Intensive Insulin Therapy in Severely Burned Pediatric Patients

A Prospective Randomized Trial

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***Rationale*: Hyperglycemia and insulin resistance have been shown to increase morbidity and mortality in severely burned patients, and glycemic control appears essential to improve clinical outcomes. However, to date no prospective randomized study exists that determines whether intensive insulin therapy is associated with improved post-burn morbidity and mortality.**

***Objectives*: To determine whether intensive insulin therapy is associated with improved post-burn morbidity.**

***Methods*: A total of 239 severely burned pediatric patients with burns over greater than 30% of their total body surface area were randomized (block randomization 1:3) to intensive insulin treatment (n = 60) or control (n = 179).**

***Measurements and Main Results*: Demographics, clinical outcomes, sepsis, glucose metabolism, organ function, and inflammatory, acute-phase, and hypermetabolic responses were determined. Demographics were similar in both groups. Intensive insulin treatment significantly decreased the incidence of infections and sepsis compared with controls ($P < 0.05$). Furthermore, intensive insulin therapy improved organ function as indicated by improved serum markers, DENVER2 scores, and ultrasound ($P < 0.05$). Intensive insulin therapy alleviated post-burn insulin resistance and the vast catabolic response of the body ($P < 0.05$). Intensive insulin treatment dampened inflammatory and acute-phase responses by deceasing IL-6 and acute-phase proteins compared with controls ($P < 0.05$). Mortality was 4% in the intensive insulin therapy group and 11% in the control group ($P = 0.14$).**

***Conclusions*: In this prospective randomized clinical trial, we showed that intensive insulin therapy improves post-burn morbidity.**

Clinical trial registered with www.clinicaltrials.gov (NCT00673309).

Keywords: insulin; burn; pediatric; sepsis; morbidity

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Intensive insulin was shown to be beneficial in critically ill patients. Currently, it is unknown whether intensive insulin therapy is associated with beneficial clinical outcomes.

What This Study Adds to the Field

Based on our study, we now propose that intensive insulin therapy should be used in severely burned patients.

The clinical implications of tight euglycemic control as published by van den Berghe and colleagues (1) significantly and rapidly changed intensive care unit (ICU) practice. Van den Berghe and colleagues (2) showed that insulin administered to maintain glucose at levels below 110 mg/dl decreased mortality, the incidence of infections, sepsis, and sepsis-associated multiorgan failure in surgical patients, reduced kidney injury, and accelerated weaning from mechanical ventilation and discharge from the ICU in medical patients. In several follow-up studies, the authors confirmed the advantageous effects of tight euglycemic control. The authors showed recently that tight euglycemic control improved mortality in pediatric ICU patients (3). Insulin given during the acute phase not only improved acute hospital outcomes but also improved long-term rehabilitation of critically ill patients over a period of 1 year (4, 5), indicating the advantage of insulin therapy. However, all studies presented by the Leuven group were unicenter trials, so various unicenter and multicenter studies followed the Leuven trials to determine whether tight euglycemic control improves outcomes in a different setting.

The results of these trials were mixed, with some showing benefits with the use of euglycemic control (6, 7). Other studies, however, failed to show improved outcomes. In contrast, some of these studies even demonstrated detrimental effects associated with tight euglycemic control and a dramatic increase in the incidence of hypoglycemia (8). Substantial discussion thus arose as to whether tight euglycemic control is beneficial. To end this discussion, a large multicenter trial was initiated: the NICE SUGAR trial. This trial enrolled more than 6,000 patients; it failed to show a beneficial outcome for critically ill patients with intensive insulin therapy (9) and delineated the risks and problems associated with this therapy. Therefore, many ICUs have now changed their tight euglycemic protocols to be less strict. Despite the aforementioned studies, none of the trials investigated whether tight euglycemic control is beneficial in severely thermally injured patients. Hyperglycemia is a hallmark of burned patients (10). During the early post-burn phases, hyperglycemia is due to an increased rate of glucose appearance along with impaired tissue extraction of glucose, leading to an increase of glucose and lactate (11, 12). The clinical relevance of hyperglycemia after a severe burn was shown in several studies in which the authors demonstrated that burn patients with poor glucose control had a significantly higher incidence of bacteremia/fungemia and mortality (13–15), indicating that hyperglycemia represents a significant clinical problem in burn patients. Currently, no prospective randomized controlled trial exists that

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examines whether tight euglycemic control is beneficial in severely burned patients. We therefore conducted this prospective randomized unicenter trial in severely burned pediatric patients and hypothesized that intensive insulin therapy is associated with improved burn-induced hypermetabolism, inflammation, and morbidity.

METHODS

Thermally injured children with burns over greater than 30% of their total body surface area (TBSA) between the years of 2000 and 2009, and who required at least one surgical intervention, were randomized to control or to intensive insulin treatment. Patients were only enrolled if subjects or their parents/legal guardians consented to the protocol used in this article. This protocol was institutional review board approved. Control patients were targeted to maintain glucose levels 140 to 180 mg/dl, whereas intensive insulin–treated patients received insulin to maintain glucose levels between 80 and 110 mg/dl. The detailed orders are shown in Figure E1 in the online supplement.

Inclusion criteria were as follows: patient is between 0 and 18 years of age and the family agrees to the study protocol; greater than 30% TBSA burn; at least one surgical intervention is necessary.

Exclusion criteria were: death upon admission; decision not to treat due to burn injury severity; presence of anoxic brain injury that is not expected to result in complete recovery; known history of AIDS, HIV, or hepatitis B–E; history of cancer within 5 years or malignancy currently under treatment; previous bilateral lower extremity amputations; inability to obtain informed consent; previous existing renal failure, liver disease, or hepatic dysfunction; preexisting type I diabetes mellitus; pregnancy.

If needed, patients were resuscitated according to the Galveston formula with 5,000 ml/m^2 TBSA burned + 2,000 ml/m^2 TBSA lactated Ringer solution given in increments over the first 24 hours. Within 48 hours of admission, all patients underwent total burn wound excision and the wounds were covered with autografts. Any remaining open areas were covered with cadaver skin/allografts. After the first operative procedure, patients were taken back to the operating room when donor sites were healed. This procedure was repeated until all open wound areas were covered with autologous skin. All patients underwent the same nutritional treatment according to a standardized protocol. The intake was calculated as 1.4 times of the predicted resting energy expenditure (REE), or 1,500 kcal/m^2 body surface and 1,500 kcal/m^2 area burned, as previously published (16–18). The nutritional route of choice in our patient population was enteral nutrition via a duodenal (Dobbhoff) or nasogastric tube.

Patient demographics (age, date of burn and admission, sex, burn size, and depth of burn) and concomitant injuries, such as inhalation injury, sepsis, morbidity, and mortality, were recorded. Inhalation injury was diagnosed by bronchoscopy along with a consistent history. Wound infection was defined as greater than 10^5 colony-forming units per gram tissue in a wound biopsy with the identification of a pathogen. Repeated counts of the same bacteria in the same location were counted as the same infection. Sepsis and infection were defined by the American Burn Association and Society of Critical Care Medicine guidelines (16, 19, 20). Multiorgan failure was defined as previously published (10). We further determined the time between operations as a measure for wound healing/reepithelization.

Glucose Metabolism

Study protocols for intensive insulin and controls are given in Figure E1. During acute hospitalization, we determined daily average blood glucose levels, daily 6:00 A.M. blood glucose levels, daily maximum glucose levels, and daily minimum glucose levels. The glucose concentration was determined in our clinical laboratory by the hexokinase assay (Siemens Healthcare Diagnostics, West Sacramento, CA). We further determined insulin requirements during acute hospitalization. At discharge, we determined glucose tolerance. Each patient had oral glucose tolerance tests (OGTTs) performed at hospital discharge or at 3 months post burn, whichever was first. Studies were performed after an overnight fast. Standard procedures consisted of a baseline blood draw for the measurement of glucose, C-peptide, and insulin levels (fasting values), followed by the glucose load (adjusted for weight by the formula: Weight $\times$ 1.75 $\times$ 2.96 ml of Glucola [up to 300 ml, one full bottle]), and subsequent measurements of serum glucose and insulin at 30, 60, 90, and 120 minutes after the glucose load. Serum glucose concentrations were quantified using a hexokinase assay on a Dimension Instrument (Dade Behring/Siemens Healthcare Diagnostics, MD). Serum insulin and C-peptide concentrations were determined by common ELISA techniques (Diagnostic Systems Laboratories/Beckmann-Coulter, Webster, TX). Total glucose and insulin secretion were assessed from the area under the 120-minute curve of glucose ($AUC_{glucose}$) and insulin ($AUC_{insulin}$) concentration using the trapezoid rule (21).

Insulin sensitivity scores. Four indices for the assessment of insulin resistance were calculated for the above-mentioned time periods using glucose and insulin values during OGTT: (*1*) the homeostasis model assessment of insulin resistance index (HOMA-IR; fasting glucose [mmol/L] $\times$ fasting insulin [mU/L]/22.5, according to Matthews and colleagues [22]); (*2*) the Quantitative Insulin Sensitivity Check Index (QUICKI; 1/[log fasting insulin (μU/ml) + log fasting glucose (mg/dl)]) according to Uwaifo and colleagues (23); (*3*) the Matsuda Insulin Sensitivity Index (Matsuda ISI; $10{,}000/\sqrt{G_0 \times I_0 \times G_{mean} \times I_{mean}}$, where G and I represent the plasma glucose [mg/dl] and insulin [mU/l] concentrations, respectively, expressing fasting [0] and mean OGTT concentrations, as described by Matsuda and DeFronzo [24]); and (*4*) the insulinogenic index (IGI; δ insulin[0–30 min] [mU/l]/δ glucose [0–30 min] [mg/dl]) according to Yeckel and colleagues (25).

Hypermetabolic Response

Body composition. Height and body weight were determined clinically 5 days after admission and at discharge. This is standard at our hospital because we define the weight and height 5 days post admission as dry weight and baseline height. Total lean body mass, fat, bone mineral density, and bone mineral content were measured by dual energy X-ray absorptiometry. A Hologic model QDR-4500W DEXA (Hologic Inc, Waltham, MA) was used to determine body composition as previously published (26–29).

Indirect calorimetry. All patients underwent resting energy expenditure (REE) measurements within 1 week after hospital admission and weekly thereafter during their acute hospitalization. All measurements of REE were performed between midnight and 5:00 A.M. while the patients were asleep and receiving continuous feeding. REE was measured using a Sensor-Medics Vmax 29 metabolic cart (Yorba Linda, CA) as previously published (18). REE was calculated from the oxygen consumption and carbon dioxide production using equations described by Mlcak and colleagues (18). The measured values were compared with predicted normal values, based on the Harris-Benedict equation, and to body mass index (18).

Cytokines, hormones, and proteins. Blood was collected from each burn patient at admission, preoperatively, and 5 days postoperatively for 4 weeks, and was used for the analysis of serum hormone, protein, and cytokines, and urine hormones. Blood was drawn in a serum-separator collection tube and centrifuged for 10 minutes at 1,320 rpm; the serum was removed and stored at -70°C until assayed. Serum hormones and acute-phase proteins were determined using high-pressure liquid chromatography, nephelometry (BNII, Plasma Protein Analyzer; Siemens Healthcare Diagnostics, West Sacramento, CA), and ELISA techniques (10). 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 seventeen inflammatory mediators (10, 30).

Organ function. Serum proteins (e.g., creatinine, bilirubin, and total protein) were determined using standard nephelometry to evaluate organ function (10).

Liver and cardiac changes. Liver ultrasound measurements in this study were made with the HP Sonos 100 CF echocardiogram (Hewlett Packard Imaging Systems, Andover, MA). The liver was scanned using an Eskoline B-scanner and liver size/volume were calculated using a formula as previously published (28, 29, 31, 32). The actual size was then compared with the predicted size.

M-Mode echocardiograms were completed as follows: at the time of the study, none of the patients presented with or previously suffered from other concomitant diseases affecting cardiac function, such as diabetes mellitus, coronary artery disease, long-standing hypertension, or hyperthyroidism. Study variables included: resting cardiac output, cardiac

index, stroke volume, resting heart rate, and left ventricular ejection fraction. Stroke volume and cardiac output were adjusted for body surface area and expressed as indexes. All cardiac ultrasound measurements were made with the Sonosite Titan echocardiogram with a 3.5-MHz transducer. Recordings were performed with the subjects in a supine position and breathing freely. M-Mode tracings were obtained at the level of the tips of the mitral leaflets in the parasternal long-axis position, and measurements were performed according to the American Society of Echocardiography recommendations. Left ventricular volumes determined at end diastole and end systole were used to calculate ejection fraction, stroke volume, cardiac output, and cardiac index. Three measurements were performed and averaged for data analysis (28, 29).

Ethics and Statistics

The study was reviewed and approved by the Institutional Review Board of the University Texas Medical Branch, Galveston, Texas. Prior to the study, each subject, parent, or child's legal guardian had to sign a written informed consent form. Analysis of variance with *post hoc* Bonferroni correction, paired and unpaired Student *t* test, chi-square analysis, and Mann-Whitney tests were used as appropriate. Data are expressed as means ± SD or SEM, as appropriate. Significance was accepted at $P < 0.05$.

Role of the Funding Source

The funding organizations played no role in the design and conduct of the study, in the collection, management, analysis, and interpretation of the data, or in the preparation, review, or approval of the manuscript.

RESULTS

Demographics

A total of 239 patients were included in this study. Randomization, exclusion reasons, and inclusion numbers are shown in Figure 1. Table 1 shows the demographic data for the two study groups. Patients treated with intensive insulin were significantly older and had a larger area of third-degree burn compared with control patients (Table 1). The incidence of inhalation injury, time from burn to admission, number of operations, and time between operations were comparable in both groups (Table 1). Patients with intensive insulin treatment had a significantly decreased incidence of infections and sepsis ($P < 0.05$) (Table 1). Eleven percent of the patients died in the control group, and 4% of patients in the intensive insulin group died ($P = 0.14$). The Kaplan-Meier survival curve is depicted in Figure E2.

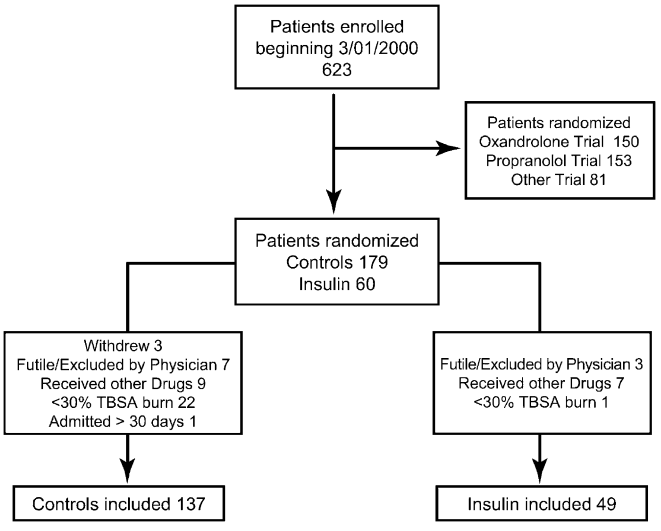

Figure 1. Randomization, exclusion reasons, and inclusion numbers. TBSA = total body surface area.

TABLE 1. PATIENT DEMOGRAPHICS

	Control ($N = 137$)	Insulin ($N = 49$)	*P* Value
Sex, M/F	79/58	32/17	
Ethnicity			
African American	6	5	
Caucasian	12	4	
Hispanic	114	40	
Other	5	0	
Age, yr	7.7 ± 5.2	10.8 ± 5.4	<0.05
Inhalation injury, n (%)	50 (37)	22 (45)	
Burn type			
Flame	114 (83)	39 (80)	
Scald	18 (13)	5 (10)	
Other	5 (3.6)	5 (10.2)	
TBSA burn, %	58 ± 16	63 ± 16	
TBSA third, %	44 ± 25	52 ± 23	<0.05
Burn to admission, d	11 ± 32	8 ± 26	
No. of ORs	3.8 ± 3.3	4.9 ± 3.3	
Time between ORs, d	5.0 ± 3.5	4.8 ± 1.4	
LOS/TBSA third degree, d/%	0.6 ± 0.3	0.7 ± 0.4	
Sepsis, no. (%)	31 (22.6)	4 (8.2)	<0.05
Mortality, no. (%)	15 (11)	2 (4)	0.14

Definition of abbreviations: F = female; LOS = length of stay; M = male; OR = operation; TBSA = total body surface area.

Data presented as means ± SD or percentages.

Significant difference between control versus insulin at corresponding time point; $P < 0.05$.

Glucose metabolism and insulin resistance. The amount of insulin given was significantly greater in the intensive insulin-treated group compared with controls ($P < 0.05$) (Figure 2A). Daily 6:00 A.M. glucose levels were significantly higher in the control group than in the intensive insulin group ($P < 0.05$) (Figure 2B). We also found that daily average, daily maximum, and daily minimum glucose levels were significantly lower in the intensive insulin group than in the control group ($P < 0.05$) (Figures 2C–2E). Control patients demonstrated 66 episodes of mild hypoglycemia (blood glucose <60 mg/dl) in 24% of the patients and 17 episodes of severe hypoglycemia (blood glucose <40 mg/dl) in 9% of the controls patients. In the intensive insulin-treated group there were 108 episodes of mild hypoglycemia in 43% of the patients and 23 episodes of severe hypoglycemia in 26% of the patients ($P < 0.05$).

OGTTs were conducted to determine whether intensive insulin administration improved insulin sensitivity. We found that intensive insulin–treated patients had significantly improved ISI HOMA and ISI Matsuda scores compared with controls, indicating improved insulin sensitivity ($P < 0.05$) (Figures 3A and 3B). The QUICKI (Figure 3C) and Insulinogenic (Figure 3D) indices were not significantly different between intensive insulin and control patients.

Hypermetabolic Response

Body composition. Patients receiving intensive insulin treatment had a significant improvement in bone mineral density, body fat, lean body mass, and body mass from admission to discharge compared with control patients ($P < 0.05$) (Figure 4).

Indirect calorimetry. As previously reported, burn injury increased REE, indicating a vast hypermetabolic response. In this study, intensive insulin treatment did not alter REE, indicating that hypermetabolism was not affected by intensive insulin treatment (data not shown).

Cytokines, hormones, and proteins. Confirming previous studies, we found that a burn injury induces vast inflammatory and acute-phase responses. Patients with intensive insulin

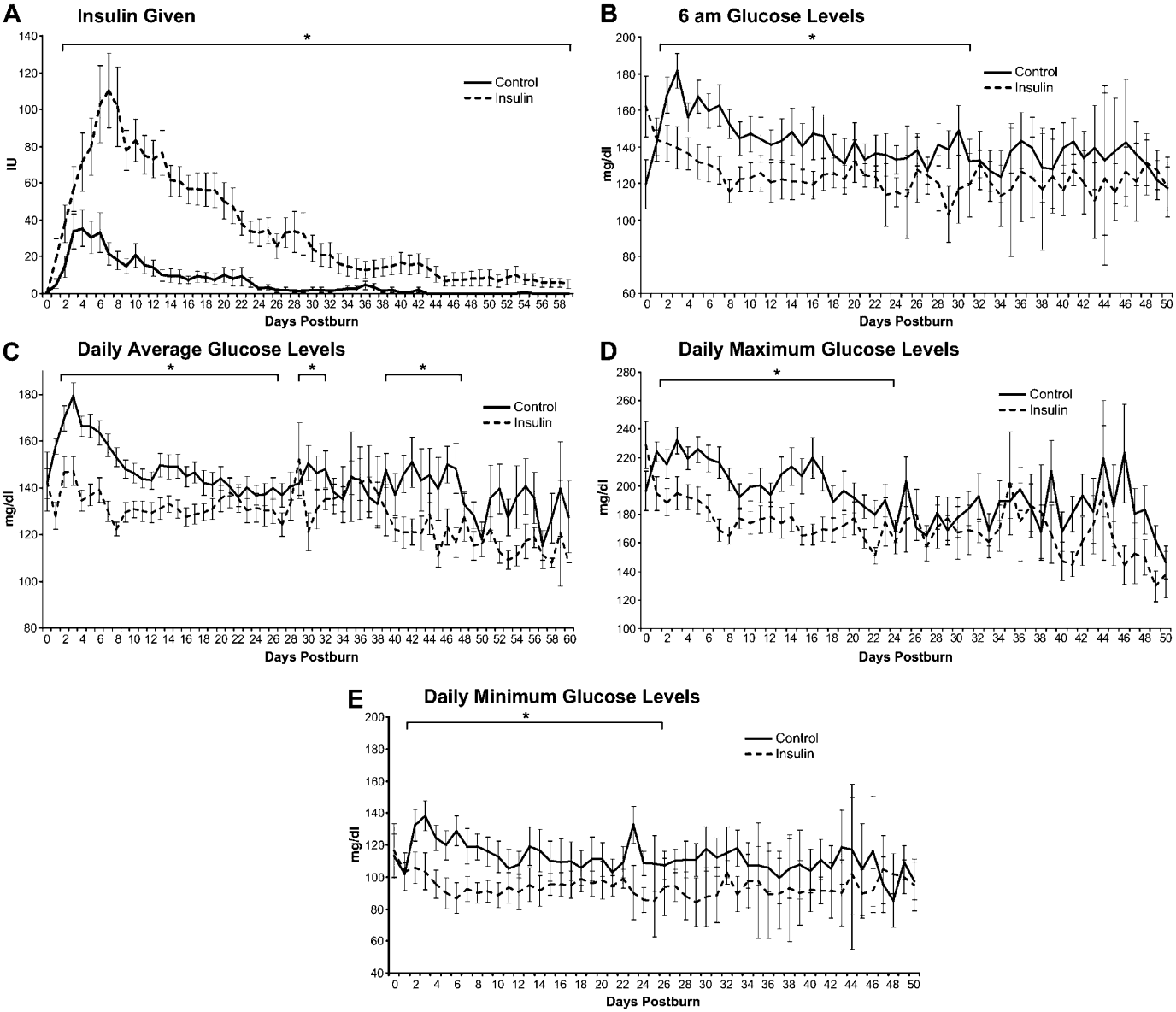

Figure 2. (*A*) Daily insulin administration. (*B*) Daily 6:00 A.M. glucose. Patients with good glucose control had significantly lower level compared with patients with poor glucose control. (*C*) Daily average glucose levels. (*D*) Daily maximum glucose levels, and (*E*) daily minimum glucose levels. *Significant difference between intensive insulin treatment versus control; $P < 0.05$.

treatment demonstrated a markedly altered inflammatory and acute-phase response. Intensive insulin treatment was associated with significantly decreased IL-6 compared with control patients ($P < 0.05$) (Figure 5A). The serum acute-phase proteins C-reactive protein (Figure 5B), complement C3 (Figure 5C), α_2-macroglobulin (Figure 5D), and haptoglobin (Figure 5E) were increased post burn. Intensive insulin treatment significantly decreased all of the aforementioned acute-phase proteins compared with controls ($P < 0.05$). The serum constitutive hepatic proteins prealbumin, transferrin, and retinol-binding protein markedly decreased and remained low up to 60 days post burn. Intensive insulin treatment significantly decreased retinol-binding protein (Figure 5F), but it had no effect on transferrin or prealbumin ($P < 0.05$).

Intensive insulin had a vast effect on fat metabolism. We measured serum free fatty acids, triglycerides, apolipoprotein A1, and apolipoprotein B. Burn injury increased all of these fat metabolites and markers. Insulin significantly decreased free fatty acids (Figure 5G), triglycerides (Figure 5H), apolipoprotein A1 (Figure 5I), and apolipoprotein B (Figure 5J) compared with controls ($P < 0.05$).

Organ function. We conducted cardiac and hepatic ultrasounds to determine cardiac function and hepatic changes. We found that insulin had no effect on cardiac function (data not shown), but significantly alleviated post-burn hepatomegaly (Figure 6A). We further determined serum markers of organ function and homeostasis. We found that burn caused increases in hepatic enzymes alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, total bilirubin, blood urea nitrogen, and creatinine levels. Intensive insulin treatment significantly decreased serum alkaline phosphatase levels (Figure 6B), total bilirubin (Figure 6C), and creatinine (Figure 6D) levels compared with control patients ($P < 0.05$). Improved serum markers of organ function were confirmed by calculating the organ function DENVER2 score. Intensive insulin patients had a significantly lower DENVER2 score, indicating improved

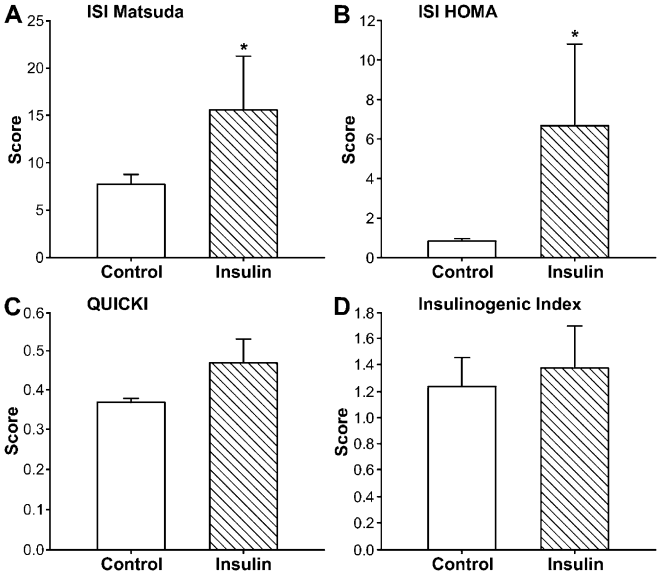

Figure 3. Intensive insulin–treated patients had significantly improved insulin sensitivity index (ISI) homeostasis model assessment (HOMA) and ISI Matsuda scores compared with control subjects, indicating improved insulin sensitivity. The Quantitative Insulin Sensitivity Check Index (QUICKI) and Insulinogenic indices were not significantly different between intensive insulin and control patients.*Significant difference between intensive insulin treatment and control; $P < 0.05$.

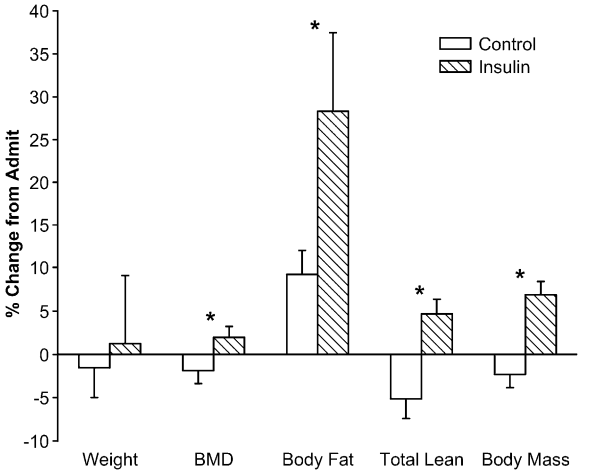

Figure 4. Body composition. Patients receiving intensive insulin treatment had a significant improvement in bone mineral density, body fat, lean body mass, and body mass from admission to discharge compared with control patients; $P < 0.05$. BMD = bone mineral density.

organ function (Figure 6E). Insulin did not affect aspartate aminotransferase, alanine aminotransferase, or blood urea nitrogen levels post burn.

DISCUSSION

The introduction of tight euglycemic control as a clinical concept (1, 2) changed modern ICU practice (6, 33). However, various recent studies found that tight euglycemic control worsened morbidity and mortality, questioning tight euglycemic control as a treatment paradigm (8, 9). The initial studies by van den Berghe and colleagues (1) indicated that if blood glucose concentrations are less than 110 mg/dl, morbidity and mortality of critically ill patients are dramatically improved. Several trials attempted to confirm the Leuven results, but the large randomized multicenter trials (e.g., VISEP or NICE) failed to demonstrate superiority of intensive insulin treatment (8, 9). In contrast, intensive insulin therapy was associated with increased hypoglycemic episodes and adverse outcomes. The reason for these two entirely different outcomes is unknown and is the subject of current speculation. However, despite the controversial clinical discussions, in many studies insulin was shown to be a beneficial adjunct. In severely burned patients, insulin given during acute hospitalization improves muscle protein synthesis, attenuates lean body mass loss, decreases hypermetabolism, and accelerates donor site healing time (34–37). Furthermore, insulin decreases the inflammatory and acute-phase responses (38–41). These data were confirmed by Hemmila and colleagues (15) and Pham and coworkers (42). In these studies, insulin administration was shown to decrease the incidence of infection and sepsis and improved post-burn morbidity. In a recent study using a rodent two-hit model, burn followed by infection with *Pseudomonas aeruginosa*, we found that low-dose insulin improved mortality as well as length of survival (43). There was no difference in mortality between groups in this prospective randomized clinical trial ($P = 0.14$); power analysis to obtain significance (i.e., power = 50%) indicated that we would need 216 patients total if patient number per group would be equal (i.e., 108 per group). With a 3:1 block randomization of patients per group (as in this study), it would require about 570 patients total. Thus, this study was underpowered to detect differences in mortality.

However, this study clearly indicates that intensive insulin therapy is beneficial in terms of post-burn morbidity. In this prospective randomized trial, we found that intensive insulin therapy significantly decreased the incidence of infections and sepsis, along with dampened acute-phase and inflammatory responses. We also showed that intensive insulin improved hepatic and renal function. The mechanisms by which insulin causes these effects are not determined, but based on this study and those by Hemmila and colleagues, Klein and coworkers, and Gauglitz and colleagues (15, 41, 43), all of which showed that insulin had antiinflammatory effects, improved organ function, and decreased incidence of infection and sepsis, we suggest that insulin exerts antiinflammatory effects, improves organ function, and most likely affects immune functions. In a recent study in the burn–sepsis model, insulin was shown to partially restore the depleted and compromised immune system (43). An improved immune function would explain the decreased infections. Insulin further improves organ homeostasis by exerting antiapoptotic promitogenic effects in liver, heart, and kidney (39, 41, 44). We hypothesize that attenuated inflammatory and acute-phase responses lead to decreased whole-body and organ catabolism. This hypothesis is supported by data from this study, in which we found that patients treated with intensive insulin had an improved body composition and organ metabolism.

One of the major limitations of this study is that we did not achieve a consistent glucose level below 110 mg/dl as recommended by van den Berghe and colleagues (1). Maintaining a continuous hyperinsulinemic, euglycemic clamp in burn patients is particularly difficult because these patients are being continuously fed large caloric loads through enteral feeding tubes in an attempt to maintain euglycemia. As burn patients require weekly operations and daily dressing changes, the enteral nutrition occasionally has to be stopped, which leads to disruption of gastrointestinal motility, difficult adjustments, and the risk of hypoglycemia. In the present study, we found that patients receiving intensive insulin treatment had an increased incidence

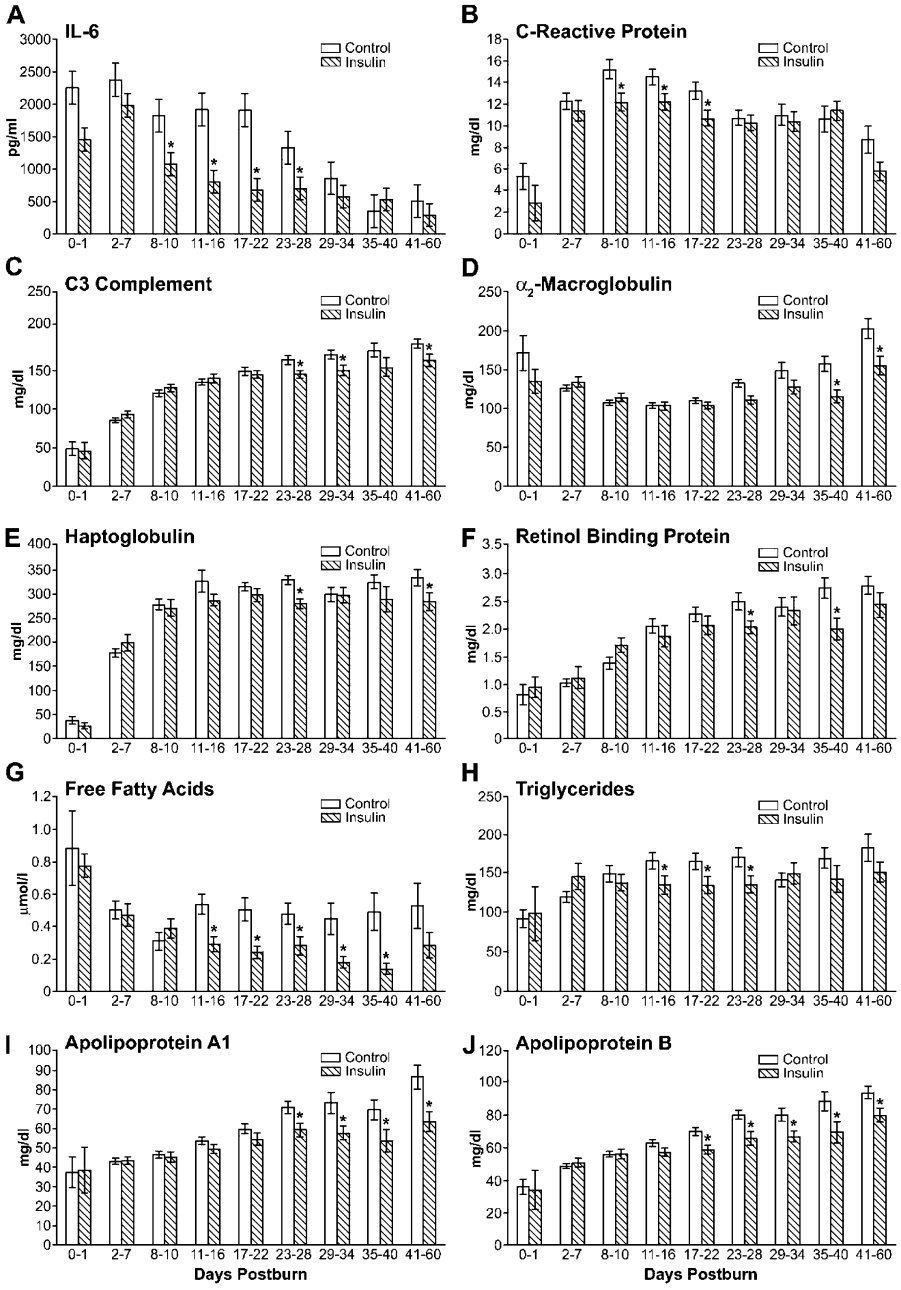

Figure 5. Intensive insulin treatment significantly decreased (*A*) IL-6 and the acute-phase proteins, (*B*) C-reactive protein, (*C*) complement C3, (*D*) α_2-macroglobulin, and (*E*) haptoglobin. (*F*) Intensive insulin treatment significantly decreased retinol-binding protein. Insulin significantly decreased (*G*) free fatty acids, (*H*) triglycerides, (*I*) apolipoprotein A1, and (*J*) apolipoprotein B compared with control subjects. Data presented as mean ± SEM. *Significant difference between intensive insulin treatment versus control at each corresponding time point; $P < 0.05$. Normal levels: IL-6: 6 ± 2 pg/ml; CRP: 0.02 ± 0.03 mg/dl; Complement C3: 140 ± 7 mg/dl; α2-macroglobulin: 265 ± 22 mg/dl; haptoglobin: 155 ± 20 mg/dl; retinol binding protein: 2.5 ± 0.3 mg/dl; free fatty acids: 0.3 ± 0.1 μmol/l; triglycerides: 110 ± 12 mg/dl; apolipoprotein A1: 100 ± 7 mg/dl; apolipoprotein B: 76 ± 4 mg/dl.

of hypoglycemia. Although 9% of control patients had episodes of severe hypoglycemia, 26% of intensive insulin treatment patients had severe hypoglycemic episodes. Thus, in the present study and in the randomized controlled trial by Vlasselaers and colleagues (3) the incidence of hypoglycemia was high. In the Vlasselaers trial, 25% of the tight insulin group suffered severe hypoglycemia, as did 80% in the less than 1-year-old subset. We emphasize that glycemic control does indeed improve outcomes in critically ill children (3) and severely burned children, but it is imperative to use a management strategy that minimizes iatrogenic hypoglycemia. Until further outcome evidence is presented, practitioners wishing to use this management should consider using consistent, validated approaches.

In the present study, we maintained blood glucose levels at 6 A.M. at 120 to 130 mg/dl, whereas control patients had 6:00 A.M. blood glucose levels of 150 to 160 mg/dl. We therefore did not see as big of a difference between groups at 6:00 A.M. glucose levels as in other trials in critically ill patients, but we believe that this difference is enough to detect physiological differences, as protein glycosylation occurs at blood glucose levels between 150 and 160 mg/dl. In addition, by not being overly strict in following the intensive insulin protocol, we are in agreement with current recommendations by several trials and guidelines. VISEP recommends blood glucose levels of 140 mg/dl and less (8), as do Finney and colleagues (6). The analysis of Preiser and Devos (7) summarized recent studies on glucose modulation. The authors recommend that given the hypoglycemic risks of intensive insulin therapy and the uncertainty of the ideal glucose level, an intermediate level of 140 mg/dl should be targeted. Also following this recommendation is the Surviving Sepsis Campaign (33). The authors recognized the lack of an ideal glucose range and the complications of hypoglycemic episodes, but recommend maintaining glucose levels below 150 mg/dl. The authors from the NICE trial also recommend glucose control to a target of 140 to 150 mg/dl to avoid both hyperglycemia and hypoglycemia.

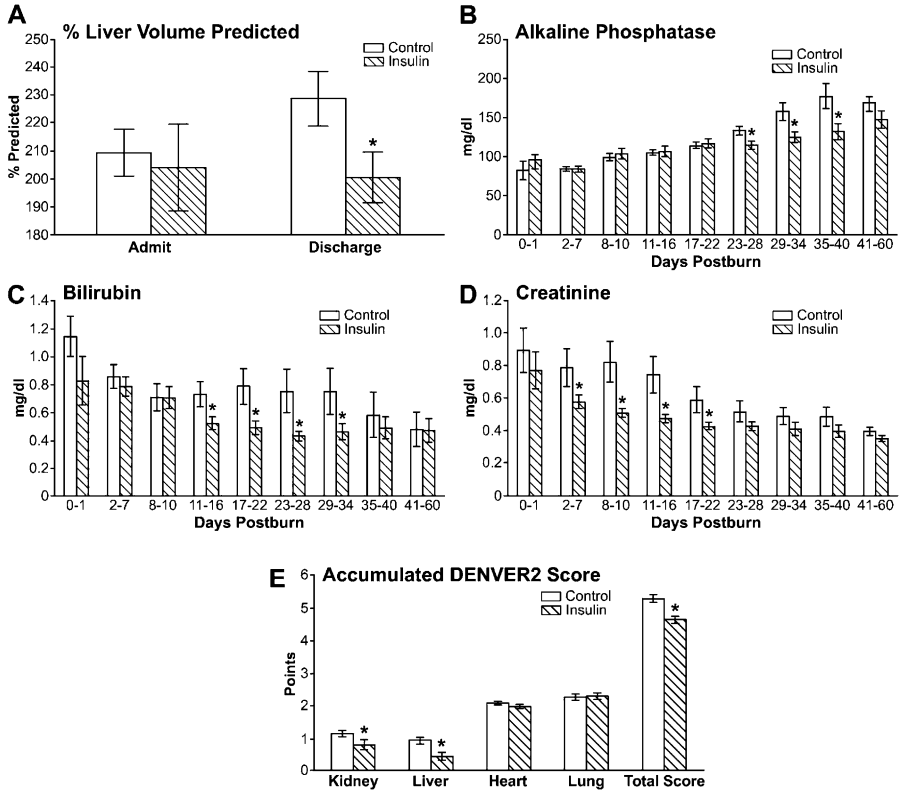

Figure 6. Good glucose control improved organ function as indicated by (*A*) attenuated hepatomegaly, and significantly decreased (*B*) serum alkaline phosphatase levels, (*C*) total bilirubin, and (*D*) creatinine levels compared with controls. (*E*) Intensive insulin patients had a significantly lower DENVER2 score, indicating improved organ function. Data presented as mean ± SEM. *Significant difference between intensive insulin treatment versus control at each corresponding time point; $P < 0.05$. Normal alkaline phosphatase: 80 ± 4 mg/dl; total bilirubin: 0.1 ± 0.02 mg/dl; creatinine: 0.2 ± 0.05 mg/dl. Normal DENVER2 score: 0.

We recently performed a trial in severely burned patients to determine which daily average and 6:00 A.M. glucose levels are associated with an improved morbidity and mortality. We analyzed approximately 300,000 glucose values and found that burn patients whose 6:00 A.M. glucose levels are at 130 mg/dl for 75% of their acute hospitalization have an improved outcome compared with patients whose glucose levels are above 140 mg/dl (unpublished data). Our data showed that the ideal glucose target is around 130 to 140 mg/dl, and that the glucose curve has a U-form shape, meaning that very low glucose levels are equally as detrimental as very high glucose levels. These data are in agreement with the aforementioned studies recommending a glucose target of 130 to 150 mg/dl. It appears that 130 to 150 mg/dl is a glucose range that does not cause protein glycosylation and is not associated with the risk of severe hypoglycemia. Given the controversy over glucose range, glucose target, risks, and detrimental outcomes associated with hypoglycemia, we thus suggest that in severely burned patients, blood glucose of 130 mg/dl should be targeted. This recommendation would be in agreement with three other clinical studies that were conducted in pediatric patients and showed similar glucose cut-off values as we presented in the present study (45–47).

Others (48–50) and we (10, 51–53) have recently investigated the underlying molecular mechanisms by which burn causes insulin resistance. Effects of insulin to maintain normoglycemia occur through the insulin-signaling cascade (48). On binding to the α-subunit on the extracellular portion of its receptor, insulin induces autophosphorylation of the β-subunit, leading to conformational changes and phosphorylation of insulin receptor substrate-1 at a critical tyrosine residue, which in turn leads to activation of the phosphatidylinositol-3 kinase (PI3K)/Akt pathway (49, 50). Recent work now suggests that stress-induced insulin resistance may in part be due to phosphorylation-based negative feedback, which may uncouple the insulin receptor or insulin receptor-associated proteins from their downstream signaling pathways, altering insulin action (50). Specifically, phosphorylation of insulin receptor substrate-1 at serine residues by various kinases may preclude its tyrosine phosphorylation by the insulin receptor tyrosine kinase, thus inhibiting insulin receptor trafficking (54).

Several recent studies linked c-Jun N-terminal kinases (JNK) and endoplasmic reticulum stress and unfolded protein response (ER stress/UPR) to insulin resistance and hyperglycemia. Post stress, JNK was activated on specific stimuli, including the presence of various cytokines, such as IL-6, and internal cues, including ER stress, all of which are present under conditions leading to hyperglycemia (54–57). We have recently shown that a severe burn causes ER stress/UPR in rodents and humans (51, 53, 58). The ER, a membranous organelle that functions in the synthesis and processing of secretory and membrane proteins, is critical in the cellular stress response (ER) (59). Certain pathological stress conditions disrupt ER homeostasis and lead to accumulation of unfolded or misfolded proteins in the ER lumen (59–61). The ER stress response limits the unfolded protein burden in the ER lumen by inhibiting translation and inducing the nuclear transcription of additional chaperone proteins. If the unfolded protein burden cannot be reversed, apoptotic cell death ensues. To cope with this stress, cells activate a signal transduction system linking the ER lumen with the cytoplasm and nucleus, called the unfolded protein response (UPR) (60, 61). ER stress is detected by transmembrane proteins that monitor the load of unfolded proteins in the ER lumen and transmit this signal to the cytosol (59). Two of these proteins, inositol-requiring enzyme-1 and PKR-like ER kinase, undergo oligomerization and phosphorylation in response to increased ER stress (59). Work in our laboratory has recently demonstrated increased phosphorylation of IRE-1 and PERK in rodents and humans after burn injury, indicating post-burn activation of ER stress–signaling pathways. We now suggest that ER stress/UPR is one of the underlying causes of post-burn insulin resistance. The effects of insulin on the ER stress/UPR are unknown, but are the focus of ongoing studies in several laboratories.

In the present study, we showed that intensive insulin therapy in severely burned patients was associated with an improved incidence of infections and sepsis, along with dampened acute-phase and inflammatory responses. We also showed that intensive insulin improved post-burn hepatic and renal function, indicating that intensive insulin therapy is beneficial for severely burned patients.

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