Mortality in Childhood-Onset Type 1 Diabetes

A population-based study

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OBJECTIVE — To describe the age- and sex-specific mortality in a cohort of young type 1 diabetic patients and to analyze the causes of death with special focus on suicide, accidents, and unexplained deaths.

RESEARCH DESIGN AND METHODS — A population-based incident childhood diabetes register, covering onset cases since 1 July 1977, was linked to the Swedish Cause of Death Register up to 31 December 2000. The official Swedish population register was used to calculate age- and sex-standardized mortality rates (SMRs), excluding neonatal deaths. To analyze excess risks for specific diagnoses, case subjects were compared with five nondiabetic control subjects, matched by age, sex, and year of death. Death certificates were collected for all case and control subjects. For case subjects with an unclear diagnosis, hospital records and/or forensic autopsy reports were obtained.

RESULTS — Mean age- and sex-SMR was 2.15 (95% CI 1.70–2.68) and tended to be higher among females (2.65 vs. 1.93, $P = 0.045$). Mean age at death was 15.2 years (range 1.2–27.3) and mean duration 8.2 years (0–20.7). Twenty-three deaths were clearly related to diabetes; 20 died of diabetic ketoacidosis. Only two case subjects died with late diabetes complications (acute coronary infarction). Thirty-three case subjects died with a diagnosis not directly related to diabetes; 7 of them committed suicide, and 14 died from accidents. There was no significant difference in traffic accidents (odds ratio 1.02 [95% CI 0.40–2.37]). Obvious suicide tended to be increased but not statistically significantly so (1.55 [0.54–3.89]). Seventeen diabetic case subjects were found deceased in bed without any cause of death found at forensic autopsy. Only two of the control subjects died of similar unexplained deaths.

CONCLUSIONS — In a well-developed health care system, there is still a significant excess mortality in young type 1 diabetic patients. We confirm a very large proportion of unexplained deaths in bed, which should be further studied. There is no clear excess death rate caused by suicide or traffic accidents among young diabetic subjects.

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Although the main part of excess mortality in type 1 diabetes is due to long-term complications, an excess death rate has also been reported from several countries in case subjects with short duration without signs of long-term complications (1–4). Except for the mortality caused by onset ketoacidosis or diabetic ketoacidosis after onset, part of the excess mortality has been unexplained deaths in bed (3).

It has been made clear in experimental studies that car driving skills may be affected by hypoglycemic episodes (5). Restrictions are also put on driver's licenses, especially type 1 diabetic subjects in Europe. The epidemiological evidence of accidents in general or traffic accident incidence among diabetic compared with control subjects has been controversial (6–9).

In the present study, we studied survival of children who were diagnosed with diabetes at age 0–14 years during the period of 1 July 1977 to 31 December 2000 by linking the Swedish Childhood Diabetes Register with the Swedish Cause of Death Register. From this nationwide cohort of >10,000 individuals, we describe the age- and sex-specific mortality rate and analyze suicide, accidents, and unexplained deaths as the causes of death in a case-control design.

RESEARCH DESIGN AND METHODS

— The research ethics committee, Umeå University, and the National Board of Health and Welfare in Sweden approved the investigation. Since 1 July 1977, in collaboration with all pediatric clinics in Sweden, recent-onset diabetic children are recorded in the Swedish Childhood Diabetes Register (10). The ascertainment of case subjects in the register varies between 96 and 99% (11,12). By December 2000, a total of 10,200 children were recorded. This case register was linked to the official Swedish Cause of Death Register. For all 78 deceased case subjects thus identified, death certificates were obtained. In addition, for all case subjects with an unclear diagnosis in death certificates, especially those who died at home and with unexplained death, hospital records and/or forensic autopsy reports were obtained. The ketoacidosis diagnosis was verified in autopsy protocols of patients who did not die in hospital and was mainly based on high levels of ketone and glucose in urine and femoral vein blood. For calculation of standardized mortality rates, we used the official Swedish population register, Statistics Sweden. Neonatal deaths (before 1 month of age) were excluded, since no diabetic case subjects had an onset before 1 month of age.

For the analysis of the excess risk of specific diagnoses, we selected from the Swedish Cause of Death Register for each deceased diabetic case subject five control

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Abbreviations: SMR, standardized mortality rate.

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

Table 1—*Age- and sex-SMRs by age at onset and age at death for 78 young childhood-onset type 1 diabetic case subjects*

	Number of observed deaths	Number of expected deaths	SMR (95% CI)
Age at onset (years)			
≤2	9	1.93	4.66 (2.13–2.85)
3–7	18	8.50	2.00 (1.17–3.20)
8–15	51	25.91	2.01 (1.50–2.63)
Age at death (years)			
0–9	7	2.34	2.99 (1.20–6.16)
10–14	10	4.21	4.38 (1.14–4.37)
15–19	29	11.11	2.61 (1.75–3.75)
20–24	21	10.23	2.05 (1.27–3.14)
25–29	10	5.31	1.88 (0.90–3.46)
30–38	1	2.14	0.47 (0.01–2.62)

subjects, matched by age, sex, and year of death. A total of 378 matched referents were obtained; 5 of them had a diabetes diagnosis and were excluded. We obtained and scrutinized the death certificates of 371 of 373 eligible individuals (two certificates missing). In case of uncertain diagnosis as noted in the certificates, we received hospital records and/or autopsy protocols. Among the diabetic subjects, two individuals had died abroad without autopsy and with no diagnosis and were excluded from analyses. Similarly, seven referent deaths were excluded for this reason.

Statistical methods

Standardized mortality rates (SMRs) were calculated using the indirect method and 95% CIs based on exact Poisson distributions. Frequencies were compared using Fisher's exact test, and differences were expressed as odds ratios.

RESULTS — A total of 78 case subjects, 49 males and 29 females, had died over the 81,600 person-years of observation and with a mean duration of diabetes of 8.2 ± 7.1 years (range 0–20.7). The mean age- and sex-SMR was 2.15 (95% CI 1.70–2.68). The SMR was higher among females than males (2.65 vs. 1.93, $P = 0.045$). Mean age at death was 15.2 ± 8.6 years (range 1.2–27.3).

Table 1 shows SMRs for different ages at onset and different ages at death. Children with an onset before the age of 2 years had an excess death rate of more than four, whereas for other age-at-onset groups the death rate was about doubled. The excess mortality in type 1 diabetic children younger than age 10 years was approximately three times. Table 2 shows the mortality in relation to duration of diabetes. A peak in mortality is indicated at 10–12 years of diabetes duration.

Causes of death among diabetic subjects

Table 3 shows the causes of deaths. Twenty-three deaths were clearly related to diabetes. Mean age at death in this group was 15.1 years (range 1.2–27.3) and mean duration of diabetes 8.2 years (range 0–20.7). Six were onset deaths. Among them, five children were younger than age 4 years, and one was age 14 years. Fourteen deaths were due to diabetic ketoacidosis. Four of them were treated in hospital, and two of them had the additional diagnosis of cerebral edema. Ten case subjects with an autopsy diagnosis of diabetic ketoacidosis were found at home, all living alone. Among the three remaining diabetes-related deaths, one was found with severe alcohol intoxication with strong suspicion of hypoglycemic death, and two case subjects (both with acute coronary infarction) had a diagnosis related to late diabetes complications.

A total of 20 deaths were classified as having an uncertain relationship to diabetes. Two of the diabetic subjects died in hospital with a diagnosis of pneumonia and bronchitis, with diabetes as a contributing cause of death. One death was associated with psychiatric disease and was described to have occurred in hospital during a hyperventilation attack. As many as 17 cases of diabetic subjects were found deceased in bed at home, without any cause of death found at thorough forensic autopsy. In all of these cases, the protocols were scrutinized. Blood and urine glucose were not high. In a few cases, glucose was estimated in eye chamber water with no clear sign of hypoglycemia. All these case subjects were found deceased in bed by close relatives, and the deaths were quite unexpected. Mean age at death in this group was 18.1 years (range 11.4–25.1) and mean diabetes duration 8.2 years (range 2.6–12.6).

Thirty-three patients died with a diagnosis not related to diabetes, of which seven were obvious suicides (four males and three females). Suicide methods were mainly hanging or headshot for males and intoxication of medicines for females. Fourteen case subjects died of other violent causes; nine died in traffic accidents, three drowned, and two had accidents at work. In the group with traffic accidents, mean age was 17.6 years (range 11.4–23.3). One (11.4 years) was bicycling, four were motorcycle drivers, and the others were car drivers.

Case-control analysis

There were 98 deaths from traffic accidents among the 364 age- and sex-matched control subjects, which gave an odds ratio for traffic accidents with diabetes of 1.02 (95% CI 0.40–2.37). Fifty-four control subjects had clearly committed suicide. The odds ratio for suicide when having diabetes was 1.55

Table 2—*Duration of diabetes and mortality*

Duration (years)	Number of deaths	At-risk population	Deaths per 1,000 (95% CI)
0	8	10,109	0.79 (0.34–1.56)
1–3	10	9,673	1.03 (1.50–1.90)
4–6	15	8,561	1.75 (0.78–2.89)
7–9	14	7,352	1.90 (1.04–3.19)
10–12	14	6,180	2.27 (1.24–3.80)
13–15	7	5,012	1.40 (0.56–2.28)
16–18	8	3,703	2.16 (0.93–4.25)
19–21	2	2,195	0.91 (0.11–3.29)
22–24	0	1,114	0.00 (0.00–3.31)

Table 3—*Causes of death*

	Diabetic subjects	Control subjects
n	78	378
Excluded among control subjects (missing certificates, diabetes)	—	7
Death abroad, no diagnosis	2	7
Death clearly related to diabetes	23	—
Death uncertain relation to diabetes	20	—
Death not related to diabetes	33	364
Suicide	7	54
Drowning	3	14
Traffic accident	9	98
Other accident	2	38
Narcotic overdose	0	10
Malignancy	2	46
Neuromuscular disease	4	22
Heart disease (except coronary infarction)	3	19
Infection	0	19
Disorder in digestive system	2	6
Inborn errors of metabolism, syndrome	1	14
Other	0	14

(0.54–3.89). Other causes of death among the 33 diabetic patients and 364 control subjects included in this analysis are given in Table 3. Notably, 10 of 364 control subjects died from an overdose of narcotic drugs, whereas none of the diabetic subjects had this diagnosis.

Among the control subjects, except for seven who died without diagnosis in a foreign country, only two individuals died with a diagnosis, which could not be classified despite a thorough autopsy; one was a 19-year-old female and the other a 17-month-old male. Both were found deceased in bed. One hundred and fifty of the 364 control subjects died from traffic accidents, drowning, or other accidents compared with 14 of 33 deaths without relationship to diabetes among the diabetic subjects, which gives an overall odds ratio for accidents of 1.05 (95% CI 0.47–2.29).

CONCLUSIONS — The present large population-based study shows that in spite of a well-developed health care system, Sweden, like many other developed countries, still reports significant excess mortality in type 1 diabetic patients before the development of late complications. While a large geographic variability in early mortality among type 1 diabetic patients has been shown (4,13), the age- and sex-standardized mortality ratio around two subjects found in our study is similar to previous reports from Sweden and other Nordic countries (1–3). A more than fourfold increase in death rate found among the youngest children, and mainly depending on onset death, underlines the importance of knowledge about the diagnosis and treatment of this disease in the youngest children. There was a significantly higher standardized mortality among females, probably reflecting that diabetes-related deaths in this age-group are not sex related, whereas young males have a higher death rate than females in the general population.

In the present study, we thoroughly analyzed the causes of death where clearly diabetic ketoacidosis is the most common diabetes-related cause. The majority of onset deaths were associated with signs of cerebral edema, as was two of the four ketoacidosis deaths treated in hospital several years after the of onset of the disease. It is notable that 10 case subjects were found deceased in their homes but were given an autopsy diagnosis of diabetic ketoacidosis. These were young adults with duration of diabetes of many years and with access to modern home blood glucose and urinary glucose testing. Such tragic deaths should have been avoidable, unless they were not intended. This possibility points to a need of improved psychosocial support in the care of these young type 1 diabetic patients.

A total of 33 deaths were classified as not related to diabetes. Certainly this classification is difficult when based on ICD codes only (14). In our study, we collected individual death certificates as well as detailed autopsy reports and hospital records. Cases classified as not related directly to diabetes were obvious suicides, accidents of different kinds, and some lethal diagnoses such as leukemia, cystic fibrosis, and severe inborn syndromes. In the case-control analysis, we found a statistically nonsignificant tendency to excess mortality of clear suicide deaths in the group of diabetic subjects. In addition, as mentioned above, suicides might have been hidden behind other diagnoses, such as ketoacidosis.

Hypoglycemia and driving accidents have been of great concern, since hypoglycemic episodes produce cognitive motor slowing, which may interfere with driving performance (5). Whether this actually leads to a higher incidence of car accidents has been controversial (6–9,15–17), and the discussion on drivers licensing in insulin-dependent diabetic subjects is continuing (18,19). In our population-based dataset covering high-risk groups for traffic accidents, we could not confirm an excess mortality. This does not exclude that involvement in accidents might be more frequent among diabetic subjects; still, the number of events was small. Young people with diabetes may be aware of the risk and may be competent to handle it properly. Also, other types of accidents have been discussed to be more prevalent among insulin-dependent diabetic subjects, but in our study no excess mortality for such reasons was noted.

Despite thorough postmortem examinations, the cause of death could not be explained in as many as 17 of these young individuals found deceased in bed in their homes compared with only 2 of 364 control subjects. This confirms the original observation by Tattersall and Gill (20) that young and otherwise apparently healthy individuals seem to run a significant risk of sudden death during sleep due to their diabetic state. Indeed, unexplained death in bed was the second most common cause of death diagnosis, comprising 22% of all deaths in this cohort. People found deceased in their homes undergo forensic autopsy according to the Swedish law. Careful examinations are then performed to exclude causes such as intoxication. The difficulty to objectively assess low blood glucose postmortem is well known, but it is still hard to believe that hypoglycemia without concomitant alcohol intoxication would lead to death, except in certain individuals who may

have a dysregulation of the counterregulatory system. Another potential mechanism that has been discussed is that hypoglycemia may trigger cardiac arrhythmia and death (20). Large epidemiological studies focusing on these unexplained deaths in young type 1 diabetic patients are warranted to find about this potentially avoidable death.

In conclusion, there is still a significant excess mortality in young type 1 diabetic patients with a short duration, where onset deaths due to ketoacidosis, especially in young children, are important to prevent. We found no clear indications of excess violent deaths or suicide. The large proportion of unexplained deaths in bed must be a focus of further studies.

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References

1. Sex differences in the mortality associated with insulin-dependent diabetes mellitus in four countries: the Diabetes Epidemiology Research International (DERI) Study. *Am J Epidemiol* 133:577–584, 1991
2. Joner G, Patrick S: The mortality of children with type 1 (insulin-dependent) diabetes mellitus in Norway, 1973–1988. *Diabetologia* 34:29–32, 1991
3. Sartor G, Dahlquist G: Short-term mortality in childhood onset insulin-dependent diabetes mellitus: a high frequency of unexpected deaths in bed. *Diabet Med* 12: 607–611, 1995
4. Podar T, Solntsev A, Reunanen A, Urbonaite B, Zalinkevicius R, Karvonen M, LaPorte RE, Tuomilehto J: Mortality in patients with childhood-onset type 1 diabetes in Finland, Estonia, and Lithuania: follow-up of nationwide cohorts. *Diabetes Care* 23:290–294, 2000
5. Cox DJ, Gonder-Frederick L, Clarke W: Driving decrements in type I diabetes during moderate hypoglycemia. *Diabetes* 42: 239–243, 1993
6. Mansell P: Diabetes and driving (Editorial). *Diabet Med* 19:617–618, 2002
7. Veneman TF: Diabetes mellitus and traffic incidents. *Neth J Med* 48:24–28, 1996
8. Cox DJ, Penberthy JK, Zrebiec J, Weinger K, Aikens JE, Frier B, Stetson B, DeGroot M, Trief P, Schaechinger H, Hermanns N, Gonder-Frederick L, Clarke W: Diabetes and driving mishaps: frequency and correlations from a multinational survey. *Diabetes Care* 26:2329–2334, 2003
9. Songer TJ, LaPorte RE, Dorman JS, Orchard TJ, Cruickshanks KJ, Becker DJ, Drash AL: Motor vehicle accidents and IDDM. *Diabetes Care* 11:701–707, 1988
10. Dahlquist G, Blom L, Holmgren G, Hagglof B, Larsson Y, Sterky G, Wall S: The epidemiology of diabetes in Swedish children 0–14 years: a six-year prospective study. *Diabetologia* 28:802–808, 1985
11. Nystrom L, Dahlquist G, Rewers M, Wall S: The Swedish childhood diabetes study: an analysis of the temporal variation in diabetes incidence 1978–1987. *Int J Epidemiol* 19:141–146, 1990
12. Dahlquist G, Mustonen L: Childhood onset diabetes: time trends and climatological factors. *Int J Epidemiol* 23:1234–1241, 1994
13. The Diabetes Epidemiology Research International (DERI) Study Group: International analysis of insulin-dependent diabetes mellitus mortality: a preventable mortality perspective. *Am J Epidemiol* 142: 612–618, 1995
14. Muhlhauser I, Sawicki PT, Blank M, Overmann H, Richter B, Berger M: Reliability of causes of death in persons with type I diabetes. *Diabetologia* 45:1490–1497, 2002
15. Eadington DW, Frier BM: Type 1 diabetes and driving experience: an eight-year cohort study. *Diabet Med* 6:137–141, 1989
16. Stevens AB, Roberts M, McKane R, Atkinson AB, Bell PM, Hayes JR: Motor vehicle driving among diabetics taking insulin and non-diabetics. *BMJ* 299:591–595, 1989
17. Kennedy RL, Henry J, Chapman AJ, Nayar R, Grant P, Morris AD: Accidents in patients with insulin-treated diabetes: increased risk of low-impact falls but not motor vehicle crashes: a prospective register-based study. *J Trauma* 52:660–666, 2002
18. Distiller LA, Kramer BD: Driving and diabetics on insulin therapy. *S Afr Med J* 86 (Suppl. 8):1018–1020, 1996
19. MacLeod KM: Diabetes and driving: towards equitable, evidence-based decision-making (Review). *Diabet Med* 16: 282–290, 1999
20. Tattersall RB, Gill GV: Unexplained deaths of type 1 diabetic patients. *Diabet Med* 8:49–58, 1991