A Major Improvement in the Prognosis of Individuals With IDDM in the Past 30 Years in Japan

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OBJECTIVE — To evaluate the time trends of mortality among individuals with IDDM in Japan.

RESEARCH DESIGN AND METHODS — A historical prospective study of two independent population-based cohorts composed of individuals who were diagnosed between 1965 and 1969 (1960s cohort) and between 1975 and 1979 (1970s cohort), which included 286 IDDM patients (onset age <18 years) for the 1960s cohort and 779 patients for the 1970s cohort, was performed. After 10 years of observation, mortality status and causes of deaths between the two cohorts were compared.

RESULTS — The age-adjusted mortality rate per 100,000 person-years of the 1960s cohort was 754 (95% CI, 471–1,141); in contrast, that of the 1970s cohort was only 196 (95% CI, 107–329) (P <0.001). The standardized mortality ratio of the 1960s cohort was 1,432 (95% CI, 898–2,161), and that of the 1970s cohort was 489 (95% CI, 267—821). Analyses of the causes of deaths revealed a marked decline in recent years in the number of deaths by acute complications and renal disease.

CONCLUSIONS — A major decline in the mortality of diabetic children in Japan may be attributed to the dramatic changes in the quality of care and medical infrastructure that occurred after the mid-1970s.

The Japanese people live longer than any other. However, the mortality rate of individuals with IDDM in Japan has appeared to be quite high compared with that of individuals with IDDM in Western countries, even in recent years (1). There is very little information concerning the temporal trends of IDDM mortality in Japan or, in fact, in any country. Therefore, as part of the Diabetes Epidemiology Research International (DERI) Mortality Study, we have conducted a follow-up study during the past 30 years to assess time trends of IDDM mortality in Japan. The present study evaluated the 10-year prognoses and the causes of deaths of two independent cohorts in Japan diagnosed between 1965 and 1979.

RESEARCH DESIGN AND METHODS

— Patients were collected from two nationwide IDDM surveys that were conducted in 1970 (2) and 1981 (3), and they fulfilled the criteria of being *1*) diagnosed with diabetes before 18 years of age, 2) placed on insulin therapy within 1 month after onset, and 3) diagnosed between 1965 and 1969 and alive as of 1 January 1970 (for the 1960s cohort) or diagnosed between 1975 and 1979 and alive as of 1 January 1980 (for the 1970s cohort). An "alive" criterion was adopted so that prevalence cohort could be modified into incidence cohort. Any patients with diabetes secondary to other conditions, such as Down's syndrome, were not included. A total of 1,065 patients was registered in this study, 286 patients from the 1960s cohort and 779 patients from the 1970s cohort. The living status for each of the patients was identified as of 1 January 1980 for the 1960s cohort and 1 January 1990 for the 1970s cohort. The degree of ascertainment of 1970s cohort was estimated to be ~60%, according to the reported incidence rate (0.8/100,000) of the Tokyo survey (1979–1981) (4), which had essentially complete ascertainment. Concerning the 1960s cohort, there was no way to estimate the ascertainment rate because no incidence data existed for this time. The ascertainment rate of 1960s cohorts was likely lower than that of the 1970s cohort. The descriptive demographic data, such as sex ratio and age of onset, for the 1960s and 1970s cohorts were similar to that of the Tokyo survey. Therefore, the cohorts appeared to be unbiased and representative of IDDM patients in Japan for this period (5).

Age-adjusted mortality rates and standardized mortality ratios (SMRs) were determined per person-years of follow-up. Cause-specific mortality rates were also calculated to compare the two cohorts. The causes of deaths were determined according to the international standards of the DERI mortality classification committee (6), and they were divided into diabetic renal disease, acute complications (i.e., diabetic ketoacidosis, hypoglycemia, etc.), accident or suicide, cardiovascular disease, infections, cancer, and others. Age adjustment for the pooled age-specific populations across the two cohorts was used. Because the distributions of person-years in our mortality follow-up were different from typical standards as the 1985 world standard population, most of the person-year fol-

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DERI, Diabetes Epidemiology Research International; SMR, standardized mortality ratio.

Table 1—*Comparison of the age-adjusted all causes, cause-specific mortality rates per 100,000 person-years, and SMRs of individuals with IDDM diagnosed between 1965 and 1969 vs. 1975 and 1979*

	1965–1969		1975–1979	
	n	Mortality rates	*n*	Mortality rates
Causes of death				
Acute complications	12	421 (216–738)	6	83 (30–181)
Diabetic renal disease	5	165 (52–388)	0	0
Suicide or accident	2	63 (8–227)	3	41 (8–120)
Cardiovascular disease	1	37 (1–204)	1	14 (0–80)
Infections	1	31 (1–171)	1	14 (0–80)
Other causes	1	37 (1–204)	3	43 (9–126)
All causes	22	754 (471–1141)	14	196 (107–329)
SMRs	1,432 (898–2,161)		489 (267–821)	

Data are *n* and 95% CI by Poisson distribution.

low-up fell in the 5- to 24-year age-group. The statistical weights used per age-group were as follows: 0.0123, 0–4 years old; 0.1225, 5–9 years old; 0.2834, 10–14 years old; 0.3421, 15–19 years old; 0.2020, 20–24 years old; 0.0362, 25–29 years old; and 0.0014, 30–34 years old. For the SMRs calculations, the background mortality rate in 1975 was used for the 1960s cohort and that in 1985 for the 1970s cohort. CIs of the mortality rates and SMRs were determined by the Poisson distribution (7). Statistical analyses were conducted with SAS computer software (8).

RESULTS — The living status of 281 of 286 subjects (98.3%) in the 1960s cohort was traced: 22 were deceased and 259 were alive. In the 1970s cohort, living status of 748 of 779 subjects (96.0%) was traced: 14 were deceased and 734 were alive. Overall, 7.8% of the 1960s cohort died; in contrast, only 1.9% of the 1970s cohort died. The age-adjusted mortality rate per 100,000 person-years of the 1960s cohort was 754 (95% CI, 471–1,141), and that of the 1970s cohort was only 196 (95% CI, 107–329). The difference was statistically significant. The analyses of the causes of the deaths revealed a marked decline in the mortality rates from acute complications and diabetic renal disease in the 1970s cohort compared with the rates of the 1960s cohort. No renal death was observed in the 1970s cohort. No differences were seen in the other causes of deaths (Table 1). The SMR of the 1960s cohort was 1,432 (95% CI, 898–2,161), and that of the 1970s cohort was 489 (95% CI, 267–821) (Table 1).

CONCLUSIONS — Before the discovery of insulin, almost all children with diabetes were destined to die within 1 or 2 years after onset (9). After insulin entered into clinical use, the prognosis of children with diabetes dramatically improved in the early 20th century (10). Studies from Pittsburgh (11), Denmark (12), and Norway (13) have demonstrated a decline in IDDM mortality; however, the decline was much more modest than that seen in Japan. In 1991, the DERI mortality study group conducted a multinational comparative study to examine major cross-country differences in the prognosis of children with IDDM using the same criteria. The study revealed that the mortality of IDDM patients in Japan was extremely high compared with that in the U.S., Finland, and Israel during 1965–1985 (1). Therefore, the present study was conducted to examine if any change had occurred in high IDDM mortality in Japan. The results revealed a marked and rapid improvement of IDDM mortality close to that of Western countries. No other report has demonstrated such a drastic increase in the life expectancy of patients with IDDM in the past 30 years.

One of the reasons for a high IDDM mortality in Japan might be the very low IDDM incidence rate compared with that of countries in Europe and North America. The rate for the Japanese is reported to be ~1/20–1/60 of that for Caucasians (14). This fact may be fortunate for Japan as a country; however, it is quite unfortunate for Japanese patients with IDDM because, in general, pediatricians do not have many opportunities to treat patients for IDDM in their clinical practice. Thus, children with diabetes may not always receive sufficient care.

Another reason for a high IDDM mortality in Japan may reside in the health care system itself, as children could not legally inject themselves with insulin before 1981. However, major health care changes occurred in the mid-1970s that affected individuals with diabetes. Free medical care for diabetic patients under the age of 18 and urine screening tests for school children started in 1974, and summer camps for children with diabetes have become instituted all over Japan during the same period. Moreover, in 1985, the Japan Diabetes Society established a national registry of authorized diabetologists to encourage internists to become diabetes specialists. Thus, a marked decline in the mortality of diabetic children in Japan may be attributed to the improvement of diabetes care and medical infrastructure in Japanese society. The major decline in acute-deaths mortality testifies to the improvement of diabetes care and education; however, acute complications still accounted for half of the deaths in the 1970s cohort and may be preventable. The decrease in the number of deaths by renal disease, which is affected by the quality of primary and long-term diabetes care (15), was also worthy of special mention. Inadequate care of diabetes and insufficient access to hemodialysis might be responsible for the renal deaths that occurred in the 1960s cohort (16). It is very unusual to observe renal deaths within a 10-year duration of diabetes; however, such patients were ob-

served in this cohort. The dramatic changes in the quality of care and the accessibility to hemodialysis that occurred in the 1970s cohort were enough to prevent avoidable premature deaths by renal disease.

Further improvements still need to occur, as Japanese children with IDDM are still five times more likely to die than children of the same age in general population. One effective strategy may be the establishment of a national center for IDDM care where every child with IDDM can receive proper and up-to-date care by the medical team. Our recent work has demonstrated that there was a significant inverse relationship between mortality rate and the number of registered diabetologists among 47 prefectures in Japan (17). It should not be a dream that a child with IDDM has the same longevity as a child without IDDM.

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APPENDIX— DERI Study Group, Japan–Teruo Kitagawa, Naoko Tajima, Nobuo Matsuura, Takayoshi Toyota, Yoshio Ikeda, Itsurou Hibi, Eishi Miki, Hiroshi Maruyama, Masahiko Kawamura, Gen Isshiki, Akira Takeda, Kaichi Kida, Yasuko Kohno, Goro Mimura, Masato Matsushima, Mayumi Aono, Shigeo Aono, Michihiko Maruyama, Kanae Shimizu, Rimei Nishimura, and Keiko Asao.

References

1. Diabetes Epidemiology Research International Mortality Study Group: Major cross-country differences in risk of dying for people with IDDM. *Diabetes Care* 14:49–54, 1991
2. Miki E, Maruyama H: Juvenile-onset diabetes mellitus in Japan: the results of the first nation-wide survey. *J Jpn Diabetic Soc* 15:38–42, 1972
3. Hibi I, Tanae A, Maruyama H, Tsuchiya H, Isshiki G, Matsuura N, Kitagawa T: Juvenile-onset type diabetes in Japan: current status. *Report of the Childhood Diabetes Research Committee*. Tokyo, Japan, Ministry of Health and Welfare, 1980–1981
4. Aagenaes O, Wannag E, Kitagawa T: Childhood diabetes in Tokyo and Oslo. *Diabetologia* 25:135, 1983
5. Tajima N, LaPorte RE, Hibi I, Kitagawa T, Fujita H, Drash AL: A comparison of the epidemiology of youth-onset insulin-dependent diabetes mellitus between Japan and the United States (Allegheny County, Pennsylvania). *Diabetes Care* 8 (Suppl. 1): 17–23, 1985
6. Diabetes Epidemiology Research International Mortality Study Group: International evaluation of cause-specific mortality and IDDM. *Diabetes Care* 14:55–60, 1991
7. Dobson AJ, Kuulasmaa K, Eberle E, Scherer J: Confidence intervals for weighted sums of Poisson parameters. *Stat Med* 10:457–462, 1991
8. SAS Institute: *SAS/STAT User's Guide, Version 6*. Cary, NC, SAS Inst., 1990
9. Krall LP, Levine R, Barnett D: The history of diabetes. In *Joslin's Diabetes Mellitus*. 13th ed. Kahn CR, Weir GC, Eds. Philadelphia, PA, Lea & Febiger, 1994, p. 1–14
10. Marks HH: Longevity and mortality of diabetics. *Am J Public Health* 55:416–423, 1965
11. Dorman JS, LaPorte RE, Kuller LH, Cruickshanks KJ, Orchard TJ, Wagener DK, Becker DJ, Cavender DE, Drash AL: The Pittsburgh Insulin-Dependent Diabetes Mellitus (IDDM) Morbidity and Mortality Study. *Diabetes* 33:271–276, 1984
12. Green A, Borch-Johnsen K, Andersen PK, Hougaard P, Keiding N, Kreiner S, Deckert T: Relative mortality of type 1 (insulin-dependent) diabetes in Denmark: 1933–1981. *Diabetologia* 28:339–342, 1985
13. Joner G, Patrick S: The mortality of children with type 1 (insulin-dependent) diabetes mellitus in Norway, 1973–1988. *Diabetologia* 34:29–32, 1991
14. World Health Organization: *Prevention of Diabetes Mellitus: Report of a WHO Study Group*. Geneva, World Health Org., 1994, p. 1–8
15. Diabetes Control and Complications Trial Research Group: The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 329:977–986, 1993
16. Matsushima M, Tajima N, LaPorte RE, Orchard TJ, Tull ES, Gower IF, Kitagawa T, Diabetes Epidemiology Research International (DERI) U.S.-Japan Mortality Study Group: Markedly increased renal disease mortality and incidence of renal replacement therapy among IDDM patients in Japan in contrast to Allegheny county, Pennsylvania, U.S.A. *Diabetologia* 38:236–243, 1995
17. Nishimura R, Agata T, Shimizu H, Matsushima M, Tajima N, and DERI study group: The relationship between medical infrastructure and IDDM mortality rate in Japan. *J Jpn Diabetes Soc* 38:689–696, 1995