Insulin Autoimmune Syndrome Diagnosis and Therapy in a Single Chinese Center

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ABSTRACT

Purpose: Insulin autoimmune syndrome (IAS) is a relatively rare cause of hypoglycemia characterized by endogenous hyperinsulinism and autoantibodies against endogenous insulin despite no prior exposure to exogenous insulin. We present a series of IAS cases and describe the clinical characteristics of these cases.

Methods: The medical records of inpatients with the final diagnosis of IAS were collected from August 2007 to August 2017 in Peking Union Medical College Hospital. Clinical characteristics and laboratory test results were summarized. The results of serum glucose, insulin, true insulin, and C-peptide testing during 5-h oral glucose tolerance tests were also summarized. Circulating immune complexes were assessed qualitatively by precipitation with polyethylene glycol (PEG) in some patients.

Findings: Sixteen patients were included in this study. Insulin autoimmune antibody test results were found positive in 12 patients and weakly positive in 1 patient. Nine patients had an insulin to C-peptide molar ratio >1, whereas 6 patients had an insulin to C-peptide molar ratio <1. Circulating immune complexes were verified in all 4 patients who had been assessed with PEG. During 5-h oral glucose tolerance tests, the C-peptide level responded earlier to the glucose tolerance and had a shorter peak value period compared with insulin, although C-peptide's fluctuation still lagged behind the glucose fluctuation. Three patients presented with self-limited disease courses or limited disease course after discontinuing use of the sulfhydryl group drugs. Some patients' symptoms were relieved after small frequent meals, and some were relieved after taking acarbose. Only 3 patients took glucocorticoids as the anti-immune therapy.

Implications: The insulin to C-peptide molar ratios were not consistently >1 in patients with confirmed diagnoses of IAS in our study, which suggested the low sensitivity of insulin to C-peptide molar ratio to detect IAS. The therapy in our study also revealed the self-limited disease course of IAS, and despite the effectiveness of anti-immunity therapy, convenient therapy, such as frequent small meals and adding acarbose, performed well in many patients. (*Clin Ther*. 2019;41:920–928) © 2019 Published by Elsevier Inc.

Key words: autoimmune diseases, hyperglycemia, insulin autoimmune syndrome, sulfhydryl group drugs.

INTRODUCTION

Insulin autoimmune syndrome (IAS) is a relatively rare cause of hypoglycemia characterized by endogenous hyperinsulinism and autoantibodies against endogenous insulin despite no prior exposure to exogenous insulin.[1,2] The first case of IAS occurred in a 52-year-old Japanese man who had markedly elevated insulin levels and no evidence of insulinoma.[1] A total of 325 patients with IAS were identified in Japan before 2007,[1] whereas a total of 58 individuals who were non-Asian (16 countries) were identified before 2009.[3] Hypoglycemia attributable to the development of antibodies to native insulin is reported

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to occur primarily among Asian populations[4] and is reported to be the third most common cause of spontaneous hypoglycemia in Japan.[5] Drugs in the sulfur or sulfydryl groups (eg, thiols with -SH), such as methimazole, captopril, hydralazine, glutathione, and clopidogrel,[6–8] were deemed to have the potential to trigger IAS. Patients with autoimmune diseases are also more likely to have IAS.

Although IAS is an important cause of hypoglycemia, hyperglycemia also occurs immediately after a meal or oral glucose challenge in individuals with IAS.[9,10] Oral glucose tolerance tests (OGTTs) can help to identify the characteristics of glucose, insulin, and C-peptide fluctuations at fasting and postprandial states. In addition, some studies have found an inversed insulin to C-peptide ratio >1 to be a distinguished characteristic of IAS.[11,12] As for the treatment, although IAS is caused by an autoimmune system disorder, low carbohydrate meals and α-glucosidase inhibitors are proven to be effective.[9,13] Besides, IAS seemed to be self-limited.[4]

IAS is likely to be underreported and possibly misdiagnosed. Case reports make up most of the literature regarding IAS. As an important cause of hypoglycemia, the characteristics of IAS have seldom been summarized. We analyzed the clinical characteristics, especially the insulin to C-peptide ratio, the OGTT results, and the treatment choice of 16 patients with IAS in a single Chinese center. This research can provide us some insights into IAS.

METHODS

The medical records of inpatients with a final diagnosis of IAS were collected from August 2007 to August 2017 in Peking Union Medical College Hospital. The diagnosis of IAS was made according to the American Endocrine Society clinical practice guideline.[4] Endogenous hyperinsulinism was documented by the findings of symptoms, signs, or both, with plasma glucose concentrations <3.0 mmol/L, plasma insulin concentrations >3.0 μU/mL, and plasma C-peptide concentrations >0.6 ng/mL.[4] Evidence of serum insulin antibodies confirmed the diagnosis of IAS. Clinical characteristics, including sex, age, disease course, symptoms, histories of previous use of sulfhydryl group drugs, and treatment, were summarized. Laboratory measurement results, including glucose, insulin, C-peptide, and true insulin during 5-h 75-g OGTTs and insulin autoimmune antibodies, were summarized.

Serum glucose, insulin, and C-peptide measurements were determined in the Department of Laboratory Medicine, Peking Union Medical College Hospital. Serum glucose was measured with an automatic biochemical analyzer (AU2700, Beckman Coulter, Brea, California). Serum insulin and C-peptide levels were measured by the automatic immunoassay system (ADVIA Centaur XP, Siemens, Munich, Germany). Serum true insulin was measured by the enzyme-linked immunosorbent assay, which was developed and performed in the Key Laboratory of Endocrinology in Peking Union Medical College Hospital. The true insulin assay had a sensitivity of 0.5 mU/L, an interassay CV of <9.0%, and no cross-reactivity to proinsulin (<0.05%).[14] Circulating immune complexes were assessed qualitatively by precipitation with polyethylene glycol (PEG) followed by insulin assay in the supernatant. Serum insulin value changes after PEG precipitation in healthy individuals were used as the control values.

Age and disease duration were presented as medians with interquartile ranges (IQRs). The glucose and insulin values during OGTTs were presented as means (SEs) unless otherwise stated. Insulin values > 300 μIU/mL and C-peptide values > 7 ng/dL during OGTTs exceeded the upper limit of the detectable range and were calculated as 300 uIU/mL and 7 ng/dL, respectively. The comparisons of glucose, insulin, and C-peptide at different time points used paired *t* tests. $P < 0.05$ was considered statistically significant. The statistical analyses were performed by SPSS statistical software, version 25 (IBM Corp, Armonk, New York).

RESULTS

From August 2007 to August 2017, a total of 16 Chinese Han patients (7 men and 9 women; median age, 53.5 years; IQR,39–60.5 years) were admitted for hypoglycemia and diagnosed with IAS (See: Table I). The median disease duration was 3 months (IQR, 1–11 months). All patients presented with some catecholamine-mediated, adrenergic neurogenic symptoms and neuroglycopenic symptoms, including tremor, palpitations, sweating, psychomotor

Table I. Demographic, symptomatic, and metabolic characteristics of patients with insulin autoimmune syndrome.*

Patient No.	Sex	Age, y	Course of Disease	Onset Time of Hypoglycemia	Use of Sulfhydryl Group Drugs	Previous History of Autoimmune Diseases	Plasma Glucose, mmol/L	Insulin. μIU/mL	C-peptide, ng/mL)	Molar Ratio Insulin/ C-peptide	IAA	Treatment	Insulin After PEG, μIU/mL
1	M	55	8 y 2 mo	Premeal	None	None	2.7	>300	6.62	>1.00	P	Separate meals	NA
2	M	65	1 y	fasting, when not eating in time	None	Interstitial lung disease	2.2	4198.27	6.28	>1.00	N	Acarbose, separate meals	183.88
3	F	39	10 d	Early in the morning	Methimazole for 15 d	None	2.1	51.8	>14	<0.08	P	Discontinuing methimazole use, separate meals	NA
4	M	59	5 m	Early in the morning, when exercising	None	None	2.1	414	1.54	5.60	P	No	NA
5	F	57	1 y	Early in the morning	None	None	1.7	1636.8†	4.70	7.26	P	No	NA
6	F	41	2 m	Early in the morning, premeal	None	None	1.2	>300	>7	Can't be calculated	P	No	NA
7	F	21	3 y 1 mo	Pre-meal, nighttime	Methimazole for 1 mo	Hashimoto thyroiditis	2.9	3.03	0.36	0.18	N	Discontinue methimazole use	NA
8	M	30	2 mo	Fasting	None	Oral lichen planus	2.1	183.2	3.01	1.27	P	Acarbose	NA
9	F	65	8 mo	Early in the morning, fasting	None	Rheumatoid arthritis	2.2	>300	5.78	>1.08	P	Prednisone 20 mg, TID, acarbose	NA
10	F	12	4 mo	Early in the morning, nighttime	None	None	1.9	131.7	6.93	0.40	P	Prednisone 5 mg once daily	NA
11	F	55	14 d			None	1.6	232.1	5.31	0.91	P	Separate meals	NA

Table I. (*Continued*)

Patient No.	Sex	Age, y	Course of Disease	Onset Time of Hypoglycemia	Use of Sulfhydryl Group Drugs	Previous History of Autoimmune Diseases	Plasma Glucose, mmol/L	Insulin. µIU/mL	C-peptide, ng/mL)	Molar Ratio Insulin/ C-peptide	IAA	Treatment	Insulin After PEG, µIU/mL
				3 h after meals, nighttime	Captopril for 1 d								
12	M	40	1 mo	Fasting, premeal	Methimazole for 20 d	Graves disease	1.5	10,732†	11.15	20.05	P	Discontinue methimazole use, separate meals	295.54
13	M	39	1 mo	Predinner	Tiopronin for 15 d	None	2.0	256.3	6.27	0.85	P	Discontinue tiopronin use	NA
14	M	52	16 d	Early in the morning	Methimazole for 2 mo	Hashimoto thyroiditis	2.8	>300	13.3	16.81	P	Discontinue methimazole use	NA
15	F	81	4 mo	3 h after lunch and dinner	Captopril for 1 y	None	1.6	53.61	5.94	0.19	N	Low glycemic index diet; adding extra meals	5.93
16	F	61	1 mo	Nocturnal	Glimepiride for 10 y	Hashimoto thyroiditis	2.8	4300†	13.37	6.70	P	Methylprednisolone 2 mg once daily	8.66

IAA = insulin autoimmune antibody; N = negative; NA = not applicable; P = positive; PEG = polyethylene glycol.

* References ranges are 5.2–17.2 IU/mL or insulin and: 0.8–4.2 ng/mL for C-peptide. The molar ratio of insulin/C-peptide was calculated as insulin (nmol/L)/C peptide (nmol/L). Insulin (nmol/L) was calculated as IU/L × 6.965/100; C-peptide (nmol/L) was calculated as ng/mL × 333/1000.

† Measurement after attenuation.

abnormalities, and cognitive impairment. In addition, low glucose values and diminished symptoms when the blood glucose level was elevated were found. The onset time of hypoglycemia varied, including before meals, early in the morning, 3 h after meals, and at night. Six patients had the histories of taking sulfhydryl group drugs, and 6 patients had histories of autoimmune diseases.

Endogenous hyperinsulinism was verified in all patients. The diagnosis of insulinoma was excluded by negative pancreatic image examination. Insulin autoimmune antibody test results were positive in 12 patients and weakly positive in 1 patient. Four patients conducted the PEG analysis, and changes of insulin values after PEG precipitation revealed the existence of insulin-binding antibodies. The diagnoses of IAS were confirmed in all patients except Patient No.7. This patient did not undergo PEG precipitation and had a negative insulin autoimmune antibody test result. However, the results of screening for other causes of endogenous hyperinsulinism were negative, and this patient had a definitive history of taking sulfhydryl group drugs. Therefore, the diagnosis of IAS was highly conceivable.

The insulin and C-peptide values of 1 patient exceeded the upper limit of the detectable range, so the molar ratio of insulin to C-peptide could not be calculated. Among the remaining 15 patients, 9 had a molar ratio of insulin to C-peptide >1, whereas 6 had a molar ratio of insulin to C-peptide <1.

A total of 12 patients underwent the 5-h 75-g OGTT, and 5 of these patients tested as having true insulin. The fluctuations of glucose, insulin, and C-peptide in all the patients are presented in Figure 1. According to the results of the OGTTs, all patients presented with fasting glucose values < 6.1 mmol/L, 5 patients presented with hypoglycemia (glucose values < 2.8 mmol/L) combined with the 2-h glucose values of >7.8 mmol/L, and 3 patients presented with hypoglycemia combined with the 2-h glucose values of 11.1 mmol/L. Two patients presented with 2-h glucose values > 7.8 mmol/L and no hypoglycemia. One patient presented with hypoglycemia without hyperglycemia. Two patients presented with normal OGTT results. Hypoglycemia appeared at the fourth and fifth hours of the 5-h OGTT. Insulin values measured at the first hour were significantly higher than those measured at 30 min (240.36 [21.57] vs 208.41 [25.23],

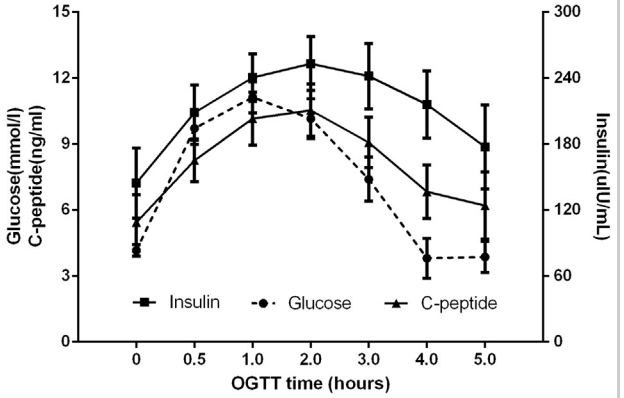

Figure 1. The glucose, insulin and C-peptide in the 5-h oral glucose tolerance tests of 12 patients with insulin autoimmune syndrome.

$P = 0.024$), whereas insulin values measured at the fourth hour were significantly lower than that those measured at the third hour (215.79 [30.70] vs 241.75 [29.75], $P = 0.045$). C-peptide values measured at 30 min were significantly higher than those measured in the fasting state (8.25 [0.97] vs 5.43 [1.26], $P = 0.004$). C-peptide values measured at the first hour were significantly higher than those measured at 30 min (10.15 [1.20] vs 8.25 [0.97], $P = 0.033$). C-peptide values measured at the third hour were significantly lower than those measured at the second hour (9.07 [1.15] vs 10.53 [1.19], $P = 0.043$). C-peptide values measured at the fourth hour were significantly lower than those measured at the third hour (6.83 [1.22] vs 9.07 [1.15], $P = 0.003$). The insulin level significantly increased between 30 and 60 min, remained high from 60 to 180 min, and significantly decreased between 180 and 240 min. However, the C-peptide level significantly increased from the beginning to 60 min, remained high from 60 to 120 min, and significantly decreased between 120 and 240 min. The fluctuations of glucose, insulin, and true insulin of 5 patients are presented in Figure 2, and data are presented as the mean in Figure 2.

Hypoglycemic symptoms of 3 patients were relieved during the in-hospital duration. The symptoms of 5 patients were relieved after discontinuation of use of the sulfhydryl group drugs alone or combined with

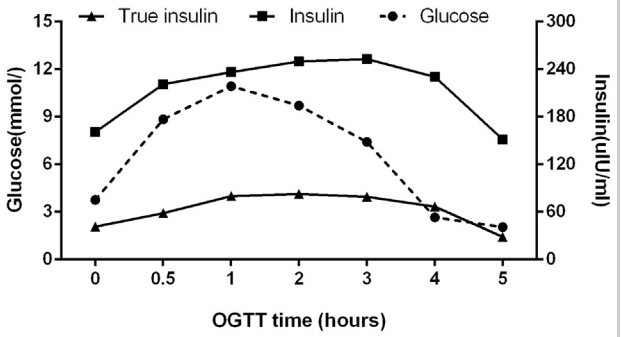

Figure 2. The glucose, insulin and true insulin of 5 patients with insulin autoimmune syndrome.

frequent small meals. The symptoms of 5 patients were relieved by frequent small meals, extra meals, low glycemic index meals, or acarbose. Three patients had been treated mainly with glucocorticoids as the anti-immune therapy.

DISCUSSION

In this study, we present a series of IAS cases, whereas most previous studies regarding IAS were case reports. In this study, we analyzed the clinical and laboratory characteristics of IAS. In addition, the characteristics of the extended OGTTs were explored deeply.

Among the 15 patients with confirmed diagnoses of IAS in our study, 9 had the insulin to C-peptide molar ratio more than 1, while 6 subjects had an insulin to C-peptide molar ratio <1. C-peptide and insulin are co-secreted from pancreatic β-cells into the portal circulation in equimolar proportions. The molar ratio of endogenous insulin to C-peptide in portal venous blood should approach but not attain or exceed a value of 1.0. In contrast, as a result of the selective extraction of insulin by the liver, this ratio should be considerably <1.0 in peripheral venous blood, even at maximal rates of insulin/C-peptide secretion. Boyko et al[15] found that the insulin to C-peptide molar ratio approximated 0.13 to 0.14 in the postabsorptive state and 0.19 an hour after the ingestion of 75 g of glucose. In cases of sulfonylurea-mediated hypoglycemia, the insulin to C-peptide ratio ranged from 0.03 to 0.21.[16–18] In the case of insulin administration, the insulin to C-peptide ratio was >1. The situation of presence of insulin-binding antibodies was considered the same as using exogenous insulin.[11] The study by Wong et al[12] also found that the insulin to C-peptide molar ratio may be reversed to >1 in the case of IAS.[12] The results in our study reveal that a relatively high insulin to C-peptide molar ratio suggests the diagnosis of IAS, but the diagnosis of IAS should not be excluded because of an insulin to C-peptide molar ratio <1. A low insulin to C-peptide ratio may be because of severe hypoglycemia, leading to the release of large amounts of C-peptide, which even exceeding the amounts of insulin binding with antibodies.

The results of OGTTs presented some specific features of IAS. Of 16 patients, 10 presented with elevated 2-h glucose values and 9 presented with hypoglycemia. A previous study[9] also found that hyperglycemia may occur immediately after a meal or oral glucose challenge in patients with IAS.[9] The study by Goldman et al[10] also found that the results of OGTTs could identify whether a patient was diabetic or nondiabetic, with or without hypoglycemia,[10] a finding consistent with our study. Censi et al[19] presented a case of IAS in which three 75-g OGTTs were conducted at different insulin autoantibody levels. The glucose states during OGTTs changed from diabetes to impaired glucose tolerance, along with the decreasing insulin autoantibodies,[19] which suggested an association between impaired glucose metabolism states and the insulin autoantibody levels. In our study, the results of OGTTs indicated that the C-peptide level responded earlier to the glucose tolerance and had a shorter peak value period compared with insulin, although C-peptide's fluctuation still lagged behind the glucose fluctuation. In addition, hypoglycemia appeared at the fourth and fifth hours in the extended OGTT. The most widely accepted hypothesis of hypoglycemia attributable to IAS is a mismatch between blood glucose and insulin concentration, secondary to the binding and release of secreted insulin by autoantibodies.[20] The action of endogenous antibodies that bind with insulin is that the initial pancreatic response to an increase in blood glucose would be ineffective in lowering the blood glucose level because that insulin binds to these endogenous antibodies, causing relatively insufficient

insulin and postprandial hyperglycemia that persists longer. This in turn results in prolonged pancreatic secretion of insulin and C-peptide in equimolar amounts, until the endogenous antibodies' binding capacity is exceeded.[10] Insulins bound with these endogenous antibodies in blood represent a reservoir[21,22]; the subsequent dissociation of insulin from these antibodies would continuously release free bioactive insulin enough to cause hypoglycemia of varying severity usually within 2−6 h or longer.[23] In our study, the prolonged elevated C-peptide peak duration caused a continuing release of insulin because of the relatively high blood glucose levels during OGTTs, which might lead to hypoglycemia after the insulin autoantibodies were largely bound with insulin and started to dissociate from these antibodies. The longer insulin peak value duration compared with C-peptide suggested the existence of insulin autoantibodies. Figure 2 clearly shows the existence of insulin antibody.

Among the 16 patients in our study, 6 had a medical history of autoimmune diseases, and 6 had a history of using sulfhydryl group drugs. IAS is considered to be associated with different medications, especially sulfhydryl group medication, and autoimmune conditions. In approximately 47% of the non-Asian patients, IAS seemed to be triggered by exposure to different medications (eg, captopril, penicillamine, pyritinol, carbimazole, imipenem, propylthiouracil, hydralazine, procainamide, isoniazid, and penicillin G). The proposed mechanism of IAS induced by medications that contain a sulfhydryl group is that the sulfhydryl group interacts with the disulfide bond of the insulin molecule, making the latter more immunogenic,[24] which allows the body to make more insulin antibodies.

The prognosis of patients with IAS in our study indicates a self-limited characteristic of IAS. Discontinuation of use of the sulfhydryl group drugs and adjusting the diet or diet mode proved to be effective in 10 of 16 patients, and 3 patients presented with a self-limited disease course without any treatment. Only 3 patients were treated with glucocorticoids as the anti-immune therapy, which suggested that these convenient methods successfully achieved disease remission. The prognoses of our patients were consistent with previous reports. In 80% of patients, IAS is a transient condition with spontaneous resolution within 3−6 months of diagnosis.[25] For those with intractable hypoglycemia, small frequent meals low in carbohydrates remain the first line of treatment; the rationale for this is to avoid postprandial hyperglycemia and thereby the stimulus for insulin secretion.[20] Glucocorticoid therapy (eg, oral prednisone 30−60 mg/d) may be useful as an adjunct therapy.[20] In the article by Lupsa et al,[9] most patients were treated with a low-carbohydrate diet, whereas only 38% of patients were treated with glucocorticoids. Recently, 2 cases of IAS were cured by administration of the immunoadsorption drug rituximab.[26,27] If sulfhydryl-containing medications were implicated, discontinuing use of the drugs led to resolution of the symptoms.[9] Acarbose has demonstrated varying success in the management of IAS.[9] Simple treatments, including discontinuing use of related drugs, small frequent meals, low glycemic index diet, and acarbose, are effective and free of the adverse effects of glucocorticoids.

CONCLUSIONS

In our study, the characteristics of IAS have been summarized in depth. The insulin to C-peptide molar ratios were not consistently >1 in patients with confirmed diagnoses of IAS in our study, which suggested the low sensitivity of insulin to C-peptide molar ratio to detect IAS. The 5-h extended OGTTs presented hyperglycemia and hypoglycemia at the same time, and the high insulin and C-peptide levels indicated the continuous release of insulin and prolonged insulin peak duration, which suggested that IAS leads to hypoglycemia in some cases. The therapy in our study also revealed the self-limited disease course of IAS, and despite the effectiveness of anti-immunity therapy, convenient therapy, such as frequent small meals, low glycemic index diet, and acarbose, performed well in many patients. This study provides more simple and effective therapy choices for IAS.

CONFLICTS OF INTEREST

The authors have indicated that they have no conflicts of interest regarding the content of this article.

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