Clinical Characteristics of Type 1 Diabetic Patients With and Without Severe Hypoglycemia

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OBJECTIVE — To investigate the frequency of severe hypoglycemia (SH) and hypoglycemic coma and to identify clinical and behavioral risk indicators in a nonselected population of type 1 diabetic patients.

RESEARCH DESIGN AND METHODS — This study involved a retrospective clinical survey of 195 consecutive patients using a questionnaire addressing the frequency of SH (i.e., help from others required) and hypoglycemic coma during the previous year, general characteristics, behavior, hypoglycemia awareness, and the Hypoglycemia Fear Survey. Data regarding diabetes, treatment, long-term complications, comorbidity, and comedication were obtained from the patients' medical records.

RESULTS — A total of 82% of subjects were receiving intensive insulin treatment, and mean ± SD HbA_{1c} was 7.8 ± 1.2%. Mean duration of diabetes was 20 ± 12 years. The occurrence of SH (including hypoglycemic coma) was 150 episodes/100 patient-years and affected 40.5% of the population. Hypoglycemic coma occurred in 19% of subjects (40 episodes/100 patient-years). SH without coma was independently related to nephropathy (odds ratio [OR] 4.8 [95% CI 1.5–15.1]), a threshold for hypoglycemic symptoms of <3 mmol/l (4.8 [1.8–12.0]), and a daily insulin dose 0.1 U/kg higher (1.3 [1.0–1.6]) (all ORs were adjusted for diabetes duration and use of comedication). Hypoglycemic coma was independently related to neuropathy (3.9 [1.5–10.4]), (nonselective) β-blocking agents (14.9 [2.1–107.4]), and alcohol use (3.5 [1.3–9.1]) (all ORs were adjusted for diabetes duration).

CONCLUSIONS — SH and hypoglycemic coma are common in a nonselected population with type 1 diabetes. The presence of long-term complications, a threshold for symptoms of <3 mmol/l, alcohol use, and (nonselective) β-blockers were associated with SH during the previous year. If prospectively confirmed, these results may have consequences for clinical practice.

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Hypoglycemia as the limiting factor in the treatment of type 1 diabetes continues to be a topical issue. Various intervention strategies such as blood glucose awareness training programs and novel methods of insulin replacement are being developed and evaluated (1–6). The question arises of how to identify those patients who most need support for and, if possible, relief from recurrent severe hypoglycemia (SH), which is defined as requiring help from others (7,8).

The results of the Diabetes Control and Complications Trial (DCCT) showed that tight glycemic control by means of intensified insulin treatment is effective in preventing and delaying microvascular complications of type 1 diabetes (7). In the DCCT, the subjects receiving intensified insulin treatment had a 3-fold increase in the incidence of SH compared with subjects treated conventionally (7,9). This substantially increased the awareness of the problem of hypoglycemia for both patients and health care workers.

In the intensified treatment group of the DCCT, several risk factors were shown to increase the risk of SH: previous episodes of SH, longer duration of diabetes, higher insulin dose at baseline, lower HbA_{1c} levels, and higher initial HbA_{1c} or a recent decrease in HbA_{1c}. Note that these risk factors were reported to explain only 8.5% of the variance in SH episodes (9).

We undertook a survey to estimate the frequency of SH and the proportion of SH episodes complicated by coma in a nonselected population of type 1 diabetic patients in daily clinical practice. We investigated the clinical and behavioral characteristics of patients who either had only a history of uncomplicated SH or who also had SH episodes complicated by coma during the previous year.

RESEARCH DESIGN AND METHODS

— All 224 consecutive type 1 diabetic patients visiting the outpatient diabetic clinic of the University Medical Center in Utrecht, the Netherlands, during a period of 6 weeks were considered for participation in the study. Eligible patients were asked to complete a set of questionnaires at that visit. Patients were excluded if insulin treatment had begun <18 months before or if the patient was unable to complete the questionnaires. Of 224 eligible patients, 13 (5.8%) were excluded, and 16 (7.1%) did not give consent to participate. Data for the remaining 195 participants are reported.

The study was approved by the Ethical Committee of the University Medical Center. Participants gave written informed consent after the nature of the study was explained to them.

SH was defined as all episodes for which help from others was required (8). SH was

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Abbreviations: DCCT, Diabetes Control and Complications Trial; OR, odds ratio; SH, severe hypoglycemia; SMBG, self-monitoring of blood glucose.

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

divided into uncomplicated SH (i.e., SH episodes not complicated by coma, seizure, or treatment with glucagon or intravenous dextrose) and hypoglycemic coma (i.e., SH complicated by coma, seizure, or treatment with glucagon or intravenous dextrose).

The data collected from the questionnaires addressed the following issues. First, the data included general characteristics such as self-care behavioral items, alcohol consumption, smoking habits, and exercise habits. Patients were divided into alcohol-using (≥2 alcohol-containing beverages/week) and non–alcohol-using subjects (≤1 beverage/week). Second, the data included the classification of hypoglycemia awareness according to Clarke et al. (10). In the present analyses, awareness was categorized into normal awareness (including inconclusive) and reduced awareness. Third, the occurrence of SH (all episodes) was noted during the previous year. Fourth, the data include the occurrence of hypoglycemic coma during the previous year. Finally, an adapted Hypoglycemia Fear Survey (11,12) was used. This survey consists of a Worry scale (maximum of 52 points on 13 items) concerning hypoglycemia-related anxiety and a Behavior scale (maximum of 40 points on 10 items) concerning hypoglycemia avoidance behavior.

Data concerning the following issues were obtained from the outpatient clinic chart blinded for the answers given in the questionnaires: diabetes duration, insulin treatment (intensive insulin treatment was defined as the administration of ≥3 insulin injections/day [basal-bolus regimen] or use of an external pump [7]), long-term diabetic complications, glycemic control (HbA_{1c} normal value 4–6%; the lowest level during the past 1.5 years was used because, in the DCCT, the risk for SH increased with lower HbA_{1c} values during treatment [9]), comorbidity, and comedication.

Long-term diabetic complications were categorized and defined as follows.

- Retinopathy (as determined by an ophthalmologist): none, background, preproliferative, and proliferative
- Nephropathy: none, microalbuminuria (30–300 mg/24 h or 20–200 mg/l at least once), and macroalbuminuria (≥300 mg/24 h or ≥200 mg/l at least once)
- Neuropathy: none, subclinical (abnormal vibration or thermic thresholds on biothesiometric examination), symptomatic (clinically apparent disturbance of sensory functions and/or tendon reflexes), and severe (ulcer and/or arthropathic changes and/or amputation) (13)
- Macrovascular: none, peripheral (clinical evidence and/or disturbance on Doppler ultrasound), and coronary (as determined by a cardiologist)

In the analyses shown, long-term complications were categorized into absent (none) and present (all other categories for that complication). In the main analysis, patients were divided into 3 groups: *1*) no SH, *2*) uncomplicated SH only, and *3*) at least 1 SH complicated by hypoglycemic coma, seizure, or treatment with glucagon or intravenous dextrose. Groups 2 and 3 were compared with group 1, which served as the reference group. If we consider groups 2 and 3 together, we use the term all patients with SH for the combined group.

Statistical analysis was performed using the statistical package SPSS Version 8.0 (SPSS, Chicago). Differences between groups were analyzed using the χ^2 test to compare proportions and unpaired Student's *t* test (and nonparametric tests if appropriate) to compare means. Adjusted odds ratios (ORs) and their 95% CIs were obtained by multiple logistical regression analysis of characteristics that may serve as predictor variables.

Because of the large number of variables included when exploring potential risk indicators for uncomplicated SH and hypoglycemic coma, respectively, only univariate associations with $P < 0.01$ are considered statistically significant. In the multiple logistical regression models, $P < 0.05$ was used as the level of significance.

RESULTS

Occurrence of SH

The characteristics of the study population are shown in the first column of Table 1. Of these type 1 diabetic patients, 40.5% reported at least 1 episode of hypoglycemia for which the assistance of another person was required during the previous year. Half of these subjects with SH (19% of the total) reported that 1 or more of their episodes had been complicated by coma or seizure or that they had received treatment with glucagon or intravenous dextrose. The total occurrence of SH episodes was 150 episodes/100 patient-years, including both uncomplicated SH and hypoglycemic coma. About one-quarter of the episodes was complicated by coma or seizure (40 episodes/100 patient-years).

Clinical risk indicators

Potential clinical risk indicators for uncomplicated SH and hypoglycemic coma are summarized in Table 1.

Demographics

Sex, age, mean age at onset of diabetes (20 ± 12 years), and BMI did not differ among the 3 groups.

Diabetes and treatment

Glycemic control in this population on average was fair, with a mean HbA_{1c} level of 7.8 ± 1.2% and an identical distribution of HbA_{1c} levels in the 3 groups (Table 1). The proportions of patients receiving intensive insulin treatment were similar. The duration of diabetes tended to be longer in the hypoglycemic coma group than in the group without SH (mean difference [95% CI] 4.9 years [0.2–9.5]; $P = 0.04$).

Complications

As shown in Table 1, the proportions of patients with long-term diabetic complications were higher in the coma group than in the patients without SH. This was only statistically significant for neuropathy ($P = 0.002$). The proportions of patients with micro- or macroalbuminuria, neuropathy, or macrovascular disease all tended to be higher in the coma group ($0.05 < P < 0.01$ after adjustment for diabetes duration).

Comedication and comorbidity

Comedication tended to be prescribed more often to patients with hypoglycemic coma compared with patients with no SH (70 vs. 48%, $P = 0.02$). No significant difference was evident in unrelated comorbidity.

More detailed analysis of the types of comedication showed a higher proportion of patients using β-blocking agents in the coma group than in the group without SH (14 vs. 2%, $P = 0.01$). All 5 patients with coma who were receiving β-blockers used nonselective β-blocking drugs, whereas the others used β_1-selective agents. For ACE inhibitors, benzodiazepines, antidepressants, diuretics, and salicylates, no significant differences among groups were detected, but group sizes were too small to allow for conclusions (data not shown).

Self-care behavior

Hypoglycemia avoidance behavior (measured with the Hypoglycemia Fear Survey Behavior scale), smoking (31%), caffeine-containing coffee drinking (≥5 cups/day in

34%), and regular exercise habits (46%) did not differ among groups.

Patients in the coma group tended to be more likely to start self-treatment of decreasing blood glucose levels earlier (already at levels of ≥4 mmol/l) than patients without SH (36 vs. 17%, $P = 0.02$) (Table 1). The coma group reported a significantly higher target as the lower limit of their treatment goals, which was reflected by a mean (95% CI) target blood glucose level of 5.5 mmol/l (4.9–6.2) compared with patients without SH and with uncomplicated SH who aimed for 4.5 mmol/l (4.3–4.7) and 4.6 mmol/l (4.2–5.0), respectively ($P = 0.005$ for coma vs. all others). The frequency of self-monitoring of blood glucose (SMBG) and the proportion of patients inclined to measure blood glucose levels at night (11%) were similar for the 3 groups.

The regular use of alcoholic beverages at an average of ≥2 beverages/week was reported by 69% of patients in the coma group and by 50% of all others ($P = 0.04$). Alcohol use in quantities >14 beverages/week was uncommon (6%) and was not related to SH.

Fear of hypoglycemia

Fear of hypoglycemia was a far heavier burden for patients with SH than for subjects who did not report any recent SH episodes ($P < 0.001$, no SH vs. all others).

Hypoglycemia awareness

The proportion of subjects categorized with reduced awareness was 51% in the group with hypoglycemic coma, 25% in the group with uncomplicated SH, and 9% in patients who did not report SH ($P < 0.001$).

Between patients who were aware and patients with reduced awareness, no differences were found regarding sex, age, level of glycemic control, duration of diabetes, comedication, comorbidity, and the presence of long-term complications (data not shown). A perceived threshold blood glucose level for hypoglycemic symptoms <3.0 mmol/l was reported more often by the uncomplicated SH group than by patients without any SH (40 vs. 18%, $P < 0.01$).

Multiple logistical regression analysis of potentially predictive risk indicators for uncomplicated SH and hypoglycemic coma

Uncomplicated SH was independently related to the following risk indicators after correction for diabetes duration and the use of any type of comedication: nephropathy (4.8 [1.5–15.1]), a threshold for hypoglycemic symptoms of <3 mmol/l (4.8 [1.8–12.0]), and a daily insulin dose 0.1 U/kg higher (1.3 [1.0–1.6]). After adjusting for diabetes duration, being in the coma group was independently related to the presence of neuropathy (3.9 [1.5–10.4]),

Table 1—*Clinical characteristics of 195 type 1 diabetic patients with no SH, uncomplicated SH, and hypoglycemic coma during the previous year*

	All patients	No SH	Uncomplicated SH	Hypoglycemic coma
n	195	114	44	37
Demographics				
Women	55	54	64	46
Age (years)	41 ± 14	40 ± 15	39 ± 12	44 ± 14
BMI (kg/m^2)	24.4 ± 3.0	24.9 ± 3.2	23.8 ± 2.4	23.7 ± 2.9
Diabetes/treatment				
HbA_{1c} (%)	7.8 ± 1.2	7.8 ± 1.2	7.7 ± 1.2	7.9 ± 1.3
HbA_{1c} distribution				
<7%	23	22	25	24
7–8%	37	38	45	27
>8%	40	40	30	49
Diabetes duration (years)	20 ± 12	19 ± 12	22 ± 10	24 ± 13
Intensive insulin treatment	82	81	86	81
Insulin dose/24 h (U/kg)	0.74 ± 0.24	0.71 ± 0.21	0.78 ± 0.23	0.79 ± 0.31
Complications				
Retinopathy	45	36	54	61
Nephropathy	19	12	26	31
Neuropathy	26	21	19	49‡
Macrovascular	12	8	12	25
Comorbidity/comedication				
Any comedication prescribed	54	48	57	70
Any comorbidity present	40	34	43	51
β-Blocking agents	4	2	2	14
Behavior				
Treating decreasing blood glucose at				
≥4 mmol/l	21	17	19	36
3–4 mmol/l	52	53	51	47
<3 mmol/l	27	30	30	17
Perceived treatment targets				
Upper limit blood glucose (mmol/l)	10.0 ± 1.8	10.0 ± 1.2	10.3 ± 2.3	10.7 ± 2.4
Lower limit blood glucose (mmol/l)	4.7 ± 1.4	4.5 ± 1.1	4.6 ± 1.3	5.5 ± 1.9*
SMBG frequency per week				
<7 times	37	35	39	41
7–21 times	40	43	39	35
≥21 times	23	22	22	24
Inclined to do SMBG at night	11	10	11	14
Alcohol intake ≥2 drinks/week	53	51	47	69
Fear of hypoglycemia				
Hypoglycemia Worry level†	14 ± 10	11.7 ± 9.2	16.5 ± 9.3*	17.3 ± 9.7*
Hypoglycemia awareness				
Reduced awareness (Clarke et al. [10])	21	9	25*	51‡
Threshold for symptoms <3.0 mmol/l	24	18	40*	27

Data are means ± SD or %. *P* values as compared with no SH. $P < 0.01$ is considered statistically significant. *$P < 0.01$; †Hypoglycemia Fear Survey Worry scale (points); ‡$P < 0.001$.

the use of (nonselective) β-blocking agents (14.9 [2.1–107.4]), and the use of alcohol (3.5 [1.3–9.1]). No other potentially predictive risk indicators independently contributed to explaining hypoglycemic coma or uncomplicated SH.

For patients regularly using alcohol (without neuropathy and not taking β-blockers) and for patients with neuropathy (no alcohol and no β-blockers), the predicted probabilities of having experienced at least 1 episode of hypoglycemic coma were 24.5 and 27%, respectively (observed probabilities: 13 of 59 [22%] and 4 of 17 [24%]). For alcohol-using patients with neuropathy (not taking β-blockers), the model predicted an average probability of being in the hypoglycemic coma group of 51% (observed probability: 9 of 19 [47%]).

CONCLUSIONS — SH and hypoglycemic coma are common complications of intensive insulin treatment. The overall incidence of SH of 150 episodes/100 patient-years affected 40.5% of this unselected population. This includes 40 episodes/100 patient-years of hypoglycemic coma, which affected 19% of this population. In comparison, in the DCCT, the intensively treated group reported an occurrence of 62 SH episodes/100 patient-years, including 16 episodes of hypoglycemic coma (7). A recent study reported an incidence of 16 episodes of hypoglycemic coma in 199 patients during a 3-month period when regular insulin was used as the mealtime insulin; this would be equivalent to 32 episodes/100 patient-years (14). The proportions of patients affected by SH (all episodes) (40.5%) and hypoglycemic coma (19%) in our study were in the same range as reported for the experimental group of the DCCT—namely 34 and 21%, respectively (9). Together with the proportions of the population affected, the occurrence rates of SH (all episodes) and hypoglycemic coma that we found illustrate the recurrent nature of SH during the study period when no specific programs to reduce SH were being applied. This recurrence of SH during the period under investigation (1 year) may indicate that SH itself contributed to an increased risk of subsequent SH, as reported previously (9).

Most studies describing the occurrence of SH have dealt with highly selected populations (e.g., the population recruited for the DCCT consisted of type 1 diabetic adults <40 years of age without advanced complications, comorbidity, or previous recurrent episodes of hypoglycemic coma [7,9]). In addition, discrepancies in definitions and assessments of SH and differences in diabetes management and patient education may explain differences in the occurrence of SH among various studies.

The conclusions that may be drawn from our observations are limited because the data were collected retrospectively and were partly self-reported. The results of this clinical survey do not allow for firm conclusions regarding whether the risk indicators that were identified for SH and hypoglycemic coma are predictive of future SH or rather reflect a response to SH. A threshold for symptoms at lower blood glucose levels may also be the result of recurrent previous hypoglycemia, which constitutes a vicious circle (15). Heightened fear of hypoglycemia, the inclination to treat decreasing blood glucose earlier, and the higher target for the lower limit of the treatment goals were considered to be most likely the result of having experienced SH or hypoglycemic coma; therefore, these variables were not included as predictor variables in the multiple logistical regression models.

Our studies suggest that the presence of long-term complications may serve as a useful clinical risk indicator of SH. This may have important implications for clinical practice. If complications have begun to appear (background or nonproliferative retinopathy), then the advantage of slowing progression by tightening glycemic control will presumably balance the increased risk of SH (7). On the other hand, in patients with severe and advanced long-term complications—especially nephropathy and proliferative retinopathy—the benefits of aiming for strict glycemic control to slow the progression or ameliorate the symptoms are questionable (15).

As reported previously, the characteristics of patients with impaired hypoglycemia awareness and patients who were aware were found to be largely similar (10). The increased proportions of patients with reduced awareness in the groups with uncomplicated SH and hypoglycemic coma are in accordance with a previous prospective study (10).

The results of this study support that the recognition of hypoglycemic symptoms and the timely treatment of decreasing blood glucose levels need to be optimized in patients with previous SH. This is consistent with a recent study demonstrating that patients with a history of SH during the previous year showed less effective behavior regarding preventing low blood glucose levels, recognizing decreasing blood glucose levels and self-treatment of hypoglycemia (16). In addition, patients experiencing SH may need support to deal with a heightened fear of hypoglycemia.

Although we often assume that alcohol consumption increases the risk of hypoglycemia in type 1 diabetes, little evidence supports this association (17,18). Results of the current study indicate an independently increased risk of hypoglycemic coma in patients consuming ≥2 alcoholic beverages/week. As reported previously, we found an increased risk of SH in patients using (nonselective) β-blocking agents (19,20).

Although determining whether long-term complications and a threshold for symptoms of <3.0 mmol/l contribute to the occurrence of SH or merely reflect a response to SH may be impossible, we speculate that their presence may be useful to predict an increased risk of future SH in clinical practice. Prudence in alcohol consumption and avoidance of nonselective β-blocking agents in type 1 diabetic patients seems to be advisable.

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