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Mortality of patients with childhood onset (0–17 years) Type I diabetes in Israel: a population-based study*

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Abstract

Aims/hypothesis. The aim of this study was to examine the mortality rate of subjects with childhood-onset Type I (insulin-dependent) diabetes mellitus in Israel.
Methods. The whole-country cohort of 1861 children and adolescents (0–17 years) with Type I diabetes, diagnosed between January 1965 and December 1993 in Israel, was analysed for mortality up to October 1996.
Results. A total of 37 deaths were identified with an ascertainment rate of 100 %. There was a significant ($p < 0.001$) excess mortality in the patients with Type I diabetes, the standard mortality ratio being three times higher than that of the general population. The causes of mortality were ketoacidosis ($n = 8$), infections ($n = 8$), chronic diabetes complications ($n = 9$), external causes ($n = 6$) and other ($n = 6$). Among the subjects who died, the prevalence of nephropathy, neuropathy and anaemia was higher in female than in male subjects. A total of 17 of the patients with diabetes who died had a central nervous disease (psychosis, mental retardation, epilepsy). There was a trend to lower mortality among the Arab cohort which did not reach statistical significance.
Conclusions/interpretation. Our data provide additional evidence that childhood-onset Type I diabetes carries an increased mortality risk when compared with the mortality risk of the non-diabetic population. [Diabetologia (2001) 44 [Suppl 3]: B 81–B 86]

Keywords Childhood Type I diabetes, mortality, population studies, ethnic distribution, diabetes in Israel.

The introduction of regional or whole-country registers of Type I diabetes has shown that the incidence of childhood diabetes is rapidly increasing in many parts of the world including Israel [1–9]. However, long-term follow-up surveys relating to the mortality rates of patients with childhood-onset Type I diabetes are rare [10–16].

In 1991 we reported on the mortality in a cohort of 614 Jewish Israeli patients with childhood-onset Type I diabetes diagnosed between the years 1965 and 1979 [17]. We have continued the whole-country registry of newly diagnosed Type I diabetic patients in Israel and report in this study on the mortality of the whole-country cohort of 1861 patients with Type I diabetes in Israel diagnosed under the age of 18 between the years 1965 and 1993 and belonging to several ethnic groups.

Subjects and methods

Definition of the study cohort. The population included in this study comprises the whole-country cohort of patients with childhood Type I diabetes ($0–17^{11}/12$ years – forthwith 0–17 years) resident in Israel and newly diagnosed between 1 January 1965 and 31 December 1993. It constitutes the Israel Registry of Type I childhood diabetes which is part of the Diabetes Epidemiology Research International (DERI) Study

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Abbreviations: SMR, standard mortality ratio.

(1965 –1979) [18] and subsequently the EURODIAB ACE Project (1980–1993) [1]. The degree of ascertainment was estimated to be over 95 %.

Altogether seven patients with associated diseases such as Bloom's syndrome, cystic fibrosis, thalassaemia major, pancreatectomy, glucocorticoid- induced diabetes and Wolfram's syndrome were excluded from this study. The total number of patients with childhood Type I diabetes for the above 1965 to 1993 period was 1861. During this period the Israeli population consisted of the following major ethnic groups: Ashkenazi Jews (European origin), non-Ashkenazi Jews (North African, Mediterranean, Middle-Eastern origin) approximately 40 % each and Israeli Arabs (18 % of the total population).

The study was approved by the Hospital Ethical Committee and the legal offices of the Ministries of Health and Interior.

Determination of death and its cause. The death of patients was ascertained from the records of hospitals where the patients were treated or died. In addition, the survival status of the cohort up to 30th October 1996 was confirmed by submitting the official identification (ID) numbers of all the 1861 patients into the computerized register of the Interior Ministry which then checked these against the National Death Registry. Ascertainment of death was 100 %. All the medical charts and the death certificates as well as six available necropsy reports for the deceased patients were reviewed and the details of their medical history including diagnosis and course of Type I diabetes complications and cause of death were noted. In instances in which more than one cause of death was cited, the primary (underlying) cause was chosen by two independent physicians. In cases of disagreement a third reviewer was consulted.

Statistical analysis. Statistical analysis was done using the SPSS programme. The incidence of mortality was calculated using several methods:

The follow-up period for each patient was calculated from the date of diagnosis (date of first insulin injection) to the date either of death or the census (30 October 1996). Standardized mortality ratios (SMRS) were calculated per 5 years using the equations of Kilpatrick [19] and Hill [20] and compared with the age adjusted mortality rate in the general population of Israel provided by the Central Bureau of Statistics in the year 1996 [21]. A SMR of 1 denotes equal mortality ratio to the general population. The 95 % CIs were calculated using Byar's approximation of Poisson's regression analysis [22]. Survival rates were calculated according to the Kaplan-Meier survival method [23], and the log-rank test was used to ascertain statistically significant differences between them.

Differences between means were calculated using the Student's *t* test.

Results

The whole-country registry in Israel for Type I diabetes (0–17 years) between the years 1965 and 1993 was carried out by the Endocrinology and Diabetes Research Unit, Beilinson and Schneider Children's Medical Centres [9]. Out of 1861 newly diagnosed patients with Type I diabetes, 37 died before 30 October 1996. The duration of observation ranged from 1 to 32 years (mean ± SD = 14 ± 8 years) providing a total of 23 877 person-years of follow-up. The differences in mortality rates between the groups were not statistically significant (Arabs vs Ashkenazi Jews, $p = 0.3$; Arabs vs non-Ashkenazi Jews, $p = 0.7$; Ashkenazi vs non-Ashkenazi Jews, $p = 0.2$) (Table 1). The mean age at diagnosis was 10.6 ± 4.4 years.

Table 1. Demographic characteristics of the diabetic cohort studied

	Population with childhood diabetes (1965–1993)	
	Cohort Studied	Deceased
Number (%)	1861 (100)	37 (100)
Sex: Male	921 (49)	17 (1.8)
Females	940 (51)	20 (2.1)
Ethnic Origin:		
Ashkenazi Jews	615 (33)	17 (2.8)
Non-Ashkenazi Jews	995 (54)	17 (1.7)
Arabs	157 (8)	2 (1.3)
Unknown	94 (5)	1
Age at Diagnosis (Years)		
0–11	1013	20 (2)
12–18	848	17 (2)

Mortality according to age at diagnosis, duration of disease, and sex. No difference in the overall mortality rate was seen when dividing the subjects into groups of under 12 and over 12 years of age. Out of 1013 patients diagnosed before 12 years of age, 20 (2.0 %) had died. Out of 848 patients diagnosed between 12 to 17 years of age, 17 (2 %) had died (Table 1). However the death of the patients diagnosed before 12 years of age occurred at a younger age than those diagnosed at 12 years of age or later (log-rank = 5.8; $p = 0.016$). There was no difference in mortality rate according to duration of disease between patients diagnosed before 12 years of age and those diagnosed later (log-rank $p = 0.89$). Notably no patient died at or shortly after diagnosis, nor did any patient die before 5 years of age.

Out of 940 female patients, 20 (2.1 %) died, and out of 921 male patients, 17 (1.8 %) died (Table 1), thus there is no difference in the mortality pattern between sexes.

In both studies there is a drop in the mortality rate in the second 6 years of duration compared with the first 6 years, with an increasing rate again in the third 6-year period. In males, the progressive increase in mortality rate with duration of disease is significant ($p < 0.004$).

Causes of death. The most frequent causes of death of the 37 patients with childhood-onset Type I diabetes were ketoacidosis (21.6 %) and infections (21.6 %) (Table 2). Out of the 8 patients who died of ketoacidosis, there were 5 females and 3 males between 8 and 37 years of age. One patient died 10 months after diagnosis, two between 7 and 14 years of disease duration. The remaining died between 14 and 19 years

Table 2. Cause of death of 37 patients with childhood-onset (0–17 years) Type I diabetes in Israel (January 1965–October 1996)

		Age at death (Years)			
		5–19	20–29	> 30	Total deaths *n* (%)[a]
Diabetes Ketoacidosis		4	4	0	8 (21.6)
Infections	Sepsis	2	1	3	6 (16.2)
	Pneumonia	0	1	0	1 (2.7)
	Peritonitis	0	0	1	1 (2.7)
	Total	2	2	4	8 (21.6)
Complications of diabetes		0	2	2	4 (10.8)
Cardiovascular	Acute MI	0	1	1	2 (5.4)
	Acute cardiomyopathy	0	1	0	1 (2.7)
	Total	0	2	3	5 (13.5)
External Causes	Homicide	1	1	1	3 (8.1)
	Traffic accident[b]	2	1	0	3 (8.1)
	Total	3	2	0	6 (16.2)
Malignancies[c]		1	1	0	2 (5.4)
Sudden death[d]		0	0	2	2 (5.4)
Others[e]		0	0	2	2 (5.4)
TOTAL		10	13	14	37 (100)

[a] percent of total deaths;
[b] hypovolaemic shock/severe brain oedema;
[c] leukaemia and cancer of the lung;
[d] including sudden death after anaesthesia for vitrectomy and asphyxia;
[e] cause of death is not known

Table 3. Chronic diabetes complications at time of death of 37 patients with childhood-onset Type I diabetes

		Age at death (Years) *n* (%)			Total deaths	Females	Males
Diabetes complications		0–19[a]	20–29	> 30	*n* (%)	*n*	*n*
Retinopathy		1 (10)	5 (38.4)	11 (78.5)	17 (46.0)	8	9
Nephropathy		2 (20)	4 (30.7)	10 (71.4)	16 (43.2)	10	6
Hypertension		2 (20)	2 (15.3)	7 (50)	11 (30.0)	5	6
Cardiovascular	Acute MI & ischaemic heart disease	0	1 (7.7)	4 (28.6)	5 (13.5)	1	4
	Cardiac insufficiency	0	1 (7.7)	5 (3.6)	6 (16.2)	6	
	Others[b]	0	1 (7.7)	1 (7.1)	2 (5.4)	2	
Neuropathy		1 (10)	1 (7.7)	8 (57.1)	10 (27.0)	6	4
Anaemia		0	4 (30.8)	4 (28.6)	8 (21.6)	7	1

[a] the youngest age at death was 5; [b] including 1 patient with each of cardiovascular angiopathy and acute cardiomyopathy; MI = myocardial carfarction

disease duration and all of these had suffered from previous hypoglycaemic and hyperglycaemic episodes.

Of the patients who had chronic diabetes complications at the time of their death, approximately half had retinopathy and/or nephropathy, and one third had hypertension (Table 3). Notably female patients had more neuropathy, acute myocardial infarction and ischaemic heart disease, nephropathy and almost all had severe anaemia, most probably related to nephropathy. In summary, 33 out of the 37 patients who died had one or more chronic diabetes complications, 2 had none and no information was available on the remaining 2 patients. Altogether 3 patients with a disease duration of over 30 years had undergone lower limb amputation.

Of the additional disorders diagnosed in the patients with diabetes, 45.9 % were connected with the central nervous system disease (Table 4). A total of 21.5 % of the patients had an associated endocrine disease, mostly of autoimmune origin.

Standardized mortality ratio (SMR). The overall SMR in the diabetes cohort with childhood-onset Type I diabetes in Israel is significantly higher for the whole group than that of the Israeli mortality statistics, especially in the younger age groups (Table 5). After 34 years of age, we found no difference in SMR between patients with diabetes and the general population.

Table 4. Additional diseases diagnosed in the 37 patients with childhood-onset Type I diabetes who died

Disease n (%)	Age at death (Years)			Total (%) deaths *n*
	0–19[a]	20–29	> 30	
Mental disorder[b]	2	5	3	10 (27.0)
Mental retardation	2	2	0	4 (10.8)
Epilepsy	1	2	0	3 (8.1)
Endocrine[c]	1	3	4	8 (21.6)
Others[d]	1	2	1	4 (10.8)

[a] the youngest age at death was 5; [b] including major depression (four patients), personality disorders, anorexia nervosa and undefined psychopathology. All had been treated previously in psychiatric clinics, some had been hospitalized; [c] Hashimoto thyroiditis, hypothyroidism, osteoporosis, diabetes insipidus and autoimmune endocrine polyglandular disease; [d] deafness, poliomyelitis, acute lymphocytic leukemia and chronic obstructive pulmonary disease

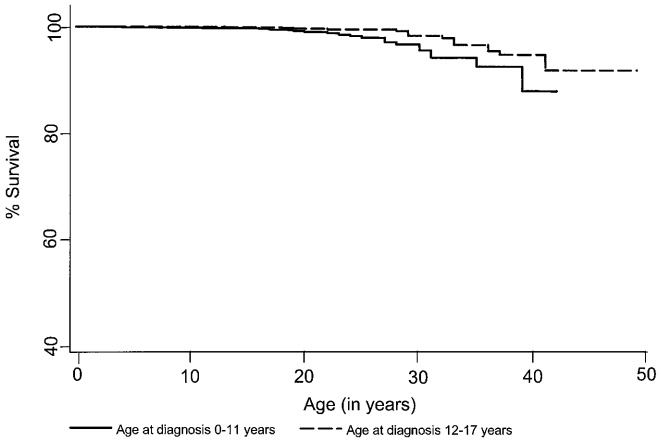

Fig. 1. Cumulative survival curve of 1861 patients with childhood-onset (0–17 years) Type I diabetes diagnosed in Israel between 1965 and 1993

Discussion

This study is one of the very few examining mortality rates during long-term follow-up of a large cohort of childhood-onset Type I diabetes in a whole-country population.

A study carried out in Estonia reviewed the survival of 340 children (0–14 years of age) diagnosed between 1980 and 1989 [14]. Another population-based cohort of 1185 children (0–14 years old) was reviewed in Austria between the years 1979 and 1990 [7]. The largest cohort studied was in Finland (5162 patients) followed between 1965 to 1985 [18]. Few other studies are based on regional population registers [13, 15, 16].

Distinct from other studies we were able to compare the mortality rate between various ethnic groups residing in the same small country and differing in the incidence of Type I diabetes [9].

Out of the 1861 patients followed for 23 877 person-years duration of diabetes, 37 died. Compared with studies available from other countries, the overall SMR rate in Israel is low both for the length of the follow-up period, i.e. 32 years in our study (with a median of 12.0 years) and for the age of the patients. The SMR seems close to that found in the Finnish population followed for a similar length of time and with a higher incidence of diabetes [4, 16]. Overall, the SMR of Type I childhood diabetes patients in Israel is three times higher than the general Israeli population. This excess mortality, compared to the general Israeli population, is particularly evident between 5–19 years of age, when it decreases, but is still significantly higher than the general population until 34 years of age. After 34 years of age, no differences in mortality rates were found between the Type I diabetic patients and the general population.

The number of deaths were distributed equally between both sexes and between the Ashkenazi and non-Ashkenazi Jews. The Arabs who represent 18% of the total population of Israel, had only 5% of the deaths in this group of diabetic patients. The Arabs also have the lowest incidence of Type I diabetes

Table 5. Standardized mortality ratio (SMR) in a cohort of 1861 subjects with childhood-onset Type I diabetes (diagnosed 1965–1993)

Age group (Years)	Israeli mortality statistics 1996			Type I diabetic cohort				
	Number of deaths	Population	Rate (1000/year)	Number of deaths	Person-years	Expected number of deaths	SMR	95%-CI
0–4	511	581400	0.8789	0	12	0.0105	0.00	0
5–9	52	547800	0.0949	2	303	0.0288	69.54	8.41–251
10–14	62	534800	0.1159	2	1357	0.1573	12.71	1.54–45.89
15–19	139	512600	0.2712	6	2476	0.6714	8.94	3.28–19.48
20–24	241	490800	0.4910	5	4258	2.0908	2.39	0.77–5.57
25–29	171	413700	0.4133	8	4796	1.9824	4.04	1.74–7.95
30–34	180	371100	0.4850	8	4586	2.2244	3.60	1.55–7.09
35–39	234	364900	0.6413	3	3649	2.3400	1.28	0.26–3.74
40–44	299	361400	0.8273	3	1787	1.4785	2.03	0.42–5.93
45–49	463	337600	1.3714	0	653	0.8956	0.00	0
Total	2352	4516100	0.5208	37	23877	12.4352	2.98	2.1–4.09

among the various ethnic groups in Israel (8 % of our cohort) [9]. A total of 10 patients died between 15 and 24 years of age, and 16 between 25 and 34 years of age. The youngest patient died aged 5 years. Duration of disease was statistically significantly related to death in the male patients only. Of note is that during the second 6 years of disease there was a decrease in mortality in both sexes compared with the first 6 or subsequent years of disease.

Although diagnosis before 12 years of age was associated with a younger age at death, the survival analysis by duration of disease did not show a statistically significant difference between the groups according to age at diagnosis (before and after 12 years of age). Of special note is that there was no death at or shortly after the onset of disease, as reported from other countries [7, 8, 13, 14, 24]. This is probably due to an awareness among the population of the early symptoms of diabetes through long standing population-oriented educational programmes [25] and easily availabile medical services.

A total of 25 (possibly 27) out of 37 causes of death (~ 73 %) can be ascribed to being directly related to the diagnosis of diabetes. The majority were due to diabetic ketoacidosis, infections or complications, which are partly preventable by improved metabolic control [26]. Several findings in our study seem of special interest: 17 (46 %) of our deceased patients had some kind of disorder of the central nervous system (Table 4). This is not mentioned in other surveys, and certainly plays a role in the motivation to maintain good metabolic control. Whether the sudden deaths belong to the "dead in bed" syndrome [8, 27] or were suicides is not clear. The traffic accidents were passive according to the information obtained.

Despite an equal distribution of deaths between the two sexes, the prevalence of nephropathy, neuropathy and anaemia was higher in the female than in the male patients, whereas cardiac disease occurred almost exclusively in males.

In conclusion, even with a relatively low mortality rate compared with other countries, a well-developed multidisciplinary team approach and a National Insurance Medical System, mortality rates in childhood-onset Type I diabetes patients in Israel remain higher than in the general population.

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