



Low Incidence of End-Stage Renal Disease in Childhood-Onset Type 1 Diabetes Followed for Up to 42 Years

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OBJECTIVE

End-stage renal disease (ESRD) is one of the most severe complications in type 1 diabetes. We aimed to estimate the cumulative incidence of ESRD in individuals with childhood-onset type 1 diabetes followed for up to 42 years.

RESEARCH DESIGN AND METHODS

Data were based on the nationwide, population-based Norwegian Childhood Diabetes Registry and included case patients with new-onset type 1 diabetes (age <15 years) who had received a diagnosis during the periods 1973–1982 and 1989–2012. Follow-up took place until the development of ESRD, death, emigration, or 30 November 2015. We estimated the cumulative incidence of ESRD by linking to the Norwegian Renal Registry.

RESULTS

Among the 7,871 patients, representing 147,714 person-years of follow-up, ESRD developed in 103 individuals (1.3%). The mean time from the diagnosis of diabetes to the development of ESRD was 25.9 years (range 12.7–39.1). The cumulative incidence of ESRD was 0.7% (95% CI 0.4–1.0) at 20 years' diabetes duration, 2.9% (2.3–3.7) at 30 years' duration, and 5.3% (4.3–6.5) at 40 years' duration. The risk of the development of ESRD was lower in women than in men (hazard ratio [HR] 0.61; 95% CI 0.41–0.91) and higher in individuals in whom diabetes had been diagnosed at 10–14 years of age compared with those in whom it was diagnosed before 10 years of age (HR 1.29; 1.06–1.56). We did not identify any significant difference in the risk of the development of ESRD between those in whom diabetes was diagnosed in 1973–1982 and in 1989–2012 (HR 0.80; 0.45–1.45).

CONCLUSIONS

We report a very low incidence of ESRD among patients with childhood-onset diabetes in Norway. The risk was lower in women compared with men and in individuals in whom diabetes was diagnosed at a younger age.

Diabetic nephropathy is one of the most serious complications of type 1 diabetes, and the presence and severity of kidney disease is closely linked to mortality (1). The incidence of end-stage renal disease (ESRD), defined as the need to start renal replacement therapy due to chronic renal failure, has been reported from several regions, and there seem to be substantial geographic variations (2–5). Studies from Finland and Sweden have indicated a lower incidence of ESRD among children in whom diabetes

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was diagnosed before age 5 years (2) or 10 years (3) compared with those in whom it was diagnosed up to age 34 years. Receiving a diagnosis in the pubertal years might give a higher risk of the development of ESRD. A declining incidence of ESRD in individuals with type 1 diabetes by more recent year of diagnosis has been reported in studies (2,4,6,7) comparing the incidence in cohorts of individuals with childhood-onset type 1 diabetes in previous decades compared with cohorts in which it was diagnosed more recently. This is in line with improved diabetes care, including better renoprotective treatment during the last 3 decades (8).

In Norway, the incidence of childhood-onset type 1 diabetes is high (9), but the incidence of ESRD in childhood-onset type 1 diabetes has not yet been assessed. To our knowledge, few studies have assessed the incidence of ESRD in nationwide cohorts with type 1 diabetes that were followed for >40 years. Therefore, the aim of this study was to estimate the cumulative incidence of ESRD by sex, age at diagnosis, and year of diagnosis of diabetes in individuals with up to 42 years of follow-up.

RESEARCH DESIGN AND METHODS

The study is based on data from the Norwegian Childhood Diabetes Registry, a population-based, nationwide registry including all new-onset cases of childhood-onset (age <15 years) diabetes in Norway (9). The study population consisted of two nationwide cohorts of individuals in whom type 1 diabetes had been diagnosed during the periods from 1 January 1973 to 31 December 1982 and from 1 January 1989 to 31 December 2012, and the completeness of ascertainment was high in both cohorts: >98% and 92%, respectively (9,10). Data from the cohort who had received diagnoses during 1973–1982 period were collected retrospectively (10). Since 1989, all case patients have been registered prospectively in the Norwegian Childhood Diabetes Registry. During the period 1983–1988, data were not collected nationwide. We excluded individuals with genetically verified monogenic diabetes, those who had received a diagnosis before 6 months of age, and those with known type 2 diabetes (11). The follow-up period for each participant was from the date of the diagnosis of type 1

diabetes to the diagnosis of ESRD, death, emigration, or 30 November 2015, whichever occurred first. To estimate the incidence of ESRD, we linked to the Norwegian Renal Registry, a nationwide registry with high completeness of ascertainment, including data on all patients in Norway receiving renal replacement therapy due to chronic renal failure since 1980 (12). ESRD was defined as the introduction of dialysis or transplantation. Survival or emigration status was obtained by linking to the National Population Registry using the unique national identification number. Mortality in individuals who had received a diagnosis of childhood-onset diabetes in 1973–1982 and 1989–2012 and had been followed up until 30 September 2013 has been described previously (11). The Norwegian Regional Committee for Research Ethics approved the study protocol (reference number 2012/1939).

We used Stata, version 13 (StataCorp LP, College Station, TX), for data handling and analyses. We estimated the cumulative incidence of ESRD by the number of years since the diagnosis of type 1 diabetes using the Kaplan-Meier method. When comparing the curves, we used the log-rank test. We also used years since the diagnosis of type 1 diabetes as the timescale in Cox regression models to estimate unadjusted and adjusted hazard ratios (HRs) with 95% CIs for the association between ESRD and age at type 1 diabetes diagnosis, sex, and calendar period of type 1 diabetes diagnosis. We assessed temporal changes in the cumulative incidence of the development of ESRD up to 26.9 years after the diagnosis of type 1 diabetes by comparing those in whom it was diagnosed in 1973–1982 and 1989–2012. We also analyzed the data considering death as a competing risk using the *stcrreg* function in Stata. We calculated the incidence rate as the number of ESRD case patients per 1,000 person-years during 5-year follow-up periods after the diagnosis of type 1 diabetes. Each person contributed to the total number of person-years of time they spent within each age band and calendar period. We used a significance level of 5%.

RESULTS

Among 7,871 individuals with type 1 diabetes, representing 147,714 person-years, we identified 103 individuals with

ESRD due to diabetic nephropathy during a mean follow-up time of 18.8 years (range 0–42.9 years). There were an additional seven case patients with ESRD caused by primary glomerulonephritis ($n = 4$), interstitial nephropathies ($n = 2$), or multisystem diseases ($n = 1$), and these case patients were not included in the analysis. Transplantation was performed in 17.5% of case patients (18 of 103 case patients). In total, 285 individuals died, and ESRD developed in 31 individuals before death. The shortest duration of diabetes before the development of ESRD was 12.7 years, and the average duration from the diagnosis of type 1 diabetes to the development of ESRD was 25.9 years (Table 1). The mean age at the development of ESRD was 35.9 years (range 22.1–48.3), with similar ages for men and women. The highest attained age at the end of the follow-up period was 57.5 years (mean 27.6). Notably, the lower mean age at the diagnosis of ESRD and the shorter time from the diagnosis of diabetes to the development of ESRD in the 1989–2012 cohort were related to the shorter follow-up period in this cohort.

The overall incidence rate of ESRD was 0.69 per 1,000 person-years (95% CI 0.57–0.85). ESRD developed in only three case patients before 15 years after the diagnosis of diabetes. However, the incidence increased substantially between 15 and 25 years after the diagnosis of diabetes; thereafter, it leveled off (Fig. 1). The cumulative incidence of ESRD was 0.7% (95% CI 0.4–1.0) at 20 years after the diagnosis of type 1 diabetes, 2.9% (95% CI 2.3–3.7) at 30 years, and 5.3% (95% CI 4.3–6.5) at 40 years. The probability of the development of ESRD was higher in men compared with women ($P = 0.017$) (Fig. 2A). There was a significantly increased risk for the development of ESRD with increasing age at the diagnosis of diabetes (Fig. 2B).

When sex, age at diagnosis, and the diagnosis period of type 1 diabetes were included simultaneously in a Cox regression model, it showed that the risk of the development of ESRD was 39% lower in women than in men (HR 0.61; 95% CI 0.41–0.91; $P = 0.016$) and 29% higher in individuals in whom diabetes had been diagnosed at 10–14 years of age compared with those in whom it had been diagnosed before 10 years of age (HR 1.29; 95% CI 1.06–1.56; $P = 0.011$). However,

Table 1—Demographic characteristics of the study population of childhood-onset (<15 years of age) type 1 diabetes in Norway, followed for ESRD, mortality, and emigration, or until 30 November 2015

	Total	Male	Female	Year of diagnosis	
				1973–1982	1989–2012
Participants	7,871 (100)	4,242 (53.9)	3,629 (46.1)	1,888 (24.0)	5,983 (76.0)
Age at diagnosis of type 1 diabetes, years	8.8 (0.6–14.9)	8.8 (0.6–14.9)	8.7 (0.6–14.9)	9.1 (0.6–14.9)	8.7 (0.6–14.9)
Duration of diabetes, years	18.8 (0–42.9)	18.7 (0–42.9)	18.8 (0–42.9)	35.8 (0–42.9)	13.4 (0–26.9)
Age at end of follow-up, years	27.6 (1.8–57.5)	27.6 (3.7–57.5)	27.5 (1.8–57.0)	44.8 (3.9–57.5)	22.2 (1.8–41.6)
Follow-up, person-years	147,714	79,381	68,333	67,411	80,303
Participants in whom ESRD developed	103 (1.3)	67 (1.6)	36 (1.0)	86 (4.6)	17 (0.3)
Incidence rates of ESRD per 1,000 person-years (95% CI)	0.69 (0.57–0.85)	0.84 (0.66–1.07)	0.52 (0.38–0.73)	1.28 (1.03–1.58)	0.53 (0.38–0.73)
Time from diagnosis of diabetes to ESRD, years	25.9 (12.7–39.1)	26.4 (14.1–39.1)	24.8 (12.7–37.4)	27.2 (16.5–39.1)	18.9 (12.7–24.6)
Age at diagnosis of ESRD, years	35.9 (22.1–48.3)	36.5 (24.1–48.3)	34.6 (22.1–45.8)	37.0 (22.1–48.3)	29.9 (22.4–38.7)
Dead	285 (3.6)	200 (4.7)	85 (2.3)	204 (10.8)	81 (1.4)
Emigrated	108 (1.4)	48 (1.1)	60 (1.7)	26 (1.4)	82 (1.4)
Deceased participants who had ESRD	31 (10.9)	22 (11.0)	9 (10.6)	27 (13.2)	4 (4.9)

Data are *n* (%) or mean (range), unless otherwise indicated.

we observed no significant difference in the risk of the development of ESRD for those in whom type 1 diabetes had been diagnosed in 1973–1982 compared with those in whom it was diagnosed in 1989–2012 up to 26.9 years after the diagnosis of diabetes (HR 0.80; 95% CI 0.45–1.45). Unadjusted HRs were similar (data not shown). We also performed a competing risk regression with death as a competing risk, and this gave very similar results.

CONCLUSIONS

In this study, we found that the incidence of ESRD in individuals with childhood-onset type 1 diabetes in Norway was low: 0.7% at 20 years after diagnosis, 2.9% at 30 years, and 5.3% at 40 years. The risk of the development of ESRD was lower in

women compared with men and in those in whom type 1 diabetes had been diagnosed at a younger age. We have shown earlier that all-cause mortality in these cohorts was elevated 3.6 times compared with the general population in Norway. The cumulative mortality at 35 years after the diagnosis of diabetes was 9.1% (95% CI 7.9–10.3). Acute complications were the leading cause of death before 30 years of age; after 30 years of age, cardiovascular death was predominant (11,13).

The cumulative incidence of ESRD in individuals with type 1 diabetes has been reported from several countries; for instance, it was estimated to be 9–11% at 25 years after the diagnosis of diabetes in the U.S. (4,6) and 7.8% at 30 years in Finland (2). Compared with these studies, we report a

very low cumulative incidence of ESRD. However, our estimates are in line with results from a Swedish study (3) that included individuals in whom type 1 diabetes had been diagnosed in 1977–1995. It is known that the incidence of ESRD is lower in Western European countries compared with, for instance, the U.S. According to a Norwegian population-based study, this could not be explained by the lower prevalence of chronic kidney disease, but rather by the lower risk of ESRD among individuals with chronic kidney disease (14). We believe that the results we report are influenced by several factors. The effect of near-normoglycemia on diabetic nephropathy was shown in the Oslo Study in 1986 (15) and resulted in recommendations of intensified insulin treatment at an early point in Norway. Also, national guidelines for the use of ACE inhibitors in normotensive patients with type 1 diabetes with microalbuminuria were available in 1995, although they had been used by many clinicians at an earlier point (16). We also believe that the low risk of ESRD may be related to the Norwegian health care system. Equal health care is provided for all patients in Norway without extra cost, independent of socioeconomic status. A Norwegian study (9) reported overt nephropathy in only 7.8% of individuals at 19–30 years after the diagnosis of diabetes in the cohort in whom childhood-onset type 1 diabetes was diagnosed in 1973–1982. Another important aspect is the fact that in the Norwegian and Swedish study populations no patients had received a

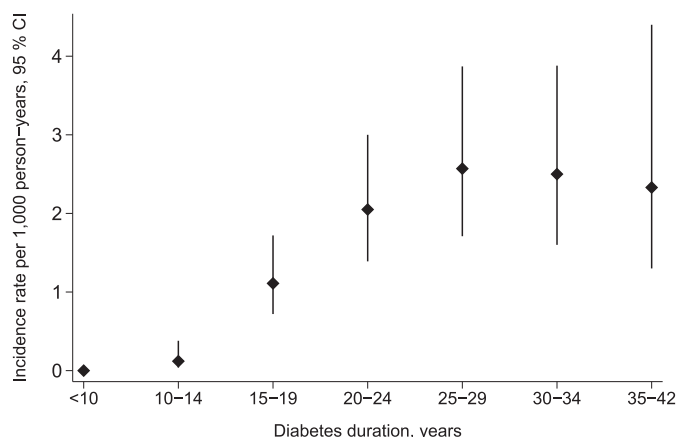


Figure 1—Incidence rates of ESRD per 1,000 person-years in 7,871 patients with type 1 diabetes who had received a diagnosis before 15 years of age during 1973–1982 and 1989–2012.

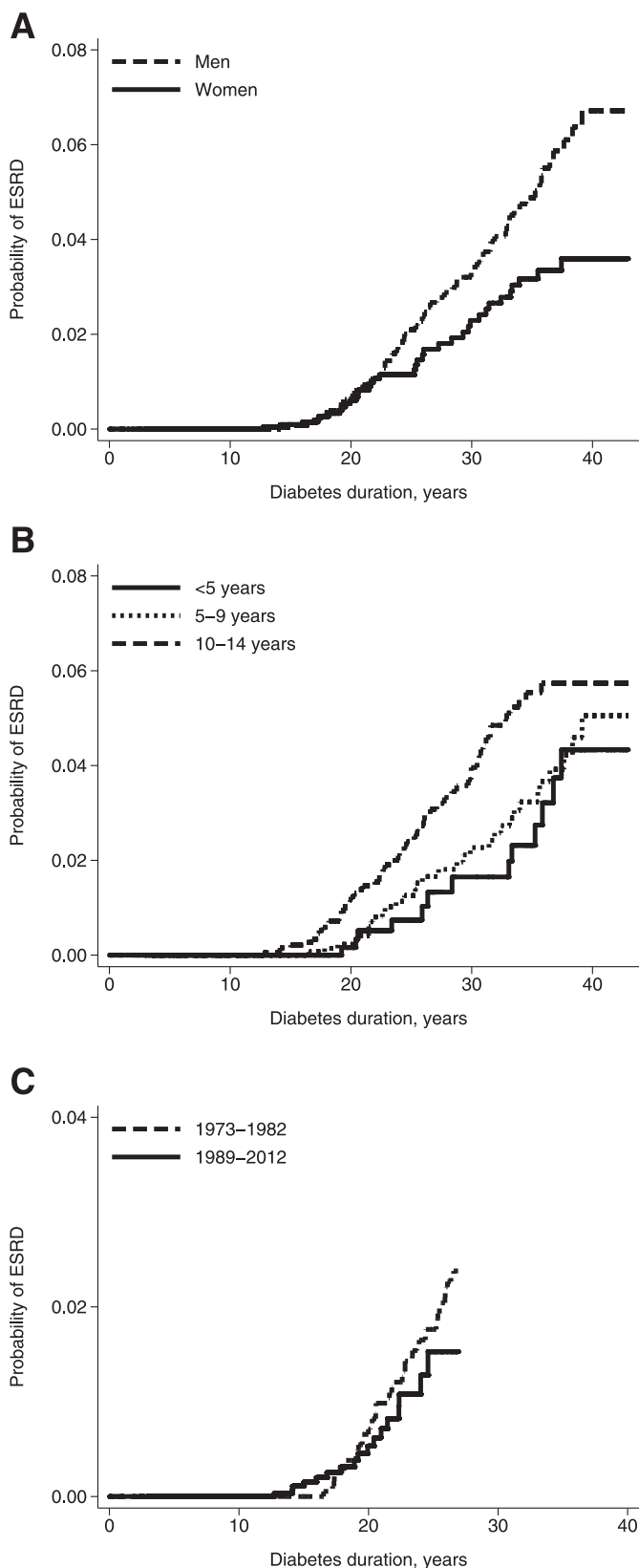


Figure 2—Cumulative incidence of ESRD in 7,871 patients with type 1 diabetes who had received a diagnosis before 15 years of age during 1973–1982 and 1989–2012. *A*: By sex, $P = 0.017$. *B*: By age at diagnosis of diabetes, $P = 0.011$. *C*: By time period of diagnosis of diabetes, $P = 0.38$. P values in *A* and *C* were calculated using the log-rank test and in *B* by the log-rank test, test for trend.

diagnosis of type 1 diabetes before 1973 and therefore probably have profited more from modern diabetes therapy, including renoprotective treatment, than patients who had received a diagnosis in earlier decades.

The more recent periods of diagnosis also pose a possible explanation for why we did not observe any significant change in the cumulative incidence of ESRD for those in whom type 1 diabetes had been diagnosed in 1973–1982 compared with in whom it was diagnosed in 1989–2012. A lower incidence of ESRD has been reported from several studies (2,4,6,8,17) when comparing type 1 diabetes cohorts in which diagnosis had been received more recently than in older cohorts. However, in our study, differences in the incidence of ESRD may appear between the two cohorts with longer durations of diabetes in individuals who had received a diagnosis in 1989–2012.

Our data support the more recent reports from Sweden (3), Finland (2), and the Diabetes Control and Complications Trial (7) showing that the peak in the incidence rate of diabetes nephropathy has been delayed compared with earlier studies from Denmark (18,19). The peak we report was at ~25–29 years after the diagnosis of diabetes; thereafter, it seemed to remain constant up to 42 years of follow-up. Our study indicates that the peak incidence of ESRD has been delayed or was probably reached at 25–29 years after the diagnosis of diabetes.

We observed a higher risk of ESRD in men with type 1 diabetes compared with women with type 1 diabetes. The cumulative incidence curve of ESRD for men and women seemed to diverge after 20 and 25 years diabetes duration. The higher risk in men is in accordance with some studies (3,6), but not all (2,20). It has been suggested that the sex difference could be explained by modifiable risk factors like blood pressure and lifestyle or renal physiology (20). There might also be sex differences in the patients' use of the health care system that may influence the development of long-term complications; for instance, women may use the available health care more frequently and be more compliant with the suggested treatment than men.

It has been indicated that young age at diagnosis of diabetes might prolong the time until the development of chronic complications (2,3,21,22). Our results

support this statement. We observed a 39% lower risk of the development of ESRD if a diagnosis of diabetes had been received before 10 years of age compared with a diagnosis being received at 10–14 years of age. Both Swedish and Finnish studies (2,3,23) have reported a lower risk of or a delay in the development of ESRD associated with being diagnosed with type 1 diabetes before 10 years of age compared with being diagnosed up to 34 years of age. We report a higher risk of ESRD if individuals had received a diagnosis of type 1 diabetes at 10–14 years of age, which might be a result of both psychological and endocrine factors that are important during the pubertal period. It is suggested that hormonal changes and poor glycemic control can accelerate the development of chronic complications (24). Also, receiving a diagnosis in puberty, a period in life represented by large psychological changes, might affect how well the patient adheres to diabetes treatment (25,26). This age is a particular challenge to the health care system to achieve good diabetes care in the patients.

This study is the first to estimate the incidence of ESRD in a cohort with childhood-onset type 1 diabetes in Norway. The study was based on two large, national registries with high completeness of ascertainment, which yielded high-quality data. Nearly all individuals in Norway in whom childhood-onset type 1 diabetes had been diagnosed during the study period were included. Another strength was analyzing the data by considering death as a competing risk; however, this did not change the results, probably because there were relatively few deaths. A limitation was the lack of clinical risk factors. However, patients with type 1 diabetes in Norway are treated according to national guidelines that are in line with recommendations from the International Society for Pediatric and Adolescent Diabetes and the American Diabetes Association. Another limitation was that we did not have data on levels of estimated glomerular filtration rate. The definition of ESRD was based purely on the introduction of dialysis or transplantation due to chronic renal failure.

In conclusion, we report a risk of the development of ESRD in individuals in Norway with childhood-onset type 1 diabetes that was lower than that reported in several

other countries (2,6,27). Receiving a diagnosis of diabetes before the pubertal period seems to imply lower risk, or a delay, in the development of ESRD.

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Author Contributions. V.G. wrote the manuscript, collected data, and organized and analyzed the data. M.S. helped with data analysis. L.C.S. supervised the data analysis. T.L. helped with data collection. G.J. contributed to initiating the study and helped with data collection. T.S. developed the study concept, initiated the study, collected data, and supervised the study. All authors contributed to interpretation of the results and to the discussion, critically reviewed the paper, and approved the final version of the article. T.S. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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