

Relationship of Hepatic Glucose Production to Growth Hormone and Severity of Malnutrition in a Population with Colorectal Carcinoma¹

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ABSTRACT

To define the influence of weight loss on the severity of metabolic abnormalities in patients with the same stage and primary site of cancer, hepatic glucose production (HGP) and nutritional status were determined in 44 patients with advanced, Stage D colorectal carcinoma and compared to values in seven cancer-free controls. The colorectal cancer patients were divided into three groups based upon percentage of ideal body weight. HGP was determined in all participants after an overnight fast by using a 3- or 4-h primed, continuous infusion of [6-³H]glucose. Fasting glucose, insulin, cortisol, thyroxine, triiodothyronine, and growth hormone values were also determined. Mean HGP was significantly elevated in colorectal carcinoma patients *versus* normal subjects (2.35 ± 0.89 (SD) mg/kg/min *versus* 1.75 ± 0.16 ; $P < 0.01$). The most severely malnourished group (ideal body weight < 90%) demonstrated the greatest increase in HGP (2.98 ± 0.73 mg/kg/min). Growth hormone mean fasting levels were significantly elevated in the colorectal carcinoma population compared to the normal subjects (2.9 ± 3.1 ng/ml *versus* 0.5 ± 0.2 ; $P < 0.001$). The most severely malnourished group also demonstrated the highest growth hormone levels. The rate of HGP was significantly correlated with fasting growth hormone levels ($r = 0.71$; $P < 0.001$) and not significantly correlated to cortisol, insulin, thyroxine, triiodothyronine, or glucose levels in carcinoma patients. Thus, the elevation in HGP seen in patients with colorectal carcinoma is related to the severity of weight loss and is associated with elevations in fasting growth hormone.

INTRODUCTION

Malnutrition is a significant complication of cancer which adversely influences patients' survival (1). The mechanism underlying the development of weight loss in cancer patients and the relationship of the weight loss to decreased patient survival has not been precisely defined. However, preliminary human studies suggest a multifactorial etiology for the development of the altered nutritional status (2, 3), especially since administration of excessive nutritional intake alone has not been helpful (4-11).

Abnormal elevations in hepatic glucose production (12-19) and Cori cycle activity (19, 20) have been commonly observed in cancer populations and may contribute up to 300-kcal loss of energy per day in these groups (19). Most published reports in this area have included relatively small numbers of patients with a range of primary sites, stage of disease, and nutritional status. Within this context, a consistent picture for counter-regulatory hormone influence on hepatic glucose production has not been defined. The current study evaluated a larger group of similarly staged cancer patients with one primary disease type having defined nutritional status. The objective was to relate HGP³ abnormalities to nutritional status and

alterations in hormonal profiles in patients with advanced colorectal carcinoma.

MATERIALS AND METHODS

A population of patients with colorectal carcinoma were studied before initiation of chemotherapy and were compared to a cancer-free control population. Patients with biopsy proven nonresectable colorectal carcinoma with or without prior malnutrition were eligible for entry. Patients with diabetes mellitus, hypothyroidism, hyperthyroidism, clinical evidence of cirrhotic liver disease, renal disease, or anemia (hematocrit < 30) were excluded. Control patients had the same selection criteria as above and had no recent history of illness or decrease in usual food intake. Cancer patients and controls were admitted to the Clinical Research Center at Harbor-UCLA Medical Center.

Fasting base-line bloods include measurements of glucose, insulin, growth hormone, cortisol, and thyroid function tests. A 3- or 4-h [6-³H]glucose primed, continuous (25 μ Ci, 14.4 μ Ci/h) infusion was started between 7 and 8 am. Over the final hour of the study, blood was drawn every 20 min for plasma glucose, insulin, and [6-³H]glucose specific activity. We have previously used primed, continuous infusions of [6-³H]glucose to determine fasting whole body glucose appearance rates according to the following formula:

$$\text{HPG (mg/h)} = \frac{r(\text{ml/h}) \times \text{SAi (dpm/ml)}}{\text{SAs (dpm/mg)}}$$

where r is the infusion rate; SAi is the specific activity of infusate; SAs is the specific activity of glucose in serum at equilibrium. Since [6-³H]glucose is metabolized to tritiated water, protein-free plasma supernatants are evaporated prior to scintillation counting when determining [6-³H]glucose specific activity according to previously described methods (21). Plasma insulin, growth hormone, cortisol, triiodothyronine, and thyroxine were measured by standard double antibody radioimmunoassay methods. Plasma glucose was measured with an Abbott ABA-100 analyzer by the method of König *et al.* (22). Chemistry profiles and serum transferrin were performed by the Clinical Chemistry Laboratory. The Clinical Research Center dietitian performed standardized measurement of anthropometry based upon established methods (23).

Data analysis was performed by using steady state isotopic equations run on the Clinfo biostatistical package. Changes in HGP rates and any relationship between degree of malnutrition and hormonal profiles were examined by analysis of variance by the Dunnett's multiple comparison test. Sample sizes of several measurements vary and are noted in the individual tables. Linear regression analysis was performed by the method of least squares. Significance was defined at $P < 0.05$.

RESULTS

Forty-four colorectal carcinoma patients and 7 cancer-free controls were enrolled and completed the study. To evaluate the influence of malnutrition on the hormonal and metabolic abnormalities present in the colorectal carcinoma patients, the population of patients was divided into three groups based upon percentage of IBW at the time of enrollment. Table 1 describes the patients' characteristics and Table 2 the nutritional assessment parameters. Liver function test, serum albumin, and transferrin levels were not different among all four groups (Table 3).

The mean HGP rate was significantly elevated in the colorectal carcinoma patients compared with the normal subjects (2.35 ± 0.89 mg/kg/min *versus* 1.75 ± 0.16 (SD); $P < 0.01$).

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³ The abbreviations used are: HGP, hepatic glucose production; IBW, ideal body weight.

Table 1 Patient characteristics

Groups	n	Age (yr)	Sex		n	Wt (kg)	n	Performance status
			M	F				
Normal subjects	7	48 ± 5 ^a	7	0	7	83 ± 12	7	0.0 ± 0.0
Colon cancer								
>110% IBW	15	59 ± 9	7	8	15	81 ± 17	14	0.9 ± 1.0
90–110% IBW	13	59 ± 10	7	6	13	58 ± 6 ^b	13	1.3 ± 1.1
<90% IBW	16	56 ± 14	11	5	16	54 ± 7 ^b	15	1.7 ± 1.0 ^b

^a Mean ± SD.^b Compared to normal subjects, $P < 0.05$ by analysis of variance with Dunnett's multiple comparison test.

Fasting plasma glucose levels were not significantly correlated with HGP rates in the carcinoma population ($r = 0.04$, $n = 44$, $P = 0.81$) nor in the normal subjects ($r = 0.63$, $n = 7$, $P = 0.13$). The most severely malnourished cancer group (IBW < 90%) demonstrated the highest elevation in HGP (2.98 ± 0.73 mg/kg/min; see Table 4). The mean fasting growth hormone level was significantly elevated in the colorectal carcinoma population compared to controls (2.9 ± 3.1 ng/ml *versus* 0.5 ± 0.2 , $P < 0.001$) with the largest elevation observed in patients < 90% IBW. In the colorectal carcinoma patients, the HGP rate was significantly correlated with fasting growth hormone levels ($r = 0.71$, $n = 27$, $P < 0.001$; see Fig. 1). and not significantly correlated to cortisol, insulin, thyroxine, triiodothyronine, or glucose levels. Serum free triiodothyronine was significantly decreased in the most malnourished group but thyroxine, triiodothyronine, cortisol, and insulin levels were not significantly different in all of the groups (Table 4).

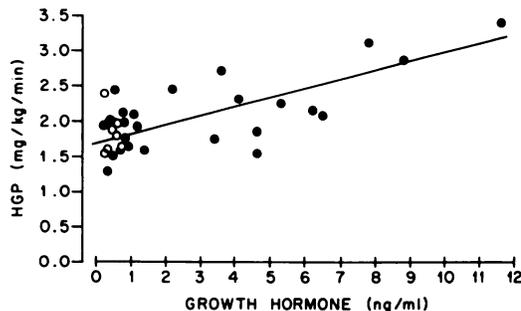


Fig. 1. Correlation in colorectal cancer patients (●) between fasting plasma growth hormone levels and the hepatic glucose production rate measured by a primed continuous infusion of [$6\text{-}^3\text{H}$]glucose ($r = 0.71$; $n = 27$; $\text{HGP} = 1.755 + 0.115 \times \text{growth hormone}$; $P < 0.001$). Elimination of the largest growth hormone value in the colorectal cancer group reduces the correlation from 0.71 to 0.59, $P < 0.005$. There was no correlation between plasma growth hormone levels and hepatic glucose production rate in the normal volunteers (○).

DISCUSSION

The metabolic factors associated with the presence of cancer cachexia have not been clearly identified. Elevated HGP has been noted in multiple types of cancer (12–19) and can be viewed as an energy costly process that could contribute to the development of cancer cachexia. Weight loss alone without the presence of cancer has not been associated with elevations in HGP (19). Insulin insensitivity in cancer patients has been described (17, 24, 25) and a blunted action of insulin at the site of the liver (19) could very well be contributing to the elevation in HGP as seen in the type II diabetic (26).

Table 2 Nutritional assessment data

Groups	IBW		BMI ^a		Fat mass		TSF		AMA		Muscle mass		Wt loss	
	n	%	n	kg/m ²	n	kg	n	mm	n	cm ²	n	kg	n	kg
Normal subjects	7	111 ± 10 ^b	7	26 ± 2	7	29 ± 16	7	16 ± 8	7	54 ± 14	7	33 ± 8	7	-1 ± 1
Colon carcinoma														
>110% IBW	15	127 ± 19 ^c	15	29 ± 5	15	47 ± 18 ^c	15	24 ± 7 ^c	15	49 ± 11	16	28 ± 7	15	1 ± 11
90–110% IBW	13	100 ± 5	13	22 ± 2 ^c	13	22 ± 12	13	15 ± 7	13	30 ± 10 ^c	13	18 ± 4 ^c	13	6 ± 7
<90% IBW	16	79 ± 11 ^c	16	19 ± 1 ^c	15	14 ± 8	13	10 ± 5	15	29 ± 9 ^c	15	19 ± 5 ^c	15	15 ± 8 ^c

^a BMI, body mass index; TSF, triceps skin fold; AMA, arm muscle area.^b Mean ± SD.^c Compared to normal subjects, $P < 0.05$ by analysis of variance with Dunnett's multiple comparison test.

Table 3 Biochemical parameters and liver function tests

Groups	Albumin		Transferrin		Aspartate amino-transferase		Lactate dehydrogenase		Alkaline phosphatase		Bilirubin	
	n	g/dl	n	mg/dl	n	IU/liter	n	IU/liter	n	IU/liter	n	mg/dl
Normal subjects	6	4.0 ± 0.3 ^a	7	238 ± 38	6	16 ± 5	6	139 ± 24	6	76 ± 17	6	0.4 ± 0.1
Colon carcinoma												
>110% IBW	14	3.9 ± 0.5	11	246 ± 60	13	40 ± 51	13	258 ± 180	14	174 ± 299	14	1.0 ± 1.6
90–110% IBW	12	3.5 ± 0.7	10	216 ± 52	12	30 ± 18	12	348 ± 223	12	235 ± 327	12	0.9 ± 1.4
<90% IBW	15	3.4 ± 0.6	11	197 ± 98	9	36 ± 33	15	421 ± 487	15	205 ± 172	15	0.5 ± 0.3

^a Mean ± SD.

Table 4 Hepatic glucose production and hormonal profile

Groups	HGP		Growth hormone		Cortisol		Insulin		Glucose		Thyroxine		Triiodothyronine		Free triiodothyronine	
	n	mg/kg/min	n	ng/ml	n	μg/dl	n	units/ml	n	mg/dl	n	μg/dl	n	ng/dl	n	pg/dl
Normal subjects	7	1.75 ± 0.16 ^a	7	0.5 ± 0.2	7	12 ± 6	7	10 ± 5	7	100 ± 7	7	7.2 ± 0.7	7	133 ± 27	5	433 ± 62
Colon carcinoma																
>110% IBW	15	1.95 ± 0.73	12	1.4 ± 1.5	13	11 ± 7	15	13 ± 11	15	101 ± 14	14	6.5 ± 2.9	14	97 ± 40	6	285 ± 174
90–110% IBW	13	2.06 ± 0.27	9	2.2 ± 2.1	10	16 ± 5	11	7 ± 2	13	95 ± 12	11	8.4 ± 2.4	11	100 ± 47	6	247 ± 125
<90% IBW	16	2.98 ± 0.73 ^b	6	7.2 ± 2.8 ^b	11	18 ± 5	15	7 ± 3	16	93 ± 9	11	7.7 ± 2.6	11	97 ± 36	7	231 ± 103 ^b

^a Mean ± SD.^b Compared to normal subjects, $P < 0.05$ by analysis of variance with Dunnett's multiple comparison test.

Counter regulatory hormone abnormalities instead of isolated insulin insensitivity may be important mediators of the process of cancer cachexia. Studies generally in small populations of cancer patients have not demonstrated elevations in 24-h urinary free cortisol levels (12, 27–29) with two exceptions. Rose *et al.* (28) studied breast, lung, and colon carcinoma and described a significant elevation in urinary free cortisol only in the colon cancer patients *versus* controls ($89 \pm 44 \mu\text{g/day}$ *versus* 57 ± 23 (SEM); $P < 0.05$). A recent study of a large population of heterogeneous cancer patients in which 50% of the patients had the diagnosis of colorectal carcinoma has demonstrated the presence of mild elevations in urinary free cortisol (317 ± 32 nmol/day *versus* 196 ± 20 (SEM); $P < 0.01$) and urinary epinephrine (39 ± 4 nmol/day *versus* 30 ± 4 (SEM); $P < 0.05$; Ref. 3). Plasma cortisol levels in several types of malignancy have previously been shown to be elevated (30–32) or normal (2, 4, 15, 33, 34), but the levels in colorectal carcinoma patients have not been previously described. The lack of a significant elevation in mean plasma cortisol levels in the present study, the lack of difference among the three groups based upon IBW, and the absence of any correlation of plasma cortisol levels with HPG rates reduces the possibility that the morning plasma cortisol levels play a primary role in the elevation of HGP in patients with colorectal cancer.

Catecholamine levels in urine of cancer patients have been found to be normal (19) or slightly elevated (3). Catecholamines were not performed in this study because recent work in normal volunteers infused with a 300-fold increase in epinephrine levels along with β adrenergic blockade did not demonstrate an increase in HGP (35), and because selective α adrenergic and β adrenergic blockade did not reduce elevated HGP rates in surgical cancer and noncancer patients (5).

Growth hormone levels are known to be elevated in several types of nonacromegalic cancers, including lung, lymphoma, breast, carcinoid, liver, laryngeal, and endometrial carcinoma (2, 34, 36–40) and in severe malnutrition (41–43). Growth hormone levels are not increased after a 9-day fast alone (44) but are commonly elevated in marasmus and kwashiorkor types of malnutrition (41, 42). None of the colorectal patient groups in this study demonstrated a significant reduction in serum albumin levels indicating little evidence of kwashiorkor type of malnutrition. In both the $<90\%$ IBW and the 90–110% IBW colorectal patient groups there was a significant and similar reduction in muscle mass and arm muscle area, suggesting a comparable degree of marasmus type of malnutrition. If the severity of malnutrition alone determines the growth hormone level, then a similar level of growth hormone in these two malnourished groups would be expected (Table 4). The fact that similar growth hormone levels were not observed in the two groups supports the hypothesis that malnutrition alone may not be responsible for the elevated growth hormone levels seen in this colorectal cancer population.

Severe liver involvement by metastatic disease can contribute to elevation in plasma growth hormone levels in cancer populations (45). However, in our colon cancer patients, differences among patient groups in this regard were not evident by liver function tests nor were liver function values correlated with growth hormone levels. The malignant process itself may be producing factors that reduce somatomedin C levels (44) and subsequently elevate growth hormone levels. Elevated growth hormone levels in normal subjects increase insulin insensitivity at the site of the liver and elevate endogenous HGP rates (46). Controlled administration of growth hormone to normal volunteers can double HGP (47), so that the observed increase in

the growth hormone level in this population of colorectal carcinoma patients and the associated increase in HGP support the hypothesis that growth hormone is contributing to the increase in HGP.

Earlier work has suggested that the elevation of growth hormone levels seen in severe marasmus may be a mechanism to prevent severe hypoglycemia in the face of prolonged starvation (43). Even though there was no history of hypoglycemia in the most malnourished group, the fasting glucose level was the lowest of all the groups. The significant correlation ($r = 0.71$) between HGP rates and plasma growth hormone level suggest that there exists a role of growth hormone and elevations in HGP in colorectal cancer patients. This study has not demonstrated causality between growth hormone and HGP but does identify the need for further research in this area.

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