

Age at Onset of Childhood-Onset Type 1 Diabetes and the Development of End-Stage Renal Disease

A nationwide population-based study

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ON BEHALF OF THE SWEDISH CHILDHOOD
DIABETES STUDY AND THE SWEDISH
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URAEMLIA*

OBJECTIVE — To analyze the impact of age at onset on the development of end-stage renal disease (ESRD) due to diabetic nephropathy in a nationwide population-based cohort with childhood-onset type 1 diabetes.

RESEARCH DESIGN AND METHODS — A record linkage between two nationwide registers, the Swedish Childhood Diabetes Registry, including 12,032 cases with childhood-onset diabetes, and the Swedish Registry for Active Treatment of Uraemia was performed. Log-rank test was used to test differences between cumulative risk curves of developing ESRD due to diabetic nephropathy in three different strata of age at onset (0–4, 5–9, and 10–14 years).

RESULTS — At a maximum follow-up of 27 years, 33 patients had developed ESRD due to diabetic nephropathy and all had a diabetes duration >15 years. In total, 4,414 patients had diabetes duration >15 years, and thus the risk in this cohort to develop ESRD was 33 of 4,414 (0.7%). A significant difference in risk of developing ESRD was found between the youngest (0–4 years) and the two older (5–9 and 10–14 years) age-at-onset strata ($P = 0.03$ and $P = 0.001$, respectively). A significant difference in the risk of developing ESRD was also found between children with prepubertal (0–4 and 5–9 years, $n = 2,424$) and pubertal (10–14 years, $n = 2000$) onset of diabetes ($P = 0.002$). No patient with onset of diabetes before 5 years of age had developed ESRD.

CONCLUSIONS — With a median duration of 21 years in this population-based Swedish cohort with childhood-onset diabetes, <1% of the patients had developed ESRD due to diabetic nephropathy, and a prepubertal onset of diabetes seems to prolong the time to development of ESRD.

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Poor glycemic control is a necessary but not sufficient factor for the development of diabetic nephropathy (1–3). Other factors, such as perinatal, hormonal, and genetic issues, seem to contribute (4,5). Puberty, in addition to

frequently noted deterioration of glycemic control, is characterized by rapid growth and hormonal changes, all factors that could promote the development of chronic diabetes complications (6–8). Thus, some clinical studies (6,9–12) but

not all (13–17) suggest that prepubertal diabetes duration may contribute less to the development of microvascular complications than pubertal and postpubertal duration. In addition, there are studies that have suggested that an onset of diabetes in the youngest age-group, age <5 years, may delay development of chronic diabetes complications such as microalbuminuria and retinopathy (18–21).

In this large population-based study we assessed the cumulative incidence of ESRD due to diabetic nephropathy in a cohort with childhood-onset diabetes with a median duration of 21 years. In addition, we analyzed the effect of age at onset on the development of ESRD due to diabetic nephropathy using two large nationwide population-based registers.

RESEARCH DESIGN AND METHODS

The Swedish Childhood Diabetes Registry

In the Swedish health care system all children aged 0–14 years with suspected diabetes are referred to pediatric departments. Since 12 July 1977, all children in Sweden with newly diagnosed insulin-treated diabetes are reported to the Swedish Childhood Diabetes Registry (SCDR). This report includes information on personal identification number, sex, county of residence, date of diagnosis (first insulin injection), date of reporting, reporting hospital, and physician. Comparison with external sources has shown that the level of ascertainment in the SCDR is 96–99% (22).

The Swedish Registry for Active Treatment of Uremia

The Swedish Registry for Active Treatment of Uraemia (SRAU) was started in 1991, registering data on all patients who were on renal replacement therapy (dialysis treatment or a functioning kidney transplant) at that time. Since then, all patients with chronic renal failure who start dialysis treatment or receive a kidney transplant are reported to SRAU. In addi-

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*Complete lists of Swedish Childhood Diabetes Study members and SRAU board members appear in the APPENDIX.

Abbreviations: ESRD, end-stage renal disease; SCDR, The Swedish Childhood Diabetes Registry; SRAU, Swedish Registry for Active Treatment of Uraemia.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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tion to treatment modality, the register includes information on the primary renal disease, age, and sex and, since 1998, also comorbidity factors of importance for survival, such as diabetes, cardiovascular disease, malignancy, and hypertension. Date of registration is defined as date of first dialysis or kidney transplantation. All patients are followed until death. All dialysis and transplant units in Sweden report data to the SRAU. A study among all patients who had died from renal disease since 1991 in five counties in Sweden showed that <5% of patients who have started treatment for chronic renal failure had not been reported to the SRAU during this period (23). Thus, in this study ESRD is defined as a need to start active treatment of uremia (e.g., dialysis or renal transplantation) due to renal failure (e.g., a glomerular filtration rate <10–15 ml/min).

The study cohort

The study population included patients born after 1 January 1963 diagnosed with childhood-onset diabetes between 1 July 1977 and 31 December 2003 and reported to the SCDR ($n = 12,032$). By using the personal identification number given to all Swedish citizens, this register was linked to the Swedish cause-of-death register, covering deaths up to 31 December 2002, and we found that altogether 100 patients (0.8%) had died, 30 patients died after >15 years, and 4 patients died after having developed ESRD due to diabetic nephropathy.

Among patients who died with a diabetes duration <15 years none had developed ESRD. When linking the SCDR to the SRAU we identified 40 patients that had developed ESRD during this period. Thirty-three (82%) of them had diabetic nephropathy as the primary cause, and of those, 4 had died at follow-up. Among these 33 patients, only 1 received a renal transplant before the start of dialysis. Seven (18%) patients had other renal diseases, i.e., polyarteritis (1), pyelonephritis (2), polycystic renal disease (1), interstitial nephritis (1), and IgA-nephritis (1). In one patient we were not able to specify the primary renal disease. These seven patients were excluded from the analyses.

The first patient from the SCDR with ESRD due to diabetic nephropathy was registered in the SRAU in 1993, and all 33 of them were diagnosed with diabetes between 1 July 1977 and 31 December 1985. None of them had diabetes duration <15 years. Thus, all patients diag-

Table 1—Clinical characteristics of the study cohort with and without ESRD

	Patients	
	With ESRD	Without ESRD
<i>n</i>	33	4,381
Sex		
Male	13 (39)	2,316 (53)
Female	20 (61)	2,071 (47)
Age at onset of diabetes (years)		
0–4	0	879 (20)
5–9	9 (27)	1,536 (35)
10–14	24 (73)	1,966 (45)
Age at onset of diabetes (years)	12.4 (5–15)	9.3 (0–15)
Time to follow-up (years)	20.5 (18–26)	21.0 (15–27)
Age at onset of ESRD (years)	30.8 (25–36)	
Time from onset of diabetes to ESRD (years)	20.0 (15–23)	

Data are median (range) or *n* (%).

nosed with diabetes between 1 July 1977 and 31 December 1985 ($n = 4,414$) comprised the study cohort used in the statistical comparisons of the effect of age at onset, since patients with a duration of diabetes <15 years were not at risk of developing ESRD in this cohort.

Age-at-onset strata

The patients were divided into three 5-year strata according to age at onset of diabetes (0–4, 5–9, and 10–14 years). We defined the two youngest age-at-onset strata as being prepubertal, thus using the age of 10 years as a proxy for puberty in both girls and boys. The study was approved by the research ethics committee of Umeå University.

Statistical methods

Data are presented as median (range) as indicated. Life tables, adjusting for diabetes duration, were constructed, and log-rank test was used to test the significance of the differences between cumulative risk curves of developing ESRD due to diabetic nephropathy in three different strata of age at onset (0–4, 5–9, and 10–14 years). Start of follow-up was defined as the onset of diabetes, i.e., first insulin injection. Time to event was defined as the time from onset of diabetes to registration in the SRAU, i.e., the first treatment on dialysis or date of transplantation. Patients were followed until an event occurred (ESRD or death) or until 31 December 2003. A *P* value <0.05 was considered statistically significant. Results are given with their 95% CIs. SPSS 11.0 for Mac OS X (Software MacKiev, Cupertino, CA) was used to analyze data.

RESULTS

Clinical characteristics of the study cohort

The crude cumulative incidence of ESRD due to diabetic nephropathy was 33 of 12,032 (0.3%). However, in the population at risk, i.e., with a diabetes duration >15 years, a total of 33 of 4,414 (0.7%) of the patients had developed ESRD due to diabetic nephropathy. The median time of follow-up in this cohort was 21 years (range 15–27) and the median time from onset of diabetes to ESRD was 20 years (range 15–23). There was no significant difference in median time of follow-up in the three different age-at-onset strata (20.3 [range 15–27], 20.5 [15–27], 20.4 [15–27] years, respectively). Table 1 shows clinical characteristics of patients with and without ESRD due to diabetic nephropathy.

Effect of age at onset on ESRD

A significant difference in the risk of developing ESRD was found between the youngest (0–4 years) and the two older (5–9 and 10–14 years) age-at-onset strata ($P = 0.03$ and $P = 0.001$, respectively). No patients with ESRD due to diabetic nephropathy were found in the 0–4 years age-at-onset group. These results are shown in Fig. 1A. Since our focus is prepubertal onset of diabetes, the two prepubertal age-groups with an onset of diabetes before the age of 10 (0–4 and 5–9 years [$n = 2,426$]) were merged, and a significant difference in the risk of developing ESRD was found between children with prepubertal and pubertal onset of diabetes ($P = 0.002$). The results are summarized in Fig. 1B.

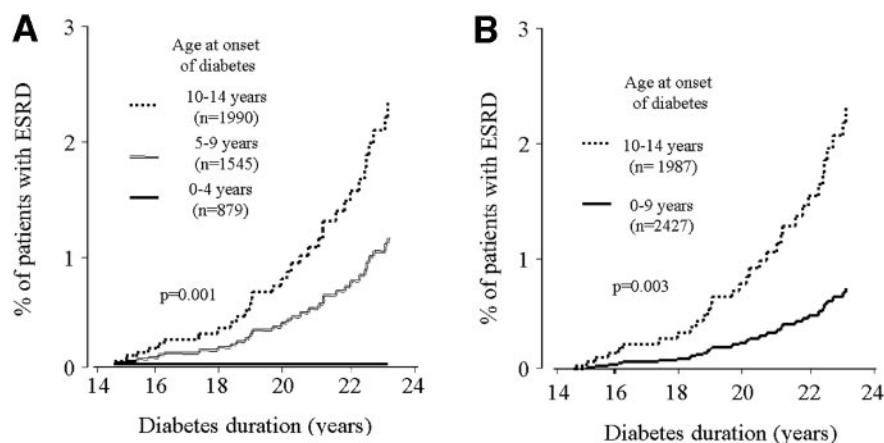


Figure 1—A: Risk of developing diabetic nephropathy and ESRD during follow-up in children 0–4, 5–9, and 10–14 years at onset of diabetes. *n*, number of patients in each age-at-onset group. B: Risk of developing diabetic nephropathy and ESRD during follow-up in children 0–9 (prepubertal) and 10–14 (pubertal) years at onset of diabetes. *n*, number of patients in each age-at-onset group.

CONCLUSIONS— In this nationwide population-based study <1% of patients with diabetes duration >15 years and a median time to follow-up of 21 years (range 15–27) developed ESRD due to diabetic nephropathy. This cumulative incidence is surprisingly low, but comparisons with previous studies are difficult to interpret since most other studies have used microalbuminuria (incipient nephropathy), macroalbuminuria (overt nephropathy), or urinary albumin-to-creatinine ratio as outcome variables and markers of diabetic nephropathy. In addition, the follow-up time varies between studies. The low prevalence of ESRD found in our study may be due to the relatively short time of follow-up, 15–27 years, since the peak incidence of diabetic nephropathy previously has been found to occur 25–30 years after the onset of type 1 diabetes (9,24). Thus, the most probable explanation of our findings would be a delay in the incidence peak of onset of ESRD. In 1996, a 35-year follow-up study from the Joslin cohort study (from 1959 and onwards) showed a cumulative risk of dialysis treatment (ESRD) of 6–7% at 20 years duration of type 1 diabetes (25). More recent studies have shown a declining incidence of diabetic nephropathy over time both in the U.S. and in Europe (9,26,27), and similar trends have also been shown in Swedish patient cohorts with respect to both incipient (28) and overt nephropathy (29). A declining incidence of ESRD or a delay in the peak incidence of onset has also been indicated by the fact that the take-on rate for type 1 diabetes in the European Dial-

ysis and Transplant Association registry has remained unchanged through the 1990s despite an increase in prevalence of type 1 diabetes and a longer survival in patients with type 1 diabetes (30). This has also been suggested by findings from the SRAU (31). However, there are other studies from Denmark and Iceland that have indicated an unchanged incidence of diabetic nephropathy (32,33). Only long-term follow-up studies in population-based cohorts may reveal such trends.

Many of the previous follow-up studies on chronic diabetes complications involve patients from specialized clinics only (Joslin, Steno, and Linköping), thus not mirroring the general population. On the other hand, population-based cohort studies may be incomplete. Our population-based cohort includes 96–99% of the cases with childhood-onset type 1 diabetes during the defined time period in Sweden, and the SRAU includes 95% of cases with ESRD. A concern with population-based prevalence studies is that they might miss patients that have already died and thus underestimate the occurrence of the disease. The death rate in young patients with diabetes is approximately twice the expected rate also at short duration (34). In this study only 70 patients died before a diabetes duration >15 years, all without a diagnosis of ESRD. In the study cohort, 30 of 4,414 patients (0.7%) had died, 4 after having developed ESRD. It is unlikely that the deaths of 26 patients without ESRD would significantly affect our results. The SRAU started in 1991, initially also collecting prevalent cases of ESRD, and none of the patients in

the SCDR then had a duration >13 years. Therefore, our study should cover the vast majority of all potential cases in the defined time period and thus represents the Swedish population at large.

To the best of our knowledge, we show, for the first time in a nationwide population-based study, that onset of diabetes before the age of 10 years, and thus prepubertal, significantly influenced the time to development of ESRD due to diabetic nephropathy. This suggests, not that the early ages of onset are protective but rather that “the clock does not run as fast” for the years before pubertal onset. A similar impact of age at onset has been indicated in a population-based study in an American and a Japanese cohort where a positive correlation between age at onset and risk of ESRD was found (35). Other studies have indicated that the prepubertal years with diabetes involve a reduced risk or a longer time to development of diabetic nephropathy and other microvascular complications, e.g., retinopathy (6,9,11,36–38). Our study and others (18–21) may also suggest that an onset of diabetes before the age of 5 years may have an additional impact on risk or the time to development of microvascular complications.

The mechanism behind this effect of age at onset is not clear, but it has been speculated that puberty, characterized by both rapid growth, hormonal changes, and worsening in glycemic control, may accelerate the processes leading to chronic diabetes complications such as ESRD. Hyperglycemia is crucial and promotes early glomerular hyperfiltration and, in addition, stimulates pathways that may influence the development of diabetic nephropathy (39,40). A role of growth hormone has been indicated (41); however, the postpubertal susceptibility to diabetic nephropathy seems to be persistent during adulthood (9). In addition, sex hormones may be of importance (42–44), with studies indicating a higher prevalence of diabetic nephropathy in men (45,46). In this study we could not confirm an association between male sex and ESRD; however, the number of patients with ESRD due to diabetic nephropathy is low and the follow-up time is limited.

In summary, at a median of 21 years of follow-up, <1% of patients with childhood-onset type 1 diabetes had developed ESRD due to diabetic nephropathy in this nationwide population-based study. A prepubertal onset of diabetes seems to prolong the time to development

of ESRD. These results should be confirmed in studies with longer follow-up, preferably including also patients with a postpubertal onset of diabetes.

APPENDIX

Members of the Swedish Childhood Diabetes Study

Lars Skogsberg (Luleå), Agne Lindh (Borås), Karin Segnestam (Eskilstuna), Kalle Snellman (Falun), Åke Stenberg and Christer Nilsson (Gällivare), Gunilla Kördel-Engberg (Gävle), Bengt Lindblad (Göteborg), Nils Östen Nilsson (Halmsstad), Jan Neiderud (Helsingborg), Herje Hörnell and Åke Lagervall (Hudiksvall), Lars Ivar Hardell (Kalmar), Hans Edenvall (Karlskrona), Gudrun Jonsell (Karlstad), Karin Larsson (Kristianstad), Bengt Hansing (Lidköping), Sture Sjöblad (Lund), Lars Stenhammar (Norrköping), Lennart Hellenberg (Nyköping), Anna Trela (Skellefteå), Marie Bourdin (Skövde), Britta Björnell (Sollefteå), Susanne Rudberg and Ingemar Zachrisson (Stockholm), Torunn Torbjörnsdotter (Huddinge), Leif Blom (Stockholm), Eva Landgren (Sundsvall), Ragnar Hanås (Udevalla), Jan Gustafsson (Uppsala), Margareta Blomgren (Visby), Nils Wramner (Trollhättan), Björn Eriksson (Västervik), Björn Jönsson (Ystad), Carl Göran Arvidsson (Västerås), Stig Edvardsson (Växjö), Ulf Ståhle (Ångelholm), Jan Åman (Örebro), Stellan Sjögren (Örnsköldsvik), and Anna-Lena Nilsson (Östersund).

Members of the board of the SRAU

Jarl Ahlmén (Göteborg), Björn Wikström (Uppsala), and Henrik Ekberg (Malmö).

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