The Impact of a Decade of Changing Treatment on Rates of Severe Hypoglycemia in a Population-Based Cohort of Children With Type 1 Diabetes

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OBJECTIVE — To determine the impact of changes to treatment on the incidence of severe hypoglycemia and its risk factors in a large population-based cohort of children with type 1 diabetes.

RESEARCH DESIGN AND METHODS — The cohort consisted of 1,335 children (age at entry 9.5 ± 4.3 years [mean ± SD], range 0–18), yielding 6,928 patient-years of data. The mean follow-up period was 4.7 ± 3.1 years (range 0–10.7). Prospective assessment of severe hypoglycemia (an event leading to loss of consciousness or seizure) and associated clinical factors and outcomes was made between 1992 and 2002. Patients were reviewed every 3 months. Data were analyzed using the negative binomial regression model.

RESULTS — A total of 944 severe events were recorded. The incidence of severe hypoglycemia increased significantly by 29% per year for the first 5 years but appeared to plateau over the last 5 years. The overall average HbA_{1c} significantly decreased (by 0.2% per year) over the whole follow-up period. An increased risk of severe hypoglycemia was associated with lower HbA_{1c}, younger age, higher insulin dose, male sex, and lower parental socioeconomic status. Of insulin therapies, only pump treatment was associated with reduced rates of severe hypoglycemia.

CONCLUSIONS — Severe hypoglycemia remains a major problem for children and adolescents with type 1 diabetes. Recent approaches to therapy may be allowing a degree of improved control without the expected increased risk of severe hypoglycemia but further monitoring will be important.

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Insulin-induced hypoglycemia remains a central problem in the management of type 1 diabetes. This is especially the case in children and adolescents in whom the ever-present dilemma between tight glycemic control and the risk of hypoglycemia adds to the considerable burden of the disease.

The last decade has seen improved understanding of the pathophysiological mechanisms leading to hypoglycemia in type 1 diabetes. Along with this, treatment approaches have also changed dramatically. The Diabetes Control and Complication Trial (DCCT) led to a fundamental shift in the goals of management (1,2). This, along with new insulins, increased use of multiple injection regimens, pump therapy, more targeted behavioral and educational methods, and new glucose-monitoring technologies have potentially altered the epidemiology of severe hypoglycemia in young patients.

It has been long recognized that it is important to survey type 1 diabetic patients to determine the risk factors for severe hypoglycemia and monitor therapeutic outcomes (3,4). Earlier reports were difficult to interpret because of methodological problems, variations in definitions of hypoglycemic episodes, and retrospective approaches. More recent reports have used a prospective study design, an approach stimulated by the DCCT experience and protocols (1). This approach, combined with careful definition of hypoglycemic events and well-described subject populations, has removed some of the limitations of cross-sectional studies (5–8).

We have previously reported (5) hypoglycemia rates in a population-based sample of children with type 1 diabetes and documented changes that followed improvements in diabetes control. Since that time, further changes in therapy have occurred. We now report the impact of these changes on the risks of severe hypoglycemia in a large cohort of childhood-onset type 1 diabetic patients.

RESEARCH DESIGN AND METHODS

— All children and adolescents with type 1 diabetes aged ≤18 years attending the diabetes clinic at Princess Margaret Hospital for Children from 1992 to 2002 were included in the study. Princess Margaret Hospital for Children is the only pediatric referral center for diabetes serving Western Australia, and almost all diagnosed children in the state are registered and treated there. Previous studies (6) have shown that this center had a case ascertainment of 99.9% for children diagnosed at <16 years of age. A total of 1,335 patients (654 boys and 681 girls) were included. Age at entry of the cohort was 9.5 ± 4.3 years (mean ± SD) with a range of 0 to 18 years. The overall

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Abbreviations: DCCT, Diabetes Control and Complications Trial; IRR, incidence rate ratio.

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

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Table 1—*Clinical characteristics of the diabetic children by age-group*

	Age-group (years)			
	<6	6–12	12–18	Total
n	268	696	371	1,335
Age at entry (years)				
Mean ± SD	3.2 ± 1.5	9.2 ± 2.0	14.7 ± 1.5	9.5 ± 4.3
Range	0–5	6–12	13–18	0–18
Age at diagnosis (years)				
Mean ± SD	3.3 ± 1.5	8.4 ± 2.8	11.6 ± 4.1	8.3 ± 4.2
Range	0.5–6	0.8–13	0.8–18.5	0.5–18.5
Sex (% girls)	51.5	53.2	46.6	51.0
HbA_{1c} (%)				
Mean ± SD	8.7 ± 1.5	8.9 ± 1.6	9.2 ± 1.9	9.0 ± 1.8
Range	4.9–14.1	4.0–14.1	4.1–14.1	4.0–14.1
Clinic visits				
Mean ± SD	24.1 ± 14.9	21.9 ± 12.3	11.7 ± 6.5	19.4 ± 12.6
Range	1–54	1–47	1–27	1–54
Years of follow-up				
Mean ± SD	5.6 ± 3.5	5.4 ± 3.1	2.8 ± 1.6	4.7 ± 3.1
Range	0–10.7	0–10.6	0–5.9	0–10.7
Socioeconomic disadvantage (%)				
Highest	42.5	40.8	40.7	41.1
Middle	24.6	24.1	20.5	23.2
Lowest	32.8	35.1	38.8	35.7
Total insulin (units · kg^{-1} · day^{-1})				
Mean ± SD	0.7 ± 0.2	0.9 ± 0.3	1.1 ± 0.4	1.0 ± 0.4
Range	0–2.6	0–2.7	0–3.8	0–3.8

follow-up period was 4.7 ± 3.1 years (range 0–10.7). The overall dropout rate was minimal (0.5%). The clinical characteristics of these patients are shown in Table 1. The index of relative socioeconomic disadvantage was calculated using the method described by the Australian Bureau of Statistics (9). The study was approved by the institution's ethics committee, and consent was obtained from all parents or caregivers.

Treatment

After initial diagnosis, parents and patients were seen by the diabetes care team, which included a pediatric diabetologist, diabetes nurse educator, dietitian, psychologist, and social worker. All children and their parents received detailed and developmentally appropriate education on how to manage the child's diabetes, which included training on the identification and treatment of hypoglycemia as well as insulin dose adjustments to allow for exercise patterns and food intake (5). Every effort was made to see the patient and their parents every 3 months. Parents were actively encouraged to use a logbook to record any changes in treatment and all adverse events, including hypoglycemic episodes. Over the decade, as information emerged concerning the importance of glycemic control in the development of diabetes complications, changes in practice were emphasized by the treating team. These included more emphasis on blood glucose testing and stricter glycemic targets. All data were collected prospectively at each clinic visit over a period of 10 years. A computerized patient record system was used to facilitate the prospective evaluation of all diabetes-related outcomes and therapy. Table 2 documents the changes in insulin therapy by calendar year. Analog therapy refers to the use of short-acting insulin analogs whether used in two, three, or four times daily insulin regimens.

Definition of outcome event

In this study we report the epidemiology of severe hypoglycemia, which was defined as an event leading to loss of consciousness or seizure. An episode of hypoglycemia not resulting in one of these effects was not considered an outcome. For each patient, total severe hypoglycemic episodes were counted for the whole follow-up period.

Statistical analysis

HbA_{1c} was measured by agglutination inhibition immunoassay at 3-month intervals in each patient (non–type 1 diabetes reference <6.2%; Ames DCA 2000) (10). For the regression model, the primary end point was the number of episodes of severe hypoglycemia for each patient during their entire follow-up period. The incidence rate for severe hypoglycemia was calculated by obtaining the total number of severe hypoglycemic events and dividing this by the total length of follow-up. Significant predictors of se-

Table 2—*Frequency of patients receiving various insulin treatment regimens by calendar year*

Year	Number of patients	Number of injections of insulin per day			Pump	Analog
		2	3	>3		
1992	348	96.0	0.3	2.3	—	—
1993	383	95.8	0.3	2.3	—	—
1994	430	97.9	0.5	1.2	—	—
1995	477	96.0	1.3	2.1	—	—
1996	509	95.3	1.6	2.8	—	—
1997	562	92.7	3.0	3.7	—	1.4
1998	597	90.6	3.2	6.0	—	12.7
1999	625	85.0	5.6	9.0	—	24.0
2000	738	80.2	9.1	9.5	0.9	22.9
2001	776	68.0	12.1	15.1	4.4	25.0
2002	801	60.2	13.9	17.1	8.2	36.0

Data are the percentage of patients on each treatment regimen. Total percent may not add to 100% because those treated with less then two injections per day are not shown in the table and because "analog" (which refers to all regimens that include short-acting insulin analogs) is a subset of insulin injections.

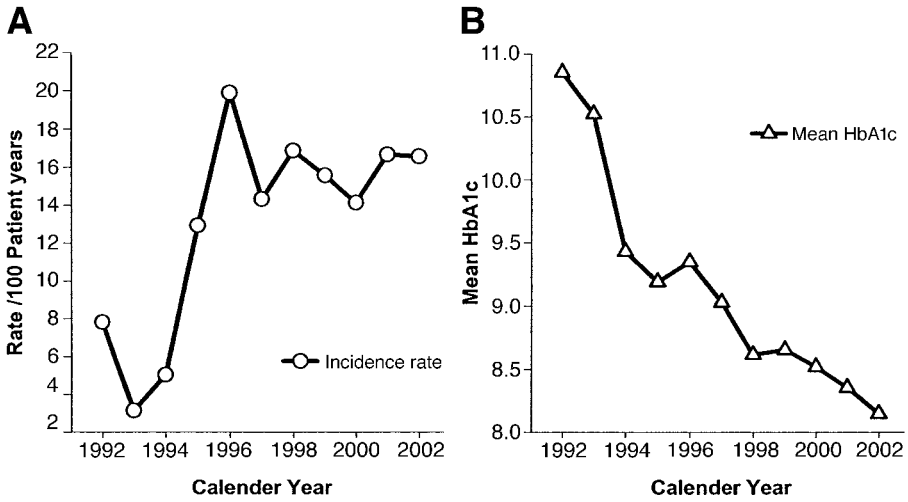


Figure 1—*Rates of severe hypoglycemia* (A) *and average HbA$_{1c}$* (B) *by calendar year.*

vere hypoglycemia were identified using univariate and multivariate negative binomial regression models. We have previously shown (11) that in order to examine factors that are associated with severe hypoglycemia, where events are recorded as counts and there are excess zero counts, use of a Poisson regression model results in a poor fit (12). It underestimates the observed number with no severe hypoglycemic events and overestimates the number with one or two severe hypoglycemic events. This is due to the problem of overdispersion, also known as extra-Poisson variation, and occurs because a single Poisson parameter is insufficient to describe the population. All statistical analyses were performed using SAS version 8.2 and Stata version 8.

RESULTS — A total of 944 severe hypoglycemic events occurred during 6,928 patient-years of follow-up. The overall incidence rate of severe hypoglycemia in 1992 was 7.8 per 100 patient-years (Fig. 1). A decade later in 2002, the incidence rate was 16.6 per 100 patient-years. The incidence rate adjusted for age and sex rose by 18% per year for the first 5 years ($z = 5.10$, $P < 0.0001$); however, no significant change in the adjusted rate of severe hypoglycemia was observed over the last 5 years of follow-up ($P = 0.962$). Of the 1,335 patients, 964 (72.2%) had no episodes of severe hypoglycemia. Of the remaining 371 children, 47% had one episode, 21% had two, and 32% had three or more.

Glycemic control

Figure 1 also shows the change in mean HbA$_{1c}$ for each year of the period of observation. The average HbA$_{1c}$ fell from 10.9 ± 1.7% in 1992 to 8.1 ± 1.5% in 2002. Overall, this represents a significant reduction in average HbA$_{1c}$ of 0.2% per year after adjusting for age and sex ($P < 0.0001$).

After adjusting for age and sex, a decrease in HbA$_{1c}$ was associated with a higher risk of severe hypoglycemia (incidence rate ratio [IRR] 0.78, 95% CI 0.73–0.84; $P < 0.0001$). A similar trend was observed in a multivariate analysis (shown in Table 3), where, for example, children with HbA$_{1c}$ <9% had rates between three and four times higher compared with children with HbA$_{1c}$ >11%.

Age and sex

Table 3 summarizes the impact of age and sex on hypoglycemic risk. A significant difference was observed between the youngest and oldest age-groups, with the youngest at highest risk (IRR 1.76, 95% CI 1.10–2.81; $P = 0.018$). The 6- to 12-year-olds had a lower risk of severe hypoglycemia compared with the oldest age-group (0.76, 0.60–0.96; $P = 0.024$). Boys had a significantly higher risk compared with girls (1.44, 1.11–1.86; $P = 0.007$). This difference was confined to the 13- to 18-year age range (1.72, 1.24–2.34; $P < 0.001$).

Other factors

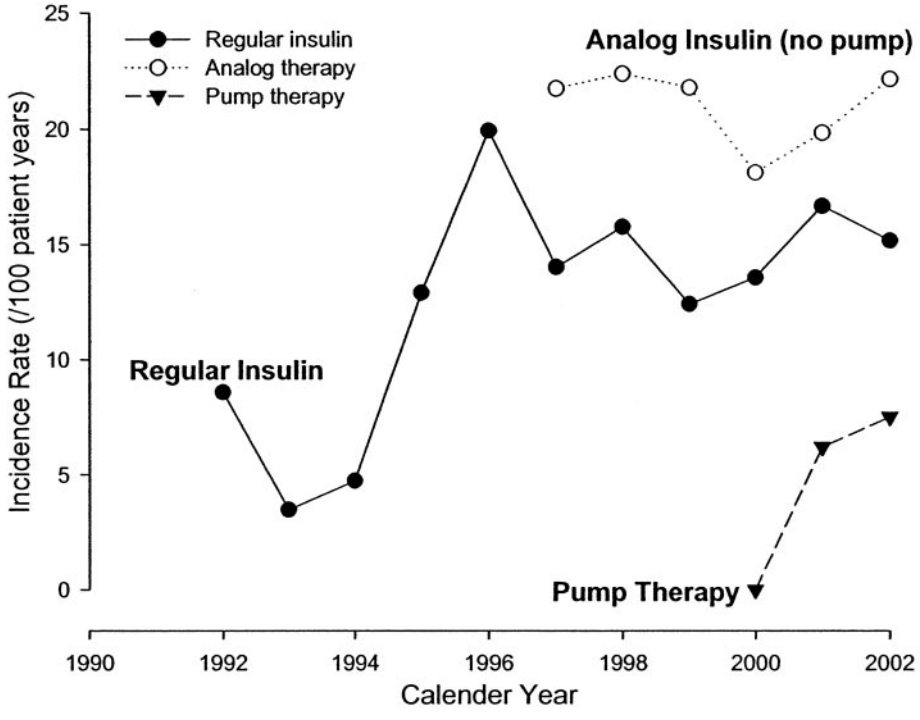
The results of a multivariate regression analysis where all of the factors were entered into a single model are summarized in Table 3. Children with a duration of diabetes of >12 months had a significantly higher risk than those with a duration of disease of <12 months. Higher insulin dose was associated with a higher risk (IRR 1.62, 95% CI 1.19–2.20; $P = 0.002$). Children in higher socioeconomic groups, i.e., whose parents' social disadvantage status was classified as lowest disadvantaged, had a significantly lower risk of severe hypoglycemia (0.73, 0.54–0.97; $P = 0.028$) compared with children whose parents' socioeconomic status was classified as both highest and middle disadvantaged.

Treatment regimens and severe hypoglycemia

The average daily insulin dose has risen significantly ($P < 0.001$) from 0.83 ± 0.34 units · kg^{-1} · day^{-1} in 1992 to 1.00 ± 0.37 units · kg^{-1} · day^{-1} in 2002. The incidence of severe hypoglycemia over time by selected insulin treatment method is shown in Fig. 2. There was no significant difference in hypoglycemia rates between those treated with regular or analog insulin (IRR 1.32, 95% CI 0.96–1.82; $P = 0.086$). The mean HbA$_{1c}$ and age over the last 4 years for these patients were 8.3 ± 1.4% and 12.2 ± 3.8 years, respectively, for those on analog insulin compared with 8.4 ± 1.6% and 10.7 ± 4.7 years, respectively, for those on regular insulin.

Children and adolescents treated with three or more injections of regular insulin per day had severe hypoglycemia rates no different from those of children and adolescents treated with two injections of regular insulin and with very similar mean HbA$_{1c}$ over the last 4 years (IRR 1.32, 95% CI 0.93–1.87; $P = 0.118$). Similarly for those treated with analog insulin, no difference was observed in risk between groups of patients having two or more than two injections (1.07, 0.70–1.64; $P = 0.757$).

The first patients to receive pump therapy were introduced in 1999. The rate of severe hypoglycemia was 7.5 per 100 patient-years by 2002. Those treated with pump therapy had significantly lower rates of severe hypoglycemia compared with those on regular insulin therapy and analogs. This difference was



Number of Patients

	1992		1994		1996		1998		2000		2002
Regular	348	383	430	477	509	556	535	501	568	582	513
Analog	-	-	-	-	-	6	62	124	162	160	222
Pump	-	-	-	-	-	-	-	-	7	34	66

Figure 2—*Incidence rate of severe hypoglycemia by insulin therapy.*

observed despite a lower mean HbA_{1c} of 7.8 ± 1.1% in the pump therapy group.

CONCLUSIONS — In this observational study, our primary objective was to analyze incidence rates of severe hypoglycemia over a decade of changing therapy. A randomized controlled trial is the ideal methodology to assess the potential impact of a particular treatment method under optimal conditions. In contrast, our approach in this report has been to descriptively examine a large population-based cohort over a prolonged period. This approach has the advantage of providing a reflection of the overall effect of contemporary therapy in a clinic setting in a representative sample. We have attempted to avoid the problems of retrospective surveys by using a prospective design in which data were recorded every 3 months to reduce the chance of false recall of hypoglycemic events. We have relied on parental reports, and this may therefore present an underestimation of the true rates of hypoglycemia. Due to the problems of defining moderate hypoglycemia, which may alter during such a long observation period, we have limited this report to severe hypoglycemia defined as the occurrence of convulsions or coma. In our previous report, we also included episodes of severe neuroglycopenia (described as "moderate" events). It is worth noting that, in that report (6), the epidemiology of these episodes, although more frequent, closely paralleled the more severe category.

Our study of 1,335 children observed longitudinally for 6,928 patient-years is one of the largest population-based cohorts with clinical data collected over a decade. The near complete ascertainment and very low dropout rate add to the strength of the study. The overall incidence of severe hypoglycemia in our sample is comparable with that of other reports, including a recent study from Denver and the cross-sectional Hvidore multicenter study (7,8,13–15). The incidence of severe hypoglycemia increased significantly during the first 5 years of the observation period. In view of the strong relationship between HbA_{1c} and hypoglycemia risk in our cohort, it is likely that this increased rate of severe hypoglycemia was associated with the rapid improvement in glycemic control over that time. The reasons for this improvement in diabetes control are likely to be multifactorial, and as the change coincided with the dissemination of DCCT results, changes in glucose targets and practice are likely to have been important. It is noteworthy that our data suggest that hypoglycemic rates have reached a plateau over the last 5 years despite continued lowering of HbA_{1c} (Fig. 1). It can only be speculated as to whether this was due to the introduction of specific insulin regimens, increased skills in the clinicians and caregivers, or a combination of these.

In our sample, individuals with a lower HbA_{1c} were at greater risk of severe hypoglycemia. This was found in other large studies, including the DCCT, but not in all studies (13,14,16,17). Adolescent boys between the ages of 13 and 18 years had a significantly higher incidence rate compared with girls. This is similar to findings from Rewers et al. (7) and is unexplained. We have also shown that children from the more disadvantaged socioeconomic groups tend to have a higher risk. Some studies have shown contrasting results, but they used a classification of socioeconomic status that was not comparable with ours (7,18). For example, Allen et al. (18) used occupation quartiles and showed no correlation, and Rewers et al. (7) used medical insurance as an indicator of low socioeconomic status and did report results similar to our findings.

For every 1-year increase in duration of diabetes, the risk of severe hypoglycemia increases by 8%. Both Rewers et al. (7) and Craig et al. (14) demonstrated a similar relationship.

Children on continuous subcutaneous insulin infusion showed a significant reduction in risk of severe hypoglycemia compared with children on injections, despite a lower mean HbA_{1c} in the pump therapy group. This is in keeping with other reports (19,20) evaluating pump therapy in children. Our findings need to be qualified, however, because in our study the numbers on pump therapy are smaller and rates have been evaluated with a relatively short follow-up period of 2 years. Neither insulin therapy with multiple injections nor analog insulin therapy was associated with fewer hypoglycemic

Table 3—*Predictors of severe hypoglycemia*

Variables	IRR	*P*	95% CI of IRR
Age-group (years)			
<6	1.8	0.018	1.1–2.8
6–12	0.8	0.024	0.6–0.9
13–18	1.0	—	—
Sex			
Male	1.4	0.007	1.1–1.9
Female	1.0	—	—
Duration of diabetes (years)			
<1	1.0	—	—
1–5	3.7	<0.001	2.3–6.0
5–9	4.8	<0.001	2.8–8.0
>9	5.3	<0.001	2.9–9.5
HbA_{1c} (%)			
<7	4.3	<0.001	2.6–7.1
7–8	3.1	<0.001	1.9–4.8
8–9	2.7	<0.001	1.8–4.3
9–10	1.8	0.014	1.1–2.8
10–11	1.1	0.747	0.7–1.8
>11	1.0	—	—
Number of injections	1.4	0.025	1.0–1.8
Insulin dose (units · kg^{-1} · day^{-1})			
<0.64	1.0	—	—
0.64–0.79	1.8	0.014	1.1–2.8
0.80–0.93	1.8	0.020	1.1–2.9
0.94–1.07	1.5	0.113	0.9–2.6
1.08–1.28	1.9	0.019	1.1–3.1
≥1.29	2.2	0.002	1.3–3.5
Social disadvantage			
Highest	1.0	—	—
Middle	0.6	0.004	0.4–0.9
Lowest	0.7	0.028	0.5–0.9

events in our sample. Other reports have suggested that severe events may be less common with analog therapy (21–23), but the relationship has not been strong in pediatric studies (24,25). The reason for the lack of difference in the analog group in the present study is not clear, but it must be considered that this is an observational study. Other factors may be operating; for example, those with recurrent hypoglycemia may have been changed to the analog insulin in an attempt to reduce the frequency of hypoglycemia.

In conclusion, severe hypoglycemia remains a major problem for children and adolescents with type 1 diabetes. Changes in therapy encompass not only insulin regimens but also glycemic targets, blood glucose monitoring, and other key aspects of diabetes management and practice. Further monitoring of newer approaches to therapy is required to determine whether improvements in glycemic control are possible without an increased risk of severe hypoglycemia.

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