Pittsburgh Epidemiology of Diabetes Complications (EDC) study, we assessed the long-term cumulative kidney complications risk in childhood-onset T1D to further address the effects of age at onset, sex, and diagnosis cohort.

RESEARCH DESIGN AND METHODS

The Pittsburgh EDC study is a representative, prospective investigation of incident cases of childhood-onset T1D diagnosed, or seen within 1 year of diabetes diagnosis, at Children's Hospital of Pittsburgh (32). Eligibility for participation comprised having been diagnosed with T1D between 1950 and 1980 and residing within 100 miles or 2.5 h from Pittsburgh, Pennsylvania. Of 1,124 eligible participants, 145 (12.9%) died before the study baseline (1986–88), 191 (17%) declined participation, 130 (11.6%) only provided survey information, and 658 (58.5%) participated in biennial assessments. Death certificates were obtained for 144 (99%) of the 145 predeceased individuals. Analyses for the cumulative incidence of micro- and macroalbuminuria were restricted to participants who attended the biennial clinical examinations during the 25-year follow-up (n = 658). For reduction of the effect of survival bias, analyses pertaining to the risk of ESRD also included participants who only provided survey data (n = 130) and the 144 predeceased individuals for whom a death certificate was available.

Urinary albumin was measured by immunonephelometry (33). Microalbuminuria was defined as an albumin excretion rate (AER) of 20–200 μg/min (30–300 mg/24 h) and macroalbuminuria as AER >200 μg/min (>300 mg/24 h) in at least two of three validated timed biennial urine collections. Persistent microalbuminuria also was assessed and defined as the presence of microalbuminuria in two consecutive biennial examinations or initiation of ACE inhibitor/angiotensin receptor blocker therapy. Onset of ESRD was defined as starting dialysis or undergoing kidney transplantation. For predeceased individuals, given the lack of more detailed information, a mention of kidney failure on the death certificate was used to determine ESRD status, and the onset of ESRD was assumed to equal the duration of diabetes at death. Because information on the actual timing of ESRD onset was not widely available among the predeceased individuals, we also assessed the combined outcome of ESRD and all-cause mortality in a sensitivity analysis. The definitions of micro- and macroalbuminuria include those who later progressed to ESRD.

Statistical Analysis

Participant characteristics were evaluated by diabetes diagnosis year (before or after 1 January 1965) by using χ^2 tests for classification variables and Student t test for continuous variables. The cumulative incidence of kidney complications was then assessed by diabetes diagnosis year, diabetes duration, sex, and age at diabetes onset by using χ^2 or Fisher exact test, as appropriate. Participants were categorized according to an age at onset of <6 years, 6–11 or 12 years (for girls and boys, respectively, to represent puberty onset), and ≥11 or 12 years. Logistic regression models also were used to evaluate whether age at onset of T1D (as a continuous and, in separate models, as a classification variable) and sex were associated with the cumulative risk of kidney complications at specific diabetes durations, ranging from 20 to 50 years in 10-year intervals. Models were adjusted for chronological age and stratified by diagnosis cohort. Analyses for the 1950–64 diagnosis cohort were not conducted at

20 years' duration because very few participants had data available. In addition, analyses for the 1965–80 cohort were not conducted at 50 years' duration because very few individuals had reached that duration by the 25-year study follow-up. All statistical analyses were conducted with SAS 9.4 software (SAS Institute, Cary, NC).

RESULTS

The composition and demographic characteristics of the EDC cohort used in this analysis are listed in Table 1. Of the total sample of 932, almost 58.2% were diagnosed between 1965 and 1980. As expected, a greater proportion of individuals who died before study initiation were diagnosed with T1D before 1965, whereas the majority of survey-only and examined participants received a T1D diagnosis within or after 1965. The mean age of the entire cohort at study initiation was 27.4 years, and the mean age at diabetes onset was 8.7 years. The age at diabetes onset was slightly greater in the more recent diagnosis cohort (8.6 vs. 8.0; P = 0.02), as was the proportion of women (52.2 vs. 45.9; P = 0.06), whereas chronological age was lower (23.3 vs. 33.0; $P <$ 0.0001). The majority of participants were Caucasian, with only ~3% being African American regardless of diagnosis cohort.

The cumulative incidences of micro- and macroalbuminuria, ESRD, and the combined outcome of ESRD and all-cause mortality by diabetes diagnosis year (before and within or after 1965) and T1D duration are shown in Table 2. Results for persistent microalbuminuria were notably similar to those for any microalbuminuria, despite the smaller sample size available for analysis, and thus results for persistent microalbuminuria are not presented here. The cumulative incidence of all four outcomes increased with longer diabetes duration. More than one-half of this T1D cohort was affected by microalbuminuria by 20 years of diabetes duration, reaching 88% by 50 years. Similarly, high rates were observed for macroalbuminuria, ranging from >27% at 20 years' duration to almost 72% by 50 years'. The cumulative incidence of both ESRD and ESRD/mortality also dramatically increased with longer duration of diabetes, exceeding 61% and 75%, respectively, by 50 years.

Figure 1*A–D* depicts the cumulative incidence of kidney disease by age at onset and duration of T1D. Generally, a lower risk of micro- and macroalbuminuria was observed with a diabetes diagnosis before 6 years of age, although this association diminished at longer diabetes durations because a greater proportion of participants developed increased proteinuria. A younger age at diabetes onset was also associated with a lower cumulative incidence of both ESRD and ESRD/mortality—associations that were apparent even at a duration of 50 years. These graphs also emphasize the enormous burden of kidney complications in the T1D population. Thus, at a duration of 40 years, the cumulative incidence of microalbuminuria among those at the lowest risk for developing kidney complications (those diagnosed before the age of 6 years) was 77.2%; the cumulative incidence of macroalbuminuria was 50.4%, ESRD 29.1%, and ESRD/mortality 42.0%.

As presented in Table 2, no reductions were observed in the cumulative incidence of either micro- or macroalbuminuria in the post-1965 compared with the 1950–64 diagnosis cohort. Indeed, rates were similar between the two cohorts at each duration of T1D. On the contrary, significant reductions were apparent in the cumulative incidences of ESRD and ESRD/mortality for the post-1965 compared with the 1950–64 diagnosis cohort. Thus, ESRD incidence was 58% and 45% lower in the more recent diagnosis cohort by 30 and 40 years of diabetes duration, respectively. For ESRD/mortality, the reduction was 53% and 35%, respectively.

Given our previous findings of an effect modification of sex on kidney disease incidence by diagnosis cohort (31), we assessed the cumulative incidence of the three outcomes of interest separately for the 1950–64 and post-1965 diagnosis cohorts. Again, a greater kidney disease risk associated with male sex appeared to be restricted to participants diagnosed with T1D between 1950 and 1964. Figure 1*E–H* shows results by sex and diagnosis cohort at 30 and 40 years of T1D duration.

A detailed breakdown of cumulative incidence by diabetes diagnosis year, sex, and age at T1D onset also is shown in Supplementary Table 1. In addition to the aforementioned findings, the results suggest that the greater kidney disease risk among men was restricted to those diagnosed with T1D between the ages of 6 and 11 (girls) or 12 (boys) years within the 1950–64 interval.

Logistic regression models for an independent effect of age at diabetes onset on the cumulative risk of kidney complications suggested that a younger age at onset is associated with lower risk, even after taking into account differences in chronological age (Table 3). However, this association was not as prominent for microalbuminuria or for longer diabetes durations and remained significant after adjustment for age and sex only for ESRD and ESRD/mortality. These associations were similar regardless of whether age at diabetes onset was used as a continuous or a categorical variable. For brevity, Table 3 shows results with age at onset used as a continuous variable. Generally, sex was not significantly associated with kidney complications after adjusting for age at onset and chronological age.

CONCLUSIONS

During a 25-year follow-up of individuals with childhood-onset T1D, we observed that kidney disease continues to affect

Table 1—Composition and demographic characteristics of the EDC cohort by T1D diagnosis before and after 1965 at study entry (1986–1988)

	Diabetes diagnosed in 1950–64 (n = 390)	Diabetes diagnosed in 1965–80 (n = 542)	P value
Cohort composition			
Predeceased	33.1 (129)	2.8 (15)	<0.0001
Survey only	9.5 (37)	17.2 (93)	
Examined	57.4 (224)	80.1 (434)	
Age at T1D onset (years)	8.0 (3.9)	8.6 (4.0)	0.02
Chronological age (years)	33.0 (7.6)	23.3 (5.6)	<0.0001
Female sex	45.9 (179)	52.2 (283)	0.06
Race/ethnicity			
Caucasian	96.7 (376)	96.9 (525)	0.85
African American	3.3 (13)	3.1 (17)	

Data are mean (SD) or percent (n).

Table 2—The 25-year cumulative incidence of microalbuminuria, macroalbuminuria, and ESRD by diagnosis cohort and duration of T1D

	Microalbuminuria		Macroalbuminuria		ESRD		ESRD/mortality	
	1950–64	1965–80	1950–64	1965–80	1950–64	1965–80	1950–64	1965–80
Duration of T1D								
20 years	—	54.7 (215/393)	—	27.1 (105/388)	14.5 (53/366)	5.5 (27/491)	24.1 (94/296)	7.9 (40/505)
					$P < 0.0001$		$P < 0.0001$	
30 years	65.2 (122/187)	70.0 (254/363)	43.3 (87/201)	39.9 (127/318)	34.6 (111/321)	14.5 (63/435)	46.9 (182/388)	21.9 (104/474)
	$P = 0.26$		$P = 0.45$		$P < 0.0001$		$P < 0.0001$	
40 years	79.0 (169/214)	81.7 (188/230)	57.1 (113/198)	57.3 (102/178)	48.5 (145/299)	26.5 (62/234)	59.9 (232/387)	39.1 (108/276)
	$P = 0.46$		$P = 0.96$		$P < 0.0001$		$P < 0.0001$	
50 years	88.0 (176/200)	—	71.8 (117/163)	—	61.3 (165/269)	—	75.1 (277/369)	—

Data are % (*n* cases/total *n*).

the majority of this population at longer diabetes durations, with the cumulative incidence of micro- and macroalbuminuria remaining essentially identical between the older and more recent diagnosis cohorts. Thus, although rates of ESRD and ESRD/mortality dramatically declined from the earlier (1950–64) to the more recent (1965–80) diagnosis cohort, >26% of the recent cohort still had a diagnosis of ESRD and >39% were affected by ESRD/mortality by 40 years of diabetes duration. Of note, >60% of individuals diagnosed with T1D during 1950–64 had a diagnosis of ESRD by 50 years' duration, while >75% had either been diagnosed with ESRD or died. These results strongly support that the improvement in ESRD rates reflects better management of nephropathy rather than its prevention. The findings also suggest that being diagnosed with T1D before 6 years of age carries a lower risk of kidney disease development, although this relationship was less pronounced at longer diabetes durations. Finally, men were more likely to develop kidney disease only among those diagnosed during 1950–64 and after the age of 6 years, whereas rates were similar by sex in the more recent diagnosis cohort.

Earlier European studies provided evidence that microvascular complications still develop among individuals with T1D at a young age, despite modern means of disease management. Thus, Olsen et al. (34) reported a prevalence of microalbuminuria of 13% among adults with T1D in their early 20s with duration of diabetes of ~12 years. Studies from Sweden also provided evidence of incipient diabetic nephropathy affecting 18% of young adults with T1D during the first 10–12 years of diabetes duration (7,35). In the current cohort, >50% of participants diagnosed in the post-1965 era developed microalbuminuria by 20 years of diabetes duration (when they were in their late 20s/early 30s), while macroalbuminuria was observed in 27.1%. In addition, the observation of similar rates between the two diagnosis cohorts with longer diabetes duration also suggests that the incidence of albuminuria has not declined over time,

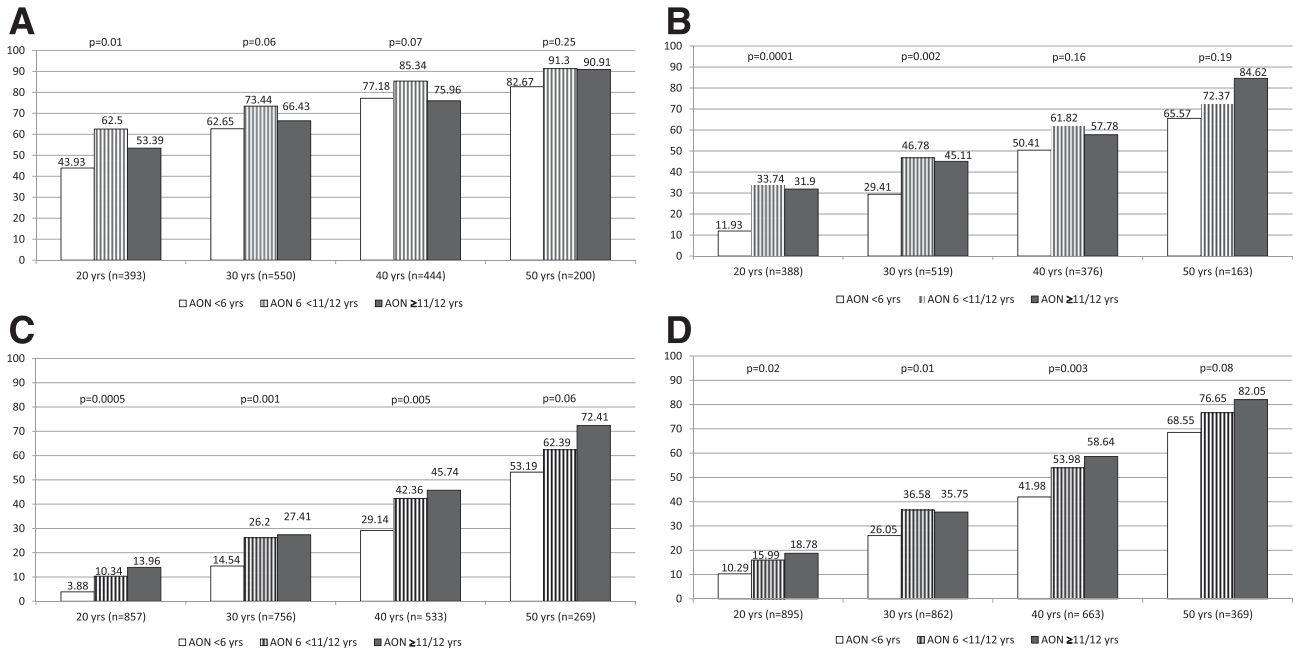

Figure 1—Cumulative incidence of kidney complications by duration of T1D, age at onset (AON), diagnosis cohort, and sex. *A*: Cumulative incidence of microalbuminuria (*A*), macroalbuminuria (*B*), ESRD (*C*), and ESRD/mortality (*D*) by AON and duration of T1D. Cumulative incidence of microalbuminuria (*E*), macroalbuminuria (*F*), ESRD (*G*), and ESRD/mortality (*H*) by sex and diagnosis cohort at 30 and 40 years of T1D duration. yrs, years.

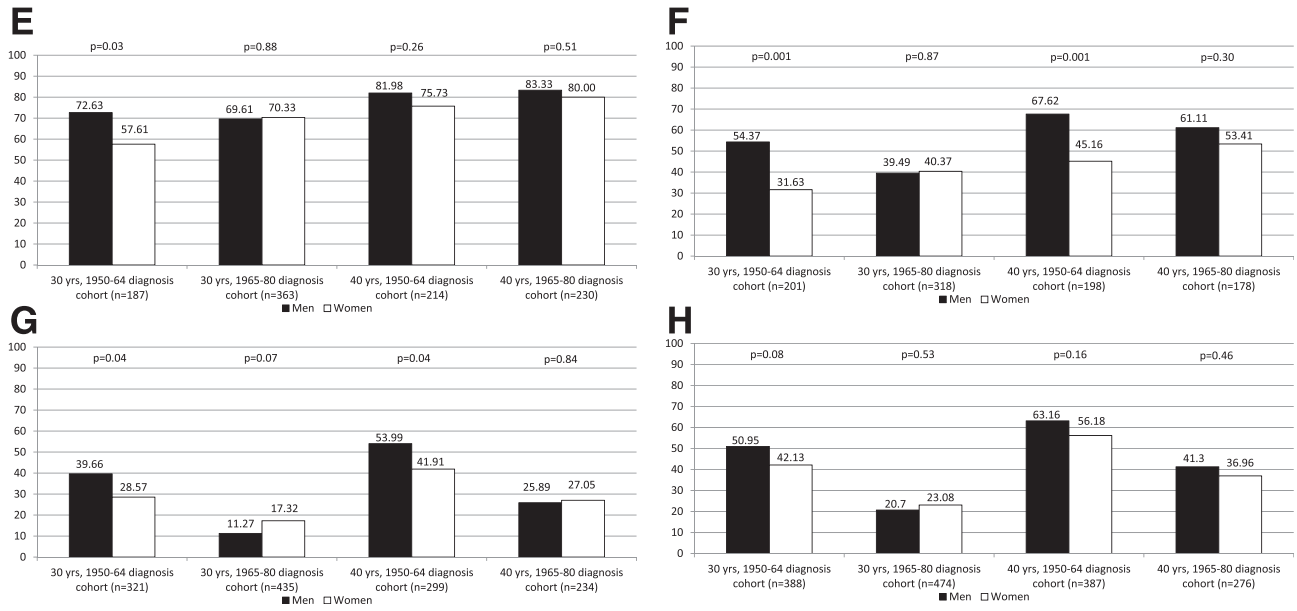

Figure 1—*Continued*.

notwithstanding the availability of prevention regimens and treatment options for kidney disease.

In the U.S., lower rates of micro- and macroalbuminuria than observed in the EDC study have been reported by Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) investigators (36,37). However, important selection differences apply to DCCT/EDIC that limit a direct comparison with the EDC cohort. The criteria for participation in the DCCT/EDIC study included a maximum diabetes duration of 5 years, age between 13 and 39 years, absence of complications at baseline, and absence of major hypertension or hypercholesterolemia. Indeed, in previous comparative analyses of the DCCT/EDIC and the subset of the EDC cohort meeting DCCT recruitment criteria, complication rates in the EDC and the DCCT/EDIC conventional treatment group (including nephropathy) were similar and, in fact, marginally higher in DCCT/EDIC (38).

It is possible, however, that renoprotective medication use has produced declines in the progression of diabetic nephropathy to ESRD. Indeed, a reduction over time in the rates of ESRD as a result of T1D was previously observed in a study conducted based on data provided by kidney registries in Europe, Canada, and Australia (39). Remarkably low cumulative incidence rates for ESRD (<1% at 21 years of diabetes duration [11] and merely exceeding 1% at 30 years' duration [12]) were reported by Swedish investigators in recent years. Moreover, the mean age at onset of kidney replacement therapy as a result of T1D increased by >3 years during 1995–2010 in Sweden, whereas the number of patients requiring such therapy decreased (40). In the EDC study, the cumulative incidence of ESRD declined dramatically in the more recent (1965–80) compared with the earlier (1950–64) diagnosis cohort by 62%, 58%, and 45% at 20, 30, and 40 years of diabetes duration, respectively. However, the cumulative incidence was still much higher in the 1965–80 diagnosis cohort (5.5%, 14.5%, and 26.5% at 20, 30, and 40 years, respectively) than that reported in Sweden (1% at 30 years) but comparable to the 20-year 6–7% risk of ESRD within the Joslin Cohort (41).

Nevertheless, not all study findings agree that rates of ESRD have dropped among individuals with T1D. Reports of unchanged or even increased rates of kidney disease have been previously brought forth by Joslin Diabetes Center investigators (8). By using data from the U.S. Renal Data System for the years 1990–2006, Krolewski (8) noted a 9% annual increase in new cases of ESRD believed to be attributed to T1D. Of note, although the proportion of individuals age <40 years declined over time, the number age 40–49 years almost doubled, suggesting that improved management in this population perhaps delayed but did not eliminate the development of ESRD in the U.S. Nonetheless, the increasing incidence of T1D and the better overall survival of the T1D population may partly explain these observations.

As previously reported by several research groups (14–18,30), we also observed that a very young age (<6 years) at diabetes onset was associated with the lowest risk of developing kidney complications later in life. Thus, our findings support the hypothesis of greater kidney disease risk associated with a T1D diagnosis after 6 years of age, with similar or greater cumulative incidences observed for a postpubertal versus prepubertal (but after 6 years) age of onset. Previous studies also reported an increased risk among individuals diagnosed with T1D during or after puberty (9–13). The reason for an increased complications risk associated with a pubertal diabetes diagnosis is not clear. Hormonal changes, especially higher androgen and lower IGF-I levels (22), during puberty and the accompanying hyperglycemia have been proposed to promote the development of kidney complications (9,19,20). However, evidence is scarce, and observations of similarly high or low incidence rates among individuals diagnosed during the pubertal period with those diagnosed before (13) or after puberty (12) weaken this hypothesis. Another potential explanation for the lower incidence among

Table 3—Logistic regression models for the prediction of the 25-year cumulative incidence of microalbuminuria, macroalbuminuria, ESRD, and ESRD/mortality from age at diabetes onset and chronological age

	Diabetes duration			
	20 years	30 years	40 years	50 years
Microalbuminuria				
Total cohort		*n* = 550	*n* = 444	
Age at onset		1.04 (0.99–1.09)	1.01 (0.95–1.08)	
Chronological age		1.00 (0.97–1.03)	1.01 (0.97–1.05)	
Women		0.78 (0.54–1.12)	0.73 (0.46–1.17)	
AIC		690.167	445.161	
1950–64 cohort		*n* = 187	*n* = 214	*n* = 200
Age at onset		1.17 (1.02–1.33)	0.98 (0.87–1.11)	0.98 (0.82–1.14)
Chronological age		0.91 (0.81–1.01)	1.09 (0.98–1.20)	1.14 (0.99–1.30)
Women		0.50 (0.27–0.93)	0.64 (0.33–1.26)	0.65 (0.27–1.56)
AIC		239.548	222.516	148.567
1965–80 cohort	*n* = 393	*n* = 363	*n* = 230	
Age at onset	1.02 (0.95–1.09)	0.97 (0.90–1.04)	0.94 (0.82–1.08)	
Chronological age	1.03 (0.98–1.08)	1.07 (1.01–1.13)	1.05 (0.93–1.20)	
Women	0.99 (0.66–1.48)	1.05 (0.67–1.66)	0.82 (0.42–1.61)	
AIC	545.410	445.202	225.426	
Macroalbuminuria				
Total cohort		*n* = 519	*n* = 376	
Age at onset		1.07 (1.02–1.12)	1.04 (0.98–1.10)	
Chronological age		1.01 (0.99–1.04)	1.00 (0.97–1.04)	
Women		0.67 (0.47–0.96)	0.52 (0.34–0.79)	
AIC		695.457	509.813	
1950–64 cohort		*n* = 201	*n* = 198	*n* = 163
Age at onset		1.19 (1.06–1.34)	1.06 (0.95–1.17)	1.06 (0.94–1.21)
Chronological age		0.88 (0.81–0.97)	0.98 (0.91–1.07)	0.98 (0.88–1.08)
Women		0.38 (0.21–0.68)	0.38 (0.21–0.69)	0.43 (0.21–0.87)
AIC		263.270	266.998	195.508
1965–80 cohort	*n* = 388	*n* = 318	*n* = 178	
Age at onset	1.07 (0.99–1.15)	1.05 (0.97–1.13)	1.01 (0.89–1.15)	
Chronological age	1.06 (0.999–1.12)	1.05 (0.996–1.11)	1.04 (0.92–1.16)	
Women	1.37 (0.86–2.18)	1.01 (0.64–1.60)	0.73 (0.40–1.33)	
AIC	440.228	422.235	248.035	
ESRD				
Total cohort		*n* = 756	*n* = 533	
Age at onset		1.07 (1.02–1.12)	1.07 (1.02–1.13)	
Chronological age		1.02 (0.99–1.04)	1.00 (0.97–1.03)	
Women		0.85 (0.60–1.20)	0.71 (0.50–1.01)	
AIC		808.087	706.064	
1950–64 cohort		*n* = 321	*n* = 299	*n* = 269
Age at onset		1.34 (1.22–1.48)	1.20 (1.11–1.29)	1.19 (1.10–1.29)
Chronological age		0.75 (0.69–0.81)	0.84 (0.79–0.89)	0.87 (0.82–0.92)
Women		0.56 (0.32–0.98)	0.62 (0.38–1.02)	0.62 (0.37–1.05)
AIC		323.906	373.734	333.904
1965–80 cohort	*n* = 491	*n* = 435	*n* = 234	
Age at onset	1.19 (1.03–1.37)	1.10 (0.999–1.20)	1.07 (0.94–1.23)	
Chronological age	1.04 (0.95–1.15)	1.05 (0.99–1.12)	1.07 (0.95–1.20)	
Women	1.41 (0.63–3.14)	1.69 (0.96–2.98)	1.07 (0.59–1.96)	
AIC	201.173	347.748	264.074	
ESRD/mortality				
Total cohort		*n* = 862	*n* = 663	
Age at onset		1.06 (1.02–1.10)	1.10 (1.05–1.15)	
Chronological age		0.99 (0.97–1.01)	0.96 (0.94–0.99)	
Women		0.81 (0.61–1.07)	0.74 (0.54–1.01)	
AIC		1,093.305	903.823	
1950–64 cohort		*n* = 388	*n* = 387	*n* = 369
Age at onset		1.39 (1.27–1.53)	1.24 (1.15–1.34)	1.19 (1.10–1.29)
Chronological age		0.72 (0.67–0.78)	0.82 (0.78–0.86)	0.87 (0.83–0.92)
Women		0.62 (0.37–1.03)	0.72 (0.46–1.14)	0.67 (0.40–1.10)
AIC		376.859	440.838	380.697
1965–80 cohort	*n* = 505	*n* = 474	*n* = 276	
Age at onset	1.12 (1.00–1.25)	1.04 (0.97–1.12)	1.05 (0.95–1.17)	
Chronological age	1.04 (0.96–1.12)	1.05 (0.999–1.11)	1.06 (0.97–1.17)	
Women	0.82 (0.42–1.57)	1.15 (0.74–1.79)	0.82 (0.50–1.35)	
AIC	275.230	493.647	362.927	

Data are OR (95% CI) unless otherwise indicated. AIC, Akaike information criterion.

patients with T1D onset at a very young age may simply relate to the early introduction and acceptance of diabetes management as part of their lives as opposed to being required to make significant lifestyle changes at a time when physical changes also occur. Thus, the observed differences in complication incidence later in life may reflect differences in diabetes control during the early years after a diagnosis according to a patient's age of onset. In addition, the pathophysiology of kidney disease among those with very early onset may be distinct. For example, previous analyses supported the existence of a disease entity characterized by loss of kidney function without prior/concurrent albuminuria, which occurred in participants with a mean age at onset of 5 years who were more likely to use higher insulin doses per body weight despite insulin sensitivity and HbA_{1c} levels similar to those in patients with albuminuria (42).

Discrepancies in study findings also exist regarding the presence or absence of sex differences in kidney complication incidence among those with T1D. Historically, men were believed to be at greater risk than women. However, we previously showed that this excess of kidney disease cases in males observed in the earlier EDC diagnosis cohort (1950–64) was no longer present in the younger cohort (1965–80) (31). The more detailed current analyses provide similar results, with any increased risk among men compared with women being restricted to those diagnosed during 1950–64 at an age between 6 and 11 (girls) or 12 (boys) years. However, previous investigators reported the presence of differences in kidney disease risk by sex. Thus, in a cohort of individuals with T1D followed since diagnosis, female sex was associated with a 79% higher risk of microalbuminuria or worse (29). Analysis of a large (n = 1,195) pediatric T1D cohort from a Midwestern pediatric diabetes clinic network provided additional support that female sex is associated with an increased risk of developing persistent microalbuminuria (P = 0.08) (30). In contrast, despite no sex differences in ESRD risk in an overall cohort of patients with T1D (17), European investigators generally observed a greater risk in men than in women among those diagnosed with T1D after 10 years of age in Finland (13) and between 20 and 34 years of age in Sweden (12). Furthermore, data from the nationwide prospective German Diabetes Documentation System survey suggested that male sex is associated with the development of macroalbuminuria (43). The reason for these discrepancies is not clear, although confounding may have played a role. Indeed, in the DCCT, although male sex was associated with AER, this relationship was completely accounted for by differences in waist-to-hip ratio (44).

In conclusion, similar to previous reports, we observed that the risk of kidney complications is lowest among individuals diagnosed with T1D at a very young age, a finding consistent with the hypothesis that pathogenesis may be different in this subgroup. Study findings also suggest that advanced kidney disease can affect the vast majority of individuals with T1D, indicating that it is not limited to a susceptible minority. Although encouraging signs exist that ESRD specifically may be declining, this seems to reflect better management and slower progression of established kidney disease rather than prevention of early disease per se. These observations are alarming because as the life expectancy of patients with T1D increases, the number affected by advanced kidney disease will also rise, with dire implications for the patient as well as for the health care system. The immediacy by which focused prevention efforts should occur is therefore evident. Such prevention efforts should expand beyond approaches targeting glycemic control and should include intensive lipid and hypertension management. Research studies aiming to identify additional, currently unknown risk factors should also be undertaken, as they may offer an opportunity for additional therapeutic targets.

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References

1. Hovind P, Tarnow L, Rossing K, et al. Decreasing incidence of severe diabetic microangiopathy in type 1 diabetes. Diabetes Care 2003;26:1258–1264
2. Brenner BM, Cooper ME, de Zeeuw D, et al.; RENAAL Study Investigators. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. N Engl J Med 2001;345:861–869
3. Lewis EJ, Hunsicker LG, Bain RP, Rohde RD; The Collaborative Study Group. The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy [published correction appears in N Engl Med 1993;330:152]. N Engl J Med 1993; 329:1456–1462
4. Lewis EJ, Hunsicker LG, Clarke WR, et al.; Collaborative Study Group. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. N Engl J Med 2001;345:851–860
5. Parving HH, Jacobsen P, Rossing K, Smidt UM, Hommel E, Rossing P. Benefits of long-term antihypertensive treatment on prognosis in diabetic nephropathy. Kidney Int 1996;49:1778–1782
6. Astrup AS, Tarnow L, Rossing P, Pietraszek L, Riis Hansen P, Parving HH. Improved prognosis in type 1 diabetic patients with nephropathy: a prospective follow-up study. Kidney Int 2005;68:1250–1257
7. Svensson M, Sundkvist G, Arnqvist HJ, et al.; Diabetes Incidence Study in Sweden (DISS). Signs of nephropathy may occur early in young adults with diabetes despite modern diabetes management: results from the nationwide population-based Diabetes Incidence Study in Sweden (DISS). Diabetes Care 2003;26:2903–2909
8. Krolewski AS. Progressive renal decline: the new paradigm of diabetic nephropathy in type 1 diabetes. Diabetes Care 2015;38:954–962
9. Dahlquist G, Rudberg S. The prevalence of microalbuminuria in diabetic children and adolescents and its relation to puberty. Acta Paediatr Scand 1987;76:795–800
10. Rogers DG, White NH, Shalwitz RA, Palmberg P, Smith ME, Santiago JV. The effect of puberty on the development of early diabetic microvascular disease in insulin-dependent diabetes. Diabetes Res Clin Pract 1987;3:39–44
11. Svensson M, Nyström L, Schön S, Dahlquist G. Age at onset of childhood-onset type 1 diabetes and the development of end-stage renal disease: a nationwide population-based study. Diabetes Care 2006;29:538–542
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. Harjutsalo V, Maric C, Forsblom C, Thorn L, Wadén J, Groop PH; FinnDiane Study Group. Sex-related differences in the long-term risk of microvascular complications by age at onset of type 1 diabetes. Diabetologia 2011;54:1992–1999
14. Schultz CJ, Konopelska-Bahu T, Dalton RN, et al.; Oxford Regional Prospective Study Group.

Microalbuminuria prevalence varies with age, sex, and puberty in children with type 1 diabetes followed from diagnosis in a longitudinal study. Diabetes Care 1999;22:495–502
15. Donaghue KC, Fairchild JM, Craig ME, et al. Do all prepubertal years of diabetes duration contribute equally to diabetes complications? Diabetes Care 2003;26:1224–1229
16. Kullberg CE, Abrahamsson M, Arnqvist HJ, Finnström K, Ludvigsson J; VISS Study Group. Prevalence of retinopathy differs with age at onset of diabetes in a population of patients with type 1 diabetes. Diabet Med 2002;19:924–931
17. 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
18. Salgado PP, Silva IN, Vieira EC, Simões e Silva AC. Risk factors for early onset of diabetic nephropathy in pediatric type 1 diabetes. J Pediatr Endocrinol Metab 2010;23:1311–1320
19. Cummings EA, Sochett EB, Dekker MG, Lawson ML, Daneman D. Contribution of growth hormone and IGF-I to early diabetic nephropathy in type 1 diabetes. Diabetes 1998;47:1341–1346
20. Cho YH, Craig ME, Donaghue KC. Puberty as an accelerator for diabetes complications. Pediatr Diabetes 2014;15:18–26
21. Rudberg S, Persson B. Serum leptin levels in young females with insulin-dependent diabetes and the relationship to hyperandrogenicity and microalbuminuria. Horm Res 1998;50:297–302
22. Amin R, Schultz C, Ong K, et al.; Oxford Regional Prospective Study. Low IGF-I and elevated testosterone during puberty in subjects with type 1 diabetes developing microalbuminuria in comparison to normoalbuminuric control subjects: the Oxford Regional Prospective Study. Diabetes Care 2003;26:1456–1461
23. McNally PG, Raymond NT, Swift PG, Hearnshaw JR, Burden AC. Does the prepubertal duration of diabetes influence the onset of microvascular complications? Diabet Med 1993;10:906–908
24. Donaghue KC, Fung AT, Hing S, et al. The effect of prepubertal diabetes duration on diabetes. Microvascular complications in early and late adolescence. Diabetes Care 1997;20:77–80
25. Kordonouri O, Danne T, Enders I, Weber B. Does the long-term clinical course of type I diabetes mellitus differ in patients with prepubertal and pubertal onset? Results of the Berlin Retinopathy Study. Eur J Pediatr 1998;157:202–207
26. Holl RW, Grabert M, Thon A, Heinze E. Urinary excretion of albumin in adolescents with type 1 diabetes: persistent versus intermittent microalbuminuria and relationship to duration of diabetes, sex, and metabolic control. Diabetes Care 1999;22:1555–1560
27. Amiel SA, Sherwin RS, Simonson DC, Lauritano AA, Tamborlane WV. Impaired insulin action in puberty. A contributing factor to poor glycemic control in adolescents with diabetes. N Engl J Med 1986;315:215–219
28. Szadkowska A, Pietrzak I, Mianowska B, et al. Insulin sensitivity in type 1 diabetic children and adolescents. Diabet Med 2008;25:282–288
29. Goñi MJ, Forga L, Ibañez B, Cambra K, Mozas D, Anda E. Incidence and risk factors involved in the development of nephropathy in patients with type 1 diabetes mellitus: follow up since onset. Can J Diabetes 2016;40:258–263
30. Raman S, Dai H, DeLurgio SA, et al. High hemoglobin A1c variability is associated with early risk of microalbuminuria in children with T1D. Pediatr Diabetes 2016;17:398–406
31. Costacou T, Fried L, Ellis D, Orchard TJ. Sex differences in the development of kidney disease in individuals with type 1 diabetes mellitus: a contemporary analysis. Am J Kidney Dis 2011;58:565–573
32. Orchard TJ, Dorman JS, Maser RE, et al. Prevalence of complications in IDDM by sex and duration. Pittsburgh Epidemiology of Diabetes Complications Study II. Diabetes 1990;39:1116–1124
33. Ellis D, Buffone GJ. New approach to evaluation of proteinuric states. Clin Chem 1977;23:666–670
34. Olsen BS, Sjølie AK, Hougaard P, et al.; Danish Study Group of Diabetes in Childhood. The significance of the prepubertal diabetes duration for the development of retinopathy and nephropathy in patients with type 1 diabetes. J Diabetes Complications 2004;18:160–164
35. Svensson M, Eriksson JW, Dahlquist G. Early glycemic control, age at onset, and development of microvascular complications in childhood-onset type 1 diabetes: a population-based study in northern Sweden. Diabetes Care 2004;27:955–962
36. de Boer IH, Rue TC, Cleary PA, et al.; Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study Research Group. Long-term renal outcomes of patients with type 1 diabetes mellitus and microalbuminuria: an analysis of the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications cohort. Arch Intern Med 2011;171:412–420
37. de Boer IH, Afkarian M, Rue TC, et al.; Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Research Group. Renal outcomes in patients with type 1 diabetes and macroalbuminuria. J Am Soc Nephrol 2014;25:2342–2350
38. Nathan DM, Zinman B, Cleary PA, et al.; Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Research Group. Modern-day clinical course of type 1 diabetes mellitus after 30 years' duration: the diabetes control and complications trial/epidemiology of diabetes interventions and complications and Pittsburgh epidemiology of diabetes complications experience (1983-2005). Arch Intern Med 2009;169:1307–1316
39. Stewart JH, McCredie MR, Williams SM; ESRD Incidence Study Group. Divergent trends in the incidence of end-stage renal disease due to type 1 and type 2 diabetes in Europe, Canada and Australia during 1998-2002. Diabet Med 2006;23:1364–1369
40. Toppe C, Möllsten A, Schön S, Jönsson A, Dahlquist G. Renal replacement therapy due to type 1 diabetes; time trends during 1995-2010—a Swedish population based register study. J Diabetes Complications 2014;28:152–155
41. 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
42. Costacou T, Ellis D, Fried L, Orchard TJ. Sequence of progression of albuminuria and decreased GFR in persons with type 1 diabetes: a cohort study. Am J Kidney Dis 2007;50:721–732
43. Raile K, Galler A, Hofer S, et al. Diabetic nephropathy in 27,805 children, adolescents, and adults with type 1 diabetes: effect of diabetes duration, A1C, hypertension, dyslipidemia, diabetes onset, and sex. Diabetes Care 2007;30:2523–2528
44. Sibley SD, Thomas W, de Boer I, Brunzell JD, Steffes MW. Gender and elevated albumin excretion in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) cohort: role of central obesity. Am J Kidney Dis 2006;47:223–232