Increasing Incidence of Hypoglycemic Coma in Children With IDDM

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Objective: To examine the incidence of hypoglycemic coma in children with insulin-dependent diabetes mellitus (IDDM) over 8 yr from 1981 to 1988 and to investigate the importance of residual β-cell function of HbA_1 levels and other variables as risk factors for hypoglycemic coma. Research Design and Methods: The study consisted of 155 children with IDDM aged <16 yr at study entry. Mean age at onset of diabetes was 7.9 yr (range 1.1–15.6 yr). We made a prospective assessment of hypoglycemic coma episodes, with a standardized questionnaire, over a total observation time of 816.6 person-yr. Three monthly clinical and laboratory examinations, which included determinations of C-peptide and HbA_1 levels, were conducted. We compared children with hypoglycemic coma (cases) with children without hypoglycemic coma (controls) in a case-control analysis matched for diabetes duration. Yearly incidence of hypoglycemic coma, calculated as the number of subjects having an attack in 1 yr divided by the cumulative number of person-years for that year, was measured. Univariate and multivariate odds ratios were calculated from logistic regression. Results: Over the first 4 yr, the average yearly incidence was 4.4/100 person-yr compared with 7.4/100 person-yr during the later 4 yr ($P < 0.0001$). This tendency was accompanied by intensification of insulin treatment with an increase in the mean number of daily injections and a decrease in mean HbA_1 levels. In the case-control analysis, absent residual β-cell function was the most important risk factor for hypoglycemic coma (adjusted odds ratio 7.8, 95% confidence intervals 2.0–31.2), followed by near-normal HbA_1 levels (adjusted odds ratio 4.5, 95% confidence intervals 1.9–10.5). Conclusions: In this group of children, improvement of glycemic control apparently led to an increase in the incidence of severe hypoglycemia. In children with recurrent hypoglycemic coma and undetectable C-peptide levels, it may be safer to aim for somewhat less tight glycemic control.
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The most important acute complication of the treatment of insulin-dependent diabetes mellitus (IDDM) in children is severe hypoglycemia (1,2). Permanent brain damage accompanied with electroencephalographic abnormalities (3,4) and specific deficits in cognitive function (5,6) have been related to previous hypoglycemia in diabetic children. On the other hand, good glycemic control is considered important for the avoidance of diabetic complications, e.g., retinopathy and nephropathy (7–9). To delay the development of these late complications, tight glycemic control, with near-normal glucose levels, has become the therapeutic goal for children with IDDM.

In adult diabetic patients, it has been shown that improved glycemic control results in an increased risk of severe hypoglycemia (10). Therefore, there may be a need to balance between the benefits and risks of improved control in children. To explore this issue, we investigated the trend in the incidence of and risk factors for hypoglycemic coma in children with IDDM over 8 yr.

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RESEARCH DESIGN AND METHODS

One hundred sixty-seven children with IDDM aged <16 yr at study entry were seen between 1 January 1981 and 31 December 1988 at the outpatient clinic of the Department of Pediatrics, University Hospital, Berne. This is the regional center for diabetes care in this age-group. Ten patients were excluded because of missing data and two because of concomitant epilepsy. The age at onset of diabetes for the remaining 155 children was between 1.1 and 15.6 yr (mean ± SD 7.9 ± 3.8 yr). These children were followed up for 63.2 ± 28 mo, giving a total patient observation time of 816.6 person-yr. Incident cases entered the population throughout the study, the last patient being included in August 1988. Exits from the population occurred when children moved outside the catchment area of the hospital or when diabetes care was taken over by the adult diabetes service or by a practicing diabetologist. At the time of diagnosis of diabetes, children were hospitalized for 3 wk. Instruction on diet, insulin treatment, measurement of urinary glucose and acetone, and measurement of blood glucose was given (11). The recognition of hypoglycemia and the treatment of mild episodes with oral carbohydrates and of severe episodes with injections of glucagon was also covered. Children and their parents were taught to register hypoglycemic episodes in a booklet also used for recording control of blood glucose. Definitions produced by the Swiss Pediatric Diabetology Group were used: grade 1, minor signs, self-management possible; grade 2, moderate signs, patient dependent on external help but no loss of consciousness; grade 3, unconciousness with documented low blood glucose and/or immediate response to glucose or glucagon (12).

The treatment schedule after diagnosis was two daily injections of a mixture of short-acting insulin (Actrapid, Novo, Copenhagen, or Velosulin, Nordisk, Copenhagen) and long-acting insulin (Monotard or Protaphan, Novo or Insulatard, Nordisk). At onset, 61% of patients used pork insulin and 39% used human insulin. Sixteen percent of the patients were transferred from pork to human insulin (Actrapid and Protaphan, Novo), because pork insulins (Novo) were withdrawn. After 1986, ~20% of patients aged ≥12 yr were transferred to a 4-injections/day treatment schedule with pen injectors. Over the study, the therapeutic goal was tightened from an initial target, that of a HbA_1 of 10% to a target of 9%.

Children were seen at three monthly intervals in the pediatric outpatient clinic. At each visit, any grade 3 hypoglycemic episodes since the previous visit were elicited prospectively with a standardized interview schedule. Physical examination included height measurement with a Harpenden stadiometer (Holtain, Crymych, UK), weight, and palpation for the assessment of lipodystrophy. Laboratory examinations included the determination of stable HbA_1 (thermostabilized column chromatography, Boehringer Mannheim, Mannheim, Germany, reference value 5.1–7.8%) corrected for the presence of fetal hemoglobin (13) and plasma C-peptide (Novo, fasting reference value 180–680 pM, postprandial reference value 970–1830 pM) and insulin antibodies (125 J ox insulin, amberlite separation, Novo; 14). HbA_1 controls (Boehringer Mannheim) were used in every HbA_1 assay with a mean coefficient of variation of 3.1% (range 1.1–4.4%). All methods were kept unchanged during the study. Postprandial samples were available in 75% of the patients and fasting samples in the other 25%. Therefore, both actual plasma C-peptide levels and the ratio of C-peptide to glucose level were analyzed. The study protocol was supervised by one of the authors (K.Z.) throughout the study.

To identify possible risk factors for hypoglycemic coma, a case-control analysis was performed. Cases were defined as children experiencing one or more grade 3 hypoglycemic events during the follow-up period. For each episode, the following variables were extracted from the clinic charts: weight, height, presence of hypertrophic lipodystrophy, insulin regimen, insulin-antibody titer, HbA_1, plasma C-peptide, and plasma C-peptide–glucose ratio. Relative weight was calculated as the actual weight divided by the weight obtained from a 50% weight-for-height percentile (11). The means of the two values from the visit before and the visit after the episode of hypoglycemia were used for the analysis. Controls were selected from the children who did not experience a hypoglycemia grade 3 episode during the follow-up period. Controls were matched to cases on diabetes duration to within 3 mo, with two controls being randomly selected from the appropriate pool of control subjects for each case episode.

Statistical analysis. The incidence of hypoglycemic coma was calculated for each year as the number of subjects having an attack in this year divided by the cumulative number of person-years for that year. Subjects were excluded from the at risk population and the person-years accumulation once they had an attack. In the case-control study, univariate and multivariate odds ratios (ORs; 15), probability values from χ^2-statistics, and 95% confidence intervals (CIs) were calculated from matched analyses with conditional logistic regression (EGRET software; 16). Hypoglycemic coma episodes formed the unit of these analyses. Time trends were investigated with unpaired two-tailed Student's t tests and χ^2-statistics with Yates correction where appropriate. Data are presented as means ± SD or proportions. $P < 0.05$ was assumed to be significant.

RESULTS

During the follow-up period, there were a total of 104 grade 3 hypoglycemic events occurring in 53 patients. Therefore, 34.2% of the IDDM patients suffered at least one episode of hypoglycemic coma over a mean follow-

up time of 63.2 mo. Seizures were present in 42% of the episodes. Of the children who had at least one episode of grade 3 hypoglycemia, 45% had at least one repeat episode. Two children had five episodes and one child had six episodes.

The incidence of grade 3 hypoglycemia generally increased over the time of the study (Fig. 1). Over the first 4 yr, the average yearly incidence was 4.4/100 person-yr compared with 7.4/100 person-yr during the later 4 yr ($P < 0.0001$). The lowest incidence was recorded in 1984 (2.7/100 person-yr), with the highest in 1987 (9.2/100 person-yr). This tendency was accompanied by a decrease in mean HbA_1 and an increase in the mean number of injections per day (Fig. 1). Mean ± SD HbA_1 was 9.86 ± 1.3 in the first half of the follow-up period but 9.48 ± 1.6 during the second half ($P = 0.04$). The corresponding figures for the mean number of daily injections were 1.9 ± 0.3 and 2.2 ± 0.7 ($P = 0.0001$). No such trend was noted for C-peptide levels or ratios of C-peptide to glucose.

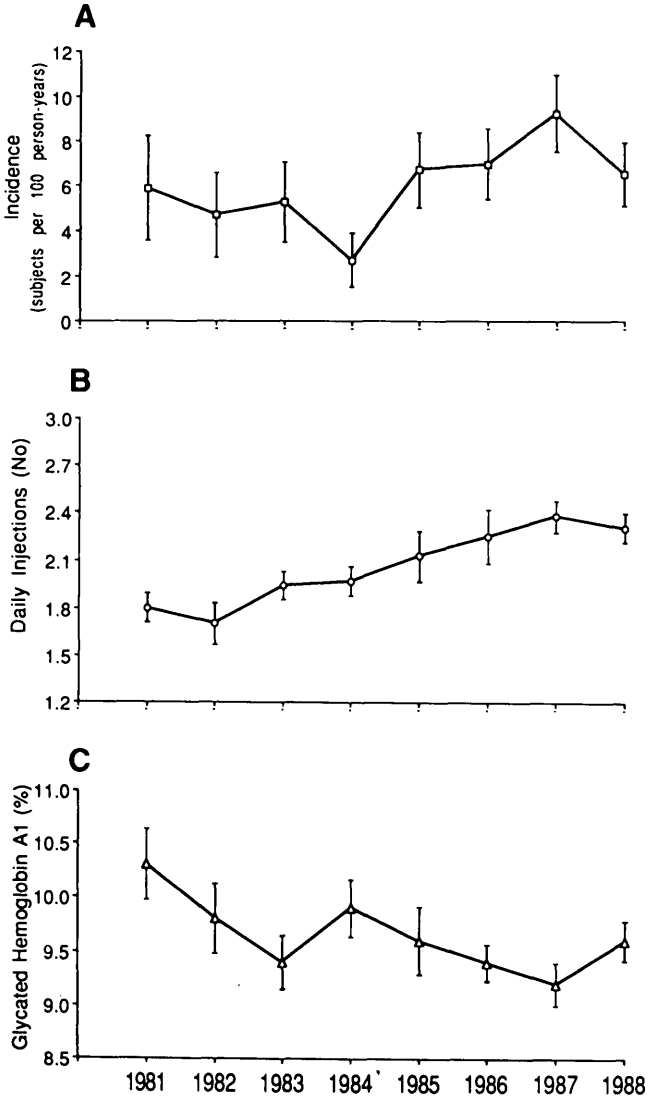

FIG. 1. Incidence of hypoglycemic coma (*A*), number of daily insulin injections (*B*), and mean HbA_1 levels (*C*) in 155 insulin-dependent diabetic children from 1981 to 1988. Values are means ± 1SE.

TABLE 1
Clinical and metabolic variables in cases with hypoglycemic coma and controls

	Cases	Controls	*P**
n	104	208	
Age (yr)	12.6 ± 4.6	13.0 ± 4.5	0.18
Males	55 (53)	88 (42)	0.073
Duration of diabetes (yr)	5.5 ± 4.0	5.4 ± 3.9	0.094
Relative weight (%)	0.77 ± 9.0	2.4 ± 10	0.19
Lipodystrophy	29 (28)	39 (10)	0.057
Daily insulin injections			0.12
1	4 (4)	10 (5)	
2	86 (82)	183 (88)	
4	14 (14)	14 (7)	
Daily insulin dose ($U \cdot kg^{-1} \cdot day^{-1}$)	0.95 ± 0.19	0.91 ± 0.28	0.12
Percentage long-acting insulin	64.6 ± 17	66.3 ± 14	0.46
HbA_1	9.00 ± 1.1	9.85 ± 1.6	<0.0001
C-peptide (pM)	36.9 ± 70	82.7 ± 130	<0.0001
C-peptide (pM)/glucose (mM)	3.7 ± 7	8.3 ± 14	<0.0001
Insulin antibodies	7.6 ± 13	4.0 ± 5	0.009

Values are means ± SD with percentages in parentheses.
*Probabilities from univariate conditional logistic regression analysis.

Case-control comparisons were based on the clinical characteristics of the cases and controls around the time of the episodes of severe hypoglycemia (Table 1). There were no marked differences with regard to age, sex, diabetes duration, and relative weight. There was a trend toward more frequent hypertrophic lipodystrophy in cases compared with controls ($P = 0.057$). The insulin regimen of the cases involved a higher total daily insulin dose and more injections than the controls, but the differences did not reach statistical significance. HbA_1 concentrations, C-peptide levels, and ratios of C-peptide to glucose were significantly lower for the case events, whereas insulin antibodies were higher.

The unadjusted ORs increased with decreasing levels of HbA_1 (test for linear trend $P = 0.0002$), indicating an increasing risk of hypoglycemic coma with improving glycemic control (Table 2). Decreasing levels of C-peptide were also associated with increased ORs for hypoglycemic coma, although the test for linear trend did not reach statistical significance ($P = 0.09$). However, absent C-peptide levels were strongly associated with the risk of hypoglycemic coma (unadjusted OR 5.9, $P < 0.0001$). These results were not materially altered when ratios of C-peptide to glucose instead of C-peptide levels were included into the model. There was a small

TABLE 2
Risk factors for hypoglycemia with coma in children with insulin-dependent diabetes mellitus

	Unadjusted odds ratio	Adjusted odds ratio*
HbA_1 (%)		
<8.5	3.3 (1.7–6.7)	4.5 (1.9–10.5)
8.5–10	1.9 (1.1–3.4)	2.4 (1.3–4.6)
>10	1.0	1.0
C-peptide (pM)		
<35	5.9 (2.3–15.1)	7.8 (2.0–31.2)
35–100	1.5 (0.76–2.9)	1.6 (0.71–3.8)
>100	1.0	1.0
Insulin antibodies/% increase	1.04 (1.01–1.08)	1.02 (0.99–1.06)
Lipodystrophy		
Present	1.8 (0.98–3.2)	1.8 (0.84–3.8)
Absent	1.0	1.0

95% confidence intervals in parentheses. Matched analysis (matched for diabetes duration) performed by logistic regression.
*Adjusted for all variables listed and age, sex, diabetes duration, and year of admission to study.

but statistically significant increase of the OR with higher levels of insulin antibodies. The presence of lipodystrophy was associated with an elevated OR; however, the 95% CIs included one. In the multivariate analysis, the ORs for HbA_1 and C-peptide were further increased, the OR for insulin-antibody concentration was decreased with 95% CIs now including one, whereas the OR for the presence of lipodystrophy remained unchanged.

A comparison of the incidence of grade 3 hypoglycemia during treatment with human insulin (35 episodes during 295.4 person-yr) and pork insulin (69 episodes during 521.2 person-yr) reveals rates of 11.8 episodes/100 person-yr and 13.2 episodes/100 person-yr (P = 0.7).

CONCLUSIONS

This longitudinal study confirms the high incidence of severe hypoglycemia in children with IDDM (1,2). The cumulative incidence in these patients, 34.2% over a mean follow-up of ~5 yr, is close to the 31.4% reported from the United States (1). Similar results were also found in a Canadian study. Over a follow-up period of 1 yr, 24 of 350 children with IDDM experienced severe hypoglycemia, giving an incidence of 6.8/100 person-yr compared with 6.5/100 person-yr in our study (17).

In this group of children, the incidence of severe hypoglycemia with coma increased over an observation period of 8 yr. The results from the case-control analysis indicate that this increase may largely be due to the concomitant improvement of glycemic control. Several studies, including a randomized controlled trial, have identified improved glycemic control as a risk factor for severe hypoglycemia (1,10,18–20). Intensification of insulin therapy, resulting in near-normal glycemic control, leads to impairment of glucose counterregulation. This involves a lowering of the glucose threshold for and a delay in epinephrine release, together with diminished hepatic glucose production (21). In well-controlled diabetic patients with low HbA_1 levels, the sensitivity of hepatic glucose production to insulin is increased compared with that of poorly controlled diabetic patients (21). Therefore, the higher risk of hypoglycemia in well-controlled diabetic patients observed in this and other studies would be expected. In the study from Canada, no relationship between HbA_1 and risk of severe hypoglycemia was found (17). This might be due to the fact that all HbA_1 levels determined during follow-up, and not only the values close to the hypoglycemic incident, were used in the analysis.

The ORs for severe hypoglycemia were considerably elevated for subjects with nondetectable C-peptide levels. To our knowledge, this finding has not been published previously, yet it confirms a long-standing clinical impression that patients in remission are less likely to develop severe hypoglycemia. Residual endogenous insulin production seems to be protective, perhaps through providing a regulatory mechanism for the prevention of severe hypoglycemia. Therefore, during threatened hypoglycemia, remaining endogenous insulin secretion into the portal system could be shut off. Because portal insulin has a strongly suppressive effect on hepatic glucose production (21), this could have an important influence in subjects with significant remaining insulin production.

Elevated insulin-antibody titers may be a further risk factor for severe hypoglycemia (22). The mechanism may again be diminished glucose counterregulation, which has been found to correlate with insulin-antibody titer (22), possibly due to delayed insulin action. In this study, the OR decreased and the effect became nonsignificant as soon as multivariate analysis adjustment was made for C-peptide levels, HbA_1 levels, and other factors. Thus, the effect seen in univariate analysis may be due to confounding through these other factors, although interpretation of multivariate coefficients is problematic when differential degrees of measurement error and intraindividual variation exist (23,24). Further studies are needed to establish if increased insulin-antibody concentrations are a risk factor for severe hypoglycemia.

Children who use human and pork insulins had a similar incidence of severe hypoglycemia over a total follow-up period of >800 person-yr, confirming the results of a previous multicenter study with a shorter observation time and a smaller number of patients (25). This is reassuring in view of the increasing evidence of hypoglycemia unawareness associated with human insulin in adult patients with long-standing diabetes (26–28).

Many factors, other than those examined in this study, are of relevance to the risk of hypoglycemia in children. These include delayed or insufficient food intake, increased exercise without concomitant increased caloric

intake, incorrect insulin dose, and inadequate insulin adaptation. Most of these are preventable by extensive education. The most important risk factor identified in this study, absent residual β-cell activity, cannot be influenced by education. In diabetic patients who have suffered a hypoglycemic coma and have undetectable C-peptide levels, it may be safer to aim at somewhat less tight blood glucose control with slightly higher levels of HbA_1.

REFERENCES

1. Daneman D, Frank M, Perlman K, Tamm J, Ehrlich R: Severe hypoglycemia in children with insulin-dependent diabetes mellitus: frequency and predisposing factors. *J Pediatr* 115:681–85, 1989
2. Travis LB: Hypoglycemia in insulin-dependent diabetes mellitus. *J Pediatr* 115:740–41, 1989
3. Gilhaus KH, Daweke H, Lülsdorf HG, Sachsee R, Sachsee B: EEG-Veränderungen bei diabetischen Kindern. *Dtsche Med Wochenschr* 31:1449–54, 1973
4. Soltesz G, Acsadi G: Association between diabetes, severe hypoglycemia, and electroencephalographic abnormalities. *Arch Dis Child* 64:992–96, 1989
5. Rovet JF, Ehrlich RM, Hoppe M: Specific intellectual deficits in children with early onset diabetes mellitus. *Child Dev* 59:226–34, 1988
6. Ryan CM: Neurobehavioral complications of type I diabetes: examination of possible risk factors. *Diabetes Care* 11:86–93, 1988
7. McCane DR, Hadden DR, Atkinson AB, Archer DB, Kennedy L: Long-term glycaemic control and diabetic retinopathy. *Lancet* 2:824–28, 1989
8. Chase HP, Jackson WE, Hoppe SL, Cockerham RS, Archer PG, O'Biran D: Glucose control and the renal and retinal complications of insulin-dependent diabetes. *JAMA* 261:1155–60, 1989
9. Klein R, Moss SE, Klein BEK, Davis MD, DeMets DL: Wisconsin epidemiologic study of diabetic retinopathy. XII. Relationship of C-peptide and diabetic retinopathy. *Diabetes* 39:1445–50, 1990
10. The DCCT Research Group: Diabetes control and complications trial (DCCT): results of feasibility study. *Diabetes Care* 10:1–19, 1987
11. Zuppinger K, Töndury P, Mullis P (Eds.): *Berner Datenbuch der Pädiatrie*. 3rd ed. Stuttgart, Germany, Gustav Fischer Verlag, 1988
12. Arbeitsgruppe der Schweizerischen Pädiatrischen Diabetologen: die Betreuung des Diabetes mellitus beim Kind. *Schweiz Rundsch Med Prax* 75:619–22, 1986
13. Mullis P, Schuler J, Zuppinger K: Increased prevalence of fetal hemoglobin in type I (insulin-dependent) diabetes mellitus. *Diabetologia* 32:227–30, 1989
14. Zuppinger K, Aebi C, Fankhauser S, Herz G, Zurbrügg RP, Schopfer K, Neri TM: Comparison of human and porcine insulin therapies in children with newly diagnosed diabetes mellitus. *Diabetologia* 30:912–15, 1987
15. Kahn KA, Sempos CT: *Statistical Methods in Epidemiology*. 2nd ed. Oxford, UK, Oxford Univ. Press, 1989
16. Breslow NE, Day NE, Halvorsen KT: Estimation of multiple relative risk functions in matched case-control studies. *Am J Epidemiol* 108:200–207, 1978
17. Bergada I, Suissa S, Dufresne J, Schiffrin A: Severe hypoglycemia in IDDM children. *Diabetes Care* 12:239–44, 1989
18. Goldstein DE, England JD, Hess R, Rawlings SS, Walker B: A prospective study of symptomatic hypoglycemia in young diabetic patients. *Diabetes Care* 4:601–605, 1981
19. Casparie AF, Elving LD: Severe hypoglycemia in diabetic patients: frequency, causes, prevention. *Diabetes Care* 8:141–45, 1985
20. Aman J, Karlsson I, Wranne L: Symptomatic hypoglycemia in childhood diabetes: a population-based questionnaire study. *Diabetic Med* 6:257–61, 1989
21. Amiel SA, Tamborlane WV, Simonson DC, Sherwin RS: Defective counterregulation after strict glycemic control of insulin-dependent diabetes mellitus. *N Engl J Med* 316:1376–84, 1987
22. Bolli GB, Dimitriadis GD, Pehling GB, Baker BA, Haymond MW, Cryer PE, Gerich JE: Abnormal glucose counterregulation after subcutaneous insulin in insulin-dependent diabetes mellitus. *N Engl J Med* 310:1706–11, 1984
23. Davey Smith G, Phillips AN: Declaring independence: why we should be cautious. *J Epidemiol Community Health* 44:257–58, 1990
24. Phillips AN, Davey Smith G: How independent are independent effects? Relative risk estimation when correlated exposures are measured imprecisely. *J Clin Epidemiol*. In press
25. Zuppinger K, Egger M, Aebi C, Schoenle E, Gschwend-Eigenmann S, Mullis P: Hypoglykämien bei Kindern mit Diabetes unter humanem oder porcinem Insulin. *Schweiz Med Wochenschr* 19:532–35, 1989
26. Berger W, Keller U, Honegger B, Jaeggi E: Warning symptoms of hypoglycemia during treatment with human and porcine insulin in diabetes mellitus. *Lancet* 1:1041–44, 1989
27. Egger M, Davey Smith G, Imhoof H, Teuscher A: Risk of severe hypoglycemia in insulin treated diabetic patients transferred to human insulin: a case control study. *Br Med J* 303:617–22, 1991
28. Egger M, Davey Smith G, Teuscher AU, Teuscher A: Influence of human insulin on symptoms and awareness of hypoglycemia: a randomized double-blind crossover study. *Br Med J* 303:622–26, 1991