Reactive Hypoglycemia Associated with Transient Hyperthyroidism in the Background of the Prediabetic Stage

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A 70-year-old woman suffered from hypoglycemic symptoms three or four hours after glucose intake for three months. At this time, the patient felt she had perspired more than in previous years. A diffuse elastic goiter without tenderness was palpable. Transient hyperthyroid state with little uptake by ¹²³I-thyroid scintigram was shown and diagnosed as silent thyroiditis. Oral glucose ingestion test (OGTT) showed normal glucose response but high insulin response and hypoglycemia occurred at 240 minutes. We diagnosed reactive hypoglycemia for glucose intake. The frequency of hypoglycemia reduced after the glucose intake decrease. Hypoglycemia did not occur after glucose intake in the euthyroid state. Then OGTT showed a borderline pattern and delayed hyperinsulinemic response. Reactive hypoglycemia may have been the result of transient hyperthyroid state in the background of the pre-diabetic stage. (Kitakanto Med J 2010 ; 60 : 151~154)

Key Words : postprandial hypoglycemia, transient hyperthyroidism, prediabetes

Introduction

Reactive hypoglycemia refers to disorders in which postprandial hypoglycemia occurs within 2–5 hours after food intake. In adults reactive hypoglycemia can be subdivided into three categories: (a) hypoglycemia after surgery of the upper gastrointestinal tract (alimentary hypoglycemia),¹ (b) hypoglycemia in patients with elevated glucose in an oral glucose tolerance test (early diabetes hypoglycemia)² and (c) idiopathic functional hypoglycemia.³ In hyperthyroid patient, beta-adrenergic hyperresponsiveness is shown.⁴ Postprandial hypoglycemia is associated with beta-adrenergic hypersensitivity.⁵ Here, we report a case of reactive hypoglycemia of transient hyperthyroidism in the background of the pre-diabetic stage.

Case report

For three months, a 70-year-old woman suffered from a sense of sleepiness or cold sweat three or four hours after food such as juice or cake intake. At this time, the patient felt she had perspired more than in

previous years. When the patient came to our hospital immediately after sensing these symptoms, the blood glucose was 60mg/dl and the immunoreactive insulin (IRI) was 5.6 μ U/ml caused by hypoglycemia.

There was no previous history of the disease. Her brother had type 2 diabetes mellitus. Other family members had no previous history of diabetes mellitus, nor were there any other previous history of the disease. She did not drink alcohol or smoke.

Physical examination showed the following: height 155cm, weight 56kg (body mass index 23.3kg/m²), blood pressure 133/66mmHg, pulse rate 88/min and temperature 36.7°C. The conjunctiva was not anemic. The thyroid was diffusely enlarged and elastic without tenderness on palpation. There were no abnormalities on the chest or abdomen. There was no lymphadenopathy. The tendon reflexes were symmetrically normal in the tetra limbs. There were no abnormalities in sensation. Finger tremors were not noted.

The laboratory data is shown in Table 1. Urinalysis, hematology, liver function, renal function and electrolytes were within a normal range. Fasting

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Table 1 Laboratory data on the admission

Urinalysis		Chemistry			
protein	(-)	AST	25mU/ml	CRP	0.1mg/dl
glucose	(-)	ALT	23mU/ml	FBG	91mg/dl
blood	(-)	LDH	177mU/ml	fasting IRI	7.8μU/ml
aceton	(-)	γ-GTP	239mU/ml	U-CPR	55μg/day
pH	5	protein	12mU/ml	Serology	
Hematology		albumin	6.6g/dl	STS	(-)
RBC	395×10 ⁴ /μl	ZTT	4g/dl	HBs Ag	(-)
Hb	12.3g/dl	TTT	7.2U	anti-HCV Ab	(-)
Ht	39.20%	BUN	6.3U	Thyroid function	
platelet	21.8×10 ⁴ /μl	Cr	9.9mg/dl	TSH	0.02μU/ml
WBC	9300/μl	UA	0.7mg/dl	free-T3	3.89pg/ml
basophil	1%	Na	4.6mg/dl	free-T4	1.39ng/ml
eosinophil	3%	K	144mEq/l	Tg-Ab	6u/ml
segment	48%	Cl	4mEq/l	TPO-Ab	0.2u/ml
lymphocyte	42%	Ca	9.6mg/dl	TBII	(-)
monocyte	7%	amylase	82su/dl		
ESR	23mm/hr	total cholesterol	193mg/dl		
		HDL-cholesterol	45mg/dl		
		triglyceride	96mg/dl		

Table 2

75g oral glucose ingestion (at admission)						
time (min (s))	0	30	60	120	180	240
glucose (mg/dl)	93	193	137	115	88	61
IRI (μU/ml)	8.0	118.3	95.4	42.8	23.5	5.2
75g oral glucose ingestion (six months later)						
time (min (s))	0	30	60	120	180	240
glucose (mg/dl)	98	163	178	145	112	85
IRI (μU/ml)	8.4	63	82.5	100.7	43	7.1

Table 3

Starvation test						
time (hour (s))	5	11	20	29		
glucose (mg/dl)	82	77	83	83		
IRI (μ U/ml)	4.5	3.2	2.7	2.1		
CPR inhibition test (regular insulin 0.1u/kg/hour)						
time (minute (s))	0	10	20	30	40	50
glucose (mg/dl)	83	85	74	53	43	36
CPR (ng/ml)	1.9	2.0	1.7	1.3	1.1	0.9
free-IRI (μ U/ml)	7.7	101.9	120	118.3	122	122.9
IRG (ng/ml)	45	205	295	305	305	303

IRI : immunoreactive insulin, IRG : immunoreactive glucagons, CPR : C-peptide immunoreactivity

plasma glucose ; 91 mg/dl, fasting IRI ; 7.8μU/ml, urine C-peptide reactivity (CPR) ; 55μg/day. There were no abnormalities in the chest X ray or electrocardiogram. TSH ; 0.02μU/ml, free-T3 ; 3.89pg/ml, free-T4 ; 1.39ng/dl, thyroglobulin antibody ; 6.0u/ml, thyroid peroxide antibody ; 0.2u/ml indicating mild hyperthyroid state due to autoimmune thyroid disease, but TSH receptor binding antibody (TBII) was negative. ¹²³I-thyroid scintigram showed little uptake (3 hrs 1.2%, 24hrs 1.2%), indicating silent thyroiditis. Although the patient felt she had perspired more than in previous years, we could find no evidence of hyper-

thyroidism. Subsequently, we diagnosed subclinical hyperthyroidism due to silent thyroiditis. 75g oral glucose ingestion test showed normal glucose response but high insulin response. However, hypoglycemic symptoms occurred 240minutes later and blood glucose 61mg/dl and IRI 5.2μU/ml (Table 2). Starvation test showed gradual IRI decrease for 29 hours and CPR inhibition test showed gradual CPR decreases, indicating the insulin secretion was not autonomous (Table 3). Arginine tolerance test showed normal IRI, CPR, immunoreactive glucagon (IRG) and GH response. Corticotropin-releasing hormone (CRH)-

Table 4
Arginine tolerance test (arginine 30g)

time (hour (s))	0	15	30	45	60	90	120
glucose (mg/dl)	87	110	129	112	95	83	82
IRI (μ U/ml)	5.2	25	47.2	49	35.9	16	5.9
CPR (ng/ml)	2.3	4.6	6.7	7.9	7.7	5.5	3.8
IRG (ng/ml)	49	310	310	240	180	130	110
GH (ng/ml)	0.75	0.84	1.25	4.57	6.85	3.21	1.56

CRH-GHRH-TRH-LHRH tolerance test

time (minute (s))	0	15	30	60	120
ACTH (pg/ml)	35	203	196	169	121
cortisol (μ g/dl)	11.3	15.1	16.1	14.6	13.0
GH (ng/ml)	0.96	3.37	4.78	6.11	1.78
TSH (μ U/ml)	0.02	0.02	0.02	0.02	0.02
prolactin (ng/ml)	3.8	40.7	36.0	26.6	20.5
LH (mIU/ml)	15.1	21.1	26.1	29.9	30.7
FSH (mIU/ml)	58.41	58.20	59.19	67.06	75.43

CRH : corticotropin-releasing hormone, GHRH : growth hormone-releasing hormone
TRH : thyrotropin-releasing hormone, LHRH : lutenizing hormone-releasing hormone

Fig. 1 Clinical course of the patient.

GH-releasing hormone (GHRH)-thyrotropin-releasing hormone (TRH)- (LH)- releasing hormone (LHRH) tolerance test showed normal ACTH, cortisol, GH and prolactin response, low LH and FSH response and no TSH response reflecting hyperthyroid state (Table 4). We diagnosed postprandial hypoglycemia for glucose intake. The frequency of hypoglycemia decreased when the patient reduced simple glucose intake or primary carbohydrate ingestion of rice or bread following vegetables, meat or fish. The hyperthyroid state had returned to euthyroid state by observation alone. After euthyroid state, hypoglycemia did not occur following glucose intake (Fig. 1). Six months later 75g oral glucose ingestion test showed borderline glucose response and delayed high insulin response. Hypoglycemic symptoms did not occur 240minutes later (Table 2). At this time TSH ; 1.81 μ U/ml, free-T3 ; 2.24pg/ml and free-T4 was 1.08 ng/dl indicating euthyroid state.

Discussion

The patient had clinical manifestation featuring postprandial hypoglycemia without using hypoglycemic drugs. The results of starvation test and CPR inhibition test did not show the presence of autonomous insulin secretion such as insulinoma. Normal IRG and GH response by arginine tolerance test and normal ACTH and GH response by CRH-GHRH tolerance test did not show insulin resistant hormone deficient state in our case. In admission 75g oral glucose ingestion test showed normal glucose response but the peak of glucose and IRI values were at 30 minutes and hypoglycemia was at 240minutes, indicating a postprandial oxyhyperglycemic pattern. Arginine tolerance test showed normal IRI and IRG response. The hypoglycemia was due to glucose responsive hypoglycemia in our case. Therefore, we diagnosed the patient as reactive hypoglycemia for glucose intake.

Alimentary hypoglycemia occurs in some patients after gastrectomy with or without gastric drainage procedure.¹ The hypoglycemia results from accelerated movement of ingested food into the small intestine, followed by rapid absorption of glucose that stimulates insulin secretion. Although upper gastrointestinal tract surgery had not been performed on the patient, she had transient hyperthyroidism due to silent thyroiditis. In hyperthyroid patients, beta-adrenergic hyperresponsiveness is shown.⁴ Beta-adrenergic blockers are used for symptomatic relief in most hyperthyroidism.⁶ Postprandial hypoglycemia is associated with beta-adrenergic hypersensitivity.⁵ Hyperthyroid associated beta-adrenergic hypersensitivity may cause reactive hypoglycemia. Although glucose metabolism

in patients with subclinical hyperthyroidism, in general, is not affected,⁷ a subclinical hyperthyroidism alone may not induce reactive hypoglycemia. We had not measured incretin such as gastric inhibitory polypeptide (GIP), which had insulinotropic action. Glucose and IRI responses are exaggerated in hyperthyroidism after oral glucose ingestion, while GIP levels are slightly higher but not statistically different in hyperthyroid subjects versus controls.⁸ The role of GIP in the hyperinsulinemia in hyperthyroid subjects may be minimal.

Reactive hypoglycemia in type 2 diabetic patients may rarely occur for decades before manifestations of the disease.² Hyperglycemia provokes a gradual increase in insulin secretion, which may persist after the disposal of the ingested glucose, leading to late hypoglycemia. Only 5% of patients with early diabetes and hypoglycemia after an oral glucose load had symptoms of hypoglycemia after meals.⁹ 75 g oral glucose ingestion test showed normal pattern at admission in our case. However, the patient's brother had type 2 diabetes mellitus. Six months later, 75 g oral glucose ingestion test showed borderline pattern and delayed hyperinsulinemic response indicating prediabetic state. Hyperthyroidism increases gluconeogenesis.¹¹ In our case oxyhyperglycemia and oxyhyperinsulinemia may be due to subclinical hyperthyroidism at admission. Six months later delayed hyperinsulinemia may not be due to end of hyperthyroid state. Reactive hypoglycemia may be partly caused by transient hyperthyroidism masked early stage pre-diabetes.

The pathogenesis of true idiopathic reactive hypoglycemia is unknown. Increased insulin sensitivity represents a feature of idiopathic reactive hypoglycemia.³ There are few data indicating that a reduced glucagon response may play a role in the development of late hypoglycemia after glucose ingestion.¹¹ Our patient had hyperinsulinemic response

after glucose ingestion and did not have a low glucagon response, indicated that the patient's hypoglycemia was not idiopathic reactive hypoglycemia.

In our case reactive hypoglycemia may be due to transient hyperthyroidism in the background of the pre-diabetic stage.

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