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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 ( $^{15}\text{N}$  Lysine), and glucose disposal (glucose tolerance test) were assessed in eight burn patients before and after a 3-day infusion of IGF-1 ( $20\text{ }\mu\text{g/kg/hr}$ ). 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 ( $40.3 \pm 2.2$  vs.  $39.1 \pm 2.3$  kcal/kg/day). However, glucose uptake was promoted, and protein oxidation decreased significantly ( $0.118 \pm 0.029$  vs.  $0.087 \pm 0.021$  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.

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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.<sup>1,2</sup> 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.<sup>3</sup> Clinical trials using growth hormone in a variety of catabolic conditions demonstrated that growth hormone was somewhat effective in conserving body proteins.<sup>4,5</sup> 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.<sup>6,7</sup> 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.<sup>8</sup> 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.<sup>9</sup> Diet and tumor necrosis factor-induced catabolism have been reversed by exogenous IGF-1 in animal and human studies.<sup>10-14</sup> 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.<sup>15,16</sup>

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 <sup>15</sup>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  $\mu$ g/kg/hr was started for each patient. Serum glucose levels were obtained at the 1/2-, 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 <sup>15</sup>N Lysine technique, as described by Wolfe, was used.<sup>17</sup> The <sup>15</sup>N Lysine was infused continuously at a rate of 0.08  $\mu$ mol/kg/min immediately after a priming dose of 6.8  $\mu$ mol/kg. In addition, the urea pool was primed by administration of 3.2  $\mu$ mol/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-

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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

$$= \text{lysine oxidation } (\mu\text{mol/kg/min}) \times 2.647.$$

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  $^{15}\text{N}$  Lysine and  $^{15}\text{N}$  urea.

$$\text{Lysine oxidation } (\mu\text{mol/kg/min}) = (\text{urea Ra})$$

$$(\% \text{ urea enrichment} / \% \text{ lysine enrichment}).$$

$$\text{Urea Ra } (\mu\text{mol/kg/min}) = (\text{urine N}) (\text{urine volume})$$

$$(1.2) / (\text{weight}) (\text{urine time}) (2.8 \text{ gm}/\mu\text{mol})$$

assuming that 20% of urea is recycled.<sup>18</sup>

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

$$\text{protein degradation} = \text{lysine Rae } (\mu\text{mol/kg/min}) \times 2.647.$$

$$\text{Lysine Ra} = \text{lysine Ra} - \text{lysine in enteral feedings.}$$

$$\text{lysine Ra } (\mu\text{mol/kg/min}) = {}^{15}\text{N Lysine infusion rate}$$

$$(\mu\text{mol/kg/min}) \times 99\% / \% \text{ lysine enrichment}$$

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:

$$\text{glucose oxidation} = \text{non-protein } \text{VO}_2 \times (\text{non-protein RQ-696}) 0.227 \text{ and fat oxidation} = (0.75 \times \text{non-protein } \text{VO}_2) / 2.019 \text{ as described by Jaquier et al.}^{19}$$

### 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  $41.6 \pm 5.6$  years and  $56 \pm 6.5\%$ , 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 ( $40.3 \pm 2.2$  vs.  $39.1 \pm 2.3$  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  $0.0447 \pm 0.011$   $\mu\text{mol/kg/min}$  to  $0.033 \pm 0.0089$   $\mu\text{mol/kg/min}$  ( $p < 0.05$ ). Lysine Rae also decreased during IGF-1 therapy from  $3.089 \pm 0.39$   $\mu\text{mol/kg/min}$  to  $2.52 \pm 0.38$   $\mu\text{mol/kg/min}$  ( $p = 0.059$ ).

## DISCUSSION

The recognition by Cuthbertson in the 1930s<sup>20</sup> 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.<sup>21</sup>

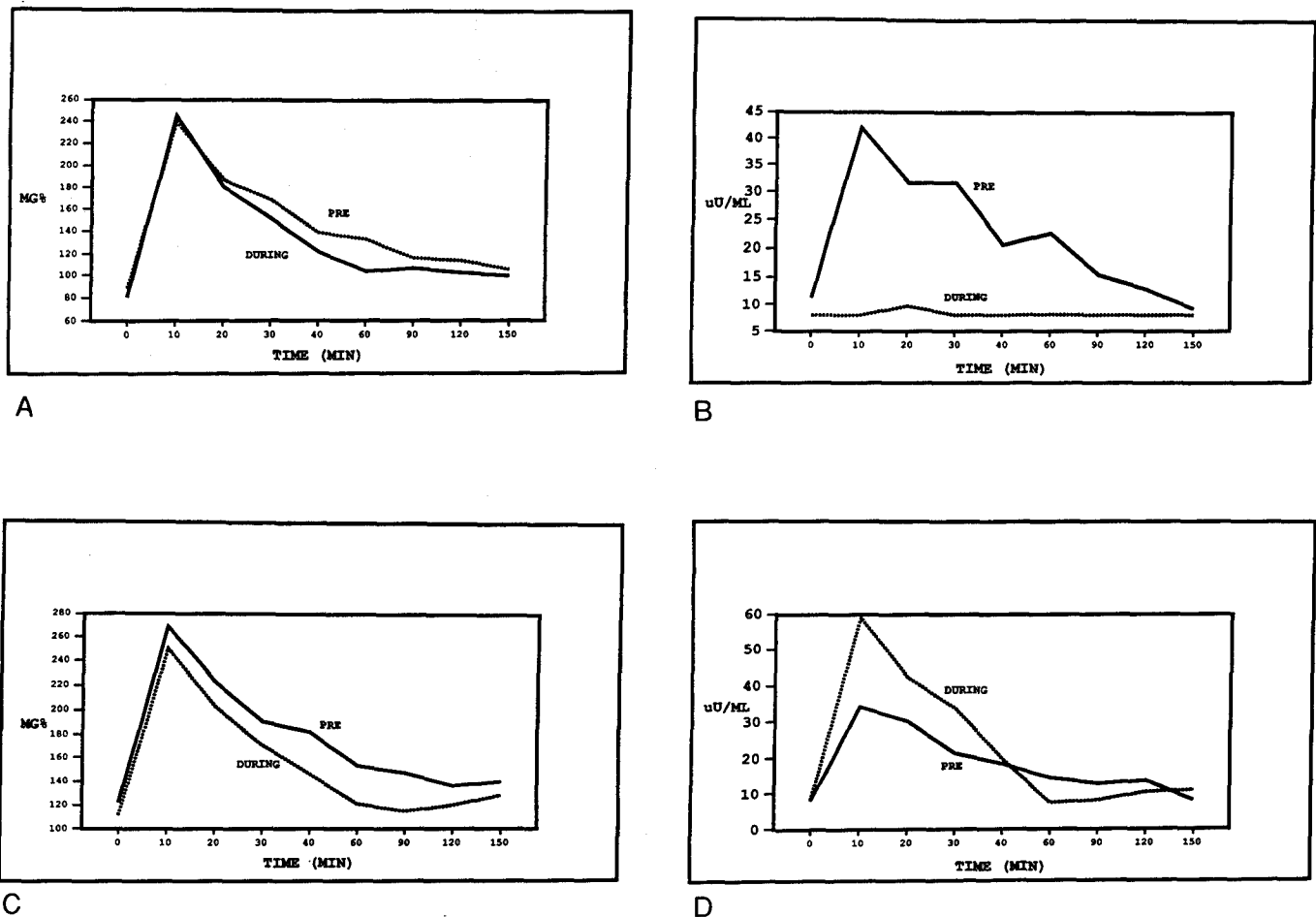
The provision of nutritional support to the injured has been noted to have a protein-sparing effect. Long and associates administered glucose and fat in varying con-

centrations to burn patients and noted that glucose was much more effective than fat in reducing nitrogen excretion.<sup>22</sup> However, limitations in glucose disposal have been reported by several investigators with a maximal oxidation rate of 6 to 7 mg/kg/min.<sup>23,24</sup> 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.<sup>25</sup> 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.<sup>26,27</sup> Jahoor and colleagues have demonstrated an intact insulin response in patients who are burned and septic patients.<sup>28</sup> 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<sup>2</sup>/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<sup>29</sup> 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.<sup>1,2,30-32</sup> Basal levels of growth hormone and IGF-1 have been reported to be low after thermal injury.<sup>33</sup> Resistance to the anabolic effects of growth hormone has been reported, especially in those patients with the most severe injury.<sup>5</sup> 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.<sup>34,35</sup>

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.<sup>10,11,36</sup> 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.<sup>14,37</sup> 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.<sup>12,13,38</sup>

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 to-

tally reverse the catabolic state because all patients remained in negative nitrogen balance, similar to the effects of insulin reported by Jahoor.<sup>28</sup> We cannot comment on whether protein synthesis was affected because incorporation of <sup>15</sup>N into muscle was not measured, although IGF-1 has been reported to increase protein synthesis *in vitro*.<sup>39</sup>

Insulin-like growth factor-1 treatment significantly inhibited glucose-stimulated insulin secretion, a finding reported by others, while maintaining glucose disposal.<sup>38</sup> 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.<sup>40</sup> 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.<sup>36</sup> 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.<sup>28</sup>

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.<sup>40</sup>

Unlike the findings in an animal study,<sup>15</sup> 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.<sup>41</sup> 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.<sup>42</sup>

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.<sup>43</sup> This approach may be particularly useful in cata-

bolic patients because IGF-1 has been shown to decrease hepatic protein synthesis, whereas growth hormone has the opposite effect.<sup>44</sup> 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.<sup>16,45</sup> 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.

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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



investigations of the metabolic response to injury by the Army Institute of Surgical Research. I have three short questions.

If glucose oxidation and fat oxidation remain unchanged and protein oxidation decreases after IGF-1 treatment, what nutrient fills the gap as a fuel source to maintain the elevated energy expenditure described in the treated patients?

Second, the measurements in this group of patients were made while enteral feedings of a high calorie-high nitrogen diet were being administered. As you know, many studies of the metabolic response to injury were carried out after at least an overnight fast by the study subjects. Do you feel that your findings would have been different if derived during fasting? And if so, how?

Third, and along the same lines, do you feel that IGF-1 administration might be dangerous if given in the absence of exogenously administered substrate in that what is at least an early survival metabolic response could be diminished? For example, could patients become dangerously hypoglycemic?

Finally, I would like to thank the Association for the privilege of membership.

**DR. DAVID N. HERNDON** (Galveston, Texas): I would like to join Dr. Goodwin in congratulating the authors on an excellent clinical research study that clearly demonstrates that this newly available recombinant product has a small but significant effect of decreasing lysine oxidation in hypermetabolic burn patients over a 3-day infusion period.

This study titillates us in its conclusion to speculate that this agent might have clinical utility. The introduction of any modulator of the host response should address risk benefits, including discussions of potential alternatives. And in that regard I would like to ask three questions.

As to clinical efficacy, I would like to ask the authors to comment on recent reports that demonstrate that when IGF-1 is given for chronic periods to AIDS patients there is an initial anabolic effect on protein metabolism but this effect disappears in the second and third week of treatment, presumably due to reciprocal increase in binding proteins which limits free IGF-1 availability. How would you prevent binding protein production from negating the effects of IGF-1 over time?

In terms of risk, could you comment on the decision of the major pharmaceutical suppliers of IGF-1 to suspend the availability for clinical trials of the agent because of five cases of Bell's palsy and three cardiac arrests in patients being studied?

Finally, insulin and insulin-like growth factor-1 exert their anabolic effects through related if not in some cases identical membrane receptors. One of the co-authors of this paper has shown a twofold improvement in protein synthesis, in fact a more dramatic improvement than shown with IGF-1, with insulin infusions in patients that are quite similar to those studied here. Might the authors be able to subserve the same therapeutic anabolic function at a lower risk and a lower price with insulin than the newly available recombinant product?

**DR. PALMER Q. BESSEY** (Rochester, New York): I, too, would like to rise to congratulate Dr. Cioffi and his associates for completing these sophisticated metabolic studies in a group of very difficult, complex, critically ill patients.

This presentation and its manuscript will join many of the other superb reports from the ISR under Dr. Pruitt's direction that have revolutionized burn care and markedly improved the outlook for victims of perhaps the most horrendous and challenging injury we face.

Dr. Cioffi and his associates tried to shift the balance between anabolism and catabolism in recovering burn patients by infusing IGF-1, an anabolic hormone. The good news is that—amazingly—it looks as though maybe they did it.

IGF-1 infusion appeared to inhibit the erosion of body protein by reducing the use of protein as a fuel for oxidation and, as Dr. Cioffi indicated, over the course of recovery from a major burn this might spare several kilograms of lean body mass and thus reduce the debility associated with recovery.

But before we rush to adopt IGF-1 as a routine therapy in our ICUs, we should consider some of the possible limitations of the study.

First, the isotopic dilution techniques are most reliable when a variety of fairly strict conditions are met. The size of the compartments or pools in which the isotope is distributed should be constant during both studies; the isotopic distribution should be in a steady state; and recycling should be negligible or certainly constant. The metabolic state of a recovering burn patient is certainly a dynamic one as he or she progresses toward recovery, so that the conditions under which these two studies were accomplished might well be different.

Dr. Cioffi, could the differences you observed in lysine kinetics be due in part to progression of the patient's convalescence? In other words, if the patients did not receive IGF-1 would the results of isotopic dilution studies done in 3-day intervals be constant or would they show similar changes?

Secondly, when you look at how all these parameters are derived or calculated through the formulas in the manuscript, you realize that the parameters here, protein oxidation and protein breakdown, are really derived from just a few primary measurements. In addition to measurements of isotopic enrichment, the calculations of the parameters depend heavily on the values of the intake of the unlabeled lysine and also on the output of urea nitrogen. Lysine intake came from absorption of lysine from the enteral feeding in the GI tract. This was assumed to be constant during these studies. Although the measurements of urea nitrogen and total nitrogen is standard, there was enough variability in the system that nitrogen balance was not statistically different before and after IGF-1.

When there are significant differences in the derived parameters but not in the primary data on which they are based, we must be cautious in our interpretation of the data. Dr. Cioffi, would you comment further on this?

But nonetheless, the burn patient is certainly the biggest metabolic challenge we face and the fact that Dr. Cioffi and his associates detected improvement in protein metabolism with IGF-1 is an exciting finding and offers the possibility of further reducing the catabolic cost of critical illness.

**DR. JOSEF E. FISCHER** (Cincinnati, Ohio): Those of us who have struggled in the area of proteolysis have probably reluctantly begun to come to the conclusion that one of the problems in the proteolytic situation is not the presence of positive factors that increase proteolysis but the absence of positive fac-

tors such as IGF-1. My simpleminded way of looking at this is that perhaps what IGF-1 does is decrease transport of amino acids from the periphery to the center.

If data are correct, and assuming that you have a 70-kilogram man, I calculated from the differences in protein, fat, and glucose oxidation that there is a difference over 24 hours of about 69 calories expended in a 70-kilogram man. So it is not surprising that a resting energy expenditure did not detect the difference in this particular group of patients.

On the other hand, I wonder—and Cleon Goodwin has already referred to this—whether you stack the deck against yourselves by giving these people and continuing 5 milligrams per kilogram a minute of carbohydrate by enteral feeding, which remained stable throughout the experiment, and whether the difference between the animal experiments, which show efficacy of IGF-1 under these circumstances, and humans, is the fact that the animals were fasted, or at least were not fed to excess, and here you had no alternative but to continue the feeding.

One possible way around this, since it would be unethical and you wouldn't want to decrease the feedings for a prolonged period of time in patients with these extensive burns, is perhaps to go back to an old technique which I know is available in the laboratory—amino acid fluxes in the unburned extremities, if such existed—in which if you fasted the patients maybe for 6 hours you probably would see the effect of IGF-1 on muscle amino acid flux and perhaps prove your point.

I do have another problem, and that's with the calculation of glucose oxidation. Since you obviously have the capacity for isotopic dilution, wouldn't it be better to derive the glucose oxidation figures from a direct test of glucose oxidation enrichment than an indirect calculation? I think it would make a very nice paper and a very nice series of studies even nicer.

It's a very nice manuscript and it was an excellent presentation.

**DR. STANLEY M. LEVENSON** (Bronx, New York): Just one brief comment. The data presented by Dr. Cioffi are very suggestive, but from the point of view of experimental design of the study, I would have liked to have seen an equal group of similar patients studied concurrently but prospectively randomized in a double-blind study to have received only the vehicle in which the insulin-like growth factor-1 was solubilized.

The reason for my suggestion is that these patients were studied at a time when their clinical and metabolic states may well be changing. I am not saying that what has been demonstrated by Dr. Cioffi and his colleagues is not the case, but their conclusion regarding the effects of the insulin-like growth factor-1 would be significantly more solid had there been an appropriate control group of patients studied concurrently.

**DR. WILLIAM G. CIOFFI** (Closing discussion): I would like to thank the discussants for their questions, and I will answer them in the order that they were asked.

Dr. Goodwin asked three questions, the first concerning the changes in glucose, fat, and protein oxidation, and why there was no observed change in resting energy expenditure. I think that Dr. Fischer answered that question, in that the decrease in

protein oxidation equates to a very small number of calories, and thus I would not expect to find a difference in resting energy expenditure.

Dr. Goodwin also asked about the use of fasting *versus* fed patients. Indeed, it is preferable to perform metabolic studies in a fasting state. However, the hypoglycemic response that you would anticipate at the infusion of 20 micrograms per kilogram per hour of IGF-1 would be prohibitive. Thus, similar to the insulin studies that Dr. Herndon alluded to, you need to supply a constant glucose infusion.

The safety of the compound, IGF-1, was questioned by both Dr. Herndon and Dr. Goodwin. Indeed, there have been several incidences of Bell's palsy and cardiac arrest in other patient populations that have been studied using IGF-1. We did not note any untoward effects in our patients. The majority of complications that have been documented, that Dr. Herndon noted, occurred in a group of AIDS patients and a group of severe insulin-dependent diabetics that were receiving much higher doses of IGF-1 than we administered.

Dr. Herndon asked about the size of the protein-sparing effect, and was it enough to really make a clinical difference. He also asked if we could obtain the same effect as Dr. Gore had previously published using higher doses of insulin. I think that the size of the effect that we documented is substantial if we take the lysine data and extrapolate it to whole body protein kinetics and then look at what would happen over the initial 30 days postburn period.

The purpose of the IGF-1 infusion was not to decrease resting energy expenditure of the patients, but to decrease the autocannibalism of lean body mass and attempt to keep protein stores, both functional and structural, intact.

If we wanted to use insulin instead of IGF-1, I think there are several problems with that approach. The study that Dr. Herndon alluded to pointed out some of those problems. In order to halve the protein oxidation rates with insulin, it required 52 units of insulin per hour and the administration of 12 milligrams per kilogram per minute of glucose to those patients.

I would hesitate to use that as a standard therapy in any intensive care unit where I would think the complications associated with hypoglycemia would be immense, and certainly much worse than they were noted to be in this study.

An additional effect of insulin is that very small infusion rates result in essentially shutting off hepatic gluconeogenesis. IGF-1 has been noted to have a similar effect, but at much higher doses, and I would hope that at the dose we employed in this study we would not observe this effect.

Dr. Bessey alluded to some of the limitations of using isotopic techniques to do these studies. I can only say that during the time period the patients were studied, their weights were stable, they were on a stable nutritional diet, and they received no exogenous nutrition other than the enteral feedings. As he noted, however, we cannot be sure they absorbed all the enteral lysine which we presented to them.

In terms of the stability of the resting energy expenditure and nitrogen metabolism in these patients, we previously reported that from postburn day 4 or 5 until at least the 30th postburn

day, resting energy expenditure and nitrogen wasting is essentially stable in this kind of burn patient.

Dr. Bessey also asked about the nitrogen balance data not being statistically different between the two groups. That data was calculated using 24-hour urine collections, while the isotope data was calculated over a 3-hour time period of the isotope infusion. I think the urine collections during the 3-hour study are much more accurate than the 24-hour urine collections in the intensive care unit.

Dr. Fischer asked why we did not use glucose isotopes rather than the metabolic cart data. I agree with him that it would be a much better study if we were able to use the glucose isotopes. We started this as a pilot and we were hoping to see if we could document a protein-sparing effect of the IGF-1 and then go on to look at its effects on glucose oxidation in a much more precise way. As Dr. Herndon commented, both Genentech and Ciba Geigy have withdrawn the compound from the market

for the present time and we are going to have to wait and see if we can get more compound.

Again, I think the most important point of the study is that we were not looking to decrease resting energy expenditure, but we were hoping to preserve lean body mass. I think we demonstrated that we can do that with IGF-1 in thermally injured patients.

Dr. Herndon, I think, had the most critical comment, and that is "Could we do the same with insulin?" Indeed, the two compounds work in a very similar fashion. IGF-1 does bind insulin receptors, and many of its effects are then modulated by the insulin receptor. However, I think in terms of clinical utility, IGF-1 would be a much safer drug to use in an intensive care unit in terms of symptomatic hypoglycemia. As I noted, it takes exceptionally high doses of insulin to get the same kind of effect that we noted with relatively modest doses of IGF-1.