Decreasing Cumulative Incidence of End-Stage Renal Disease in Young Patients With Type 1 Diabetes in Sweden: A 38-Year Prospective Nationwide Study

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OBJECTIVE

Diabetic nephropathy is a serious complication of type 1 diabetes. Recent studies indicate that end-stage renal disease (ESRD) incidence has decreased or that the onset of ESRD has been postponed; therefore, we wanted to analyze the incidence and time trends of ESRD in Sweden.

RESEARCH DESIGN AND METHODS

In this study, patients with duration of type 1 diabetes >14 years and age at onset of diabetes 0–34 years were included. Three national diabetes registers were used: the Swedish Childhood Diabetes Register, the Diabetes Incidence Study in Sweden, and the National Diabetes Register. The Swedish Renal Registry, a national register on renal replacement therapy, was used to identify patients who developed ESRD.

RESULTS

We found that the cumulative incidence of ESRD in Sweden was low after up to 38 years of diabetes duration (5.6%). The incidence of ESRD was lower in patients with type 1 diabetes onset in 1991–2001 compared with onset in 1977–1984 and 1985–1990, independent of diabetes duration.

CONCLUSIONS

The risk of developing ESRD in Sweden in this population is still low and also seems to decrease with time.

Diabetic nephropathy is a devastating complication to diabetes. It can lead to end-stage renal disease (ESRD), which demands renal replacement therapy (RRT) with dialysis or kidney transplantation. In addition, diabetic nephropathy is associated with increased risk of cardiovascular morbidity and mortality (1,2). As a nation, Sweden, next to Finland, has the highest incidence of type 1 diabetes in the world (3), and the incidence of childhood-onset diabetes is increasing globally (4,5). The incidence of ESRD caused by diabetic nephropathy in these Nordic countries is fairly low as shown in recent studies, 3–8% at maximum 30 years' of diabetes duration (6,7). This is to be compared with studies from Denmark in the 1980s that showed a cumulative incidence of diabetic nephropathy of 41% at 40 years of diabetes duration. Older, hospital-based cohort studies found that the incidence of persistent proteinuria

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seemed to peak at 25 years of diabetes duration; after that, the incidence levels off (8,9). This implies the importance of genetic susceptibility as a risk factor for diabetic nephropathy, which has also been indicated in recent genome-wide scan studies (10,11). Still, modifiable factors such as metabolic control are clearly of major importance in the development of diabetic nephropathy (12–15). Already in 1994, a decreasing incidence of diabetic nephropathy was seen in a hospital-based study in Sweden, and the authors concluded that this was mainly driven by better metabolic control (16). Young age at onset of diabetes has previously been found to protect, or postpone, the development of ESRD caused by diabetic nephropathy, while diabetes onset at older ages is associated with increased risk (7,9,17). In a previous study, we found that age at onset of diabetes affects men and women differently (7). Earlier studies have indicated a male predominance (8,18), while our previous study showed that the incidence of ESRD was similar in men and women with diabetes onset before 20 years of age, but with diabetes onset after 20 years of age, men had increased risk of developing ESRD compared with women. The current study analyzes the incidence of ESRD due to type 1 diabetes, and changes over time, in a large Swedish population-based cohort with a maximum follow-up of 38 years.

RESEARCH DESIGN AND METHODS

Study Population

The Swedish Childhood Diabetes Register (SCDR) is a nationwide research register that started on 1 July 1977. All patients with incident type 1 diabetes who are younger than 15 years of age and resident in Sweden at the time of diagnosis are enrolled after informed consent from parents. Only patients who are insulin treated from diagnosis are registered. Internal and external validation has shown 96–99% ascertainment rate (19). The Diabetes Incidence Study in Sweden (DISS) records incident diabetes cases in the age-group between 15 and 34 years since 1 January 1983. Each clinic appoints a contact physician, who is responsible for reporting new cases. Classification of diabetes in DISS was initially made according to the World Health Organization classification but changed to the American Diabetes Association classification criteria in 1992. When antibodies and C-peptide levels were used to check, $<$10% of the patients with type 1 diabetes were misclassified (20). The level of ascertainment has been shown to be 82–91%, depending on the method of validation (21). The National Diabetes Register (NDR) started in 1996. It is a national prevalence register where patients with diabetes (any type) are registered and followed yearly for quality assessment from the age of 18 years. Nurses and doctors report to the register for at least one annual appointment; data are transmitted electronically to the register. All patients give written or oral consent to be registered. More than 90% of clinics report to the NDR (22). A validation of correct diagnosis has been made in a large cohort in NDR, showing $>$90% accuracy of diagnosis (23). The DISS and NDR provided data on cases of diabetes with onset after 15 years of age.

ESRD was defined according to the need to start active RRT. For retrieval of information on ESRD, the SCDR, NDR, and DISS were linked to the Swedish Renal Registry (SRR), using the Swedish unique personal identity code. All dialysis and renal transplantation units in Sweden report their patients to the SRR, which has been active since 1991. All patients are asked to give informed consent for registration, and very few choose not to be registered. A validation study has shown that at least 95% of patients with RRT are reported to SRR (24). For obtainment of date of death, the diabetes registers were linked to the Swedish Cause of Death Register.

Earlier studies have shown that it takes $\sim$15 years to develop persistent proteinuria and another 10 to proceed to ESRD (9,25). In the current study population, no patients developed ESRD because of type 1 diabetes at a duration $<$14 years; thus only patients with diabetes duration of $\geq$14 years were included in the study. By the end of 2015, the SCDR included 10,322 patients with type 1 diabetes with diabetes duration $>$14.0 years. The NDR contributed 7,630 cases of type 1 diabetes with onset at 15–34 years of age, and the DISS register added 808 unique individual cases. In the NDR, only the year of diabetes onset is registered—not the full date. For calculations of duration, all were given starting date 30 June (midpoint estimate) of the given year.

The study was approved by the regional ethics review board at Umeå University and the ethics committee at Statistics Sweden, according to the Swedish law on research ethics, and performed in accordance with the Declaration of Helsinki.

Statistical Analysis

Age at onset of diabetes was divided into three groups: 0–9, 10–19, and 20–34 years. Incidence rates of ESRD were calculated as number of cases divided by number of years at risk in the different diabetes duration groups: 14–19, 20–24, 25–29, and $\geq$30 years. Every individual contributes to the total person-years with the time they spend within each duration interval. We used the website http://openepi.com and function http://openepi.com/PersonTime1/PersonTime1.htm for calculation of the CI of the interval rate. The results from the Rothman/Greenland method were given in the tables (26). Incidence rates in different calendar year groups were analyzed; the periods were 1977–1984, 1985–1990, and 1991–2001. These periods were chosen because the guidelines for more intensive treatment were issued in 1982 and we considered a likely adjustment time to be 2 years. This also gave us cohorts of approximately the same time length and equal numbers of patients at risk. Cox regression analyses were performed to estimate hazard ratios (HRs) of developing ESRD, adjusted for age at follow-up and sex. The time at risk was calculated from onset of diabetes until ESRD (i.e., date of first treatment with RRT), death, loss to follow-up, or the end of the study (31 July 2015). Kaplan-Meier analyses may overestimate the cumulative incidence if death is censored in the same way as when censoring for other reasons; therefore, all calculations of cumulative incidence were analyzed with death as a competing risk. This method provides a more accurate estimate, since it accounts for death as an event that eliminates the risk of ESRD. The R statistical software, version 2.5.1 (R Foundation for Statistical Computing) (available from http://www.r-project.org/index.html), with the function "cuminc" from the "cmprsk" package, was used for calculations with death as a competing risk event. The "smooth.spline()" function in R was used for Fig. 1. The other statistical analyses were performed using SPSS, version 23.0, for Windows.

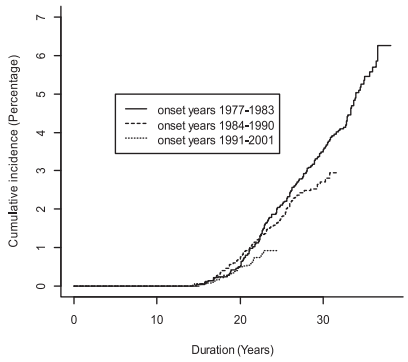

Figure 1—Cumulative incidence of ESRD due to type 1 diabetes with onset in different calendar year periods. There is a significant decrease in cumulative incidence between the earlier periods and the period 1991–2001.

RESULTS

Demographics

A total of 18,760 unique patients were included in the study: 10,560 (56%) men and 8,200 (44%) women. The mean age at the end of the study was somewhat lower for women, 38.9 years, compared with 40.2 years for men. Women tend to develop type 1 diabetes about a year earlier than men: mean age 15.0 years for women compared with 16.5 years for men. There was no difference regarding mean diabetes duration between men and women in the study (23.8 years for women and 23.7 years for men). A total of 317 patients had developed ESRD due to diabetes. The maximum diabetes duration was 38.1 years for patients in the SCDR and 32.6 years for the NDR and the DISS. The median time from onset of diabetes to ESRD was 22.9 years (minimum 14.1 and maximum 36.6). Table 1 shows the numbers of males and females with and without ESRD, the duration of diabetes to ESRD, and the number of deaths associated with and not associated with ESRD at different ages at diabetes onset. At follow-up, 77 patients with ESRD and 379 without ESRD had died (Table 1). The risk of dying during the course of the study was almost 12 times higher among the ESRD patients (HR 11.9 [95% CI 9.3–15.2]) when adjusted for sex and age. Males had almost twice as high a risk of dying as female patients (HR 1.7 [95% CI 1.4–2.1]), adjusted for ESRD and age.

Long-term Incidence Rate and Cumulative Incidence of ESRD

The overall incidence rate of ESRD during 445,483 person-years of follow-up was 0.71 per 1,000 person-years. Table 2 shows the incidence rate by 1,000 person-years at different diabetes duration intervals. The incidence rate increases with diabetes duration. For patients with diabetes onset at 0–9 and 10–19 years of age, there was an increase in incidence up to 36 years of duration; at longer durations, the number of cases is too small and results must be interpreted with caution. With diabetes onset at 20–34 years of age the incidence rate increases until 25 years of diabetes duration, and then a decrease can be observed (Table 2).

In comparison of different time periods, the risk of developing ESRD was lower in patients with diabetes onset in 1991–2001 compared with onset in 1977–1984 (HR 3.5 [95% CI 2.3–5.3]) and 1985–1990 (HR 2.6 [95% CI 1.7–3.8]), adjusted for age at follow-up and sex. Figure 1 shows the cumulative incidence of ESRD at different diabetes durations, divided by calendar year of diabetes onset.

Effect of Age at Onset and Sex on Development of ESRD

Table 3 shows the cumulative incidence of ESRD at different diabetes durations in different age-at-onset groups, adjusted for death as competing risk. The lowest risk of developing ESRD was found in the group with onset of diabetes before the age of 10 years—both for males and females (Supplementary Fig. 1). With this group as reference, males diagnosed with diabetes at 10–19 or 20–34 years of age had increased risk of ESRD (HR 2.4 [95% CI 1.6–3.5] and HR 2.2 [95% CI 1.4–3.3]), respectively. For females, the risk of developing ESRD was also increased with diabetes onset at 10–19 years of age (HR 2.4 [95% CI 1.5–3.6]); however, when diabetes was diagnosed after the age of 20 years, the risk of developing ESRD was not increased compared with an early onset of diabetes (HR 1.4 [95% CI 0.8–3.4]).

There were no significant differences between males and females in any age-at-onset group. With age at diabetes onset 20–34 years, there was a tendency toward higher risk for males (HR 1.5 [95% CI 0.96–2.35]).

CONCLUSIONS

By combining data from the SCDR, DISS, and NDR registers and identifying ESRD cases via the SRR, we have included close to all patients with type 1 diabetes in Sweden with diabetes duration >14 years who developed ESRD since 1991. The cumulative incidence of ESRD in this study is low: 5.6% (5.9% and 5.3% for males and females, respectively) at maximum 38 years of diabetes duration. For the first time, we could see a clear decrease in ESRD incidence in Sweden by calendar year of diabetes onset. The results are in line with a recent study from Norway that reported a modest incidence of 5.3% after 40 years of diabetes duration (27). In the current study, we found a decrease in the incidence rate after 25 years of diabetes duration in the group with diabetes onset at 20–34 years. With age at onset of diabetes 0–9 or 10–19 years, the ESRD incidence

Table 1—Time from diabetes onset to ESRD and number of deaths with and without ESRD, by age at diagnosis and sex, in patients with duration of type 1 diabetes >14 years

	Males					Females				
				Deaths					Deaths	
Age at onset of diabetes (years)	Without ESRD	With ESRD	Time to ESRD, years	Without ESRD	With ESRD	Without ESRD	With ESRD	Time to ESRD, years	Without ESRD	With ESRD
0–9	3,073 (98.9)	34 (1.1)	27.2 (23.4–32.5)	60 (2.0)	10 (29.4)	2,926 (99.0)	31 (1.0)	25.2 (21.1–30.2)	35 (1.2)	8 (25.8)
10–19	3,531 (97.5)	91 (2.5)	22.8 (20.0–26.6)	76 (2.2)	20 (22.0)	2,709 (97.5)	70 (2.5)	22.3 (18.7–26.7)	31 (1.1)	18 (25.7)
20–34	3,767 (98.3)	64 (1.7)	21.2 (17.5–25.0)	129 (3.4)	14 (21.9)	2,437 (98.9)	27 (1.1)	21.7 (18.6–24.6)	48 (2.0)	7 (25.9)
0–34	10,371 (98.2)	189 (1.8)	23.1 (20.0–26.6)	265 (2.6)	44 (23.3)	8,072 (98.4)	128 (1.6)	22.6 (19.3–27.0)	114 (1.4)	33 (25.8)

Data are median (interquartile range) or *n* (%). Percent deaths given within each group based on number of patients with or without ESRD.

Table 2—Incidence rates per 1,000 person-years at different diabetes duration intervals

Age at onset of diabetes (years)	Diabetes duration intervals (males/females)			
	14–19 years	20–24 years	25–29 years	30–38 years
0–9	0.07 (0.009–0.5)/0.4 (0.2–0.9)	1.3 (0.7–2.4)/1.0 (0.5–2.0)	1.9 (1.0–3.5)/1.6 (0.8–3.2)	4.0 (2.3–7.0)/3.1 (1.6–6.0)
10–19	1.2 (0.8–1.8)/1.7 (1.2–2.6)	3.5 (2.5–4.9)/2.5 (1.6–3.9)	3.5 (2.3–5.4)/3.2 (2.0–5.2)	4.1 (2.4–7.3)/4.1 (2.2–7.7)
20–34	1.3 (0.8–1.9)/0.6 (0.3–1.2)	2.5 (1.7–3.7)/2.4 (1.4–3.9)	3.1 (1.9–5.19)/1.3 (0.5–3.5)	0/2.0 (0.3–14.5)
0–34	0.9 (0.7–1.2)/0.9 (0.7–1.2)	2.5 (2.0–3.2)/1.9 (1.4–2.6)	2.9 (2.2–3.8)/2.1 (1.5–3.1)	3.6 (2.4–5.4)/3.5 (2.2–5.4)

Data in parentheses are 95% CIs.

rate increases until 35 years of diabetes duration, but owing to the limited number of patients with longer duration we cannot determine whether the peak incidence has been reached or not. We can, however, conclude that the onset of ESRD has been postponed at least 10 years compared with that in older prospective cohort studies (8,9).

The lower cumulative incidence of ESRD in patients with diabetes onset 1991–2001 compared with earlier cohorts is of interest. We believe that the prolonged diabetes duration before ESRD can be attributed to more intense self-care education efforts and improved care of patients with type 1 diabetes in Sweden during the later years. It is known that the metabolic control in the first years of diabetes is important for the risk of later complications (15), and, as shown in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC), intense insulin treatment from onset of diabetes rendered a lower risk of developing renal complications (28). Most of the patients in our registers have benefitted from modern diabetes treatments. In 1982, intensive insulin treatment and home blood glucose monitoring were already recommended by the Swedish Pediatric Association Working Group for Diabetes in Children, in the nationwide Diabetes in Childhood Care Program (29). Moreover, active prevention of diabetic nephropathy, by introduction of ACE inhibitors in individuals with persistent microalbuminuria, was recommended in national guidelines from the Swedish Pediatric Association issued in 1996 (30). In adults, national guidelines for treatment of diabetes were issued by the Swedish Board of Health and Welfare. These guidelines, first issued in 1996, also involve intensive treatment of blood pressure and lipids, including ACE inhibition and statins, for persons with type 1 diabetes (31). In addition, all health care visits and medicines are free of charge up to the age of 18 years. Also, regardless of age, insulin, syringes, and glucose monitoring devices are always free of charge in Sweden. The health care system in Sweden is provided for by the government, and there are extensive subsidies to make the access to health care as equal as possible. Patients with onset of diabetes in the late 1970s or early 1980s, however, may have had limited resources in their first years with diabetes since new treatment regimens, such as blood glucose monitors and inhibition of the renin angiotensin system, were not yet introduced. In other Nordic countries (27,31) with similar social welfare systems and well-developed national guidelines, the incidence of ESRD due to type 1 diabetes is also low. Discrepancies in the intensity of diabetes care could be part of the explanation behind the higher incidence numbers (13% and 18% after 30 years of diabetes) observed in other countries (32,33). This was also implied in a multinational study on variation of HbA_{1c} level within and between countries published recently (34). Sweden had the lowest mean HbA_{1c} level and also the least variation between different centers. The U.S. had a higher mean HbA_{1c} but still had low variation between centers.

In our study, we did not find any statistically significant differences in risk of developing ESRD between males and females, but among the patients with diabetes onset at the age of 20 years and older, we saw a trend toward increased risk of ESRD for males. This was also shown in a study from Finland by Harjutsalo et al. (35) but only after 40 years of diabetes duration. In a Norwegian study by Gagnum et al. (27), an increased risk for ESRD was found among male patients after a shorter follow-up and in a younger-age-at-onset group. On the other hand, a recently published study by Costacou and Orchard (33) showed that an onset in later calendar years rendered a higher or equal risk of ESRD for females depending on duration of diabetes, so the difference between males and females regarding risk of ESRD remains to be elucidated.

In conclusion, this large population-based study shows a low incidence of ESRD in Swedish patients with onset of type 1 diabetes after 1977 and an encouraging decrease in risk of ESRD, which is probably an effect of improved diabetes care. We confirm that young age at onset of diabetes protects against,

Table 3—Cumulative incidences of ESRD with death as a competing risk

Age at diagnosis (years)	Duration of type 1 diabetes (males/females)			
	20 years	25 years	30 years	35 years
0–9	0 (0–0.2)/0.3 (0–0.6)	0.7 (0.4–1.2)/0.8 (0.4–1.3)	1.7 (1.1–2.5)/1.5 (1.0–2.3)	3.9 (2.6–5.6)/2.8 (1.8–4.1)
10–19	0.8 (0.5–1.2)/1.1 (0.7–1.5)	2.5 (1.9–3.3)/2.3 (1.7–3.0)	4.2 (3.3–5.3)/3.7 (2.8–4.8)	6.5 (5.0–8.4)/5.8 (4.1–7.8)
20–34	0.8 (0.5–1.2)/0.4 (0.2–0.7)	2.0 (1.5–2.7)/1.6 (1.0–2.3)	3.4 (2.6–4.5)/2.2 (1.4–3.3)	—
0–34	0.6 (0.4–0.8)/0.6 (0.4–0.8)	1.8 (1.5–2.2)/1.5 (1.2–1.9)	3.2 (2.7–3.8)/2.5 (2.0–3.0)	5.4 (4.4–6.5)/4.1 (3.2–5.1)

Data are % (95% CI). The cumulative incidence with death as a competing risk takes into account that death is an event competing with the risk of developing ESRD.

or prolongs, the time until development of severe complications.

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