Protein and Energy Metabolism with Biosynthetic Human Growth Hormone after Gastrointestinal Surgery

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The effect of biosynthetic human growth hormone (BSHGH) on postoperative protein and energy metabolism has been studied in patients who had major gastrointestinal surgery. Seven patients received placebo and seven patients received BSHGH, 0.1 mg/kg/24 h, for the first six postoperative days. Mean total nitrogen excretion was significantly lower with BSHGH (31.5 ± 2.4 g N) (2287 ± 160 mmol) than with placebo (42.7 ± 3.1 g N) (3049 ± 219 mmol) over the 6-day study period. The mean daily measured energy expenditure over days 3–6 was higher with BSHGH (31.3 ± 1.8 kcal/kg LBM/24 h) (131 ± 7 kJ/kg LBM/24 h) than with placebo (27.6 ± 0.8 kcal/kg LBM/24 h) (114 ± 2 kJ/kg LBM/24 h). Fat oxidation with BSHGH (2.05 ± 0.26 mg/kg LBM/24 h) was greater than with placebo (1.5 ± 0.17 mg/kg LBM/24 h) and protein oxidation was less with BSHGH (0.68 ± 0.07 g/kg LBM/24 h) than with placebo (0.9 ± 0.09 g/kg LBM/24 h) on days 1–6. Postoperative nitrogen turnover (BSHGH 943 ± 174 mg N/kg LBM/24 h, placebo 557 ± 50 mg N/kg LBM/24 h) (BSHGH 67 ± 13 mmol/kg LBM/24 h, placebo 40 ± 4 mmol/kg LBM/24 h), protein synthesis (BSHGH 5.31 ± 1.09 g prot/kg LBM/24 h, placebo 2.54 ± 0.33 g prot/kg LBM/24 h) and protein breakdown (BSHGH 5.90 ± 1.09 g prot/kg LBM/24 h, placebo 3.48 ± 0.31 g prot/kg LBM/24 h) were greater with BSHGH. On the first postoperative day serum insulin and blood glucose levels were higher with BSHGH than with placebo, and on days 4 and 7 serum somatomedin-C levels were significantly elevated. This study shows that BSHGH alters postoperative protein and energy metabolism by reducing protein oxidation and increasing fat oxidation with raised rates of whole body nitrogen turnover.

CUTHBERTSON'S DESCRIPTION of increased excretion of nitrogen, sulphur, phosphorus, and calcium after injury, which implied breakdown and oxidation of protein greater than could be accounted for by damage at the injury site alone, has led to the concept that a systemic response to injury exists.[1]

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This results in increased protein and energy substrate oxidation and an increased metabolic rate.[2] Neuronal and hormonal factors have been implicated in the mediation of this response.[3] The net effect of these changes is to erode protein and energy substrate stores at a time when nutritional intake is often reduced. If these resources are already reduced at a time of injury, the ability to heal wounds, combat infection, and breathe adequately may be impaired, leading to increased morbidity and mortality.[4] Even the well nourished may experience periods of debility after the injury of major surgery, which may relate to reduction of protein reserves and energy stores.[5]

Shortly after its identification, growth hormone was shown to have anabolic effects on protein metabolism, and Cuthbertson et al. were able to abolish negative nitrogen balance in fed rats subjected to fracture of the femur by using a bovine pituitary extract.[6] Human pituitary growth hormone has been investigated in the context of surgery by Johnson and Hadden[17] and Roe and Kinney[8] and in major burns by Soroff et al.[9] and Wilmore et al.[10] Further study has been limited by the availability of human pituitary hormone. Biosynthetic human growth hormone (BSHGH) (Somatonorm, KabiVitrum, Stockholm, Sweden) produced by recombinant DNA technology from an *Escherichia coli* host, has become available recently. BSHGH is identical to human growth hormone but with the addition of a methionyl residue at the N-terminal position.

This study investigates the effects of BSHGH on energy substrate and whole body protein metabolism in patients who have major gastrointestinal operations without nutritional support.

TABLE 1. *Patient Details*

Patient	Sex	Age (yrs)	Weight (kg)	LBM (kg)	Diagnosis	Operation
Patients receiving BSHGH						
2	F	29	59	42	Duodenal ulcer	Partial gastrectomy
5	M	72	76	53	Carcinoma rectum	A/P resection
7	M	52	66	48	Duodenal ulcer	Partial gastrectomy
11	M	76	79	57	Chronic jejunocolic fistula	Jejunocolic resection
13	F	75	43	32	Colovaginal fistula	Sigmoid colectomy
15	F	59	64	51	Carcinoma sigmoid colon	Left hemicolectomy and hysterectomy
16	M	73	81	62	Carcinoma sigmoid colon	Left hemicolectomy
Mean ± SD		62 ± 17	67 ± 13	49 ± 10		
Patients receiving placebo						
1	M	66	72	57	Carcinoma rectum	Anterior resection
3	F	71	64	44	Carcinoma stomach	Total gastrectomy
4	M	56	90	66	Prior resection for diverticulitis	Reversal of Hartmann's
9	F	75	53	37	Carcinoma cecum	Right hemicolectomy
10	F	86	63	41	Carcinoma sigmoid colon	Left hemicolectomy
12	F	51	56	45	Rectovaginal fistula	A/P resection
14	M	71	62	52	Carcinoma esophagus	Ivor-Lewis
Mean ± SD		68 ± 12	66 ± 12	49 ± 10		

LBM = lean body mass. A/P = abdominoperineal.

Patients and Methods

Sixteen patients due to have major gastrointestinal surgery were allocated at random to receive 0.1 mg/kg of BSHGH or placebo by intramuscular injection at 8:00 P.M. on the day of operation and at the same time for the following 6 postoperative days. Patients who were diabetic, had disturbed liver function, were taking steroids, had sepsis, weight loss of more than 10%, or disseminated malignancy were not considered for study. Two patients had development of septic complications during the course of the study and were excluded from further analysis. Seven patients received BSHGH and seven patients received placebo. The details of sex, age, weight, and lean body mass (LBM) from skinfolds,[11] diagnosis, and operative procedures are shown in Table 1. All patients had an uncomplicated postoperative course during the study. Postoperative analgesia was provided by continuous intravenous morphine sulphate (six in each group) or by morphine epidural injection.

In the preoperative studies, patients were allowed fluids by mouth, to provide 400 kcal/24 h with negligible nitrogen intake. After operation they received a regimen of saline and 5% dextrose solution providing 400 kcal/24 h (1675 kJ/24 h). Water by mouth was introduced when indicated and dietary intake was begun after the sixth day.

Blood samples were drawn for substrate and hormone levels on the control day before operation and on the first, fourth, seventh, and ninth postoperative days between 8:00 A.M. and 9:00 A.M.

Indirect calorimetry was done before operation and on the first 6 postoperative days between 10:00 A.M. and 12:00 P.M. Resting energy expenditure (REE) was determined from oxygen consumption and carbon dioxide production, using Weir's formula.[12] Oxygen and carbon dioxide concentration were measured with paramagnetic and infrared analysers, respectively, gas flow was measured by a Fleisch pneumatochograph incorporated in a mobile system giving a visual display and a continuous printout of results (Calostar, Fenyves & Gut, Basel, Switzerland[13]). Rates of substrate oxidation were calculated from oxygen consumption, carbon dioxide production, and urinary nitrogen excretion by MacHattie's formulae.[14]

Urine for total nitrogen excretion was collected throughout the study period. Total nitrogen was measured by a semiautomated Kjeldahl technique. Nitrogen turnover was measured before operation and on the third to fourth postoperative days using a primed continuous infusion of ^{15}N glycine for 24 hours.[15] Isotope enrichment of urinary urea over the second 12-hour period of infusion was measured by mass spectrometry. Whole body nitrogen turnover was calculated by dividing the infusion rate of ^{15}N tracer by the urinary urea enrichment with ^{15}N at plateau.[16] Whole body protein synthesis was derived by subtracting total urinary nitrogen excretion from turnover. In the absence of nitrogen

TABLE 2. *Total Urinary Nitrogen Excretion, g N/24 h (mmol/24 h)*

Day	0	1	2	3	4	5	6
Placebo	5.9 ± 1.5	8.6 ± 0.6	8.0 ± 1.4	7.3 ± 1.0	7.0 ± 0.8	6.6 ± 1.7	5.3 ± 0.8
	(422 ± 107)	(616 ± 43)	(572 ± 97)	(517 ± 68)	(497 ± 57)	(469 ± 122)	(378 ± 57)
BSHGH	5.4 ± 0.8	7.0 ± 1.0	6.8 ± 1.2	4.4 ± 0.4*	4.5 ± 1.0	5.0 ± 1.0	3.9 ± 0.6
	(387 ± 58)	(501 ± 70)	(485 ± 89)	(315 ± 25)*	(318 ± 74)	(354 ± 65)*	(277 ± 45)

* $p < 0.05$.

intake, whole body protein breakdown corresponds to the rate of nitrogen turnover. Synthesis and breakdown values are converted to grams of protein by multiplying by 6.25. Serum growth hormone, insulin, and somatomedin-C were each measured by radioimmunoassay. Blood glucose was measured by the glucose oxidase method. Results are expressed as mean and SEM. Statistical analysis is nonparametric by the Mann-Whitney U test.

Informed consent was obtained from the patients and the study was approved by the District Ethical Committee.

Results

No adverse effects attributable to the studies or the giving of placebo or BSHGH were encountered. For technical reasons, nitrogen turnover studies were not completed in the preoperative period on three patients (2 placebo, 1 BSHGH) and one patient (BSHGH) in the postoperative period. Total nitrogen excretion over the first 6 postoperative days was 31.5 ± 2.4 g (2267 ± 160 mmol N) for those receiving BSHGH, significantly less than 42.7 ± 3.1 g (3049 ± 219 mmol N) for those with placebo ($p < 0.01$). Results for each day are shown in Table 2 and Figure 2. The mean REE on days 1 and 2 of 28.8 ± 1.4 and 31.7 ± 1.8 kcal/kg LBM/24 h (121 ± 6 and 133 ± 9 kJ/kg LBM/24 h) with placebo and BSHGH, respectively, were not significantly different, but over days 3–6 the REE of 31.3 ± 1.8 (131 ± 7 kJ/kg LBM/24 h) with BSHGH was significantly higher than that with placebo (27.6 ± 0.8, $p < 0.05$) (114 ± 2 kJ/kg LBM/24 h). Although respiratory quotient over days 1–6 was consistently lower in patients receiving BSHGH (0.79 ± 0.02) than patients receiving placebo (0.81 ± 0.02), the difference was not significant. Fat oxidation (BSHGH 2.05 ± 0.26 g/kg LBM/24 h and placebo 1.51 ± 0.17) was significantly higher with BSHGH (Fig. 1). Carbohydrate oxidation (BSHGH 2.10 ± 0.36 g/kg LBM/24 h and placebo 2.09 ± 0.36) was similar and corresponded to dextrose infusion rates of 2.11 ± 0.21 g/kg LBM/24 h for BSHGH and 2.12 ± 0.17 for placebo; protein oxidation (calculated from nitrogen excretion, Fig. 2) was significantly lower with BSHGH than with placebo (0.68 ± 0.07 g/kg LBM/24 h and placebo 0.92 ± 0.09, mean for days 1–6, $p < 0.05$).

Whole body nitrogen turnover, protein synthesis, and breakdown results are shown in Table 3. All values were similar in the preoperation period but after operation, nitrogen turnover, protein synthesis, and breakdown rates were significantly higher in the group receiving BSHGH. In five patients receiving placebo and six patients receiving BSHGH in whom nitrogen turnover was measured before and after operation, turnover decreased to a mean of 75% (range: 61–87%) of control in those with placebo, whereas with BSHGH turnover in-

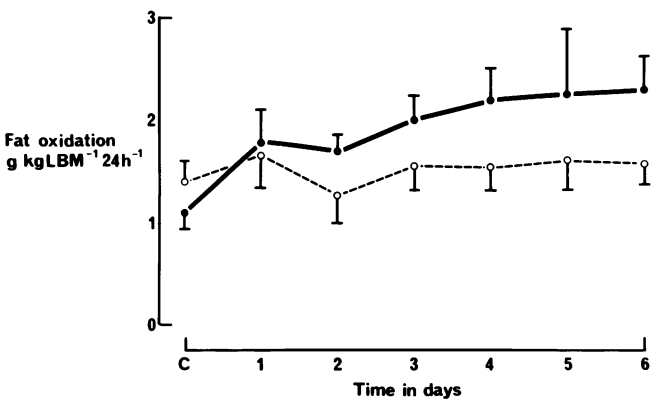

FIG. 1. Fat oxidation with BSHGH (● —— ●) and placebo (O --- O) for the control preoperative day (C) and postoperative days 1–6 expressed as mean ± SEM.

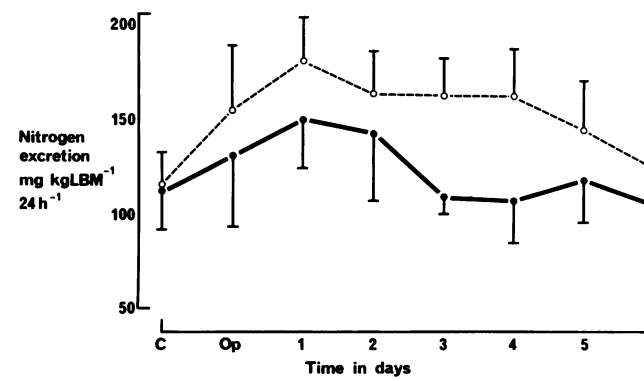

FIG. 2. Total urinary nitrogen excretion with BSHGH (● —— ●) and placebo (O - - - O) for the control preoperative day (C) and postoperative days 1–6 expressed as mean ± SEM.

TABLE 3. *Results of Whole Body Protein Metabolism Measurements (Mean ± SEM)*

	No. of Patients	Nitrogen Turnover mg/kg LBM/24 h (mmol/kg LBM/24 h)	Protein Synthesis g/kg LBM/24 h	Protein Breakdown g/kg LBM/24 h
BSHGH				
Before operation	6	764 ± 66 (55 ± 51)	4.04 ± 0.48	4.78 ± 0.41
After operation	6	943 ± 174* (67 ± 13)	5.31 ± 1.09*	5.90 ± 1.09*
Placebo				
Before operation	5	815 ± 78 (58 ± 6)	4.31 ± 0.54	5.09 ± 0.44
After operation	7	557 ± 50 (40 ± 4)	2.54 ± 0.33	3.48 ± 0.31

* $p < 0.05$ (Postoperative placebo *vs.* postoperative BSHGH).

creased to a mean of 126% (range 81–212%). After operation, whole body protein synthesis expressed as a percentage of breakdown was higher with BSHGH (89 ± 3) than placebo (72 ± 5, $p < 0.05$). The preoperative values were 84 ± 4 and 84 ± 3, respectively.

Serum growth hormone, somatomedin-C, and insulin were all raised in those receiving BSHGH as shown in Table 4. Elevations in serum growth hormone and insulin levels were significant on the first postoperative day and returned to control values by the ninth day, 3 days after the study period. The raised levels of somatomedin-C in patients receiving BSHGH became significant on the fourth and seventh days and were still significantly higher than those of patients receiving placebo on the ninth day. These changes in hormonal profile were accompanied by elevated blood glucose in patients receiving BSHGH (Table 4), which was sufficient to produce slight glycosuria in some patients.

Discussion

The reduction in nitrogen excretion and elevation of metabolic rate and of fat oxidation shown in this study are in keeping with the findings of Cuthbertson et al.[6] and of Roe and Kinney,[8] confirming that BSHGH has similar metabolic effects to growth hormone derived from pituitary glands. In contrast, the study of Johnston and Hadden failed to show an improvement in nitrogen balance with pituitary growth hormone after herniorrhaphy.[7] The lesser degree of trauma, and resulting magnitude of negative nitrogen balance, occurring with hernia repair may explain the difference from the current study. Soroff et al.[9] and Wilmore et al.[10] both demonstrated increased retention of nitrogen, elevation of metabolic rate, and decreased respiratory quotient in severely burned patients given growth hormone.

Initially, Wilmore suggested that adequate nutritional

TABLE 4. *Serum Hormone and Blood Glucose Levels*

Day	0	1	4	7	9
Serum growth hormone,* μ/L					
BSHGH	3 (3–36)	43 (24–54)‡	6 (4–10)	6 (3–23)	3 (3–8)
Placebo	3 (3–6)	3 (3–12)	3 (3–22)	3 (3–5)	3 (3–10)
Serum Somatomedin-C,† μ/mL					
BSHGH	0.66 ± 0.14	0.68 ± 0.11	1.06 ± 0.18‡	1.29 ± 0.18‡	0.64 ± 0.17‡
Placebo	0.65 ± 0.13	0.49 ± 0.11	0.34 ± 0.08	0.37 ± 0.13	0.30 ± 0.08
Serum insulin,† (μmol/mL)					
BSHGH	29 ± 6	123 ± 50‡	81 ± 21	69 ± 19	34 ± 6
Placebo	28 ± 15	38 ± 9	30 ± 9	23 ± 6	27 ± 9
Blood glucose,† mg/100 mL (mmol/L)					
BSHGH	104 ± 10 (5.8 ± 0.6)	214 ± 34 (12.0 ± 1.9)‡	190 ± 30 (10.6 ± 1.7)	164 ± 30 (9.2 ± 1.8)	102 ± 7 (5.7 ± 0.4)
Placebo	97 ± 6 (5.4 ± 0.3)	142 ± 1 (7.9 ± 1.2)	124 ± 10 (6.9 ± 0.6)	133 ± 15 (7.4 ± 0.9)	121 ± 12 (6.7 ± 0.6)

* Median (range).
† Mean ± SEM.
‡ Different from placebo, $p < 0.05$.

intake was necessary for growth hormone to produce a nitrogen sparing effect; but more recent data from Manson and Wilmore,[17] obtained from studies on healthy human subjects receiving hypocaloric intravenous feeding, have refuted this. They have demonstrated that with an intake of 1070 kcal/d and 11.3 g N/d growth hormone improves nitrogen retention and increases fat oxidation. The results of this study indicate that growth hormone can alter metabolism with minimal (400 kcal/24 h) (1675 kJ/24 h) nutritional intake.

Nitrogen balance is an index of net whole body protein balance. If whole body nitrogen turnover is measured, nitrogen intake and excretion can be used to derive rates of whole body protein synthesis and breakdown.[16] The ^{15}N from glycine has been shown to be widely distributed among the other amino acids,[18] and although growth hormone has been shown to decrease the plasma level of most amino acids[19] there does not appear to be a specific effect on glycine metabolism. In the absence of evidence for a specific metabolic pathway between glycine and urea (which is affected by growth hormone to produce a decrease in transfer of the amino nitrogen of glycine to urea), the decrease in ^{15}N enrichment of urinary urea from which the increase in nitrogen turnover with growth hormone is derived is interpreted as being an effect on whole body protein metabolism and not a specific effect of growth hormone on glycine metabolism.

The improved nitrogen balance seen with administration of growth hormone occurs with a postoperative protein synthesis rate of 209% of the corresponding synthetic rate for placebo and a breakdown rate of 170% of placebo, indicating a relative increase in synthesis to breakdown of 39%. In the absence of exogenous protein intake, the amino acids for protein synthesis will be derived from breakdown and the expression of synthesis as a percentage of breakdown will give a value for the recycling of protein and, hence, the efficiency of protein metabolism. After operation there was a decrease in recycling of protein of 12% compared with before operation in the placebo group and an increase of 5% with growth hormone, there being a 17% improvement in the efficiency of protein metabolism after surgery when growth hormone is given.

The diversion of amino acids as potential gluconeogenic substrates from oxidative to synthetic pathways when growth hormone is given results in a reduction of a mean of 51 kcal/d (214 kJ/d) derived from protein oxidation. The increased energy production of 264 kcal/d (1105 kJ/d) from fat oxidation is in excess of that required to compensate for the shortfall from protein oxidation by a mean of 213 kcal/d (892 kJ/d). It is likely that this excess in oxidation of fat is a result of the specific action of growth hormone on increasing lipolysis and free fatty acid oxidation.[19] This is seen as an overall increase in energy expenditure, most notably in the last 4 days of the study.

A diabetogenic effect of growth hormone producing increases in blood glucose and serum insulin has been described[19] and is confirmed in this study. Serum levels of growth hormone, somatomedin-C, and insulin were all affected by growth hormone administration. Growth hormone stimulates secretion of somatomedin-C from the liver[20] and the gradually increasing levels of somatomedin-C during growth hormone administration suggest a direct action of growth hormone. Insulin levels are highest when blood glucose peaks and decreases as the glucose levels fall, suggesting that insulin levels are not primarily affected by growth hormone administration but relate to the blood glucose level. Because both somatomedin-C and insulin are capable of increasing rates of protein synthesis it is not possible to determine in this study if the elevated levels of either hormone, or growth hormone itself, are responsible for the raised rate of protein synthesis.

These studies were designed to investigate the effect of growth hormone administration on postoperative metabolism and have clearly demonstrated improved protein economy and increased fat oxidation in patients with minimal nutritional intake. The suggestion that somatomedin-C is a mediator of the protein responses is worthy of further investigation; however, this will only be possible if somatomedins can be synthesized and produced in sufficient quantites by recombinant DNA technology. This study has not specifically studied clinical outcome but it is unlikely that this will be affected by these metabolic changes. The importance of the data obtained here is to provide information that can be used to evaluate the effect of growth hormone on nutrient (particularly intravenous) utilization in not only producing more efficient use of expensive materials but perhaps in reducing the quantities of nutrients that require administration, thus allowing greater use of peripheral (as opposed to central) vein feeding.

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