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Treatment with α-Glucosidase Inhibitor for Severe Reactive Hypoglycemia: A Case Report

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Abstract. Gastrectomy or vagotomy may result in reactive hypoglycemia, which, in some cases, can reduce the plasma glucose levels to 30–40 mg/dl due to rapid digestion and absorption of food, especially carbohydrates. It also occurs sometimes in patients on hemodialysis, where it is a potentially lethal complication. Because insulin has a longer half-life due to lack of renal degradation, hypoglycemia can be induced by insulin in patients with renal failure.

We treated a patient with frequent episodes of severe hypoglycemia, that were sometimes accompanied by convulsions. He had undergone total gastrectomy 8 years before and had been maintained on hemodialysis for 3 years. Hyperinsulinemia caused by oxyhyperglycemia associated with post-gastrectomy led to severe hypoglycemia in this patient because of the lack of renal insulin degradation. Since nutritional treatment did not successfully manage his reactive hypoglycemia, an α-glucosidase inhibitor, acarbose, was administered to treat his oxyhyperglycemia. This therapy was very effective and he has not had any recurrence of reactive hypoglycemia since the initiation of the therapy.

Key words: Alimentary hypoglycemia, Post-gastrectomy, Chronic renal failure, α-Glucosidase inhibitor, Counter-regulatory hormone

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SYMPTOMS of hypoglycemia, such as weakness, perspiration, hunger, nausea, anxiety and tremors, can occur from one to two hours after a meal in patients with gastrectomy or vagotomy. This hypoglycemia is due to the rapid digestion and absorption of food, especially carbohydrates, that has been dumped into the duodenum. Glucose rapidly enters the bloodstream and causes oversecretion of insulin, which later results in hypoglycemia.

Renal failure interferes with the metabolism of glucose and insulin, since insulin is mainly metabolized in the kidneys and liver. The half-life of insulin is appreciably prolonged in renal failure due to the lack of renal insulin degradation. Because insulin consequently remains in the blood for a long time, hypoglycemia can be induced in patients with renal failure [1]. Therefore, severe hypoglycemia is likely to occur in post-gastrectomy patients with renal failure.

There are several treatments for the dumping syndrome, such as nutritional treatment [2] and octreotide [3, 4]. However, nutritional treatment alone is not always successful; octreotide injection therapy is invasive and expensive. Recently, diabetes mellitus with especially postprandial hyperglycemia has been treated by α-glucosidase inhibitors. These medications act by delaying carbohydrate absorption [5]. We treated a patient with frequent episodes of severe hypoglycemia after gastrectomy, who was compli-

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cated by chronic renal failure (CRF) on hemodialysis (HD), using an α-glucosidase inhibitor acarbose.

Case Report

A 64-year-old Japanese man was admitted to our hospital for assessment and treatment of hypoglycemia. He had undergone total gastrectomy and Roux-en-Y anastomosis for gastric carcinoma on May 31, 1991. At that time, renal dysfunction due to chronic glomerulonephritis as well as impaired glucose tolerance was detected. Although he was instructed to eat 6 divided small meals in a day to control reactive hypoglycemia, he frequently suffered from hypoglycemic episodes characterized by hunger, weakness, sweating, dizziness and palpitations that occurred 1–2 hours after meals.

On October 15, 1996, he complained of dyspnea and was admitted to another hospital. Chronic renal failure (CRF) and decompensated congestive heart failure were diagnosed, and HD was started. He was advised to begin a high calorie and high carbohydrate diet because of his CRF on HD. Subsequently, on two occasions, he developed hypoglycemic coma with convulsions. The first episode occurred after eating a cake in 1996 and the next was after drinking alcohol in January 1999. Although he denied taking high carbohydrate foods or drinking alcohol after those episodes, he sometimes had hypoglycemia unawareness with a plasma glucose concentration of 30–40 mg/dl. On June 16, 1999, he was admitted to our hospital for management of his reactive hypoglycemia.

On admission, his blood pressure was 150/80 mmHg, the pulse rate was 80 beats per min, and the body temperature was 36.8°C. He had slightly pale conjunctivae and an apical systolic murmur. He did not have any abnormal skin pigmentation (e.g. acanthosis nigricans). Liver dysfunction was not detected by serum chemistry. His HbA1c level was 5.0% and his glycosylated albumin level was 20.4%. He did not have diabetic neuropathy or retinopathy. Insulin autoantibody and insulin receptor antibody were not detected. HD was performed three times a week, for four hours each time. He was placed on a diet of 2000 kcal/day, comprising 290 g of carbohydrate, 75 g of protein and 65 g of fat, and the meals were divided into six times per day. He also took fat- and protein-rich snacks, including cheese. Although his plasma glucose concentration frequently went down to 40–60 mg/dl in the postprandial period, hypoglycemic symptoms were not observed at this level of glycemia. The patient was informed about the aims of the present study and his written consent was obtained.

Methods

Glucagon injection test was performed with 1 mg of intravenous glucagon (Glucagon Novo Nordisc, Denmark). Plasma glucose and serum C-peptide immunoreactivity (CPR) were measured before and 6 min after injection. Meal tolerance test was performed with 600 kcal test meal comprising 75 g from carbohydrate, 25 g from protein and 20 g from fat. Acarbose 100 mg was taken just before each meal.

Serum IRI, CPR, GH, ACTH and cortisol were measured using IRMA methods. Glucagon was measured by RIA method, and catecholamines were measured by high-performance liquid chromatography.

Results

48-h fasting test

The patient was fasted for 48 hrs. His plasma glucose level was above 70 mg/dl and serum IRI was under 2.5 μU/ml during the test (Table 1). He had no spontaneous hypoglycemia or hyperinsulinemia. These results suggested that his hypoglycemia was not induced by abnormal insulin secretion, such as insulinoma or insulin autoimmune syndrome.

Glucagon injection test

To evaluate insulin secretion, 1 mg of glucagon

Table 1. Fasting test

Time (hrs)	12	24	36	48
Plasma glucose (mg/dl)	98	83	82	78
IRI (μU/ml)	3.6	2.5>	2.5>	2.5>
CPR (ng/ml)	4.2	3.4	2.3	2.3

Table 2. Glucagon injection test

Time (min)	0	6
Plasma glucose (mg/dl)	78	80
IRI (μU/ml)	2.5>	22
CPR (ng/ml)	2.3	4.3

was injected. After the glucagon injection, serum CPR level increased from 2.3 to 4.3 ng/ml (Table 2). This result suggests that his pancreatic β-cells possessed good insulin secreting ability.

Meal tolerance test

In the meal tolerance test, the baseline glucose concentration was 87 mg/dl, and rapidly increased to 333 mg/dl at 30 min after meal (Fig. 1). Elevation of insulin concentration was recognized after the increase of glucose concentration. The baseline insulin concentration was 4.8 μU/ml, and it rose to 350 μU/ml after 30 min and 560 μU/ml after 60 min. This increase of insulin was likely to be a reaction to the observed hyperglycemia. The glucose concentration decreased rapidly to 63 mg/dl 120 min after meal. The insulin level gradually decreased to 340 μU/ml after 90 min, to 62 μU/ml after 120 min and to 22 μU/ml after 180 min. Although he was hypoglycemic after 120 min, he had no symptoms of hypoglycemia.

Counterregulatory hormone

To investigate the counterregulatory hormone response to his reactive hypoglycemia, glucagon, GH, catecholamines, ACTH and cortisol were measured during the meal tolerance test. At baseline, there was no deficiency in his counterregulatory hormone levels. Glucagon and catecholamines are two important classes of hormones that play a role in glycogenolysis in the hypoglycemic state. In his case, concentration of catecholamines only marginally increased (except norepinephrine that decreased), and no obvious glucagon response was observed during the decreasing glycemia (Fig. 2).

Meal tolerance test with acarbose administration

Acarbose 100 mg was administered before the meal tolerance tests. The maximum plasma glucose level was 182 mg/dl after 100 mg of acarbose. Reactive hypoglycemia was not observed with acarbose ad-

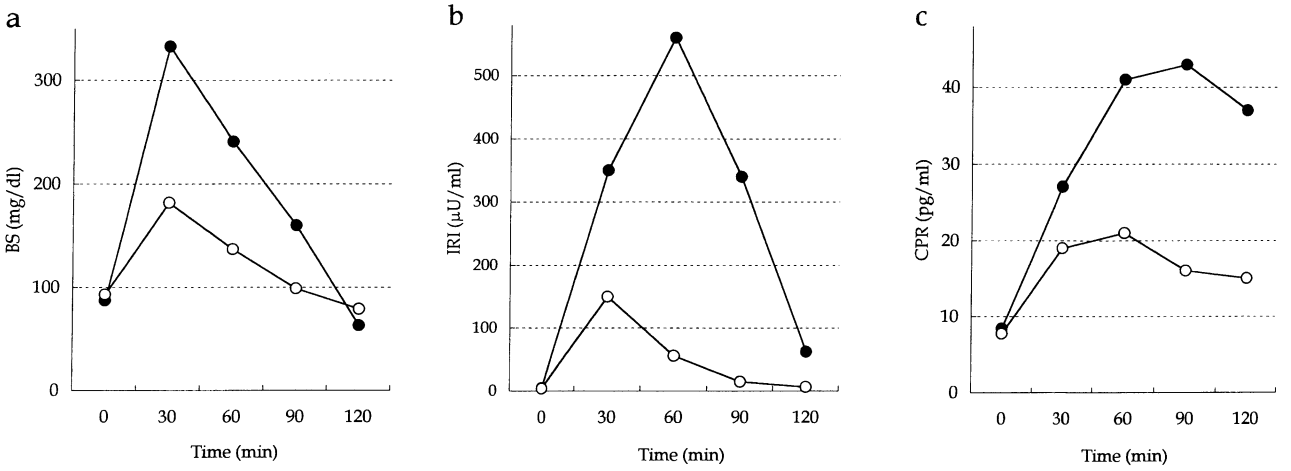

Fig. 1. Meal tolerance test. Meal tolerance test was performed with 600 kcal test meal comprising 75 g from carbohydrate, 25 g from protein and 20 g from fat. The baseline glucose concentration was 87 mg/dl, and this rapidly increased to 333 mg/dl at 30 min after the meal. His baseline insulin concentration was 4.8 μU/ml, and it rose to 350 μU/ml after 30 min and to 560 μU/ml after 60 min. The glucose concentration decreased rapidly to 63 mg/dl at 120 min after the meal. His insulin level was mildly decreased to 340 μU/ml after 90 min, 62 μU/ml after 120 min. Acarbose 100 mg was then administered before the meal tolerance tests. Maximum plasma glucose was 182 mg/dl after 100 mg of acarbose (a). Maximum insulin concentration was reduced to 150 μU/ml after acarbose administration (b). CPR was also decreased (c). closed circle; no medicine, open circle; on acarbose 100 mg.

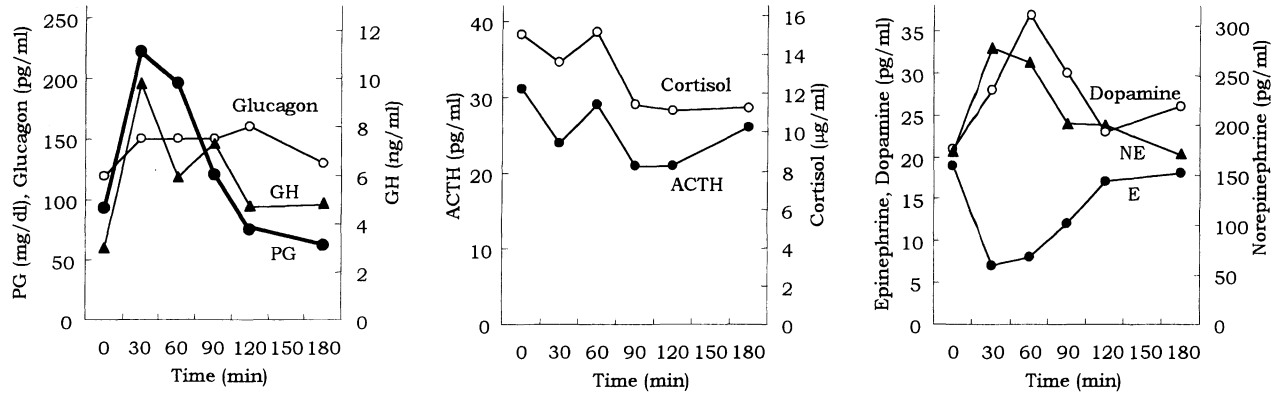

Fig. 2. Response of counterregulatory hormones to hypoglycemia. To investigate the response of counterregulatory hormones to reactive hypoglycemia, glucagon, GH, catecholamines, ACTH and cortisol were measured during the meal tolerance test. There was no deficiency of these counterregulatory hormones. However, catecholamines only marginally increased (except norepinephrine that decresed), and no obvious glucagon response was observed.

ministration (Fig. 1a). The maximum insulin concentration was 150 μU/ml after acarbose administration (Fig. 1b). The increase of plasma glucose and the response of insulin were suppressed by acarbose. CPR was also reduced after acarbose administration (Fig. 1c).

Discussion

Gastrectomy or vagotomy may result in persistent gastrointestinal symptoms, including reactive hypoglycemia. Some patients with this hypoglycemia can have a glucose concentration as low as 30–40 mg/dl [2, 6]. Our patient had unequivocal episodes of convulsions, and his glucose concentrations might have been lower than this level on such occasions. Impairment of insulin disposal due to renal failure may also have exaggerated the level of hypoglycemia caused by hyperinsulinemia after his oxyhyperglycemia. Moreover, altered carbohydrate metabolism is a well-recognized complication of CRF [7], and hypoglycemia sometimes occurs in those patients having CRF with or without dialysis, which is a potentially lethal complication [8–12]. In addition, patients with CRF on HD have been reported to have high risk of being unable to respond to hypoglycemia and of being unaware of it [1]. Although glucose intolerance due to peripheral insulin resistance is common in patients with CRF [10, 13, 14], insulin sensitivity is significantly improved after starting dialysis [15, 16]. Insulin levels tend to be elevated and the half-life of insulin is appreciably prolonged due to the loss of renal insulin degradation. Furthermore, impaired hepatic gluconeogenesis, glycogenolysis, and substrate availability have also been implicated in patients with CRF. It was recently reported that renal gluconeogenesis plays an important role in counterregulation for hypoglycemia [17, 18]. In our patient, hyperinsulinemia led to more pronounced hypoglycemia possibly because of the failure of renal insulin degradation, as well as the persistence of normal insulin sensitivity.

In healthy people and diabetic patients without renal failure, the most important counterregulatory hormone is glucagon, which restores euglycemic state after hypoglycemic events [19–23]. It has been reported that patients on dialysis are capable of secreting normal amounts of epinephrine, but are unable to adequately raise the levels of ACTH, cortisol or GH [24, 25]. On norepinephrine, it has been reported to respond poorly to hypoglycemia in patients on HD [24]. On the other hand, there was one report in which glucagon responded well to hypoglycemia in a patient on HD [1]. In our patient, counterregulatory hormones, such as ACTH, cortisol and catecholamines (except norepinephrine that decreased) only slightly increased during the period of glycemic decrease, nor did glucagon respond. These findings can be ascribed to the frequent episodes of hypoglycemia that are believed to cause blunted response of counterregulatory hormones

[26–28]. In addition, although the morning GH concentration was high, and GH responded paradoxically to hypoglycemia, this phenomenon is sometimes observed in patients with CRF [29, 30].

Some molecules, such as GLP-1, potentiate insulin secretion [31], and excessive secretion of such insulinotropic hormones, stimulated by rapid entry of nutrients into the intestine, may cause hyperinsulinemia. In our case, although the entry of nutrients into the bowel as well as their calorific value should be unchanged with or without acarbose, the oxyhyperglycemia was suppressed by acarbose and the increase of the serum IRI concentration was also suppressed. This suggests that hyperinsulinemia was a reaction against the hyperglycemia and was not related to GLP-1.

There are several treatments for reactive hypoglycemia associated with post-gastrectomy. The primary objective of dietary modification is to restore nutritional status and a comfortable lifestyle for the patient. Proteins and fats are better tolerated than carbohydrates because they are more slowly hydrolyzed. Therefore, it is recommended to prescribe a diet containing high fat and high protein with low content in simple carbohydrates in order to achieve and maintain optimum weight and nutritional status for such patients. The important nutritional rules are to avoid concentrated sweets, and to eat separate small meals a day. However, this nutritional care is not always successful in patients with reactive hypoglycemia. Several studies have shown that the symptoms of reactive hypoglycemia are ameliorated by long-acting somatostatin analogue, octreotide [32–35]. It has also been reported that octreotide is an effective treatment for reactive hypoglycemia itself [3], and that it can be used for the long-term treatment of reactive hypoglycemia due to gastrectomy [4]. However, it is expensive and invasive as it requires injection. α-Glucosidase inhibitors are less expensive oral agents used for diabetic patients with postprandial hyperglycemia to reduce digestion and absorption of nutrients such as starch, sucrose, and maltose. In our patient, it is of note that hypoglycemia did not occur after acarbose administration. In summary, the treatment with acarbose was effective in a patient with post-gastrectomy reactive hypoglycemia complicated by CRF on HD without any side effects.

References

1. Jackson MA, Holland MR, Nicholas J, Talbot M, Spencer H, Lodwick R, Fuhrmann C, Forster D, Macdonald IA (1999) Occult hypoglycemia caused by hemodialysis. *Clin Nephrol* 51: 242–247.
2. Khoshoo V, Roberts PL, Loe WA, Golladay ES, Pencharz PB (1994) Nutritional management of dumping syndrome associated with antireflux surgery. *J Pediatric Surg* 29: 1452–1454.
3. D'Cruz DP, Reynard J, Tatman AJ, Kopelman PG (1989) Long-term symptomatic relief of postprandial hypoglycaemia following gastric surgery with a somatostatin analogue. *Postgrad Med J* 65: 116–117.
4. Mackie CR, Jenkins SA, Hartley MN (1991) Treatment of severe postvagotomy/postgastrectomy symptoms with the somatostatin analogue octreotide. *Br J Surg* 1991, 78: 1338–1343.
5. Bischoff H (1994) Pharmacology of a-glucosidase inhibition. *Eur J Clin Invest* 24: 3–10.
6. Bellini F, Sammicheli L, Ianni L, Pupilli C, Serio M, Mannelli M (1998) Hypoglycemia unawareness in a patient with dumping syndrome: report of a case. *J Endocrinol Invest* 21: 463–467.
7. Majais SK, Fadda G (1989) Carbohydrate metabolism in end-stage renal disease. (1989) *Semin Dial* 2: 46–53, 1989.
8. Block MB, Rubenstein AH (1970) Spontaneous hypoglycemia in diabetic patients with renal insufficiency. *JAMA* 213: 1863–1866.
9. White MG, Kurtzman NA (1971) Hypoglycemia in diabetes with renal insufficiency. *JAMA* 215: 117.
10. Greenblatt DJ (1974) Insulin sensitivity in renal failure. Fatal hypoglycemia following dialysis. *New York State J Med* 74: 1040–1041.
11. Avram MM, Wolf RE, Gan A, Pahilan AN, Paik SK, Iancu M (1984) Uremic hypoglycemia. A preventable life-threatening complication. *New York State J Med* 84: 593–596.
12. Tzamaloukas AH, Avasthi PS (1992) Hypoglycemia during hemodialysis in diabetics treated with insulin. *Nephron* 61: 470–471.
13. Eidemak I, Feldt-Rasmussen B, Kanstrup IL, Nielsen SL, Schmitz O, Strandgaard S (1995) Insulin resistance and hyperinsulinaemia in mild to moderate progressive chronic renal failure and its association with aerobic work capacity. *Diabetologia* 38: 565–572.
14. Mek RH (1996) Insulin resistance in uremia: effect of

dialysis modality. *Pediatr Res* 40: 304–308.
15. Foss MC, Gouveia LM, Moyses Neto M, Paccola GM, Piccinato CE (1996) Effect of hemodialysis on peripheral glucose metabolism of patients with chronic renal failure. *Nephron* 73: 48–53.
16. Scmitz O (1991) Glucose metabolism in non-diabetic and insulin-dependent diabetic subjects with end-stage renal failure. *Dan Med Bull* 38: 36–52.
17. Cersosimo E, Garlick P, Ferretti J (1999) Insulin regulation of renal glucose metabolism in humans. *Am J Physiol* 276: E78–E84.
18. Meyer C, Dostou JM, Gerich JE (1999) Role of the human kidney in glucoes counterregulation. *Diabetes* 48: 943–948.
19. Sacca L, Perez G, Carteni G, Trimarco B, Rengo F (1977) Role of glucagon in the glucoregulatory response to insulin-induced hypoglycemia in the rat. *Hormone Metab Res* 9: 209–212.
20. Ensinck JW, Palmer JP (1976) Dominant inheritance of large molecular weight species of glucagon. *Metabolism* 25: 227–232.
21. Rizza RA, Cryer PE, Gerich JE (1979) Role of glucagon, catecholamines, and growth hormone in human glucose counterregulation. Effects of somatostatin and combined alpha- and beta-adrenergic blockade on plasma glucose recovery and glucose flux rates after insulin-induced hypoglycemia. *J Clin Invest* 64: 62–71.
22. Exton JH, Mallette LE, Jefferson LS, Wong EH, Friedmann N, Miller TB Jr, Park CR (1970) The hormonal control of hepatic gluconeogenesis. *Recent Prog Hormone Res* 26: 411–421.
23. Amiel S (1991) Glucose counter-regulation in health and disease: current concepts in hypoglycaemia recognition and response. *Q J Med* 293: 707–727.
24. Ramirez G, Brueggemeyer C, Ganguly A (1988) Counterregulatory hormonal response to insulin-induced hypoglycemia in patients on chronic hemodialysis. *Nephron* 49: 231–236.
25. Rosman PM, Benn R, Kay M, Tito J, Wallace EZ (1984) Cortisol binding in uremic plasma. I. Absence of abnormal cortisol binding to corticosteroid-binding globulin. *Nephron* 37: 160–165.
26. Pampanelli S, Fanelli C, Lalli C, Ciofetta M, Sindaco PD, Lepore M, Modarelli F, Rambotti AM, Epifano L, Di Vincenzo A, Bartocci L, Annibale B, Brunetti P, Bolli GB (1996) Long-term intensive insulin therapy in IDDM: effects on HbA1c, risk for severe and mild hypoglycaemia, status of counterregulation and awareness of hypoglycaemia. *Diabetologia* 39: 677–686.
27. Lingenfelser T, Renn W, Sommerwerck U, Jung MF, Buettner UW, Zaiser-Kaschel H, Kaschel R, Eggstein M, Jakober B (1993) Compromised hormonal counterregulation, symptom awareness, and neurophysiological function after recurrent short-term episodes of insulin-induced hypoglycemia in IDDM patients. *Diabetes* 42: 610–618.
28. Veneman T, Mitrakou A, Mokan M, Cryer P, Gerich J (1993) Induction of hypoglycemia unawareness by asymptomatic nocturnal hypoglycemia. *Diabetes* 42: 1233–1237.
29. Ramirez G, O'Neill WM, Bloomer HA, Jubiz W (1978) Abnormalities in the regulation of growth hormone in chronic renal failure. *Arch Intern Med* 138: 267–271.
30. Haffner D, Blum WF, Heinrich U, Mehls O, Tonshoff B (1997) Impaired postprandial regulation of insulin-like growth factor binding protein-1 in children with chronic renal failure. *J Clin Endocrinol Metab* 82: 2832–2835.
31. Toft-Nielsen M, Madsbad S, Holst JJ (1998) Exaggerated secretion of glucagons-like peptide-1 (GLP-1) could cause reactive hypoglycemia. *Diabetologia* 41: 1180–1186.
32. Long RG, Adrian TE, Bloom SR (1985) Somatostatin and the dumping syndrome. *Br Med J Clin Res Ed* 290: 886–888.
33. Hopman WP, Wolberink RG, Lamers CB, Van Tongeren JH (1988) Treatment of the dumping syndrome with the somatostatin analogue SMS 201–995. *Ann Surg* 207: 155–159.
34. Primrose JN, Johnston D (1989) Somatostatin analogue SMS 201–995 (octreotide) as a possible solution to the dumping syndrome after gastrectomy or vagotomy. *Br J Surg* 76: 140–144.
35. Tulassay Z, Tulassay T, Gupta R, Cierny G (1989) Long-acting analogue of somatostatin—SMS 201–995—is highly effective in the prevention of clinical symptoms related to the dumping syndrome. *Ann Surg* 210: 250–252.