Amino Acid, Glucose, and Lipid Kinetics After Palliative Resection in a Patient With Glucagonoma Syndrome

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Glucagon excess causes catabolic changes, including enhanced glucose production, lipolysis, and amino acid oxidation. In this study, we evaluate the metabolic effects of debulking surgery on a patient with glucagon-producing tumor. Stable isotope tracer methods were used to measure glucose, glycerol, and α-ketoisocaproic acid (αKICA) rates of appearance (Ra) into plasma. Measurements were obtained 25 days after surgery in the basal state and during hormonal suppression of glucagon production by infusing somatostatin with insulin replacement. Basal plasma glucagon concentration (14,100 pg/mL) remained high after debulking surgery. Somatostatin infusion decreased plasma glucagon concentration to 6,735 pg/mL and basal substrate kinetics (α-KICA Ra from 1.97 to 1.48 μmol/kg/min; glucose Ra from 16.89 to 11.56 μmol/kg/min; and glycerol Ra from 3.33 to 2.74 μmol/kg/min). We conclude that debulking surgery fails to adequately suppress glucagon production and the alterations in substrate metabolism associated with excess glucagon. In these patients, somatostatin therapy can be an effective method to suppress secretion of glucagon and help attenuate its catabolic effects.

GLUCAGONOMAS ARE rare glucagon-secreting islet cell tumors that can cause profound metabolic effects including weight loss, muscle wasting, hypoaminoacidemia, and hyperglycemia.[1] In a previous case study, we found that alterations in amino acid, glucose, and lipid kinetics contributed to the clinical abnormalities observed in this patient population.[2] Although complete tumor excision is the optimal treatment for glucagonomas, unresectable metastatic lesions are present in up to 50% of patients, and tumor recurrence can occur after apparent complete resection. Therefore, palliative therapy by debulking the tumor mass and providing a long-acting somatostatin analogue (Sandostatin; Sandoz Pharmaceuticals, Minneapolis, MN) to inhibit glucagon secretion is an option for selected patients and has been shown to resolve glucagonoma-induced skin lesions and diabetes.[3-6] However, little is known about the effectiveness of palliative therapy on the abnormalities in substrate metabolism associated with glucagonoma syndrome.

The present study was undertaken to evaluate the effect of palliative surgical therapy on the metabolic abnormalities associated with glucagonoma. Amino acid, glucose, and lipid kinetics were determined during postabsorptive basal conditions and during somatostatin infusion plus insulin replacement after partial tumor resection in a patient we previously evaluated before surgery.[2]

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CASE REPORT

A 46-year-old woman presented with a history of a migratory erythematous rash and weight loss. A skin biopsy was obtained, and dermatopathology was consistent with necrolytic migratory erythema. Serum glucagon concentration was markedly elevated at 10,040 pg/mL (normal, 25 to 250 pg/mL). An abdominal computed tomography (CT) scan showed a 5-cm tumor in the tail of the pancreas and metastases throughout the liver. The patient was admitted to the hospital for a surgical debulking procedure. After 4 days of therapy with intravenous amino acids and subcutaneous octreotide, partial pancreatectomy to remove the primary tumor and left hepatectomy to remove many of the metastatic lesions were performed. However, the right lobe of the liver still contained multiple metastatic lesions. Histologic and immunohistochemical evaluations of the primary and metastatic lesions were consistent with glucagonoma.

The patient's postoperative course was uneventful, and she did not experience any serious complications. Her diet was advanced as tolerated, and she was eating a regular diet within 7 days after surgery. She lost 2.7 kg of body weight after surgery, but was weight stable for 1 week before the metabolic studies were performed, 25 days after surgery.

Methods

Study protocol. An isotope infusion study was performed 25 days after surgery. The patient had not received intravenous amino acids or octreotide since her operation. After the patient fasted overnight (10 hours), intravenous lines were inserted into the antecubital vein of 1 arm for infusion of isotopes and into the contralateral dorsal hand vein, which was heated, for arterialized venous sampling.[7] Baseline blood and breath samples were obtained to determine background isotopic enrichments. After a bolus infusion of [^{13}C] sodium bicarbonate (1.68 mmol/kg) was given, primed-constant infusions of [1-^{13}C] leucine (16.8 μmol/kg priming dose and 0.28 μmol/kg/min continuous infusion), [6,6-^{2}H] glucose (26.7 μmol/kg priming dose and 0.33 μmol/kg/min continuous infusion), and [1,1,2,3,3-^{2}H] glycerol (1.5 μmol/kg priming dose and 0.10 μmol/kg/min continuous infusion) were infused for 270 minutes. At 120 minutes, a continuous infusion of somatostatin (0.12 mg/kg/min) and insulin (0.2 mU/kg/min) was started and continued until the end of the isotope infusion protocol. Blood and breath samples were taken at 90, 100, 110, and 120 minutes to measure basal plasma hormone concentrations, leucine,[8] glucose,[9] and glycerol[10] kinetics. Blood and breath samples were taken at 240, 250, 260, and 270 minutes to measure the effect of somatostatin plus insulin replacement on plasma hormone concentrations and substrate kinetics. Measurements made from the 4 samples obtained from each study condition were averaged to obtain 1 value for the basal period and 1 value for the

somatostatin plus insulin period. Blood samples were obtained at 120 and 270 minutes to determine plasma glucagon,[11] insulin,[12] C-peptide,[13] glycerol,[14] free fatty acids,[14] and glucose concentrations.[9] Oxygen consumption, carbon dioxide production, and resting energy expenditure (REE) were measured by indirect calorimetry between 90 to 120 minutes and 240 to 270 minutes by using a 2900 metabolic cart (Sensormedics, Lorba Linda, CA).

The study was approved by the Institutional Review Board, and the experimental protocol was performed in the General Clinical Research Center after informed consent was obtained from the patient.

Calculations. Substrate (glucose, glycerol, and amino acid) kinetics were calculated by using isotope tracer dilution methods. The dilution of a tracer infused into the bloodstream by the release of endogenous unlabeled substrate permits the assessment of endogenous substrate rate of appearance (Ra) in plasma. Glucose, glycerol, and of α-ketoisocaproic acid (αKICA) Ra were calculated using Steele's equation for physiologic and isotopic steady state conditions.[15] Determination of αKICA enrichment allows an estimation of leucine release from intracellular protein breakdown because αKICA is derived directly from and is in equilibrium with intracellular leucine. Leucine oxidation rate (an index of net protein catabolism) was obtained from the product of carbon dioxide production and the isotopic enrichment of exhaled carbon dioxide. Nonoxidative leucine disposal rate (an index of protein synthesis) was obtained from the difference between leucine Ra and leucine oxidation. Resting energy expenditure was calculated from oxygen consumption and carbon dioxide production measurements.[16]

RESULTS

Plasma hormone and substrate concentrations during basal conditions and during somatostatin plus insulin infusion are shown in Table 1. Plasma glucagon concentration did not decrease despite debulking a large portion of the visible tumor. Basal plasma insulin and glucose concentrations were higher at the time of the isotope infusion study performed after surgery compared with values obtained before the operation.[2] During the somatostatin plus insulin infusion, plasma glucagon concentration decreased by 50%, but the value was still much higher than normal. Somatostatin infusion suppressed endogenous insulin secretion; plasma C-peptide concentration was below the assay limit of detection. Insulin replacement during somatostatin infusion was not adequate to maintain preinfusion basal levels, and plasma insulin concentration decreased by 50%.

Leucine, glucose, and lipid kinetics during basal conditions and during somatostatin plus insulin are shown in Table 2. Intracellular leucine (αKICA) Ra, leucine oxidation, and nonoxidative leucine disposal were lower after surgery compared with values obtained preoperatively.[2] Glucose Ra was greater after than before surgery. Somatostatin plus insulin infusion decreased amino acid, glucose, and glycerol kinetics.

Table 1. Plasma Hormone and Substrate Concentrations During Basal Conditions and Somatostatin Plus Insulin Infusion

	Basal	Somatostatin Plus Insulin
Glucagon (pg/mL)	14,100	6,735
Insulin (mU/mL)	20	10
C-peptide (ng/mL)	2.8	<0.47
Glucose (mg/dL)	188	164
Glycerol (μmol/L)	100	80
Free fatty acids (μmol/L)	2,000	1,290

Table 2. Substrate Kinetics During Basal Conditions and Somatostatin Plus Insulin Infusion

	Basal	Somatostatin Plus Insulin
Intracellular leucine Ra	1.97	1.48
Leucine oxidation	0.57	0.48
Nonoxidative leucine disposal	1.40	1.00
Glucose Ra	16.89	11.56
Glycerol Ra	3.33	2.74

NOTE. Values are in μmol/kg/min.

Measured REE was 26 kcal/kg/d. This value is identical to the value predicted by the Harris-Benedict equation.[17]

DISCUSSION

Many patients with glucagonoma syndrome undergo partial tumor resection because of unresectable lesions and metastatic disease. In the present case report, we evaluated the effect of palliative surgical therapy on the metabolic abnormalities associated with glucagonoma syndrome. Amino acid, glucose, and lipid kinetics were determined 25 days after surgery during basal conditions and during somatostatin infusion plus insulin replacement in a patient who we previously studied before operation.[2] The results of these metabolic studies show that hyperglucagonemia persists after only partial tumor resection and is responsible for continued alterations in substrate metabolism. However, further inhibition of pancreatic-tumor hormone secretion by infusing somatostatin decreased plasma glucagon concentration, as well as the rates of protein breakdown, synthesis, net protein catabolism, glucose production, and rate of lipolysis.

Excess glucagon increases the rates of protein breakdown,[18] glucose production,[19] and lipolysis.[2] Despite resecting a large portion of our patient's tumor, plasma glucagon concentration remained more than 100 times higher than the mean values we have observed in normal volunteers.[2] Our results show that the presence of persistent hyperglucagonemia was responsible for increased amino acid, glucose, and lipid kinetics in our patient, because these parameters decreased towards normal values when plasma glucagon concentration declined during somatostatin plus insulin infusion. It is unlikely that the simultaneous infusion of insulin, which also affects amino acid,[20] glucose,[21] and lipid metabolism[22,23] was responsible for the slower kinetics, because plasma insulin concentration was actually lower during somatostatin infusion than during basal conditions. The infusion of somatostatin did not normalize plasma glucagon concentration in our patient, and considerable hyperglucagonemia was still present. Therefore, the normalization of substrate kinetics during somatostatin infusion may have been possible because of a general downregulation of glucagon action that occurs with chronic glucagon excess.[24]

It is possible that other factors may have influenced substrate metabolism in our patient. First, although our patient was weight stable at the time of the metabolic studies, she had lost approximately 10 kg (17%) of her initial body weight before surgery and an additional 2.7 kg after the operation. The

presence of chronic undernutrition, which decreases proteolysis,[25-27] may explain why her basal rate of whole-body protein breakdown, as measured by αKICA Ra, was lower compared with values observed in normal volunteers.[2] However, the decline in αKICA Ra during somatostatin infusion suggests that proteolysis would have been even lower without the presence of hyperglucagonemia. Second, surgical stress itself can cause insulin resistance, which would affect amino acid, glucose, and lipid kinetics. However, insulin resistance usually resolves within 2 weeks after operation, and it is unlikely that operation-induced insulin resistance was still present 25 days after operation.[28] Third, it is possible that pancreatic resection and diminished islet cell mass limited the capacity for pancreatic insulin secretion. However, our patient had elevated basal plasma insulin concentrations, suggesting that insulin secretion was not diminished by surgery.

This study shows that debulking surgery alone may fail to adequately suppress glucagon production and the metabolic abnormalities caused by glucagon-producing tumors. Additional therapy with a long-acting somatostatin analogue can further decrease circulating glucagon levels, protein breakdown, net protein loss, glucose production, and lipolysis caused by hyperglucagonemia.

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