

Severe Hypoglycemia in Type 2 Diabetes : A Hospital-based Retrospective Study

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Abstract

Background and Purpose : For patients with diabetes, severe hypoglycemia has a significant economic impact and adverse effect on quality of life. The aim of this study was to assess the incidence of and risk factors for severe hypoglycemia among patients with type 2 diabetes. **Methods** : We evaluated a cohort of 1195 patients with type 2 diabetes followed in the outpatient clinic of Mackay Memory Hospital, Taitung, Taiwan from January 1 through December 31, 2004. Medical records were retrospectively reviewed for demographics, medical history, duration of diabetes, results of laboratory tests, and current diabetes therapy. We used univariate and multivariate logistic regression to determine risk factors for severe hypoglycemia. **Results** : The overall incidence of severe hypoglycemia was 7.4%. Patients on insulin therapy had higher incidence than patients on oral hypoglycemic agents alone (17.8% vs. 6.3% $P < 0.001$). Multiple logistic regression showed that the risk of severe hypoglycemia increased with older age ($P < 0.001$), lower educational level ($P = 0.02$), HbA_{1c} level lower than 7.0% ($P < 0.001$), current insulin therapy ($P < 0.001$), and impaired renal function ($P = 0.01$) **Conclusion** : Older age, lower educational level, HbA_{1c} ≤ 7 , current insulin therapy and impaired renal function are risk factors of severe hypoglycemia in type 2 diabetes. (J Intern Med Taiwan 2006; 17: 73-77)

Key Words : Severe hypoglycemia, Risk factors, Type 2 diabetes

Introduction

Hypoglycemia is the most common endocrine emergency. It has a significant economic impact and impairs quality of life in patients with diabetes¹. Mild hypoglycemia induces unpleasant symptoms and emotional distress². However, severe hypoglycemia

may cause profound brain dysfunction³ and may be associated with fatal vascular events, such as myocardial infarction, stroke, and cardiac arrhythmias⁴⁻⁶.

Hypoglycemia is common in type 1 diabetes, with mild, self-treated episodes occurring as frequently as 1 to 2 episodes a week. The incidence of severe hypoglycemia in type 1 diabetes ranges from

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0.62 to 1.6 episodes per patient per year⁷⁻⁹. In people with type 2 diabetes, though, the frequency of severe hypoglycemia is generally considered to be low^{10,11}. Nevertheless, it may be becoming more common. The Diabetes Control and Complications Trial (DCCT) and United Kingdom prospective Diabetes Study (UKPDS) trials in type 1 and type 2 diabetes have proved that the risk of vascular complications is strongly correlated with HbA_{1c} levels and the duration of poor glycemic control. Extensive evidence supports the efficacy of intensive glucose management in decreasing micro- and macrovascular complications^{8,11}. Stricter glucose control goals and earlier introduction of insulin in type 2 diabetes lead to a consequent increase in the risk of severe hypoglycemia¹². However, there is little information on the frequency of and risk factors for severe hypoglycemia in type 2 diabetes in the typical clinical practice setting. Moreover, less is known about hypoglycemia in minority populations with low literacy levels, where tight glycemic control might be more difficult to attain. The aim of this study was to assess the incidence of and risk factors for severe hypoglycemia among patients with type 2 diabetes treated in the outpatient center of a regional hospital in Taitung, Taiwan.

Methods

Study Design

We examined records from the outpatient clinic of Mackay Memory Hospital Taitung, Taiwan from January 1 through December 31, 2004. We studied a cohort of 1442 adults with type 2 diabetes mellitus (diagnosed according to American Diabetes Association criteria¹³) who had at least 3 outpatient appointments during the study period. Their medical records were reviewed for demographics, medical history, duration of diabetes, results of laboratory tests, and current diabetes therapy. Severe hypoglycemia was defined as loss of consciousness or other major alteration of mental status requiring the assistance of another person for reversal. Impaired re-

nal function was defined as a creatinine clearance of less than 80 mL/min, as estimated using the Cockcroft-Gault formula¹⁴. Patients' educational level was stratified to two levels with the cut-point at the beginning of junior high school. Type of therapy was classified to diet, oral hypoglycemic agents and insulin three groups. In insulin group we included patients prescribed with insulin alone or both insulin and oral hypoglycemic agents. HbA_{1c} levels were categorized as $\leq 7\%$ and $> 7\%$. We measured HbA_{1c} level using an Affinity High Performance Liquid Chromatography (HPLC) assay (Primus CLC-385, reference range 4.5% to 5.7%).

Statistical analyses

Descriptive statistics included means, standard deviation, and percentages. We performed an unpaired 2-tailed t-test to analyze continuous variables and a Wald z-test for categorical variables. We used univariate and multivariate logistic regression to determine the risk factors for severe hypoglycemia. Statistical analysis of the data was performed using Stata version 8.0 (Stata Corporation, Texas, USA).

Results

A total of 1195 patients were included in this study, 247 excluded because of incomplete demographic or laboratory data. The subjects were predominantly non-aboriginal, with males and females almost equally represented. The majority (757/1195, 63.3%) were either illiterate or had only an elementary school education, and four fifths of the patients were being treated with oral hypoglycemic agents (Table 1).

The mean HbA_{1c} level was significantly lower in patients whose diabetes was managed by means of diet alone ($6.1\% \pm 0.7$), followed by those managed with oral agents alone ($7.6\% \pm 1.8$), or with insulin ($8.1\% \pm 2.0$). The incidence of severe hypoglycemia was 7.4% (88 of 1195). Patients receiving insulin therapy had a higher incidence than did patients on oral agents alone (23/129, 17.8% vs. 65/1036, 6.3%, $P < 0.001$). None of 30 patients treated with diet alone

had severe hypoglycemia.

By univariate logistic regression, age ($P < 0.001$), educational level ($P < 0.001$), HbA_{1c} ($P < 0.001$), insulin therapy ($P < 0.001$), and renal dysfunction ($P < 0.001$) were associated with severe hypoglycemia (Table 1). Significant risk factors by multiple logistic regression included older age ($P < 0.001$), lower educational level ($P = 0.02$), HbA_{1c}

level lower than 7.0% ($P < 0.001$), current insulin therapy ($P < 0.001$) and impaired renal function ($P = 0.01$). After insulin therapy and a lower HbA_{1c}, the highest odds ratios (OR) were associated with renal impairment (2.46, 95% CI 1.21 to 4.99) and lower educational level (OR 2.16, 95% CI 1.14-4.12) (Table 2).

Table 1. Demographic and clinical Characteristics of study cohort and univariate analysis on risk of severe hypoglycemia

	No.(%)	P-value
Total	1195	
Age, mean \pm SD	61.9 \pm 12.1	<0.001
Diabetes duration, mean \pm SD	7.1 \pm 5.0	0.39
Gender		0.08
Female	598 (50%)	
Male	597 (50%)	
Ethnicity		0.39
Aborigines	217 (18.2%)	
Non-aborigines	978 (81.8%)	
Education Level		<0.001
< Junior high school	757 (63.3%)	
\geq Junior high school	438 (36.7%)	
HbA _{1c}		<0.001
\leq 7%	510 (42.7%)	
> 7%	685 (57.3%)	
Impaired renal function	65 (5.4%)	<0.001
Type of diabetes therapy		<0.001*
Diet alone	30 (2.5%)	
Oral hypoglycemic agents	1036 (86.7%)	
Insulin	129 (10.8%)	

*Type of diabetes therapy: insulin vs. oral hypoglycemic agents

Table 2. Risk factors for severe hypoglycemia by multivariate analysis

	Odds Ratio (95% CI)	P-value
Age by annual increments	1.03 (1.01-1.06)	<0.001
Diabetes duration by annual increments	0.97 (0.93-1.02)	0.29
Gender	0.85 (0.53-1.36)	0.49
Ethnicity	1.08 (0.56-2.08)	0.82
Educational level, < Junior high school vs. \geq Junior high school	2.16 (1.14-4.12)	0.02
HbA _{1c} , \leq 7% vs. > 7%	3.60 (2.14-6.03)	<0.001
Type of diabetes therapy, insulin vs. oral hypoglycemic agents	5.26 (2.83-9.78)	<0.001
Impaired renal function	2.46 (1.21-4.99)	0.01

Discussion

In our study, we found an overall incidence of severe hypoglycemia of 7.4%, but it varied with the type of diabetes therapy. Patients receiving insulin had a higher incidence than did patients on oral agents alone (17.8% vs. 6.3%). A population-based study reported the incidence of severe hypoglycemia in type 2 diabetes was 7.3% with insulin and 0.8% with oral agents¹². Christopher et al reported among 1055 patients with type 2 diabetes in a diabetes center a 0.5% incidence of severe hypoglycemia with insulin and none with oral agents¹⁵. The latter study more closely resembled our study which was also in a specific clinical practice setting. Although this study was limited by retrospective nature and we may miss severe hypoglycemic episodes that were not treated at our hospital. Incidence of severe hypoglycemia could be underestimated. However, the overall incidence of severe hypoglycemia in our series was considerably higher. Also our results paralleled the other in that severe hypoglycemia was more common in insulin-treated patients than in those treated with oral agents or diet alone.

As in previous investigations¹⁶⁻¹⁸, our study demonstrated that older age increased the risk for severe hypoglycemia. There are several possible explanations for this finding. First, ageing per se modifies the counterregulatory hormone and symptom responses to hypoglycemia, resulting in a loss of adrenergic symptoms¹⁹. Second, inconsistent eating patterns or missed meals are not uncommon in elderly²⁰. Third, age-associated decreases in hepatic oxidative enzyme activity may interfere with the metabolism of oral hypoglycemic agents²¹. Finally, older patients may be more likely to have impaired renal function, which we found to be an independent risk factor for severe hypoglycemia. We did not, however, find a direct correlation between age and renal dysfunction. Several mechanisms for the development of hypoglycemia in the setting of renal insufficiency have been proposed, including reduction of renal gluconeogenesis and decreased clearance of insulin and oral hypoglycemic agents^{22,23}.

Low literacy is an important barrier to good care for patients with diabetes^{24,25}. Our study documented this as a risk factor for severe hypoglycemia, one that is presumably modifiable. Better communication and patient education materials appropriate to patients' literacy level would be expected to reduce the risk. Such methods need to be developed and tested to ensure that optimal care is provided regardless of educational level.

Not surprisingly, the incidence of severe hypoglycemia increases as mean HbA_{1c} levels fall²⁶. We found the risk increased as the HbA_{1c} level approached the American Diabetes Association goal of less than 7.0%. The patients who have a lower HbA_{1c} level should be encouraged to be more diligent about meal planning, flexible insulin and other drug regimens and frequent self-monitor blood sugar.

The incidence of severe hypoglycemia in this study appeared to be higher than that reported elsewhere, although the risk factors we identified are similar to those identified by other investigators.

Identifying patients at risk for severe hypoglycemia is essential if we are to develop better strategies to prevent this complication of treatment for diabetes.

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一區域醫院第2型糖尿病人嚴重低血糖之研究

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摘 要

嚴重低血糖常影響糖尿病人生活品質，而且加重其經濟負擔。本回溯性研究針對2004年1月至12月在台東馬偕紀念醫院門診追蹤之1195位第2型糖尿病人，依個人資料、生化數據及處方藥物，統計其嚴重低血糖之發生率，並以單變項及多變項回歸分析相關危險因子。結果顯示嚴重低血糖之總發生率為7.4%，使用胰島素治療之病患嚴重低血糖發生率高於只使用口服降血糖藥物者(17.8% vs. 6.3% $P < 0.001$)。而年紀大($P < 0.001$)、低教育程度($P = 0.02$)、糖化血色素低於7($P < 0.001$)、是否使用胰島素治療($P < 0.001$)及腎功能不全者($P = 0.01$)較易發生嚴重低血糖。