A novel diagnostic model for insulinoma

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Abstract

The aim is to describe a simple and feasible model for the diagnosis of insulinoma. This retrospective study enrolled 37 patients with insulinoma and 44 patients with hypoglycemia not due to insulinoma at the First Affiliated Hospital of Guangxi Medical University. General demographic and clinical characteristics; hemoglobin A1c (HbA1c), insulin and C-peptide concentrations; and the results of 2-hour oral glucose tolerance tests (OGTT) were recorded, and a logistic regression model predictive of insulinoma was determined. Body mass index (BMI), HbA1c concentration, 0-hour C-peptide concentration, and 0-hour and 1-hour plasma glucose concentrations ($P < 0.05$ each) were independently associated with insulinoma. A regression prediction model was established through multivariate logistics regression analysis: Logit p = 7.399+(0.310×BMI) - (1.851×HbA1c) - (1.467×0-hour plasma glucose) + (1.963×0-hour C-peptide) - (0.612×1-hour plasma glucose). Using this index to draw a receiver operating characteristic (ROC) curve, the area under the curve (AUC) was found to be 0.957. The optimal cut-off value was − 0.17, which had a sensitivity of 89.2% and a specificity of 86.4%. Logit P≥-0.17 can be used as a diagnostic marker for predicting insulinoma in patients with hypoglycemia.

Introduction

Insulinoma is one of the most common functional pancreatic neuroendocrine tumors, originating from pancreatic β cells [1]. Its clinical manifestations include hyperinsulinemia with hypoglycemia syndrome [2]. The incidence of insulinoma in the general population has been estimated to be 1–4 per million people, but this may be an underestimate, as insulinomas have been reported in 0.8–10% of persons autopsied [3]. Insulinoma is often misdiagnosed as epilepsy, psychosis, or cerebrovascular disease [4–6]. More than half of patients require at least 3.6 years to be properly diagnosed, with many patients never being diagnosed correctly. Brain damage due to persistent hypoglycemia is irreversible and can lead to neurological sequelae. Therefore, early diagnosis and treatment are essential for good patient prognosis [7].

At present, the 72-hour fasting test is the standard method of diagnosing insulinoma. About 80% of patients can be diagnosed within 24 hours, and 100% can be diagnosed within 72 hours [8]. Many patients, however, refuse to participate in 72-hour fasting tests because they were unable to tolerate the distress caused by hunger, thus hindering the diagnosis of insulinoma. Insulinoma can also be diagnosed by administration of the GLP1 peptide analogue exendin-4, followed by single-photon emission computed tomography (SPECT) [9]. Although this assay has a sensitivity of 95%, the need for costly equipment and inspections has limited the application of this method to the diagnosis of insulinoma. A simple and convenient diagnostic method is therefore needed.

By consulting the literature, patients with insulinoma will have changes in plasma glucose, C-peptide, and insulin due to the massive secretion of insulin [10–13], and 72% of patients will gain weight [14], we selected indicators related to the assessment of insulin, including insulin, plasma glucose, C-peptide, and HbA1c concentrations, as well as patient demographic and clinical characteristics. These indicators were utilized to establish a diagnostic model based on single factor analysis and multi-factor logistic regression analysis. The present study shows that this diagnostic model was better able to diagnose than Fajans' and Turner's indices.

Materials And Methods

Patient Selection

This study included 81 patients with hypoglycemia who were admitted to the First Affiliated Hospital of Guangxi Medical University from January 2012 to September 2021, including 37 patients with insulinoma and 44 with hypoglycemia of other etiologies. Insulinoma was confirmed by pathological examination of tissue samples following surgical resection or following ultrasound-guided fine needle endoscopic aspiration biopsy. Patients were included in the insulinoma group if they had hypoglycemia with Whipple's triad (hypoglycemic manifestation, plasma glucose level < 2.8 mmol/l, and improvement in the symptoms after taking in glucose) and positive results (plasma glucose levels ≤ 40mg/dl, insulin ≥ 36 pmol/l, C-peptide ≥ 200 pmol/l, proinsulin ≥ 5 pmol/l, β-hydroxybutyrate ≤ 2.7 mmol/l and absence of plasma or urine sulfonylurea metabolites)

on the 72-hour fasting test. Patients were included in the control group if they had hypoglycemia not due to insulinoma with Whipple's triad and negative results on the 72-hour fasting test, but due to other causes, such as hyperthyroidism, subtotal gastrectomy, severe liver disease, etc. Patients with incomplete clinical data were excluded (Fig.1). The study protocol was approved by the Ethics Committee of the First Affiliated Hospital of Guangxi Medical University.

Pathological examination of tissue specimens

Immediately after isolation, specimens were fixed in 10% formaldehyde solution and stained with hematoxylin-eosin. All samples were evaluated by two experienced pathologists.

Clinical and laboratory index testing

Age, sex, height, and weight were recorded for each patient, and body mass index (BMI) was calculated as kg/m2. HbA1c concentrations were measured, and all patients underwent 75 g OGTT, as recommended by the World Health Organization. Venous blood samples were obtained directly before (0 min) and during the OGTT (30, 60, and 120 min). Glucose, C-peptide, and insulin concentrations were measured at 0, 1 and 2 h. Plasma glucose concentration was measured by the hexokinase method on a Cobase e702 analyzer (Roche, Germany). C-peptide and insulin concentrations were measured by electrochemiluminescence (Shanghai Enzymelink Biotechnology Corp.), according to the manufacturer's instructions; and HbA1c concentrations were measured using a glycated hemoglobin instrument (BioRad Variant Ⅱ).

Statistical analyses

Normally distributed continuous variables were reported as mean ± standard deviation and compared by independent sample t tests. Non-normally distributed continuous variables were reported as median [first quartile, third quartile] and compared by independent sample rank sum tests. Categorical variables were reported as number (%) and compared by chi-square tests. Multivariate stepwise logistic regression analysis was used to evaluate the diagnostic value of the developed model, with receiver operating characteristic (ROC) curves delimiting the value and areas under the curve (AUC) compared using normal Z tests. All statistical analyses were performed using SPSS 24.0 software, with $P<0.05$ considered statistically significant.

Results

Characteristics of Patients in the Insulinoma and Control Groups

The demographic and clinical characteristics of the 81 patients with hypoglycemia, including 37 with and 44 without insulinoma, are shown in Table 1. Age, sex and 1-hour insulin, 2-hour insulin and 2-hour C-peptide concentrations in these two groups did not differ significantly ($P>0.05$). In contrast, BMI was significantly higher, and HbA1c, 0-hour C-peptide, 0-hour insulin, 0-hour plasma glucose, 1-hour and 2-hour plasma glucose concentrations were significantly lower in the insulinoma than in the control group. Of the 37 insulinoma patients, six (16.2%), 27 (73.0%), and four (10.8%) had tumors of maximum diameters < 1 cm, 1-2cm, and > 2cm, respectively. Of these 37 tumors, 13(35.1%) were located in the head, 11 (29.7%) in the body, and 13 (35.1%), in the tail of the pancreas. Thirty-six (97.3%) insulinoma were single and one (2.7%) was multiple. Of the 44 patients in the control group, 15 (34.1%) had preprandial hypoglycemia, 28 (63.6%) had of postprandial hypoglycemia, and one (2.3%) had induced hypoglycemia.

Construction of a diagnostic model for insulinoma

Single factor analysis yielded seven meaningful indicators, including BMI, and HbA1c, 0-hour C-peptide, 0-hour insulin and 0-hour, 1-hour and 2-hour plasma glucose concentrations ($P<0.05$ each; Table 1). Multiple logistic regression analysis identified five factors significantly and independently associated with the occurrence of insulinoma, including higher BMI and 0-hour C-peptide concentration and lower HbA1c, 0-hour plasma glucose, and 1-hour plasma glucose concentrations ($P<0.05$ each; Table 2). These five factors were incorporated into a regression prediction model, calculated using the formula: Logit

P=7.399+(0.310×BMI) - (1.851×HbA1c) -(1.467×0-hour plasma glucose) + (1.963× 0-hour C-peptide) - (0.612×1-hour plasma glucose).

Predictive value of Logit P, Fajans' index and Turner's index for the diagnosis of insulinoma

ROC curve analysis was used to compare the diagnostic performances of the Logit P, Fajans' index and Turner's index for the diagnosis of insulinoma. The Logit P insulinoma diagnostic model described in this study was found to have a higher accuracy rate, than either Fajans' or Turner's index (Table 3, Fig.2).

Discussion

The present study describes the use of general clinical characteristics and biochemical indicators to establish a simple and feasible model for the diagnosis of insulinoma. This model was highly sensitive and accurate and may provide a simple and rapid method to diagnose insulinoma in patients with hypoglycemia and can be used in outpatients to diagnose insulinoma patients, which is helpful for diagnosis of more outpatients with insulinoma.

Insulinoma can cause severe metabolic disorders. Long-term hypoglycemia can cause irreversible damage to nerve tissue, and even endanger the life of the patient in severe cases [15]. Therefore, early diagnosis and treatment are required. Insulinomas can be diagnosed qualitatively or based on localized factors [16]. Qualitative diagnosis mainly relies on clinical manifestations and laboratory tests. At present, the 72-hour fasting test is the standard method for the qualitative diagnosis of insulinoma [6, 17–19]. An insulin-to-glucose ratio > 0.3 at the onset of hypoglycemia may provide a basis for diagnosing insulinoma. Many patients refuse to take the 72-hour fasting test, due to its being a painful experience and its accompanying risk of hypoglycemia. A retrospective analysis of the results in 69 patients with confirmed insulinoma showed that 20 (29.0%) had negative results on 72-hour fasting tests [20], indicating that negative results on 72-hour fasting tests cannot completely rule out a diagnosis of insulinoma [21]. Insulinomas can also be diagnosed by imaging modalities, including ultrasound, CT, MRI, and endoscopic ultrasound (EUS), although the positivity rates of these noninvasive examinations are not high, with preoperative CT and MRI having sensitivity rates of 72% and 75%, respectively [22]. EUS, another minimally invasive method, was found to have a sensitivity of 94% [23], although its sensitivity was largely dependent on the operator's technique and experience. The sensitivities of EUS in detecting insulinomas in the head and body of the pancreas were high, at 95% and 98%, respectively [24], whereas its sensitivity in detecting lesions in the pancreatic tail was much lower, ranging from 37%-50% [25, 26]. Of the 37 patients pathologically diagnosed with insulinoma in the present study, 32 (86.5%) underwent EUS, with all 32 having space-occupying lesions, of minimum diameter 5.6 mm, in the tail of pancreas. The insulinoma patients included in our model included four false-negative cases, all of whom had tumors < 1cm in size. These findings suggested that application of this model yielded errors in patients with atypical clinical symptoms due to the small size of these tumors. Other methods, such as PET-CT and GLP-1 receptor imaging, have been shown superior to MRI and CT in diagnosing insulinomas. However, their clinical application is limited due to the high costs of examinations.

Weight gain is a significant manifestation of insulinoma. Due to the frequent occurrence of hypoglycemia symptoms, patients can relieve symptoms such as palpitation, tremor, and dizziness through eating [27]. According to a retrospective study, 72% of patients with insulinoma have gained weight [14]. In our study, the BMI of insulinoma patients was in the overweight range, while the BMI of the control group was within the normal range. Among the biochemical indicators, the HbA1c of patients in the insulinoma group was significantly lower than that in the control group, which suggests that the plasma glucose of patients with insulinoma has been low for a long time. Combining plasma glucose, insulin and C-peptide, insulinoma patients have higher fasting insulin and fasting C-peptide than the control group, indicating that insulinoma patients are more likely to have fasting hypoglycemia symptoms. After taking 75g anhydrous glucose powder, the indicators of insulinoma group, including 1-hour plasma glucose and 2-hours plasma glucose, are lower than the control group. Considering that insulinoma patients release a large amount of insulin, the improvement of plasma glucose level after taking anhydrous glucose powder is still relatively slow. The effect of insulinoma on patients' plasma glucose is a relatively long-lasting process, which is extremely harmful to the human body.

Insulinomas are relatively rare and differ in clinical symptoms, making this condition easy to miss and misdiagnose [28–30]. A clear diagnosis of insulinoma is a prerequisite for standardized treatment. Fajans' and Turner's indices are often used to evaluate the role of insulin release from pancreatic beta cells in regulating plasma glucose. Compared with indices, our model was more accurate and more reliable. A similar model of diagnosing insulinoma includes fasting insulin, fasting C-peptide, 1-hour C-peptide, and 2-hour insulin concentrations [31]. The AUC of this model was 0.97, with a sensitivity of 86.5% and a specificity of 95.2%. That model could not be validated because the sample size was too small. Incorporation of our data into this model yielded an AUC of 0.957, a: sensitivity of 70.3%; and a specificity of 65.9%. The sensitivity and specificity of this model were lower than those of a model based on fasting plasma glucose and HbA1c concentrations in 82 patients with insulinoma and 100 normal controls [32]. Because this control group consisted of normal persons, the results may not be as accurate. Similarly, this model could not be validated because of the small sample size. Compared with these earlier models, which used control groups consisting of normal healthy individuals, our model used a control group consisting of patients with hypoglycemia not caused by insulinoma, making our model more reliable. In addition, our model combined BMI with glucose-related indicators and used both single factor and multi-factor analysis to obtain the optimal formula. The data included in our model consisted of routine screening parameters for patients with hypoglycemia, providing this model high clinical feasibility and easy implementation.

This study had several limitations, such as the exclusion of patients with incomplete data, thus reducing the sample size. Moreover, this study was a single-center retrospective study, which may have introduced selection bias. Moreover, the small sample size prevented verification of the model. Additional studies, in larger numbers of patients, are needed to verify the accuracy of this model in diagnosing insulinomas. We will continue to collect general information of insulinoma patients and laboratory test results to further verify the model.

Conclusion

In this study, the insulinoma diagnostic model constructed with non-invasive indicators has good diagnostic value, which is of great significance to discover more patients with insulinoma. In order to improve the stability of this model, it needs to be verified in more insulinoma patients.

Declarations

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Disclosure

The authors declare that there are no conflicts of interest regarding the publication of this paper.

Statement of Ethics

This retrospective review study involving human participants was in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The Human Investigation Committee (IRB) of The First Affiliated Hospital of Guangxi Medical University approved this study. Informed consents (Consent to Participate and Consent to Publish) were obtained from all participants, if participants are under 18, from a parent and/or legal guardian.

Data availability

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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Tables

Table 1

Baseline demographic and clinical characteristics of patients in the insulinoma and control groups

Index	Insulinoma Group (n=37)	Control Group (n=44)	$t/z/\chi^2$	p
Age (years)	48.00 (37.50, 53.00)	50.00 (36.50, 76.00)	1.546	0.122
Sex(male/female)	14/23	25/19	2.900	0.089
BMI (kg/m^2)	25.61±4.52	22.54±3.68	3.373	**0.001**
HbA1c (%)	4.71±0.44	5.44±0.66	5.705	**<0.001**
0-hour plasma glucose (mmol/L)	2.87±1.07	4.15±0.90	5.856	**<0.001**
0-hour C-peptide (ng/ml)	2.79 (1.88, 3.68)	1.79 (1.16, 2.81)	3.110	**0.002**
0-hour insulin (pmol/l)	92.98 (52.17, 146.68)	30.65 (21.29, 54.25)	4.191	**<0.001**
1-hour plasma glucose (mmol/L)	6.47±2.19	8.33±2.70	3.365	**0.001**
1-hour C-peptide (ng/ml)	6.76±3.75	8.42±4.15	1.866	0.066
1-hour insulin (pmol/l)	385.10 (244.35, 562.45)	362.15 (198.46, 772.18)	0.057	0.955
2-hour plasma glucose (mmol/L)	5.89±2.30	7.07±2.87	2.022	**0.047**
2-hour C-peptide (ng/ml)	6.65 (4.14, 8.04)	7.52 (4.92, 10.64)	1.531	0.126
2-hour insulin (pmol/l)	384.30 (191.90, 642.95)	285.26 (152.80, 456.95)	1.071	0.284

Data are mean ± SD or median [Q1,Q3], Abbreviations:

BMI, body mass index; HbA1c, hemoglobin A1c. P values represent between-group comparisons.

Table 2

Multiple logistic regression analysis of factors affecting the occurrence of insulinoma

Index	B	SE	Wals	P	OR	95%OR	
						Lower limit	Upper limit
BMI (kg/m^2)	0.310	0.140	4.905	0.027	1.363	1.036	1.793
HbA1c (%)	-1.851	0.830	4.967	0.026	0.157	0.031	0.800
0-hour plasma glucose (mmol/L)	-1.467	0.568	6.679	0.010	0.231	0.076	0.702
0-hour C-peptide (ng/ml)	1.963	0.787	6.226	0.013	7.124	1.524	33.308
0-hour insulin (pmol/l)	-0.001	0.009	0.010	0.922	0.999	0.981	1.018
1-hour plasma glucose (mmol/L)	-0.612	0.255	5.742	0.017	0.542	0.329	0.895
2-hour plasma glucose (mmol/L)	-0.026	0.222	0.014	0.906	0.974	0.630	1.506
Constant	7.399	4.483	2.724	0.099	1634.863		

Abbreviations: BMI, body mass index; HbA1c, hemoglobin A1c; B, Partial regression coefficient value; SE, Standard error; Wals, Wald chi-square value; P, probability; OR, odds ratio.

Table 3

Diagnostic efficacy of the Logit P model, Fajans' index, and Turner's index

Project	Cut off	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)	AUC (95%CI)	*P*
Logit P	-0.17	89.2	86.4	84.6	90.5	87.7	0.957(0.920-0.994)	0.001
Fajans' index	0.77	81.1	77.3	75.0	82.9	79.0	0.835(0.745-0.926)	0.001
Turner's index	261.69	59.5	90.9	84.6	72.7	76.5	0.746(0.624-0.867)	0.001

Fajans' index = immunoreactive insulin/glucose; Turner's index = insulin * 100/(glucose - 30). Abbreviations: PPV, positive predictive value; NPV, negative predictive value; AUC, area under the curve; CI, confidence interval.

Figures

Figure 1

Flowchart of the sample selection.

Figure 2

Receiver operating characteristic (ROC) curves of the LogitP model, Fajans' index, and Turner's index for predicting insulinoma. Logit p=7.399+(0.310×BMI)-(1.851×HbA1c)-(1.467×0-h plasma glucose)+(1.963×0-h C-peptide)-(0.612×1-h plasma glucose); Fajans' index = immunoreactive insulin / glucose ; Turner's index = insulin * 100/(glucose - 30).

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