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Factors associated with an inadequate hypoglycemia in the insulin tolerance test in Japanese patients with suspected or proven hypopituitarism

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Abstract. We attempted to identify the predictors of an inadequate hypoglycemia in insulin tolerance test (ITT), defined as a blood glucose level higher than 2.8 mmol/L after insulin injection, in Japanese patients with suspected or proven hypopituitarism. A total of 78 patients who had undergone ITT were divided into adequate and inadequate hypoglycemia groups. The relationships between the subjects' clinical parameters and inadequate hypoglycemia in ITT were analyzed. Stepwise logistic regression analysis identified high systolic blood pressure (SBP) and high homeostasis model assessment of insulin resistance (HOMA-IR) as being independent factors associated with inadequate hypoglycemia in ITT. Receiver operating characteristic (ROC) curve analysis revealed the cutoff value for inadequate hypoglycemia was 109 mmHg for SBP and 1.4 for HOMA-IR. The areas under ROC curve for SBP and HOMA-IR were 0.72 and 0.86, respectively. We confirmed that high values of SBP and HOMA-IR were associated with inadequate hypoglycemia in ITT, regardless of the degree of reduction of pituitary hormone levels. Furthermore, the strongest predictor of inadequate hypoglycemia was obtained by using the cutoff value of HOMA-IR. Our results suggest that HOMA-IR is a useful pre-screening tool for ITT in these populations.

Key words: Insulin tolerance test, Hypopituitarism, Insulin, Homeostasis model assessment of insulin resistance

INSULIN TOLERANCE TEST (ITT) plays an important role as the gold standard for the evaluation of patients with suspected growth hormone deficiency (GHD) [1], and is also widely used for the diagnosis of secondary adrenal insufficiency [2, 3]. Despite its widespread use in clinical practice, among the unresolved problems that remain, a significant one pertains to the selection of the appropriate dose of insulin for the test. Adequate hypoglycemia is not always induced with a standard dose of insulin in ITT. Lee *et al*. reported that significant hypoglycemia was not achieved in 33 out of 76 patients following pituitary surgery [4]. Conversely, since excessive dose of insulin could cause severe hypoglycemia in certain patients, ITT is contraindicated in those with a history of epilepsy or ischemic heart disease, as hypoglycemia can worsen their clinical condition. Therefore, establishing the appropriate protocol for ITT is essential for achieving optimal degree of hypoglycemia as well as preventing avoidance of the test for fear of triggering adverse events.

It has been reported that body mass index (BMI) or body weight, and/or fasting blood glucose are important determinants of the dose of insulin required to achieve optimal degree of hypoglycemia in ITT in European and Australian patients with pituitary disease [4-6]. In addition, it is assumed that other metabolic parameters such as lipid profile, hepatic function, and insulin resistance could be associated with the efficacy/inefficacy of the stimulus in ITT. To date, however, there have been few reports to identify the predictors of an inadequate hypoglycemia in ITT, including metabolic parameters other than BMI and blood glucose. In the present study, we attempted to identify such factors in Japanese patients with suspected or proven hypopituitarism.

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Materials and Methods

Patients

We conducted a retrospective review of clinical records of all consecutive inpatients admitted to Hokkaido University Hospital in Sapporo from April 2004 to December 2014 with suspected or proven hypopituitarism. The major inclusion criterion was patients who had undergone ITT. We excluded patients with the following: acromegaly, Cushing's disease, diabetes mellitus diagnosed in accordance with the criteria proposed by the Japan Diabetes Society [7], severe liver dysfunction, severe nephropathy associated with eGFR <30 mL/min/1.73 m^2 and malignancy because they might interfere with insulin sensitivity or analyses. Impaired glucose tolerance, impaired fasting glucose and diabetic type were defined as non-diabetes mellitus. In the end, 78 patients were eligible for evaluation. The study was conducted with the approval of the Institutional Review Board of Hokkaido University Hospital (014-0351). Data from this study were disclosed on the website of Hokkaido University Hospital in accordance with the ethical guidelines for medical and health research involving human subjects in Japan.

Clinical and laboratory evaluation

Body weight and height of the subjects were measured with a calibrated scale after they had removed their shoes and any extra clothing. Body weight was used to calculate BMI and dose of insulin. Venous blood samples were collected at rest in the morning after subjects had fasted overnight for measurement of the levels of fasting plasma glucose (FPG), glycated hemoglobin (HbA1c), insulin, triglyceride (TG), total cholesterol (T-Cho), high-density lipoprotein cholesterol (HDL-Cho), aspartate aminotransferase (AST), alanine aminotransferase (ALT), adrenocorticotropic hormone (ACTH), growth hormone (GH), thyroid-stimulating hormone (TSH), luteinizing hormone (LH), follicle-stimulating hormone (FSH), and prolactin (PRL). These parameters were measured using commercially available assay kits. The degree of insulin resistance was calculated by the homeostasis model assessment of insulin resistance (HOMA-IR) as insulin (μU/mL) × FPG (mmol/L) / 22.5 [8].

Insulin tolerance test

ITT was performed on all subjects by an experienced endocrinologist. The patients were asked to fast from 2100 h on the day before the test, and if they were on hydrocortisone replacement therapy, the morning dose of hydrocortisone was canceled on the day of ITT. All tests were conducted at 0900 h. We injected regular insulin and took venous blood samples at 0, 30, 60, 90 and 120 mins after insulin injection for measuring the blood levels of glucose, GH, ACTH and cortisol. Bedside measurement of blood glucose was carried out every 15 mins. The standard insulin dose of 0.1 unit/kg was administered to all patients, in principle. An insulin dose in ITT that yielded a plasma glucose level below 2.8 mmol/L was defined as an adequate hypoglycemia, while that which yielded a plasma glucose level of over 2.8 mmol/L was defined as an inadequate hypoglycemia [9]. The test was terminated by administering intravenous glucose, in cases with severe adverse events and prolonged hypoglycemia. After the test was completed, the patients were given a meal.

Statistical analysis

Age, gender, BMI, blood pressure, glucose metabolism, lipid metabolism, liver function, and basal pituitary hormone levels were compared between adequate and inadequate hypoglycemia groups using chi-square test, Mann-Whitney *U*-test or an unpaired *t*-test. Results are shown as mean ± standard deviation for non-skewed variables and median (interquartile range) for positively skewed variables. In these significant variables, multivariate analysis was performed by logistic regression with stepwise forward selection in which the significance level for inclusion of variable was 0.2 to identify factors independently associated with an inadequate hypoglycemia. Variables with a high degree of multicollinearity were eliminated. A receiver operating characteristic (ROC) curve analysis was used to define the cutoff values indicative of an inadequate hypoglycemia in ITT. P values of <0.05 were considered to denote statistical significance. Statistical analyses were carried out with JMP 11 (SAS Inc., Cary, NC, USA).

Results

Table 1 shows the underlying diseases in our patients. Out of the 78 patients, 26% each had non-functioning pituitary adenoma and craniopharyngioma. Others included a history of neonatal asphyxia, dissection of pituitary stalk, and history of operations for meningioma, trigeminal schwannoma, dysembryoplastic

neuroepithelial tumor, *etc*. The insulin dose in ITT was adequate for inducing significant hypoglycemia in 64 (82%) patients (adequate hypoglycemia group), but inadequate in the remaining 14 (18%) (inadequate hypoglycemia group) (Table 2). Mean nadir plasma glucose levels in the adequate and inadequate hypoglycemia groups were 2.0 ± 0.5 mmol/L and 3.6 ± 0.7 mmol/L, respectively (p<0.001). There was no difference in dose of insulin per kilogram body weight between the two groups. BMI, SBP, and FPG, HbA1c, insulin, HOMA-IR, TG, T-Cho, AST and ALT were higher in the inadequate hypoglycemia group than in the adequate hypoglycemia one, while HDL-Cho and GH were significantly lower in the inadequate hypoglycemia group than in the adequate hypoglycemia one. There were no differences in the other basal pituitary hormone levels, including those of ACTH, TSH, LH, FSH or PRL between the two groups. As shown in Table 3, a stepwise logistic regression analysis identified a high SBP and high HOMA-IR as being independent factors associated with an inadequate hypoglycemia in ITT, after stepwise selection was performed to take into consideration BMI, SBP, HbA1c, HOMA-IR, TG, T-Cho, HDL-Cho, AST, and GH levels.

Table 1 Underlying pituitary etiology in the patients

	n
Pituitary adenoma	25
Non-functioning	20
Prolactinoma	4
Details unknown	1
Craniopharyngioma	20
Germinoma	10
Rathke's cleft cyst	6
Sheehan syndrome	1
Lymphocytic hypophysitis	1
Langerhans cell histiocytosis	1
Idiopathic growth hormone deficiency	1
Others	13

Table 2 Baseline characteristics of the patients in the adequate and inadequate hypoglycemia groups

	Adequate hypoglycemia	Inadequate hypoglycemia	p value
N	64	14	
Age (years)	44 ± 16	40 ± 12	0.314
Females/males	38/26	6/8	0.259
BMI (kg/m^2)	22.8 ± 3.7	26.7 ± 4.8	0.001
SBP (mmHg)	111 ± 15	123 ± 17	0.009
DBP (mmHg)	71 ± 12	78 ± 15	0.063
FPG (mmol/L)	4.9 ± 0.7	5.5 ± 0.5	0.007
HbA1c (%)	5.39 ± 0.37	5.69 ± 0.29	0.010
Insulin (μU/mL)	4.0 (2.6-5.3)	9.4 (6.2-13.3)	< 0.001
HOMA-IR	0.85 (0.62-1.15)	2.14 (1.42-3.28)	< 0.001
TG (mg/dL)	112 (87-159)	219 (155-299)	< 0.001
T-Cho (mg/dL)	199 ± 41	225 ± 29	0.033
HDL-Cho (mg/dL)	63 ± 18	50 ± 19	0.022
AST (IU/L)	24 ± 11	34 ± 16	0.005
ALT (IU/L)	19 (12-35)	38 (25-50)	0.008
Insulin dose (U/kg)	0.093 ± 0.023	0.086 ± 0.036	0.408
ACTH (pg/mL)	24.08 (13.98-45.85)	24.00 (7.91-38.09)	0.711
GH (ng/mL)	0.18 (0.10-0.56)	0.03 (0-0.20)	0.010
TSH (μU/mL)	1.14 (0.06-2.27)	0.76 (0.09-2.80)	0.814
LH (mIU/mL)	2.3 (0-5.7)	1.3 (0-3.1)	0.203
FSH (mIU/mL)	5.4 (0.3-11.1)	1.9 (0-7.1)	0.126
PRL (ng/mL)	13.3 (7.2-24.5)	11.3 (3.7-14.2)	0.162

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; HOMA-IR, homeostasis model assessment of insulin resistance; TG, triglyceride; T-Cho, total cholesterol; HDL-Cho, high-density lipoprotein cholesterol; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ACTH, adrenocorticotropic hormone; GH, growth hormone; TSH, thyroid-stimulating hormone; LH, luteinizing hormone; FSH, follicle-stimulating hormone; PRL, prolactin.

Table 3 Univariate and stepwise logistic regression analysis to identify the inadequate hypoglycemia factors in the ITT

	OR univariate	95% CI	*p* value	OR multivariate	95% CI	*p* value
BMI	1.28	1.10-1.54	0.003	1.27	0.96-1.78	0.114
SBP	1.05	1.01-1.09	0.015	1.06	1.01-1.14	0.038
HbA1c	10.17	1.72-80.22	0.016	15.20	0.99-432.36	0.070
HOMA-IR	1.66	1.17-2.95	0.023	1.75	1.14-2.98	0.015
T-Cho	1.01	1.00-1.03	0.047	1.02	1.00-1.06	0.081

R^2=0.4738. Logistic regression with stepwise selection were performed considering BMI, SBP, HbA1c, HOMA-IR, TG, T-Cho, HDL-Cho, AST, and GH as potential factors independently associated with an inadequate hypoglycemia. ITT, insulin-tolerance test; OR, odds ratio; 95% CI, 95% confidence interval; BMI, body mass index; SBP, systolic blood pressure; HbA1c, glycated hemoglobin; HOMA-IR, homeostasis model assessment of insulin resistance; TG, triglyceride; T-Cho, total cholesterol; HDL-Cho, high-density lipoprotein cholesterol; AST, aspartate aminotransferase; GH, growth hormone.

Using an ROC analysis, the cutoff values for predicting an inadequate hypoglycemia in ITT were 109 mmHg for SBP and 1.4 for HOMA-IR (Table 4). The area under the ROC curve of SBP and HOMA-IR were 0.72 and 0.86, respectively (Table 4 and Fig. 1). The cutoff value of HOMA-IR showed a larger area under the ROC curve than that of SBP, and the sensitivity and specificity of the HOMA-IR cutoff for predicting an inadequate hypoglycemia in ITT were 83.3% and 83.1%, respectively (Table 4). The area under the ROC curve integrating SBP and HOMA-IR was 0.85, which was lower than that found in HOMA-IR alone.

Ten patients (12.8%) developed adverse events during the test. Of them, 5 patients had drowsiness and three developed palpitations. The others had confusion, dizziness, and listlessness. Mean nadir blood glucose level and insulin dose in these patients were comparable to those in the other patients who did not experience any adverse events (2.1 *vs*. 2.3 mmol/L and 0.096 *vs*. 0.091 U/kg, respectively).

Table 4 Cutoff values of the inadequate hypoglycemia factors in the ITT

	Cutoff value	AUC	Sensitivity (%)	Specificity (%)
SBP (mmHg)	109	0.72	92.9	56.3
HOMA-IR	1.4	0.86	83.3	83.1

ITT, insulin-tolerance test; AUC, area under the receiver operating curve; SBP, systolic blood pressure; HOMA-IR, homeostasis model assessment of insulin resistance.

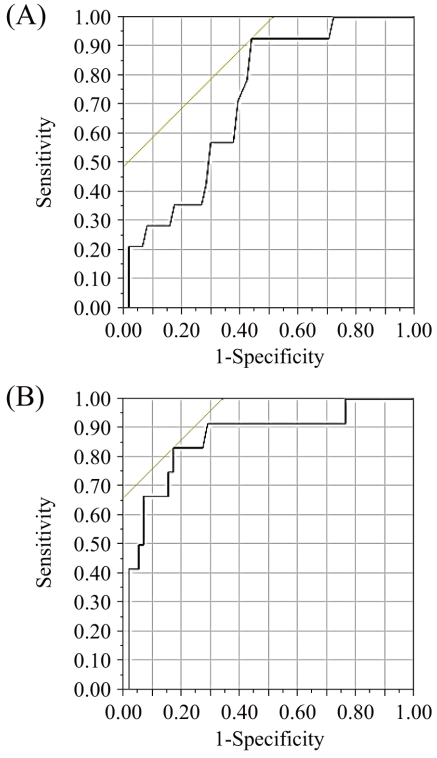

Fig. 1 Receiver operating characteristic curves (ROC) analysis for identifying the cutoff values of (**A**) systolic blood pressure (SBP) and (**B**) homeostasis model assessment of insulin resistance (HOMA-IR) for determining efficacy/inefficacy of stimulus in ITT.

Discussion

The present study sought to determine the factors associated with an inadequate hypoglycemia in ITT in Japanese patients with suspected or proven hypopituitarism. Multivariate analysis identified two factors, namely, a high SBP and high HOMA-IR, as being useful for predicting inadequate hypoglycemia in ITT. The best prediction, with the highest sensitivity and specificity for predicting inadequate hypoglycemia in ITT, was obtained using the cutoff value of HOMA-IR, the area under the ROC of which was larger than that of SBP. Thus, we recommend the use of HOMA-IR as a screening tool for predicting an inadequate hypoglycemia in ITT.

ITT is considered to be the gold standard for assessment of the pituitary-adrenal axis and GH profile [1-3]. A well-known risk factor of the test is related to hypoglycemia, with the literature describing cases of death or serious adverse events related to ITT [10-12]. Furthermore, ITT may increase the risk in patients with seizure disorders, cardiovascular disease, and cerebrovascular disease [1]. Some reports have shown that the degree of hypoglycemia is related to the adverse events of ITT [13, 14], while others have reported that adverse events are infrequent and are not correlated with the severity of hypoglycemia [5, 6, 15]. Our study showed that both mild and serious adverse events are uncommon during ITT, when care is taken to exclude older patients and those with a history of ischemic heart disease or epilepsy. These observations suggest that ITT can be a safe test if the patients are carefully selected in advance. Some have proposed alternative tests to ITT [1, 16-20]. However, many clinical centers have adopted the practice of ITT and most of the current data in the literature regard ITT as a standard reference. Therefore, it is important to obtain the optimal degree of hypoglycemia without adverse events by choosing an accurate insulin dose for ITT.

In the literature to date, BMI or body weight, and/or FPG are considered to be important factors affecting the adequacy of hypoglycemia during ITT in European and Australian patients with pituitary disease [4-6]. These results indicate that the factors affecting the severity of hypoglycemia during ITT are primarily related to metabolic factors, and not to anterior pituitary hormone levels. Consistent with these reports, the anterior pituitary hormone levels in our present study were not key factors affecting the adequacy of hypoglycemia during ITT. Furthermore, there were no significant differences in the proportion of final diagnosis of anterior hormone deficiency to ACTH, GH, TSH, GnRH or PRL between adequate hypoglycemia and inadequate hypoglycemia groups (data not shown).

There are some strengths to the present study. First, we evaluated other metabolic parameters such as blood pressure, lipid profile, hepatic function, and insulin resistance, which were not evaluated in previous studies. Second, we showed that HOMA-IR is useful as the novel predictor besides factors such as BMI, body weight, and/or FPG as shown in previous studies [4-6]. Third, in the present study, the method of statistical analysis is also different from that used in previous studies [4-6]. Our statistical process may be interpreted as the ability to predict whether an inadequate or adequate hypoglycemia will occur in ITT.

HOMA-IR was developed in 1985 by Matthews *et al*. [21] to determine the degree of insulin resistance. It is a convenient indirect marker of insulin resistance. Although the hyperinsulinemic-euglycemic clamp technique is considered as the gold standard for evaluating insulin resistance [21], it was not performed in our study, because it is time-consuming, expensive, and labor-intensive. Previous reports have shown a good correlation between insulin resistance measured by HOMA-IR and that measured by glucose clamp technique in both nondiabetic and diabetic subjects [21-23]. Thus, when used as a surrogate marker of insulin resistance, HOMA-IR may serve as an alternative to hyperinsulinemic-euglycemic clamp technique.

There are also some limitations to the present study. First, due to its retrospective nature, we were unable to adapt the dose of insulin per kilogram body weight to achieve an adequate hypoglycemia in ITT. A prospective study that ensures an adequate dose of insulin per kilogram body weight depending on HOMA-IR levels is warranted. Next, the sample size in our study was small, which might have limited its statistical power. Further, since we did not include patients with acromegaly, Cushing's disease or diabetes mellitus, our findings would not be applicable to patients with these diseases. Finally, since all patients in the present study were Japanese, it is not clear whether our results would also be applicable to non-Japanese patients.

In conclusion, this study demonstrated that a high HOMA-IR level, regardless of anterior pituitary hormone levels, is a strong predictor of an inadequate hypoglycemia in ITT. Thus, HOMA-IR is to be considered as a new and important screening tool for predicting an inadequate hypoglycemia in ITT.

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Disclosure

None of the authors have any potential conflicts of interest to declare associated with this research.

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