Hypoglycemia: Incidence and Clinical Predictors in a Large Population-Based Sample of Children and Adolescents With IDDM

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OBJECTIVE — To determine the frequency of moderate and severe hypoglycemia and to identify clinical predictors associated with its occurrence in a large population-based sample of children and adolescents with IDDM.

RESEARCH DESIGN AND METHODS — A total of 657 patients (age: 12.1 ± 4.4 years, mean ± SD) were included in the study, yielding 1,449 patient-years of data. A prospective assessment of severe hypoglycemia (an event resulting in a seizure or coma) and moderate hypoglycemia (an event requiring assistance of another, excluding severe episodes) was made over a 3-year period. Patients and caregivers detailed episodes of significant hypoglycemia (moderate and severe events) and these were recorded at each 3-month clinic visit along with HbA_{1c}. Data were analyzed using generalized estimating equation models fitted with the exchange correlation structure.

RESULTS — The overall incidence of severe events was 4.8/100 patient-years and of moderate events was 13.1/100 patient-years. Over 3 years, severe events occurred in 8.5% of children and moderate events occurred in 26.9%. Significant hypoglycemia was rare in the first 12 months after diagnosis. Rates of hypoglycemia were increased in children <6 years of age versus >6 years of age (40.9 vs. 16.6/100 patient-years, age ≤6 years vs. age >6 years, $P < 0.001$). Rates of hypoglycemia doubled when HbA_{1c} fell below 8%, and children with HbA_{1c} <7% had a threefold increase in both moderate and severe hypoglycemia (e.g., severe episodes 14.9 vs. 4.1/100 patient-years, HbA_{1c} ≤7% vs. HbA_{1c} >7%, $P < 0.001$). Most severe events were seizures, and 75% of them occurred at night. The majority of events were related to missed meals or increased activity. However, in 38% no predisposing factor was evident.

CONCLUSIONS — Newly diagnosed children appear to be protected from severe hypoglycemia. Rates increase with lower glycated hemoglobin, especially when mean HbA_{1c} is <8.0%. Younger children, who may be more susceptible to the adverse effects of neuroglycopenia, are at a particular risk of significant hypoglycemia.

A number of reports have examined the epidemiology of significant hypoglycemia in both children and adults with IDDM (1–9). The aim of these studies has been to prevent serious hypoglycemic episodes by an improved understanding of the clinical factors associated with their development. This has become more relevant with the recognition of the importance of hypoglycemic events in limiting attempts to achieve normoglycemia in patients with IDDM.

The majority of the larger studies examining the epidemiology of hypoglycemia in children represent data collected during the 1970s and 1980s (1–4). However, changes in insulin regimens and greater emphasis on better metabolic control facilitated by glucose monitoring and availability of HbA_{1c} measures may have altered the incidence of hypoglycemia. Although reports agree as to the relatively high frequency of severe hypoglycemia in children, variations in methods of defining and reporting hypoglycemia make comparisons between these studies difficult. Furthermore, there are reported differences in the relative importance of recognized predisposing factors. Daneman et al. (2), for example, in a retrospective survey, found lower HbA_{1c}, younger age, and longer diabetes duration to be relevant. However, Bergada et al. (3), in a prospective study, found no relationship between incidence of hypoglycemia and metabolic control, age, or IDDM duration. Bhatia and Wolfsdorf (4), also using a prospective survey, found lower HbA_{1c} to be a factor, but not age. Such differences may reflect methodological differences as well as variations in sample size and clinic populations, and highlight the need for further information.

Surveys of adult IDDM populations have also provided information that is varied (5–8). Furthermore, it is difficult to extrapolate the findings of these studies to younger patients because of the differences in treatment regimens, in behavior, and in responses to hypoglycemia between adults and children. These differences were highlighted recently by the higher incidence of severe hypoglycemia reported in the adolescent subgroup of the Diabetes Control and Complications Trial (DCCT) in both the conventional and the intensive treatment arms (9–11).

In the present study, we aimed to characterize the incidence and clinical predictors of moderate and severe hypoglycemia in a large group of children and adolescents with IDDM over a 3-year period using a prospective study design. The children surveyed include all children with IDDM from the population of Western Australia and thus represent a wide range of metabolic control and age.

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DCCT, Diabetes Control and Complications Trial; PMH, Princess Margaret Hospital.

Table 1—*Clinical characteristics of subjects*

Age group	<6 years	6–12 years	>12 years	Total (0–18 years)
n	83	240	334	657
Age (years)	4.3 ± 1.2	9.8 ± 1.5	14.9 ± 1.8	12.1 ± 4.4
Sex (M:F)	44:39	126:114	174:160	344:313
Duration of IDDM (years) (range)				4.7 ± 3.7 (0–18)
HbA_{1c} (%)	8.9 ± 1.4	8.8 ± 1.6	9.3 ± 1.5	9.1 ± 1.6
Percentage of subjects with HbA_{1c}:				
<8%	28.5	28.3	25.9	26.5
8–10%	65.4	64.5	61.9	63.3
>10%	6.1	7.1	12.2	10.2

Data are *n*, means ± SD (range), or %.

RESEARCH DESIGN AND METHODS

Patients

All diabetic children and adolescents attending the diabetes clinic at Princess Margaret Hospital (PMH) during the 3-year period from May 1992 to April 1995, inclusive, were included in the study. Over this time, a total of 657 patients between 0 and 18 years old were enrolled, yielding 1,449 patient-years of data. A total of 211 children were diagnosed with IDDM during the 3 years. Clinical characteristics of the subjects are shown in Table 1.

PMH is the only pediatric referral center for diabetes servicing the state population, and nearly all diagnosed children aged <15 years are registered and treated regularly at that center. This is confirmed by the Western Australian childrens' diabetes register, which has a case ascertainment rate >99% (12).

All patients at school (<17 years) are treated twice a day with insulin. Of the older subjects (≥17 years), 8 (26%) were treated using multiple daily injections. All subjects and parents had undergone standard diabetes education, including details concerning the recognition and treatment of hypoglycemia as well as insulin adjustment. All parents and patients had been educated as to the standard goals of therapy and were encouraged to achieve optimal metabolic control by the diabetes care team. Parents and patients routinely adjust insulin according to home glucose levels to allow for exercise patterns and food intake. All caregivers had access to glucagon and had been instructed in its use.

Definitions

Moderate hypoglycemia was defined as hypoglycemia requiring the assistance of another person for treatment, and severe hypoglycemia was defined as an event resulting in coma or convulsion. In this report, "significant hypoglycemia" is used to describe the combined total of moderate and severe hypoglycemia. For younger children (<5 years) the definition of moderate hypoglycemia is troublesome, as all symptomatic episodes may be described by this definition as "moderate." As a result, at that age, we counted as moderate only those events with obvious neuroglycopenia, manifesting as confusion or drowsiness and requiring immediate treatment, but where the child could be treated with oral carbohydrate and did not necessitate glucagon therapy.

Protocol

Data was collected prospectively over a 3-year period. Patients and/or parents and caregivers were asked to record any moderate or severe episodes when they occurred, along with details of the event. A standardized data collection form was used. In addition, patients/parents were asked to contact a diabetes team member after a severe episode.

Patients were seen in clinic every 3 months, and on each attendance a detailed history was obtained by the physician about any episode of moderate or severe hypoglycemia since the previous visit. The patients were questioned about the circumstances surrounding the event. The mode of treatment was also recorded. Over the 3-year study, 97% of all subjects attended a minimum of four visits per year. For all patients, HbA_{1c} was determined at each 3-month visit. This was measured by agglutination inhibition immunoassay (Ames DCA 2000, non-IDDM reference <6.2%).

Statistical analysis and procedures

Demographic data are expressed as means ± SD. The data were analyzed using generalized estimating equation models (13,14) that were fitted with the exchange correlation structure. These models are an extension of multivariate logistic regression analysis that are designed to account for multiple or repeated measures on the same subject. *P* values <0.05 were considered significant. Factors analyzed included the following: sex, IDDM duration (≤1 year, 1–5 years, 5–9 years, >9 years), HbA_{1c} (≤7%, 7%–8%, etc.), and age (≤6 years, 6–12 years, >12 years).

RESULTS — During the 3-year study, a total of 70 severe and 190 moderate hypoglycemic episodes were recorded. Thus, the overall incidence of severe episodes was 4.8/100 patient-years and of moderate episodes was 13.1/100 patient-years, giving a total incidence of significant hypoglycemia of 17.9/100 patient-years. Over the 3-year period, severe episodes occurred in 8.5% of the children and moderate episodes occurred in 26.9%. Of those who experienced one severe episode, 32% had a repeat of a severe event during the 3 years. No significant differences were noted between boys and girls in rates of hypoglycemia.

Children who had diabetes for <1 year had a reduced incidence of severe hypoglycemia (0.8 vs. 5.5/100 patient-years: diabetes duration ≤1 year vs. duration >1 year, $P < 0.001$). Thereafter, duration of diabetes was unrelated to the incidence of hypoglycemia (Fig. 1).

The incidence of hypoglycemia was further analyzed in three age groups: ≤6 years, 6–12 years, and >12 years (see Table 1). Fig-

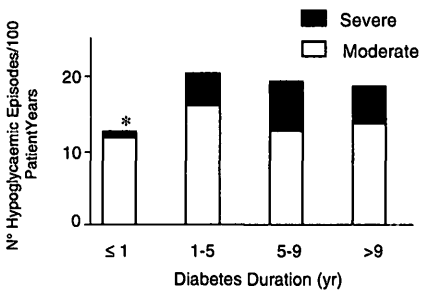

Figure 1—*Rates of moderate and severe (seizure/coma) hypoglycemia at differing periods of diabetes duration. A duration <1 year was associated with a significantly reduced incidence of severe hypoglycemia (P < 0.001).*

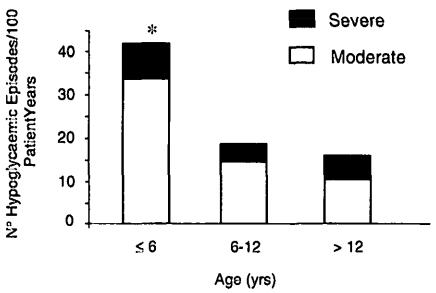

Figure 2—*Rates of moderate and severe (seizure/coma) hypoglycemia for three age groups (≤6 years, 6–12 years, >12 years). The incidence of events was highest in the youngest age group (P < 0.001).*

ure 2 shows results of this analysis. As shown, the youngest group had the highest incidence of hypoglycemia with a total of 40.9 events/100 patient-years in comparison with the rates in >6-year-olds of 16.6. The total incidence of hypoglycemia for those >12 years was 14.9 events/100 patient-years. In the youngest group, the rate of severe hypoglycemia was ~50% higher than in older children (7.2 vs. 4.7 episodes/100 patient-years, <6 years vs. >6 years, $P < 0.05$). Over the 3 years, 14.5% of the younger children reported severe hypoglycemia and 47% reported moderate hypoglycemia. The effect of younger age was independent of diabetes duration and HbA_{1c}.

The relationship between the HbA_{1c} closest to the event and the incidence of hypoglycemia is shown in Fig. 3. As shown, the incidence of hypoglycemic episodes increased sharply at an HbA_{1c} below 8%. Children with HbA_{1c} <7% had a rate of significant hypoglycemia of 47.1/100 patient-years. The incidence of severe hypoglycemia was increased threefold above the mean when HbA_{1c} fell below 7% (14.9 vs. 4.1 episodes/100 patient-years, HbA_{1c} ≤7% vs. HbA_{1c} >7%, $P < 0.001$). Rates of both moderate and severe hypoglycemia doubled at an HbA_{1c} between 7 and 8%. This effect was independent of age, duration of diabetes, or method of insulin therapy and was even more pronounced when subjects with duration <1 year were excluded from analysis; for example, at HbA_{1c} <7%, the rate of severe episodes is 16.8/100 patient-years (vs. 14.9/100 patient-years with those with duration <1 year included). Analysis of HbA_{1c} for each patient in the year following a severe episode indicated no effect on subsequent HbA_{1c}. Further, analysis of HbA_{1c} in the 12 months before the event did not indicate that hypoglycemic events followed a change in HbA_{1c}.

Description of events

Most (92%) severe episodes were seizures rather than comas. In 62% of severe episodes, a potential precipitating factor could be identified. In 31%, a missed or delayed meal was reported, and in 19% there had been greater than usual physical activity. Also, 4% reported the associated use of alcohol, and 8% of events were related to an incorrect insulin dose. Overall, 10% reported that no warning symptoms of hypoglycemia usually occur.

Of the severe episodes, 81% occurred at home, 9% occurred in the car (none drivers), 5% at school, and 5% at camp; 75% of the episodes occurred at night, 55% happened while the patient was asleep, 15% were in the morning, and 5% each in the afternoon and the evening. Glucagon was used as treatment in 55% of severe cases, and in 35% of cases, medical attention was sought. In 30% of cases, oral carbohydrate was the only treatment.

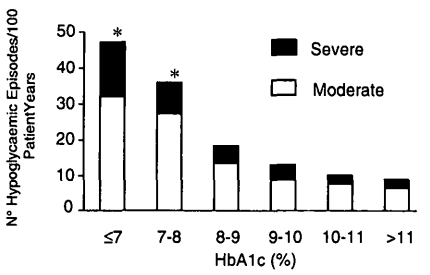

Figure 3—*Rates of moderate and severe (seizure/coma) hypoglycemia according to HbA_{1c} closest to the event. The incidence of hypoglycemia increased when HbA_{1c} fell below 8% (P < 0.001).*

CONCLUSIONS — In this study, we have determined the incidence of moderate and severe hypoglycemia in a large population-based sample of children with IDDM. In all, 1,449 patient-years of data were analyzed. A prospective study design was used to minimize underreporting, but since it is possible that further episodes were unrecognized or unreported, the rates described may well be an underestimate. Despite this, we found high rates of hypoglycemia; overall 14.9% of children experienced an episode of moderate or severe hypoglycemia per year. Further, the incidence of significant hypoglycemic events was 17.9 episodes/100 patient-years, (i.e., 4.8 severe events/100 patient-years and 13.1 moderate events/100 patient-years). These figures for severe hypoglycemia are similar to those of Bergada et al.(3) and Egger et al. (15). Egger et al. (15) described an incidence of 6.5 severe events/100 patient-years in 155 IDDM children. The overall incidence of moderate and severe hypoglycemia combined in the present study is less than the rate of 24.1/100 patient-years for significant hypoglycemia in the conventionally treated group reported in the DCCT (16). However, comparison is difficult because that study included adults; patient selection was different, and subjects had longer diabetes duration.

The definition of grades of hypoglycemia has varied between studies and may be a potential source of difficulty for comparisons. Recently, the DCCT reports defined severe hypoglycemia as any event requiring assistance and identified seizures/coma as a subset of this. The present study was commenced prior to this becoming more standard reporting practice. We have limited "severe events" to seizure/coma and used "moderate" to describe other episodes requiring assistance. We have reported the data as it was collected rather than change definitions after the completion of the study. This difference, however, should not preclude direct comparisons as the definitions have been carefully documented.

Examination of risk factors showed that a duration of diabetes >1 year, age <6 years, and HbA_{1c} <8% are all associated with significantly increased risk. Children with IDDM appear to be protected from severe hypoglycemia in the 1st year of diagnosis. Although previous reports have not described an effect of diabetes duration on hypoglycemia incidence in childhood (3,15), these studies did not specifically look at the newly diagnosed group alone. It is difficult to explain the protection in the 1st year: lower insulin doses associated with residual β-cell function may be a factor. Alternatively, patients may pay more attention to the details of diabetes care at this early stage. Finally, it may be speculated that counterregulatory responses are more efficient in the 1st year.

To examine the effect of age, we divided our sample into three age groups that corresponded to three developmental stages in childhood (i.e., preschool, ≤6 years; early/intermediate school, 6–12 years; high school/adolescence, >12 years). The finding that children <6 years of age had double the

risk of older children is of concern, since this younger age group may be more susceptible to the adverse effects of neuroglycopenia (17–19). It is possible that the increased incidence was due to the difficulty in defining moderate hypoglycemia in very young children, since all episodes at this age will require some assistance for treatment. However, we were careful to include only those episodes where there were clear signs of significant neuroglycopenia. Furthermore, the higher rates for severe hypoglycemia, which is clearly defined, are consistent with the results for moderate hypoglycemia. Although there is little data available with which to compare these findings, Daneman et al. (2) in a large retrospective survey also found younger children reported severe hypoglycemia more frequently (2). A number of factors may contribute to a higher incidence at this age. First, it is possible that parents of older children may underreport episodes in comparison to the more anxious parents of younger children. On the other hand, this is not likely to change rates of reporting of seizures. Other potential factors at this age include, for example, the irregular and often difficult eating habits of young children, the sporadic nature of their exercise habits, their inability to identify and alert caregivers about hypoglycemic symptoms, and smaller dose of insulin, facilitating relatively large increases when errors in dosage are made. In view of the uncertainty regarding the neurological consequences of hypoglycemia in younger children, it may be appropriate to consider a higher target HbA_{1c} in this age group compared to older children.

We found a strong relationship between HbA_{1c} and incidence of hypoglycemia. This contrasts with some other studies in children (3,4). The finding, that an HbA_{1c} <7% increased the risk of severe and moderate hypoglycemia threefold and that an HbA_{1c} value between 7 and 8% was associated with a double risk, is similar to data from the DCCT, which found a threefold risk in the intensively treated group, compared to those in the standard treatment group (10). All our patients are on conventional therapy, reinforcing the conclusion that the level of glycemic control is the important factor rather than the mode of therapy.

In approximately two-thirds of the cases, regarding precipitating events for hypoglycemia, a recognized possible precipitant, such as extra physical activity, missed or delayed meals, use of alcohol, or incorrect insulin dosage, was identified. The identification by the patient of these precipitants is significant, because it implies that the education of patients can be targeted to improve their ability to anticipate and prevent hypoglycemia.

In this study, we have shown that rates of moderate and severe hypoglycemia are disturbingly high. Young children and those with HbA_{1c} <8% are at particularly high risk. The finding that most severe episodes were preceded by a recognizable precipitant suggests that repetitive education may help reduce the incidence of hypoglycemia. Attempts to achieve improved metabolic control in children with IDDM must be accompanied by efforts to minimize the risk of significant hypoglycemia, particularly in the younger age group.

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