Risk Factors for Frequent and Severe Hypoglycemia in Type 1 Diabetes

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OBJECTIVE — To determine the risk of frequent and severe hypoglycemia and the associated demographic and clinical risk factors.

RESEARCH DESIGN AND METHODS — Demographic and diabetes self-management factors were measured in 415 subjects followed prospectively for 4–6.5 years of type 1 diabetes duration as participants in a population-based incident cohort. Blood samples were collected up to three times yearly to test glycosylated hemoglobin (GHb) levels. Reports of frequent (2–4 times/week) and severe (lost consciousness) hypoglycemia as well as other diabetes self-management data were collected by questionnaires.

RESULTS — Frequent hypoglycemia was common (33 and 35% of participants reported this on the 4- and 6.5-year questionnaires, respectively), whereas severe hypoglycemia occurred much less often. Better glycemic control (odds ratio [OR] 1.3 per 2% decrease in GHb, 95% CI 1.1–1.5) and more frequent self-monitored blood glucose (1.5 per blood glucose check, 1.3–1.7) were independently related to frequent hypoglycemia. The association of frequent hypoglycemia with intensive insulin therapy increased with age. Better glycemic control (1.5 per 2% decrease in GHb, 1.2–2.0) and older age were related to severe hypoglycemic reactions. No sociodemographic factors other than age increased the risk of hypoglycemia.

CONCLUSIONS — Frequent hypoglycemia was common in a population representing the full range of glycemic control in the community. Intensive insulin management and blood glucose monitoring independently predicted frequent but not severe hypoglycemia. This information may be useful for updating patients such that minor changes in diabetes management might decrease the daily burden of this condition while maintaining intensive insulin therapy.

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Hypoglycemia is the most common acute complication of type 1 diabetes (1). Onset is usually rapid, and symptoms range from very mild to severe enough to cause brain damage or death (2,3). Results of the Diabetes Control and Complications Trial (DCCT) (4) increased emphasis on intensive insulin treatment but also drew attention to the accompanying risk of hypoglycemia with such therapy, particularly in adolescents.

The frequency of and risk factors for moderate and/or severe hypoglycemia in young adults were described in studies conducted in clinic- or hospital-based samples (5–8), the DCCT (9), one national cross-sectional study from France, and a limited number of population-based cohort studies (10–12). From these studies, it is clear that a history of hypoglycemia (6,9,13) and intensive insulin therapy (9) is an important predictor. Findings regarding other factors such as age, sex, duration of diabetes, and glycemic control are not consistent across studies. The frequency of all levels of hypoglycemia has not been reported. Also, no large population-based cohort has been studied prospectively to determine the relationship of both intensive insulin therapy and glycemic control to frequent and severe hypoglycemia. A prospective population-based cohort is essential for examining temporal trends and risk factors in individuals representing the full range of diabetes care in the community.

We studied longitudinally a large population-based cohort of children, adolescents, and young adults with type 1 diabetes in Wisconsin to determine the incidence and demographic and clinical risk factors associated with both frequent and severe hypoglycemia.

RESEARCH DESIGN AND METHODS

Population

The current analysis includes 415 of 597 individuals initially enrolled from 1987–1992 in an incident cohort of individuals aged 0–29 years when type 1 diabetes was diagnosed and living in 28 Wisconsin counties. Nearly all hospitalized children (aged 0–9 years) (97.1%) and most adolescents (aged 10–19 years) (81.8%) were identified initially. A total of 23% of hospitalized adults (aged 20–29 years) were identified. Details of recruitment and case ascertainment were published previously (14). These participants, followed from their fourth to sixth and a half year duration of diabetes during 1991–1996, returned at least two mailed questionnaires with information about hypoglycemia and diabetes management. At least one blood specimen was collected from each of these participants within the 30-month follow-up. This time frame was selected because glycemic control is generally stabilized by 30 months after diagnosis of type 1 diabetes (14). Participants were representative of the entire cohort, except that they were younger (an average of 1 year), more likely to be white (by 4%), and were more likely to have private

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Abbreviations: DCCT, Diabetes Control and Complications Trial; GHb, glycosylated hemoglobin; OR, odds ratio; SMBG, self-monitored blood glucose.

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

health insurance (by 3%). Due to missing glycosylated hemoglobin (GHb) and other values, the multivariable analysis was based on 350 subjects.

Data collection

Demographic information was collected by telephone interview 2–3 months after diagnosis of diabetes. An occupation-based socioeconomic level indicator was assigned using the scheme of Stevens and Cho (15). Scores between 14 and 90 designated the lowest to highest socioeconomic levels. For two-parent households, the higher of the two levels was used in the analysis. Questionnaires were mailed every 6 months after enrollment to collect information about hypoglycemia, insulin treatment, and health insurance. If health insurance information was not provided on the mailed questionnaire, data from the medical record at diagnosis were used. The mailed questionnaire asked subjects how many times they experienced an insulin reaction in the last 6 months, how many times they needed someone to help but did not lose consciousness when their blood glucose level was low, and how many times they lost consciousness during an insulin reaction. Frequent hypoglycemia was defined as approximately two to four times per week or more, and severe hypoglycemia was defined as loss of consciousness during an insulin reaction. Severe hypoglycemia did not include those who needed help but did not lose consciousness, because our sample included a large number of young children, who might require help with any level of hypoglycemia. For purposes of this study, intensive insulin therapy was defined as three or more insulin injections daily ($n = 411$) or the use of an insulin pump ($n = 4$).

Blood samples were collected for determination of total glycosylated hemoglobin at each routine clinic visit or every 4 months if no visit was scheduled. Details of specimen collection have been published previously (16).

Specimen processing and testing

Whole blood was tested at the study's central laboratory within 7 days of collection for GHb by Isolab Glyc-Affin microcolumn affinity chromatography (Akron, OH). The nondiabetic mean ± SD was 5.52 ± 0.77%. Details of this assay were published previously (16).

Table 1—*Sample description, Wisconsin Diabetes Registry Project*

Factors	$n = 415$
Age at diagnosis (years)*	10.6 ± 6.6
Age group at time of study (years)	
<5	2.9
5–14	57.8
15–24	30.4
25–34	8.9
Sex (% female)	48.7
Race (% white)	96.6
Mother's education (years)	13.7 ± 2.2
Family's highest parental occupation code*	47 ± 21
25th percentile	26
50th percentile	47
75th percentile	65
Health insurance (% private)	93.8
Mean GHb (%)†	11.5 ± 2.4

Data are means ± SD or %. *$n = 403$ reporting occupation: example occupations, 41 legal assistants, 46 nurses; 26 printing machine operators, 65 statisticians; †mean of within-individual mean GHb level.

Statistical methods

Means, standard deviations, and percentages were used for a description of the sample. Analyses were performed using SAS statistical software (SAS Institute, Cary, NC) (17). Odds ratios (ORs) adjusted for other factors were calculated by generalized estimating equations using SAS PROC GENMOD (17) with an exchangeable working correlation (18). *P* values were determined from the asymptotic *Z* test obtained from the coefficient divided by its standard error. The mean GHb was computed for each individual by taking the average of all GHb measurements during the corresponding 6-month period. Comparison of univariate results from all subjects having data on a given risk factor with those from subjects included in the multivariable analyses did not reveal any notable differences. The potential effect of noncompliance with study protocol was investigated by including the return rate of questionnaires in the model as a main effect and as interaction effects with important covariates. Variables, two-way interaction effects, and higher-order terms significant at $P < 0.05$ were retained in the multiple regression models.

RESULTS — Descriptive demographic and glycemic control information is provided in Table 1. The cohort subjects are predominantly white, are almost equally distributed by gender, have fairly well-educated mothers, and generally have parents with white-collar occupations. Most participants were 5–14 years of age (Table 1) and ~28% were <10 years of age at the time of the study. A total of 6% of the population had public health insurance or no health insurance during the study period. Glycemic control was generally less than optimal. Mean GHb values for the group as a whole, those ever intensively treated, those with frequent hypoglycemia, and those with severe hypoglycemia were 11.5, 11.5, 11.2, and 10.8%, respectively.

Frequent hypoglycemic reactions were reported by 33 and 35% of subjects at 4 and 6.5 years' duration of diabetes, respectively, whereas severe hypoglycemic reactions were reported by 7 and 4% at these time points. The frequency of subjects on intensive insulin therapy increased considerably from 51 to 65% during the study interval. The mean frequency of daily self-monitored blood glucose (SMBG) was similar at 3.1 ± 1.4 (means ± SD), as was the mean GHb of 11.0–11.2 ± 2.3% for the 4-year compared with 6.5-year follow-up.

Results of univariate analysis showed that lower GHb, intensive insulin therapy, and more frequent SMBG were associated with increased risk of frequent hypoglycemic reactions (Table 2), whereas only lower GHb was associated with severe hypoglycemic reactions. Univariate analysis of sociodemographic factors showed that white individuals were at increased risk for frequent hypoglycemia.

Table 2—*ORs from univariate analyses of diabetes management and demographic and socioeconomic factors*

	Frequent hypoglycemia (n = 415 subjects, 2,020 observations)	Severe hypoglycemia (n = 415 subjects, 1,987 observations)
GHb (%)*	1.1 (1.1–1.3)	1.3 (1.1–1.4)
Intensive insulin therapy†	1.6 (1.3–1.9)	1.0 (0.6–1.5)
SMBG (times/day)	1.4 (1.3–1.5)	1.1 (1.0–1.3)
Age (years)	1.0 (1.0–1.0)	1.0 (1.0–1.0)
Female	1.1 (0.7–1.4)	1.5 (1.0–2.0)
White race	2.5 (1.5–3.4)	2.4 (0.4–4.3)
Mother's education (years)‡	1.1 (1.0–1.1)	1.0 (0.9–1.2)
Occupation code§		
Quartile 2 vs. quartile 1	0.8 (0.5–1.4)	0.8 (0.4–1.6)
Quartile 3 vs. quartile 1	1.1 (0.7–1.8)	0.7 (0.4–1.5)
Quartile 4 vs. quartile 1	1.2 (0.7–1.9)	0.9 (0.5–1.7)
Health insurance‖		
Medicaid versus other	0.7 (0.2–2.9)	10.5 (1.2–95.7)
Private versus other	2.1 (0.7–6.3)	2.4 (0.3–17.2)
Frequent hypoglycemia	—	1.3 (0.9–2.0)

Data are OR (95% CI) obtained from generalized estimating equations and robust standard errors. *n = 351 subjects, 1,419 observations for frequent, n = 350 subjects, 1,398 observations for severe; †three or more insulin injections per day or using insulin pump; ‡n = 413 subjects, 2,000 observations for frequent, n = 411 subjects, 1,967 observations for severe, §n = 403 subjects, 1,958 observations for frequent, n = 401 subjects, 1,925 observations for severe.

No other demographic variables were related to severe hypoglycemic reactions. Medicaid insurance was related to an increased risk of severe hypoglycemia, although the study included few individuals with public insurance. In univariate analysis, frequent hypoglycemia was not related to severe hypoglycemia (Table 2).

Multivariable analyses showed that better glycemic control (OR 1.3 per 2% decrease in GHb, 95% CI 1.1–1.5) and more frequent SMBG (1.5 per blood glucose check, 1.3–1.7) were related to frequent hypoglycemia (Table 3). There was also a significant interaction between age and intensive therapy. Multivariable analyses showed that better glycemic control (1.5 per 2% decrease in GHb, 1.2–2.0) and older age were related to severe hypoglycemic reactions, whereas intensive insulin therapy and SMBG were not significantly related. The relationship of severe hypoglycemia with age was not linear, as can be seen in Table 3. The risk of severe hypoglycemia leveled off somewhat after 15 years of age. Individuals with public insurance were found to be at greater risk for severe hypoglycemia by multivariable analyses (data not shown). However, these results are based on very few observations (four severe hypoglycemic events among those with public insurance).

Table 3—*ORs from multivariable analyses of factors related to hypoglycemia*

Risk factors for frequent hypoglycemia	
GHb (per 2% decrease)	1.3 (1.1–1.5)
Intensive insulin therapy	
At 5 years of age	0.6 (0.3–1.2)
At 15 years of age	1.4 (1.0–2.0)
At 25 years of age	3.2 (1.8–5.7)
SMBG	1.5 (1.3–1.7)
Risk factors for severe hypoglycemia	
GHb (per 2% decrease)	1.5 (1.2–2.0)
Age*	
5 years of age	2.2 (1.1–4.5)
15 years of age	5.7 (1.3–24.4)
25 years of age	6.0 (1.4–26.0)

Data are OR (95% CI) obtained from generalized estimating equations and robust standard errors. *At 5, 15, and 25 years of age compared with age 0.

CONCLUSIONS — This large population-based cohort study established that both intensive insulin therapy and better glycemic control increased the risk of *frequent* hypoglycemia. The risk of *severe* hypoglycemia was increased by better glycemic control but not by intensive therapy in our population, which contrasts with results from the DCCT (9). This may be due to the inclusion of children younger than 13 years in our study and not in the DCCT. Although no other population-based studies of the simultaneous effect of intensive insulin therapy and glycemic control on hypoglycemia have been reported, population-based studies and studies of select populations have shown relationships of one of these factors with increased risk of hypoglycemia (10–12,19,20). Our study does not support a synergistic effect of glycemic control and intensive insulin therapy on the risk of hypoglycemia (either frequent or severe).

Our finding that SMBG predicted increased frequency of hypoglycemia was not unexpected. However, this is the first report of an independent effect of SMBG on hypoglycemia after taking intensive insulin therapy and glycemic control into account. Univariate relationships between SMBG and hypoglycemia have been reported, but no multivariable analyses were available (5,21). This finding provides additional information for clinicians who wish to identify individuals at high risk for hypoglycemia.

In this first study of frequent hypoglycemia (i.e., approximately two episodes of any severity per week), the high proportion of this generally poorly controlled population reporting frequent hypoglycemia suggests that significant improvement in diabetes management is needed to prevent both extremes in blood glucose levels. The rates of severe hypoglycemia are fairly comparable to those reported previously and may indicate a slight decline with duration (8,11,22). These rates are a conservative estimate of severe hypoglycemia because our study limited the definition to those who reported losing consciousness.

Our demographic findings regarding the risk of hypoglycemia with increased age provide new information. Most other studies with comparably aged populations showed no univariate relationship between age and hypoglycemia, similar to our univariate findings. However, in a multivariable model that included glycemic control, the effect of age seen in our population was not present in multivariable analyses in most others. It is difficult to compare our results regarding age with those of the DCCT due to absence of chil-

dren and examination of age at baseline in the clinical trial compared with age at the time of hypoglycemia in our study. Our results contrast those from an Australian population-based cohort that showed an increased risk among younger children (11). The Australian report differed from ours with respect to levels of glycemic control and its lack of intensive insulin therapy data. Race and socioeconomic level as described by occupation code were not related to hypoglycemia after adjustment for age, glycemic control, and insulin therapy. There were too few nonwhites and public health insurance participants in this study to fully examine these issues.

This is the first report to compare frequent hypoglycemia with severe hypoglycemia in a population-based study. Our findings suggest that frequent hypoglycemia does not necessarily flag those who will have life-threatening episodes. Some bias related to hypoglycemia unawareness and self-report may effect our findings. However, with a similar finding in their clinic population, Goldgewicht et al. (21) suggested that patients striving for "perfect" control were prone to frequent mild hypoglycemia, whereas patients with a less aggressive approach toward glycemic control were prone to severe hypoglycemia. Our data showing that 40% of individuals with severe hypoglycemia had multiple episodes are consistent with several reports from non–population-based studies (9,21).

In summary, our findings confirm that intensive insulin therapy and better glycemic control increase the risk of hypoglycemia and that the rate of frequent episodes and life-threatening episodes is unacceptably high several years after diagnosis of diabetes. Our community-based data, along with our knowledge of the natural history of this condition, suggest that health care providers consider updating their patients who are several years postdiagnosis with preventive strategies such as insulin modifications (e.g., minor changes in dose or newer insulin analogs) or minor dietary changes (e.g., light snacks at high-risk times) while maintaining intensive insulin therapy. Lessening the individual daily burden of this condition without compromising long-term health may be possible.

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