Hypoglycemia in Patients With Type 2 Diabetes Mellitus

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Background: Although hypoglycemia is the most common complication of intensive diabetes therapy, there is little information about risk factors for hypoglycemia in patients with type 2 diabetes mellitus.

Objective: To determine the prevalence and predisposing factors for hypoglycemia in patients with type 2 diabetes.

Methods: Retrospective, cross-sectional analysis set in an outpatient specialty diabetes clinic. We included those patients who had baseline and follow-up visits from April 1 through October 31, 1999. Hypoglycemia was defined as typical symptoms relieved by eating, and/or blood glucose level of less than 60 mg/dL (3.3 mmol/L). Univariate and multivariate logistic regression were used to determine the contributions to hypoglycemia of age, sex, diabetes duration, body mass index (calculated as weight in kilograms divided by the square of height in meters), fasting plasma glucose level, glycosylated hemoglobin (HbA1c) level, type of therapy, and previous episodes at the follow-up visit.

Results: We studied 1055 patients. Prevalence of hypoglycemic symptoms was 12% (9/76) for patients treated with diet alone, 16% (56/346) for those using oral agents alone, and 30% (193/633) for those using any insulin (P<.001). Severe hypoglycemia occurred in only 5 patients (0.5%), all using insulin. Multiple logistic regression analysis demonstrated that insulin therapy, lower HbA1c level at follow-up, younger age, and report of hypoglycemia at the baseline visit were independently associated with increased prevalence of hypoglycemia. There were no significant predictors of severe hypoglycemia.

Conclusions: Mild hypoglycemia is common in patients with type 2 diabetes undergoing aggressive diabetes management, but severe hypoglycemia is rare. Concerns about hypoglycemia should not deter efforts to achieve tight glycemic control in most patients with type 2 diabetes.

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Hypoglycemia is a significant complication of diabetes therapy. Although mild hypoglycemia causes unpleasant symptoms and disrupts patients’ daily activities, severe hypoglycemia can result in coma, seizures, and death. Moreover, recurrent episodes of mild hypoglycemia can alter the counterregulatory response to decreased blood glucose levels and lead to hypoglycemia unawareness, placing patients at increased risk for development of severe hypoglycemia. Recurrent hypoglycemia has also been found to decrease quality of life in patients with diabetes.

Although hypoglycemia is well recognized as a problem in management of type 1 diabetes mellitus, less is known about hypoglycemia in patients with type 2 diabetes mellitus. The Diabetes Control and Complications Trial (DCCT) found a 3-fold greater incidence of severe hypoglycemia in a group of patients with type 1 diabetes undergoing intensive treatment compared with those treated less aggressively. In contrast, the feasibility trial of the Veterans Affairs Cooperative Study on Glycemic Control and Complications in Type II Diabetes (VA CSDM) showed an increase in mild and moderate, but not severe, hypoglycemia in patients undergoing intensive treatment, whereas the Kumamoto study showed no increase in mild or severe episodes in patients with type 2 diabetes undergoing intensive treatment compared with those undergoing less intensive treatment. Although the United Kingdom Prospective Diabetes Study (UKPDS) showed an increase in hypoglycemia in patients with type 2 diabetes assigned to the intensive protocol arm, it was largely a study of monotherapy, and many patients had elevated glucose levels.

While these studies have assessed hypoglycemia in controlled research settings, there is little information on the frequency of hypoglycemia in typical clinical
METHODS AND RESEARCH DESIGN

SETTING

The study was conducted at the Diabetes Clinic of the Grady Health System, Inc, Atlanta, Ga. The clinic serves a predominantly African American population and provides care for approximately 900 new and 5000 returning patients each year. Plasma glucose level is measured at each visit, and glycosylated hemoglobin (HbA1c) level is determined onsite every 2 to 3 months. Patients are initially examined by a nurse provider who provides diabetes education and makes recommendations for changes in therapy. Patients then undergo reevaluation by an endocrinologist who makes final treatment decisions. The clinic management protocol emphasizes lifestyle modification and an attempt to reduce the use of pharmacologic agents during the first 2 months after initial presentation. If adequate glycemic control is not attained after 2 months, pharmacologic therapy is instituted (or increased), and the goal of near normoglycemia is pursued aggressively. Pharmacologic therapy is advanced using a stepped-care approach, beginning with a single oral agent (long-acting glipizide, glyburide, or metformin), and then progressing to combination oral agents, oral agents plus bedtime insulin, and finally multiple-dose insulin regimens. The goal for glycemic control is HbA1c level of less than 7.0%.

DESIGN

We examined patient visits from April 1 through October 31, 1999. Patients were included in the analysis if they had received a diagnosis of type 2 diabetes mellitus (by clinical criteria described previously), had been followed up in the Diabetes Clinic for at least 2 months (to avoid the period of deintensification of therapy), and had had at least 2 visits during the study period (baseline and study follow-up visits). Data from the baseline visit were collected to allow hypoglycemia at baseline to be assessed as a contributing factor to hypoglycemia at follow-up. The prevalence of hypoglycemia and other information presented in the results are based on data collected at the follow-up visit.

Data from every patient visit at the Grady Diabetes Clinic are entered into a computerized registry. These data include information on demographics, laboratory test values, current diabetes therapy, and any changes in therapy made at the visit. Answers to the following questions about hypoglycemia are also entered into the database: (1) How many times was your blood glucose level low since the last visit? (2) What was the lowest home glucose monitoring value obtained during these episodes? (3) Were there symptoms associated with these episodes? and (4) How many times did you need help from someone else to treat your low blood glucose level? Hypoglycemia was thus assessed at baseline and follow-up visits.

DEFINITION OF HYPOGLYCEMIA

For purposes of the analysis, mild hypoglycemia was defined as patient report of typical symptoms of hypoglycemia (eg, sweating, tremulousness, hunger, and/or dizziness) that were relieved by eating, or patient report of home glucose monitoring values of less than 60 mg/dL (<3.3 mmol/L). The cutoff blood glucose level of 60 mg/dL (3.3 mmol/L) was selected to define biochemical hypoglycemia because it is the approximate level at which counterregulatory systems are normally activated and nondiabetic individuals may begin to experience neuroglycopenic and adrenergic symptoms characteristic of hypoglycemia. To estimate the prevalence of biochemical hypoglycemia that would have been obtained if all patients had monitored their capillary blood glucose level during reported symptoms, the number of patients reporting blood glucose levels of less than 60 mg/dL (<3.3 mmol/L) during symptoms was divided by the number of patients reporting any glucose measurement during symptoms. This proportion was then multiplied by the total prevalence of reported hypoglycemic symptoms to yield an estimated prevalence of biochemical hypoglycemia. Severe hypoglycemia was defined as loss of consciousness or other major alteration of mental status caused by hypoglycemia that required the assistance of another person to treat the condition.

At clinic visits, plasma glucose levels were measured using the glucose oxidase method. We measured HbA1c level using a turbidimetric immuno-inhibition assay (reference range, 3.5%-6.0%) (Roche, Basel, Switzerland).

ANALYSIS

Statistical analysis was conducted using commercially available software (Statview 5.0; SAS Institute Inc, Cary, NC). We used analysis of variance and unpaired 2-tailed t tests to compare means between subgroups of patients and χ² analysis to compare frequency of events between groups. We performed univariate and multivariate logistic regression to determine clinical predictors of hypoglycemia. P<.05 was considered significant.

RESULTS

A total of 2279 patients had visits during the study period. Of these, 1022 patients (44.8%) had only a baseline visit and therefore were not included in the study. Patients who had only a baseline visit were not significantly different from those with baseline and follow-up visits, except that they were slightly younger (59.4 vs 61.0 years; P=.002) and had slightly lower fasting plasma glucose values (154 vs 168 mg/dL [8.6 vs 9.3 mmol/L]; P=.01). There was no difference in the prevalence of hypoglycemia between the groups at the baseline visit. Of the 1257 patients with a baseline and a follow-up visit, 202 (16.1%)...
had incomplete hypoglycemia data and were excluded. Compared with those who were included in the study, these patients had shorter duration of diabetes (9.4 vs 10.8 years; *P* = .03) and higher fasting plasma glucose values (168 vs 154 mg/dL [9.3 vs 8.6 mmol/L]; *P* = .01).

A total of 1055 patients were included in the study. Data on patient demographics, glycemic control, and distribution of type of diabetes therapy are shown in Table 1 and Table 2. Patients were predominantly female and nearly all were African American. Patients had an average age of 61 years, average body mass index (BMI; calculated as weight in kilograms divided by the square of height in meters) of 33, average fasting plasma glucose level of 152 mg/dL (8.4 mmol/L), and average HbA1c level of 7.6%. Average HbA1c level was significantly lower in patients whose diabetes was managed by means of diet alone (6.0%) compared with those managed by means of oral agents alone (7.0%) or insulin (8.1%) (*P* < .001). Most patients (92.7%) were treated with some form of pharmacologic therapy, and 60.0% were treated with insulin (alone or in combination with oral hypoglycemic agents). Long-acting glipizide accounted for 85.6% (326/381) of sulfonylurea use, glyburide for 14.2% (326/381) of sulfonylurea use, metformin for 15.7% (60/381), and glimepiride for 0.3% (1/381). Patients had a higher prevalence of hypoglycemia than patients in the diet-only group (30.5% [193/633] vs 11.8% [9/76]; *P* < .001), and patients treated with a combination of insulin, metformin, and sulfonylurea (triple therapy) had a 2-fold increase in any hypoglycemia compared with other patients treated with insulin (61.5% [8/13] vs 29.8% [185/620]; *P* = .01).

Results of capillary home blood glucose monitoring values at the time of reported hypoglycemia obtained in 46.1% of patients. Those who reported monitoring of capillary blood glucose levels during hypoglycemia were slightly older (61 vs 58 years; *P* = .04) and had lower HbA1c levels (7.1% vs 7.7%; *P* = .01) than those who did not, but otherwise there were no significant differences between the 2 groups. There was also no significant difference in the proportion of patients reporting a blood glucose level measurement during hypoglycemic symptoms among those treated with diet alone (5/9 [55.6%]), oral agents alone (30/56 [53.6%]), insulin, and a single oral agent (79/185 [42.7%]), or triple therapy (5/8 [62.5%]) (*P* = .35). Blood glucose level readings during the reported hypoglycemia ranged from 17 to 75 mg/dL (0.9-4.2 mmol/L), with a median of 55 mg/dL (3.1 mmol/L) (Figure 2); 74 (62.2%) of 119 readings were less than 60 mg/dL (3.3 mmol/L). Patients treated with pharmaco-
logic therapy tended to have lower reported blood glucose values during hypoglycemia than did those treated with diet alone ($P = .06$, Kruskal-Wallis test), whereas patients treated with diet alone reported significantly fewer values of less than 60 mg/dL ($<3.3$ mmol/L) than did those treated with pharmacologic agents (20.0% [1/5] vs 64.0% [73/114]; $P = .047$). Only 1 blood glucose value in the diet-only group was less than 60 mg/dL (3.3 mmol/L), indicating that most patients treated with diet alone did not have biochemical hypoglycemia.

Since the report of hypoglycemia in each group of patients includes subjects with measured blood glucose levels of at least 60 mg/dL ($\geq 3.3$ mmol/L), we estimated the prevalence of biochemical hypoglycemia that would have been obtained if all patients had monitored their glucose values during symptoms. The estimated prevalence of biochemical hypoglycemia was 2.4% for patients treated with diet alone (among the 11.8% of diet-treated patients reporting hypoglycemia), 1 of the 5 patients undergoing glucose level measurement during symptoms reported glucose levels of $<60$ mg/dL ($<3.3$ mmol/L). The estimated prevalence of biochemical hypoglycemia was 9.4% for patients treated with oral agents alone (among the 16.2% of patients reporting hypoglycemia), 18 of the 31 patients undergoing glucose level measurement during symptoms reported glucose levels of $<60$ mg/dL ($3.3$ mmol/L), and 19.9% for patients treated with insulin (among the 30.5% of patients reporting hypoglycemia), 58 of the 89 patients undergoing glucose level measurement during symptoms reported glucose levels $<60$ mg/dL ($3.3$ mmol/L).

An associated cause was reported by 147 (57.0%) of 258 patients who reported hypoglycemia. The most common event associated with hypoglycemia was a missed meal (119 patients [80.9%]), followed by use of medications in doses greater than those prescribed (8 patients [3.4%]), exercise (5 patients [3.4%]), and other (12 patients [8.2%]). There were no differences between groups as to the events associated with hypoglycemia.

Univariate logistic regression demonstrated that patients treated with insulin were more likely to report hypoglycemia than patients in other treatment groups ($P = .001$). Similarly, patients who reported any hypoglycemia at the baseline visit were more likely to report hypoglycemia at the follow-up visit ($P < .001$). In addition, fasting plasma glucose level at the time of the follow-up visit and being in the highest age quartile (age $>70$ years) were negatively correlated with any hypoglycemia ($P < .001$ and $P = .03$, respectively). Race, sex, duration of diabetes, BMI, and follow-up HbA1c level were not predictors of hypoglycemia by univariate analysis. We also performed multiple logistic regression analysis, which showed that lower follow-up HbA1c level ($P = .006$), use of any insulin therapy ($P = .005$), younger age ($P = .04$), and report of hypoglycemia at the baseline visit ($P < .001$) were all independent predictors of any hypoglycemia at the follow-up visit (Table 3). Race, sex, duration of diabetes, BMI, and whether diabetes medication therapy was increased at the baseline visit did not predispose to hypoglycemia. Figure 3 shows the relationship between follow-up HbA1c values and the prevalence of hypoglycemia in patients receiving different types of diabetes therapy, illustrating the trend toward increasing prevalence of both reported and estimated biochemical hypoglycemia with decreasing HbA1c level.

Severe hypoglycemia was rare and was reported by only 5 patients (0.5%) at the follow-up visits studied (Table 4). Patients 1 and 2 suffered loss of consciousness and required transport to the emergency department by emergency medical services (EMS). Patients 3 and 4 were taken to the emergency department by EMS but did not lose consciousness, and patient 5 was treated at home by EMS without loss of consciousness. Age, sex, race, diabetes duration, BMI, follow-up fasting

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**Table 3. Results of Multiple Logistic Regression Analysis for Predicting the Occurrence of Any Hypoglycemia**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio (95% Confidence Interval)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constant</td>
<td>1.42</td>
<td>. .</td>
</tr>
<tr>
<td>Age per year</td>
<td>0.98 (0.97-1.00)</td>
<td>.03</td>
</tr>
<tr>
<td>Male sex</td>
<td>0.81 (0.55-1.19)</td>
<td>.25</td>
</tr>
<tr>
<td>Race†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>1.15 (0.43-3.08)</td>
<td>.78</td>
</tr>
<tr>
<td>Hispanic</td>
<td>0.68 (0.13-3.62)</td>
<td>.65</td>
</tr>
<tr>
<td>Other</td>
<td>1.34 (0.38-4.72)</td>
<td>.65</td>
</tr>
<tr>
<td>Diabetes duration, per year</td>
<td>0.99 (0.97-1.01)</td>
<td>.55</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>0.99 (0.97-1.01)</td>
<td>.31</td>
</tr>
<tr>
<td>HbA1c at follow-up visit (per 1% increase)</td>
<td>0.67 (0.78-0.96)</td>
<td>.008</td>
</tr>
<tr>
<td>Sulfonylurea therapy at follow-up visit</td>
<td>1.54 (0.95-2.52)</td>
<td>.08</td>
</tr>
<tr>
<td>Insulin therapy at follow-up visit</td>
<td>3.44 (2.07-5.73)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Had hypoglycemia at baseline</td>
<td>2.65 (1.80-3.80)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Medicinal therapy increased at baseline</td>
<td>1.00 (0.69-1.44)</td>
<td>&gt;.99</td>
</tr>
</tbody>
</table>

*BMI indicates body mass index; HbA1c, glycosylated hemoglobin level.
†Based on comparison with African American patients.
plasma glucose level, follow-up HbA1c level, type of diabetes therapy, hypoglycemia at the baseline visit, and whether diabetes medication therapy was increased at the baseline visit were not significant predictors of severe hypoglycemia by univariate or multivariate logistic regression.

COMMENT

In this cross-sectional study, we found a high prevalence of any form of reported hypoglycemia in an urban African American population with type 2 diabetes (24.5%), but a low prevalence of severe hypoglycemia (0.5%). As expected, the prevalence of any hypoglycemia was dependent on type of diabetes therapy. Patients receiving triple therapy had the highest prevalence, followed by those receiving insulin therapy alone or with a single oral agent, those receiving oral hypoglycemic agents alone, and those receiving diet therapy alone. It is not clear why those patients receiving triple therapy had such a high prevalence of hypoglycemia. Although mean HbA1c level for the group was not unusually low (7.4%), it may be that these patients represent a group whose diabetes is more difficult to manage. In all treatment groups, the prevalence of any hypoglycemia tended to increase as HbA1c level decreased. The highest prevalence was seen in patients receiving insulin therapy who had an HbA1c level of less than 7.0%.

Surprisingly, 9 (11.8%) of the 76 patients treated with diet alone reported some hypoglycemic symptoms, although only 1 patient reported biochemical hypoglycemia. Measurement error may explain the apparent biochemical hypoglycemia in the single patient reporting a blood glucose level of 42 mg/dL (2.3 mmol/L) during symptoms, as such low glucose levels were not reported by this patient at subsequent visits. It is possible that the hypoglycemia-like symptoms reported by some diet-treated patients were unrelated to low blood glucose levels and were, instead, nonspecific symptoms, perhaps related to hunger or anxiety. All patients who attend the Grady Diabetes Clinic are instructed about symptoms of hypoglycemia, including patients treated with diet. In addition, 47 (61.8%) of the 76 patients treated with diet alone at the time of the study had previously been treated with pharmacologic agents and might have experienced hypoglycemia before. Pohl et al18 studied nondiabetic subjects who underwent insulin-induced hypoglycemia and then were told they were to receive a second insulin injection but were actually given isotonic sodium chloride solution; such subjects reported more neuroglycopenic symptoms than did those who had been told they were to receive a second injection of isotonic sodium chloride solution. A similar phenomenon of expectant hypoglycemia might occur in diet-treated patients who are warned about hypoglycemia, particularly those who had been receiving pharmacologic therapy in the past.

Another interesting finding was that older age did not predispose patients to hypoglycemia in our population, although previous reports have suggested that older age is associated with hypoglycemia.19,20 Although older patients in our study were less likely to receive insulin therapy (potentially making their risk for hypoglycemia lower), they also had lower average HbA1c levels (potentially making their risk higher). Several factors may contribute to lower prevalence of hypoglycemia in older patients. First, activity levels in the elderly are likely to be lower than those in younger patients, making exercise-associated hypoglycemia less likely. Second, eating habits may be more regular in the elderly, so that missed meals causing hypoglycemia are less of a problem. Older patients may also have atypical symptoms21 or be less symptomatic during mild hypoglycemia, and therefore not report as many episodes. Nevertheless, as life expectancy increases, older patients should benefit more from good glycemic control, and fear of hypoglycemia should not discourage attempts at achieving American Diabetes Association goals in the elderly.

The small number of patients with severe hypoglycemia made it difficult to establish significant predic-
regression also showed lower HbA1c levels and a report accordingly, our results also support those of Jennings et al,24 although patients treated with oral agents in our study comparable to the prevalence in diet-treated patients. Accordingly, our results also support those of Jennings et al,24 although patients treated with oral agents in our study had an average HbA1c level of 7.0% vs 11.0% in theirs (ref-

Hypoglycemia can be an important limiting factor in the treatment of patients with type 2 diabetes. Our results suggest that aggressive management aimed at achieving near-normal glucose levels is associated with increased risk for hypoglycemia as HbA1c level approaches the American Diabetes Association goal of less than 7.0%. However, fear of severe hypoglycemia should not deter the attempt to achieve tight glycemic control. Those patients who are younger or have a lower HbA1c level may be at higher risk for hypoglycemia and should be encouraged to be more diligent about meal planning, home monitoring of glucose levels, and symptom awareness. Finally, older patients may not be particularly prone to hypoglycemia and therefore should not be disqualified from intensive control of blood glucose level on the basis of risk for hypoglycemia alone.

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Correction

Errors in “Comment” Section. In the original investigation by Jacobsen et al titled “Increase in Weight in All Birth Cohorts in a General Population,” published in the February 12 issue of the ARCHIVES (2001;161:466-472), an error occurred in the “Comment” section on page 469. The fifth sentence in the second paragraph should have read: “The cross-sectional and longitudinal results are compatible in that younger men have a larger increase in BMIs than older men.” Also, on page 472 the reference number in the fifth sentence of the second paragraph should have been 13 (Midthjell et al) and not 11 (Jacobsen and Thelle).