The Pittsburgh Insulin-dependent Diabetes Mellitus (IDDM) Morbidity and Mortality Study

Mortality Results

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SUMMARY

A follow-up study of 1966 patients with insulin-dependent diabetes mellitus (IDDM) who were diagnosed at Children's Hospital of Pittsburgh (CHP) between 1950 and 1981 has been completed. The mean age of the population at follow-up was 21.2 yr with a mean duration of IDDM of 12.9 yr. Nine percent of the patients were deceased, a sevenfold excess in mortality compared with the U.S. population. The relative increase in mortality was greater for females than males and greater for blacks than whites. Before age 20, the primary excess in mortality was at onset of IDDM, or within 6 mo after onset, and was due to acute diabetic complications. After age 20, the annual mortality risk was approximately 2%, which was more than 20 times greater than for the U.S. population. Renal disease was responsible for the majority of these deaths. There was a reduced risk of dying for diabetic patients who were diagnosed between 1966 and 1971 compared with patients diagnosed during earlier years. DIABETES 33:271–276, March 1984.

Before the introduction of insulin therapy in 1922 by Banting and Best, few children with insulin-dependent diabetes mellitus (IDDM or type I diabetes) survived more than 1 or 2 yr after the onset of symptoms.[1] After insulin came into clinical use, a dramatic increase in the life expectancy among patients with IDDM was observed. In spite of this significant reduction in mortality, IDDM patients still experience a markedly reduced life span compared with nondiabetic individuals.[1]

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There are few reports that have examined the life expectancy of patients with IDDM. Publications from the Joslin Clinic have indicated that the mortality risk for young diabetic patients was between 12 and 14 times higher than that of the general population, and that there was a marked increase in mortality after 35 yr of age.[1-5] Similar results were obtained from a follow-up study of patients with IDDM from Denmark.[6,7] Approximately one-half of this population died before reaching 50 yr of age. The study from Denmark, as well as the above mentioned reports from the Joslin Clinic,[1-5] have been questioned because of potential biases in patient selection. The Steno Hospital in Denmark and the Joslin Clinic are two major referral hospitals for diabetic patients. The Denmark study included many individuals whose first visit occurred 10 or more years from the onset of diabetes. Therefore, the study was potentially biased by an over-representation of individuals with diabetic complications.[6] The Joslin study reduced this selection bias by limiting their cohort to cases who were seen within 1 yr of the diagnosis of IDDM and who were Massachusetts residents.[5] There was, however, no attempt in the Joslin studies to determine the representativeness of the population.

Sultz et al.[8] described the mortality experience of 389 IDDM patients from Erie County, New York, who were diagnosed between 1946 and 1961. During the 15-yr follow-up period, seven cases had died. The data indicated that 2% of the children in this cohort died during the first 10 yr of diabetes. Although the sample size was small, this is, to our knowledge, the only published population-based mortality study that has been completed for IDDM.

The current investigation was undertaken to document the mortality and morbidity experience of a large population, representative of IDDM patients who are diagnosed during childhood. The focus of this report is to describe the mortality of patients with IDDM in relation to age, race, sex, as well as age at onset and duration of IDDM.

METHODS

The records for all IDDM patients who were seen at Children's Hospital of Pittsburgh (CHP) from 1950 through 1981

have been identified. These records form the basis of our CHP registry of cases. The eligibility criteria for the current study were: (1) the individual was less than 17 yr of age at onset of IDDM, (2) the child was on insulin therapy at the time of discharge from the hospital, and (3) the initial diagnosis of IDDM was made at CHP or the patient was seen at CHP within 1 yr of diagnosis.

From the total population of 1966 cases, the mortality status of 1894 (96%) was determined as of January 1, 1982. Family history surveys have been obtained from 94% of the total group. A medical questionnaire was also completed by 93% of the 735 diabetic patients who were diagnosed before 1965. Copies of death certificates were obtained for deceased patients to ascertain the causes of death.

Life-table analyses[9] were employed to examine the mortality rates in the population by duration of IDDM. To determine age-specific mortality rates, the number of deaths that occurred within each age group was divided by the number of person-years of IDDM within that age group. These age-specific rates were then used to calculate age-adjusted mortality rates by the direct method,[10] using the total diabetic population as the standard. The mortality rates for the diabetic population were compared with those for the general population through the calculation of standardized mortality ratios (SMR). Cause-specific analyses were completed after coding the cause of death according to the Eighth Revision of the International Classification of Diseases and Causes of Death.[11] The analyses were conducted by employing the program "OCMAP" developed by Marsh and Preininger.[12]

RESULTS

Demographic characteristics. Table 1 presents the demographic characteristics of the 1894 patients. There were similar numbers of males and females and over 95% of the population was white. The average age at onset of IDDM for the total population was 8.1 yr, and the average age of the surviving patients as of January 1, 1982 was 21.2 yr. Previous analyses have determined that over 60% of the patients from the population-based Allegheny County IDDM Registry are seen at CHP. Moreover, the demographic characteristics in Table 1 parallel those seen in our IDDM registry for Allegheny County.[13] This cohort, therefore, appears to be very similar to our population-based registry.

TABLE 1
Demographic characteristics, CHP IDDM registry, 1950–1981 [N = 1894 of 1966 cases (96%)]

Characteristic	N	Percent
Year of birth		
1930–1939	25	1.3
1940–1949	290	15.3
1950–1959	634	33.5
1960–1969	720	38.0
1970–1981	225	11.9
Sex		
Male	951	50.2
Female	943	49.8
Race		
White	1806	95.4
Black	88	4.6
Year of IDDM onset		
1950–1959	435	23.0
1960–1969	601	31.7
1970–1979	704	37.2
1980–1981	154	8.1
Age at IDDM onset (yr)		
0–5	537	28.4
6–9	591	31.2
10–16	766	40.4
Living status		
Alive	1730	91.3
Deceased	164	8.7

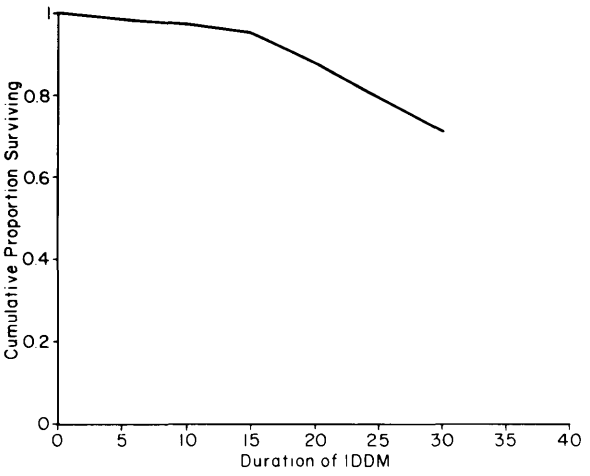

FIGURE 1. Cumulative survival plotted by duration of IDDM.

Overall mortality experience. As shown in Table 1, 8.7% of this young population was deceased, with an average age at death of 23 yr. Life-table analysis of the overall mortality of the cohort by duration of IDDM is presented in Figure 1. This represents approximately 25,000 person-years of follow-up for the 1894 cases (mean duration of follow-up = 12.9 yr). As presented, 3% of the patients died during the first 10 yr after the diagnosis of diabetes, 12% by 20 yr, and 29% by 30 yr of diabetes.

Age-specific mortality. The age-specific mortality of the diabetic population was examined by sex and race and compared with that of the U.S. population. Neonatal deaths are the primary cause of mortality during the first year of life for the general population, but are very infrequent in the diabetic population. Therefore, all deaths under the age of 1 yr were excluded from these analyses. At every age group, and for both sexes, the mortality of white diabetic patients was markedly increased compared with that of the U.S. white population. Results for white males and for white females are presented in Tables 2 and 3, respectively. The overall increase in mortality was higher for female patients (SMR = 1153) than for male patients (SMR = 540, $P < 0.05$). Examination of the age-specific SMRs revealed that the mortality of the diabetic population was 2–30 times higher than that of the U.S. population. The magnitude of the increased mortality was particularly striking among patients 25–40 yr of age. More than 2% of these patients died per year, which is approximately a 20-fold excess in mortality compared with the U.S. population.

Sixteen children (0.8%) died at onset of IDDM and an additional 3 patients died within the first 6 mo after the diagnosis of diabetes. Standardized mortality rates were recalculated after excluding these 19 patients (column 6 in

TABLE 2
Diabetic population, white males; age-specific mortality rates per 1000 person-years and standardized mortality ratios (SMR)

Age (yr)	Observed deaths	Person-years	Mortality rate/1000	Overall SMR	Adjusted SMR‡
1–4	1	424	2.4	261	—
5–9	5	1694	3.0	633*	253
10–14	4	3003	1.3	283	141
15–19	8	3115	2.6	182	182
20–24	15	2191	6.8	363*	363*
25–29	21	1320	15.9	947*	947*
30–34	18	608	29.6	1728*	1728*
35+	8	185	43.2	2057*	2057*
Total	80	12540	6.4	540*	499*

Age-adjusted mortality rate = 6.5/1000 person-years.
*Significant at the 1% level.
†SMR calculated by excluding cases who died within 1 yr of IDDM onset.

Tables 2 and 3). With the exception of the 1–4-yr age group for females, the mortality among diabetic patients, although increased, was not significantly greater than for the U.S. population until age 20 yr. The results indicate that the most dangerous period for patients with IDDM is at onset and during the first 6 mo after onset of symptoms. After this period, the risk is markedly reduced.

Sex differences in mortality. The overall age-adjusted mortality rates were similar for males (6.5/1000) and females (5.7/1000). However, there was considerable variation in the sex ratios of the age-specific mortality rates. Although females had higher mortality rates than males in the younger age groups, the trend was reversed among the older age groups, where a twofold excess in mortality was observed among males.

Racial differences in mortality. As a result of the small number of deaths among blacks in the CHP diabetic population (N = 11), these data were not analyzed by sex. However, the sex ratio among black patients was similar to that for white patients, and no significant sex differences in mortality were observed. Overall, the age-adjusted mortality rate among blacks (12.3/1000) was approximately twice the rate among whites (6.1/1000).

To determine if the higher mortality rates among black patients could be explained by the racial differences in mortality that are observed in the general population,[14] SMRs were calculated by comparing white diabetic patients with the U.S. white population and black diabetic patients with the U.S. black population. It was apparent that the relative excess in mortality was higher for black patients (SMR = 968) than for white patients (SMR = 711). This suggests that insulin-dependent diabetes may have a greater impact on mortality among black patients compared with white patients. The causes of death among black versus white patients were also examined and found to be similar. Diabetic ketoacidosis and coma accounted for 17% of the deaths among whites and for 18.2% among blacks. The proportions of deaths due to other causes were also comparable between the races.

Differences in mortality by age at onset of IDDM. Figure 2 presents the relationship between age at onset of IDDM and mortality risk. For each age at onset group, an increase in age was associated with a marked increase in mortality. However, little variation was observed in the mortality patterns for the three age at onset groups. The age-specific mortality rates for patients diagnosed before 5 yr of age were similar to the rates for patients with older ages at onset, as illustrated by the overlapping confidence intervals.

These results are of critical importance in trying to examine the independent effects of duration of diabetes and age on

TABLE 3
Diabetic population, white females; age-specific mortality rates per 1000 person-years and standardized mortality ratios (SMR)

Age (yr)	Observed deaths	Person-years	Mortality rate/1000	Overall SMR	Adjusted SMR‡
1–4	6	315	19.0	2606*	869†
5–9	7	1502	4.7	1437*	411
10–14	7	2927	2.4	882*	378
15–19	4	2793	1.4	270	270
20–24	10	1986	5.0	823*	823*
25–29	24	1192	20.1	3055*	3055*
30–34	8	550	14.6	1699*	1699*
35+	0	192	—	—	—
Total	66	11457	5.8	1153*	926*

Age-adjusted mortality rate = 5.7/1000 person-years.
*Significant at the 1% level.
†Significant at the 5% level.
‡SMR calculated by excluding cases who died within 1 yr of IDDM onset.

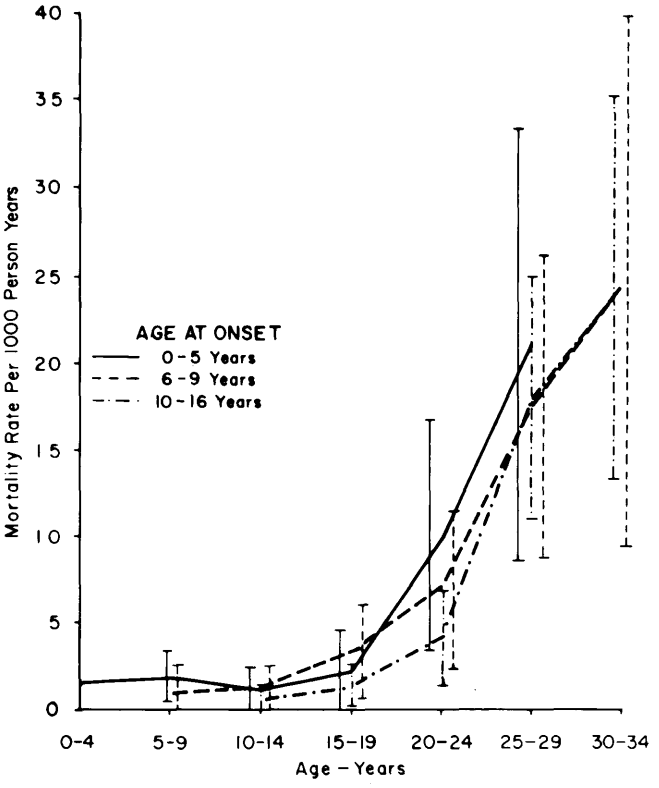

FIGURE 2. Age-specific mortality rates per 1000 person-years and 95% confidence intervals by age at onset of IDDM, excluding 19 deaths within 1 yr of IDDM onset.

the mortality risk. The age-specific mortality rates did not differ significantly by age at onset. At every age, patients with a younger age at onset have had a longer duration of diabetes than those diagnosed at a later age. The results, therefore, suggest that age is more highly associated with mortality risk than the duration of diabetes.

Cohort differences in mortality. During the past 30 yr, there have been major advancements in the treatment of IDDM. The mortality experience of children diagnosed with IDDM in the early 1950s was, therefore, compared with those diagnosed in the later years. The mean ages at onset were similar for each cohort. Comparing children diagnosed in the 1950s and early 1960s with those diagnosed after 1966, there was an overall significant reduction in 5- and 10-yr mortality for the 1966–1971 cohort (Table 4). In addition, there was a dramatic reduction in onset mortality. Although 1.7% of the children diagnosed between 1950 and 1957 died at onset, the mortality risk in later years was 0.5%. This represents more than a threefold reduction in mortality risk. However, the mortality at 15 and 20 yr of diabetes did not differ significantly by year of diagnosis. It was important to determine if this improvement in survivorship was exclusively the result of a reduction in the number of deaths occurring shortly after IDDM onset, or resulted from a decline in long-term mortality. The mortality probabilities were, therefore, recalculated by excluding all deaths that occurred during the first year of diabetes, and are presented in Table 5. Comparing the 1958–1965 cohort with the 1950–1957 cohort, the elimination of the deaths within 1 yr of onset accounted for the slight improvement in long-term mortality. However, the 1966–1971 cohort still showed a lower mortality, both at 5- and 10-yr duration, which approached statistical significance.

Cause-specific mortality. Analyses of the causes of death obtained from death certificates confirmed that the majority of deaths were due to renal disease, as presented in the total mortality results in Figure 3. The largest proportion of the deaths occurring before 10 yr of age were due to acute complications, including ketoacidosis and coma. These conditions were also responsible for one-half of the deaths among patients 10–19 yr of age. In addition, deaths unrelated to diabetes were common in this age group. Renal disease was not a major cause of death among these young patients. This is in sharp contrast to what was observed for patients dying between 20 and 29 yr of age. In this age group, renal disease accounted for more than one-half of the deaths. Among patients 30 yr of age or older, the proportion of deaths due to renal disease was similar to that observed for patients 20–29 yr of age. Cardiovascular mortality was also a significant cause of death among older diabetic patients.

Standardized mortality ratios were also calculated by cause of death and are presented in Table 6 for white males and white females. As illustrated, the mortality from renal disease in the diabetic cohort was excessive when compared with the U.S. population. However, the number of cardiovascular deaths in this young population was more than 11 times greater than what would be expected among nondiabetic individuals of the same age. Of interest was that neither cancer mortality nor mortality resulting from accidents was increased.

TABLE 4
Cumulative probability of dying within a given duration of IDDM by year of IDDM diagnosis

Year of diagnosis	Duration of IDDM				
	≤1 yr	≤5 yr	≤10 yr	≤15 yr	≤20 yr
1950–1957 (N = 291)	1.7%	3.1%	4.1%	6.2%	14.5%
1958–1965 (N = 473)	0.9%	1.9%	3.6%	5.3%	12.9%‡
1966–1971 (N = 423)	0.5%	0.7%	1.4%		
	P < 0.05	P < 0.05	P < 0.05	NS	NS

‡Probability calculated for years 1958–1961, N = 249.

TABLE 5
Cumulative probability of dying within a given duration of IDDM by year of IDDM diagnosis, excluding deaths within the first year of diabetes

Year of diagnosis	Duration of IDDM			
	≤5 yr	≤10 yr	≤15 yr	≤20 yr
1950–1957 (N = 286)	1.4%	2.4%	4.5%	12.9%
1958–1965 (N = 469)	1.0%	2.7%	4.4%	11.4%‡
1966–1971 (N = 421)	0.2%	0.9%		
	P = 0.06	P = 0.07	NS	NS

‡Probability calculated for years 1958–1961, N = 245.

DISCUSSION

Insulin-dependent diabetes mellitus is the most prevalent chronic disease in children other than asthma.[8] Surprisingly, little is known about the degree to which IDDM is a direct or indirect cause of death in children and adults. In this report, the mortality experience of a large, well-defined, and representative population of newly diagnosed IDDM patients has been presented.

The results of these analyses demonstrate that, overall, IDDM patients had a sevenfold excess in mortality risk compared with the U.S. population of the same age. The relative increase was greater for female patients than for male patients, which was most likely a reflection of the sex differential in mortality that is observed for the U.S. population, but lacking among individuals with IDDM.

Mortality among patients less than 20 yr of age was frequently the result of children dying at onset of IDDM or within 6 mo after the onset of symptoms. This indicates that the critical period for the increased mortality risk is at onset or shortly afterward. After the first 6 mo of diabetes, the risk of dying was markedly reduced and not significantly greater than for the general population until age 20 yr.

The racial difference in mortality is of particular interest. In Allegheny County, whites are about 50% more likely to develop IDDM than blacks.[13] However, once diabetes develops, it appears as if IDDM is more likely to be fatal for blacks than for whites. In addition, there were no major differences in the causes of death for blacks and whites. The results are similar to the findings of Sultz in a much smaller sample size.[8] Although these results were based on a small number of black patients, the differences in the incidence, as well as the mortality risk, suggest that IDDM among blacks may have different characteristics than IDDM among whites, and may reflect racial heterogeneity of the etiology and severity of IDDM.

Our results indicate that age was a much more important determinant of mortality than duration of diabetes. This relationship between duration of diabetes and mortality has also been demonstrated at the Joslin Clinic and the Steno Hospital in Denmark.[5–7] It has been argued that these data indicate that the duration of diabetes is not highly related to the risk of mortality.[5] Alternatively, the findings could be the result of the limited variability of duration of IDDM in this cohort, which is due to the narrow range of the ages at onset (< 17 yr). Future research will be needed to examine the true relationship between duration of IDDM and mortality with a broader range of age at onset than that employed in the current research.

Differences in mortality were also observed by a decade of diagnosis. An overall significant reduction in mortality was observed for patients with onset of IDDM between 1966 and 1971 compared with individuals diagnosed during earlier

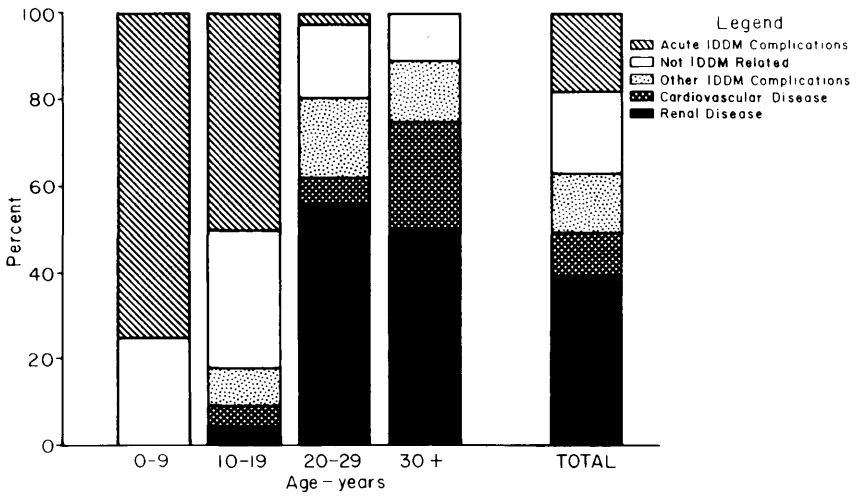

FIGURE 3. Distribution of causes of death by age at death.

TABLE 6
Standardized mortality ratios (SMR) by cause of death

Cause of death	White males		White females	
	Number of deaths	SMR	Number of deaths	SMR
All causes	80	540*	66	1153*
All malignant neoplasms	1	85	2	236
Cardiovascular disease	8	1137*	7	1591*
Renal disease	34	55618*	24	56163*
Accidents and suicide	6	57	4	146

*Significant at the 1% level.

years, even when the deaths occurring within the first year of diabetes were eliminated. These results are very encouraging and are indicative of an improvement in the long-term prognosis of IDDM patients. The increase in survival was not a result of the decline in mortality in the general U.S. population. During the 1950–1981 period, not only was there a decline in the mortality rates for diabetic patients, but there was also a marked reduction in the SMRs. The decrease in the number of deaths occurring at diabetes onset during the late 1960s, as well as the reduction in 5- and 10-yr mortality, may reflect improvements in medical care, better diabetes education, and/or changes in life-style habits.

The reduction in mortality does not appear to be specific to the Pittsburgh area. Recent vital statistics reports from the state of Pennsylvania have revealed that during 1970 and 1971, 29 individuals under age 20 yr died and had diabetes listed as the primary cause of death on the death certificates. However, during 1979 and 1980, only 5 people under 20 yr of age died of diabetes.[15] The results from Pittsburgh and the state of Pennsylvania, therefore, suggest a marked reduction in mortality for young insulin-dependent diabetic patients.

The results of these analyses indicate that the second most prevalent chronic disease in children, IDDM,[8] is still associated with a marked increase in mortality. Future epidemiologic research is needed to identify why some individuals with IDDM die prematurely, whereas others have a survival experience similar to the nondiabetic population. Through this knowledge, it may be possible to identify the risk factors for morbidity and mortality, which, if altered, may reduce the likelihood of early complications and premature death.

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