Mortality in Patients With Childhood-Onset Type 1 Diabetes in Finland, Estonia, and Lithuania

Follow-up of nationwide cohorts

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OBJECTIVE — To assess mortality of population-based cohorts of childhood-onset type 1 diabetic patients from the Eastern European countries of Estonia and Lithuania and compare this information with recent data from Finland.

RESEARCH DESIGN AND METHODS — Estonian (n = 518) and Finnish (n = 5,156) type 1 diabetic cohorts were diagnosed between 1980 and 1994, and the Lithuanian (n = 698) cohort was diagnosed between 1983 and 1994. The mortality of these cohorts was determined in 1995. Life-table analysis, Cox survival analysis with covariates, and standardized mortality ratios (SMRs) were used. Causes of death were analyzed.

RESULTS — Survival after 10 years duration of type 1 diabetes was similar in Estonia (94.3%) and Lithuania (94.0%), but much higher in Finland (99.1%). In the Cox survival analysis with covariates, the country of origin and age at diagnosis were found to be significant predictors of mortality. The SMR for the Estonian cohort was 4.35 (95% CI 2.25–7.61), the highest for the Lithuanian cohort was 7.55 (4.89–11.15), and the lowest for the Finnish cohort was 1.62 (1.10–2.28). The most common cause of death in Estonia and Lithuania was diabetic ketoacidosis (DKA), and in Finland, it was violent causes. No deaths from late complications of diabetes have been documented so far in any of the three countries.

CONCLUSIONS — Our results demonstrate a high rate of short-term deaths due to DKA and inferior survival of childhood-onset type 1 diabetic patients in Estonia and Lithuania compared with Finland. In Finland, the survival of childhood-onset type 1 diabetic patients has improved and is only slightly inferior to that of the background population.

Diabetes Care 23:290–294, 2000

Before the discovery of insulin in 1922, the diagnosis of type 1 diabetes at an early age was associated with a 100% mortality in a few years as a result of diabetic ketoacidosis (DKA). Since the introduction of insulin into the therapy of type 1 diabetes, the life expectancy for patients with type 1 diabetes has improved dramatically. However, the quality of life and the life expectancy of type 1 diabetic patients still lag behind that of the background population (1). Even today, type 1 diabetes leads to a two- to tenfold excess risk of mortality in developed countries, whereas in developing countries, a large proportion of type 1 diabetic patients die within a few years of diagnosis (1,2).

The majority of mortality studies on type 1 diabetic patients have come from countries where finances for the care of type 1 diabetic patients are relatively abundant. Based on the results of mortality studies, one can judge whether a health care system performs well, what the predictors are, and where the potential for reducing mortality lies. Until now, there has been a shortage of data on mortality in type 1 diabetes in the Eastern European countries. The purpose of the present study was to estimate the mortality of population-based cohorts of childhood-onset type 1 diabetic patients from the Eastern European countries of Estonia and Lithuania and compare it with the latest data from Finland.

RESEARCH DESIGN AND METHODS

In all three countries, the diagnostic criteria for type 1 diabetes were those defined by the World Health Organization DIAMOND project, as follows: *1*) diagnosis of diabetes; *2*) placed on insulin before age 15; and *3*) permanent residency in the country at the time of the first insulin administration (2).

Case ascertainment

Estonia. Patients from the Estonian population-based childhood-onset type 1 diabetes registry that contains information on newly diagnosed cases since 1980 (3) were followed up. The registry covers the whole nation and is at least 95% complete. Reports from district pediatricians served as the primary source of information. Medical records of the Republic Endocrinology Center were the secondary source of information. Secondary case verification was, in essence, a capture-mark-recapture technique and yielded an estimated completeness of 95%.

The Estonian study population consisted of two subcohorts. The first one com-

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Received for publication 11 May 1999 and accepted in revised form 12 November 1999.

Abbreviations: DERI, Diabetes Epidemiology Research International; DKA, diabetic ketoacidosis; SMR, standardized mortality ratio.

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

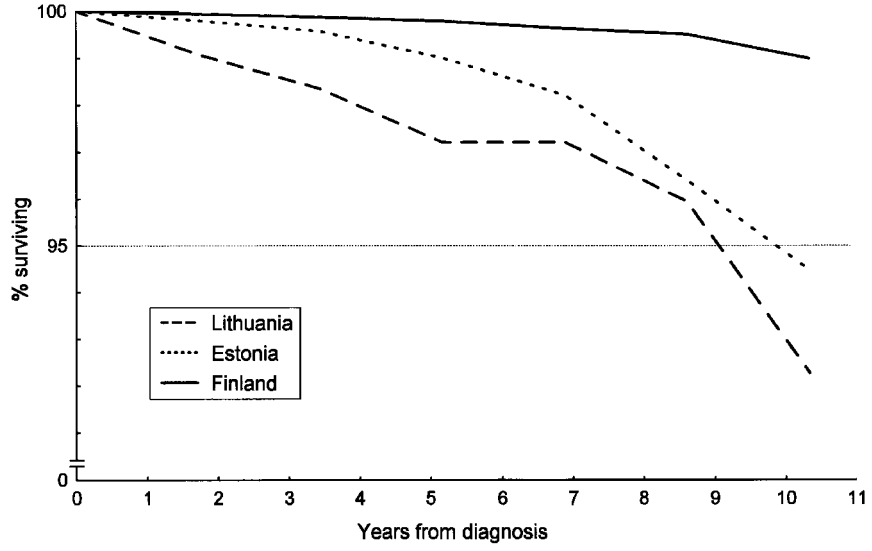

Figure 1—*Survival curves for the Estonian, Lithuanian, and Finnish type 1 diabetic cohorts.*

prised 310 children diagnosed with type 1 diabetes in Estonia between 1 January 1980 and 31 December 1988, inclusive. The survival status of this subcohort was determined as of 1 January 1992. The second cohort comprised 208 children diagnosed between 1 January 1989 and 31 December 1994, inclusive. The survival status of this group was determined by 1 July 1995.

Several approaches were used to determine the mortality status of patients. Attending physicians were asked to note the last date the patient had visited the office or had been hospitalized. Additional information was obtained from currency change lists. Currency change took place in Estonia in mid-1992, and all at least 16-year-old individuals on the list had to be alive on 1 January 1992. In a minority of cases untraceable by these methods, phone interviews were conducted and/or letters mailed. The survival status of the cohort diagnosed between 1989 and 1994 was determined via the National Death Registry of Estonia. Follow-up information was available for 309 of 310 patients of the first subcohort and all 208 of the second one. The only untraceable case was censored 1 week after diagnosis as the onset death of the patient was excluded. Seven patients had emigrated and were censored at the date they were last known to be alive.

Information on the causes of death was gathered by investigators through review of hospital records, interviews with physicians and relatives, and autopsy reports, whenever available. Mortality data for the Estonian background population were obtained from the Central Statistics Bureau of Estonia.

Lithuania. Data were obtained from the nationwide childhood type 1 diabetes register. From 1983 to 1994, 698 patients were registered. Since 1983, data have been collected prospectively using annual reports from regional pediatricians/endocrinologists. As a secondary data source, annual statistics from the Ministry of Health were used. Since 1989, medical records from the inpatient childhood endocrinology department of the University Hospital of Kaunas, where all newly diagnosed diabetic children are hospitalized, were used as the main data source. Annual reports from regional pediatricians/endocrinologists remained an independent secondary source for case ascertainment (4,5). The completeness of the registry exceeded 95%.

For the mortality follow-up, all 698 patients diagnosed with type 1 diabetes from 1 January 1983 to 1 January 1995 were followed up. The survival status of this cohort was determined as of 1 January 1995. A special questionnaire was prepared in order to get information on the living status of patients. Questions were preferably answered by patients, but if they were too young, the questionnaire was filled in by the parents. If the questionnaire was not returned, the investigators searched for the information using other methods: telephone calls, visiting patients at home, or using information provided by endocrinologists. Follow-up information was available for all 698 cases. Deaths were ascertained by comparing the date of diagnosis and the date of death from the Department of Death Registry at the state archives. Each cause of death was analyzed according to ICD-9 using a copy of the death certificate and the autopsy report. Data on mortality of the background population by age-groups were obtained from the National Department of Statistics.

Finland. The Social Insurance Institution's Central Drug Register was used for identification of childhood-onset type 1 diabetic cases for the period of 1980–1986. It includes all patients on insulin. Since 1987, data from the prospective nationwide register for childhood diabetes, which includes all new type 1 diabetic cases in Finland, were used. Hospital records of incident cases were used as a main data source. Data from the Social Insurance Institution served as an independent data source for case ascertainment (6–8). The completeness of the data was estimated to approach 100%.

Mortality of these two cohorts was determined by 1 July 1995. The causes of death were taken from the database of the National Death Registry. The vast majority of the deceased cases were autopsied. Mortality data of the background population were obtained from Statistics Finland.

Statistical analysis

Life-table analysis was used to assess the survival of the childhood-onset type 1 diabetic cohorts (9). Cox survival analysis with covariates was used to evaluate the effects of age at diagnosis, sex, country of origin, and period of diagnosis (1980–1944, 1985–1989, and 1990–1994) on the survival of the cohorts (9). Crude mortality rate was calculated as the number of deaths divided by the number of accumulated person-years. Annual age-standardized mortality rates were calculated using the European population as standard. Standardized mortality ratios (SMRs) for all-cause mortality were computed using the computer software package Person-Years (10). The 95% CIs of SMR were calculated assuming the Poisson distribution of deaths.

RESULTS

The mean duration of follow-up was 7.7 ± 4.4 (mean ± SD) years (range 0.1–15.5) in Finland, 6.1 ± 3.2 years (0.0–12.8) in Estonia, and 5.8 ± 3.4 (0.0–12.7) years in Lithuania. The median age at diagnosis of type 1 diabetes in Estonia, Lithuania, and Finland was 9.6, 9.4, and 8.5 years, respectively. The mean age at diagnosis was 9.2, 9.1, and 8.3 years in these three countries, respectively. The high-

Table 1—*Predictors of mortality of type 1 diabetic patients in Estonia, Lithuania, and Finland (summary of Cox models)*

	Coefficient	SEM	*t*	*P*	Risk ratio
Center	−2.154	0.385	−5.595	<0.01	0.12
Sex	−0.157	0.244	−0.643	>0.2	0.85
Age at diagnosis	0.128	0.035	3.631	<0.01	1.14
Period of diagnosis	−0.384	0.23	−1.671	>0.1	0.68

Center (Estonia and Lithuania pooled vs. Finland) and sex (M/F) were included in the model as categorical variables. Period (1980–1984, 1985–1989, and 1990–1994) and age at diagnosis were included as continuous variables.

est possible attained age was 30 years. The total number of person-years accumulated during follow-up was 3,164 in Estonia, 4,081 in Lithuania, and 39,486 in Finland.

During follow-up, 12 individuals (8 men/4 women) (2.3%) died in Estonia, 25 (12 men/13 women) (3.6%) in Lithuania, and 32 (20 men/12 women) (0.6%) in Finland. Mortality at onset of diabetes was low in all three participating countries. During the first week after diagnosis, one death was reported for Estonia, two for Lithuania, and none for Finland.

The crude annual mortality rate among the Estonian cohort was 373.2 per 100,000 person-years; the highest rate was documented in Lithuania (612.7), and the lowest in Finland (81.0). The annual age-standardized mortality rates, using the European population as standard, were 403.8, 749.8, and 122.1 per 100,000 person-years, respectively. The survival curves were very similar in Estonia and Lithuania and differed much from the one in Finland (Fig. 1). Survival of the cohorts was best in Finland, where 99.96% of cases were still alive after 1 year, 99.8% after 5 years, and 99.1% after 10 years. In Estonia, the corresponding survival rates were 99.8%, 99.0%, and 94.3%, and in Lithuania, they were 99.4%, 97.3%, and 94.0%, respectively. Of the covariates studied in the Cox models—country of origin, sex, age at diagnosis, and period of diagnosis—the country of origin and age at diagnosis affected the survival significantly (Table 1).

Compared with mortality in the background population, the best survival was found in Finland, with an SMR of 1.62, followed by 4.35 in Estonia and 7.55 in Lithuania (Table 2). No statistically significant sex differences could be established for SMRs in any of the three countries. In all countries, however, females tended to have higher SMRs than males. SMRs for males and females were 4.14 and 4.86 in Estonia and 5.28 and 12.56 in Lithuania. In Finland, the SMR for men was 1.38 vs. 2.26 for women. The SMR in all three countries pooled was 1.41 (1.00–1.93) in men and 2.59 (1.72–3.74) in women (data not shown in Table 2). The SMR values by age at diagnosis in the 0- to 4-, 5- to 9-, and 10- to 14-year-old age-groups were 1.25, 6.39, and 5.26 in Estonia, 4.00, 6.24, and 9.30 in Lithuania, and 0.41, 1.22, and 2.42 in Finland, respectively.

In Estonia and Lithuania, deaths were most often due to acute diabetes-related complications, e.g., DKA (Table 3). DKA accounted for 50% of deaths in Estonia and for 44% of deaths in Lithuania. In Finland, 22% of deaths were due to DKA, and most of the deaths of type 1 diabetic patients were the result of violent causes. No deaths were due to chronic microvascular complications of type 1 diabetes in any of the three countries.

The mean age at death was highest in Finland (18.7 ± 0.9 years), followed by Estonia (16.4 ± 1.6) and Lithuania (14.7 ± 1.2).

CONCLUSIONS

Only a small amount of information is available on mortality of type 1 diabetic patients in most countries. This certainly applies to Eastern Europe. Here we report mortality of population-based type 1 diabetic cohorts from the Baltic states of Estonia and Lithuania and contrast it with data from Finland. Mortality in type 1 diabetic patients in Finland has been extensively studied already (11–13). Finland is a country with a geographic proximity to the two Baltic states, has a higher living standard and the highest incidence of type 1 diabetes in the world. During 1983–1992, the average age-standardized incidence per 100,000 per year was 35.0 in Finland, 10.2 in Estonia, and 7.1 in Lithuania (5). Despite the relatively small size of the population-based cohorts from Estonia and Lithuania and the short follow-up, these data should give a general estimate of the potential differences in the survival of type 1 diabetic patients in these three countries in the immediate past.

There are inherent difficulties in uniform interpretation of the results of mortality studies. Generalizations regarding the prognosis of patients with type 1 diabetes in epidemiological studies are impaired by great intraindividual variations and methodological differences (14). The most frequent problems are the following: *1*) studies not covering the same time periods; *2*) application of different diagnostic criteria of type 1 diabetes; *3*) potential selection bias; *4*) varying duration of follow-up; and *5*) different methods of presenting the results. Most of the published studies are clinic-based, from hospitals that specialize in diabetes care, and not necessarily representative of the general type 1 diabetic population. Only a few studies have been population-based (15–18). We tried to avoid the above-mentioned pitfalls in our study design as much as possible.

Table 2—*SMRs and 95% CIs in Estonian, Lithuanian, and Finnish type 1 diabetic cohorts by sex, 1980–1995*

Study group	Cases followed up (*n*)	Accumulated person-years (*n*)	Deaths Observed (*n*)	Deaths Expected (*n*)	SMR	95% CI of SMR
Estonia	518	3,164	12	2.756	4.35	2.25–7.61
Men	269	1,649	8	1.93	4.14	1.79–8.15
Women	249	1,516	4	0.823	4.86	1.32–12.44
Lithuania	698	4,081	25	3.309	7.55	4.89–11.15
Men	360	2,093	12	2.274	5.28	2.73–9.22
Women	338	1,988	13	1.035	12.56	6.69–21.47
Finland	5,156	39,487	32	19.81	1.62	1.10–2.28
Men	2,798	21,677	20	14.499	1.38	0.84–2.13
Women	2,358	17,810	12	5.31	2.26	1.17–3.95

Table 3—*Distribution of causes of death of Estonian, Lithuanian, and Finnish type 1 diabetic cohorts by sex, 1980–1995*

	Estonia				Lithuania				Finland			
	Men		Women		Men		Women		Men		Women	
Cause of death	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
DKA	4	50	2	50	5	42	6	46	4	20	3	25
Accident, suicide, homicide	3	37	0	0	1	8	2	15	11	55	3	25
Neoplasm	1	13	1	25	2	17	0	0	1	5	1	8
Infection	0	0	0	0	4	33	4	31	1	5	1	8
Other	0	0	1	25	0	0	1	8	3	15	4	33
Total	8	100	4	100	12	100	13	100	20	100	12	100

Survival of the patients in the Estonian and Lithuanian cohorts was quite similar, as expected. Both countries were part of the former Soviet Union and subject to similar health care practices. The Finnish cohort had better survival compared with that in the two Baltic countries for several reasons. Type 1 diabetes is much more common in Finland than in the Baltic states. Thus, the society, health care system, and physicians in Finland are much more experienced in taking care of diabetic patients. Second, a higher living standard in Finland has enabled enough resources for self-monitoring and education of patients. Also, the quality of insulin has been better in Finland than in Estonia and Lithuania, where mostly Soviet-made insulin with varying potency was used, at least until 1991. Large-scale self-monitoring of blood glucose was not feasible in the former Soviet Union until the beginning of the 1990s. Patient education was quite neglected, and the role of patients in the treatment of type 1 diabetes was not given enough importance. In accord with this observation, in Japan, where the incidence of type 1 diabetes is low, a major improvement in the survival of type 1 diabetic patients has been seen over the years and attributed mostly to changes in the quality of care and medical infrastructure (19). Some authors have offered barriers to health care, basically financial ones, as the reason for the ethnic differences in mortality (20). Inferior survival of the Estonian and Lithuanian cohorts is hardly explainable by inequalities in access to health services compared with Finland.

Mortality in the general populations of Estonia and Lithuania has been found to be much higher than that in the developed countries bordering the Baltic Sea (21). Compared with the background population, the survival of childhood-onset type 1 diabetic patients in the two Baltic states is also worse than it is in Sweden and Norway (17,18), where the SMR is ~2, and similar to that in a recent study from Japan (19). Some caution should be exercised when comparing mortality data of type 1 diabetic patients diagnosed during different periods. Mortality of type 1 diabetic patients has declined during recent decades compared with earlier in this century (17), and the Estonian and Lithuanian cohorts were diagnosed later than those in the Swedish and Norwegian studies.

Mortality of Finnish type 1 diabetic patients has declined a little from that reported in the Diabetes Epidemiology Research International (DERI) Study, where patients diagnosed in 1965–1979 were included. The SMRs were 1.93 and 1.62 in the DERI Study (11) and in our study, respectively; the SMR is now approaching that of the background population (12). When the mortality rate of the diabetic cohort was compared with the value in the background population, the SMRs in males and females did not differ significantly in any of the participating countries. In Finland, the difference between men and women SMRs has become slightly larger compared with earlier DERI Study results. Mortality is similarly increased in younger and older-onset patients in Estonia and Lithuania compared with Finland.

The most frequent cause of death in Estonia and Lithuania was DKA, the main killer of the pre-insulin era. These deaths could potentially have been prevented. The occurrence of violent death was also high, particularly in Finland. Fatal hypoglycemia as the cause of death was rare. This agrees with the pattern emerging from other studies, i.e., that in patients with a shorter duration of type 1 diabetes, the most frequent causes of death are related to acute complications (DKA, hypoglycemia) and violence (13,15,16,18,22). Reduction in the frequency of DKA seems to be the most feasible approach in reducing overall mortality in patients with type 1 diabetes of short duration in Estonia and Lithuania. Considering the short follow-up and age of the cohorts, no deaths were due to chronic complications of type 1 diabetes.

In conclusion, the short-term survival of childhood-onset type 1 diabetic patients in Estonia and Lithuania is inferior compared with that in Finland. We can only speculate on the cause of our observations, but data suggest the importance of patient education and self-monitoring as possible means to reducing the excess mortality of type 1 diabetic patients in the Baltic states and perhaps in other Eastern European countries. In Finland, the survival of childhood-onset type 1 diabetic patients has improved and is only slightly inferior to that of the background population.

Acknowledgments— This study was supported by European Community Contract BMH1 CT92 0043, and Estonian Science Foundation Grant 4325.

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