

Postprandial Reactive Hypoglycemia in an Oldest-old Patient Effectively Treated with Low-dose Acarbose

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Abstract. We recently encountered a 96-year-old Japanese woman who suffered from frequent hypoglycemia. Endocrinological and imaging data eliminated the possibility of insulinoma, whereas oral glucose tolerance testing revealed impaired glucose tolerance and subsequent reactive hypoglycemia. The patterns between insulin or C-peptide secretions and glucose excursions demonstrated that the discrepancy occurred in the late postprandial stage. Administration of small doses of alpha-glucosidase inhibitor (α -GI) dramatically inhibited the rapid rise and subsequent precipitous fall of plasma glucose. Reactive hypoglycemia may be one of the important cause of hypoglycemia in the elderly, and α -GI could effectively and safely prevent such hypoglycemic attacks in those patients.

Key words: Reactive hypoglycemia, Oldest-old patient, Oral glucose tolerance test, Oral sucrose tolerance test, Alpha-glucosidase inhibitor

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REACTIVE hypoglycemia is a rare pathophysiological condition in which hypoglycemic symptoms occur postprandially [1, 2]. Dumping syndrome after gastrointestinal surgery is the most frequent cause, but some cases can be caused by mild diabetes mellitus, hormone-deficient status, insulinoma, drugs, or other rare mechanisms including fructose intolerance, or may be idiopathic. Patients with mild diabetes mellitus or impaired glucose tolerance may suffer from reactive hypoglycemia if excessive delayed insulin secretion occurs when the blood glucose levels are decreasing. Alpha glucosidase inhibitor (α -GI), which is used for the treatment of postprandial hyperglycemia due to its ability to inhibit carbohydrate digestion, has been found to prevent reactive hypoglycemia patients by blunting the delayed hypersecretion of insulin [3–7]. Here we report an oldest-old patient with reactive

hypoglycemia and impaired glucose tolerance, whose hypoglycemic symptoms were effectively relieved with low-dose α -GI, acarbose.

Case

A 96-year-old woman was admitted to our hospital from a nursing home because of frequent hypoglycemic episodes of unknown origin. Five weeks earlier, she was brought urgently to a nearby hospital due to loss of consciousness and hypoglycemia (17 mg/dl). Intravenous injection of 10 g glucose restored her consciousness state and she returned to the nursing home. One week later, a similar hypoglycemic coma occurred and she was brought to another hospital. Her blood glucose level was 59 mg/dl, and intravenous glucose injection was again performed. Following this episode, she was admitted to the hospital, but was discharged one week later because physical examination and abdominal ultrasound revealed no abnormalities and there were no apparent hypoglycemic episodes observed during the hospitalization. However, 6 days after discharge,

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another hypoglycemic episode occurred. To prevent hypoglycemic attacks, she was given supplementary sugar 5 times a day at 6:00, 10:00, 15:00, 21:00, and 24:00 (5 g each time). Nevertheless, similar hypoglycemic events, including disturbance of consciousness, still frequently occurred. These episodes were observed anytime during the day, but most frequently before supper. She was referred to our hospital for further examination.

On admission, physical examination revealed her height to be 134.2 cm and weight 29.0 kg; her BMI was 16.1 kg/m². She was almost completely deaf because of certain auditory dysfunction suffered in her infancy, but could communicate by writing. A moderate systolic ejection murmur was heard on the 2nd right sternal border, which was afterward identified by

echocardiography to be due to aortic valve stenosis. She had no history of alcohol consumption, and had never undergone any alimentary surgery or administration of any oral hypoglycemic agents or insulin.

Laboratory and endocrine data on admission are shown in Table 1. Serum levels of immunoreactive insulin (IRI) and C-peptide were normal after overnight fasting. Blood hemoglobin A1c was 5.3%. The serum levels of pituitary and adrenal hormones, ACTH, cortisol, GH, and TSH, which may affect plasma glucose levels, were normal. Furthermore, because no significant abnormality was detected by either brain MRI or abdominal CT, insufficiencies in the pituitary or adrenal glands were not the cause of the hypoglycemic attacks. Insulin antibody levels were below the normal range. The tumor markers CEA and CA19-9 were normal.

We examined the possibility of insulinoma. Abdominal CT scanning showed no obvious pancreatic mass. As we could not obtain the serum samples at the exact time of a hypoglycemic attack, we subsequently performed a 48-hour fasting test. We observed that the blood glucose levels were above 70 mg/dl throughout the entire fasting period, and that serum insulin and c-peptide levels were completely suppressed during the test (Fig. 1). Taken together her hypoglycemia was not induced by insulinoma or an IGF-II-secreting tumor such as a non-islet cell tumor. The counterregulatory hyperglycemic hormones, glucagons (218 pg/ml) and cortisol (37.6 µg/dl), were sufficiently secreted at the end of the fasting test.

Table 1. Laboratory data on admission

Urinalysis	
Protein	(-)
Glucose	(-)
CBC	
WBC	4430/mm ³
RBC	4.14 × 10 ⁶ /mm ³
Hb	11.5 g/dl
Hct	35.1%
Plt	24.6 × 10 ⁴ /mm ³
Blood Chemistry	
TP	7.2 g/dl
Alb	3.5 g/dl
GOT	24 IU/l
GPT	11 IU/l
LDH	185 IU/l
ALP	296 IU/l
BUN	10 mg/dl
Cre	0.5 mg/dl
T-Chol	177 mg/dl
TG	63 mg/dl
CEA	3.4 ng/ml
CA19-9	<1 U/ml
Glucose	76 mg/dl
HbA1c	5.3%
Endocrinological data	
IRI	3.4 µU/ml
C-peptide	1.0 ng/ml
TSH	8.48 µIU/ml
ft3	2.42 pg/ml
ft4	1.01 ng/dl
ACTH	22.1 pg/ml
Cortisol	29.8 µg/dl
GH	0.28 ng/ml
LH	36.1 mIU/ml
FSH	69.9 mIU/ml
Insulin Ab	5.1%

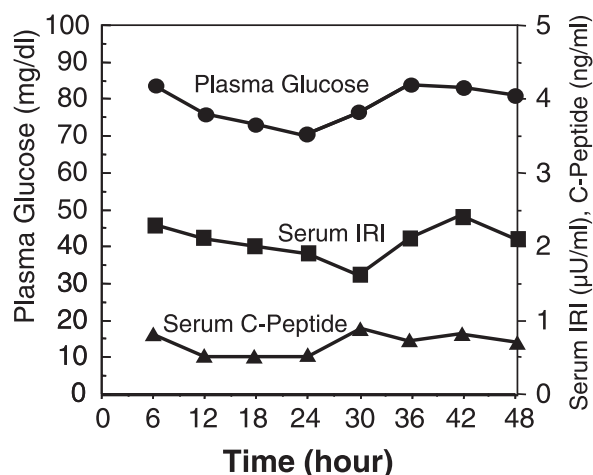


Fig. 1. Forty-eight hour fasting test. Plasma glucose (●) serum IRI (■) and C-peptide (▲) concentrations were measured for 48 hours after the last food intake.

Next, to elucidate the time when a hypoglycemic attack was liable to occur in daily life, we followed the circadian change in the blood glucose level in the patient for several days with self-monitoring blood glucose (SMBG) equipment (Medisafe, Terumo, Tokyo, Japan). SMBG tests were performed 4 times a day, before every meal and at bedtime. Interestingly, hypoglycemia was observed exclusively before supper (17:30) approximately once every two days (Table 2A). The hypoglycemic levels were between 50–70 mg/dl and no consciousness disturbance including coma occurred. However, the patient frequently complained of palpitations when her blood glucose level decreased.

Because of the regularity of the hypoglycemic attacks, we suspected they might indicate postprandial reactive hypoglycemia. Thus we performed a 50 g oral glucose tolerance test (OGTT). Plasma glucose, serum insulin and C-peptide were followed for up to 6 hours. As shown in Fig. 2, the glucose level at 120 min was as high as 186 mg/dl, which categorizes this patient as having impaired glucose tolerance. Peak insulin level was 97 μ U/ml at 120 min, and this delayed hypersecretion continued to 180 min, and resulted in a prominent decrease of blood glucose between 180–240 min, followed by a nadir of 49 mg/dl at 300 min. We concluded from these data that consistent hypersecretion of insulin was the cause of hypoglycemia in this case.

Finally, we investigated the effect of alpha-glucosidase inhibitor on the hypoglycemic attack. Fifty gram oral sucrose tolerance tests (OSTT) were performed

with or without acarbose. The patient was given 50 g sucrose (in 150 ml water) with or without acarbose (50 mg) in the first draught of the solution. Plasma glucose, IRI, and C-peptide were monitored at 0, 30, 60, 120, 180, 240, 300, 360, and 420 min. The two tests were performed 4 days apart. As shown in Fig 3, sucrose load without acarbose resulted in a significant increase in plasma glucose (243 mg/dl), IRI (55.0 μ U/ml), and C-peptide (8.4 ng/ml) levels, which peaked at 120 min postload, as in the case in OGTT. The glucose nadir was 70 mg/dl at 360 min. No hypoglycemic symptoms were observed during the test. Acarbose dramatically changed the glycemic response; the peak glucose (148 mg/dl) and insulin (23.2 μ U/ml) levels were significantly decreased, and the glucose nadir level (101 mg/dl, 420 min) was significantly increased, resulting in a decrease in the area under the concentration curve (AUC) in each graph.

After these studies, the patient was prescribed 50 mg acarbose before each meal (150 mg per day). Since beginning medication, no significant side effects have occurred and the SMBG data show no hypoglycemia, including before supper (Table 2B). After she was discharged to her nursing home, no hypoglycemic episodes including hypoglycemic coma have been observed.

Table 2. Daily profile of self-monitored blood glucose (SMBG). A; Before, B; After starting acarbose treatment (150 mg per day)
Glucose levels under 70 mg/dl are underlined.

A.				
Date	6:30	11:30	17:30	21:00
May 3	83	83	65	83
May 4	93	72	73	103
May 5	77	72	<u>54</u>	135
May 6	84	101	<u>54</u>	73
B.				
Date	6:30	11:30	17:30	21:00
June 6	75	89	83	113
June 7	75	88	114	89
June 8	88	93	84	106
June 9	99	93	101	106

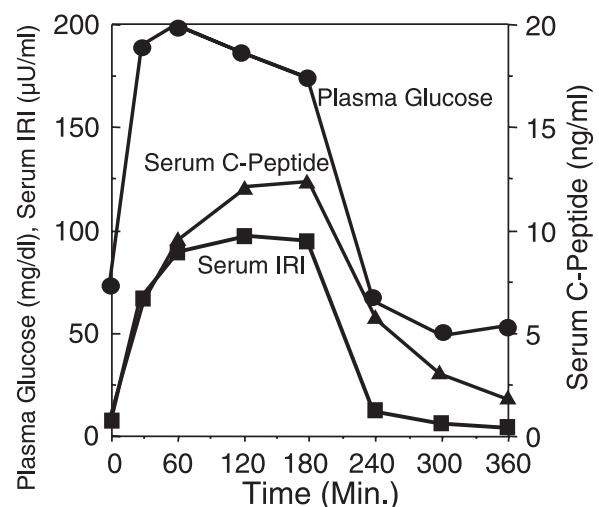


Fig. 2. Fifty gram oral glucose tolerance test (50 g OGTT). Plasma glucose (●) serum IRI (■) and C-peptide (▲) concentrations were measured until 360 min after glucose load.

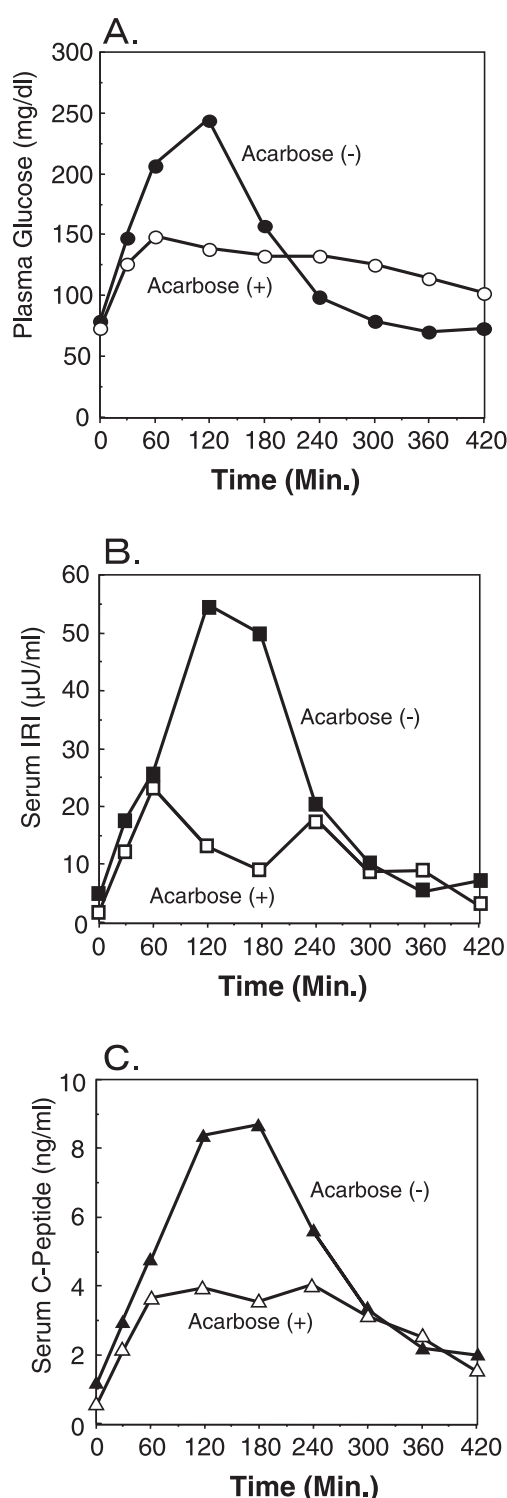


Fig. 3. Fifty gram oral sucrose tolerance test (50 g OSTT). Plasma glucose (A), serum IRI (B), and C-peptide (C) concentration were measured until 420 min after sucrose load only (solid symbols) or after the sucrose load plus 50 mg acarbose administration (open symbols).

Discussion

We encountered an oldest-old woman who suffered from hypoglycemic episodes of uncertain origin. She had no apparent history of diabetes mellitus and thus no history of prescription of oral hypoglycemic agents or insulin. Insulinoma, a non-islet cell tumor and other endocrine disorders such as hypopituitarism were incompatible with our case. We could not eliminate the possibility of an insulin-like growth factor-II (IGF-II) secreting tumor, which is, however, highly unlikely because no tumor mass was detected in CT imaging and serum tumor marker levels were within the normal range.

The regularity of the timing of the hypoglycemic episodes and results of OGTT revealed this case to be one of postprandial reactive hypoglycemia. The causes of reactive hypoglycemia are various. Hofeldt classified postprandial reactive hypoglycemia into five categories: alimentary hypoglycemia, diabetes mellitus, hormonal, deficient early hepatic gluconeogenesis, and idiopathic [1]. Dumping syndrome after gastrointestinal surgery is the most frequent cause, but this patient had no history of abdominal surgery. It has been reported that patients with mild diabetes mellitus or impaired glucose tolerance can experience reactive hypoglycemia, because excessive insulin is discharged in the late period, which may cause a severe drop in plasma glucose levels [2]. Although she had never been diagnosed with impaired glucose tolerance before, the OGTT pattern showed moderately high glucose levels, and subsequent extremely high insulin levels at 120 min after the challenge, which may categorize this case as diabetic reactive hypoglycemia. From this point of view, the frequent prophylactic intake of sugar at the nursing home might have damaged the hypoglycemic response, whereas certain foods with low glycemic indices, such as brown rice or rye bread, could have lessened the risk of hypoglycemic events. Although we did not measure postprandial levels of norepinephrine or glucagons, age-related decreases in these counterregulatory hormones secreted as plasma glucose levels fall might influence the onset of hypoglycemia.

It is of interest that a glucose nadir was observed at around 300–360 min after meals or the glucose/sucrose challenge in this case. The cause of the extremely slow reactivity is uncertain. Some previous reports have shown that the augmentation of insulin secretion in

reactive hypoglycemia is mediated by a preceding secretion of incretins, a series of gut hormones with insulinotropic activity, including glucagon-like peptide-1 (GLP-1) [3, 8]. Although serial measurement of GLP-1 concentrations was not performed, certain changes in the incretin response, probably due to attenuated gastrointestinal motility with age, might have been responsible for the extremely delayed insulin hypersecretion in this case. Further studies are needed to clarify the relationship between incretin and aging.

In OSTT, we could not induce apparent hypoglycemia. This was probably because the 50 g load of sucrose was quantitatively insufficient. A 75 g challenge might have been enough, but she was unable to tolerate such an overload. However, the delayed and sustained (up to 180 min) insulin hypersecretion and subsequent prominent glucose decrease, observed in OGTT, were reproducible.

Alpha glucosidase inhibitor (α -GI) is used to treat postprandial hyperglycemia since it slows the absorption of carbohydrate. Acarbose, a kind of α -GI, has been found to prevent the postprandial hypersecretion of insulin and reactive hypoglycemia [3–7]. Similarly,

in this case, it dramatically attenuated the early glucose excursions and insulin rise, and significantly raised the glucose nadir level. This result confirmed that this hypoglycemic agent could be used for the prophylaxis of postprandial hypoglycemia.

It has been reported that gastrointestinal side-effects such as ileus occasionally accompany α -GI use [9], especially in elderly patients. In this case, however, no such adverse effects were observed. In previous studies, patients were given 100 mg acarbose at each meal [4–6], whereas the patient in this study was given 50 mg. This low-dose administration may be safe and sufficiently effective for the oldest-old patients.

In conclusion, we experienced a case of reactive hypoglycemia associated with an oldest-old patient, which was effectively treated with acarbose. It is reported that the prevalence of undiagnosed impaired glucose tolerance has increased recently, especially in the elderly [10]. It is considered that among elderly patients with hypoglycemia of unknown etiology, diabetic reactive hypoglycemia may be hidden, and so it is recommended that OGTT be performed and the data be followed up for 5–6 hours in those patients.

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