Mortality of Childhood-Onset IDDM Patients

A cohort study in Havana City Province, Cuba

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OBJECTIVE — To determine the survival pattern and the underlying cause of death in a cohort of childhood-onset IDDM subjects from Havana City Province, Cuba.

RESEARCH DESIGN AND METHODS — This was a descriptive study carried out on a historical cohort of IDDM subjects with disease onset before 15 years of age in Havana City Province, Cuba. The cohort was assembled from several sources. Subjects were diagnosed from 1965 to 1980, and their vital status was assessed at 31 December 1991. Cumulative survival rate was calculated by the Kaplan-Meier method, and a univariate analysis was performed. To test survival differences between groups, the Cox-Mantel test was used. To compare the cohort mortality with the general population, standardized mortality ratios by sex and age were calculated. Specific causes of death were determined by a committee examining death certificates, clinical records, and necropsy reports.

RESULTS — A total of 504 subjects were identified, and the mean follow-up time was 17.5 years. Of the subjects, 70 (13.9%) had died at 31 December 1991. Overall, the cohort had a 71% cumulative survival rate at 25 years of IDDM duration. There were no survival differences according to sex or calendar period of IDDM diagnosis. Statistically significant differences were found among age-at-diagnosis groups. The group with a peripubertal age at diagnosis showed the worst prognosis. The cohort experienced 8.5 times the all-causes death rate, compared with the general population. Renal disease accounted for almost half the deaths.

CONCLUSIONS — IDDM subjects from Havana City Province, Cuba, showed a better survival pattern than IDDM subjects from other developing countries. However, when compared with IDDM populations from developed countries, there is a survival reserve to be achieved by reducing mortality due to renal disease and infections.

Mortality data for cohorts of people with IDDM from developing countries are lacking. This might be due to the relatively low prevalence of the disease and the inevitable problems in identification of subjects and ascertainment of death (1,2).

IDDM mortality cohort studies from developed countries have shown a significantly higher risk of premature death for IDDM subjects compared with the general population (3–6). Major cross-country differences in risk-of-dying for people with IDDM have been reported (7).

Worldwide, Cuba is among the countries with low IDDM incidence. The country has a reported annual incidence of 3 cases per 100,000 inhabitants in the 0–14 year age-group (8). However, people with IDDM present a public health problem because of premature mortality and chronic morbidity (4–7).

A single National Public Health System has been running in Cuba for more than 35 years, providing free medical care and covering the entire population. Death certificates are completed by medical doctors for every death in the country. The National System of Public Health Statistics collects and produces data of recognized quality. Thus, identification and follow-up of children with diabetes are feasible.

As far as the authors are aware, this is the first report of a study performed on a large cohort of people with IDDM followed up for a long time in a developing country.

RESEARCH DESIGN AND METHODS

A cohort of IDDM subjects was defined by age at diagnosis of IDDM (<15 years of age), place of residence at IDDM diagnosis (Havana City Province), and date of IDDM diagnosis (1 January 1965 to 31 December 1980).

Inclusion into the cohort began at diagnosis of IDDM, and the patients were followed until they died, emigrated, or until 31 December 1991. Emigrated subjects were censored at the date of migration. Subjects with unknown status at the end of the study were censored at the date of the last medical consultation.

To estimate the number of subjects we would expect in such a cohort, we examined Havana City Province data from the National Registry of IDDM subjects with onset before 15 years of age. This Registry has been running since 1979, and in 1990, it was enrolled as a participating center of the World Health Organization (WHO) Multinational Project for Childhood Diabetes (DiaMond Project) (9). The average annual number of incident cases between 1979 and 1990 in the province was 30. Thus, the estimated number of IDDM subjects during the 15-year period of cohort formation (1965–1980) is 450, assuming no temporal changes in the disease incidence and population demographics.

We assembled our cohort from several sources. Between 1965 and 1980, there was a single health care center (Hospital Dr. Pedro Borrás Astorga), where all children diagnosed with IDDM and living in Havana City Province attended. At age 15 years, they were all referred to another center for teenage diabetes (Diabetics Care Centre, National Institute of Endocrinology). In this center, a registry, including all data from the pediatric health care center, was

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SMR, standardized mortality ratio.

Table 1—*Main epidemiological features of the Havana City cohort*

Characteristic	*n*	Percentage
Sex		
Male	259	51.4
Female	245	48.6
Birth year		
1950–1959	82	16.3
1960–1969	340	67.5
1970–1979	82	16.3
Age at diagnosis		
0–4	182	36.0
5–9	155	31.0
10–14	167	33.0
Year of diagnosis		
1965–1969	121	24.0
1970–1974	165	32.7
1975–1980	218	43.3
IDDM duration (years)		
0–4	8	2.0
5–9	15	3.0
10–14	164	33.0
15–19	178	35.0
20–24	103	20.0
25–26	36	7.0
Life-death status		
Alive	400	79.4
Deceased	70	13.9
Migrated	23	4.5
Unknown	11	2.2

Table 2—*Cohort and population cumulative survival rate according to attained age*

Attained age (years)	Cumulative survival rate, %			
	Cohort (age-at-onset groups)			General population*
	0–4	5–9	10–14	
5	97.9	98.2	98.2	98.2
10	97.9	97.9	97.9	97.9
15	97.3	97.6	97.6	97.6
20	94.4	95.6	96.4	97.1
25	87.9	88.1	93.4	96.4
30	75.6	82.1	79.7	95.7
35	—	62.2	72.7	94.9
40	—	—	68.1	93.9

*Havana City Province, 1986–1987.

maintained. Those on this registry were included in the cohort.

Some children with IDDM may have died before they could be referred to the pediatric health care center. Therefore, we examined necropsy records of pathology archives at pediatric hospitals in Havana City for the study period.

All residents of Cuba have a unique identity number at the Identity Card and Population Registry. This number was used to obtain the subjects' vital status at 31 December 1991. All deaths and migrations in Cuba are registered here.

Since information on death certificates is imprecise (10,11), we attempted to obtain more detailed information from clinical records and necropsy reports (if performed), using a similar approach to that used by the Diabetes Epidemiology Research International (DERI) Epidemiology Mortality Group (12).

After all deaths in the cohort were identified, attempts were made to obtain copies of the medical records (including the last hospitalization if the subject died in a hospital), autopsy reports, and death certificates. Standardized forms were used for all data collection. Information on cause of death was obtained from death certificates in 90% of deceased subjects, from necropsy reports in 64.3%, and from medical records in 31.4%.

A one-paragraph summary on terminal events was then prepared. The three members of the mortality classification committee independently coded the main cause of death and secondary causes that contributed to that death. Eventually, all the information was evaluated by the committee, which collectively decided the most likely underlying cause of death for every deceased subject.

Statistical procedures

Cumulative survival rate was calculated by the Kaplan-Meier method. Statistical significance for group differences was assessed using the Cox-Mantel test. The analyses were carried out using software for univariate survival data analysis (Ludwig Institute for Cancer Research, Sao Paulo branch, Brazil, 1989). Havana City population data for 1986–1987 was used to compare survival rates in the cohort with that of the general population.

To determine the cohort's excess mortality, we calculated standardized mortality ratios (SMRs) by sex and age, and 95% CI of SMRs were calculated assuming the Poisson distribution. The specific mortality of the Cuban general population in 1990 was used as the standard.

RESULTS — A total of 504 subjects (245 females and 259 males) were identified through the mentioned sources. Seven (1.4%) were identified from the necropsy records at pediatric hospitals. Vital status information was available on 470 subjects (93.3%), and the mean follow-up time was 17.5 years (range 0–26). During the follow-up, 70 (13.9%) individuals died, of whom 33 were female (13.5% of females), and 37 were male (14.3% of males). The characteristics of the cohort are shown in Table 1.

Table 2 shows the survival pattern of IDDM subjects compared with the general population of the same age. For each age-at-diagnosis group, the cumulative survival rate starts to diverge from the population cumulative survival rate when the group has been suffering from the disease for at least 10–15 years.

No differences were found in cumulative survival rate by sex ($P = 0.7$) or by year of diagnosis ($P = 1.0$; Figs. 1 and 2). However, significant differences were found in cumulative survival rate among age-at-diagnosis groups ($P < 0.01$). Those subjects who were diagnosed at an older age (10–14 years) had poorer survival rates than those diagnosed at either 0–4 years or 5–9 years of age (Fig. 3).

Overall, the cohort experienced 8.5 times the all-cause mortality compared with the Cuban general population. Female subjects tended to have somewhat higher SMRs than male subjects; 10.0 (95% CI 6.9–14.6) vs. 7.5 (95% CI 5.3–10.3), respectively.

The distribution of specific causes of death is shown in Fig. 4. There were no statistical differences between sexes ($\chi^2 = 2.13$, 4 df, $P = 0.71$). Almost half the deaths in both sexes were due to renal disease. Infections were another important cause of death.

CONCLUSIONS — We believe this is the first report from a developing country on a large cohort of people with IDDM with prolonged follow-up.

We are confident that we ascertained that the vast majority of children with dia-

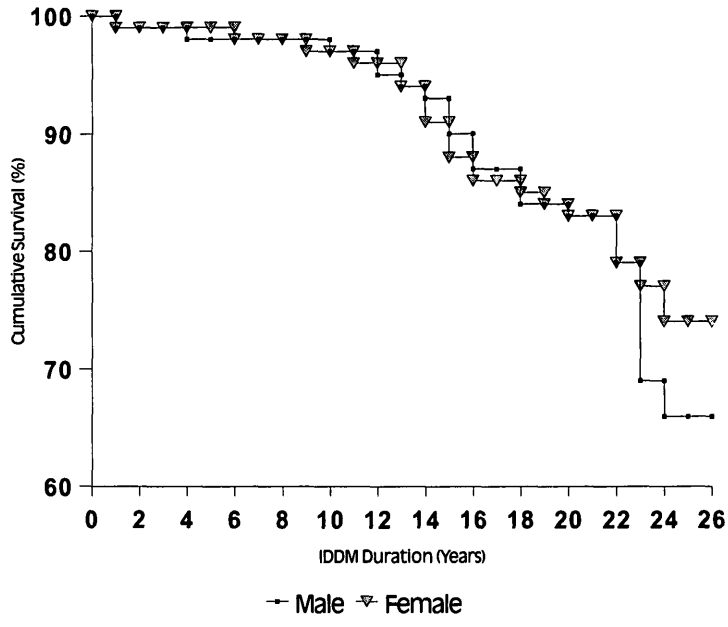

Figure 1—*Survival rate by sex.*

betes, as the number of people in the cohort, was much higher than expected. Further, the Cuban health care system is highly accessible, literacy levels in the population are high, and the disease has a striking acute onset.

We attempted to capture all deaths occurring before referral to the Pediatric Health Centre by searching necropsy records at pediatric hospitals in Havana City Province. This data source may not have been complete for all deaths. However, we managed to obtain up to nine subjects from that data source, and the proportion of people dying <15 years of age in Cuba is small.

Although 23 subjects (4.5%) had emigrated at the end of the study period, we assumed there was no relationship between severity of disease and migration because free health care (including renal transplant) has been offered for the whole population in the country.

It was not possible for us to rule out any contribution made to the survival results by possible confounders (i.e., year of diagnosis or birth year effect) because we used a univariate analysis.

In this report, we compare our results with the results from other reports. However, it is important to take into account that comparison with other studies is difficult because of methodological differences, including differences in the age-groups and the standard populations.

The similarity between the survival of IDDM subjects compared with the general population for the first 10–15 years of disease duration may be due to the avoidance of early deaths. We believe it was due to an early diagnosis, the availability of insulin, and qualified medical care. This observation is consistent with previous findings from Israel, where the cumulative mortality of young IDDM subjects resembled that of the general population during the first 15 years of disease duration (13).

Our results are consistent with previous international results regarding the lack of sex differences in survival rates among IDDM subjects whose onset of diabetes occurs in childhood (4,14,15). Where differences have been found, they have been accounted for by deaths due to accidents and violence, and not by diabetes-related diseases or complications (10).

Children with onset at peripubertal ages had a worse prognosis than children with an early onset. This confirms previous observations from other countries (7,16). The DERI Mortality Study Group has found that among IDDM subjects with onset <18 years of age, those who developed the disease <9 years of age had better survival rates than those who developed the disease later (7). A cohort study at the Children's Hospital of Pittsburgh found that individuals with a peripubertal onset of diabetes had a higher risk of mortality than those with a prepubertal onset (16).

Further research is needed to find out whether such differences among age-at-onset groups were due to a different pathogenesis of disease according to age at onset or to difficulties in achieving good and long-lasting metabolic control in subjects with peripubertal onset. The latter might reflect personal, family, and medical difficulties in dealing with the particular psychosocial characteristics of teenagers. Another possible explanation could be that

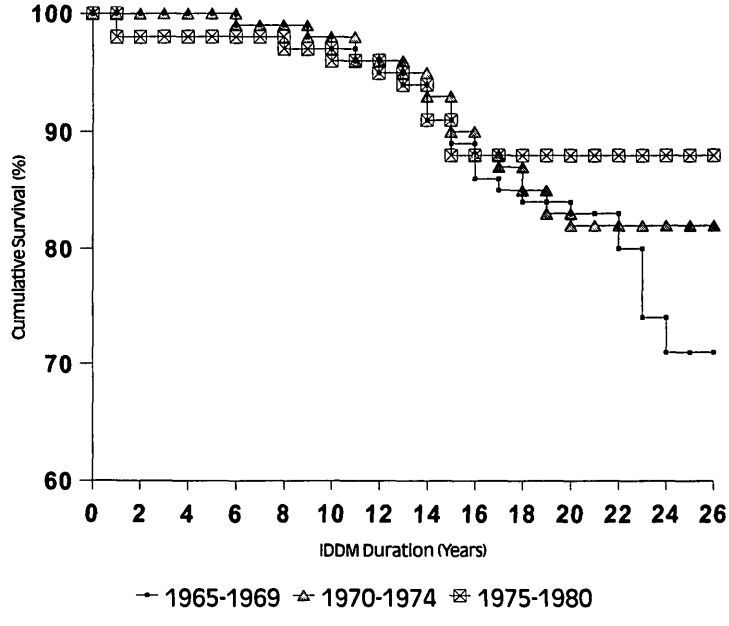

Figure 2—*Survival rate by year of IDDM diagnosis.*

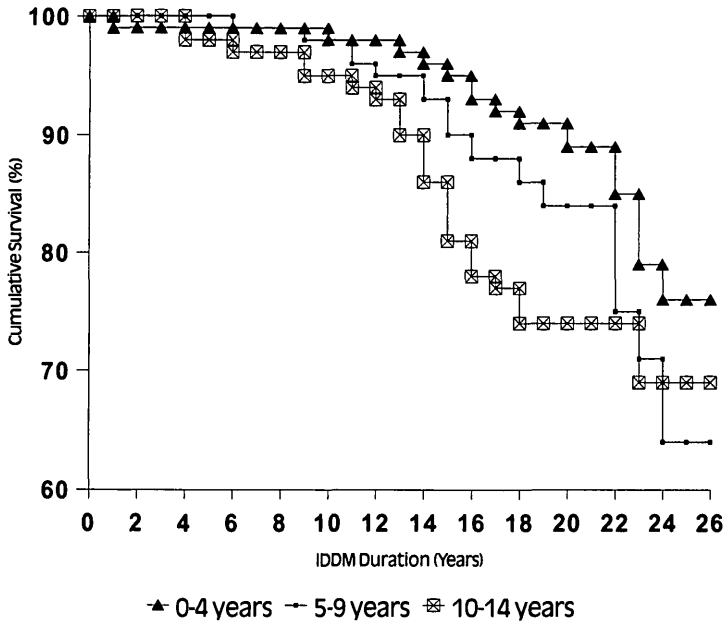

Figure 3—*Survival rate by age at diagnosis.*

the time of onset to time of diagnosis in the peripubertal population may be longer than in the younger population, leading to a longer period of potential organ damage.

This study had shown that Cuban IDDM subjects with onset before 15 years of age have a much better prognosis compared to other developing countries. Data from the African continent have shown an unfavorable position for the African population when it comes to diabetes-associated mortality (IDDM or NIDDM). A study from Tanzania, including IDDM and NIDDM subjects, has shown a 60% survival rate at 5 years of diabetes duration (1). This effect is probably caused by poor access to health care, missed diagnosis, and the unavailability of insulin in most African countries (1,2).

However, the survival of our cohort was inferior compared with cohorts from developed countries. The DERI Mortality Study Group have found better survival probabilities for IDDM subjects with onset before 18 years of age in four countries (7). This was particularly true when diabetes duration was >10 years. After 20 years of disease duration, our cohort had a cumulative survival rate of 84%, considerably less than the 97%, the 95%, and the 94% reported cumulative survival rate at the same years of follow-up for the Finnish, Israeli, and Allegheny County cohorts, respectively (7). At 25 years of disease duration, our cohort had a cumulative survival rate of 71%, showing a rapid decline in the survival probabilities of the subjects.

Compared with the general population, the mortality of childhood-onset IDDM subjects in this cohort is higher than that of developed countries (10). Only Japan has shown an excess mortality of a level similar to our own. Although there was no statistical difference between the sexes in survival, our finding of a greater excess mortality in female subjects is similar to previous findings in other countries (10). It seems that the female survival advantage seen in the general population does not persist in IDDM (18).

The fact that almost half the deaths were due to renal disease could be related both to age of the subjects and to the duration of their disease. Similar findings from other countries have shown that this is the more relevant cause of death for IDDM subjects at these ages (4,17,19). However, others have reported a fewer proportion of deaths due to this cause (12).

We show that infections are an important cause of death in this cohort. This finding was supported by reports from developed countries (10). An extensive Brazilian necropsy study showed infections to be the main cause of death among diabetic subjects, although no separation between IDDM and NIDDM was made (20).

No statistical differences were found in cause-specific mortality by sex. Such differences have been found in other countries (10); however, they were due mainly to violent deaths and not to causes directly associated with diabetes.

Our results show better survival in childhood-onset IDDM patients compared with other developing countries. However, there are clear improvements to be made when compared with developed countries. This could be achieved by reducing mortality from renal disease and infections.

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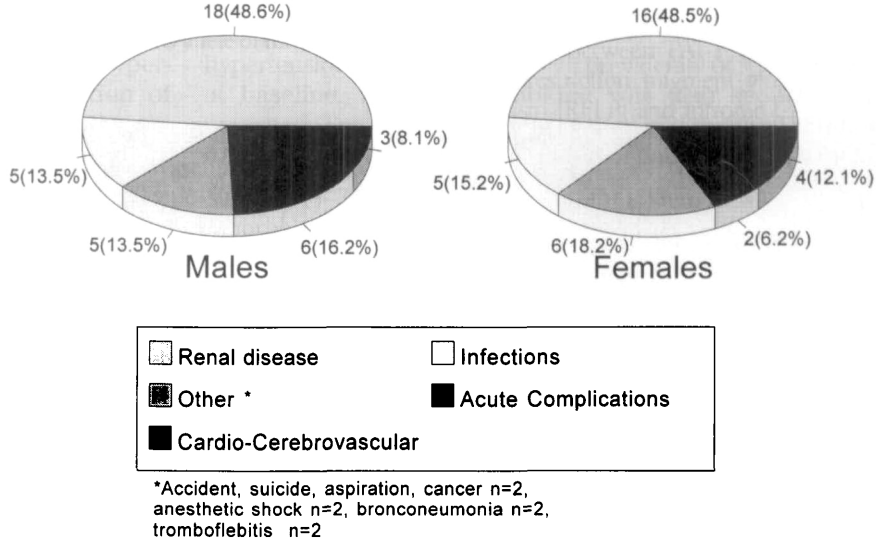

Figure 4—*Causes of death by sex.*

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