Glucose Metabolism in Cachectic Patients with Colorectal Cancer

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ABSTRACT

We have studied a defined group of 12 weight-losing patients with metastatic colorectal cancer to evaluate the occurrence of and possible relationship between those determinants of carbohydrate metabolism which have been reported to occur commonly in cancer cachexia. The rates of endogenous glucose production and recycling via lactate (Cori cycle) were measured following an infusion of 50 to 100 µCi of [1-14C]glucose. Compared to an age-related group of control subjects without cancer, significantly elevated rates of glucose production [136.4 ± 9.0 (S.E.) versus 101.0 ± 4.6 mg/kg/hr; p < 0.01] and recycling (43.0 ± 7.2 versus 15.4 mg/kg/hr; p < 0.01) were observed. Values for glucose production and recycling ranged from normal to markedly elevated. Glucose tolerance was then determined following a p.o. glucose load of 40 g/sq m in 10 of the 12 patients. Compared to control subjects, all showed a significantly delayed clearance of glucose (p < 0.01) and a blunted insulin-secretory responsiveness (p < 0.025). Increased glucose production and recycling was only observed in the presence of carbohydrate intolerance, but the latter occurred in a manner which seemed independent of the rate of glucose turnover.

In order to obtain an estimate of hepatic glycogen reserves, glucagon, 15 ng/kg/min, was infused over 40 min in seven subjects. A significantly blunted glycemic response was observed in the cancer patients compared to controls (Δ25.0 ± 6.9 versus 55.8 ± 8.5 mg/dl; p < 0.025). Neither the rate of glucose production nor the glycemic response to glucagon appeared to correlate with the immediate antecedent caloric intake. An apparent relationship was observed, however, between increased glucose production and recycling and a lack of response to infused glucagon, probably reflecting decreased glycogen stores in the face of an increased glucose requirement by the patient.

We have shown that diverse abnormalities of carbohydrate metabolism commonly occur in cancer cachexia and that significant metabolic heterogeneity may be expected, despite a uniform diagnosis. These results should prove useful in the interpretation and development of clinical studies on cancer cachexia.

INTRODUCTION

Reports that carbohydrate intolerance occurs with increased frequency in cancer patients have appeared in the medical literature over the past several decades (8, 17, 21, 23). Because carbohydrate intolerance may be associated with factors such as starvation (1), inactivity (18, 19), sepsis (9), and composition of the antecedent diet (25, 28), any of which may preexist in cancer cachexia, the primacy of cancer cannot be established as the reason for this observation. More recently, we (13, 22) and others (3, 27) have observed increased rates of endogenous glucose production in some cachectic patients. Elevated rates of endogenous glucose production are almost entirely accounted for by increased glucose recycling via lactate (the Cori cycle), reflecting increased hepatic gluconeogenesis (13, 15). Because hepatic glucose production is normally controlled by the action of insulin, patients with elevated rates of glucose production would be anticipated to show some measure of insulin resistance or hypoinsulinemia. Equally, depleted liver glycogen would be anticipated in anorectic patients with increased rates of endogenous glucose production and this, in part, may account for earlier reports of a decreased glycemic response to infusions of epinephrine (24) in some cancer patients.

The interpretive difficulties inherent in these diverse reports are compounded by the heterogeneous study population and the nonspecific nature of the metabolic findings. In this study, we have attempted to evaluate the occurrence, magnitude, and possible relationship between carbohydrate intolerance, estimated hepatic glycogenolysis, and rates of endogenous glucose utilization and recycling in a defined group of patients with metastatic colorectal cancer who were homogeneous with respect to diagnosis and to the fact that they were cachectic as a result of progressive cancer.

MATERIALS AND METHODS

Patient Subjects. Twelve patients with histologically proven adenocarcinoma of the colon or rectum agreed to participate in the study. All patients had metastatic disease and all had previously received chemotherapy with a 5-fluorouracil-containing drug regimen. There were 6 male and 6 female patients whose ages ranged from 39 to 84 years (mean, 68 years). At the time of study, all patients had lost between 10 and 20% of premorbid body weight. All patients were considered to have recovered adequately from the effects of prior oncological therapy, and were adequately hydrated, and were without acid-base disturbance. All were anorectic at the time of study. Prior to study, no patient was acutely ill, none was febrile, and none received glucocorticoids, chemotherapy, radiation therapy, or surgery during the preceding 3 weeks. Clinical performance status ranged from 1 to 3 (Zubrod scale), and no patient was completely bed confined. Life expectancy was estimated to be more than 60 days in all cases, and all patients were considered to have adequate base-line renal, hepatic, pulmonary, and cardiac function. Control subjects were selected from a group of older volunteers who ages ranged from 50 to 72 years (mean, 63 years) and who weighed from 53.2 to 81.1 kg (mean, 68.9 kg). The control group consisted of 3 male and 3 female healthy subjects who were without history of major complicating illness.

Clinical Procedures and Methodology. Patients were admitted to the Clinical Research Unit of the Lankenau Medical Research Center for a 5-day period. During the first, second, and fourth days, the patients were acclimated to their surroundings, encouraged to ambulate as tolerated, and ate ad libitum with free choice from a house diet. Estimates of caloric intake were obtained by 48-h dietary recall in the initial 2 patients and by the Bowes and Church technique of nutrient analysis of

1 Supported by NIH Research Grant CA-20960 and Biomedical Research Support Grant 5-S07-RR-05585.
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Received March 13, 1984; accepted August 17, 1984.

CANCER RESEARCH Vol. 44, December 1984

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second- and fourth-day food consumption in subsequent patients. Unconsumed food was weighed, and the caloric intake was calculated using standard tables.

After an overnight fast of 10 to 14 hr, the rate of endogenous glucose production and glucose recycling via lactate (Cori cycle) was measured by an isotope tracer technique on Day 3, following the rapid injection of 50 to 100 μCi of [1-14C]glucose as described previously (13, 22). Immediately following the completion of the glucose turnover study, an infusion of glucagon, 15 ng/kg/min, was commenced and maintained for over 40 min. This rate of glucagon infusion was chosen because, in normal subjects, it will override the insulin response to induced glycemia (2).

Blood samples were obtained at 0-, 10-, 20-, 30-, and 40-min intervals for glucagon and plasma glucose determinations. Blood samples for glucagon determinations were collected in trasyol (500 kIU/ml). FBA and immunoreactive insulin were determined by the method of Hales and Randle (10), plasma FFA was determined by the method of Dole and Hohorst (11), and plasma glucose was determined using Glucostat reagent (Worthington Biochemical Corp., Freehold, NJ).

Values are expressed as means. Statistically significant differences between values were determined with the t test for small samples (26).

RESULTS

The plasma glucose response to a p.o. glucose load in 10 of the 12 cancer patients is shown in Chart 1, and the results are compared to those of control subjects. The peak plasma glucose concentration was not significantly different in the cancer patients and control subjects, but glucose clearance was significantly delayed (p < 0.01). All of the cancer patients were actively losing weight at the time of study, and all patients were considered to demonstrate impaired carbohydrate tolerance on the basis of delayed glucose clearance.

Coincident with the attenuated glycemic response to glucose loading, the insulin responsiveness was blunted markedly in the cancer patients, as shown in Chart 1 (p < 0.025). No differences, however, were found in basal insulin concentration (14.9 ± 2.0 μunits/ml in the cancer patients compared to 15.8 ± 1.7 μunits/ml in the controls). By contrast, basal glucagon concentration in the cancer patients was approximately twice that of control subjects (24.2 ± 48.1 versus 112.2 ± 16.8 pg/ml), although these differences were not statistically different.

No differences were observed in basal FFA concentration (0.98 ± 0.05 μEq/liter in the cancer patients versus 0.95 ± 0.08 μEq/liter in the controls). Equally, the FFA response to oral glucose loading was not significantly different between the 2 groups (Chart 2). By contrast, basal plasma lactate concentration was elevated significantly in the cancer patients (1.18 ± 0.07 compared to 0.75 ± 0.07 mm in the controls; p < 0.01). Lactate concentration rose as expected, in response to oral glucose loading in both groups, but was higher in the cancer patients at all time periods except ½ and 1 hr during the 4-hr study (p < 0.01) (Chart 2).

In 12 cancer patients, the mean rate of basal glucose production was 136.4 ± 9.0 compared to 101.0 ± 4.6 mg/kg/hr in the controls (p < 0.01). The increased glucose production seen in the cancer patients was accounted for entirely by significantly increased Cori cycle activity (glucose to lactate to glucose), which was 43.0 ± 7.2 mg/kg/hr in the cancer patients versus 15.4 ± 0.9 mg/kg/hr in the controls (p < 0.01). Rates of endogenous glucose production and recycling in the cancer patients ranged from normal in 2 patients to markedly elevated. No apparent correlation was observed between the rate of glucose production or recycling and the peak glucose concentration, delay in glucose clearance, or degree of insulin responsiveness. While increased glucose production and recycling was observed only in the
The response to glucagon infusion is shown in Chart 3. In 7 cancer patients studied, the mean rise in plasma glucose concentration in response to glucagon was 25.0 ± mg/dl compared to 57.8 ± 8.5 mg/dl in the controls (p < 0.025). No apparent correlation was noted between the estimated caloric intake (mean, 1688 kcal/24 hr; range, 932 to 2579 kcal/24 hr) and the rate of endogenous glucose production and recycling or the glycemic response to glucagon. Those patients with the highest rates of glucose production and recycling, however, had the least response to glucagon infusion, suggesting that hepatic glycogen was depleted as a result of increased glucose requirements rather than decreased caloric intake.

**DISCUSSION**

Reports that abnormal carbohydrate metabolism occurs with increased frequency in cancer patients have appeared sporadically in the medical literature over several decades (8, 17, 21, 23). The interpretative difficulties inherent in these data are compounded by the heterogeneous study populations, the lack of age-matched controls, and the nonspecific nature of the metabolic findings. For these reasons, we thought it was important to study a defined, homogeneous group of cachectic patients with a common solid tumor such as metastatic colorectal cancer.

In contrast to earlier reports (8, 17, 21, 23), all of our patients showed carbohydrate intolerance, as evidenced by delayed clearance of glucose and reduced insulin-secretory responsiveness to oral glucose loading. This was probably due to the fact that all of our patients were cachectic and all were actively losing weight at the time of study. Our findings are similar to the more recent reports of Schein et al. (23) and Chlebowski et al. (3), except that we did not observe heightened peak glucose concentrations compared to controls. The difference in peak glucose concentrations may result from the lower quantity of glucose administered in this study and the difference in study populations. Despite evident glucose intolerance, it is important to recognize that our patients had normal fasting glucose, insulin, and FFA concentrations. Glucagon concentration, on the other hand, was increased in the cancer patients compared to controls, although the differences were not statistically significantly different. While not reported previously, to our knowledge, elevated glucagon levels would be anticipated in a weight-losing catabolic state such as cancer cachexia.

Confirming reports of others (20), the FFA response to oral glucose loading in the cancer patients was not significantly different from the controls. In the face of a blunted insulin response to glucose loading, this observation seems surprising. A possible explanation lies in the relatively increased sensitivity of lipolysis, as opposed to glucose uptake, to the action of insulin.

As expected from previous reports (12, 13), fasting lactate concentrations were higher in the cancer patients. Lactate concentration is known to rise following a glucose load (7), and we have observed previously a modest hyperlactatemia during i.v. hyperalimentation with solutions of hypertonic glucose in some cancer patients (14). Because we have shown earlier that patients with metastatic colorectal cancer have increased rates of endogenous lactate production (12), the higher values seen in the cancer patients throughout the glucose tolerance test probably reflect increased lactate formation in response to glucose.

In an earlier study, we observed markedly increased rates of glucose production and Cori cycle activity in roughly 50% of a heterogeneous group of weight-losing cancer patients (13). In our group of patients with metastatic colorectal cancer, glucose production and Cori cycle activity were increased in 10 of 12 patients. Observed values ranged from normal to markedly elevated. Because endogenous glucose production is normally controlled by the actions of insulin, we have speculated that patients with increased rates of glucose production but normal plasma insulin concentration may be insulin resistant. In these same patients, we have also shown delayed glucose clearance and a blunted insulin-secretory responsiveness. Although the mechanisms which lead to delayed carbohydrate clearance in cancer cachexia are not known, the phenomenon in this study occurred in a manner which was independent of the rates of glucose production and recycling.

We have speculated also that, in patients with elevated rates of glucose recycling, glycogen stores may be depleted. Although depleted liver glycogen would be anticipated in anorectic patients with elevated glucose requirements, this has not, to our knowledge, been investigated systematically but may be inferred from earlier reports of a decreased blood glucose response to infusions of epinephrine (24). Our findings of a significantly decreased glycemic response to glucagon in the cancer patients is in general agreement with previous studies but requires special comment. Although patient numbers are small, no apparent relationship was observed between the estimated caloric intake and the responsiveness to glucagon infusion. An inverse relationship, however, appeared to exist between the glycemic response to glucagon and the rate of glucose production and recycling, suggesting that hepatic glycogen was depleted as a result of increased glucose requirement by the tumor and host, rather than by a simple decrease in caloric intake.
We have shown that diverse abnormalities of carbohydrate metabolism occur commonly in cancer cachexia and that significant metabolic heterogeneity may be expected, despite a uniform diagnosis. While patients with increased endogenous glucose production all demonstrated carbohydrate intolerance in response to a p.o. glucose load, the converse was not true. An apparent relationship was observed between increased glucose production and recycling and a lack of response to infused glucagon, probably reflecting decreased glycogen stores in the face of an increased glucose requirement by the patient. The results of this investigation should prove useful in the development and interpretation of future studies of potential anticachectic agents.

ACKNOWLEDGMENTS

We are indebted to Maureen Donohue, Linda Bell, Patricia Nojunas, R.N., and Laura Savard, R.N., for excellent technical assistance.

REFERENCES

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