Postprandial Reactive Hypoglycemia Treated with a Low-dose Alpha-glucosidase Inhibitor: Voglibose May Suppress Oxidative Stress and Prevent Endothelial Dysfunction

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Abstract

We encountered a 62-year-old woman who experienced frequent episodes of hypoglycemia. She was diagnosed with postprandial reactive hypoglycemia according to the results of oral glucose and sucrose tolerance tests, having undergone an endocrinological examination and image inspection. The administration of low-dose voglibose, an alpha-glucosidase inhibitor (α -GI), improved the glucose fluctuations and inhibited hypoglycemic symptoms. Voglibose is also known to diminish oxidative stress and maintain endothelial function after hyperglycemia. An α -GI might effectively prevent hypoglycemic symptoms and endothelial dysfunction by suppressing oxidative stress in such cases.

Key words: postprandial reactive hypoglycemia, alpha-glucosidase inhibitor, oral tolerance test, oxidative stress, endothelial function

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Introduction

Reactive hypoglycemia is a relatively uncommon meal-induced hypoglycemic disorder. Dumping syndrome after gastrointestinal surgery is the most frequent cause, while bariatric surgery (which interferes with incretin hormones), endocrinopathies (such as insulinoma), mild diabetes mellitus (including impaired glucose tolerance), drugs, or other rare mechanisms, can also cause this condition (1, 2). Idiopathic reactive hypoglycemia also occurs in some patients. Furthermore, if excessive delayed insulin secretion occurs while the blood glucose levels are decreasing, then hypoglycemia can be seen in apparently healthy individuals, typically several hours after a meal with a high glycemic load, especially in patients with mild diabetes mellitus or impaired glucose tolerance (2).

Many studies have reported postprandial hyperglycemia as a major cause of a mechanism that induces oxidative stress and endothelial dysfunction (3, 4). However, upon review of the literature, we have not found any case reports that dem-

onstrate whether high glucose levels and subsequent extremely high insulin levels induce oxidative stress and endothelial dysfunction.

Alpha-glucosidase inhibitors (α -GIs) are anti-diabetic agents that improve postprandial hyperglycemia, one of the most common abnormalities in the early phase of type 2 diabetes. The mechanism of action is the inhibition of carbohydrate digestion. It is known that α -GIs prevent reactive hypoglycemia by adjusting insulin secretion (5, 6).

Through this case report, we aimed to assess the effect of α -GIs and investigate induced oxidative stress and endothelial dysfunction.

Case Report

The patient was a 62-year-old woman who was admitted to our hospital for the assessment and treatment of hypoglycemia. A few days prior to admission, she was urgently brought to a nearby hospital due to the loss of consciousness, hypoglycemia (blood glucose, 28 mg/dL) and high insulin levels (8.8 μ U/mL). Intravenous administration of 20 g

Table. Laboratory Data on Admission.

【Blood cell count】		Glu	102 mg/dL
WBC	5000 / μ L	Insulin	6.4 μ U/mL
RBC	404 $\times 10^4$ / μ L	C-peptide	1.72 ng/mL
Hb	12.8 g/dL	GAD antibody	negative
Ht	39.8 %	Anti-insulin antibody	negative
Plt	23.4 $\times 10^4$ μ L	HbA1c	4.9 %
【Biochemistry】		GA	15.3 %
TP	7.2 g/dL	1.5-AG	19.5 μ g/mL
Alb	4.1 g/dL	【Pituitary Hormone】	
T-Bil	0.5 mg/dL	GH	0.5 ng/mL
BUN	9.0 mg/dL	IGF-1	157 ng/mL
Cr	0.4 mg/dL	TSH	1.70 μ IU/mL
Na	141 mEq/L	LH	29.3 mIU/mL
K	4.3 mEq/L	FSH	71.0 mIU/mL
Cl	104 mEq/L	PRL	10.5 ng/mL
AST	29 U/L	【Thyroid Hormone】	
ALT	29 U/L	F-T4	1.1 ng/dL
LDH	210 U/L	F-T3	2.7 pg/mL
CPK	155 U/L	【Adrenal gland Hormone】	
CEA	2.1 ng/mL	Time	6:00 21:00
CA19-9	0.8 ng/mL	ACTH (pg/mL)	18.6 27.3
		Cortisol (μ g/dL)	14.0 8.4

of glucose reversed her hypoglycemic state. The following day, she again fell into a hypoglycemic coma and was brought to the same local hospital. She was referred to our hospital for further investigation into the cause of hypoglycemia.

On this admission, the patient's height was 152 cm. She had a body weight of 42.0 kg, body mass index (BMI) of 18.0 kg/m², blood pressure of 96/63 mmHg, and body temperature of 36.8°C. Physical and neurological findings did not reveal any obvious abnormalities. She had no history of alcohol consumption. Her past surgical history was significant for an operation for breast cancer at 52 years of age, however, she had not undergone any alimentary surgery or received any oral hypoglycemic agents or insulin. The patient's mother and younger brother both had diabetes mellitus. Laboratory data on this admission are shown in Table. Fasting blood test results revealed a normal blood glucose level of 102 mg/dL. Serum levels of immunoreactive insulin (IRI) and C-peptide were also normal. Blood HbA1c was 4.9%, and she tested negative for anti-insulin antibodies. The serum levels of pituitary, adrenal and thyroid hormones were near the normal ranges. Moreover, abdominal computed tomography and magnetic resonance imaging did not reveal any abnormal findings in the pancreas. According to these results, the possibility of secondary hypoglycemia was thoroughly ruled out.

Because we eventually suspected that these results might indicate postprandial reactive hypoglycemia, we performed 50-g and 75-g oral glucose tolerance tests (OGTTs) and measured the glucose levels using a continuous glucose monitoring system (iPro[®]2, Medtronic MiniMed Inc., Northridge, USA). As shown in Fig. 1, the glucose levels decreased between 240 and 300 minutes during both the 50-g and 75-g OGTTs. Therefore, we repeated the 75-g OGTT to specifically measure the plasma glucose, along with the serum levels of IRI and C-peptide, which were followed for

Figure 1. Results of 50- and 75g oral glucose tolerance tests. The plasma glucose levels were measured by continuous glucose monitoring (CGM). The glucose nadir was at approximately 60 mg/dL and 10 g of glucose was administered.

up to 240 minutes (Fig. 2). The results showed that this patient had impaired glucose tolerance, which was induced by high serum IRI and C-peptide levels at 120 minutes, and consequently, she experienced hypoglycemia due to the delayed hypersecretion of insulin.

To investigate the effect of an α -GI on the patient's hypoglycemic episodes, production of oxidative stress and induction of endothelial dysfunction by postprandial hyperglycemia before hypoglycemia caused by the hypersecretion of insulin, we performed 100-g oral sucrose tolerance tests with or without 0.2 mg of voglibose. The production of reactive oxygen metabolites (ROMs) was measured using the d-ROMS test (Diacron, Grosseto, Italy) and endothelial function was assessed using the EndoPAT 2000 device (Itamar Medical Ltd., Caesarea, Israel). The plasma glucose, IRI, C-peptide, and d-ROM levels were monitored at 0, 30, 60, 120, 180, and 240 minutes. Regarding endothelial function, we monitored the reactive hyperemia index (RHI) before and after the start of the sucrose tolerance test (0 and 240 minutes), and these measurements were performed 2 days apart. As shown in Fig. 3, voglibose improved the glucose fluctuations after the sucrose tolerance test. The peak glucose, IRI, and C-peptide levels were decreased, resulting in a disappearance of the patient's signs and symptoms of hypoglycemia. After she was discharged, the patient no longer exhibited any hypoglycemic symptoms or a coma while using 0.2 mg of voglibose at the time of excessive carbohydrate intake.

Discussion

The present case report describes a 62-year-old woman who experienced frequent hypoglycemia due to the postprandial hypersecretion of insulin. A diagnosis of postprandial reactive hypoglycemia was made according to the finding of decreased blood glucose levels accompanied by symptoms after a glucose or sucrose tolerance test. The

Figure 2. Results of a 75-g oral tolerance test. The plasma glucose (A), serum IRI (B) and C-peptide (C) levels were measured for 240 minutes.

Figure 3. Results of a 100-g oral sucrose tolerance test. The plasma glucose (A), serum IRI (B), and C-peptide (C) levels, oxidative stress (d-ROMs) (D), and endothelial function (box in D) were measured for 240 minutes.

patient had no apparent history of diabetes mellitus and thus no history of prescription of oral hypoglycemic agents or insulin. In order to eliminate the possibility of an endocrine

disorder, in particular an insulinoma, we performed 48-hour fasting blood tests. Her glucose levels, as measured by continuous glucose monitoring (CGM), were above 70 mg/dL

in the fasting period, and the serum IRI and C-peptide levels were substantially suppressed during the fasting period (data not shown). It has been reported that a patient who has impaired glucose tolerance can experience postprandial reactive hypoglycemia caused by the secretion of excessive insulin in the late period after a meal (1, 7), which may cause severely decreased plasma glucose levels. Although her postprandial glucose levels monitored by CGM did not increase after food intake in the hospital (1,600 kcal/day), the result of a 75-g OGTT showed an impaired glucose tolerance pattern with slightly high glucose levels at 120 minutes and delayed hypersecretion of insulin at 120 minutes.

We also performed 100-g oral sucrose tolerance tests in the current patient to validate the effects of the α -GI voglibose. It has been found that α -GIs prevent the postprandial hypersecretion of insulin and reactive hypoglycemia (5, 6, 8). In this case, voglibose attenuated the blood glucose levels and subsequent insulin increase, and her symptoms of hypoglycemia disappeared. According to these results, voglibose may be a prophylactic drug for hypoglycemia when used at meals with an excessive intake of carbohydrates.

Reactive hypoglycemia has been reported to be associated with irregularities in hormonal and/or cerebral mechanisms involved in glucose homeostasis, such as increased insulin secretion due to increased secretion of glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) (9). Therefore, the measurement of active GLP-1 was performed at 0, 30, 60, 120, and 180 minutes in the 100-g sucrose tolerance test with or without voglibose. The change in the GLP concentration [Δ GLP-1: max concentration (pmol/L) minus the baseline concentration] did not differ with the presence or absence of voglibose. The Δ GLP-1 was 6.79 (14.12 pmol/L at 30 minutes minus 7.33 pmol/L at 0 minute) without voglibose and 7.16 (11.29 pmol/L at 30 minutes minus 4.13 pmol/L at 0 minute) with voglibose. Accordingly, we did not observe a significant increase in the concentration of active GLP-1 with or without voglibose. Unfortunately, we were unable to measure the concentration of GIP-1.

Recently, a commercially available assay of "organic peroxides," known as the d-ROMs test, has become available (10, 11). This assay is relatively inexpensive and can be performed in minutes. In a recent report, the d-ROMs assay was used to assess the effectiveness of various antioxidant treatment strategies (11). We observed that the patient's oxidative stress induced by postprandial hyperglycemia, as demonstrated by a reduction in the d-ROM levels, improved with voglibose treatment. Additionally, it has been reported that a potential mechanism by which postprandial hyperglycemia impairs endothelial function is the generation of reactive oxygen species (ROS) (12).

It is known that postprandial hyperglycemia induces endothelial dysfunction and oxidative stress. Oxidative stress appears to be a key player of endothelial dysfunction. The precise mechanism of the increase in oxidative stress

through glucose spikes remains unknown (13). However, recent studies have shown that protein C, NAD(P)H, or inflammatory markers are activated in response to a glucose spike, which causes the production of superoxide through the activation of these pathways (14).

Moreover, hyperinsulinemia is also known to activate NAD(P)H in an experimental rat model of aortic endothelial (15). Thus, insulin may also cause endothelial dysfunction through downstream effects on NAD(P)H oxidase and superoxide anion production.

α -GIs reduce postprandial hyperglycemia without postprandial hyperinsulinemia, successfully reducing oxidative stress and improving endothelial function (16).

In this case, voglibose may also improve endothelial function as demonstrated by the RHI. Because this report is a single case report, a greater accumulation of cases is necessary to demonstrate that voglibose reduces oxidative stress and improves endothelial function.

In summary, we experienced a patient with postprandial reactive hypoglycemia without type 2 diabetes mellitus who was effectively treated with low-dose voglibose. For such cases, we recommend that OGTT and sucrose tolerance tests be performed to diagnose and validate the effects of α -GIs. In addition, according to our results, this is the first case report to demonstrate that postprandial reactive hypoglycemia may impair the endothelial function in patients with impaired glucose tolerance, which could be improved by the use of voglibose prior to the intake of excessive amounts of carbohydrates.

The authors state that they have no Conflict of Interest (COI).

References

- Hofeldt FD. Reactive hypoglycemia. *Endocrinol Metab Clin North Am* **18**: 185-201, 1989.
- Tamura Y, Araki A, Chiba Y, Horiuchi T, Mori S, Hosoi T. Postprandial reactive hypoglycemia in an oldest-old patient effectively treated with low-dose acarbose. *Endocr J* **53**: 767-771, 2006.
- Moreno PR, Fuster V. New aspects in the pathogenesis of diabetic atherothrombosis. *J Am Coll Cardiol* **44**: 2293-2300, 2004.
- Ceriello A. Postprandial hyperglycemia and diabetes complications: is it time to treat? *Diabetes* **54**: 1-7, 2005.
- Pagano G, Marena S, Corgiat-Mansin L, et al. Comparison of miglitol and glibenclamide in diet-treated type 2 diabetic patients. *Diabete Metab* **21**: 162-167, 1995.
- Peter S. Acarbose and idiopathic reactive hypoglycemia. *Horm Res* **60**: 166-167, 2003.
- Sørensen M, Johansen OE. Idiopathic reactive hypoglycaemia: prevalence and effect of fibre on glucose excursions. *Scand J Clin Lab Invest* **70**: 385-391, 2010.
- Aoki C, Suzuki K, Yanagi K, Satoh H, Niitani M, Aso Y. Miglitol, an anti-diabetic drug, inhibits oxidative stress-induced apoptosis and mitochondrial ROS over-production in endothelial cells by enhancement of AMP-activated protein kinase. *J Pharmacol Sci* **120**: 121-128, 2012.
- Mitrakou A, Ryan C, Veneman T, et al. Hierarchy of glycemic thresholds for counterregulatory hormone secretion, symptoms, and cerebral dysfunction. *Am J Physiol* **260**: E67-E74, 1991.

10. Cesarone MR, Belcaro G, Carratelli M, et al. A simple test to monitor oxidative stress. *Int Angiol* **18**: 127-130, 1999.
11. Cornelli U, Terranova R, Luca S, et al. Bioavailability and anti-oxidant activity of some food supplements in men and women using the D-ROMS test as a marker of oxidative stress. *J Nutr* **131**: 3208-3211, 2001.
12. Sheetz MJ, King GL. Molecular understanding of hyperglycemia's adverse effects for diabetic complications. *JAMA* **288**: 2579-2588, 2002.
13. Kato K, Node K. Therapeutic potential of α -glucosidase inhibitors to prevent postprandial endothelial dysfunction. *Int Heart J* **55**: 386-390, 2014.
14. Ceriello A, Esposito K, Piconi L, et al. Oscillating glucose is more deleterious to endothelial function and oxidative stress than mean glucose in normal and type 2 diabetic patients. *Diabetes* **57**: 1349-1354, 2008.
15. Kashiwagi A, Shinozaki K, Nishio Y, et al. Endothelium-specific activation of NAD(P)H oxidase in aortas of exogenously hyperinsulinemic rats. *Am J Physiol* **277**: E976-E983, 1999.
16. Meugnier E, Faraj M, Rome S, et al. Acute hyperglycemia induces a global downregulation of gene expression in adipose tissue and skeletal muscle of healthy subjects. *Diabetes* **56**: 992-999, 2007.

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