Mortality Trends in Type 1 Diabetes

The Allegheny County (Pennsylvania) Registry 1965–1999

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OBJECTIVES — To investigate long-term mortality and its temporal trends as of 1 January 1999 among the 1,075 patients with type 1 diabetes (onset age <18 years, diagnosed between 1965 and 1979) who comprise the Allegheny County population-based registry.

RESEARCH DESIGN AND METHODS — Overall, sex- and race-specific mortality rates per person-year of follow-up were determined. Standardized mortality ratios were also calculated. Survival analyses and Cox proportional hazard model were also used. Temporal trends were examined by dividing the cohort into three groups by year of diagnosis (1965–1969, 1970–1974, and 1975–1979).

RESULTS — Living status of 972 cases was ascertained as of January 1, 1999 (ascertainment rate 90.4%). The mean duration of diabetes was 25.2 ± 5.8 (SD) years. Overall, 170 deaths were observed. The crude mortality rate was 627 per 100,000 person-years (95% CI 532–728) and standardized mortality ratio was 519 (440–602). Life-table analyses by the Kaplan-Meier method indicated cumulative survival rates of 98.0% at 10 years, 92.1% at 20 years, and 79.6% at 30 years duration of diabetes. There was a significant improvement in the survival rate between the cohort diagnosed during 1965–1969 and that diagnosed during 1975–1979 by the log-rank test ($P = 0.03$). Mortality was higher in African-Americans than in Caucasians, but there were no differences seen by sex. The improvement in recent years was seen in both ethnic groups and sexes.

CONCLUSIONS — An improvement in long-term survival was observed in the more recently diagnosed cohort. This improvement is consistent with the introduction of HbA_1 testing, home blood glucose monitoring, and improved blood pressure therapy in the 1980s.

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The introduction of insulin into clinical use in the 1920s dramatically changed the life of children with type 1 diabetes. Before that time, onset of the disease meant almost certain death. Results from the Joslin Clinic showed that 10-year survival of patients diagnosed as having diabetes in the 1930s was higher than 90% (1). More recently, a follow-up study from the Children's Hospital of Pittsburgh reported that the mortality of subjects diagnosed between 1950 and 1981 was seven times higher than that of the general population as of 1982 (2). The study also showed that the 10-year mortality decreased from 4.1 to 1.4% during this period. However, these results do not necessarily represent the mortality of the total diabetic population, because the study was hospital-based.

The Diabetes Epidemiology Research International (DERI) group conducted an international study comparing the mortality (as of 1 January 1990) of patients diagnosed between 1965 and 1979 in population-based registries from four countries: U.S. (Allegheny County, PA), Finland, Japan, and Israel. The mortality in Allegheny County was five times higher than that of the general population (3–5). European reports of population-based studies from Norway (6) and the U.K. (7,8) suggest that the mortality of children with type 1 diabetes was two to three times higher than that of the general population. The report from the U.K. also noted that the standardized mortality ratios (SMRs) decreased from 981 to 238 during the period 1940–1989 (8). However, very limited information is available in the U.S. regarding time trends in mortality with duration of diabetes of >10 years for patients diagnosed in recent years (9). This is particularly important because medical care improved greatly with the advent of self-monitoring blood glucose (10), HbA_{1c} (11), and angiotensin-converting enzyme inhibitor use (12) in recent years. Therefore, the current study assessed the long-term mortality and temporal trends in prognosis for the subjects diagnosed between 1965 and 1979 with follow-up of at least 19 years. Differences in ethnic group (African-American versus Caucasian) and sex were also examined.

RESEARCH DESIGN AND METHODS

— Subjects were identified from the type 1 diabetes incidence registry in Allegheny County, PA, which was developed through periodic review of hospital records and validated by contact with pediatricians in the community (13). This is the same cohort as studies in earlier DERI reports (3–5) and has been fully described previously (3–5,13) with the degree of ascertainment estimated to be >95% (13). Inclusion criteria were a diagnosis of diabetes before 18 years of age between 1 January 1965 and 31 December 1979, residence in Allegheny County, PA, at onset, and administration of insulin beginning at the time of diagnosis. Persons were excluded if they had developed

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

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Demographic profile of study population (Allegheny County Registry, U.S., 1965–79)*

	Sex		Race		Year at onset			
	Male	Female	Caucasian	African-American	1965–1969	1970–1974	1975–1979	Total
n	558	517	995	79	353	391	331	1,075
Living status confirmed (%)	502 (90.0)	470 (90.9)	906 (91.1)	65 (82.3)	320 (90.7)	355 (90.8)	297 (89.7)	972 (90.4)
Male (%)	558 (100)	—	524 (52.7)	34 (43.0)	178 (50.4)	213 (54.5)	167 (50.4)	559 (52.0)
Caucasian (%)	524 (93.9)	471 (91.1)	955 (100)	—	326 (92.4)	366 (92.4)	303 (91.5)	996 (92.7)
Year at onset	1971.9 ± 4.1	1971.8 ± 4.1	1971.9 ± 4.1	1971.8 ± 44	1967.2 ± 1.4	1972.0 ± 1.4	1976.8 ± 1.5	1971.9 ± 4.1
Age at onset	11.0 ± 4.3	10.8 ± 4.0	10.9 ± 4.2	11.4 ± 4.3	10.6 ± 4.4	10.7 ± 4.1	11.5 ± 4.0	10.8 ± 4.2
Mean duration of diabetes	25.5 ± 5.0	24.9 ± 6.2	25.3 ± 5.6	23.6 ± 6.4	28.7 ± 6.2	25.2 ± 4.9	21.3 ± 2.6	25.2 ± 5.8
Person-years of follow-up	14,188.25	12,904.7	25,199.84	1,872.6	10,184.9	9,878.2	7,029.8	27,092.9

Data are means ± SD, unless otherwise indicated. Age at onset for the subjects diagnosed between 1975–1979 was significantly higher than those of 1965–1969 and 1970–1974 by Tukey's multiple comparison of analysis of variance ($P = 0.01$).

diabetes from a secondary cause, i.e., diabetes associated with cystic fibrosis or Down's syndrome and steroid-induced diabetes. As of 1 January 1980, 1,075 eligible cases were identified from the Allegheny County registry.

Initially, permission was obtained from the hospital of diagnosis to contact the attending or referring physician for each eligible case. Upon approval, permission was then obtained from the attending/referring physician to contact their patients by letter and then phone for the initial follow-up (conducted in 1985). To ascertain the living status of cases as of 1 January 1999, contact was again made first by letter with a questionnaire and a consent form. If the subjects did not respond to this questionnaire, they were contacted by phone. If the whereabouts of subjects were not confirmed by these procedures, tracking through the Social Security Death Index (www.ancestry.com) and the National Death Index was also used (14). These procedures were approved by the Institutional Review Board of the University of Pittsburgh.

Analysis

Overall, sex- and race-specific mortality rates per person-year of follow-up were determined. To assess the temporal trends of mortality, the total cohort was divided into three groups by year of diagnosis (1965–1969, 1970–1974, and 1975–1979). Temporal trends were also assessed by race and sex. The χ^2 test for trend was used to assess the trends of mortality. Life-table analyses by the Kaplan-Meier method were performed. Log-rank test was used to determine the statistical difference between the survival curves both overall and by sex, race, and diagnosis cohort. Although performed, the more detailed analyses (e.g., by diagnosis cohort within race) are limited by small sample size. The SMRs were calculated considering dynamic calendar date and age with reference to the National Vital Statistics Report (15). Person-years were partitioned by decade and age, sex, race, and calendar year. Similar specific background mortality rates covering the same period were used for calculation of SMRs. To investigate the effects of sex, age at diagnosis, race, and year at diagnosis (1965–1969, 1970–1974, and 1975–1979), Cox proportional hazard model was used. The 95% CIs were determined based on the Poisson distribution (16). Statistical analyses were conducted with SAS software (17).

RESULTS — As of 1 January 1999, the living status of 972 of the 1,075 total cases was confirmed (90.4%). There were no statistical differences between the traced and missing cases in age at onset (mean + SD 10.6 + 4.0 vs. 10.7 + 3.7 years, respectively; mean year at onset 1971 + 4.1 vs. 1972.1 + 4.0, respectively) and sex (51.6 vs. 55.7% male, respectively). However, African-Americans were less likely to be traced than Caucasians (93.3% of Caucasians were traced vs. 86.8% of African-Americans). The demographic details by race and sex are listed in Table 1. Age at onset for the subjects diagnosed between 1975 and 1979 was significantly higher than those diagnosed in 1965–1969 and 1970–1974 ($P = 0.01$). Overall, 170 deaths were observed (17.5%) (Table 2). The mean duration of diabetes of the cases at death or censoring was 25.2 ± 5.8 (SD) years. Overall, the mortality rate was 627 per 100,000 person-years (95% CI 532–728). Sex, race, and temporal morbidity data are shown in Table 2. The mortality of African-Americans was significantly higher that that of the Caucasians ($P < 0.05$); however, the difference was less marked when race-specific SMRs were compared. The mortality rate in women tended to be higher than in men; the SMR for women (1,041) was substantially higher than for men (325).

At 20-year duration of diabetes (Table 2), a significant improvement in mortality by diagnosis cohort was seen ($P < 0.01$). However, no difference in mortality was noted by either sex or race at 20 years duration of diabetes.

Life-table analyses of the total cohort by the Kaplan-Meier method indicated that the cumulative survival was 98% at 10 years, 92.1% at 20 years, and 79.6% at 30 years (Fig. 1*A*). Little difference was seen by sex (Fig. 1*B*), although the survival curve of African-Americans (Fig. 1*C*) was significantly worse than that of Caucasians, especially after 25-year duration of diabetes ($P < 0.0001$). The survival rate of the 1975–1979 cohort (Fig. 1*D*) was significantly higher than that of the 1965–1969 cohort ($P = 0.03$). Between 10 and 20 years duration of diabetes, 8.4% of the subjects died in the earliest cohort (1965–1969), whereas only 3.5% of the subjects died in the latest cohort (1975–1979) (Fig. 1*D*). The analyses of temporal trend of mortality showed a declining trend for both Caucasians and African-Americans; however, this was not significant in either race. In African-Americans, >20% of the subjects died at 20 years duration of diabetes in the

Table 2—*Mortality rates and standardized mortality ratios by sex, race, and year at onset (Allegheny County Registry, U.S., 1965–1979, 20+ years follow-up)*

	Sex		Race		Year at onset			
	Male	Female	Caucasian	African-American	1965–1969	1970–1974	1975–1979	Total
Deceased (*n*)	81	89	144	26	92	57	21	170
Mortality rate	571	690	571	1,388	903	577	299	627
(95% CI)	(447–670)	(551–846)	(478–672)	(895–2,012)	(729–1,094)	(440–736)	(182–451)	(532–728)
SMR	325	1,041	530	645	677	488	281	519
(95% CI)	(255–398)	(832–1,277)	(443–623)	(416–934)	(546–821)	(372–622)	(171–424)	(440–602)
Deceased (*n*) at 20 years duration of diabetes	35	40	67	8	33	27	15	75
Mortality rate at 20 years duration of diabetes	310	389	335	508	457	345	229	347
(95% CI)	(210–422)	(282–522)	(217–360)	(207–948)	(318–627)	(225–487)	(124–363)	(253–459)
SMR at 20 years duration of diabetes	222	776	387	327	492	367	235	367.0
(95% CI)	(151–303)	(562–1,042)	(251–416)	(133–610)	(342–676)	(239–519)	(127–372)	(267–484)

95% CIs according to the Poisson distribution are given in the parentheses. Mortality rate of African-Americans is significantly higher than that of Caucasians ($P < 0.05$). At 20 years duration of diabetes, the time trend in mortality rates was significant ($P = 0.01$).

oldest cohort (1965–1969); however, only 11% of the subjects died at 20 years duration of diabetes in latest cohort (1975–1979). In the oldest cohort, more than half of the African-Americans had died at the 30 years duration of diabetes (Fig. 1*E* and *F*). Cox proportional hazard model indicated that the cohort diagnosed between 1975 and 1979 had significantly lower risk of death compared with those diagnosed between 1965 and 1969 (risk ratio 0.51 [1975–1979/1965–1969], 95% CI 0.30–0.85). Risk for those diagnosed between 1970 and 1974 did not differ from those diagnosed from 1965 to 1969 (0.86 [1970–1974/1965–1969], 0.61–1.23). In the model, older age at diagnosis (1.12/1-year, 1.08–1.17) and African-American race (1.68 [African-American/Caucasian], 1.35–2.10) but not sex (1.20 [female/male], 0.88–1.62) were significantly associated with higher risk of death.

CONCLUSIONS — The present study confirmed living status and temporal trends in mortality in a population-based cohort in Allegheny County, PA, with a 19-year minimum and a 34-year maximum follow-up (duration) of diabetes. In accordance with recent reports from developed countries, the mortality in Allegheny Country, PA, was higher than that of the general population with an overall SMR of 519 (95% CI 440–672). Likewise, a study from Leicestershire, U.K., followed 845 type 1 diabetes patients diagnosed between 1940 and 1989 and reported a decrease in the SMR from 938 in the 1940s to 238 in the 1980s (8), although clearly this decrease was dated from an earlier time point. However, in a more recent study (cases diagnosed between 1973 and 1982 compared with 1988), the SMR in Norway has also been reported to have decreased from 1,908 to 207 (6). Although our results are somewhat worse than these European data, differences in methodology (including our longer follow-up) and populations studied make comparisons difficult. Nonetheless, our previous DERI report indicated a 61% greater relative risk of death in Allegheny County as of 1990 (SMR = 485, 95% CI 368–627), compared with Finland (331, CI 291–394).

The reasons for a higher mortality in the U.S. may relate to the costly health care system for diabetes (5); the high financial burden may keep patients from frequent contact with physicians. In Finland and Norway, where mortality was reported to be lower, free medical care is provided for type 1 diabetes. Greater contact with a diabetes specialist care team has also been suggested to be related to a reduced risk of death in Pittsburgh (18). Another component of the higher mortality in the U.S. is the higher mortality of African-Americans, which has previously been reported as a twofold excess mortality in the same cohort (19). The difference in prognosis after 20 years duration of diabetes was evident. However, because the mortality in the general population is also higher in African-Americans, the SMRs for diabetes are relatively similar in both African-Americans and Caucasians. Thus, the poorer prognosis for African-Americans with type 1 diabetes reflects an underlying general ethnic disparity rather than a diabetes-specific entity. No difference in the mortality rates by sex was apparent in the current analysis, which is consistent with a previous report (20). However, the SMR for women was significantly higher than that of men, reflecting the lower background mortality in women.

Several studies have examined temporal trends in mortality associated with type 1 diabetes. In a study from Denmark, based on 2,930 type 1 diabetic patients diagnosed before the age of 31 years between 1933 and 1972, the relative mortality of type 1 diabetes decreased as calendar years at diagnosis increased after 1950 during this period (21). The study from the U.K., based on 845 patients diagnosed between 1940 and 1989, reported a major decline in mortality and SMRs by decade of diagnoses, especially between the 1940s and the 1950s. However, there were no clear differences in survival curves by decade of diagnosis between 1950 and 1980. A mortality study from Cuba showed that no improvement was observed in mortality of the cases diagnosed between 1965 and 1980 (22).

In the present study, mortality, especially after 15 years duration of diabetes,

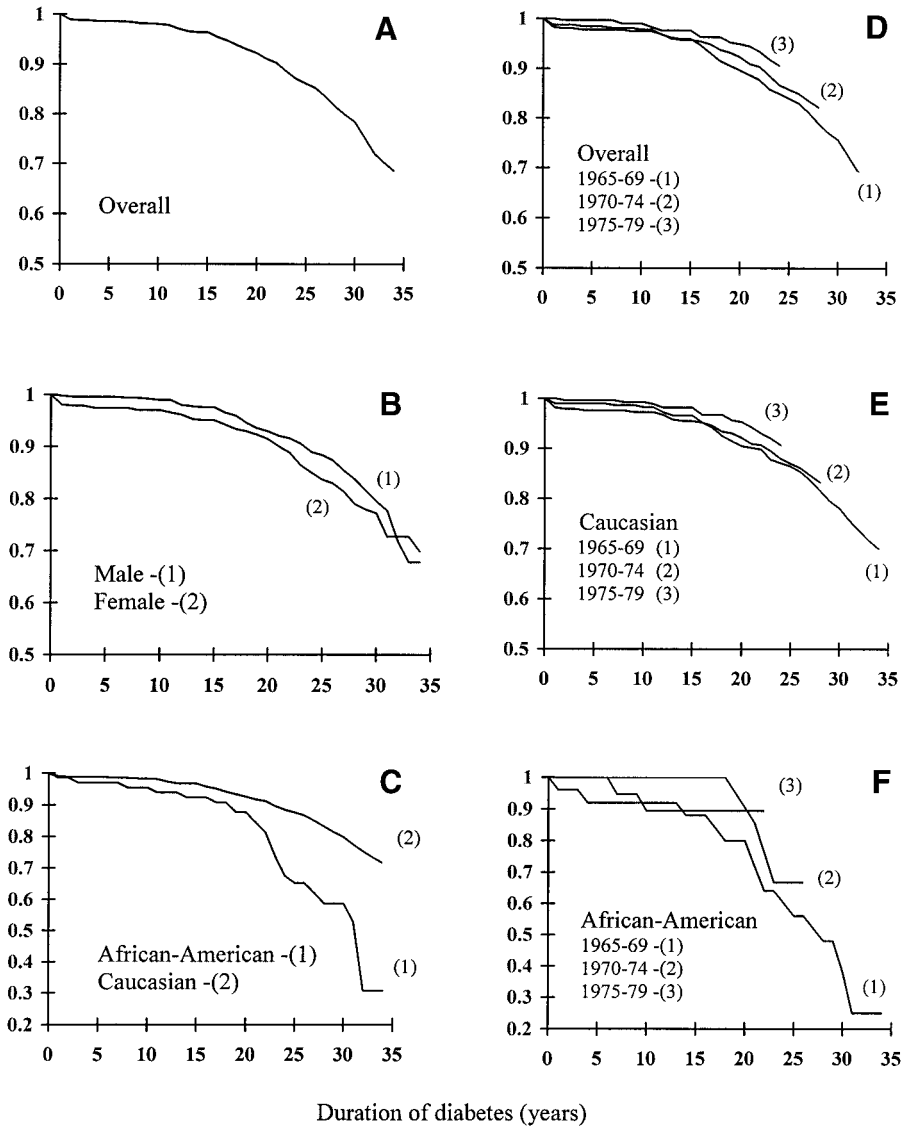

Figure 1—*Life-table analyses by sex, race, and the temporal trend of individuals with type 1 diabetes diagnosed in Allegheny County, PA, between 1965 and 1979.* P *values were calculated by log-rank test.* C: *African-American vs. Caucasian,* P > *0.0001.* D: *1965–69 vs. 1975–79,* P = *0.03. There were no statistical differences in* B, E, *and* F.

has declined during the last 30 years. The decline was most evident for the cases diagnosed in 1975–1979 compared with 1965–1969. SMRs at 20-year duration of diabetes showed a decreasing tendency (Table 2) over the study period, indicating that the improving prognosis of diabetic children was greater than that of the general population. In this report, the prognosis of African-Americans is much worse than that of Caucasians after 25 years of diabetes. However, the decline in mortality seemed to be similar in both Caucasians and African-Americans.

The timing of these improvements is consistent with the introduction of HbA_1 testing, home blood glucose monitoring, and improved blood pressure therapy in the 1980s. The reason for the improvement of the cohort diagnosed in 1975–1979 may reflect an improvement in the prevention of life-threatening, long-term diabetic complications such as end-stage renal disease. To test this hypothesis, the cause of death of all deceased patients is being determined. Death certificates from almost all of the deceased patients are available. However, because the cause of death as stated on the death certificate is often inaccurate or not recorded in a standard manner, a review of medical records at the time of death and next-of-kin interviews are being conducted to determine underlining cause of death in a standardized manner in accordance with DERI procedures (4). These data, hopefully, will aid in developing strategies to prevent premature deaths due to type 1 diabetes.

As part of DERI study, international comparison between Japan (n = 1,410) and Finland (n = 5,148) of the mortality of the childhood-onset type 1 diabetes cases diagnosed between 1965 and 1979 was performed as of 1995 (23). As shown previously, as of 1985 and 1990, Finland had a lower mortality rate compared with Japan. Finland showed no improving tendency when mortality of the cases diagnosed between 1975 and 1979 was compared with that of 1965–1969. The 15-year survival rates were 96.3 (1965–1969) and 96.6% (1975–1979), respectively. In Japan, as already reported (24), a dramatic improvement has been observed between 1969 and 1979 with 15-year survival rates of 87.6% in 1965–1969 increasing to 96.0% in 1975–1979. The present study suggests that the improvement of mortality up to 15 years duration of diabetes of type 1 diabetes patients may have reached a plateau. Further cause-specific analyses are needed to determine whether any further improvement in the first 15-year duration is possible.

One limitation of the current study is that the living status of 10% of cases was not determined. This partially reflects the lack of residence registration in the U.S. and the fact that the Social Security numbers of the patients were not recordable when the registry was started. This would be particularly helpful for tracing women who married after initial registration and who are very difficult to locate after they have changed their surnames. However, because we have used the National Death Index for the duration between 1980 and 1998, it is likely that we have identified most of the deceased patients in the cohort as long as the patients died in the U.S. Therefore, it is likely that our results are not biased and that the mortality rates presented here may be a little overestimated; the denominator may be proportionally higher because the missing patients are likely to be alive.

In conclusion, this study shows that the long-term mortality of children with type 1 diabetes has been improving in re-

cent years, reflecting, in all probability, the better glycemic control and blood pressure treatment available since the early 1980s. Encouraging improvements are seen in African-Americans, as well as Caucasians, although survival continues to be worse in African-Americans. Continued follow-up and cause-specific analyses of death will, hopefully, help to further document and explain improvement in mortality and suggest strategies to reduce mortality to background level.

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