Acute Complications and Drug Misuse Are Important Causes of Death for Children and Young Adults With Type 1 Diabetes

Results from the Yorkshire Register of Diabetes in Children and Young Adults

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OBJECTIVE — To examine mortality rates and causes of death among subjects diagnosed with type 1 diabetes aged ≤29 years.

RESEARCH DESIGN AND METHODS — Subjects with type 1 diabetes from a population-based register in Yorkshire, U.K., diagnosed between 1978 and 2004 were linked to the U.K. National Health Service Central Register for death notifications. Deaths were coded using ICD-9 (1979–2000) and ICD-10 (2001–2005). Standardized mortality ratios (SMRs) were calculated using expected numbers of deaths from U.K. mortality rates by cause of death and age at diagnosis.

RESULTS — A total of 4,246 individuals were followed up, providing 50,471 person-years of follow-up. Mean follow-up length was 12.8 years for individuals aged 0–14 years and 8.3 for those aged 15–29 years. Overall, 108 patients died, of whom 77 (71%) were male. A total of 74 (1.7/1,000 person-years) deaths occurred in inidividuals aged 0–14 years and 34 (4.6/1,000 person-years) in those aged 15–29 years. The SMR was 4.7 (95% CI 3.8–5.6) overall, similar for males and females, but higher for individuals aged 15–29 years (SMR 6.2 [95% CI 4.3–8.6]) compared with those aged 0–14 years (4.2 [3.3–5.3]). The SMR rose with increasing disease duration. A total of 47 of 108 deaths (44%) occurred from diabetes complications, 32 of which were acute and 15 chronic. Twenty-two percent ($n = 24$) of deaths were attributed to accidents or violence (SMR 2.1 [95% CI 1.4–3.2]), including six suicides. Sixteen percent of all deaths were related to drug misuse (including insulin but excluding tobacco and alcohol) (SMR 6.4 [95% CI 3.7–10.2]).

CONCLUSIONS — Subjects with type 1 diabetes diagnosed under 30 years of age had a 4.7-fold excess mortality risk. Nearly half of the deaths were due to acute or chronic complications of diabetes. Drug misuse–related deaths may be an emerging trend in this population warranting further investigation.

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Abbreviations: NHSCR, National Health Service Central Register; ONS, Office for National Statistics; SMR, standardized mortality ratio.

In recent years, there has been a trend toward more intensive insulin regimens using multiple daily injections and pump therapy for children and young adults with type 1 diabetes (1–3). This trend should improve long-term glucose control, help avoid the chronic complications of diabetes, and, in theory, reduce mortality rates in subjects with type 1 diabetes.

The literature contains a number of studies focusing on mortality among those who develop type 1 diabetes in childhood (4–15), but few data exist on risk and causes of death in those diagnosed before 30 years of age. One U.K. analysis of individuals aged 0–29 years (7) demonstrated an excess mortality risk ranging from 2 to 6 times that of the general population for individuals aged ≤40 years. Older teenagers and young adults constitute a transitional group between children and adults and often fall out of health care provision. They have also been neglected in research studies and, due to differences in the delivery of care among individuals aged 15–29 years, mortality risks may differ from those in children aged 0–14 years.

The generation of robust mortality data relies on comprehensive and accurate information about subjects who have diabetes and their date and cause of death. To examine mortality trends, we were able to utilize a population-based diabetes register in the north of England linked to the national population database and thereby obtained death notifications and details. The aim of the study was to obtain information on the causes of death in young people diagnosed under 30 years of age, thereby informing clinicians about how better to manage their patients prospectively.

RESEARCH DESIGN AND METHODS

— Patient details were extracted from the Yorkshire Register of Diabetes in Children and Young Adults, a population-based database with ascer-

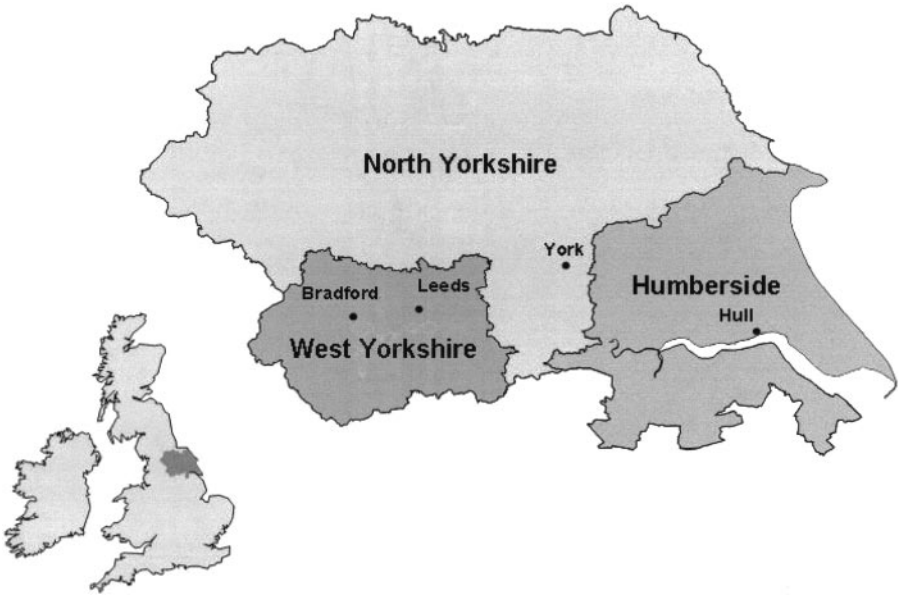

Figure 1—*Study area covered by the former Yorkshire Regional Health Authority in relation to the British Isles.*

tainment rates exceeding 98% (16). The Yorkshire Register is unique in England, as it captures clinical and demographic data on all individuals aged 0–29 years in the geographical area of the former Yorkshire Regional Health Authority. The Yorkshire Region (Fig. 1) covers an area of 12,000 km^2 and includes a total population of 3.5 million, of whom 1.4 million are aged 0–29 years.

Information was obtained on subjects who were newly diagnosed under 15 years of age between 1978 and 2004 in the whole of the Yorkshire Region and between 1991 and 2004 for case subjects diagnosed under 30 years of age in West Yorkshire only. The county of West Yorkshire comprises ~60% of the population of the Yorkshire Region. Diagnosis of type 1 diabetes was based not only on insulin treatment from diagnosis but also on using complete clinical information contained within the patient's medical records according to standard criteria (17). Patients whose diagnosis was uncertain were reassessed by local clinical experts (H.J.B. and Dr. Fiona Campbell, Consultant Pediatrician, Leeds, U.K.).

Death notifications and coding

Each patient's vital status (alive/dead) was obtained by linking individuals from the Yorkshire Register to the National Health Service Central Register (NHSCR) using their National Health Service number. The NHSCR retains information on the current location of every individual in the U.K., their vital status, and whether they have emigrated. Notifications from the NHSCR were received up to September 2006 to ensure all patients were followed up until 31 December 2005.

Details of patients who had died were obtained from the Office for National Statistics (ONS) General Registry Office, which provided us with copies of the death certificate. The underlying cause of death was coded according to ICD-9 for those dying between 1979 and 2000 and ICD-10 for those dying between 2001 and 2005 (18). Quality and consistency of mortality data are maintained by the ONS through automation of the coding process, a procedure established in 1993 (19). Bridge coding (19) was used to align ICD-9 causes of death with ICD-10 causes of death. Full death certificate information was used to reallocate cause of death for those for whom the underlying cause was reported as "diabetes" but whose death was related to specified complications, e.g., chronic renal failure or cardiovascular complications. In instances where the cause of death was unknown/uncertain, the coroner would ask for an autopsy and hold an inquest, irrespective of age (20); findings from these investigations and any other available documentation were also used to assign the underlying cause of death.

A particular focus of the study examined the number of deaths caused by drug misuse, as we noticed a number of certifications mentioning this. Drug-related deaths were defined according to the standard classification used by the ONS (20–21) based on the following codes: mental and behavioral disorders due to drug use (excluding alcohol and tobacco), insulin poisoning, intentional self-poisoning/poisoning by drugs, and accidental poisoning by drugs (21). Careful scrutiny of the death certificate was made to ensure the cause was assigned correctly for each subject in conjunction with toxicology or coroner reports because almost all drug-related deaths required an inquest.

Statistical analyses

A person-years–at risk analysis was used to compare mortality in the cohort (by sex, current age, time since diagnosis, and calendar period) with that in the background U.K. population (22). Cause-specific U.K. mortality rates were extracted by sex, 5-year calendar period, and 5-year age-group and were used to calculate the number of deaths expected in the cohort—based on the accrued person-years within each sex/period/age group were it to have experienced U.K. mortality rates—and SMRs were obtained as the ratio of observed to expected number of deaths. CIs for SMRs were derived assuming a Poisson distribution (23).

RESULTS — Patients diagnosed aged 0–14 years (n = 3,349) and 15–29 years (n = 897) (Table 1) were included and provided 50,471 person-years of follow-up. Mean length of follow-up was 12.8 years (range 0.9–27.9) for the younger and 8.3 years (0.3–14.9) for the older group at diagnosis. Only 10 patients (0.2%) were untraceable.

Overall, 108 (2.5%) patients died, of whom 77 (71%) were male. A total of 74 (1.7 per 1,000 person-years) deaths occurred in the younger diagnosed group and 34 (4.6 per 1,000 person-years) in the older diagnosis group (Table 1). The SMR was 4.7 (95% CI 3.8–5.6) overall and nonsignificantly higher for individuals aged 15–29 years (6.2 [95% CI 4.3–8.6]) than for children (4.2 [3.3–5.3]). Risk of death was similar for male and female patients diagnosed under 15 years of age (Table 1) but nonsignificantly higher for female patients (7.5 [3.4–14.3]) compared with male patients (5.8 [3.8–8.6]) aged 15–29 years at diagnosis.

Risk of death was significantly elevated in all attained age-groups and at every time point since diagnosis (Table 2), although no significant linear relationship

Table 1—*Standardized mortality ratios by sex and age at diagnosis for patients diagnosed with type 1 diabetes in Yorkshire, 1978–2004*

	n	Deaths observed (expected)	Standardized mortality ratio (95% CI)
Age at diagnosis (years)			
0–14 (Yorkshire)			
Male subjects	1,742	52 (12.3)	4.2 (3.2–5.5)
Female subjects	1,607	22 (5.3)	4.1 (2.6–6.3)
Total	3,349	74 (17.7)	4.2 (3.3–5.3)
15–29 (West Yorkshire)	568	25 (4.3)	5.8 (3.8–8.6)
Male subjects			
Female subjects	329	9 (1.2)	7.5 (3.4–14.3)
Total	897	34 (5.5)	6.2 (4.3–8.6)

was observed between increasing disease duration and mortality using Poisson regression. SMRs increased steadily by calendar period of diagnosis (Table 2), exhibiting a fivefold increased risk of death since 1995.

Cause-specific SMRs showed that risk of death was significantly higher for all causes than for the background population, excluding cancer and stroke patients (Table 3). Almost one-half (44% [n = 47]) of all deaths were related to complications of diabetes (including heart disease, stroke, or renal disease). Mortality was high for deaths attributed to respiratory (SMR 5.6 [95% CI 1.8–13.0]) and mental (7.5 [3.4–14.3]) disorders. A further one-fifth of fatalities (n = 24) was related to accidents or violence (2.1 [1.4–3.2]), 6 of which were confirmed suicides (2.5 [0.9–5.4]). The excess risk of death due to accidents and violence was nonsignificantly higher for female patients (3.4 [1.4–6.9]) than for male patients (1.9 [1.1–3.0]). There were 19 deaths of "other" (n = 13) or "unknown" (n = 6) causes (3.3 [2.0–5.1]).

Thirty-two deaths were due to acute and fifteen to chronic complications. Deaths from acute complications were comprised of 14 from diabetic ketoacidosis, 2 from hyperglycemia (where the death certificate did not mention diabetic ketoacidosis), 8 from hypoglycemia, and 8 unspecified cases. Male patients constituted 25 of 32 (78%) deaths from acute complications. Deaths from acute complications occurred evenly throughout the cohort by attained age. Deaths associated with chronic complications included six from ischemic heart disease, one from stroke, and eight from renal failure (six of which occurred in female patients).

Drug misuse was related to 16% of all deaths (17 of 108) (SMR 6.4 [95% CI 3.7–10.2]). In this group, female patients (n = 5) had a nonsignificantly higher SMR (8.8 [2.9–20.6]) compared with male patients (5.7 [2.9–10.0]). The majority (71%) of these deaths (n = 17) occurred between the ages of 20 and 29 years, and 6 of these deaths were associated with insulin overdose: 3 confirmed suicides and 3 possible suicides. The remaining 11 deaths were accounted for by abuse of prescription drugs (n = 3, analgesics) and nonprescription drugs (n = 8, mainly opiates).

CONCLUSIONS — The Yorkshire Register data have enabled an investigation of mortality rates on 4,200 subjects diagnosed continuously from 0–29 years of age, comprising one of the largest and most recent population-based series in this age range. The Yorkshire Register is 98% complete in terms of ascertainment, and subjects were linked to a National Health Service register to provide a virtually complete level (99.8%) of tracing, with only 10 individuals lost to follow-up. This produced notifications of 108 deaths and detailed information on the precise cause of death.

Since publication of the results of the Diabetes Control and Complications Trial in 1993 (24), tight glycemic control has been an emphasis of the treatment for patients with type 1 diabetes. This should lead to a decrease in the occurrence of chronic complications of diabetes and thereby decrease number of deaths from them. In addition, intensive insulin treatment and enhanced patient education, with frequent out-patient supervision and close contact with a diabetes specialist nurse, should theoretically avoid or reduce the occurrence of the acute diabetes complications of ketoacidosis and severe hypoglycemia. Therefore, it is of interest to examine the causes and

Table 2—*Number of deaths and mortality risk by attained age, time since diagnosis (duration), and calendar period for patients diagnosed with type 1 diabetes in Yorkshire, 1978–2004*

	Deaths observed (expected)	Standardized mortality ratio (95% CI)
Total deaths	108 (23.2)	4.7 (3.8–5.6)
Attained age (years)		
0–4	3 (0.4)	6.8 (1.4–19.9)
5–9	3 (0.8)	3.7 (0.8–10.7)
10–14	5 (1.7)	2.9 (0.9–6.7)
15–19	16 (5.0)	3.2 (1.8–5.2)
20–24	22 (5.3)	4.2 (2.6–6.3)
25–29	30 (4.6)	6.6 (4.4–9.4)
30–34	19 (3.5)	5.4 (3.2–8.4)
35–39	9 (1.5)	5.8 (2.7–11.0)
40–44	1 (0.2)	4.1 (0.1–22.8)
Time since diagnosis (years)		
0–4	24 (6.4)	3.7 (2.4–5.6)
5–9	30 (6.2)	4.8 (3.3–6.9)
10–14	21 (4.9)	4.3 (2.7–6.6)
15–19	22 (3.2)	6.8 (4.3–10.4)
>20	11 (2.4)	4.5 (2.3–8.1)
Period of diagnosis		
1978–1984	1 (0.7)	1.4 (0.0–7.6)
1985–1989	3 (1.7)	1.8 (0.4–5.1)
1990–1994	12 (3.3)	3.7 (1.9–6.4)
1995–1999	32 (5.9)	5.4 (3.7–7.7)
2000–2005	60 (11.5)	5.2 (4.0–6.7)

Table 3—*Standardized mortality ratios by cause of death for patients diagnosed with type 1 diabetes in Yorkshire, 1978–2004*

	ICD-10 code	Deaths observed (expected)	Standardized mortality ratio (95% CI)
Cause of death			
Diabetes	E10-E14	32 (0.1)	356 (243–502)
Ischemic heart disease	I20-I25	6 (0.3)	9.6 (7.2–42.7)
Stroke	I60-I69	1 (0.4)	2.5 (0.1–14.0)
Renal disease	N00-N09	8 (0.0)	5,481 (2,367–∞)
Respiratory failure	J00-J98	5 (0.9)	5.6 (1.8–13.0)
Neoplasms	C00-C97, D00-D48	4 (3.3)	1.2 (0.3–3.1)
Mental disorder	F00-F99	9 (1.2)	7.5 (3.4–14.3)
Accidents and violence (including suicide)	S00-T98, V00-Y98	24 (11.2)	2.1 (1.4–3.2)
Suicide	X60-X84	6 (2.4)	2.5 (0.9–5.4)
Other/unknown causes	By subtraction	19 (5.8)	3.3 (2.0–5.2)
All causes		108 (23.2)	4.7 (3.8–5.6)

rates of death in a cohort of subjects diagnosed in childhood and young adult life. Previously, studies have focused on mortality of subjects diagnosed in childhood (4–15), but more recently, those diagnosed in early adult life have been examined. For example, one study noted that young adults with type 1 diabetes had a raised SMR, but the SMR was even higher in those with type 2 diabetes (25).

Risk of death for children and young adults with type 1 diabetes in Yorkshire was four and six times that of the background population. Acute complications accounted for approximately one-third of all deaths, emphasizing that, despite modern intensive education and insulin treatment, such deaths continue to occur. Similarly, chronic complications including cardiac, renal, and cerebrovascular causes continued to arise and subsequently proved fatal.

Previously published data from the U.K. (7) showed an SMR range of 3.6–4.4 for female patients but one notably lower (2.5–2.9) for male patients with a similar length of follow-up, whereas our present data showed a similar SMR for both sexes. We previously found that male patients seemed to be at greater risk than female patients for developing microvascular complications such as renal failure and severe retinopathy (26). The risk of death was significantly elevated at every time period since diagnosis, reaching seven times the background population for individuals living with diabetes aged 15–19 years, but the risk did not increase linearly with increasing duration of diabetes. SMRs increased by period of diagnosis, especially since 1990, when individuals aged 15–29 years were first registered. U.K. data reported from 1999 for deaths occurring in individuals under 20 years of age, in which diabetes was mentioned on the death certificate, showed an SMR of 2.3 (6); diabetic ketoacidosis was the cause of death in the majority of these cases (69 of 83).

Mortality data on Norwegian children showed that deaths from acute complications and violent causes constituted about one-third each of the total (27). In our study, 22% of the deaths were due to violence or accidents, in agreement with previous U.K. data (8), but these are a common cause of death in this age-group in the general population. Seventeen individuals died as a result of drug misuse, with a higher SMR for female than male individuals and a peak in the number of such deaths occurring between the ages of 20 and 29 years. Our findings also revealed that six of these fatalities were due to insulin overdoses, although we were unable to establish whether these were accidental or not. The remaining 11 patients in this group died due to opiate, cocaine, or analgesic misuse. In addition, a male subject aged 29 years, whose cause of death was inconclusive, had toxicological evidence of recent amphetamine and 3,4-methylenedioxy-*N*-methylamphetamine (MDMA) use, but he was not thought to have died of an overdose of these drugs. Another male subject aged 33 years, whose cause of death was uncertain, had a history of psychotic illness, intravenous amphetamine abuse, repeated suicide attempts, and erratic insulin usage with recurrent hypoglycemia and ketoacidosis. Our findings were based on examination of full toxicology/coroners' reports to ensure that risk of misclassification of cause of death attributable to drug misuse was minimized. However, we acknowledge that this approach may be a conservative estimate because there were 19 deaths classified as "other/unknown" for which no further information was available.

These are important new findings for clinicians treating young people with type 1 diabetes, as we have identified a propensity for young-adult subjects to misuse drugs or take insulin overdoses. A previous survey of young adults with type 1 diabetes found that street drug misuse was common (28). In their study of psychosocial and socioeconomic risk factors for premature death in young people, Laing et al. (29) found an odds ratio of 4.6 for past drug misuse but did not comment on drug misuse as a cause of death. A history of psychiatric disorder was noted in 10 of the 37 deaths in the childhood-onset diabetes cohort in Israel (30). In our study, drug misuse was mentioned on the death certification, and this factor was therefore actively involved as a cause of death. Furthermore, in most cases, we were able to obtain information on the nature of the drugs involved following detailed scrutiny of coroners' reports. One may speculate whether some diabetic young adults are drawn into a drug culture because of their familiarity with injection techniques or as a result of a psychological maladaptation as a consequence of their diabetic condition. Alternatively, type 1 diabetes, with its prospect of long-term complications, may engender a fatalistic or reckless behavior pattern in this age-group. There may therefore be an emerging trend for young people with type 1 diabetes to misuse drugs, which warrants further examination in future studies.

The cause of death was uncertain in 19 cases, and we were interested to see if any of these suggested the dead-in-bed

syndrome (31). This still appears to constitute a significant number of cases in some series (13). Only one case was found inexplicably dead in bed, following a full postmortem examination and toxicology report. However, as that syndrome has been linked to hypoglycemia or autonomic neuropathy, some of our other unexplained cases may also have died from these causes. A proportion of the fatalities attributed to uncertain causes is likely to have been related to diabetes and accidents/violence, suggesting that we may have underestimated the true number in our diabetes population. In conclusion, subjects diagnosed with type 1 diabetes in childhood and early-adult life showed significantly increased mortality from acute and chronic diabetic complications, with death due to or associated with drug misuse or insulin overdose as an emerging feature.

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