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# Growth Hormone, Alone and in Combination With Insulin, Increases Whole Body and Skeletal Muscle Protein Kinetics in Cancer Patients After Surgery

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## Objective

To investigate the impact of growth hormone, alone and in combination with insulin, on the protein kinetics of patients with upper gastrointestinal (GI) tract cancer who have undergone surgery and are receiving total parenteral nutrition (TPN).

## Summary Background Data

Patients with malignancies of the upper GI tract are at increased risk for malnutrition and perioperative death and complications. Standard nutritional support has not significantly altered outcome. Growth hormone (GH) and insulin have been shown to have some benefit in patients with cancer; however, their action in patients undergoing resection has not previously been studied.

## Methods

Thirty patients undergoing surgery for upper GI tract malignancies were prospectively randomized into one of three nutritional support groups after surgery: 10 patients received standard TPN, 10 received TPN plus daily injections of GH, and 10 received daily GH, systemic insulin, and TPN. The patients underwent a protein kinetic radiotracer study on the fifth day after surgery to determine whole body and skeletal muscle protein kinetics.

## Results

Patients who received standard TPN only were in a state of negative skeletal muscle protein net balance. Those who received GH and insulin had improved skeletal muscle protein net balance compared with the TPN only group. Whole body protein net balance was improved in the GH and the GH and insulin groups compared with the TPN only group. GH and insulin combined did not improve whole body net balance more than GH alone. GH administration significantly increased serum IGF-1 and GH levels. Insulin infusion significantly increased serum insulin levels and the insulin/glucagon ratio.

## Conclusion

Growth hormone and GH plus insulin regimens improve protein kinetic parameters in patients with upper GI tract cancer who are receiving TPN after undergoing surgery.

Patients with cancer frequently have cachexia as part of the advanced malignant process. Cancer cachexia describes a group of symptoms, signs, and metabolic alterations that occur in the cancer-bearing host that result in involuntary weight loss and decreased nutrient intake. Although cachexia can be associated with any malignancy, patients with upper gastrointestinal (GI) tract malignancies are at significantly increased risk for malnutrition and weight loss.[1] These patients not only exhibit anorexia, dysphagia, and obstructive symptoms as a result of their GI tract tumor, but are also subject to alterations in protein metabolism secondary to the neoplastic process.[2] The resulting clinical impact of cachexia is significant, and numerous studies have demonstrated that the extent of malnutrition correlates with increased rates of perioperative morbidity and mortality.[3,4] In patients with upper GI tract cancer who do not undergo surgery, any degree of weight loss has been associated with decreased median survival.[1] The further catabolic stress of

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major surgery increases the risks of cancer-related malnutrition.

The negative impact of cancer cachexia on clinical outcome has resulted in extensive investigation of total parenteral nutrition (TPN) support in patients with cancer, especially those with GI tract malignancies.[5–7] However, only one of these prospective trials investigating TPN in the perioperative period demonstrated a significant decrease in rates of major complications or death.[6]

The failure of TPN to improve clinical outcome has led to significant interest in the use of potential anabolic adjuncts. Insulin is a potent anabolic agent and has been shown to improve protein kinetics with both short-term and long-term infusions in patients with cancer.[8–10] Growth hormone (GH) has also been studied as an anabolic agent and has been shown to increase lean body mass[11] and result in an increase in nitrogen balance and a decrease in wound infection and hospital stay[12] in patients undergoing surgery. However, few studies have investigated the use of GH in patients with cancer. Our laboratory investigated the effect of GH before surgery in patients with cancer and showed an increase in whole body protein net balance, but no significant change in skeletal muscle kinetics. When GH was combined with short-term insulin infusion, both skeletal muscle and whole body protein net balances were increased.[13] The only other published report of GH administration in patients with cancer examined 10 patients who did not undergo surgery; it found that GH increased anabolism only in patients who were not malnourished.[14]

This study was undertaken to determine the effect of GH, alone and in combination with insulin, on protein kinetics in patients with upper GI tract cancer who received TPN after surgery.

## METHODS

### Subjects

All subjects were admitted to the Gastric and Mixed Tumor or Thoracic Surgery Service at Memorial Sloan-Kettering Cancer Center and underwent complete resection of their upper GI tract (esophageal, gastric, or pancreatic) malignancy. The study was performed under an Institutional Review Board-approved protocol, and informed written consent was obtained before enrollment into the study. Patients with a history of thyroid disease or insulin-dependent diabetes mellitus were excluded from the study, as were patients requiring medications known to alter intermediary metabolism or metabolic rates, such as beta blockers.

### Study Design

The study was conducted as a prospective, randomized trial in which 30 patients were randomized to receive one of three nutritional regimens, ten patients per treatment group, after surgery. Before surgery, patients underwent a prestudy evaluation that included a history and physical examination, determination of height, weight, and skinfold thickness, and documentation of weight loss. Phlebotomy was performed to determine hormone levels, a complete blood count, and a biochemical screening profile, including liver function tests.

At the time of surgery, once tumor resectability had been determined, a central venous catheter was inserted and the patient was randomized to receive one of three nutritional regimens starting on day 1 after surgery. The TPN group received standard TPN; the GH group received a daily injection of recombinant human GH and TPN; the GH plus insulin group received daily GH, systemic insulin, and TPN. The randomization was conducted in cooperation with the randomization office at Memorial Hospital.

Nutritional support and hormone administration were started on the first day after surgery and continued until day 5, when all patients underwent a protein kinetic metabolic study to determine whole body and skeletal muscle protein kinetics. Growth hormone, IGF-1, insulin, glucagon, and C-peptide levels were measured each morning during the study period. A biochemical screening profile and complete blood count were obtained on days 1, 3, and 5.

### Nutritional Support and Hormone Administration

Total parenteral nutrition was administered through a central venous catheter. The TPN was composed of 1 g/kg amino acids (Travasol 10%; Baxter, Deerfield, IL), 1000 kcal/day dextrose, 500 ml of 20% lipid emulsion (Intralipid; Baxter), trace element solution (American Regent; Shirley, New York, NY), and a multivitamin mixture (Lyphomed, Deerfield, IL). The total volume of TPN per 24-hour period was 2000 ml (500 cc of intralipid solution plus 1500 cc of the amino acid and dextrose solution). Patients were kept *non per os* (NPO) throughout the study period. All medications were mixed in normal saline, and no dextrose was provided as part of any intravenous fluid outside of the TPN.

Patients in the GH and GH plus insulin groups received 0.1 mg/kg GH (Biotropin; Biotechnology General Corp., Iselan, NJ) per day subcutaneously at 6 PM starting on day 1 and continuing through day 4. For patients in the GH plus insulin group, 1.4 units/kg of regular human insulin (Eli Lilly, Indianapolis, IN) was added to the standard daily TPN formula. This delivered a continuous infusion of 1 mU/kg of insulin per minute. The insulin-enriched TPN and standard TPN formulas were isocaloric and isonitrogenous and differed only in the addition of insulin in the GH plus insulin group. Before the initiation of the insulin-enriched TPN on day 1, a graded bolus of 400 mU/m$^2$ of regular human insulin was administered over 10 minutes to patients in the GH plus insulin group. The TPN with insulin was started immediately after the bolus was completed. During the 10-minute bolus period and at least 2 hours after the commencement of the insulin-enriched TPN, serum glucose was closely monitored using a bedside serum glucose analyzer

(Beckman, Fullerton, CA), and a variable infusion of 50% dextrose was adjusted according to a sliding scale to prevent hypoglycemia. Once a stable serum glucose level was achieved, glucose levels were monitored by fingerstick values every 8 hours, and the 50% dextrose infusion was adjusted according to a sliding scale designed to maintain euglycemia. Patients in the TPN or GH group also underwent fingerstick glucose monitoring every 8 hours throughout the study period but were not allowed to receive exogenous insulin.

## Protein Kinetic Study

On day 5, all patients underwent a protein kinetic metabolic study consisting of a 2-hour isotope infusion period followed by a 45-minute sampling period. The studies were performed at the bedside with the patient resting in a supine position. At 7 AM on day 5, a primed continuous infusion of 1-(1-$^{14}$C) leucine (bolus 17 $\mu$Ci, infusion 11.6 $\mu$Ci/hour) and L-(ring 2,6-$^{3}$H) phenylalanine (bolus 34 $\mu$Ci, infusion 41 $\mu$Ci/hour) was started through the indwelling central venous catheter. A 3.6-$\mu$Ci bolus of $^{14}$C sodium bicarbonate was also given intravenously to prime the bicarbonate pool.[15] All radiotracer infusates (Du Pont, Boston, MA) were sterilized by passage through a 0.2-$\mu$m sterilizing filter, and all dilutions were prepared with sterile normal saline.

During the isotope infusion period, an arterial catheter was placed into the radial artery of the hand after confirmation of adequate collateral hand blood flow. An 18-gauge, 2″ catheter was also inserted in a retrograde fashion into an antecubital vein to allow deep venous sampling from the forearm. After 2 hours of isotope infusion, when radiotracer specific activity was at steady state, samples of arterial and deep venous blood were obtained at 15-minute intervals, and forearm blood flow was measured by capacitance plethysmography.[16] Expired air was collected into a solution of hyamine hydroxide, designed to trap 1 mmol of $CO_2$ per vial.[17] Total $CO_2$ production over a 5-minute period was collected by a metabolic measuring cart (Sensor Medics, Yorba Linda, CA).

## Sample Analysis

All blood samples were placed on ice immediately after collection. Serum and plasma were then stored at −70°C for subsequent analysis. Plasma for $\alpha$-ketoisocaproate (KIC) determination was deproteinized with 50% sulfosalicylic acid, and the ketoacids were extracted by cation exchange resin (AG 50W-X8; Bio-Rad, Richmond, CA). Phenylalanine and KIC specific activities were then determined by high-performance liquid chromatography separation and subsequent beta scintillation counting of the appropriate fractions. Levels of GH, IGF-1, insulin, glucagon, and C-peptide were determined using standard radioimmunoassay. Specific activity of expired $CO_2$ was determined by beta scintillation counting of expired breath samples.

## Calculations

### *Whole Body*

Whole body leucine kinetics were calculated using a stochastic, two-pool model of whole body protein metabolism.[18] Using this model, whole body leucine turnover, or flux ($Q$), is represented by the equation:

$$Q = S + Ox = B + I(\mu\text{mol/kg per minute})$$

where $S$ is the rate of nonoxidative leucine disappearance, or protein synthesis; $Ox$ is the rate of leucine oxidation; $B$ is the endogenous rate of leucine appearance, or protein breakdown; and $I$ is the rate of infusion of exogenous leucine. $Q$ is defined as the rate of amino acid flow through the free amino acid pool into protein and other metabolic pathways.

Using a reciprocal pool model,[19] the specific activity of KIC is used to represent the immediate precursor pool of leucine incorporation into protein. $Q$ can then be calculated by the equation:

$$Q = F/SA_{KIC}(\mu\text{mol/kg per minute})$$

where $F$ equals the rate of infusion of $^{14}$C leucine (dpm/min) at steady state and $SA_{KIC}$ is the specific activity of KIC (dpm/mol) in plasma at steady state.

The rate of leucine oxidation ($Ox$) can be calculated as follows:

$$Ox = E/(K \times SA_{KIC})(\mu\text{mol/kg per minute})$$

where $E$ is the rate of appearance of $^{14}CO_2$ in expired breath (dpm/min) and $K$ is a derived correction factor to take into consideration the incomplete recovery of metabolic bicarbonate pool measured as expired $CO_2$ ($K = 0.81$).[15] When $I$ is a known constant, the rate of leucine appearance, or protein breakdown, can be calculated from $B = Q - I$, and the rate of nonoxidative leucine disappearance, or protein synthesis, can be calculated from $S = Q - Ox$. Whole body net balance of leucine ($NB$) is then calculated as the difference between protein synthesis and breakdown:

$$NB = S - B(\mu\text{mol/kg per minute}).$$

### *Skeletal Muscle*

A systemic infusion of L-(ring-2,6-$^{3}$H) phenylalanine with measurement of steady-state amino acid exchange kinetics across the forearm muscle bed was used to determine the rates of skeletal muscle protein synthesis and degradation and net balance. The venous plasma pool was used as the reference pool.[20] As previously described, steady-state arterial and venous samples were analyzed for phenylalanine concentration and specific radioactivity. According to this model of skeletal muscle protein kinetics:

$$Ra = Art_{phe} \times F \times ([SA_{art}/SA_{ven}] - 1)$$

$$NB = (Art_{phe} - Ven_{phe}) \times Flow$$

$Rd = NB - Ra$(nmol/100 g forearm tissue per minute).

*Ra* is the rate of appearance of phenylalanine in the plasma and reflects skeletal muscle breakdown. *Rd* is the rate of disappearance of phenylalanine from the plasma and reflects skeletal muscle protein synthesis. *NB* is the net balance of phenylalanine across the skeletal muscle bed. $Art_{phe}$ and $Ven_{phe}$ are the measured arterial and venous concentrations of phenylalanine, respectively, and $SA_{art}$ and $SA_{ven}$ represent the specific activity of L-(ring-2,6-$^3$H) phenylalanine in the arterial and venous plasma, respectively. *F* is forearm plasma flow.

## Statistics

To evaluate the independent effects of the nutritional regimens, protein kinetic parameters between the treatment groups were analyzed using the Wilcoxon rank-sum test. To evaluate changes in hormone levels and blood chemistries between the treatment groups and over the course of the study period, analysis of variance with repeated measures was used with Bonferroni adjustment when appropriate (SPSS software). Significance was defined as $p < 0.05$. Results are expressed as mean ± SEM.

## RESULTS

Before surgery, 66 patients were recruited into the study. Of these, 27 were never randomized because their tumors were unresectable (n = 23) or they needed intensive care unit treatment after surgery (n = 4). Thirty-nine patients were randomized and began treatment; 30 patients completed the trial. Two subjects were removed for hyperglycemia (GH and GH plus insulin groups). Five patients required transfer to the intensive care unit and were removed from the study because they were considered to be under a more significant metabolic stress (GH, n = 3; TPN, n = 2). One patient in the GH group refused reinsertion of an inadvertently pulled central venous catheter, and one patient in the GH group refused to undergo the metabolic study.

Patient characteristics and primary tumor types are shown in Table 1. There was no difference among the three groups with respect to height, weight, percentage of weight loss from preillness weight, percentage of lean body mass, and percentage of ideal body weight, as determined by skinfold thickness (biceps, triceps, subscapular, iliac crest). There were no significant differences among or within the groups with respect to hematologic parameters, electrolytes, liver function tests, or vital signs.

Subjects in the GH plus insulin group received significantly more calories over the entire study period (11,622 ± 659 kcal, $p < 0.05$) than those in the TPN (9394 ± 104 kcal) and GH (9119 ± 73 kcal) groups. There was no difference in total calories delivered between the TPN and GH groups. The extra calories provided to the GH plus insulin group resulted from the 50% dextrose used to maintain euglycemia. Daily caloric intake was greater in the GH plus insulin group than in the TPN or GH group, also as a result of the 50% dextrose infusion. Fingerstick glucose monitoring demonstrated that by day 4, patients in the GH group became significantly hyperglycemic compared with the GH plus insulin group. The patients in the GH group also had an elevated urine glucose level compared with the other two groups (results not shown).

**Table 1. PATIENT CHARACTERISTICS**

| | TPN N = 10 | GH N = 10 | GH + INS N = 10 |
|---|---|---|---|
| Male/female | 8/2 | 5/5 | 8/2 |
| Age (yr) (range) | 65.8 ± 4.1 (50–84) | 60.2 ± 3.0 (46–74) | 63.1 ± 2.2 (52–75) |
| % Weight loss | 4.8 ± 1.2 | 3.8 ± 1.1 | 6.7 ± 1.5 |
| Malignancy | | | |
| Pancreas | 4 | 1 | 2 |
| Stomach | 2 | 4 | 4 |
| Esophagus | 4 | 5 | 4 |

p = N.S. All results reported as mean ± standard error of the mean. TPN = total parenteral nutrition; GH = growth hormone; GH + Ins = growth hormone plus insulin.

## Hormone Levels

Figure 1 demonstrates the changes in serum insulin levels over the course of the study. Starting on day 2, the insulin level in the GH plus insulin group (117.8 ± 21.1 μU/ml) was significantly elevated compared with the level before surgery (24.0 ± 2.7 μU/ml, $p = 0.005$) and with the TPN (37.7 ± 6.4 μU/ml, $p < 0.05$) and GH (42.1 ± 6.9 μU/ml, $p < 0.05$) groups. The insulin level in the GH plus insulin group remained significantly elevated throughout the remainder of the study period compared with the other groups. Also, starting on day 3 the mean insulin level in the GH group was significantly elevated compared with the TPN group (53.5 ± 8.1 μU/ml *vs.* 28.4 ± 6.5 μU/ml, $p < 0.05$). C-peptide hormone levels were measured as a reflection of endogenous insulin secretion; on day 5, the levels were significantly elevated in the GH group (6.58 ± 0.66 ng/ml) compared with the TPN group (4.03 ± 0.61 ng/ml, $p < 0.05$) and the GH plus insulin group (4.23 ± 0.59 ng/ml, $p < 0.05$), demonstrating that the elevated insulin levels seen in the GH group were from release of endogenous insulin.

There were no differences among or within the groups with respect to glucagon levels, but there was a significant elevation in the insulin/glucagon ratio in the GH plus insulin group starting on day 2 (1.20 ± 0.22) compared with

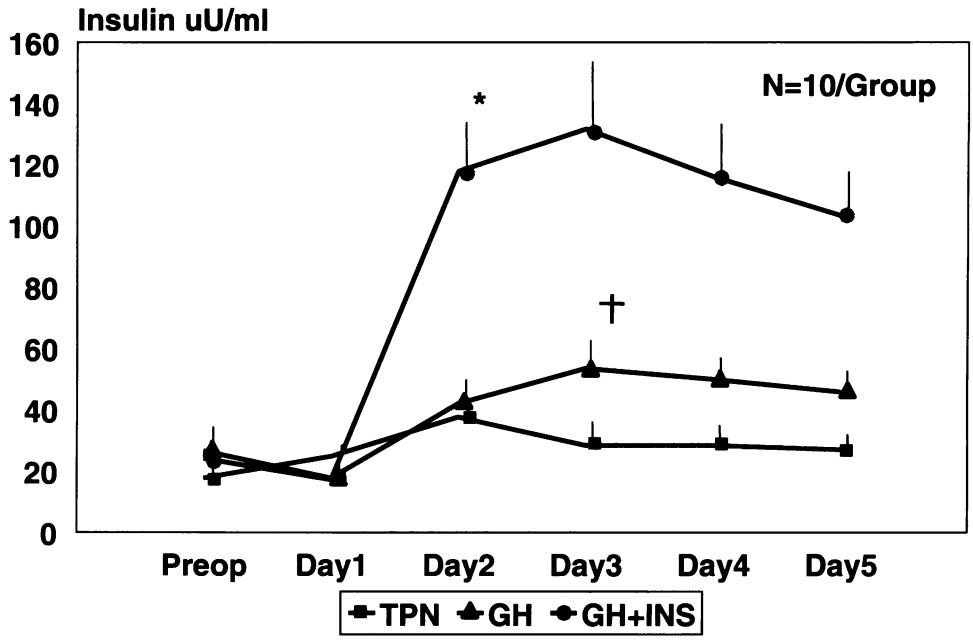


**Figure 1.** Insulin levels (μU/ml). *, $p < 0.05$ *vs.* total parenteral nutrition (TPN), growth hormone; †, $p < 0.05$ *vs.* TPN. All data are presented as mean ± standard error of the mean. TPN, total parenteral nutrition group; GH, growth hormone group; GH+Ins, growth hormone plus insulin group.

pretreatment values (0.22 ± 0.03, $p < 0.05$) and the TPN (0.25 ± 0.05, $p < 0.05$) and GH groups (0.42 ± 0.11, $p < 0.05$).

Growth hormone levels are shown in Figure 2. Both GH-treated groups (GH and GH plus insulin) had significantly elevated GH levels starting on day 2 (33.4 ± 3.8 and 39.4 ± 4.5 ng/ml, respectively; $p < 0.05$ *vs.* before treatment) compared with pretreatment levels (day 1 levels: GH, 3.68 ± 1.2 ng/ml; GH plus insulin, 3.64 ± 1.0 ng/ml). Although there was a decline in GH levels over the course of the study period, they remained significantly elevated compared with the pretreatment period in both GH-treated groups. In addition, starting on day 2 and for the remainder of the study period, GH levels in the GH and GH plus insulin groups were significantly elevated compared with the TPN group (day 2: 3.06 ± 0.9 ng/ml, $p < 0.05$).

IGF-1 levels are shown in Figure 3. There was a significant decrease in IGF-1 levels after surgery in all three treatment groups from the baseline level before surgery to day 1 after surgery. In both the GH-treated groups, GH treatment increased IGF-1 levels significantly compared with day 1 measurements starting on day 3, and the levels continued to rise throughout the study period in both groups. Although GH treatment elevated the IGF-1 mea-

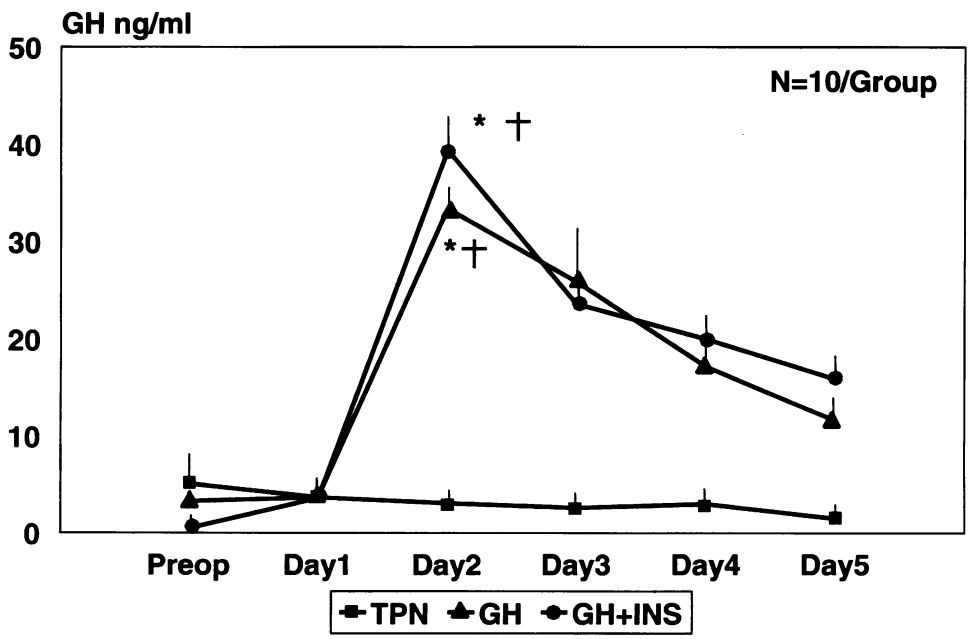


**Figure 2.** Growth hormone levels in ng/ml. *, $p < 0.05$ *vs.* total parenteral nutrition group; †, $p < 0.05$ *vs.* presurgical and day 1. All data are presented as mean ± standard error of the mean. TPN, total parenteral nutrition group; GH, growth hormone group; GH+Ins, growth hormone plus insulin group.

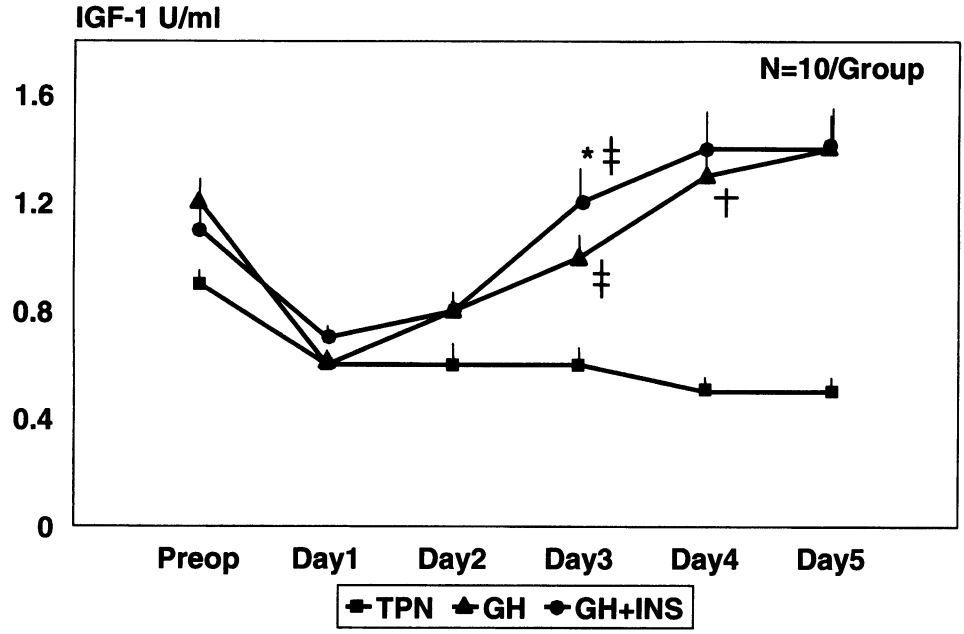


**Figure 3.** IGF-1 levels (U/ml). *, $p < 0.05$ *vs.* total parenteral nutrition group; †, $p < 0.05$ *vs.* total parenteral nutrition group; ‡, $p < 0.05$ *vs.* day 1. All data re presented as mean ± standard error of the mean. TPN, total parenteral nutrition group; GH, growth hormone group; GH+Ins, growth hormone plus insulin group.

surements back to the range before surgery, the levels did not become significantly greater than the values before surgery. Starting on day 3, the GH plus insulin group had a significantly elevated IGF-1 level (1.20 ± 0.19 U/ml) compared with the TPN group (0.58 ± 0.09 U/ml, $p < 0.05$), and starting on day 4, the GH group had significantly elevated IGF-1 levels (1.26 ± 0.17 U/ml) compared with the TPN group (0.48 ± 0.07 U/ml, $p < 0.05$).

## Protein Kinetics

Whole body protein kinetic data are shown in Figure 4. The nonoxidative rate of leucine disappearance (Rd), a reflection of protein synthesis, was not significantly altered by the administration of GH or GH plus insulin. Similarly, the endogenous rate of leucine appearance (Ra), a reflection of protein breakdown, was not significantly influenced by treatment. Whole body protein net balance, however, was significantly improved by treatment with both GH (0.17 ± 0.02 μmol leucine/kg per minute, $p < 0.005$) and GH plus insulin (0.14 ± 0.02 μmol leucine/kg per minute, $p = 0.05$) compared with TPN alone (0.05 ± 0.03 μmol leucine/kg per minute). Although whole body protein net balance was significantly increased by GH and GH plus insulin treatment compared with TPN alone, the combination of GH and

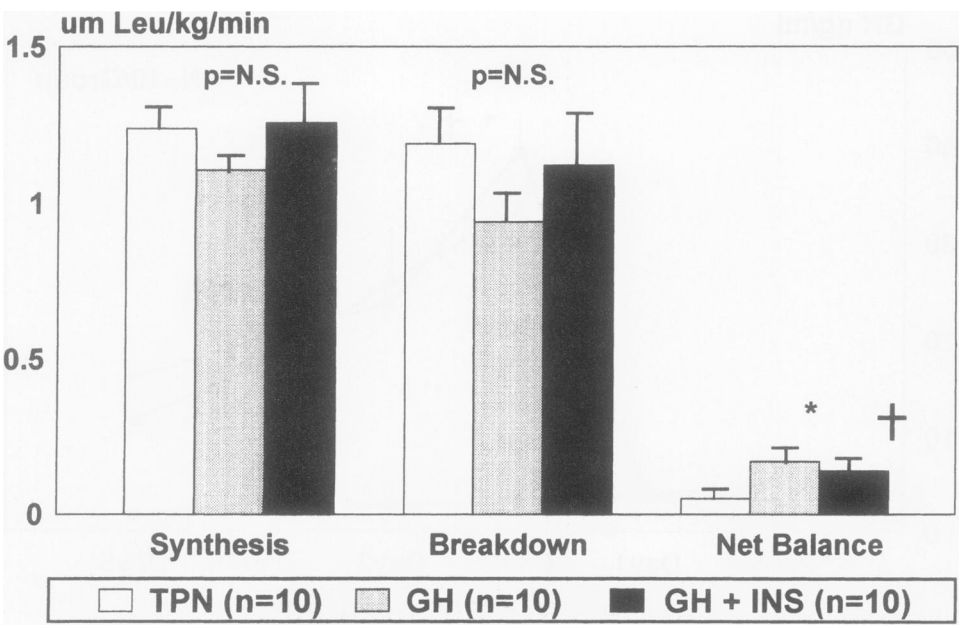


**Figure 4.** Whole body protein synthesis, breakdown, and net balance (μm leucine/kg per minute). *, $p < 0.005$ *vs.* total parenteral nutrition group; †, $p = 0.05$ *vs.* total parenteral nutrition group. All data are presented as mean ± standard error of the mean. TPN, total parenteral nutrition group; GH, growth hormone group; GH+Ins, growth hormone plus insulin group.

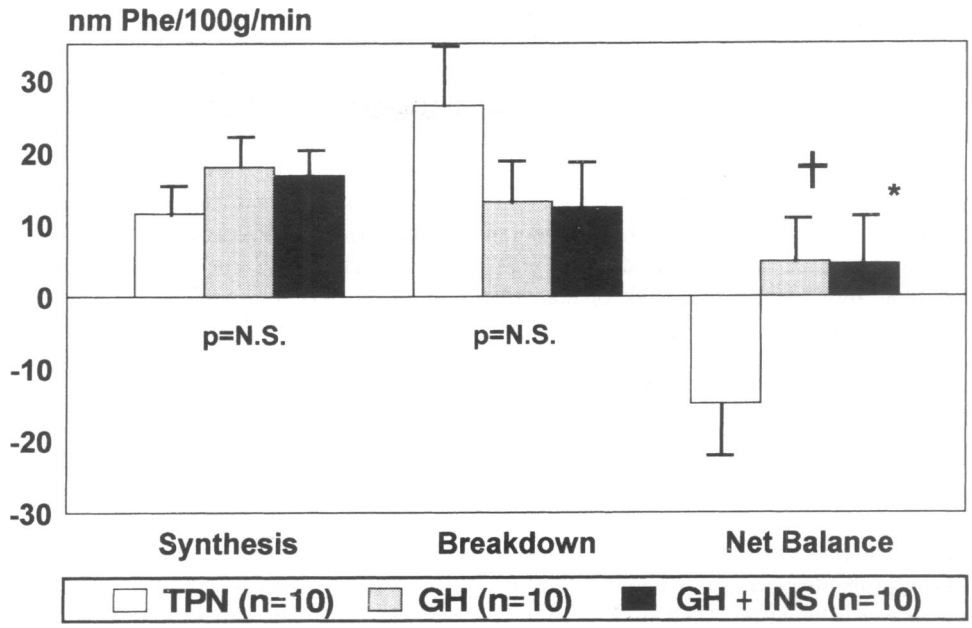


**Figure 5.** Skeletal muscle protein synthesis, breakdown, and net balance (nm phenylalanine/100 g forearm tissue per minute). *, p = 0.01 *vs.* total parenteral nutrition group; †, p = 0.15 *vs.* total parenteral nutrition group. All data are presented as mean ± standard error of the mean. TPN, total parenteral nutrition group; GH, growth hormone group; GH+Ins, growth hormone plus insulin group.

insulin did not significantly improve net balance above the increase seen with GH alone.

Skeletal muscle protein kinetic data are shown in Figure 5. Skeletal muscle protein synthesis, measured by the rate of disappearance (Rd) of phenylalanine (Phe), was increased, although not significantly, by treatment with GH and GH plus insulin compared with treatment with TPN alone. Skeletal muscle protein breakdown, measured by the rate of appearance (Ra) of phenylalanine, was decreased, although not significantly, by GH and GH plus insulin treatment compared with treatment with TPN alone. The skeletal muscle net protein balance for the TPN only group was in a state of significant negative net balance (−14.93 ± 6.64 nmol phenylalanine/100 g per minute). Treatment with GH improved skeletal muscle net balance, although not significantly, compared with TPN alone (GH: +4.86 ± 5.68 nmol phenylalanine/100 g per minute; not significant *vs.* TPN). Treatment with GH plus insulin, however, significantly improved skeletal muscle protein net balance compared with TPN (GH plus ins: +4.50 ± 5.04 nmol phenylalanine/100 g per minute; p = 0.01 *vs.* TPN). The combination of GH and insulin, however, did not significantly increase skeletal muscle protein net balance compared with GH alone.

## DISCUSSION

Patients with malignancies of the upper GI tract are at increased risk for developing malnutrition.[3] The added catabolic stress of antineoplastic treatment (surgery, chemotherapy, or radiation therapy) in these patients may result in an increase in death and complications, an important factor considering the more frequent use of neoadjuvant and multimodal cancer treatment. Nutritional status before surgery has been shown to correlate with perioperative outcome,[4] and weight loss in patients with GI tract malignancies correlates with decreased median survival.[1]

Considering the negative clinical impact of cancer cachexia, nutritional support has become an extensively investigated field of research. TPN has been studied as a means of reversing the malnutrition seen in patients with cancer and potentially decreasing perioperative morbidity and mortality rates. Although TPN has been shown to improve some parameters of protein metabolism in patients with cancer,[21] there is no conclusive evidence that these biologic changes translate into improved clinical outcome. Of the prospective trials examining the effect of TPN in patients with cancer, only one has demonstrated a significant decrease in perioperative morbidity and mortality rates, and that study has been criticized for the high complication rate.[6] In fact, the use of TPN in patients with cancer undergoing surgery has been associated with an increased rate of infectious complications.[7,22]

Without conclusive data supporting the use of TPN in patients with cancer, the potential use of anabolic agents in conjunction with parenteral nutrition has become a significant area of investigation. Although insulin[10] and GH[13] have been studied in these patients, the impact of GH and the combination of GH and insulin have not been previously investigated in patients with an upper GI tract malignancy after surgery.

In this study, we compared the peripheral and whole body protein kinetic effects of three nutritional regimens (standard TPN, daily GH plus standard TPN, and daily GH, systemic insulin, plus standard TPN) in patients with cancer after surgery. We demonstrated that treatment with either GH or GH plus insulin significantly increased whole body

protein net balance when compared with treatment with TPN alone. The combination of GH plus insulin, however, did not significantly improve whole body protein net balance compared with GH treatment alone. Patients receiving only standard TPN treatment were in a state of negative skeletal muscle net balance on the fifth day after surgery. Although GH treatment increased skeletal muscle synthesis, decreased breakdown, and increased protein net balance compared with the TPN group, these changes did not reach statistical significance. The lack of statistical significance may be a result of a wide variability in the skeletal muscle data; with an increased sample size, these changes may become significant. The combination of GH plus insulin significantly increased skeletal muscle protein kinetics into a positive net balance range, and the treatment also significantly improved the net balance compared with TPN. Although GH plus insulin increased skeletal muscle synthesis and decreased breakdown, these levels did not reach significance, probably because of wide variability. Skeletal muscle kinetic calculations take into account forearm plasma flow as determined by capacitance plethysmography. Although there is a learning curve involved in performing this procedure, all measurements were performed by one of two investigators with experience in capacitance plethysmography, and there were no significant differences between the treatment groups with respect to forearm plasma flow. Therefore, we believe that the observed protein kinetic improvements are a result of treatment and that the lack of statistical improvements seen with some of the skeletal muscle protein data is not the result of operator error.

Administration of GH in both GH-treated groups resulted in a significant increase in serum GH levels starting on the morning of day 2, approximately 13 hours after the first dose. Serum GH levels were significantly elevated compared with pretreatment values and with the TPN only group. GH levels peaked on day 2 and then decreased over the course of the study, but they remained significantly elevated at the completion of the study.

Because the anabolic actions of GH are mediated through IGF-1, it is critical to demonstrate that serum IGF-1 levels can be significantly elevated by GH administration when attempting to show a treatment effect. The use of 0.1 mg/kg per day of GH was based on previous work in our laboratory.[13] In the current study, we demonstrated that serum IGF-1 levels significantly decreased in response to surgical stress (presurgical levels *vs.* day 1 after surgery), and this postsurgical response occurred in all three treatment groups. Treatment with GH, however, significantly elevated serum IGF-1 levels back to presurgical levels (in both the GH and GH plus insulin groups) and significantly elevated the IGF-1 levels compared with the TPN group. In fact, the TPN group continued to demonstrate a decrease in serum IGF-1 levels throughout the study period, revealing a potential mechanism for catabolic changes after surgery.

As expected, the GH plus insulin group demonstrated a sustained increase in serum insulin levels. The insulin levels were dramatically increased compared with pretreatment levels and with the TPN and GH groups. C-peptide levels, a reflection of endogenous insulin secretion, were moderately elevated in the GH plus insulin group and were not significantly different from the levels seen with standard TPN treatment. This confirms that the elevated insulin levels in the GH plus insulin group were a result of the infused exogenous insulin. The serum insulin level in the GH group became significantly elevated compared with the TPN group. This corresponded with a significant increase in the C-peptide level in the GH group, confirming that the elevated insulin level in the GH group was a result of endogenous insulin secretion in response to the significant hyperglycemia observed in these patients.

Studies have shown that high-dose glucagon treatment in normal fasting humans increases nitrogen losses.[23] In this study, there were no significant differences among the groups with respect to glucagon levels. One study[24] has proposed, however, that it is not the absolute levels of insulin or glucagon that determine the protein metabolic actions of these hormones, but that it is the insulin/glucagon ratio that is most important. In our study, we were able to elevate the insulin/glucagon ratio with GH plus insulin treatment.

Although all patients in this study received an isonitrogenous diet, the GH plus insulin group received more total calories as a result of the 50% dextrose infusion used to maintain euglycemia in the setting of the systemic insulin infusion. It can be argued, therefore, that the extra dextrose calories, and not the hyperinsulinemic state, may account for the improved protein kinetics in this group. Studies, in fact, have demonstrated that overfeeding with carbohydrate calories can have a nitrogen-sparing effect.[25] It would not be possible to provide the high-dose systemic insulin infusion necessary to produce significantly elevated serum insulin levels without dextrose supplementation. Similarly, without a hyperinsulinemic state it is possible that any extra glucose provided would not be used for anabolism and would be disposed of in the urine. In fact, in our study, the GH group had significantly elevated urine glucose levels throughout the study period, consistent with the demonstrated hyperglycemia and only moderately elevated insulin levels. The TPN only group persistently demonstrated elevated urine glucose levels. It was the GH plus insulin group who demonstrated virtually no glycosuria, even though they were receiving the extra 50% dextrose load intravenously. It is presumed that the hyperinsulinemic state allowed the extra carbohydrate calories to be used as substrate for the improved whole body and skeletal muscle protein net balance demonstrated in this group.

The potential hazards of nutritional support in this study relate to the hormone supplementation. No patient had a pneumothorax or developed line sepsis from TPN administration. Treatment with GH did result in hyperglycemia, and two patients were removed from the study at the discretion of the attending surgeon. For the purpose of this study,

subjects were not allowed to receive insulin outside of the predetermined insulin infusion in the GH plus insulin group. The hyperglycemia associated with GH administration would otherwise be treated with an insulin sliding scale, and this has been used, even in the home setting, in long-term GH administration. Two GH patients were removed from the study for fluid retention, a known effect of GH administration. These patients were in the immediate postsurgical period, however, and whether the fluid retention was a result of surgery or GH administration could not be determined. A continuous intravenous insulin infusion, as delivered to the GH plus insulin group, presents potential hazards, although no patient had evidence of clinical hypoglycemia. It is possible that the hyperglycemic effect of GH counterbalanced the hypoglycemic insulin effect, making both hormones safer to deliver in the GH plus insulin group.

Although all patients in this study underwent curative tumor resection, the potential tumor-promoting effect of GH must be addressed. Studies have examined the effect of GH on tumor-bearing rats, and although neither tumor weights nor volumes increased in GH-treated rats with methylcholanthrene-induced sarcomas,[26,27] an increase in the aneuploid/diploid ratio of the tumor cells was demonstrated.[26] One *in vivo* study has documented that rats exposed to N-butyl-N-(4-hydroxybutyl) nitrosamine (BBN) in drinking water developed more bladder tumor deposits after GH treatment than did control animals exposed only to BBN.[28] A different study, however, demonstrated that animals with subcutaneously implanted prostate tumors developed fewer metastatic lung deposits with GH treatment than did control animals not treated with GH.[29]

In humans, no study has addressed the impact of GH on tumor recurrence after surgical resection. Reports in the literature, however, have implicated long-term GH replacement in the recurrence of central nervous system tumors and leukemia in a population of children deficient in GH. A recent comprehensive report by the National Cooperative Growth Study, which monitored 19,000 children, representing 47,000 patient-years of GH treatment, concluded that there was no evidence of increased tumor recurrence.[30] Therefore, when complete resection or other appropriate antineoplastic treatment is administered, we believe that GH may be given to patients with cancer for short-term nutritional support.

To summarize, GH treatment significantly raises serum IGF-1 levels and abrogates the decrease in IGF-1 levels seen after surgical stress. Continuous administration of regular insulin raises both the serum insulin level and the insulin/glucagon ratio. GH administration, in the presence of TPN, improves whole body protein net balance, and the combination of GH plus insulin, in the presence of TPN, improves skeletal muscle and whole body protein net balance. The addition of insulin to GH treatment does not increase protein net balance above those levels seen with GH alone. We conclude from this study that GH and GH plus insulin, in the presence of TPN, improve protein kinetic parameters in patients with upper GI tract cancers after surgery. Because the addition of insulin did not markedly improve kinetics over GH alone, and considering the ease of GH management, we believe, based on the above data, that GH is the preferred anabolic additive. Improved protein kinetics, however, represent biochemical changes. A larger trial, with clinical endpoints, examining the impact of GH alone or in combination with insulin on morbidity and mortality rates in patients with cancer should be undertaken.

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