Adjuvant Recombinant Human Growth Hormone Does Not Augment Endogenous Glucose Production in Total Parenteral Nutrition–Fed Multiple Trauma Patients

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Hyperglycemia and insulin resistance are well-known, consistent responses to severe injury. The purpose of this study was to investigate the mechanism for the further exaggerated hyperglycemia due to adjuvant recombinant human growth hormone (rhGH) treatment in multiple trauma patients. We have measured in 20 adult severely injured, highly catabolic, hypermetabolic, multiple trauma patients, the glucose kinetics (appearance, clearance, oxidation, and recycling) once in the basal state (study I), 48 to 60 hours after injury but before starting nutritional therapy, and again (study II) after 7 days of intravenous nutrition (1.1 times resting energy expenditure, 250 mg nitrogen [N]/kg/d) with or without adjuvant rhGH. Group H (n = 10) randomly received daily (8 AM) rhGH (0.15 mg/kg/d) and group C (n = 10) received the vehicle of infusion. Adjuvant rhGH treatment in intravenously fed trauma patients (1) increases plasma insulin-like growth factor-1 (IGF-1) and insulin concentrations, (2) improves N balance, and (3) exaggerates the hyperglycemic response without affecting endogenous glucose output, glucose oxidation, or recycling. The mechanism for the hyperglycemic hyperinsulinemia in trauma may be due to a defective nonoxidative glucose disposal, as well as inhibition of glucose transport activity into tissue cells.
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THE EARLY catabolic flow phase of severe trauma is characterized by increased mobilization and loss of protein sources, accelerated rate of fat mobilization, and hyperglycemia. Glucose is a necessary major energy source and a potent regulator of metabolic and physiologic functions, with extensive mechanisms for close regulation of the blood glucose concentration. Glucose intolerance is the hallmark of the injured state and the posttraumatic hyperglycemia is found to be mainly due to an increased hepatic glucose output, and not to a decreased ability of the tissues to extract glucose from the plasma.[1,2] Efficient management of this early, crucial, injury period with a more effective way of preserving lean body mass is imperative for the early uncomplicated recovery. Several adjuvant therapies[3-12] were advocated to facilitate accomplishment of these goals, and the promising one among them seems to be the growth hormone (GH) infusion,[10-12] which has direct as well as indirect hormonal mediator and substrate effects.

An acute deficiency in the circulatory levels of GH had been found in multiple trauma victims during the early catabolic flow phase of severe injury.[13] At this stage, adjuvant administration of recombinant human growth hormone (rhGH) promotes protein anabolism in parenterally fed trauma patients and improves the utilization efficiency of protein flux.[11] Along with the preservation of protein conservation, the metabolic effects of rhGH administration in trauma victims include stimulation of lipolysis and reesterification.[12] Development of diabetes or insulin resistance with hyperglycemia due to GH administration has been a concern since the beginning of this treatment in healthy subjects.[14] Treatment of adults with GH deficiency (GHD), using rhGH, resulted in fasting hyperglycemia with no detectable change in overall glucose turnover,[15] as was observed after similar treatment of normal short children[16] and normal adults.[17] Glucose uptake by muscle was invariably inhibited, not enhanced, by infusion of rhGH in normal men.[18]

Deficiency in glucose transport was suggested for the reduced glucose uptake and inhibited oxidation in burn patients.[19] With injured subjects who have an inherent stress-induced glucose intolerance, any additional insulin resistance may limit the usefulness of GH. The mechanism behind the further exaggerated hyperglycemia and hyperinsulinemia due to adjuvant rhGH in trauma patients[12] is not fully understood.

In the present study, we investigated the glucose production, oxidation, and indices of recycling once in the early flow phase of injury before nutritional intervention, and again after 1 week of parenteral nutrition with or without daily rhGH injection in acutely traumatized patients. The purpose of the study was to examine the mechanism of the hyperglycemic effects of adjuvant rhGH in multiple trauma victims.

MATERIALS AND METHODS

Subjects

Twenty adult patients who had recently suffered trauma were studied after admission to the Intensive Care Unit of the Level I Trauma Center at St Joseph's Hospital and Medical Center in Phoenix, AZ. The protocol had been reviewed and approved by the institutional review board. Written informed consent was obtained following explanation of the study to the patient or legal representative. Relevant patient characteristics on admission are listed in Table 1 and the individual diagnoses were reported previously.[11] The studies were initiated within 48 to 60 hours after the patients sustained multiple injuries, while they were receiving maintenance fluids and electrolytes but no calories or nitrogen (N).

None of the patients were septic, and none had diabetes mellitus, liver dysfunction, renal insufficiency, malignant disease, or multiple organ failure. They appeared to be well nourished before injury. On admission, the injury severity was determined by

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Table 1. Patient Characteristics

No. and sex	17M/3F
Age (yr)	46.3 ± 5.0
Weight (kg)	83.4 ± 6.0
BMI (kg/m^2)	27.2 ± 1.2
ISS	30.6 ± 2.1
REE (% BEE)	141 ± 5
RQ	0.74 ± 0.02
N loss (g N/d)	19.2 ± 2.2
N loss (mg N/kg/d)	214 ± 15
Plasma glucose (mg/dL)	139 ± 10
Plasma albumin (g/dL)	2.6 ± 0.1

NOTE. Values are the mean ± SEM.
Abbreviations: M, male; F, female.

the Injury Severity Score (ISS) based on the Abbreviated Injury Score (AIS) of the three most serious anatomic injuries.[20] All had at least one major and multiple minor injuries, with ISS values ranging from 17 to 50 with a mean of 30 ± 3. The trauma team evaluated and resuscitated the patients according to individual requirements. All patients required ventilator support during the basal study (fractional inspired oxygen up to 40%) and four patients were weaned off mechanical ventilation during the 7-day nutritional therapy. Most of the patients (14 of 20) were involved in motor vehicle crashes and sustained multiple skeletal fractures with extensive soft tissue damage. Four patients were victims of penetrating wounds to the abdomen, chest, or face; one patient had an accidental fall resulting in multiple fractures, and another patient was admitted with a closed head injury and multiple fractures after his experimental airplane crashed into a tree.

Experimental Study Protocol

Twenty-four–hour urine collections through a Foley catheter were initiated and continued until the end of the study. When the medical status of the patients became stable and resuscitation was complete, a blood sample was drawn from each patient in the morning through an existing arterial line for basal substrate and hormone measurements. This occurred 48 to 60 hours after injury during the early stages of the catabolic phase of severe injury. The patients were weighed (Flexicair MC3; Support System, Charleston, SC) in the morning and the daily weights were recorded.

Gas Exchange Indirect Calorimetry

Oxygen consumption ($\dot{V}O_2$), carbon dioxide production ($\dot{V}CO_2$), and respiratory quotient (RQ) were measured using the metabolic cart (Horizon Metabolic Measurement Cart; Sensormedics, Anaheim, CA). All of the patients were on ventilator support and the exhaled flow was directly connected to the metabolic cart. The instrument was calibrated before each measurement and the stability of the instrument conditions was observed for at least a 10-minute equilibration period. Then the test measurement was performed over a 20-minute period of continuous sampling. One-minute averages of $\dot{V}O_2$, $\dot{V}CO_2$, and RQ were calculated. Means of $\dot{V}O_2$ and $\dot{V}CO_2$ during the 20-minute period, along with the urinary total N excretion, were used to calculate the resting energy expenditure (REE) and substrate oxidation rates.[21,22] Predicted basal energy expenditure (BEE) was calculated by the appropriate Harris–Benedict equation, taking into consideration age, gender, height, and weight.[23]

Glucose Kinetic Study

A primed-constant infusion of sterile and nonpyrogenic (6-^{3}H)glucose and (U-^{14}C)glucose (ICN Radiochemicals, Irvine, CA) in normal saline was administered to all subjects for 130 minutes. After a bolus priming dose over a 2-minute period, the continuous infusion followed. The infusion rates of each of the isotopic glucose solutions during this period were 2.0 nCi/kg/min. The priming dose to infusion rate ratio was 80:1 for each isotope.[24] The bicarbonate pool was primed with 60 nCi/kg of $NaH^{14}CO_3$.[25] A calibrated infusion pump (IMED, San Diego, CA) was used to ensure a constant infusion rate. During this constant continuous infusion of isotopes, arterial blood samples (5 mL each) were drawn at 110, 120, and 130 minutes to determine the specific radioactivities of the isotopic glucoses. The expired gas was collected at 5-minute intervals (105 to 110, 115 to 120, and 125 to 130 minutes) in plastic bags for specific activity of CO_2 in the breath gas. The experimental procedures did not interfere with patient care. None of the subjects exhibited glucosuria during this study.

At the end of this basal glucose kinetic study (study I) in each patient, nutritional support was started and continued for 7 days with or without rhGH bolus administration. At the end of 7 days of nutritional support, the glucose kinetic study and gas-exchange measurements were repeated (study II) while the patients were receiving full nutritional support. Glucose kinetic studies I and II were started at 10:00 AM.

Nutritional Support

At the end of study I, intravenous feeding (total parenteral nutrition [TPN]) with necessary electrolytes, minerals, trace elements, and vitamins via a central venous catheter was initiated and continued for 7 days. All patients were given continuous infusion of nutrients at a constant rate for the duration of the study. The TPN diet contained 250 mg N/kg/d as commercially available balanced free amino acid (AA) mixture (10% Aminosyn; Abbott Laboratories, North Chicago, IL) and the energy requirements were based on 1.1 times the measured REE. Nonprotein calories were provided as dextrose. To prevent essential fatty acid deficiency, 500 mL of 10% lipid emulsion (Intralipid® 10%; Kabi Vitrum, Alameda, CA) was given intravenously over an 8-hour period on day 3. During this nutritional therapy, the patients were randomized to receive (group H, n = 10) or not to receive (group C, n = 10) intramuscular rhGH (Somatropin; Genentech, South San Francisco, CA) every day at 8 AM (after morning blood sampling) at a dose of 0.15 mg/kg/d. Twenty-four–hour urine collection for daily N balance and renal function, and morning blood samples for Blood urea nitrogen (BUN) and hormonal measurements were continued. All patients tolerated the intravenous nutritional regimen and had an uncomplicated course during this period.

Repeat Glucose Kinetic Study (study II)

At the end of 7 days of continuous feeding, the glucose kinetic study was repeated as described previously with infusion of the labeled glucoses as the TPN continued. Study II was intended to document the effects of rhGH in modifying the catabolic state of injury during the flow phase with adequate nutritional support.

Chemical Methods

For measurement of radioactivity in glucose, blood samples were taken into heparinized tubes and the plasma was separated and stored at −20°C until assay. Plasma (1 mL in duplicate) was deproteinized by adding 2 mL of 5.36% (wt/vol) $Ba(OH)_2$, 2 mL of 5% $ZnSO_4 \cdot 7H_2O$, and 5 mL of distilled water, vortexed and centrifuged for 15 minutes at 10,000 rpm. The supernatant was sequentially passed through anion and cation exchange columns (hydrogen AG50W-X8, formate AG1-X8; Bio-Rad Laboratories, Richmond, CA). This will eliminate all of the ionic species. The wash was passed through another column containing AGI (borate

form) resin. Glycerol was eluated by a boric acid wash and the glucose was finally eluated by 0.5 mol/L acetic acid. The eluate was freeze-dried, suspended in 1 mL water, and an aliquot in triplicate (10 uL) was used to determine the glucose concentration with a glucostat analyzer (Glucose Analyzer II; Beckman, Fullerton, CA). A known volume (400 μL), in duplicate, was mixed with scintillation cocktail (Ready Safe; Beckman) and counted in a dual-channel scintillation counter (Model SL3801; Beckman). Corrections for efficiency and overlapping were done with the use of calibrated external standards, and the automatic quench compensation mode of the "H Number" method of Beckman built into the instrument. The specific activity of the expired $^{14}CO_2$ was determined by trapping it from the dried, expired air in a solution of hyaminehydroxide (1.0 mmol), using 0.1% phenolphthalein solution as an indicator. Trapped $^{14}CO_2$ was then mixed with 15 mL of the scintillation cocktail and counted as described previously.

Plasma levels of glucose, albumin, and BUN were determined using standard procedures in a microcentrifugal analyzer (Multistat Plus III; Instrumentation Laboratories, Lexington, MA). Commercial radioimmunoassay (RIA) kits (Diagnostic Products, Los Angeles, CA) were used to determine insulin, C-peptide, cortisol, and glucagon. Plasma GH and insulin-like growth factor-1 (IGF-1) levels were determined by the RIA method using kits from Nichols Institute Diagnostics, San Juan Capistrano, CA. Plasma IGF-1 was measured after acid-ethanol extraction from its carrier proteins. Total N in urine was measured with a chemiluminescence digital nitrogen analyzer (Antek Instruments, Houston, TX).

Calculations

The specific activity of both the isotopic glucoses were obtained by dividing the respective radioactivity (dpm) by the amount (mg) of glucose. An isotopic steady state was present in all subjects as judged by a plateau of specific activity (±3%). The successful priming of the bicarbonate pool gives an isotopic steady state in expired CO_2. This is a valid method for measuring glucose kinetics in many pathological conditions,[24-27] including trauma.[1]

Glucose Turnover

When the isotopic plateau of glucose tracer is reached in plasma, the rate of appearance of glucose on plasma (Ra) equals the rate of disappearance of glucose (Rd), and this rate is collectively called glucose turnover (GTO). With the nonrecycled radioactive isotope [(6-^{3}H)glucose], the rate of glucose appearance at the steady state can be calculated[24,27] using the Steele equation[28] for steady state:

$$\text{GTO} = \text{Ra} = \text{Rd, (mg/kg/min)} = (\text{F/SA}) \quad (1)$$

where F is the rate of isotope infusion (dpm/kg/min) and SA is the specific activity (dpm/mg) of 6-^{3}H glucose.

Glucose Recycling

Following uptake by tissues, glucose can be converted into three-carbon fragments, which are transported to the liver and converted (recycled) back to glucose. The Ra of glucose in the plasma that is due to recycled glucose is calculated[29] by the constant infusion of two tracers, one where the tracer atom is not recycled (6-^{3}H glucose) and one where the tracer atom can be recycled (U-^{14}C glucose). The carbon-labeled isotope underestimates the rate of glucose appearance. Thus in the absence of any exogenous supply of glucose,

Glucose recycling (mg/kg/min)

$$= \text{Ra}[6\text{-}^3\text{H}]\text{glucose} - \text{Ra}[\text{U}^{14}\text{C}]\text{glucose} \quad (2)$$

and

% glucose recycling

$$= 100 \times \text{glucose recycling/Ra}[6\text{-}^3\text{H}]\text{glucose} \quad (3)$$

Glucose Oxidation

Under steady-state conditions, the rate of glucose oxidation can be calculated from the data obtained from [U-^{14}C] glucose infusion,[30]

% glucose uptake oxidized

$$= \frac{^{14}CO_2 \text{ excretion (dpm/min)} \times 100}{\text{rate of } [^{14}\text{C}]\text{glucose infusion (dpm/min)} \times \text{K}} \quad (4)$$

This provides the percentage of plasma glucose that is being taken up by tissues and directly oxidized. A constant (K) is required because not all $^{14}CO_2$ formed at the cellular level is expired in the breath but some is retained in the body bicarbonate pool. The constant K for a traumatized man in fasting basal conditions is 0.85 and TPN-fed conditions is 1.0.[31]

Glucose oxidation (mg/kg/min)

$$= \%\text{ glucose uptake oxidized} \times \text{GTO(mg/kg/min)}/100 \quad (5)$$

This is the rate of oxidation of glucose that has been cleared from the blood directly by the tissues and oxidized.

% $\dot{V}CO_2$ from glucose

$$= \frac{\text{glucose oxidation (μmol/kg/min)} \times 6 \times 100}{\dot{V}CO_2 \text{ (μmol/kg/min)}} \quad (6)$$

This is the percentage of expired CO_2 derived directly from glucose oxidation. The factor 6 is required since 1 mol of glucose gives rise to 6 mol of CO_2.

Glucose Clearance

This is the amount of blood cleared of glucose per minute and given by:

Glucose clearance (mL/kg/min)

$$= \frac{\text{GTO(mg/kg/min)}}{\text{blood glucose concentration (mg/mL)}} \quad (7)$$

Hepatic Glucose Production

Under basal conditions (study I), hepatic glucose production (HGP) is the same as GTO, since there is no intake. However, during TPN (study II), HGP is Ra minus glucose intake.

Statistical Methods

Statistics were calculated on a GB/STAT (Dynamic Microsystem, Silver Spring, MD) program loaded on an IBM-PC computer (Armonk, NY). Paired *t* tests were used to test statistical significances of the differences between study I and study II parameters in each group. Analysis of variance for repeated measures (two-way ANOVA) were used to test differences between treatment and control groups.[32] Coefficients of correlation were determined by standard procedures using the least squares method. Variance of the mean was expressed as the standard error of the mean (SEM). A P value $\leq .05$ was considered statistically significant.

RESULTS

Nutritional effects on the glucose kinetics of severely injured patients were studied, once in the basal condition before the initiation of therapy, and again after 7 days of adequate nutritional support with or without daily rhGH supplement. Clinical characteristics of the enrolled trauma patients are listed in Table 1 and the individual diagnosis were reported previously.[11] The altered plasma hormonal parameters and N balance due to intravenous nutrition with (group H) or without (group C) adjuvant rhGH are listed in Table 2.

The two groups of patients were of similar body weight, body mass index, and ISS and were equally hypermetabolic (REE = 41% higher than their predicted BEE), and highly catabolic (daily N excretion = 19 g). Provision of intravenous nutrients for 7 days with daily rhGH infusion significantly improved the N balance (-41 ± 18 mg N/kg/d for patients receiving rhGH and -131 ± 14 mg N/kg/d for patients without rhGH; $P \leq .01$). This improvement in N retention was also reflected in the significantly low BUN (15.2 ± 2.3 *v* 22.4 ± 1.5, mg/dL, $P = .025$) in the rhGH group.

The plasma levels of GH and IGF-1 in the basal trauma conditions were significantly ($P = .05$) low, compared with the reported[13] normal values in healthy subjects. Although pulsatile GH secretion persisted in injured patients, the mean 8 AM GH concentration was not different from the 24-hour integrated GH concentration.[33] Provision of nutrients alone without rhGH increased IGF-1 levels by 74% from basal; however, with rhGH, they were increased by 230%. This indicates the stimulation of IGF-1 secretion by exogenous GH. TPN alone for 7 days doubled the plasma GH level, but with exogenous rhGH it was increased by 560%. Nutrition with or without adjuvant rhGH had no effect on the counterregulatory hormones, cortisol and glucagon. However, insulin levels were significantly more increased in rhGH patients. Hyperglycemia was also more exaggerated with adjuvant rhGH, and occurred in the presence of hyperinsulinemia. The effects of nutrition on the kinetic parameters of glucose production and utilization are listed in Table 3. In the basal study, there was no significant difference between the two groups of trauma patients. The slightly elevated glucose production rate at baseline (3.5 ± 0.2 *v* 4.4 ± 0.7, P = NS) was due to higher values (9.39 and 6.66) in two control patients. Both groups received equivalent amounts of glucose during the second study. Although TPN increased the plasma glucose level, administration of rhGH further enhanced significantly ($P < .05$) the hyperglycemia. Glucose clearance in group C patients was increased from a basal value of 2.9 ± 0.3 to 3.8 ± 0.3 mL/kg/min ($P < .05$) during TPN, an increase of 31%. However, there was no change in group H patients (2.5 ± 0.2 to 2.7 ± 0.2). The groups with or without adjuvant GH were similar in suppressing (45%) hepatic glucose output, increasing (30%) V_{CO_2}, and increasing (140%) glucose oxidation. There was no significant correlation between day 7 GH or IGF-1 concentrations in plasma and absolute glucose oxidation rates. Hepatic glucose output was similar in both groups of patients in studies I and II, and the percent glucose recycling was also similar in the two groups.

There was a significant linear correlation ($r = .74$; $P = .001$) between the plasma glucose level and plasma glucose Ra in both studies of trauma patients (Fig 1). Under basal conditions (study I), plasma Ra was the same (by definition) as the rate of HGP, since there was no exogenous intake. During TPN (study II), the endogenous production was suppressed significantly and still held a significant ($r = .68$; $P = .005$) linear relationship with the plasma glucose Ra (Fig 2). This amount of glucose intake (4.7 ± 0.5 mg glucose/kg/min) could not completely suppress the endogenous HGP, confirming previous reports from septic[34] and injured[35] patients. The extent of glucose recycling through three carbon fragments under basal conditions (12%) is similar to that reported (9.8%) in normal subjects.[1] During TPN with or without rhGH supplementation, the extent of glucose recycling remained unchanged.

DISCUSSION

Intramuscular administration of rhGH during intravenous nutritional support, in critically ill multiple trauma patients, exaggerated the hyperglycemic response, despite a concurrent increase in plasma insulin levels. This hyperglycemia is found to be not due to enhanced HGP or defective oxidation. Defective nonoxidative disposal (glycogen synthesis and storage/lipogenesis) may be one of the mechanisms responsible for the observed increase in hyperglycemia with

Table 2. Plasma, Hormonal Profile, and Nitrogen Balance

	Normals* (uninjured)	Trauma: Study I		Trauma: Study II	
		Group H	Group C	Group H	Group C
Insulin (uIU/mL)	7.5 ± 0.67	12.9 ± 1.6	15.1 ± 2.6	185 ± 20†	77 ± 22
GH (ng/mL)	2.92 ± 0.93	1.18 ± 0.24	0.99 ± 0.47	9.87 ± 2.41†	2.84 ± 0.72
IGF-1 (ng/mL)	228 ± 21	74 ± 15	87 ± 20	231 ± 36†	168 ± 19
Cortisol (μg/dL)	14 ± 2	23 ± 3	23 ± 4	20 ± 2	23 ± 2
Glucagon (pg/mL)	—	61 ± 28	99 ± 33	87 ± 29	116 ± 28
Epinepherine (pg/mL)	90 ± 20	223 ± 60	173 ± 34	163 ± 25	174 ± 29
Norepinepherine (pg/mL)	223 ± 59	816 ± 105	748 ± 155	654 ± 97	575 ± 36
N balance (mg N/kg/d)	—	−223 ± 25	−206 ± 17	−41 ± 18†	−131 ± 14

NOTE. Values are the mean ± SEM; n = 10 in each trauma group.

*Normal values from Surgery 111:495, 1992[13] and Clin Nutr 11:352, 1992.[48]

†$P \leq .05$ *v* patients without rhGH (group C).

Table 3. Glucose Kinetics in rhGH-Treated Trauma Patients

Variable	Study I (Basal)		Study II (TPN)	
	Group H (+rhGH)	Group C (−rhGH)	Group H (+rhGH)	Group C (−rhGH)
Glucose plasma level (mg/dL)	138 ± 9	150 ± 13	256 ± 25	202 ± 17*
Glucose appearance (mg/kg/min)	3.45 ± 0.23	4.38 ± 0.71	6.57 ± 0.64	7.67 ± 0.81
Glucose clearance (mL/kg/min)	2.53 ± 0.16	2.92 ± 0.27	2.73 ± 0.22	3.84 ± 0.26*
Glucose intake (mg/kg/min)	0	0	4.64 ± 0.48	4.80 ± 0.64
Hepatic output (mg/kg/min)	3.45 ± 0.23	4.38 ± 0.71	1.84 ± 0.21	2.80 ± 0.48
$\dot{V}CO_2$ (mL/min)	223 ± 19	287 ± 44	303 ± 22	346 ± 6
Plasma glucose oxidized (mg/kg/min)	0.86 ± 0.17	1.06 ± 0.16	1.84 ± 0.52	2.71 ± 0.55
Glucose uptake oxidized (%)	29.1 ± 5.4	21.5 ± 1.9	34.2 ± 6.2	36.5 ± 6.3
Glucose recycling (%)	12 ± 2	13 ± 1	10 ± 2	8 ± 2

NOTE. Values are the mean ± SEM; n = 10 in each group.
*$P < .05$ when the % change from study I was compared between groups H and C.

rhGH. Glucose output might have been inhibited by hyperglycemia per se, independent of an increase in insulin levels. This mechanism is unlikely in normal subjects.[18] Other possibilities for the hyperglycemic, hyperinsulinemia during rhGH supplementation include impaired glucose transport activity into tissue cells as suggested for burn patients.[19] A significant postreceptor defect may have contributed to the observed insulin resistance.[36]

Glucagon is known to induce increased hepatic output of glucose. In these trauma patients, administration of rhGH did not influence the plasma glucagon levels and this is consistent with the unchanged HGP. Influence of GH on glucose metabolism apparently varies with the endocrine and metabolic setting in which it interacts. In normal, postabsorptive man, during euglycemic hyperinsulinemic clamp, GH induced less insulin-mediated suppression of hepatic glucose output.[37] In contrast, when insulin levels were in the normal range, GH had no influence on the hepatic glucose output.[36,38,39] Additionally, glucose turnover was not influenced by GH in postabsorptive subjects with type I diabetes,[40] or in short-term fasting normal subjects,[41] consistent with our findings in trauma patients. This seems to be a common in vivo response to GH administration.

Glucose clearance rate was increased by 31% in the control group C, whereas there was no change in GH-treated group H. This suggests that glucose transport was impaired in the GH-treated group. Our data show a strong correlation between glucose Ra and plasma glucose concentration, suggesting that increased glucose appearance is indeed related to the expansion of the plasma glucose pool, irrespective of whether patients are receiving GH or not. However, the fact that glucose appearance was lower in the GH-treated group adds strength to the contention that clearance was compromised in group H.

GH has both an early insulin-like and a later anti-insulin-like effect on glucose metabolism.[18] The early effect (very shortly after the hormone is given) appears to result from an increase in cellular permeability and is attained only with very large local concentrations of the hormone. The later anti-insulin-like effect may reside in peripheral tissues[36] and also insulinotropic subjects.[18] The inability to overcome the defect in glucose metabolism at high plasma insulin concentrations suggests that a significant postreceptor defect contributes to the observed insulin resistance.[36] IGF-1 has been suggested to have a predominant role in determining glucose disposal,[42] which could offset part of the insulin resistance induced by GH.[43]

The diabetogenic action of rhGH in the rat is due to a combination of inhibition of insulin suppression of hepatic glucose output and inhibition of the uptake and subsequent utilization of glucose in skeletal muscles.[44] Although it is well recognized in normal subjects that insulin stimulates overall in vivo glucose disposal, and that glucose disposal

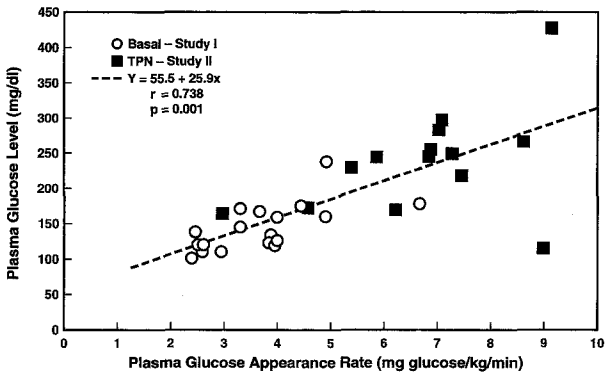

Fig 1. Correlation between plasma glucose level (Y) and plasma glucose appearance (x) in trauma victims (Y = 55.5 + 25.9×; $r = .74$; $P = .001$).

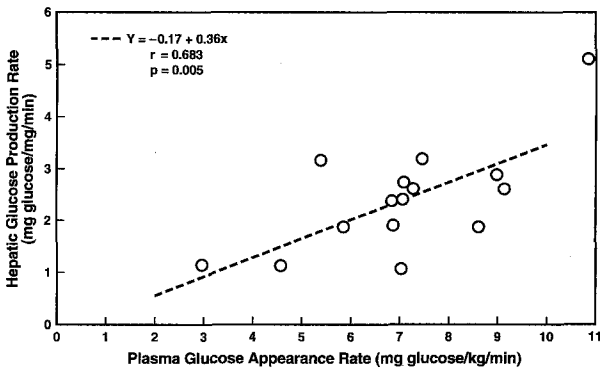

Fig 2. Correlation between endogenous hepatic glucose production rate (Y) and plasma glucose appearance(x) in TPN-fed trauma victims. Y = −0.17 + 0.36x; $r = .68$; $P = .005$. Under basal conditions, glucose production rate is the same as glucose Ra since there is no intake.

increases with elevation in plasma glucose concentration as a result of mass action, glucose transport, instead of intracellular glucose metabolism, is rate-limiting for in vivo glucose uptake over a range of glucose flux rates induced by hyperglycemia and hyperinsulinemia.[45]

Infusion of rhGH in normal man inhibited, not enhanced, glucose uptake by muscle.[18] Similarly GH also inhibited the glucose transport activity in erythrocytes.[46] GLUT-4 is the major glucose transporter isoform expressed in skeletal muscle. A translocation of the GLUT-4 transporter from an intracellular pool to the cell surface was suggested for the similar molecular events underlying IGF-1 and insulin actions on glucose uptake in skeletal muscle.[47] A defect in such translocation of the GLUT-4 transporter may perhaps be responsible for the inhibition of glucose transport activity during rhGH supplementation in trauma patients. These considerations suggest that more investigations are warranted to understand the regulation of cellular glucose uptake inhibition. It is also possible that the resetting of glucose homeostasis secondary to GH supplementation occurs acutely; hence, it may be necessary to perform a similar study in the early postinjection period to uncover the changes in kinetics responsible for the hyperglycemia.

In summary, exogenous adjuvant rhGH to trauma patients is associated with a hyperglycemic response that is not due to enhanced HGP or defective oxidation. This occurs in the presence of significantly increased plasma insulin levels. Impaired glucose transport activity into tissues cells and/or defective nonoxidative glucose disposal may be the cause of hyperglycemia. Frequent monitoring of glucose levels is needed during rhGH adjuvant treatment.

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