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Impact of Stress-Induced Diabetes on Outcomes in Severely Burned Children

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Abstract

Background—Post-burn hyperglycemia leads to graft failure, multiple organ failure, and death. A hyperinsulinemic-euglycemic clamp is used to keep serum glucose between 60-110mg/dL. Because of frequent hypoglycemic episodes, a less stringent sliding scale insulin protocol is used to maintain serum glucose levels between 80-160mg/dL following elevations above 180mg/dL.

Study Design—We randomized pediatric patients with massive burns into two groups – patients receiving sliding scale insulin to lower blood glucose levels (n=145) and those receiving no insulin (n = 98) to determine the differences in morbidity and mortality. Patients 0-18 years old with burns covering 30% of the total body surface area and not randomized to receive anabolic agents were included in this study. Endpoints included glucose levels, infections, resting energy expenditure (REE), lean body mass, bone mineral content (BMC), fat mass, muscle strength, and serum inflammatory cytokines, hormones, and liver enzymes.

Results—Maximal glucose levels occurred within 6 days of burn injury. Blood glucose levels were age dependent with older children requiring more insulin, $p < 0.05$. Daily maximum and daily minimum, but not 6am, glucose levels were significantly different based on treatment group, $p < 0.05$. Insulin significantly increased REE and improved BMC, $p < 0.05$. Each additional wound infection increased incidence of hyperglycemia, $p = 0.004$. There was no mortality in patients not

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receiving insulin, only in patients who received insulin ($p < 0.004$). Muscle strength was increased in patients receiving insulin ($p < 0.05$).

Conclusions—A subset of severely burned children develops burn-induced hyperglycemia. Length of stay was reduced in the no insulin group, and there were no deaths in this group. Administration of insulin positively impacted BMC and muscle strength, but increased REE, hypoglycemic episodes, and mortality. New glucose-lowering strategies may be needed.

Keywords

Burn; insulin; children; bone mineral content; hypermetabolic response; hypercatabolic response; resting energy expenditure

World-wide, more than 10 million people were burned in 2009, with more than 381,000 burn injuries reported in the United States alone.¹ Patients with burns over 30% or more of total body surface area (TBSA) develop a hypermetabolic response, characterized by a catecholamine and corticosteroid surge, catabolism, lipolysis, immune suppression, inflammation, insulin resistance, and hyperglycemia.²⁻³ Inadequate protein synthesis occurring alongside elevated protein breakdown results in the loss of lean body mass (LBM).⁴ The catabolic response is not limited to muscle, as shown by concurrent reductions in fat mass and bone mineral content (BMC).⁵ These changes in body composition lead to alterations in glucose homeostasis.⁶ Hyperglycemia occurs alongside an increased rate of glucose appearance,⁷ reduced glucose extraction from the blood by tissue – especially muscle,⁸ and insulin resistance.⁹⁻¹⁰ In hyperglycemic burn patients, more infections, greater catabolism, significant skin graft loss, and higher mortality are reported.¹¹ Although many of the sequelae related to poor glucose control occur acutely, perturbations in glucose metabolism may persist up to three years following initial burn insult, indicating long term alterations in glucose homeostasis.⁶ Adequate glucose control is necessary for improving patient outcomes. The current standard of care for managing hyperglycemia in severely burned patients is to administer insulin. We have demonstrated that intensive insulin therapy for tight glycemic control can be beneficial in severely burned children, with associated significant improvements in lean body mass, reductions in infections and sepsis, and decreased prevalence of multiple organ failure.¹² Patients receiving intensive insulin therapy did experience significantly more mild and severe hypoglycemic episodes compared to control patients, however.

The implementation of tight glycemic control protocols for critically ill patients has become controversial following Van Den Berghe's report that outcomes in critically ill patients were improved with intensive insulin.¹³ Further studies have shown increased morbidity and mortality in patients receiving intensive insulin.¹⁴⁻¹⁷ As even a single episode of hypoglycemia is independently associated with increased mortality in critically ill patients,¹⁸ the ranges for glycemic control protocols have been expanded recently per the recent American College of Physicians recommendation that glucose levels be maintained between 140 to 200 mg/dL in all ICU patients in order to avoid hypoglycemic episodes.¹⁹

Currently, our standard of practice is to administer insulin when blood glucose levels exceed 180 mg/dL (10 mmol/dL). Insulin is then administered according to a sliding scale. Review

of insulin administration revealed that at least half of pediatric patients with increased glucose never received insulin to decrease post-burn hyperglycemia. We then conducted a study to determine whether insulin, when administered in this manner, had independent effects on glucose levels, body composition, resting energy expenditure (REE), muscle strength, hormones, serum markers, liver function, and mortality, and whether these effects were dose dependent. The data from this study are presented here.

Methods

Patients

Six thousand five hundred seventy three severely burned children were admitted to our institution from 1998 to 2013. Of these, 1,035 patients with burns over 30% of the total body surface area (TBSA) were consented and randomized to studies of various anabolic agents administered acutely and long-term post injury. Two hundred forty three patients were randomized to the control group or to the previously published intensive insulin trial. Of these patients, 98 did not receive insulin while 100 patients received insulin by sliding scale when blood glucose >180mg/dL. Forty-five received intensive insulin therapy reported elsewhere¹² (Figure 1).

Patients enrolled in the study were between 0 and 18 years of age at the time of injury, with burns over 30% of TBSA, admitted within 7 days of burn injury, and required at least one operative intervention. Exclusion criteria included the following: inability to obtain informed consent; presence of preexisting conditions including hepatitis, AIDS, HIV, diabetes, or malignancy within the past 5 years; anoxic brain injury; chemical burns; and due to the severity of the injury, decision not to treat. Insulin was administered according to a sliding scale (Table 1) to reduce glucose levels below 180mg/dL or maintain them between 80-110mg/dL for patients randomized to the intensive insulin cohort. Glucose concentrations were assessed daily while patients were hospitalized during the acute admission period. Sporadic episodes of hyperglycemia episodes were reported but not treated due to delays in clinical team response. This study was part of a large clinical trial (www.clinicaltrials.gov, NCT00675714) evaluating the outcomes of burn survivors after administration of therapeutic agents such as oxandrolone, propranolol, intensive insulin, and the combination of oxandrolone and propranolol. Informed written consent approved by the Institutional Review Board of The University of Texas Medical Branch (Galveston, TX) was obtained from a legal guardian before enrollment in the study. Children older than 7 years assented to participate. This study adhered to ethical standards set forth by the Declaration of Helsinki (1975, revised 1983-2008).

Nutritional Support and Wound Care

At the time of admission, resuscitation was achieved per the Galveston formula (a total of 5,000 ml/m² TBSA burned + 2,000 ml/m² TBSA lactated Ringer's solution given during the first 24 hours). All subjects were taken to the operating suite within 48 hours of admission, and burn wounds were excised followed by application of autograft or allograft. For 3 days patients then remained on bed rest which was followed by daily ambulation until the next

operative intervention. Until the wounds healed, patients underwent sequential staged excision and grafting.

Nutrition was provided by nasoduodenal tube in the form of Vivonex TEN® enteral nutrition (composition: 82% carbohydrate, 15% protein, and 6% fat). Dietary intake was calculated to provide $1,500 \text{ kcal/m}^2 \text{ TBSA} + 1,500 \text{ kcal/m}^2 \text{ TBSA}$ burned during the first week, after which it was modified to provide 1.4 times the resting energy expenditure (REE) (see Indirect Calorimetry below). Throughout hospitalization, caloric replacement remained constant. Nutritional status was monitored by assessing levels of albumin, pre-albumin, and retinol-binding protein.

Patient Demographics and Injury Characteristics

Patient age, sex, and injury characteristics including the size and depth of the burn were recorded at the time of admission. Age-appropriate diagrams were used to determine burn size.²⁰ Conditions such as inhalation injury, sepsis, morbidity, and mortality were also recorded during the acute hospitalization. Inhalation injury was diagnosed by confirmation of the presence of soot, charring, mucosal necrosis, airway edema, or inflammation during fiber optic bronchoscopy, which was performed on all patients 24 hours after admission. Chest scintiphotograms, estimation of extra vascular lung water, and measurements of serum carboxyhemoglobin were also used for diagnostic purposes.

Indirect Calorimetry

All patients underwent weekly REE measurements during their acute hospitalization using the Sensor-Medics Vmax 29 metabolic cart (Yorba Linda, CA). Studies were performed while the patients were asleep between midnight and 5 AM. Inspired and expired gas compositions were sampled and analyzed at 60-second intervals. Values for carbon dioxide production and oxygen volume consumption were recorded when they were at a steady state for 5 min. Measured values were compared with predicted normal values based on the Harris-Benedict equation and body mass index (BMI).²¹⁻²³ Respiratory quotient was also calculated.

Body Composition

Dual energy x-ray absorptiometry (DEXA) was used to measure whole body fat, visceral fat, LBM, BMC, and bone mineral density (BMD) (QDR-4500W Hologic, Waltham, MA). Calibration was performed daily using a spinal phantom in the lateral, anteroposterior, and single beam modes. A tissue bar phantom was used to calibrate individual pixels to accurately identify air, lean mass, bone, or fat.²⁴

Muscle Strength

We assessed muscle strength in a subset of patients. These patients were ages 7 to 17 years. Assessments were done once within 6 months post burn, but always post-discharge. Strength assessments were performed using the Biodex System 3 dynamometer (Biodex Medical Systems) using instructions provided Biodex Medical. We have previously described in detail this methodology.²⁵ Peak torque values corrected for body weight were obtained.

Values were also corrected for gravitational movements of the lower leg and the lever arm. Assessments were done at an angular speed of 150 degrees per second.

Measurement of Hormones, Proteins, and Cytokines

Blood and urine were collected from each patient for analysis of hormone, protein, liver enzyme, and cytokine levels at admission; during the acute stay; at discharge; and at follow-up appointments. Blood was collected in serum-separator collection tubes and centrifuged for 10 minutes at 1,320 rpm. The serum was removed and stored at -80°C until assayed. Serum cortisol, transferrin, α 2-macroglobulin, and apolipoprotein A1 were determined using HPLC and ELISA as previously published.²⁶ The Bio-Plex Human Cytokine 17-Plex panel was used with the Bio-Plex Suspension Array System (Bio-Rad, Hercules, CA) to profile expression of the following seventeen inflammatory mediators: IL-1 β , IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-12, IL-13, IL-17, granulocyte colony-stimulating factor, granulocyte-macrophage colony stimulating factor, interferon- γ , monocyte chemoattractant protein-1, macrophage inflammatory protein-1 β , and tumor necrosis factor. The manufacturer's protocol was followed as previously published.²⁷⁻²⁸

Infections

In wound biopsies, infections were defined as more than 10⁵ colony forming units per gram of tissue, and the pathogen was identified, as previously described.²⁹ Incidence of pneumonias and sepsis were extracted from the medical record. Sepsis was diagnosed according to the American Burn Association consensus definition.³⁰

Statistical Analysis

Data are presented as the mean $\pm$ standard deviation (SD) or standard error of the mean (SEM). The relation between each measured response to treatment group (no insulin or received insulin), number of infections, age, gender, TBSA, time post-burn, and presence of inhalation injury, were modeled using generalized additive mixed models; the models account for nonlinear effects on the response due to time post-burn and age, and also account for repeated measures correlation by blocking on subject. Responses were power or log transformed to approximation of the normal distribution, as appropriate. Negative binomial models were used to model the relationship between hyperglycemia or hypoglycemic and treatment group, infections, age, TBSA, and inhalation injury. Statistical analyses were performed using R statistical software (version 3.0.1).³¹ All statistical tests assumed a 95% level of confidence.

Results

Patient Disposition and Demographics

Demographics and burn injury characteristics differed significantly between the no insulin and insulin groups (Table 2). Patients in the insulin group were older ($p < 0.001$), with larger burns ($p < 0.001$), and more inhalation injuries ($p < 0.001$). In the insulin group, the length of hospital stay was significantly greater ($p < 0.001$). All patients in the no insulin group survived. Mortality was 12% in the insulin group, $p = 0.001$. Although a significant difference in the number of surgeries between groups was noted, inclusion of additional

factors such as age, TBSA, and infections demonstrated that the number of surgeries was not related to the administration of insulin, but rather to the burn size and number of infections sustained.

Glucose Metabolism and Insulin Resistance

Patients who did not require insulin maintained significantly lower daily average blood glucose concentrations throughout hospitalization, $p<0.001$ (Figure 2a). A significant finding in this study was that hyperglycemia in severely burned children is age-related (Figure 2b). Younger children were less likely to experience hyperglycemic episodes, while older children with larger burns required larger doses of insulin more frequently ($p<0.0001$, Figure 2c). There was a 9% increase in hyperglycemic episodes for each year increase in age ($p<0.0001$). Similarly, larger burns were associated with hyperglycemia; each percent increase in TBSA was associated with a 3% increase in hyperglycemic episodes ($p<0.0001$). Insulin administration was associated with a 35% reduction in hyperglycemic episodes ($p=0.0015$).

The average daily dose administered to those requiring insulin was 8.3 ± 11.6 IU (average $\pm$ standard error). During the entire hospitalization period, the average cumulative amount of insulin administered to the patients was 1570 ± 263 IU (average $\pm$ standard error). Patients received insulin administration for 15 ± 1.3 days (average $\pm$ standard error). Younger patients were less likely to receive insulin based on their blood glucose levels. Poor glucose control was seen in those patients requiring more than 200IU of insulin in a single day, suggesting that insulin administration beyond 200IU may not be effective (Figure 2d).

Insulin administration was associated with significantly more hypoglycemic episodes. Eight patients (8%) in the no insulin group experienced a total of 10 mild hypoglycemic episodes (defined as blood sugar 40-59 mg/dL). Fifty two episodes of mild hypoglycemia were reported in 63 patients (43%, $p<0.0001$) in the insulin group. Similar results were found for severe hypoglycemic episodes when glucose levels dropped below 40mg/dL. Two patients (2%) in the no insulin group experienced severe hypoglycemia three times. In the no insulin group, 20 patients (14%) experienced 42 severe hypoglycemic events, $p<0.001$.

Indirect Calorimetry

Insulin was associated with significantly increased percent of predicted REE by 9.4% ($P=0.009$), indicating that hypermetabolism was significantly increased. Increases in both the REE and the percent of predicted REE were proportional to the amount of insulin administered within the prior 24 hours as well as the cumulative amount administered. (Figure 3) There was no difference in respiratory quotient between the two groups.

Body Composition

Insulin-treated patients had a significantly higher BMC, lower percentage of whole body and visceral fat mass, and increased lean mass than their no insulin counterparts, ($P<0.001$) (Table 3). These differences were apparent during the first month post injury and most persisted throughout the first year following injury. Significance was lost for visceral adipose tissue at time points greater than 1 month post burn. When adjustments were made

for time, age, and insulin administration utilizing the generalized additive modeling technique, lumbar BMC alone remained significantly different (Figure 4).

Muscle Strength

Muscle strength, expressed as peak torque/kg body weight, was significantly greater in the group of patients receiving insulin relative to the group of patients that did not receive insulin (Figure 5, $p < 0.05$). The group of patients that received insulin produced an average of 97.8 Newton-meters of peak torque per kilogram of body weight versus 80.2 Newton-meters of peak torque by kilogram of body weight produced by the patients not receiving insulin.

Hormones, Proteins, and Cytokines

Three sets of analyses were performed to determine whether serum analyte concentrations varied based on treatment group (ever received insulin), and whether a relationship existed between the serum concentrations and the administration of insulin within the prior 24 hours or the total amount of insulin administered during hospital stay (Table 4-5). Transferrin, cortisol, α 2-macroglobulin, and apolipoprotein A1 were all significantly reduced in patients receiving insulin for the duration of hospitalization (Figure 6a-d). Proinflammatory cytokines TNF, MIP-1 β (CCL4), and IL-1 β are increased with insulin administration for the duration of the study (Figure 6e,f,g). Anti-inflammatory cytokine IL-10 is also elevated in the insulin treatment group for the entire 30 day period (Figure 6h). A summary of the hormones, proteins, and cytokines that are influenced by the 24 hour or cumulative amounts of insulin administered are presented in Tables 4 and 5.

Infections

Each infection was associated with a 6% increase in hyperglycemic episodes ($p=0.004$). There were no differences in incidence of sepsis or pneumonias between the two groups.

Mortality

Mortality was significantly higher in the insulin group ($p<0.001$). All patients in the no insulin group survived, while 17 patients given insulin did not survive. Insulin administration and TBSA were related to mortality ($p = 0.023$). The hazard ratio was approximately 1.92, meaning that patients receiving insulin died at 1.92 times the rate of those patients not receiving insulin during the study period.

Discussion

Stress induced diabetes frequently occurs following a severe burn injury.^{6, 9-10, 32-33} Hyperglycemia commonly occurs early during the acute post-burn phase. In burned patients, hyperglycemia is associated with morbidities such as increased infections, pneumonias, septic episodes, and hypermetabolic and catabolic responses.^{7, 11, 34} In order to reduce these sequelae, the most frequent therapeutic intervention has been the administration of insulin.

In critically ill patients administered insulin to maintain glucose levels below 110mg/dL, Van den Berghe et al reported decreases in mortality, infections, and sepsis.¹³ Tight glycemic control has no effect, however, on infections, mortality, length of stay, or multi-organ failure incidence in pediatric cardiac surgery patients.³⁵ In burn patients, the effects of insulin have been extensively studied. More recently, we have shown that insulin resistance is persistent in severely burned children, lasting for at least three years.³²

In order to evaluate the impact of insulin on outcomes following a severe burn injury, we studied only patients who were not randomized to receive other anabolic or anti-catabolic therapeutics. We evaluated only those patients randomized to control or to insulin. Overall, we found that serum glucoses were maintained well. In this analysis, we also found a significant relationship between age and the development of hyperglycemia. Younger children with smaller burns were less likely to require insulin to reduce high blood glucose compared to older children with larger burns. Patients receiving insulin had a higher mortality (12%), while there were no deaths in the. We wondered whether this was related to the dose of insulin, to hyperglycemia, or to hypoglycemic events. Rest energy expenditure was higher in patients receiving insulin, indicating that patients receiving insulin were more hypermetabolic. Episodes of hyperglycemia or hypoglycemia, or infections, were not related to this increase in metabolism.

Previously we have shown in a randomized, controlled trial that intensive insulin therapy, to maintain blood glucose between 80 and 110 mg/dL caused significant improvements in lean body mass, bone mineral density, and reductions in inflammation, infections, fat metabolism, and acute phase proteins.¹² Hypoglycemia was greatest in the intensive insulin cohort. These patients experienced higher rates of both mild (24% of control patients versus 43% of intensive insulin patients) and severe (9% versus 26%). Significant improvements in insulin sensitivity were also seen in the patients receiving intensive insulin therapy. Despite the clear benefit of administering intensive insulin to these severely burned patients, the impact of hypoglycemic incidents should not be underestimated. In critically ill patients, a single episode of hypoglycemia has been associated with increased mortality.¹⁸ We therefore determined the impact of hypoglycemia on burn patient outcomes.

The effects of hypoglycemic episodes on post-burn outcomes were evaluated. In patients who had one or more hypoglycemic events, we found significant perturbations of the metabolic and inflammatory responses, more septic episodes, greater prevalence of multiple organ failure, and more deaths. These studies supported the notion that mortality in critically ill children could be reduced by normalizing glucose.³⁶ Adequate glucose control is essential for ensuring reductions in morbidity and mortality.³⁷

Determination of the ideal glucose range for severely burned children was of paramount importance. In 287 patients, the effect of good versus poor glucose control was compared. Hyperglycemia was shown to be a strong predictor of adverse outcomes.³⁸ Reductions in morbidity and mortality were found when the daily average glucose was maintained below 140 mg/dL. When glucoses were maintained below 130mg/dL, the hypermetabolic response was reduced as well. Significant decrements in infections and sepsis, along with subsequent mortality, accompanied reduction of blood glucose levels in severely burned children. These

studies showed the necessity of controlling blood glucose levels, but raised the question – what is the effect of insulin itself following a severe burn injury.

One of the most surprising findings of our study was the significant increase in REE with insulin treatment. Energy expenditure is significantly elevated following burn injury.^{3, 26} Previously we had shown that intensive insulin administration had no effect on resting energy expenditure, therefore concluding that intensive insulin therapy did not impact hypermetabolism.¹² In this study, however, we found a profound increase in REE in patients receiving insulin with no increase in the respiratory quotient, bringing the mechanism of insulin action into question. Over the past several decades, investigators have tried to determine whether insulin acts as an anabolic or catabolic agent. Studies of normal, prediabetic, and diabetic individuals have shown that energy expenditure is related to metabolic abnormalities. Menendez et al undertook to determine what the true effect of insulin was on resting energy expenditure in order to address controversial findings within the field.³⁹ In a comparison of 4U/kg to 8U/kg of fast acting insulin in an animal model, no effects on REE were found at the lower insulin concentration despite a 30% reduction in blood glucose concentrations. At the higher dose of insulin, however, a significant increase in REE was found along with a 68% decrease in blood glucose concentrations. They further found that the respiratory quotient was increased with administration of the higher dose of insulin, and that this was linked to enhanced thermogenesis in animals utilizing carbohydrates as the main source of energy. The findings in humans have remained discordant regarding the relationship of insulin to energy expenditure as well. In a study of 560 Pima Indians, metabolic rates were found to be higher in those patients with diabetes and in those who had impaired glucose tolerance.⁴⁰ These differences were credited to the ontogeny of metabolic abnormalities occurring as the diabetic state develops.⁴⁰ The increase in energy expenditure in diabetic or insulin resistant subjects has been postulated to be related to the progression of the disease, and occur early during development of diabetes, preceding hyperglycemia. It is thought that energy expenditure increases are driven by accelerated protein turnover, gluconeogenesis, and futile substrate cycling, among other factors. Metabolic abnormalities have been credited with energy expenditure changes, in a manner independent from body composition changes. Individuals with impaired glucose tolerance had higher sedentary metabolic rates than those with normal glucose tolerance, but lower than those with diabetes. More recently, Ikeda et al examined the relationship between insulin (endogenous secretion and exogenous administration) and basal energy expenditure in 58 Japanese patients with type 2 diabetes; despite good glycemic control, insulin levels were negatively correlated with energy expenditure, such that higher insulin levels correlated with reduced basal energy expenditure. The differences between the results of these studies may reflect variation between the patient populations being studied. Genetic factors relating to ethnicity exist for development of diabetes. Additionally, the differences in metabolic state may contribute to the effects on energy expenditure that are related to the administration of insulin. Increases in REE with increased insulin administration are thought to be related to the transition to utilizing fatty acids as the precursors for gluconeogenesis, providing another area for further elucidation in our patients in future studies.

Additional aspects of our study provide new avenues for study in severely burned children. The significant decrease in cortisol in patients administered glucose, coinciding with a

decrease in blood sugar but a concomitant increase in inflammatory markers may indicate an effect on the immune system. Despite an increase in inflammatory markers, we did not find evidence of an effect of insulin on incidence of infection. Our work also demonstrated a significant increase in bone mineral content with insulin administration. The effect of insulin on bone mineral content and on bone strength is difficult to determine as the insulin resistance status of the patient plays a large role in whether insulin has an effect or not.⁴¹ It has proven quite difficult to separate the direct and indirect effects of insulin on bone.

Our current findings are notable in that a relationship between the incidence of hyperglycemia and increasing age and burn size was demonstrated for the first time. The significant increase in risk of hyperglycemia occurs with each year of age or percent of TBSA burned. In patients receiving large cumulative doses of insulin, the efficacy of insulin on decreasing blood glucose levels seems to be lost, indicating that incorporation of additional glucose-lowering strategies may be of benefit. Insulin can be safely administered although continuous monitoring of blood glucose concentrations is necessary. Patients in the no insulin group rarely became hypoglycemic. High percentages of both mild and severe hypoglycemic events were found in patients receiving insulin, demonstrating the need for heightened monitoring of blood glucose levels in patients receiving insulin.

In conclusion, our findings provide strong evidence that insulin administration may be a dual edged sword in severely burned patients. While blood sugar levels need to be maintained below 180 mg/dL, if not 130mg/dL,³⁸ the potential for hypoglycemia needs to be kept in mind. We found improvements in bone mineral content with insulin administration. The increased mortality and risk of earlier death with insulin administration have not been found previously and are likely due to the cause of insulin resistance rather than due to insulin itself. In burned patients, greater hypermetabolism with insulin treatment needs to be studied more in order to determine whether this is a dose-dependent phenomenon. Exploration of other anti-glucose strategies for use in preventing hyperglycemia may enable even greater improvements in patient outcomes than we have seen to date.

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Abbreviations

BMC	bone mineral content
BMD	bone mineral density

DEXA	dual energy x-ray absorptiometry
ICU	intensive care unit
IU	international units
LBM	Lean body mass
REE	resting energy expenditure
SD	standard deviation
SEM	standard error of the mean
TBSA	total body surface area

Figure 1.
Consort diagram.

2a

2c

2d

Figure 2.

Effect of insulin and age on blood glucose levels. Data are represented as the GAM-derived value with the 95% confidence interval denoted as grey bars. A) Patients receiving glucose had lower daily maximum glucose. B) Age influenced blood glucose concentrations. C). Older children require the administration of more insulin when compared to younger children. D) Insulin administration of >200 IU is associated with decreased glucose control.

Figure 3. Change in resting energy expenditure with insulin administration. Data are represented as the GAM-derived values with the 95% confidence interval denoted as grey bars.

Figure 4.

Change in lumbar bone mineral content. Data are represented as the GAM-derived values with the 95% confidence interval denoted as grey bars.

Figure 5. Effect of insulin on muscle strength at the time of discharge. Data are expressed as mean $\pm$ SEM. * $P < 0.05$ vs. control.

6a

6b

6c

6d

Figure 6.

Effect of insulin on serum levels of (A) transferrin, (B) cortisol, (C) α_2 -macroglobulin, (D) apolipoprotein A1, (E) tumor necrosis factor α , (F) macrophage inhibitory protein 1 β , (G) interleukin 1 β , and (H) interleukin 10. Data are expressed as GAM derived values with the 95% confidence interval denoted as grey bars.

Table 1

Insulin sliding scale. Serum glucose checked hourly with bedside glucometer (GLU STAT strip, Nova Biomedical, Waltham, MA).

Glucose (mg/dL)	180-219	220-259	260-299	300
Insulin dose (μ /kg)	0.04	0.06	0.08	1.00

Table 2
Patient Demographics

Variable	No Insulin (n=98)	Insulin (n=145)	P value
Age (years)	5±4	10±5	<0.0012
Male, No. (%)	57 (58%)	85 (59%)	0.92
% TBSA Burned	51±13	60±17	<0.001
% TBSA 3 rd Degree Burned	33±21	48±25	<0.001
Burn mechanism, No. (%)			<0.001
Flame	57 (58)	106 (73)	
Scald	37 (38)	20 (14)	
Electrical	3 (3)	19 (13)	
Contact	1 (1)	0 (0)	
Burn to admission (days)	3±2	2±2	<0.001
Length of Stay in ICU (days)	21±11	33±28	<0.001
Length of Stay per % Burn	0.4±0.2	0.6±0.4	<0.001
Mortality, No. (%)	0 (0)	17 (12%)	0.001

Data are expressed as the mean±SD. TBSA: total body surface area.

Table 3
Insulin administration significantly improves body composition assessed by dual energy x-ray absorptiometry up to 12 months post-burn injury

Parameter/BSA	No Insulin(N=98)	Insulin(N=145)	P Value
1 Month			
WB BMC ($\times 10^{-4}$ g/cm ²)	750 $\pm$ 60	1040 $\pm$ 30	<0.001
WB BMD ($\times 10^{-4}$ g/cm ⁴)	0.82 $\pm$ 0.02	0.77 $\pm$ 0.01	0.11
WB Fat ($\times 10^{-4}$ g/cm ²)	7970 $\pm$ 370	7780 $\pm$ 250	0.12
WB %Fat ($\times 10^{-4}$ %/cm ²)	55 $\pm$ 6	26 $\pm$ 1	<0.001
WB Mass ($\times 10^{-4}$ g/cm ²)	25500 $\pm$ 880	30000 $\pm$ 540	<0.001
WB Lean ($\times 10^{-4}$ g/cm ²)	16750 $\pm$ 860	21160 $\pm$ 420	<0.001
LS BMC ($\times 10^{-4}$ g/cm ²)	23 $\pm$ 2	26 $\pm$ 1	0.03
LS BMD ($\times 10^{-4}$ g/cm ⁴)	0.80 $\pm$ 0.04	0.67 $\pm$ 0.01	0.002
VAT Mass ($\times 10^{-4}$ g/cm ²)	220 $\pm$ 30	150 $\pm$ 8	0.02
VAT Volume ($\times 10^{-4}$ cm ⁴)	235 $\pm$ 30	160 $\pm$ 8	0.02
VAT Area (cm ⁴)	45 $\pm$ 6	32 $\pm$ 2	0.02
3 Months			
WB BMC	830 $\pm$ 50	1020 $\pm$ 20	<0.001
WB BMD	0.80 $\pm$ 0.02	0.75 $\pm$ 0.01	0.08
WB Fat	8490 $\pm$ 470	8490 $\pm$ 240	0.90
WB %Fat	45 $\pm$ 5	27 $\pm$ 1	<0.001
WB Mass	27400 $\pm$ 1040	31000 $\pm$ 480	0.007
WB Lean	18100 $\pm$ 920	21300 $\pm$ 380	<0.001
LS BMC	25 $\pm$ 2	27 $\pm$ 1	0.37
LS BMD	0.76 $\pm$ 0.04	0.64 $\pm$ 0.01	0.02
VAT Mass	180 $\pm$ 20	190 $\pm$ 8	0.71
VAT Volume	190 $\pm$ 20	210 $\pm$ 9	0.70
VAT Area	40 $\pm$ 4	40 $\pm$ 2	0.72
12 Months			
WB BMC	780 $\pm$ 30	950 $\pm$ 10	<0.001
WB BMD	0.80 $\pm$ 0.02	0.70 $\pm$ 0.01	<0.001
WB Fat	7800 $\pm$ 310	8330 $\pm$ 210	0.71
WB %Fat	41 $\pm$ 3	23 $\pm$ 1	<0.001
WB Mass	26000 $\pm$ 640	32000 $\pm$ 400	<0.001
WB Lean	17500 $\pm$ 490	22500 $\pm$ 280	<0.001
LS BMC	23 $\pm$ 1	27 $\pm$ 1	0.08
LS BMD	0.75 $\pm$ 0.03	0.58 $\pm$ 0.01	<0.001
VAT Mass	180 $\pm$ 12	190 $\pm$ 6	0.77
VAT Volume	200 $\pm$ 13	200 $\pm$ 6	0.77

Parameter/BSA	No Insulin(N=98)	Insulin(N=145)	P Value
VAT Area	38 ± 2	39 ± 1	0.78

Data presented as means ± sem. **BMC**: Bone mineral content; **BMD**: Bone mineral density; **BSA**: Body surface area; **LS**: Lumbar Spine; **VAT**: Visceral adipose tissue; **WB**: Whole Body.

Table 4

Abundance of serum proteins is altered with insulin.

analyte	different by treatment group	relationship to insulin administered within prior 24 hrs	relationship to total insulin administered
Transferrin	0.001	0.2	<0.001
Apolipoprotein A1	0.002	0.006	<0.001
a2 macroglobulin	0.013	<0.001	<0.001
T3 uptake	0.049	0.001	0.024
IGF1/BP3	0.004	0.48	0.091
cortisol	0.026	0.35	0.9
insulin	0.32	<0.001	0.026
haptoglobin	0.719	0.023	0.033
Apolipoprotein B	0.953	<0.001	<0.001
free fatty acids	0.44	0.005	0.612
retinol binding protein	0.499	0.835	0.0018
a1-acid glycoprotein	0.593	0.306	0.034
prealbumin	N	0.46	<0.001
complement C3	0.786	0.27	<0.001
Testosterone	0.92	0.527	0.27
IGF-1	0.151	0.6087	0.368
total T4	0.32	0.209	0.241
Free T4	0.628	0.004	0.748
parathyroid hormone	0.77	0.24	0.089
growth hormone	0.78	0.672	0.15
triglycerides	0.8	0.15	0.357
osteocalcin	0.843	0.519	0.347
estradiol	0.914	0.44	0.929
Progesterone	0.96	0.22	0.125

Table 5
Abundance of Serum Cytokines is Altered with Insulin

analyte	different by treatment group	relationship to insulin administered within prior 24 hrs	relationship to total insulin administered
MIP-1b	0.003	0.003	0.057
IL-1b	0.014	0.014	0.083
TNF-a	0.025	0.024	0.901
IL-10	0.033	0.032	0.007
IL-4	0.715	0.715	0.038
MCP-1	0.923	0.923	<0.001
IL-8	0.063	0.063	<0.001
G-CSF	0.114	0.114	<0.001
IL-2	0.224	0.224	0.012
IL-6	0.26	0.26	<0.001
IL-7	0.081	0.081	0.56
IL-12p20	0.261	0.261	0.47
GM-CSF	0.275	0.275	0.21
IL-13	0.293	0.293	0.12
IL-5	0.053	0.053	0.71
IFN-g	0.448	0.448	0.004
IL-17	0.458	0.457	0.96