Major Cross-Country Differences in Risk of Dying for People With IDDM

Diabetes Epidemiology Research International Mortality Study Group

Objective: Little is known concerning global differences in the risk of premature death for individuals developing youth-onset insulin-dependent diabetes mellitus (IDDM). The Diabetes Epidemiology Research International Study was developed to examine the mortality patterns of four population-based cohorts of IDDM cases from Allegheny County, Pennsylvania (n = 1000), Finland (n = 5146), Israel (n = 681), and Japan (n = 1428). Research Design and Methods: All subjects were diagnosed as having diabetes, were <18 yr old at onset, were taking insulin at the time of hospital discharge, and were diagnosed between 1 January 1965 and 31 December 1979. The living status as of 1 January 1985 was determined. Results: Overall, there were 182 deaths. Life-table analysis revealed that at 20-yr duration of diabetes, 5.5% of the cohort had died in Allegheny County in contrast to only 3.1% in Finland and 4.6% in Israel ($P < 0.01$). Follow-up for an additional 3 yr in the United States and Finland revealed major differences in the 30- to 39-yr age-group, with 3.9 times greater premature mortality in the U.S. cohort compared with the Finnish group (overall mortality 2.3 vs. 0.6%, respectively). The Japanese cohort was developed in a somewhat different manner than the other three; therefore, the populations of the U.S., Finland, and Israel were reconfigured to make them directly comparable to that of Japan. The Japanese cohort exhibited markedly higher age-adjusted mortality rates (n/100,000 person-yr of diabetes) than the other three (Japan 681, U.S. 230, Finland 171, and Israel 131). Conclusions: These data indicate that young adult IDDM subjects are at an increased risk of premature death, there are differences in the mortality risk across countries, and both the U.S. and Japan have the major problem of an apparently excessive premature death rate among young people who have diabetes. *Diabetes Care* 14:49–54, 1991

Before the discovery of insulin, the onset of childhood diabetes represented almost certain death; few children survived >1 or 2 yr (1). After insulin entered into clinical use, life expectancy for the newly diagnosed patient with diabetes dramatically increased (2). However, even as insulin became available, it became apparent that childhood diabetes was still associated with marked excessive premature mortality (2,3).

Only half a century has elapsed since the introduction of insulin, yet, as Panzram (3) and, more recently, Borch-Johnsen (2) have indicated, we still know little about why one child dies at the onset of insulin-dependent diabetes mellitus (IDDM), another develops life-terminating complications, and a third survives essentially complication free (3). One approach to address the question of differential prognosis is the cross-cultural assessment of mortality associated with IDDM in populations that are distinctively different in terms of genetics, life-styles, and/or medical care. However, there is little information concerning population differences in IDDM mortality.

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The mortality studies that have been published are from the northeastern United States and northern Europe (2–14), and therefore, may provide only limited insight into global differences in the most serious complication of diabetes death. Each study used somewhat different methodologies and designs, making it impossible to test the hypothesis that the prognosis of IDDM varies across populations.

To test the hypothesis of cross-population differences in IDDM prognosis, the Diabetes Epidemiology Research International (DERI) Mortality Study was initiated in 1986. The study has evaluated mortality in comparable population-based cohorts from four distinctly different countries (Allegheny County, PA [U.S.]; Finland; Israel; and Japan). These areas were selected because they were racially and culturally diverse, had advanced diabetes-care systems, had major cross-population differences in the risk of developing childhood diabetes, and had comparable population-based cohorts (15). Of particular importance, there were also different patterns in the background mortality. This makes it possible to determine whether the mortality of IDDM patients parallels the general population or whether diabetes is such a potent determinant of mortality that it overshadows other factors related to death, thus resulting in a similar prognosis across these populations (16).

RESEARCH DESIGN AND METHODS

The standardized criteria for inclusion into the study were that each subject was diagnosed as having diabetes before the age of 18 yr, was placed on insulin, was diagnosed from 1 January 1965 to 30 December 1979, and was from the defined population of one of the four study areas. Cases of diabetes secondary to other causes, such as steroid-induced diabetes or diabetes associated with cystic fibrosis or Down's syndrome, were excluded.

Mortality follow-up for Allegheny County, Finland, and Israel could begin at the diagnosis of IDDM because the patients were identified from incident cohorts. However, for Japan, the patients were identified from two prevalence cohorts. First we present the analysis of the incidence cohorts, and then we address the prevalence cohorts.

Allegheny County, Pennsylvania. The Allegheny County registry consists of 1063 patients diagnosed between 1965 and 1979 (17). It is a population-based registry developed through the review of hospital records and validated by identifying cases through contact with pediatricians in the community. The degree of ascertainment is well over 95%. The mortality follow-up procedure consisted of writing to each hospital to seek permission to contact the attending or referring physician. We obtained permission from the attending/referring physician to determine the mortality status of the patients by phone and letter tracing. The mortality status was determined for 1000 subjects (94%).

Finland. All patients diagnosed as having diabetes and requiring insulin receive medication free of charge and are registered by the National Social Insurance Institution (18). To obtain insulin, the patient/parents must sign an application and receive a certificate from the physician. All of these certificates were validated with medical records to identify the date of diagnosis of diabetes and to verify insulin use. Ascertainment approached 100%. There were 5146 cases registered during 1965–1985.

Mortality was determined through record linkage of the drug registry to the National Death Registry with the use of the nationwide unique individual identification numbers. Ascertainment of mortality status was 100%.

Israel. In Israel, it was necessary to establish a population-based registry as the first step. The medical records were reviewed for 23 hospitals and 10 diabetes clinics throughout Israel. Several secondary sources were used to check ascertainment. Individuals excluded from the military because of diabetes were identified. Insulin prescriptions for the major health-insurance group in Israel (Kupat-Holim) were reviewed. Finally, a letter was sent to all physicians who would probably see IDDM patients, asking them to report cases fulfilling the criteria for the study. From these approaches, the completeness of the registry was estimated to be >95%. During the period 1965–1979, 611 patients were registered.

The mortality status of the members of the Israel cohort was determined by record linkage of the individual personal identification numbers and demographic characteristics to the National Death Registry. Ascertainment of mortality approached 100%.

Japan. The cohort in Japan was identified in a somewhat different manner than those for the other three countries. The cohort was established from two nationwide diabetes surveys conducted in 1970 and 1981 (19,20). From these surveys, 1428 patients were identified who fulfilled the criteria for the study. The surveys identified at least 75% of the eligible people in Japan (19,20). This was estimated by comparing the incidence calculated from the surveys (0.6/100,000 per yr) with that determined from a population-based survey during the same period (0.8/100,000 per yr) (19,20). This estimate, albeit crude, indicates that a large percentage of all youth-onset patients in Japan were identified. The cases from the surveys were supplemented with 84 patients from the population-based Hokkaido registry, which had >90% ascertainment (21).

The primary approach used to determine mortality consisted of recontacting the original hospitals where the patients were initially identified. If the living status of the patients could not be determined from the medical institution, more in-depth tracing was instituted through government medical records and direct contact with the families. Follow-up was achieved on 1394 of 1428 patients (97.8%).

Analyses. Life-table analysis by duration of IDDM was conducted. The Wilcoxon test was used to test the significance of the differences among the curves (22). Cox's

regression analysis was used to multivariately assess the effect of country while controlling for potential covariates (22).

Age-specific mortality rates and standardized mortality ratios (SMRs) were determined per person-year of follow-up with the OCMAP program by Marsh and Preininger (23). The 1975 background mortality rates for each country were used for the SMR calculations (16). The 95% confidence intervals (CIs) were determined with the Poisson distribution (24). Age adjustment by the direct method with the pooled age-specific population distributions across the four populations was used (25). The pooled age-specific population distribution was used rather than more common standards such as the 1980 U.S. census year or other standard populations because the distribution of the person-years in the DERI mortality follow-up was different from the typical standards, most of the person-year follow-up being in the 15- to 24-yr age-group. The weights used per age group were 0–4 yr, 0.0079; 5–9 yr, 0.0743; 10–14 yr, 0.1934; 15–19 yr, 0.2990; 20–24 yr, 0.2594; 25–29 yr, 0.1329; 30–34 yr, 0.0317; 35–39 yr, 0.0015. Mortality rates are presented throughout the text followed by 95% CIs in parentheses. The few individuals lost to follow-up (U.S. 6%, Japan 2.2%) were excluded from the analyses.

RESULTS

Overall, there were 182 deaths: 34 in Allegheny County, PA; 91 in Finland; 9 in Israel; and 48 in Japan. Figure 1 presents the life-table results showing mortality by duration of IDDM for the U.S., Finland, and Israel. These were highly significant differences ($P = 0.0008$). By 10 yr of duration, 1.7% of the U.S. patients had died in contrast to 0.8% in Finland and 0.5% in Israel. By 20 yr of duration, 5.5% in the U.S. had died in contrast to 3.1% in Finland and 4.6% in Israel. The differences by country were still highly significant when controlling for age at onset, sex, and year of diagnosis with Cox regression (23). The age-specific mortality rates, 95% CIs, and

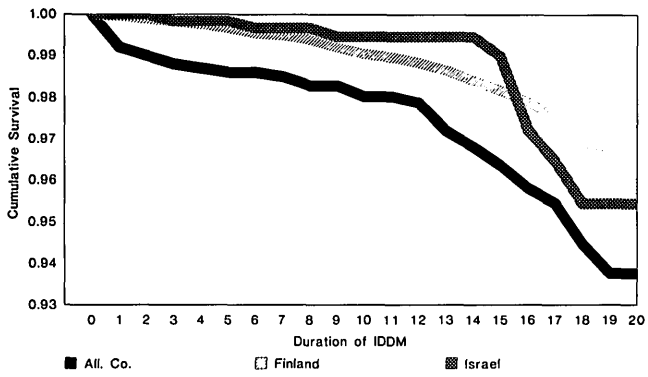

FIG. 1. Life-table analysis of insulin-dependent diabetes mellitus (IDDM) mortality by duration, comparing Allegheny County, PA; Finland; and Israel.

number of deaths are presented in Table 1 by pediatric (0–14 yr of age), youth (15–24 yr of age), and adult (25–37 yr of age) categories. In the pediatric and adult categories, the rates in the U.S. were consistently greater than those in the other two countries. The overall age-adjusted rate per 100,000 person-yr of IDDM for the U.S. (298) was much higher than that in Finland (167), or Israel (131). Japan was not included because of how the cohort was established.

Of particular concern was the apparent excess premature mortality in the U.S. It was possible to follow the Allegheny County and Finnish cohorts another 3 yr to 1 January 1988. During the 3-yr period an additional 30 deaths occurred in Allegheny County and 45 in Finland. Life-table analyses revealed highly significant differences between the U.S. and Finland ($P < 0.0001$). At 24 yr of duration of diabetes, 14.2% of the Allegheny County cohort had died in contrast to only 4.9% of the cohort in Finland. Because of the increased follow-up and therefore increased number of person-years, it was possible to compare the mortality rates in the oldest age-group (30- to 39-yr-olds). In the U.S., there were 19 deaths in this age-group during the overall period, representing a mortality rate of 2.3%/yr (2334/100,000 person-yr of IDDM; 95% CI, 1400–3641/100,000). This was markedly elevated in comparison with the Finnish rate per year of 0.6% (606/100,000 person-yr of IDDM; 95% CI, 396–891/100,000). The rate in the U.S. IDDM cases represented an excess risk that was 49 times that in the background population. Whereas in Finland mortality among IDDM cases was only 11 times that in the general population.

To compare the results from the U.S., Finland, and Israel with Japan, we needed a somewhat different definition of the cohorts. As presented in METHODS, the Japanese cohort was identified from two nationwide surveys, one in the early 1970s and the second in the early 1980s. The patients in the Japanese registry were those diagnosed between 1965 and 1969 who were alive as of January 1970 and individuals diagnosed between 1970 and 1979 who were alive as of January 1980. It was possible to use exactly the same criteria for the cohorts from the U.S., Finland, and Israel, making these cohorts directly comparable to the Japanese prevalance cohorts. Thus, in the U.S., Finland, Israel, and Japan for patients diagnosed between 1965 and 1969, follow-up began as of January 1970, rather than date of diagnosis, and for patients diagnosed in 1970 and 1979, follow-up began as of January 1980. As with the initial analysis, mortality status was determined as of 1 January 1985.

This approach reduced the overall number of deaths from 182 to 147. Restriction of the cohorts in this manner, however, had only a marginal effect on the age-adjusted rates (*n*/100,000), comparing the incidence cohorts with prevalence cohorts (U.S. 298 vs. 238, Finland 167 vs. 171, and Israel 131 vs. 159), indicating that very similar patterns of mortality were seen with the restriction of the cohorts. The cut points would exclusively have their effect in the du-

TABLE 1
Age-specific mortality patterns per 100,000 person-yr of diabetes

	Pediatric	Young adult	Adult
	0–14 yr of age	15–24 yr of age	25–37 yr of age
Allegheny County	230 (110–423)	140 (45–326)	817 (422–1430)
Finland	81 (49–126)	131 (94–117)	400 (270–572)
Israel	30 (10–167)	163 (81–292)	380 (78–1110)

The 95% confidence intervals by Poisson distribution are given in parentheses.

ration period shortly after onset, when few deaths are expected.

Figure 2 presents the age-adjusted rates for IDDM patients by country compared with the age-adjusted background mortality rates. Four facts are immediately evident: *1*) the mortality rate of the IDDM cohort in Japan was much greater than that of the other countries; *2*) in all areas, the IDDM patients were at markedly increased risk of premature death compared with the background population; *3*) there was considerably more variability in mortality for IDDM patients (the highest IDDM mortality rate was 4.6 times higher than the lowest) than for the background mortality (the highest background mortality rate was only 1.4 times higher than the lowest rate); and *4*) the area having the highest IDDM mortality, Japan, had the lowest background mortality for the population of the same age. Statistical analyses bore out these observations. IDDM patients were almost 10 times more likely to die in Japan than the general population (SMR = 992, $P < 0.01$). In contrast, for the other countries, the excess mortality was only about twice that of the background population (Israel 159, Finland 193, Allegheny County 231).

Figure 3 presents the mortality differences by country and age-at-diagnosis groups. It was particularly striking that there was little difference in the mortality experiences of the youngest age-at-diagnosis groups; large differences appeared in the 10- to 14- and 15- to 17-yr-old age-at-diagnosis groups. At follow-up, 20% of the Japanese cohort diagnosed at 15–17 yr of age had died compared to <8% of the individuals in the other three countries. The relationships between premature mortality and sex also varied by country. There was a significant 2.5-fold excess premature mortality in males in Finland; in contrast, there was no significant difference in mortality by sex for the other three areas (unpublished observations).

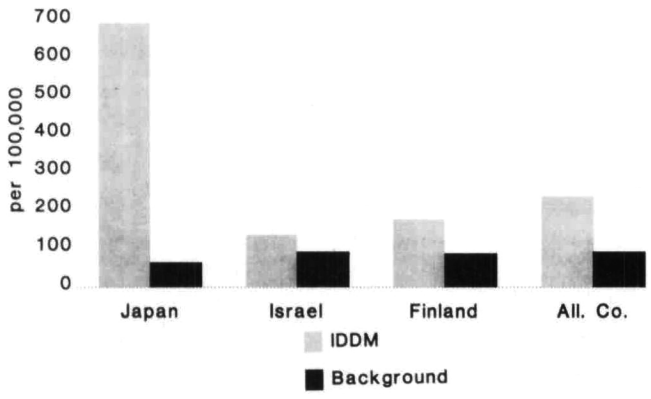

FIG. 2. Annual age-adjusted mortality rates for insulin-dependent diabetes mellitus (IDDM) patients and general population (Japan, Israel, Finland, and Allegheny County, PA).

CONCLUSIONS

IDDM is a potent determinant of death; however, as evidenced in this article, the risk varies dramatically with where a child lives. In all countries, individuals who have diabetes are at a marked increased risk for death, with the highest mortality in Japan. The U.S. was intermediate. In comparison, IDDM cohorts in Finland and Israel had uniformly low rates. There was a pronounced age-at-diagnosis effect between countries, with the greatest differences among countries occurring when IDDM was diagnosed after age 9.

It is unlikely that the factors responsible for the country difference in IDDM mortality are the same as those producing mortality in the general population. Evidence for this comes from the mortality gradient across the diabetic population being almost 10 times greater than that for the general population, and the mortality rates for the IDDM population did not parallel the rate in the general population. In fact, the relationship was opposite: the highest diabetic mortality rate was in Japan, where the overall background mortality was the lowest.

We might speculate as to why the mortality for IDDM cases in Japan was so high. The increased rate may be a function of the rarity of the condition. A pediatrician or internist may see only one case of IDDM in his/her lifetime. Therefore, diabetes care and education have been limited in contrast to the other countries. In addition, approaches to the management of diabetes during the era of the study in Japan were clearly different than in the other three countries. For example, it has been only within the last 15 yr that IDDM patients have been allowed to inject their insulin themselves; before this time, they needed to see their physicians daily for their insulin. It is also likely that there has been much greater variability of care across the 500 hospitals in

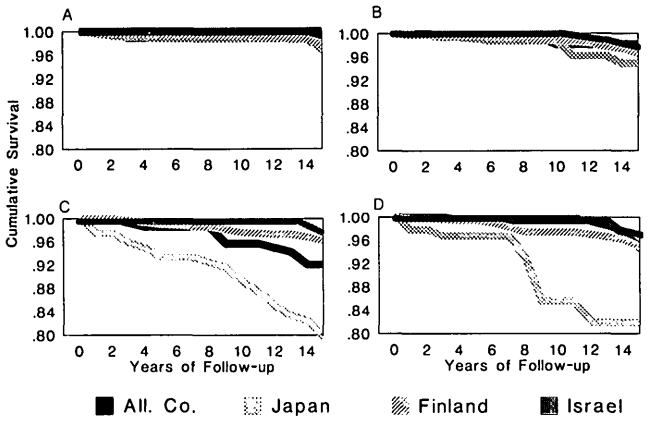

FIG. 3. Life-table analysis of insulin-dependent diabetes mellitus mortality by age at diagnosis. *A*: 0–4 yr; *B*: 5–9 yr; *C*: 10–14 yr; *D*: 15–17 yr.

which the patients were identified in Japan compared with the other areas of investigation (Allegheny County, Finland, or Israel). Thus, rapid changes have occurred in diabetes management in Japan. It will be important to monitor the mortality over time to evaluate the changing patterns of mortality. One might be concerned that the increased rate in Japan was a bias because of the somewhat different manner in which the prevalence cohorts were determined. However, we feel that these are true differences, because the incidence and prevalence cohorts for the other countries yielded almost identical results, suggesting that tailoring the cohorts to be comparable to Japan did not bias the results. Moreover, there were major differences in the long-duration diabetes groups where the use of the "alive" criteria would have no effect. In addition, the patients represented a large percentage of the total population of IDDM patients in Japan at the time of the surveys. For these reasons, we believe that the markedly high rate in Japan cannot be an artifact resulting from the method in which patients were identified and compared.

The data for Allegheny County revealed a distressing excess premature IDDM mortality in adults compared with Finland. In the 30- to 39-yr age-group, an extraordinary 2.3% of individuals died each year, which is almost 50 times the risk of dying for the general population in the U.S. It is critical to determine why the U.S. rate is four times higher than that of Finland. One might speculate that this could be explained by differences in the risk factors for mortality between the two areas. For example, Dorman et al. (26) found that for older individuals, life-style factors such as low education, lack of physical activity, smoking, and alcohol consumption were risk factors for premature death (26–28). Therefore, we hypothesize that the marked excess mortality for older individuals with IDDM in the U.S. compared with Israel and Finland may be the result of health habits. Alternatively, the excess mortality may be the result of barriers to care.

The results of this study are in accord with the previous reports from northern Europe and the U.S., which have demonstrated a significantly elevated mortality among IDDM patients compared with the general population (2–14). Both the Danish and Pittsburgh studies found similar age-at-diagnosis results where there appeared to be an increased mortality for individuals developing diabetes after puberty. In this study, it was striking that it was in the >9-yr-old age at diagnosis that the greatest cross-country differences in mortality rates appeared. This may be the result of there not being a sufficiently large number of deaths in the youngest age-at-diagnosis groups, because they were still quite young at follow-up. Alternatively, these may be true differences, which implies that the factors responsible for cross-country differences in IDDM mortality only surface in the later diagnosis ages, perhaps beyond puberty. Continued follow-up will permit a more thorough examination of these differences. Sex differences have been suggested (2); however, this is the first evidence that the sex differences in mortality risk may vary across countries.

Comparing the mortality rate of IDDM cohorts from the U.S., Israel, Japan, and Finland, we notice vast differences. It is apparent that the diagnosis of IDDM need not equal a death sentence, as it did in the early 1900s. Instead, there appears to be considerable heterogeneity in how the diagnosis of IDDM predicts premature death, with a major determinant being where the child lives. We hope that the factors creating this cross-cultural variation can be identified and modified for all children who develop diabetes, so that IDDM patients in all countries will someday have a risk of dying no different than that for people who do not have diabetes.

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