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SHORT COMMUNICATION

Cause-specific mortality trends in a nationwide population-based cohort of childhood-onset type 1 diabetes in Japan during 35 years of follow-up: the DERI Mortality Study

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Abstract
Aims/hypothesis The aim of this study was to investigate long-term, cause-specific mortality trends among patients with childhood-onset type 1 diabetes in Japan.
Methods Individuals included in the study had received a diagnosis of type 1 diabetes at age <18 years between 1965 and 1979. All individuals were followed up for their survival status until 1 January 2005. The causes of death were divided into end-stage renal disease (ESRD), acute diabetic complications (ADC), accident/suicide, cardiovascular disease (CVD), infections, cancers, others (non-diabetic/diabetic) and unknown. The cause-specific mortality trends were expressed according to the follow-up period and year of diagnosis.
Results A total of 1,385 patients were enrolled in the study, and the survival status of 1,324 was confirmed. Mortality rate at the 35 year follow-up (per 100,000 person-years) was 659.3, and the standardised mortality ratio (SMR) was 10.7. The SMR at the 25 year follow-up markedly declined from 19.3 in the 1965–1969 diagnosis group to 6.6 in the 1975–1979 diagnosis group. Approximately 40% died of ADC among those with <10 years of follow-up. A similar proportion of individuals died of ESRD among those with 10–19 years of follow-up. The longer the duration of follow-up, the lower the mortality from ADC and the greater the mortality from CVD.
Conclusions/interpretation In Japanese people with childhood-onset type 1 diabetes of more than 20 years of duration, CVD was the leading cause of death, as is the case among similar white people. The longer the duration of diabetes, the more attention should be paid to preventing CVD.

Keywords Cause of death · Mortality · SMR · Type 1 diabetes

Abbreviations

ADC	Acute diabetic complications
CVD	Cardiovascular disease
DERI	Diabetes Epidemiology Research International
ESRD	End-stage renal disease
SMR	Standardised mortality ratio

Introduction

The annual incidence of type 1 diabetes mellitus among children in Japan is 2.4 per 100,000, which is 1/24th of the 57.6 ratio seen in Finland [1], a country with one of the highest incidences of type 1 diabetes in the world. Whether the low incidence of the disease might be related to underlying conditions that would affect the clinical course of type

Members of the DERI study group are given in the Appendix.

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1 diabetes is unknown, as there are few population-based studies investigating the long-term prognosis. Therefore, the population-based Diabetes Epidemiology Research International (DERI) mortality study was launched in 1986 as an observational international collaborative study that brought together diabetes researchers from Finland, the USA, Israel and Japan.

In 1991, the study issued its first report demonstrating that Japanese patients with type 1 diabetes had a much worse prognosis than did similar patients in Finland, the USA and Israel, with the most frequent cause of death being end-stage renal disease (ESRD) [2, 3]. The current study has evaluated the latest data identifying living status and cause-specific mortality trends in Japan, as of 2005.

Methods

Individuals The study comprised participants who received a diagnosis of type 1 diabetes at <18 years of age between 1965 and 1979; these data were retrieved from two nationwide surveys conducted on childhood-onset diabetes in 1970 and 1981, as described elsewhere [2]. Type 1 diabetes was defined as requiring initiation of insulin therapy after diagnosis. Individuals who received their diagnoses between 1965 and 1969 started follow-up on 1 January, 1970, and those who received their diagnoses between 1970 and 1979 started follow-up on 1 January, 1980. All individuals were alive on the day when the follow-up started.

This cohort comprised 1,385 patients, 23 fewer than were evaluated in the survey that determined living status as of 1995 [4], owing to a correction for misclassifications and violations of the inclusion criteria discovered during the past 10 years. Case-ascertainment of the cohort was estimated to be 75%, according to the reported type 1 diabetes incidence rate (0.8 per 100,000 person-years) during that period. The representativeness of the cohort to the target population is discussed elsewhere [2, 5].

Methods of follow-up A questionnaire to confirm an individual's vital status was mailed to each individual's attending physician every 5 years (Electronic supplementary material [ESM] questionnaire). All individuals were followed up until 1 January 2005. Any individual whose status was unknown was further followed up by certificates of registry or copies of his or her family register with the approval of the Ministry of Justice. Survival status was expressed in terms of mortality rate and standardised mortality ratio (SMR).

Determination of causes of death The causes of death were determined by the DERI mortality classification committee [3] based on the information from attending physicians or death certificates. The causes of death were divided into nine categories: (1) ESRD, (2) acute diabetic complications (ADC), (3) accident/suicide, (4) cardiovascular disease (CVD), (5) infections, (6) cancers, (7) other non-diabetic causes, (8) other diabetic causes, and (9) unknown.

Statistical analysis SMRs were calculated by using the annual mortality rates and the annual cause-specific mortality rates from 1970 to 2004 released by the Japanese Ministry of Health, Labour and Welfare. The 95% CIs were calculated by using the Poisson distribution [6]. Statistical analyses were conducted by using SAS 9.3 (SAS Institute, Cary, NC, USA). A p value less than 0.05 was considered to be statistically significant (two-sided test). The study was approved by the institutional review board of Jikei University School of Medicine and was carried out in accordance with the Declaration of Helsinki.

Results

Among the total of 1,385 children with type 1 diabetes (556 boys and 829 girls; mean [± SD] age at diagnosis, 8.8±4.1 years), 1,101 were confirmed as alive as of 2005, and 223 deaths were observed. Of the 61 individuals whose status remained unknown, their last confirmed status before 2005 was used for analysis. The mean duration of diabetes was 27.9±6.5 years, with a mean follow-up of 24.4±6.4 years, and a mean age at death of 30.7±8.4 years.

All-cause mortality and SMRs The mortality rate (per 100,000 person-years) and the SMR at 35 year follow-up were 659.3 and 10.7 (95% CI 9.3, 12.1), respectively. The mortality rate was shown to be higher among male than female participants (778.1 vs 580.5); however, the SMR was lower among men than women (9.6 vs 14.3), because of a higher mortality rate among men in the general population. The mortality at 25 year follow-up was considerably improved in the 1975–1979 diagnosis group compared with that in the 1965–1969 diagnosis group (SMR, 6.6 vs 19.3).

Cause-specific mortality and SMRs Overall, the leading causes of death were ESRD and CVD, followed by ADC (Table 1). ESRD was also the most frequent cause of death in the 1965–1969 diagnosis group, at 42% of all causes of death. However, it decreased dramatically in the 1975–1979 diagnosis group. In men, the leading causes of death were CVD, ADC and infections. ESRD was the fourth highest cause of death in men. In women, ESRD was the highest cause of death, followed by CVD, and ADC.

Total cause-specific SMRs at 35 year follow-up, and at 25 year follow-up for the 1965–1969 and 1975–1979

Table 1 Cause-specific mortality rates among patients with childhood-onset type 1 diabetes in Japan by sex and by year of diagnosis

Cause of death	Overall		Men		Women		1965–1969 diagnosis group		1975–1979 diagnosis group	
	Deaths (*n*)	Mortality rate at 35 year follow-up	Deaths (*n*)	Mortality rate at 35 year follow-up	Deaths (*n*)	Mortality rate at 35 year follow-up	Deaths (*n*)	Mortality rate at 25 year follow-up	Deaths (*n*)	Mortality rate at 25 year follow-up
ESRD	51	150.8 (111.4, 197.4)	14	103.7 (60.0, 170.0)	37	182.0 (129.4, 248.0)	32	522.2 (348.6, 722.3)	6	33.3 (14.5, 71.2)
CVD	40	118.3 (85.7, 158.8)	21	155.6 (95.0, 234.7)	19	93.5 (55.0, 142.5)	8	130.5 (53.6, 243.5)	13	72.2 (37.2, 118.7)
ADC	38	112.4 (77.8, 151.7)	19	140.8 (82.8, 214.7)	19	93.5 (55.0, 142.5)	13	212.1 (109.1, 348.6)	14	77.8 (45.0, 127.5)
Infections	34	100.5 (70.3, 139.0)	18	133.4 (82.8, 205.5)	16	78.7 (47.2, 125.0)	11	179.5 (86.9, 310.9)	8	44.5 (18.3, 82.9)
Accident/suicide	21	62.1 (37.9, 93.7)	12	88.9 (49.5, 150.7)	9	44.3 (21.9, 82.5)	5	81.6 (32.1, 182.4)	8	44.5 (18.3, 82.9)
Unknown	18	53.2 (33.0, 82.0)	11	81.5 (39.4, 141.2)	7	34.4 (16.2, 67.7)	3	49.0 (13.3, 132.2)	6	33.3 (14.5, 71.2)
Other non-diabetic causes	13	38.4 (19.8, 63.2)	6	44.5 (19.4, 95.0)	7	34.4 (16.2, 67.7)	1	16.3 (0.8, 86.9)	4	22.2 (7.6, 53.3)
Other diabetic causes	6	17.7 (7.7, 37.9)	3	22.2 (6.1, 60.0)	3	14.8 (4.0, 39.9)	3	49.0 (13.3, 132.2)	1	5.6 (0.3, 29.6)
Cancers	2	5.9 (1.0, 19.8)	1	7.4 (0.4, 39.4)	1	4.9 (0.3, 26.2)	0	0 (0, 53.6)	1	5.6 (0.3, 29.6)
All causes of death	223	659.3 (573.9, 746.1)	105	778.1 (627.5, 935.7)	118	580.5 (479.9, 687.7)	76	1,240.2 (960.2, 1,537.7)	61	339.0 (261.3, 428.8)

Mortality rates are expressed per 100,000 person-years. Values in parentheses are 95% CIs

diagnosis groups, respectively, are as follows: CVD, 13.8/16.9/11.6; infections, 46.9/61.7/27.3; accident/suicide, 2.1/2.6/1.6; cancers 0.5/0.0/0.6. Details of cause-specific SMRs and their trends are available in the ESM Tables 1 and 2.

Among fatal ADC, diabetic ketoacidosis was the most frequent (50.0%), followed by diabetic coma unspecified (28.9%), and hypoglycaemia (21.1%). In the accident/suicide category, suicide was the most frequent (57.1%). In the CVD category, cerebral haemorrhage was the most frequent (37.5%), followed by myocardial infarction (20.0%) and heart failure (17.5%). Among the fatal infections, sepsis was the most frequent (35.3%), followed by pneumonia (29.4%). The cancers, of which two patients died, were Wilms' tumour and gastric cancer. Other non-diabetic causes of death included gastric ulcer (15.4%) and pancreatitis (15.4%). Among other diabetic causes, gangrene was the most frequent (50.0%).

We found that the longer the duration of follow-up, the lower the mortality from ADC, and the greater the mortality from CVD (Fig. 1).

Discussion

In our previous report in 1991 [3], ESRD and ADC were the leading causes of death, and CVD was rare. However, the current analyses have revealed that the longer the duration of follow-up, the higher the percentage of CVD in total death, with CVD becoming the leading cause of death at the 30–35 year follow-up period. The increasing trend of CVD-related mortality was also reported in the USA DERI cohort [7]. For the Japanese general population, the age-adjusted CVD-related mortality rate has decreased in recent years [8], and it is known that mortality due to CVD is relatively low compared with that in the white population [9]. Therefore, it is interesting to reveal this increasing trend of CVD-related mortality in the Japanese DERI cohort.

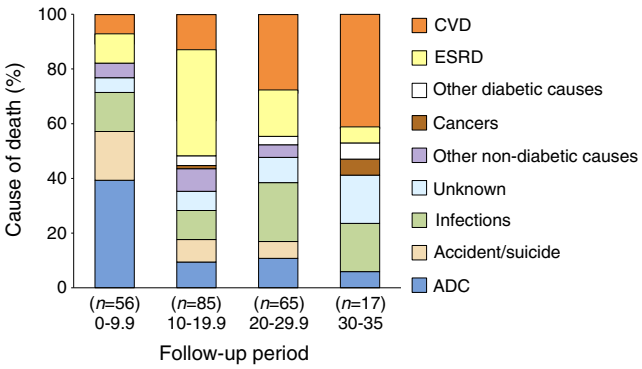

Fig. 1 The causes of death according to follow-up period in patients with childhood-onset type 1 diabetes in Japan

Our previous report in 1995 revealed that the ESRD-related mortality risk in our cohort was 2.57 times higher than that seen in the USA DERI cohort [10]. The large difference in ESRD-related mortality between these two countries was reduced considerably after the 30 year follow-up. The ESRD-related mortality rate (per 100,000 person-years) in 2008 in the USA cohort was 88.5 in men and 129.0 in women [7], thus becoming closer between the two countries, particularly among men. It was more difficult to initiate dialysis during the late 1960s and 1970s in Japan because of the limited number of dialysers, and the fact that many families were reluctant to pay for dialysis treatment until a medical care benefit system that covered high-cost healthcare was established in 1981. Moreover, working men were more likely than women to be given priority to receive dialysis or to be offered it at an earlier stage in their disease.

The SMR for infections was 46.9 overall. It was particularly high in the 1965–1969 diagnosis group and declined by half in the 1975–1979 diagnosis group. A marked improvement in both the management of type 1 diabetes and in infectious diseases might have ameliorated the SMR of premature death. The SMR for cancer was 0.5. Although patients with type 2 diabetes have a higher risk of cancer than has the general population, the main contributing mechanism is insulin resistance [11], which is not usually seen in type 1 diabetes in Japan [12]. A limitation of the present study is that individuals' clinical data, such as glycaemic status, hypertension or dyslipidaemia, were not considered in the analysis.

In conclusion, the mortality risk for a patient receiving a diagnosis of childhood-onset type 1 diabetes in Japan between 1965 and 1979 was 10.7-fold higher than that of the general Japanese population at the 35 year follow-up. However, the SMR at the 25 year follow-up markedly improved from 19.3 in the 1965–1969 diagnosis group to 6.6 in the 1975–1979 diagnosis group. As the duration of follow-up increased, ADC contributed less and CVD contributed more to mortality. As in white populations, among Japanese people the longer the duration of type 1 diabetes, the more attention should be paid to preventing CVD.

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Contribution statement AM collected data, edited the database, analysed data and wrote the manuscript. YO and HS collected data and edited the database. RN collected data, edited the database and reviewed/edited the manuscript. KU interpreted the data and reviewed the manuscript. NT designed and started the study, collected data, constructed the database and reviewed/edited the manuscript. All authors critically revised the manuscript and approved the final version of the manuscript.

Appendix

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