ANNALS OF SURGERY
Vol. 220, No. 3, 310–319

Insulin-Like Growth Factor-1 Lowers Protein Oxidation in Patients with Thermal Injury

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Objective

The effect of insulin-like growth factor-1 (IGF-1) on energy expenditure and protein and glucose metabolism in a group of patients with thermal injury was determined.

Summary Background Data

Accelerated protein catabolism is a constant feature of the hypermetabolic response to thermal injury. Insulin-like growth factor-1 has been reported to minimize protein catabolism and normalize energy expenditure in animal models of thermal injury.

Methods

To determine the efficacy of IGF-1 in human burn patients, resting energy expenditure (metabolic cart), whole body protein kinetics ($^{N}15$ Lysine), and glucose disposal (glucose tolerance test) were assessed in eight burn patients before and after a 3-day infusion of IGF-1 (20 μg/kg/hr). All patients were fluid-resuscitated uneventfully and were without obvious infection at the time of study. Enteral nutrition was administered at a constant rate before and during the IGF-1 infusion.

Results

Resting energy expenditure was not altered by IGF-1 (40.3 ± 2.2 *vs.* 39.1 ± 2.3 kcal/kg/day). However, glucose uptake was promoted, and protein oxidation decreased significantly (0.118 ± 0.029 *vs.* 0.087 ± 0.021 g/kg/d, $p < 0.05$) by IGF-1. In addition, insulin secretion, in response to a glucose challenge, was blunted.

Conclusions

Insulin-like growth factor-1 therapy has a beneficial effect in preserving lean body mass during severe stress conditions by minimizing the flux of amino acids toward oxidation.

Accelerated protein catabolism is a constant feature of the hypermetabolic response to thermal injury. Current nutritional support regimens using high calorie and protein enteral or parenteral solutions do not completely reverse net protein catabolism and have little effect on the accelerated rate of protein breakdown. Attempts to limit catabolism by experimental treatment with growth hormone have been promising under certain conditions.[1,2] The administration of pharmacologic doses of growth hormone to fasting adult humans resulted in a protein

sparing effect, but has failed to stimulate protein synthesis in other studies.[3] Clinical trials using growth hormone in a variety of catabolic conditions demonstrated that growth hormone was somewhat effective in conserving body proteins.[4,5] However, the most severely ill patients did not improve their nitrogen balance. In addition, growth hormone is an insulin antagonist and may exacerbate stress-induced insulin resistance.

In 1972, Daughaday proposed that growth hormone regulates the hepatic synthesis and release of IGF-1, which is considered to be one of the potential mediators of the anabolic effects of growth hormone.[6,7] In patients who are critically ill, growth hormone has been shown to have reduced effectiveness in stimulating the release of IGF-1, thus, possibly explaining the failure of growth hormone to reverse catabolism in some patients.[8] Data confirming the role of IGF-1 in the regulation of growth, metabolism, and differentiation have expanded remarkably during the last decade, and the recent availability of recombinant IGF-1 has provided the opportunity to study its biologic potential.[9] Diet and tumor necrosis factor-induced catabolism have been reversed by exogenous IGF-1 in animal and human studies.[10–14] More importantly, IGF-1 has been shown to limit postburn hypermetabolism and reduce gut atrophy and bacterial translocation in rodent models after severe burn injury, suggesting a potential role for this compound in the treatment of patients with thermal injury.[15,16]

The purpose of this trial is to determine the effects of a continuous infusion of recombinant human IGF-1 on the catabolic response to thermal injury in adult burn patients.

METHODS

Study Protocol

Eight adult patients with burns of more than 25% of their body surfaces, who were admitted to the U.S. Army Institute of Surgical Research or the burn center at the Medical College of Virginia within 48 hours of injury, were enrolled. After obtaining informed consent, a medical history was elicited and a baseline physical examination was performed for each patient. Within 72 hours of injury, resting energy expenditure was measured by indirect calorimetry (Deltatrac, Sensor-Medics, Anaheim, CA), and enteral feedings were initiated at a rate sufficient to meet the patients' estimated calorie and protein needs. The calorie-to-nitrogen ratio was maintained at 150 to 1. The enteral feedings were continued at the same rate, protein content, carbohydrate content, and fat content for the duration of the study. Oral intake was not allowed during the study period. Excision and grafting of the burn wounds were performed during this stabilization period as required. After 3 days of stable nutritional intake, the following studies were obtained: indirect calorimetry, body weight measurements, serum IGF-1, IGF-1 binding protein and glucose levels, 24-hour urine samples for 3-methyl-histidine, urinary urea nitrogen and total urinary nitrogen excretions, intravenous glucose tolerance tests, and ^{15}N Lysine studies to measure whole body protein oxidation and degradation. After completion of these baseline studies, an intravenous infusion of IGF-1 at a rate of 20 μg/kg/hr was started for each patient. Serum glucose levels were obtained at the ½-, 1-, 4-, and 6-hour time points after initiation of the IGF-1 and every 6 hours thereafter. After 3 days of therapy, all baseline studies were repeated.

For each patient, a modified intravenous glucose tolerance test was performed by administering a 50% aqueous glucose solution (0.5 g/kg ideal body weight) for 90 seconds. Four milliliter-blood samples for insulin and glucose levels were obtained before the bolus and at 10, 20, 30, 40, 60, 90, 120 and 150 minutes after the glucose challenge. The enteral feedings were not stopped during this study, and this was the only intravenous glucose that the patients received.

To estimate whole body protein oxidation and degradation, the ^{15}N Lysine technique, as described by Wolfe, was used.[17] The ^{15}N Lysine was infused continuously at a rate of 0.08 μmol/kg/min immediately after a priming dose of 6.8 μmol/kg. In addition, the urea pool was primed by administration of 3.2 μmol/kg of N-14,15 urea. Sterile nonpyrogenic amino acid was dissolved in sterile saline, and the solution was infused at a rate that did not exceed 25 mL/hr. After 1 hour of constant infusion, plasma samples were obtained every hour for 3 hours. Hourly urine samples were collected during this time.

Analysis of Samples

Whole blood was collected in ice-cold heparinized tubes and stored in an ice bath until completion of the study, at which time the plasma was separated and stored at −20 C until analysis. Enrichment of plasma lysine was determined from its N-acetylpropyl ester derivative with a gas chromatography mass spectrometry system (5985 B Hewlett Packard, Palo Alto, CA), using chemical ion-

Presented at the 114th Annual Meeting of The American Surgical Association; April 7–9, 1994; San Antonio, Texas.

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Accepted for publication April 11, 1994.

ization and monitoring ions at m/e 273.2 and 274.2. The isotopic enrichment of plasma urea was measured from its bistrimethylsilyl derivative also by a gas chromatography mass spectrometry system. Electron impact ionization allowed monitoring at m/e 189 and 190. Plasma IGF-1, growth hormone, and IGF-1 binding proteins levels were measured by radioimmunoassay.

Calculations

The rate of protein oxidation (g/kg/day) was estimated from the rate of lysine oxidation:

protein oxidation

= lysine oxidation (μmol/kg/min) × 2.647.

Lysine oxidation was calculated from the rate of appearance of labeled urea in the urine (urea Ra [rate of appearance]) and the plasma enrichment of ^{15}N Lysine and ^{15}N urea.

Lysine oxidation (μmol/kg/min) = (urea Ra)

(% urea enrichment/% lysine enrichment).

Urea Ra (μmol/kg/min) = (urine N) (urine volume)

(1.2)/(weight) (urine time) (2.8 gm/μmol)

assuming that 20% of urea is recycled.[18]

The rate of protein degradation (g/kg/day) was estimated from the rate of appearance of endogenous lysine (Lysine Rae) in the plasma:

protein degradation = lysine Rae (μmol/kg/min) × 2.647.

Lysine Ra = lysine Ra − lysine in enteral feedings.

lysine Ra (μmol/kg/min) = ^{15}N Lysine infusion rate

(μmol/kg/min) × 99%/% lysine enrichment

The plasma insulin and glucose levels from the glucose tolerance test were plotted, and the area under each curve was calculated to yield an estimate of the disposal of glucose and the amount of insulin secretion prompted by the glucose bolus. The rate of glucose and fat oxidation (g/min) were estimated from the indirect calorimetry data using the following formulae:

glucose oxidation = non-protein VO_2 × (non-protein RQ-696) 0.227 and fat oxidation = (0.75 × non-protein VO_2)/2.019 as described by Jaquier et al.[19]

Data Analysis

All before and during IGF-1 data were compared using a paired T test and the BMDP (BMDP, Los Angeles, CA) statistical package.

Table 1. HORMONE AND BINDING PROTEIN LEVELS

	IGF-1 ng/mL	IGF-1 BP-2 ng/mL	IGF-1 BP-3 ng/mL	Growth Hormone ng/mL
Before				
Mean	83.4	1274	494	1.98
SEM	13.4	302	36	0.41
During				
Mean	675*	1738*	723*	0.78*
SEM	42.6	313	56	0.028

* $p < 0.05$ compared with levels before treatment.

RESULTS

Eight patients were enrolled in the study; mean age and burn size were 41.6 ± 5.6 years and 56 ± 6.5%, respectively. All patients completed the protocol, and no untoward effects of the IGF-1 were noted. Specifically, symptomatic hypoglycemia did not occur in any patient, although one patient had a serum glucose of 58 mg/dL coincident with the stoppage of enteral feedings secondary to tube dislodgement. All patients had a significant rise in their serum IGF-1 levels with a concomitant decrease in growth hormone levels while receiving IGF-1. Circulating levels of IGF-1 binding proteins 2 and 3 also were increased (Table 1). Resting energy expenditure did not change during treatment (40.3 ± 2.2 *vs.* 39.1 ± 2.3 kcal/kg/day), and all patients demonstrated a significant increase in resting energy expenditure over normal (Table 2).

Insulin and C-peptide levels were depressed significantly from baseline values by the IGF-1 infusion. Glucose and fat oxidation rates were not altered by the IGF-1 (Table 3). The glucose tolerance test (GTT) confirmed the insulin-like properties of the IGF-1 in this patient co-

Table 2. REE VALUES BEFORE AND DURING IGF-1

Patient	Before kcal/kg/day	During kcal/kg/day
1	37.6	40.4
2	46.1	45.25
3	41.06	41.06
4	43.4	43.9
5	50.8	41.5
6	38.7	43.7
7	27.9	25.0
8	36.9	31.6

Table 3. GTT RESULTS AND OXIDATION RATES

	Glucose Curve Area	Insulin Curve Area	Glucose Oxidation mg/kg/min	Fat Oxidation mg/kg/min
Before				
Mean	26,197	4628	3.82	2.198
SEM	3016	868	0.18	0.14
During				
Mean	24,582	2943*	3.74	2.09
SEM	4177	853	0.21	0.15

* $p < 0.05$ compared with levels before treatment.

hort. Insulin secretion, as indexed by the area under the insulin curves, was suppressed significantly by the IGF-1 infusion during the GTT in six of the eight patients. However, the area under the glucose curves was not affected by the IGF-1, indicating the same level of glucose disposal despite the blunted insulin response. Two patients demonstrated little suppression despite elevated serum levels of IGF-1 (Fig. 1A-D).

No patient was in positive nitrogen balance during the study period. Nitrogen balance did become slightly less negative during the IGF-1 infusion, although this difference was not significant (Table 4). lysine oxidation decreased significantly during the IGF-1 infusion from 0.0447 ± 0.011 μmol/kg/min to 0.033 ± 0.0089 μmol/kg/min ($p < 0.05$). Lysine Rae also decreased during IGF-1 therapy from 3.089 ± 0.39 μmol/kg/min to 2.52 ± 0.38 μmol/kg/min ($p = 0.059$).

DISCUSSION

The recognition by Cuthbertson in the 1930s[20] that even relatively minor trauma results in hypermetabolism and a state of catabolism characterized by negative nitrogen balance has prompted investigators to search for means of promoting anabolism and preventing catabolism to improve the treatment of the injured. This self-induced state of "autocannibalism," the extent of which is quite severe in burn patients, can result in a significant loss of lean body mass. Although short-term benefits of this self-destructive response to injury have been postulated, the long-term muscle wasting and impaired immune response have a significant impact on outcome and recovery because survival rates have been reported to be inversely proportional to the loss of lean body mass.[21]

The provision of nutritional support to the injured has been noted to have a protein-sparing effect. Long and associates administered glucose and fat in varying concentrations to burn patients and noted that glucose was much more effective than fat in reducing nitrogen excretion.[22] However, limitations in glucose disposal have been reported by several investigators with a maximal oxidation rate of 6 to 7 mg/kg/min.[23,24] Administration of glucose in excess of this limit results in an accentuated metabolic response and catecholamine secretion, thereby placing increased stress on the patient. In addition, parenteral nutrition has been noted only to increase protein synthesis and not alter protein breakdown in septic humans.[25] The failure of nutritional support alone to reverse or at least match the erosion of lean mass and the apparent defect in glucose use have led to attempts to modify the hormonal environment characteristic of the post-injury state.

Insulin has been documented to improve nitrogen balance in trauma patients, although this effect has been reported to be short lived by some.[26,27] Jahoor and colleagues have demonstrated an intact insulin response in patients who are burned and septic patients.[28] In these patients, the maximal effectiveness of insulin to suppress protein breakdown was intact but was insufficient to normalize the negative flux of amino acids. Of particular note was the dose of insulin required to achieve these results; 500 $mU/m^2/min$ or approximately 52 units/hr. The safety of such high-dose insulin therapy in terms of maintaining euglycemia in a critically patient in an ICU environment is a persistent clinical concern.

The 1974 report by Wilmore et al. that states that growth hormone increased nitrogen retention in patients with thermal injury and receiving adequate calories and nitrogen[29] sparked interest in this treatment modality. These direct anabolic actions subsequently have been reported in pediatric burn patients, postoperative patients, patients with chronic obstructive pulmonary disease, patients receiving parenteral nutrition, and healthy volunteers treated with steroids.[1,2,30–32] Basal levels of growth hormone and IGF-1 have been reported to be low after thermal injury.[33] Resistance to the anabolic effects of growth hormone has been reported, especially in those patients with the most severe injury.[5] This lack of effect appears to be secondary to a failure of growth hormone to elicit an IGF-1 response. This, in concert with the negative effects of growth hormone such as increased lipolysis and insulin antagonism, make it a relatively unattractive candidate with which to counter post-injury catabolism.[34,35]

Reports that implicate IGF-1 as the mediator of the anabolic effects of growth hormone and others that demonstrate that basal levels of both growth hormone and IGF-1 are low after injury have led to trials of IGF-1 replacement in various animal models. Insulin-like growth factor-1 has been shown to reverse diet induced catabolism in fasted rats and lambs by reducing protein break-

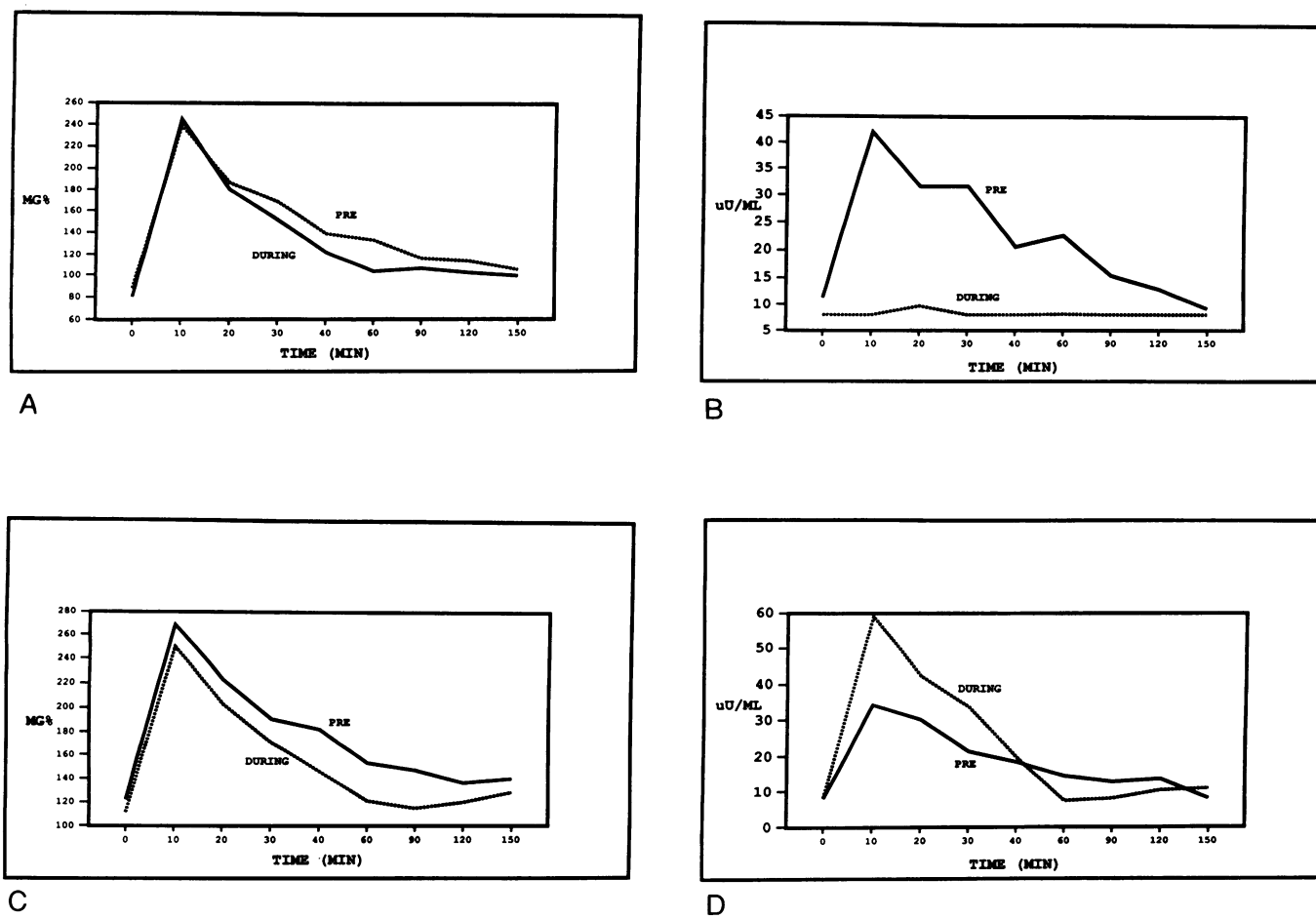

Figure 1. (A) Peripheral blood glucose levels during the GTT before and during IGF-1 infusion are depicted for patient 2. Note the similar rate of glucose disposal. (B) Insulin levels obtained during the GTT before and during IGF-1 infusion are depicted for patient 2. Note the sustained blunted insulin response while the patient received IGF-1. (C) Glucose levels during the GTT for patient 4 both before and during IGF-1. (D) Insulin levels during the GTT for patient 4. Although insulin secretion was not depressed by IGF-1 administration, an anabolic effect was observed.

down and promoting protein synthesis.[10,11,36] In attempts to partially mimic the hormonal milieu of injury, other investigators have studied the effects of IGF-1 in animals pretreated with dexamethasone or tumor necrosis factor.[14,37] In both cases, the anabolic effects of IGF-1 were preserved, indicating a potential role for this compound in the treatment of injured man. In normal volunteers, IGF-1 has been shown to reduce nitrogen wasting by decreasing protein breakdown and oxidation while inhibiting insulin secretion and promoting glucose oxidation.[12,13,38]

We have documented that the short-term anabolic effects of IGF-1 are preserved after severe thermal injury in a group of patients who were receiving full nutritional support. Insulin-like growth factor-1 inhibited lysine oxidation significantly while decreasing protein breakdown despite the inhibition of insulin secretion. It did not totally reverse the catabolic state because all patients remained in negative nitrogen balance, similar to the effects of insulin reported by Jahoor.[28] We cannot comment on whether protein synthesis was affected because incorporation of ^{15}N into muscle was not measured, although IGF-1 has been reported to increase protein synthesis *in vitro*.[39]

Insulin-like growth factor-1 treatment significantly inhibited glucose-stimulated insulin secretion, a finding reported by others, while maintaining glucose disposal.[38] However, IGF-1 did not increase oxidative and nonoxidative glucose disposal in this group of severely stressed patients as has been reported in normal volunteers.[40] A similar finding has been reported in fasted lambs, in which a low-dose infusion of IGF-1 resulted in a protein sparing effect without an increase in glucose oxidation.[36] That this lack of effect on glucose oxidation represents a

Table 4. PROTEIN KINETICS

	Lysine Enrichment %	Urea Enrichment %	Protein Oxidation gm/kg/day	Protein Breakdown gm/kg/day	Nitrogen Balance gm/day
Before					
Mean	3.08	0.02245	0.1183	8.184	−10.6
SEM	0.19	0.004	0.029	0.64	3.3
During					
Mean	4.32	0.02225	0.0874*	6.678†	−7.8
SEM	0.52	0.0035	0.0212	1.01	3.8

* $p < 0.05$ compared with levels before treatment.
† $p = 0.059$ compared with levels before treatment.

dosing phenomena is supported by the study of Jahoor and co-workers, in which they documented that the peripheral effect of insulin on glucose metabolism is intact in patients with thermal injury and that in the aforementioned lamb study, a higher dose of IGF-1 resulted in both protein sparing and increased glucose oxidation.[28]

The inhibition of insulin secretion by IGF-1 was not linked to its protein-sparing effect as shown in two patients in whom IGF-1 did not suppress insulin secretion but did promote protein sparing. This dichotomy is particularly confusing because it is believed that both the IGF-1-mediated inhibition of insulin secretion and the protein-sparing effects of IGF-1 are mediated via IGF-1 receptors, although some investigators have suggested that the protein-sparing effects are mediated via insulin receptors.[40]

Unlike the findings in an animal study,[15] we did not observe an effect of IGF-1 on resting energy expenditure. This is not surprising because glucose and fat oxidation rates were maintained at pretreatment levels, and others have reported the lack of an lipolytic effect of IGF-1.[41] In light of that and because protein oxidation accounts for only a small fraction of the resting energy expenditure, one would not expect a significant impact of the IGF-1 on the metabolic rate of these patients.

Circulating levels of IGF-1 binding proteins 2 and 3 were increased after the administration of IGF-1; whether this represents anything more than the anticipated response to increased levels of IGF-1 remains uncertain. The binding proteins are thought to play a role in regulating the amount of free IGF-1, thus, limiting the bioavailability of the hormone, although IGF-1 bp3 has been reported to potentiate the action of IGF-1 under certain conditions.[42]

It has been suggested that growth hormone and IGF-1 should be administered simultaneously in an attempt to take advantage of the combined anabolic effects of each.[43] This approach may be particularly useful in catabolic patients because IGF-1 has been shown to decrease hepatic protein synthesis, whereas growth hormone has the opposite effect.[44] Moreover, the addition of IGF-1 to growth hormone therapy may abrogate the negative effects of growth hormone, such as insulin resistance and its lipolytic effect.

The clinical implications of these effects may be substantial because IGF-1 has been shown to improve wound healing in corticosteroid-treated rats and reduce gut atrophy and bacterial translocation in an ovine model of thermal injury.[16,45] Extrapolation of our short-term infusion data suggests a potential sparing of 3.24 kg of lean body mass, or almost 5% of body weight, in a 70-kg adult during the initial 30 days after injury. The lack of untoward effects in our patients and the fact that euglycemia was maintained by provision of only 5 mg/kg/min of enteral glucose would indicate that IGF-1 potentially is safer than insulin. In light of the complications—both acute and long term—of autocannibalism of lean body mass, treatment with IGF-1 holds promise as a means to improve the metabolic support of injured persons, shorten hospital stay, and accelerate convalescence.

Acknowledgment

The authors thank Ciba-Geigy for supplying the IGF-1.

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Discussion

DR. CLEON W. GOODWIN, JR. (New York, New York): This paper is an especially outstanding example of the long line of