Octreotide improves early dumping syndrome potentially through incretins: a case report

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Abstract. Dumping syndrome, or rapid gastric emptying, is a frequent complication after gastric surgery. In this case, the patient was a 47-year-old woman who 10 years previously had undergone distal gastrectomy with Billroth I reconstruction for early-stage gastric cancer. She presented with symptoms of weakness, headache, palpitation, sweating, dizziness and significant fatigue between one and two hours after a meal. Because a 75g oral glucose tolerance test (75g-OGTT) induced both acute postprandial tachycardia (within 1 hour) and postprandial hypoglycemia, we diagnosed this patient with early and late dumping syndrome. Dietary measures and acarbose improved symptoms of late dumping syndrome but did not prevent the symptoms of early dumping syndrome such as postprandial tachycardia, weakness, headache, palpitation, and dizziness. We therefore used the somatostatin analogue octreotide, which has been reported as an effective therapy for early dumping syndrome. Octreotide prevented the symptoms of early dumping syndrome, especially postprandial tachycardia, but caused postprandial hyperglycemia. Glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinoitropic polypeptide (GIP) were completely suppressed during the 75g-OGTT following subcutaneous injection of octreotide. No change was observed in vasoactive intestinal polypeptide (VIP), which is the gastrointestinal peptide hormone generally responsible for early dumping syndrome, suggesting possible contribution of incretins in early dumping syndrome of this patient.

Key words: Dumping syndrome, GLP-1, Octreotide

Material and Methods

Laboratory analyses

Blood samples were taken after an overnight fast. Plasma glucose concentrations were measured with the hexokinase G6PD UV method. Serum insulin concentrations were measured with a chemiluminescent enzyme immunoassay. Serum triglyceride concentrations were determined by Enzymatic method. Serum total cholesterol concentrations were measured by a cholesterol dehydrogenase ultraviolet method. Serum HDL cholesterol concentrations were determined by a direct method (Cholestest®N HDL, Sekisui Medical, Japan). Hemoglobin A1c (NGSP) levels were measured by high performance liquid chromatographic assay (HPLC). Serum total GIP and active GLP-1 were measured by ELISA (Merck-Millipore, Darmstadt, Germany). Serum VIP were measured by RIA (DiaSorin, Italy).
was 108/82 mmHg, her body temperature was 35.4°C, and her pulse rate was 60 beats/min and regular. Her palpebral conjunctivae were not anemic, and her bulbar conjunctivae were not icteric. Her oral mucous membrane was not dry. No vascular murmurs were heard in the cervical region. The thyroid gland was not palpable. Her heart sounds were clear, with no audible murmurs. Breath sounds were clear, and no rales were heard. The abdomen was flat and soft, and bowel sounds were hyperactive. There was no pretibial edema, and capillary refilling time was one second. She had a history of operations: for appendicitis at 13 years of age, Billroth I gastrectomy for early-stage gastric cancer at 37 years of age, and removal of gallstones (also at 37 years of age). She had no family history of diabetes mellitus or cancer. She had a past history of smoking (eight cigarettes/day), but had quit seven years prior to admission. At the time of admission she did not drink alcohol regularly, and had no allergies. Table 1 shows her laboratory data on admission, indicating no major abnormality.

The patient’s Sigstad’s score was 21 points on admission [4], strongly suggesting that her symptoms were related to dumping syndrome. We initially performed a 75g-OGTT to estimate whether early or late dumping syndrome was primarily responsible for inducing her symptoms. The results showed that peak insulin was observed at 30 minutes and was associated with symptoms after 1 hour (Fig. 1). Using continuous glucose monitoring systems (CGMS) we also observed postprandial hypoglycemia, indicating that her symptoms were related to late dumping syndrome (Fig. 2A). Although insulinoma might be ruled out due to fasting hypoglycemia with CGMS, we didn’t proceed 72h fasting test because her symptoms are limited in postprandial state. Next, the effect of treatment with acarbose was analyzed with CGMS. Administration of acarbose improved postprandial hyperglycemia and prevented postprandial hypoglycemia (Fig. 2B). However, her symptoms (except fatigue) remained after acarbose administration. We therefore concluded that her symptoms were mainly due to early dumping syndrome.

In addition to avoiding carbohydrate-rich foods and having more frequent meals with smaller portions, we advised her not to drink any liquid or lie down for 30 minutes after meal. However, this resulted in very little improvement to her symptoms. We therefore tested the effect of octreotide on early dumping syndrome with 75g-OGTT (Fig. 3). Oral glucose challenge increased glucose and insulin concentration ever with acarbose.

**Case Report**

A 47-year-old woman, who 10 years previously had undergone distal gastrectomy with Billroth I reconstruction for early-stage gastric cancer, presented with symptoms of weakness, headache, palpitation, sweating, dizziness and significant fatigue one to two hours after meals. She was diagnosed with dumping syndrome and advised to avoid carbohydrate-rich foods and to eat more frequent meals of a smaller portion size. However, she was referred to our clinic in March 2011, because the symptoms of early dumping syndrome, particularly fatigue after meals, persisted despite a reduction of carbohydrate intake. She was then prescribed acarbose for late dumping syndrome (postprandial hypoglycemia), but her symptoms persisted. She was therefore admitted to our hospital for examination and therapy.

On admission, she was 152 cm tall and weighed 48.5 kg, with a body mass index of 21.0. Her blood pressure was 108/82 mmHg, her body temperature was 35.4°C, and her pulse rate was 60 beats/min and regular. Her palpebral conjunctivae were not anemic, and her bulbar conjunctivae were not icteric. Her oral mucous membrane was not dry. No vascular murmurs were heard in the cervical region. The thyroid gland was not palpable. Her heart sounds were clear, with no audible murmurs. Breath sounds were clear, and no rales were heard. The abdomen was flat and soft, and bowel sounds were hyperactive. There was no pretibial edema, and capillary refilling time was one second. She had a history of operations: for appendicitis at 13 years of age, Billroth I gastrectomy for early-stage gastric cancer at 37 years of age, and removal of gallstones (also at 37 years of age). She had no family history of diabetes mellitus or cancer. She had a past history of smoking (eight cigarettes/day), but had quit seven years prior to admission. At the time of admission she did not drink alcohol regularly, and had no allergies. Table 1 shows her laboratory data on admission, indicating no major abnormality.

Octreotide is not approved for dumping syndrome in Japan. We obtained fully informed consent before its administration.

75 g oral glucose tolerance test

75 g-OGTT used standard procedures. Briefly, we administered a 75g anhydrous glucose load after a 14-h fast and obtained fasting, 5, 10, 15, 30, 60, 90 and 120 minutes samples from an antecubital vein. Serum insulin and C-peptide concentrations were measured at 0, 5, 10, 30, 60, 90 and 120 minutes. Plasma GIP and GLP-1 concentrations were measured at 0, 15, 30, 60, 90 and 120 minutes. Plasma VIP concentrations were measured at 0, 15, 30 and 60 minutes. To test the effect of acarbose and octreotide on the symptoms after glucose loading, 100 mg of oral acarbose or/and subcutaneous injection of 50 µg octreotide were administered 30 minutes before glucose loading. In addition to the collection of blood samples, we performed blood pressure and heart rate measurements every three minutes from 0 to 30min during the 75 g-OGTT.

Continuous glucose monitoring

Continuous glucose monitoring was performed with CGMS-Gold® (Medtronic, USA). To calibrate CGM, we asked a patient to measure six times fingerstick blood glucose values a day to maintain the calibration of the CGMS (One-touch®, Lifescan, USA).

**Ethical issue**

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**Case report**

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Table 1  Laboratory data on admission

<table>
<thead>
<tr>
<th>WBC</th>
<th>3800/μL</th>
<th>AST</th>
<th>271U/L</th>
<th>Cl</th>
<th>104mEq/L</th>
<th>LH</th>
<th>9.8mIU/mL</th>
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<td>ALT</td>
<td>201U/L</td>
<td>Ca</td>
<td>8.8mg/dL</td>
<td>FSH</td>
<td>11.1mIU/mL</td>
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<td>HgB</td>
<td>13.7g/dL</td>
<td>LDH</td>
<td>154IU/L</td>
<td>P</td>
<td>3.0mg/dL</td>
<td>PRL</td>
<td>6.98ng/mL</td>
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<td>Ht</td>
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<td>γ-GTP</td>
<td>9U/L</td>
<td>Uric Acid</td>
<td>5.1mg/dL</td>
<td>GH</td>
<td>5.94ng/mL</td>
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<td>MCV</td>
<td>93fl</td>
<td>CPK</td>
<td>771U/L</td>
<td>HbA1c (NGSP)</td>
<td>5.1%</td>
<td>ACTH</td>
<td>17.8pg/mL</td>
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<td>MCH</td>
<td>31.2pg</td>
<td>BUN</td>
<td>12.8mg/dL</td>
<td>Anti-insulin antibody</td>
<td>&lt;125nU/mL</td>
<td>Cortisol</td>
<td>9.0μg/dL</td>
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<td>PLT</td>
<td>24.5×10^5/μL</td>
<td>Cre</td>
<td>0.71mg/dL</td>
<td>f-T4</td>
<td>1.16ng/dL</td>
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<td>138mEq/L</td>
<td>f-T3</td>
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<td>TSH</td>
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WBC, white blood cell; RBC, red blood cell; HgB, hemoglobin; Ht, hematocrit; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; PLT, platelet; TP, total protein; T-Bil, total bilirubin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; γ-GTP, gamma-glutamyl transpeptidase; CPK, creatine phosphokinase; BUN, blood urea nitrogen; Cre, creatinine; Na, sodium; Cl, chloride; K, potassium

Fig. 1  75 g-OGTT without any medications
Hypoglycemia was observed at 60 minutes after administration of oral glucose load.

Fig. 2  Continuous glucose monitoring (CGM) over 24 hours
CGMS was used to compare glucose profiles before and after administration of acarbose 100 mg three times a day with meals.
Blood pressure remained stable, but her heart rate increased ~15bpm 5min after the glucose load (Fig. 3A). In contrast, subcutaneous administration of 50 μg octreotide prevented postprandial tachycardia and completely improved her symptoms (Fig. 3B). We measured plasma vasoactive intestinal polypeptide (VIP), glucagon-like peptide-1 (GLP-1), glucose-dependent insulinotropic polypeptide (GIP), glucose, and serum insulin and C-peptide during the 75g-OGTT (Fig. 3, 4). Administration of Octreotide suppressed both insulin and C-peptide, and increased plasma glucose. Plasma VIP concentration did not change significantly during

![Graph A: 75g OGTT (Acarbose 100mg)](image)

![Graph B: 75g OGTT (Acarbose 100mg + Octreotide 50μg subcutaneous injection)](image)

**Fig. 3** 75 g-OGTT with and without octreotide 50 μg in addition of acarbose 100 mg three times a day. In order to evaluate the effect of octreotide on late dumping syndrome (postprandial hypoglycemia) and early dumping syndrome (postprandial tachycardia), octreotide was administrated 30 minutes before 75 g-OGTT. Right figures show the changes in systolic (upper solid line) and diastolic (lower solid line) blood pressures and in pulse rate (dotted line).

**Fig. 4** The change of plasma GIP, GLP-1 and VIP concentrations in 75 g-OGTT with and without octreotide 50 μg in addition to acarbose 100 mg three times a day.
the 75g-OGTT with and without octreotide treatment. In contrast to VIP, GLP-1 and GIP concentrations were greatly increased during the 75g-OGTT, but this effect was completely suppressed by octreotide treatment. These data suggested that octreotide treatment might normalize the patient’s symptoms through alterations in GLP-1 or GIP, but not through VIP.

**Discussion**

Two mechanisms are proposed to underlie the pathogenesis of early dumping syndrome. First, the arrival of hyperosmolar contents to the duodenum causes fluid to move from the intravascular component into the intestinal lumen. This movement may lead to a decrease in the volume of circulating fluid, tachycardia and, rarely, syncope [5]. Second, several gastrointestinal peptide hormones (including enteroglucagon, peptide YY, pancreatic polypeptide, vasoactive intestinal polypeptide (VIP), glucagon-like peptide 1 (GLP-1) and neurotensin) induce systemic hemo-concentration and hypotension through splanchnic vasodilation [6, 7]. In contrast, the pathogenesis of late dumping syndrome is thought to be due to hypoglycemia resulting from GLP-1, induced by rapid delivery of nutrients into the duodenum, stimulating insulin release in the beta cells [8].

In this case, a 75g-OGTT induced acute postprandial tachycardia (within 1 hour) and postprandial hypoglycemia [9]. We therefore diagnosed both early and late dumping syndrome. As the first step of medical therapy for late dumping syndrome, acarbose is recommended [7]. Acarbose inhibits carbohydrate absorption in the small intestine and prevents postprandial hypoglycemia through reduction of insulin concentration. This drug also inhibits postprandial hypotension and tachycardia by retarding gastric emptying rate, and thus reducing the speed of delivery of high osmolality nutrients into the duodenum [10, 11]. We therefore thought that acarbose would improve the symptoms of both late and early dumping syndrome. Acarbose completely inhibited the symptoms of late dumping syndrome, but did not improve the symptoms of early dumping syndrome.

Somatostatin analogs such as octreotide have been used successfully in the treatment of early dumping syndrome [12-15], although octreotide does have problems, including being expensive and having adverse events, such as gallstone formation, prolonged QT and pain at the injection site. Octreotide can retard gastric emptying rate, retard transit through the small bowel, inhibit the release of gastrointestinal hormones, inhibit insulin secretion and inhibit postprandial vasodilation [7]. Octreotide is significantly effective for early dumping syndrome, although it may be less effective in the long term than in the short term [16].

Recently, Myint *et al.* reported a 42 year old woman with hyperinsulinaemic hypoglycaemia after gastric bypass [17]. In their report, octreotide therapy significantly improved the patient’s symptoms and GLP-1 response. In our case, administration of octreotide also prevented the symptoms of early dumping syndrome, particularly postradial tachycardia. Octreotide suppressed not only plasma GLP-1 but also GIP concentration within 15 minutes during 75 g-OGTT. Somatostatin receptors exist as five isoforms (SSTR1-SSTR5), of which sst5 is expressed by the rat L-cell and the rodent K-cell [18, 19]. Somatostatin inhibits GIP and GLP-1 secretion from small intestinal cultures through SSTR5 [17]. Peripheral GLP-1 receptor ligand administration caused tachycardia [20, 21], but exendin-(9-39), the GLP-1 receptor antagonist, blocked the response in rats [22]. Yamamoto *et al.* reported the relation between GLP-1 and early dumping syndrome. They concluded that increasing catecholamine through the effect of GLP-1 on the central nervous system, which activates catecholamine neurons, might produce the symptoms of early dumping syndrome [23]. GLP-1 might confound postprandial hypotension and tachycardia by enhancing insulin-mediated vasodilatation through an increase in nitric oxide production [24, 25]. Moreover, recent studies of a long-acting GLP-1 derivative administered to healthy subjects and patients with type 2 diabetes showed a higher incidence of adverse events (notably headache, dizziness, nausea, and vomiting) after active treatment than after placebo [26, 27]. Thus, exaggerated plasma GLP-1 might be responsible for the symptoms of early dumping syndrome. We observed inhibition of GIP by octreotide in this case. However, the role of GIP in early dumping syndrome is unclear.

This study has several limitations. Although octreotide improved symptoms of dumping syndrome, octreotide inhibits both insulin secretion *per se*, and incretins, during a 75g-OGTT. It is difficult to conclude whether the inhibitory effects of octreotide on incretins are a direct effect of GLP-1 on vasodilatation or an indirect effect via insulin secretion from pancreatic β-cells. We were also unable to measure enteroglucagon, pep-
tide YY, pancreatic polypeptide and neurotensin. It is possible that octreotide improved symptoms through one of these hormones. Further study is necessary to explore this. We treated this patient with octreotide for several times, but did not continue this therapy because of the past history of cholelithiasis and postprandial hyperglycemia.

In conclusion, octreotide is an effective treatment for early dumping syndrome, but causes adverse effect, such as postprandial hyperglycemia. The data shown here suggest that increased secretion of GLP-1 and GIP might be an alternative mechanism leading to the occurrence of early dumping syndrome.

Acknowledgments

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References


