

Impaired Awareness of Hypoglycemia in Insulin-Treated Patients with Type 2 Diabetes

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Abstract

Impaired Awareness of Hypoglycemia (IAH) is associated with Severe Hypoglycemia (SH). This study investigated the actual state of hypoglycemia, including IAH, in patients with Type 2 Diabetes. A questionnaire survey on hypoglycemia and patient-physician communication was conducted in 331 patients with insulin-treated Type 2 Diabetes patients at 16 hospitals and clinics. The rate of IAH was 22.1%. Glycemic control at an HbA1c level <7.0% was a significant risk factor of IAH (odds ratio (OR): 2.12; 95% Confidence Interval (CI): 1.22-3.68; P =0.01), along with a male sex and lower body mass index. Concerning talking about hypoglycemia with physicians, patients with IAH showed a similar frequency of talking with physicians as patients without IAH, while patients with SH communicated more frequently than those without SH. Considering the prevalence of IAH, physicians should be conscious of the IAH-associated factors and talk more about hypoglycemia.

Keywords: Type 2 Diabetes; Hypoglycemia; Impaired awareness

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Introduction

The prevalence of Type 2 Diabetes is globally increasing, and the International Diabetes Federation has

predicted that the number of people with diabetes will increase from 366 million to 552 million by 2030 [1]. In Japan, the estimated number of people with diabetes was approximately 6.9 million in 1997, 7.4 million in 2002, and 8.9 million in 2007 [1]. Severe Hypoglycemia (SH) is associated with a higher risk of cardiovascular disease-related mortality and morbidity [2, 3].

Impaired Awareness of Hypoglycemia (IAH) in insulin-treated patients with Type 2 Diabetes has been reported to be associated with the presence of SH [4]. However, little is known regarding the actual states of hypoglycemia, including IAH, in Japan. The aim of the study was therefore to survey the states of hypoglycemia and patient-physician communication among insulin-treated patients with Type 2 Diabetes.

Materials and Methods

Subjects

We recruited 331 adult patients with Type 2 Diabetes at 16 hospitals and clinics nationwide in Japan. Inclusion criteria were: 1) over 20 years, 2) Type 2 Diabetes, 3) insulin treatment, 4) patients regularly attended the surveyed hospitals and clinics. Exclusion criteria were: 1) children and young patients under 20 years old, and 2) Type 1 Diabetes mellitus.

Ethics

The study was approved by the ethical committee at National Hospital Organization Kyoto Medical Center.

Study measures

Clinical data such as the insulin regimen and diabetic complications were collected from their physicians. The self-administrated questionnaire was distributed and retrieved between 2006 and 2010. Patients completed the questionnaire to assess hypoglycemia and patient-physician communication. Hypoglycemia was defined as blood sugar ≤ 50 mg/dL (2.8 mmol/L) or symptoms of dizziness, blurry vision, confusion, and/or sweating that the patient was able to resolve without assistance [5, 6]. Similar symptoms that required external assistance were defined as SH [7, 8]. IAH was based on a

patient's ability to recognize hypoglycemia on the basis of symptoms, defining the answer categories of "never," "seldom," and "sometimes" as impaired, and "often" and "always" as normal hypoglycemia awareness [9]. Favorable glycemic control to prevent diabetic complications was defined as HbA1c < 7% [10] according to "Kumamoto declaration 2013". Current smoking and alcohol drinking were recorded as previously shown [11]. Patient-physician communication regarding hypoglycemia and strategies to avoid it was based on the answer categories "never" and "seldom" as poor communication, and "sometimes" and "often" as favorable communication, in response to "how often do you talk about hypoglycemia and strategies to avoid it with your physician?"

Statistics

Data are presented as the mean $\pm$ standard deviation or percentage. Student's t-test or the chi-square test was used to compare data between the groups. A stepwise logistic regression analysis model was used to identify the significant factors. The Statistical Package for the Social Sciences (SPSS ver. 20.0, IBM Corp., New York, USA) was used for these analyses. A two-tailed p-value < 0.05 was considered significant.

Results

The rate of IAH was 22.1%. There were no significant differences in clinical characteristics, such as the age, diabetes duration, prevalence of hypoglycemia, insulin regimen, and diabetic complications, between patients with and without IAH (Table1). The rates of alcohol drinking and smoking in males were significantly higher than in females (22.5 vs. 1.4%; $p < 0.01$, and 30.9 vs. 12.2%; $P < 0.01$, respectively). A stepwise logistic regression analysis revealed that glycemic control at an HbA1c level < 7.0% was a significant risk factor of IAH (odds ratio (OR): 2.12; 95% Confidence Interval (CI): 1.22-3.68; $P = 0.01$), along with a male sex (OR: 1.89; 95% CI: 1.06-3.38; $P = 0.03$) and a BMI level (OR: 0.89; 95% CI: 0.82-0.97; $P = 0.01$). Concerning talking about hypoglycemia with physicians, patients with IAH showed a similar frequency of talking with physicians as patients without IAH (76.1 vs. 71.4%; $P = 0.44$, respectively), while patients with SH

communicated more frequently than those without SH (90.9 vs. 70.3%; $P = 0.01$, respectively).

Discussion

Main findings

An acquired complication of insulin therapy is IAH, whereby the ability to perceive the onset of hypoglycaemia often becomes diminished or absent [12]. While the prevalence of IAH was lower than that in previous studies of patients with Type 1 Diabetes [13], the current survey showed that IAH is not uncommon in insulin-treated patients with Type 2 Diabetes in Japan. Although tight glycemic control with insulin treatment is crucial for preventing diabetic complications, the risk of hypoglycemia increases [10, 14]. The current survey found that a male sex, higher BMI, and lower HbA1c levels were significantly correlated with IAH. A previous study of a French population (including patients with Type 1 and 2 Diabetes) described that aging, a higher BMI, and lower HbA1c levels were significantly correlated with IAH [15]. The results of the association between IAH and HbA1c levels observed in the current survey are consistent with those of that study [15], while the result regarding the BMI was opposite to that of the previous study [15]. Such contradictory results regarding the association between IAH and BMI could not be explained in this survey. Because the BMI levels are inversely associated with the β -cell function, and insulin secretion function, in Asian populations [16], an impaired β -cell function may increase the risk of IAH in insulin-treated populations with Type 2 Diabetes. The reason why a male sex is an independent risk factor for IAH is unclear, but one of the common causes of hypoglycemia is alcohol drinking [17], and so future research including alcohol consumption is needed to clarify these issues.

The current survey found that patients with SH talked less about hypoglycemia with their physicians. Patient education and the appropriate use of modern insulin analogues, insulin pumps, and continuous glucose monitoring are the main therapeutic strategies for reducing hypoglycemia, especially IAH [17, 18]. Favorable patient-physician communication regarding hypoglycemia and related information can prevent SH.

Table 1: Clinical data of patients with and without impaired awareness of hypoglycemia (IAH)

Variables	With IAH (n=73)	Without IAH (n=258)	P-value
Age, years	64.3 (10.6)	60.9 (12.1)	0.03
Male, %	68.5	54.7	0.04
Current smoking, %	28.8	21.4	0.19
Alcohol drinking, %	17.8	12.4	0.23
Diabetes duration, years	18.1 (9.9)	15.6 (9.6)	0.05
Injection regimen			
1 time per day	5.5	7.0	0.75
2 times per day	34.2	37.7	
3 times per day	35.6	29.2	
≥4 times per day	24.7	26.1	
Daily insulin dose, units	0.46 (0.23)	0.44 (0.21)	0.44
Sulfonylureas, %	14.1	12.7	0.75
Biguanides, %	18.3	24.4	0.28
Alpha-glucosidase inhibitors, %	21.1	16.3	0.34
Thiazolidine, %	1.4	5.7	0.13
Body mass index, kg/m ²	23.1 (3.0)	24.7 (3.9)	<0.01
HbA1c, %	7.3 (1.0)	7.7 (1.2)	<0.01
Patients with HbA1c <7%	49.3	29.8	<0.01
Retinopathy, %	52.1	44.7	0.27
Nephropathy, %	49.3	44.6	0.47
Neuropathy, %	42.3	43.8	0.81
Atherosclerosis, %	26.8	18.4	0.12
Hypoglycemia, times per month	1.3 (1.9)	1.2 (1.9)	0.49

Data are means (standard deviation) or percentage.

Strengths and limitations

The strengths of the current survey include recruitment of patients at hospitals and clinics nationwide in Japan. Because patients who regularly attended the medical centers were

recruited, they could fully respond to the questionnaire. However, this study had several limitations. The causes of the results cannot be determined because of the cross-sectional nature of the survey. The data were from a self-administered questionnaire, and we did not evaluate objective measures of

blood glucose. These limitations should be addressed in future research.

In conclusion, the current survey found that IAH was not uncommon among insulin-treated patients with Type 2 Diabetes in Japan. Aging, a lower BMI, and lower HbA1c levels were significantly correlated with IAH. The patients with SH talked less about hypoglycemia with their physicians. To improve the actual states of hypoglycemia, physicians should be conscious of the factors associated with IAH, and should talk more about hypoglycemia in insulin-treated patients with Type 2 Diabetes in Japan.

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