Usefulness of hemoglobin A1c and glycated albumin measurements for insulinoma screening: an observational case-control study

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Abstract

Background: Insulinoma represents hypoglycemia as a predominant symptom; the autonomic symptoms may be resolved by chronically recurrent hypoglycemia resulting in the persistence of non-specific symptoms alone. Therefore, it has been estimated that there are many patients in whom the disease takes longer to diagnose and has remained undiagnosed. Although some parameters exist for the definitive diagnosis of the disease, there are currently no indices for early screening. Indices of glycemic control, hemoglobin A1c (HbA1c), and glycated albumin (GA) may be useful for the screening of patients with insulinoma having chronic hypoglycemia because the values become low in such a condition. Because there are no articles that have reported the point, we examine the effective cutoff values of HbA1c and GA for the diagnosis of insulinoma in the present study.

Methods: In a multicenter cross-sectional study, 31 patients with insulinoma were included for comparison with 120 control subjects with normal glucose tolerance based on 75 g oral glucose tolerance tests whose characteristics were matched to the patients. The primary outcomes were optimal cutoff values of HbA1c and GA for the screening of insulinoma.

Results: HbA1c was significantly lower in the insulinoma group at 4.7 ± 0.4% compared to the healthy control group at 5.7 ± 0.3% (p < 0.001), and GA was significantly lower in the insulinoma group at 11.6 ± 1.8% compared to the healthy control group at 14.5 ± 1.0% (p < 0.001). According to a receiver operating characteristic (ROC) analysis, optimal cutoff values of HbA1c and GA for the diagnosis of insulinoma were 5.0 and 12.4%, respectively. Area under the curve values of HbA1c and GA were 0.970 and 0.929, respectively, showing no significant difference (p = 0.399).

Conclusions: In the present study, HbA1c and GA values in patients with insulinoma were significantly lower compared to the healthy controls, and effective cutoff values for screening were shown in the diagnosis of insulinoma for the first time. HbA1c and GA can be useful indices for insulinoma screening. Because malignant insulinoma have a similar diagnostic process to that of benign insulinoma, these could be useful for malignant insulinoma.

Keywords: Insulinoma, HbA1c, Glycated albumin, Hypoglycemia

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Background
Insulinoma is a tumor derived from pancreatic beta cells that produce excessive insulin as the most common pancreatic neuroendocrine tumor. The predominant symptoms of the disease are autonomic and neurologic manifestations due to hypoglycemia. However, the autonomic symptoms accompanied by hypoglycemia may be resolved, and then only non-specific symptoms that do not seem to be hypoglycemic manifestations persist in patients with chronically recurrent hypoglycemia [1, 2]. For such a reason, it is suggested that the diagnosis may take at least 3.6 years in over half the patients [3], and many patients are often undiagnosed [4, 5]. Approximately 5–10% of insulinoma are malignant with distant metastasis at diagnosis [6], and early detection is very important.

Classic diagnostic criteria of insulinoma are based on Whipple’s triad (hypoglycemic manifestation, plasma glucose level < 50 mg/dL, and improvement of the symptoms with glucose intake); 72-h fasting and mixed diet tests with glucose intake); 72-h fasting and mixed diet tests have been performed for a definitive diagnosis [7]. However, there are no effective early screenings in patients with persistent non-specific symptoms alone.

Indices of glycemic control, hemoglobin A1c (HbA1c) and glycated albumin (GA) may be useful for screening patients with insulinoma having chronic hypoglycemia because the values become low in such a condition while no relevant information has been reported. In the present study, we examine the effective cutoff values of HbA1c and GA as indices of early screening for the diagnosis of insulinoma.

Methods
Study patients
Among patients with insulinoma who visited one of three medical institutions attending the multicenter study (Hospital of University of Occupational and Environmental Health, Kobe University Hospital, and Keio University Hospital), 31 patients who met the following inclusion criteria were included in the study. The inclusion criteria included (1) all ages and both sexes, (2) any number of subjects in the insulinoma and healthy control groups were 31 (10 males and 21 females) and 120 (36 males and 84 females), respectively. No significant differences in age (58.3 ± 19.7 years vs. 57.3 ± 3.0 years; p = 0.390) were observed between the groups. FPG was significantly lower in the insulinoma group at 51.3 ± 15.3 mg/dL compared to the healthy control group at 75.3 ± 10.3 mg/dL.

Measurements
Total of 120 individuals with normal glucose tolerance confirmed by 75 g OGTT were included in the study. Plasma glucose levels were measured by the hexokinase method. HbA1c, expressed as the National Glycohemoglobin Standardization Program value [10], was measured by high performance liquid chromatography. GA was determined by the enzymatic method using albumin-specific proteinase, ketoamine oxidase, and albumin assay reagent (Lucica GA-L; Asahi Kasei Pharma Co., Tokyo, Japan) [11].

Statistical analyses
The values are indicated as mean ± standard deviation. Kolmogorov-Smirnov normality tests showed normal distributions for FPG and GA but not for age, BMI, HbA1c, and IRI. As for intergroup tests, unpaired t- and Mann-Whitney U tests were performed for data with a normal distribution and those without a normal distribution, respectively. In addition, chi-squared tests were conducted for comparisons between sexes. Receiver operating characteristic (ROC) curves were drawn to calculate areas under the curves and 95% confidence intervals for determination of the most distinguishable values of HbA1c and GA for the screening of insulinoma. For comparison of the diagnostic discrimination between HbA1c and GA, the areas under the curves (AUC) were compared by DeLong’s test. The significance level was p < 0.05. SPSS Statistical Software 25.0 (SPSS Inc., Chicago, IL) was used for the analyses.

Results
The subject characteristics are shown in Table 1. The numbers of subjects in the insulinoma and healthy control groups were 31 (10 males and 21 females) and 120 (36 males and 84 females), respectively. No significant differences in age (58.3 ± 19.7 years vs. 57.3 ± 3.0 years; p = 0.608) and BMI (24.4 ± 4.3 kg/m² vs. 23.9 ± 2.2 kg/m²; p = 0.390) were observed between the groups. FPG was significantly lower in the insulinoma group at 51.3 ± 15.3 mg/dL compared to the healthy control group at 75.3 ± 10.3 mg/dL.
93.0 ± 6.2 mg/dL (p < 0.001). On the other hand, fasting IRI was significantly higher in the insulinoma group at 17.0 ± 16.3 μU/mL compared to the healthy control group at 4.6 ± 2.1 μU/mL (p < 0.001).

HbA1c was significantly lower in the insulinoma group at 4.7 ± 0.4% compared to the healthy control group at 5.7 ± 0.3% (p < 0.001), and GA was significantly lower in the insulinoma group at 11.6 ± 1.8% compared to the healthy control group at 14.5 ± 1.0% (p < 0.001). Then, ROC curves were drawn to calculate the AUCs and 95% confidence intervals for determination of the most distinguishable values of HbA1c and GA for the screening of insulinoma. The sensitivities, specificities, positive/negative predictive values, and positive/negative likelihood ratios by the cutoff value of HbA1c and GA are summarized in Table 2 and Table 3. The optimal cutoff value of HbA1c for the screening of insulinoma was determined to be 5.0% [AUC = 0.971; 95% CI, 0.918–0.990 (Table 2)]. Moreover, the optimal cutoff value of GA for screening of insulinoma was determined to be 12.4% [AUC = 0.929; 95% CI, 0.788–0.979 (Table 3)]. AUC of HbA1c and GA were 0.970 and 0.929, respectively (Fig. 2), showing no significant difference (p = 0.221).

### Discussion

The present study indicated that HbA1c and GA values in patients with insulinoma were significantly lower than those in the healthy control by showing the effective cutoff values for the screening of insulinoma. Furthermore, AUCs in the ROC curves for screening of insulinoma were comparable between HbA1c and GA.

Insulinoma is a tumor, accounting for 70 to 80% of functional pancreatic neuroendocrine tumors, and most of the conditions are sporadic benign legions and single small highly vascular tumors [12]. The incidence of insulinoma in the general population was estimated to be one to four cases per million person-years [13]. In the meantime, the incidence was reported to be higher (0.8 to 10.0%) in some studies with autopsy, suggesting that insulinoma has been undiagnosed in many patients [4, 5]. The predominant symptoms of insulinoma include autonomic and neurologic manifestations due to hypoglycemia [14]; the autonomic symptoms accompanied by hypoglycemia may be resolved, and then only non-specific symptoms that do not seem to be hypoglycemic manifestations persist in patients with chronically recurrent hypoglycemia [1, 2]. Long-term exposure to chronic hypoglycemia may result in adaptation of the central nerve system to chronic
hypoglycemia and lead to difficulty in recognizing hypoglycemia in most patients. In such cases, asymptomatic hypoglycemia can cause the loss of symptoms even with very low plasma glucose [15]. Symptoms of fasting hypoglycemia have occurred in 73% of patients with insulinoma. However, the residual 27% of patients have developed symptoms in both the fasting state and after meals or only after meals [16], and therefore detection of the symptoms can be delayed, especially in those cases. No screening methods have been reported for insulinoma.

The present study showed that HbA1c and GA could be useful as parameters in the early screening for the diagnosis of insulinoma for the first time.

Whipple's triad has been known as findings that can be suspected with insulinoma (presyncope in the fasting state, plasma glucose level < 50 mg/dL during attacks, and improvement of the symptom with glucose intake). Hypoglycemia has usually developed with autonomic regulation of insulin secretion in the fasting state, and fasting IRI measurement is therefore required for the diagnosis. In the present study, AUCs in the ROC curves of HbA1c and GA were similarly high in diagnoses of insulinoma, indicating that the precision of HbA1c and GA was as high as the screening tests.

Approximately 5–10% of insulinoma are malignant with distant metastasis at diagnosis [6], early detection is very important. The main clinical manifestations of malignant insulinoma are hypoglycemia-related symptoms and some malignant insulinoma tumors are diagnosed as benign pancreatic tumors [17]. This study didn’t include malignant insulinoma. Because malignant insulinoma have a similar diagnostic process to that of benign insulinoma [17], HbA1c and GA could be useful for malignant insulinoma screening.

This study had some limitations. The first was that the controls were individuals with normal glucose level. Those parameters could be good indices for screening, but should be investigated in subjects with hypoglycemia if used for the diagnosis of insulinoma. The second was that this research was a retrospective study with a small sample size. Further investigation of the results obtained from this study in a larger prospective cohort study is warranted.
Conclusions
In the present study, HbA1c and GA values in patients with insulinoma were significantly lower compared to the healthy controls, and effective cutoff values for screening were shown in the diagnosis of insulinoma for the first time. HbA1c and GA can be useful indices for insulinoma screening in patients with chronic hypoglycemia.

Abbreviations
BMI: Body mass index; FPG: Fasting plasma glucose; GA: Glycated albumin; HbA1c: Hemoglobin A1c; IRI: Immunoreactive insulin; ROC: Receiver operating characteristic

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Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors’ contributions
MK conceived the study. KT statistical analyses. KT, AM, YH, WO, YS, IK, HI and SI carried out data collection. YO and YT contributed to interpretation of the data. All authors were involved in manuscript drafting/revision and approved the final manuscript.

Ethics approval and consent to participate
This study observed the Declaration of Helsinki and current ethical codes and was approved by the ethics committee at the University of Occupational and Environmental Health. This research is not a clinical study, and was approved by the ethics committee at the University of Kitakyushu, Fukuoka 807-8555, Japan. 2Division of Diabetes and Endocrinology, Department of Internal Medicine, Kobe University Graduate School of Medicine, Hyogo 650-0017, Japan. 3Department of Internal Medicine, Kio University School of Medicine, Tokyo 160-8582, Japan. 4Department of Internal Medicine, Kawanishi City Hospital, Hyogo 666-0195, Japan. 5Department of Internal Medicine, Hakuhokai Central Hospital, Hyogo 669-0963, Japan.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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