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THE PATHOPHYSIOLOGIC RESPONSE TO SEVERE BURN INJURY

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Abstract

Objective—To improve clinical outcome and to determine new treatment options, we studied the pathophysiologic response postburn in a large prospective, single center, clinical trial.

Summary Background Data—A severe burn injury leads to marked hypermetabolism and catabolism, which are associated with morbidity and mortality. The underlying pathophysiology and the correlations between humoral changes and organ function have not been well delineated.

Methods—Two hundred forty-two severely burned pediatric patients [>30% total body surface area (TBSA)], who received no anabolic drugs, were enrolled in this study. Demographics, clinical data, serum hormones, serum cytokine expression profile, organ function, hypermetabolism, muscle protein synthesis, incidence of wound infection sepsis, and body composition were obtained throughout acute hospital course.

Results—Average age was 8 ± 0.2 years, and average burn size was 56 ± 1% TBSA with 43 ± 1% third-degree TBSA. All patients were markedly hypermetabolic throughout acute hospital stay and had significant muscle protein loss as demonstrated by a negative muscle protein net balance (−0.05% ± 0.007 nmol/100 mL leg/min) and loss of lean body mass (LBM) (−4.1% ± 1.9%); $P < 0.05$. Patients lost 3% ± 1% of their bone mineral content (BMC) and 2 ± 1% of their bone mineral density (BMD). Serum proteome analysis demonstrated profound alterations immediately postburn, which remained abnormal throughout acute hospital stay; $P < 0.05$. Cardiac function was compromised immediately after burn and remained abnormal up to discharge; $P < 0.05$. Insulin resistance appeared during the first week postburn and persisted until discharge. Patients were hyperinflammatory with marked changes in IL-8, MCP-1, and IL-6, which were associated with 2.5 ± 0.2 infections and 17% sepsis.

Conclusions—In this large prospective clinical trial, we delineated the complexity of the postburn pathophysiologic response and conclude that the postburn response is profound, occurring in a timely manner, with derangements that are greater and more protracted than previously thought.

INTRODUCTION

Despite improvements in mortality over the last decade, postburn morbidity is tremendous and remains a challenge for clinicians. We and others have shown that after a severe thermal injury, patients are hypermetabolic, disabled, and debilitated over a period of at least 24

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months.[1, 2] There is growing evidence that pathophysiologic responses that occur immediately or early after burn will affect long-term outcome of severely burned patients.[1, 3] The inflammatory response starts immediately after burn and persists for up to several months.[3] The hypermetabolic response following major burn is characterized by a hyperdynamic response with increased body temperature, oxygen and glucose consumption, CO_2 production, glycogenolysis, proteolysis, lipolysis, and futile substrate cycling.[4–7] This hypermetabolic response begins on the fifth day post-injury and continues up to 24 months postburn causing loss of lean body mass (LBM), loss of bone density, muscle weakness, and poor wound healing.[1, 4, 8] The hypermetabolic response is associated with a marked acute phase response that persists for 8–12 weeks after the initial insult.[9, 10]

Hypermetabolism is further associated with alterations in the endocrinologic response. The hypothalamic-pituitary-organ-hormonal axis acts as a regulator of many organ and cellular functions; however, it has been suggested that a hormonal dysbalance is present following a burn injury.[11] In critically ill patients, a biphasic endocrine response is present, which encompasses an acute and a long-term phase.[12] The acute phase is characterized by low effector hormones due to target-organ resistance.[12] The long-term phase encompasses the hypothalamic suppression of the endocrine axes which contributes to the low serum levels of the subsequent target organ hormones.[12] Several clinical trials with the goal to correct hormonal dysbalances in critically ill patients have been ineffective or even harmful because of a lack of understanding of the pathophysiologic mechanisms.

Despite the identification and delineation of fragments of the postburn responses, no large prospective clinical trial examining the major responses during the postburn acute phase has been conducted. The purpose of the present study was to characterize the pathophysiologic responses postburn in terms of hypermetabolism, inflammation, hormonal and body composition changes, organ function, and muscle protein synthesis in a large prospective clinical trial in order to understand pathophysiologic mechanisms and develop new specific treatment options to improve outcome of severely burned patients.

PATIENTS AND METHODS

All thermally injured children with burns over 30% of their total body surface area (TBSA) who required surgery and consented to an IRB-approved experimental protocol between 1998 and 2007, and were admitted to our burn unit and required at least one surgical intervention were included in this study. If needed, patients were resuscitated according to the Galveston formula with 5000 cc/m^2 TBSA burned + 2000 cc/m^2 TBSA lactated Ringer's 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 autograft. Any remaining open areas were covered with homograft. After the first operative procedure, patients were taken back to the operation theater 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 1500 kcal/m^2 body surface + 1500 kcal/m^2 area burn as previously published.[13–15] The nutritional route of choice in our patient population was enteral nutrition via a duodenal (Dobhof) or nasogastric tube. Parenteral nutrition was only given in rare instances if the patient could not tolerate tube feeds.

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. Sepsis was defined as a positive blood culture or pathologic tissue identifying the pathogen during hospitalization or at autopsy, in combination with at least 3 of the

following: leucocytosis or leucopenia (>12,000 or <4,000), hyperthermia or hypothermia (>38.5 or <36.5°C), tachycardia (>150 BPM in children), refractory hypotension (systolic BP <90 mmHg), thrombocytopenia (platelets <50,000/mm^3), hyperglycemia (serum glucose >240 mg/dl), and enteral feeding intolerance (residuals > 200 cc/hr or diarrhea > 1 L/day) as previously published.[13, 14, 16] We further determined time between operations as a measure for wound healing/re-epithelization. We propose that the time between operations was indicative when donor sites were healed and thereby allowed determination of wound healing.

Indirect calorimetry

As part of our routine clinical practice, all patients underwent resting energy expenditure (REE) measurements within one week following hospital admission and weekly thereafter during their acute hospitalization. All REE measurements were performed between midnight and 5 a.m. while the patients were asleep and receiving continuous feeding. Resting energy expenditure was measured using a Sensor-Medics Vmax 29 metabolic cart (Yorba Linda, CA) as previously published.[15] The REE was calculated from the oxygen consumption and carbon dioxide production by equations described by Weir et al.[15] Measured values were compared to predicted norms based upon the Harris-Benedict equation and to body mass index (BMI).[15] For statistical comparison, energy expenditure was expressed both as absolute REE, and as the percentage of the basal metabolic rate predicted by the Harris-Benedict equation.

Muscle protein synthesis

The degree of peripheral muscle protein net balance, taking into account synthesis and breakdown, was quantified using stable isotope tracers. Protein net balance was measured in a subset of 60 severely burned pediatric patients. Protein kinetic studies were performed between 5:00 and 7:00 a.m., on post-operative day five after the first excision and grafting procedure. Because phenylalanine is neither synthesized nor degraded in the peripheral tissues (it is metabolized only in the liver), measurement across the leg reflects the net balance of protein synthesis and breakdown. Blood samples were taken simultaneously from an ipsilateral femoral artery and vein for this determination. Indocyanine green was used to determine leg blood flow. The blood concentration of unlabeled phenylalanine was determined by gas chromatography-mass spectrometry (GCMS) using the internal standard approach and the tert-butyldimethylsilyl esters, as previously described.[17] Indocyanine green concentrations were determined spectrophotometrically at λ=805 mm on a Spectronic 1001 (Bausch and Lomb, Rochester, NY). As phenylalanine is neither synthesized nor degraded in the periphery, the difference in concentration of this substrate in the femoral arterial and venous plasma pools reflects the net balance of leg skeletal muscle protein synthesis and breakdown. The net balance (NB) was calculated and standardized for leg volume by the following equation: $\mathrm{NB}=(\mathrm{C}_A-\mathrm{C}_V)\bullet \mathrm{BF}$, where C_A and C_V are the blood-free amino acid concentrations of the femoral artery and vein, and BF is leg blood flow in cc/min/100 ml leg. Leg blood flow was determined from a modification of Fick's equation. BF was normalized for each patient by leg volume. Subject weight, leg circumference at prescribed points relative to anatomic landmarks, and the distances between these points were used to mathematically model leg volume.[17]

Body composition

Height and body weight were determined clinically 5 days after admission and at discharge. Total LBM, fat, bone mineral density (BMD), and bone mineral content (BMC) were measured by dual energy x-ray absorptiometry (DEXA). A hologic model QDR-4500W

DEXA (Hologic Inc, Waltham, MA) was used to determine body composition as previously published.[1, 2, 18, 19]

Hormones, proteins, and cytokines

Blood and/or urine was collected from burn patients at admission, pre-operatively, and 5 days post-operatively for 4 weeks for serum hormone, protein, cytokine and urine hormone analysis. Blood was drawn in a serum-separator collection tube and centrifuged for 10 minutes at 1320 rpm; the serum was removed and stored at −70°C until assayed.

Serum hormones and acute phase proteins were determined using HPLC, nephelometry (BNII, Plasma Protein Analyzer Dade Behring, MD), and ELISA techniques. 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 interleukin [IL-1β, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-12p70, IL-13, IL-17, granulocyte colony stimulating factor (GCSF), granulocyte macrophage colony stimulating factor (GMCSF), interferon-gamma (IFN-γ), monocyte chemoattractant protein-1 (MCP-1), macrophage inflammatory protein-1 beta (MIP-1β), and tumor necrosis factor (TNF). The assay was performed according to the manufacturer's instructions. Briefly, serum samples were thawed and then centrifuged at 4500 rpm for 3 minutes at 4°C. Serum samples were then incubated with microbeads labeled with specific antibodies to one of the aforementioned cytokines for 30 minutes. Following a wash step, the beads were incubated with the detection antibody cocktail, each antibody specific to a single cytokine. After another wash step, the beads were incubated with streptavidin-phycoerythrin for 10 minutes, washed, and the concentrations of each cytokine were determined using the array reader.[3, 18–20]

Urine creatinine, creatinine clearance, and cortisol were determined by standard laboratory techniques.

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 was calculated using a formula as previously published.[10, 18, 19, 21] Actual size was then compared to 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 (CO), cardiac index (CI), stroke volume (SV), resting heart rate (HR) and left ventricular ejection fraction (LVEF). 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 EF, SV, CO and CI. Three measurements were performed and averaged for data analysis.[18, 19]

Physical function testing

In a subgroup analysis, we assessed physical function which involved muscle strength and cardiopulmonary function. Studies were conducted in a timeframe ranging from

immediately after ICU discharge up to 6 months postburn. Physical function was assessed in 46 burned patients (age: 13±0.5, height: 152±2 cm, weight: 48±3 kg). The results were compared with 46 age-matched non-burned control children (age: 12±0.4, height: 154±3 cm, weight: 59±3 kg). Age and height were similar in both groups, however body weight was statistically significantly less in the burn group when compared to the control group, $p<0.05$. Prior to muscle strength testing, the patient was familiarized with the exercise equipment and instructed on proper weight lifting techniques. Strength testing was conducted using a Biodex System-3 dynamometer (Shirley, NY) as previously published.[22–24] Values of peak torque were calculated by the Biodex software system. The highest peak torque measurement between the two trials was selected. Peak torque was corrected for gravitational moments of the lower leg and the lower arm.[22–24]

To determine peak oxygen consumption, patients underwent a standardized treadmill exercise test on day two using the modified Bruce protocol as part of their standard clinical outpatient evaluation. Heart rate and oxygen consumption were measured and analyzed using methods previously described.[22–24]

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 (ANOVA) with post hoc Bonferroni correction, paired and unpaired Student's t-test, Chi-square analysis, and Mann-Whitney tests were used where appropriate. Data are expressed as means±SD or SEM, where appropriate. Significance was accepted at $p<0.05$.

RESULTS

Demographics

Two-hundred forty-two severely burned children were included in the present study. Patients' demographics are shown in Table 1. Patients were, on average, 8 years of age, 41% were females and 59% were males. Patients suffered from a severe burn injury with 56% TBSA and a third-degree burn of 43% TBSA. Length of hospital/ICU stay was 31 days which results in 0.55 days per percent TBSA burn. Patients were taken back to the OR every 8^{th} day and required on average 4 operations. Minor infections occurred in 44% of the patients, while sepsis occurred in 18%, multi-organ failure in 21%, and 8% of our severely burned patients died (Table 1).

Indirect calorimetry

Percent predicted REE increased immediately postburn and peaked at 2 weeks postburn. Predicted REE decreased over time, but remained elevated at discharge indicating marked hypermetabolism (Figure 1, n=212).

Peripheral skeletal muscle net balance

Stable isotope infusions were used to measure muscle protein synthesis and breakdown to determine net protein balance in severely burned patients (n=59) and unburned young adults (n=5) (Figure 2 A–C). These patients were selected as they had a complete set of stable isotope studies during week 1 and 3 postburn. There was no selection bias in choosing these patients and their demographics are similar to the entire cohort. Peripheral muscle protein synthesis was not different at week 1 and week 3 postburn when compared to unburned young adults (Figure 2A). Ninety-five percent confidence interval for protein breakdown is 130 to 202 nmol/100 ml leg/min at 1 week and 112 to 172 nmol/100 ml leg/min at 3 weeks postburn, which are both significantly above the normal value, indicating that muscle

protein catabolism is twice the normal value (Figure 2B). Likewise, the 95% confidence interval for protein net balance is −27 to +26 nmol/100 ml leg/min at 1 week and −9 to +39 nmol/100 ml leg/min at 3 weeks postburn, which is significantly worse than normal values (Figure 2C).

Body composition

Severe burn causes marked changes in body composition during acute hospitalization. Severely burned children lost about 2% of their body weight (−5% LBM, −3% BMC, and −2% BMD) from admission to discharge. Total fat and percent fat increased from admission to discharge by 3% and 7%, respectively (Figure 3, n=105).

Hormones, proteins and cytokines

Serum acute phase proteins were markedly increased postburn (n=125–200 per time point). Serum complement C3 and α_2-macroglobulin demonstrated a slow but significant increase over time (Figure 4A–B). Serum haptoglobin, α_1-acidglycoprotein, and CRP demonstrated a 4–10-fold increase almost immediately postburn and remained significantly elevated through acute hospital stay (Figure 4C–E). Serum constitutive hepatic proteins pre-albumin, transferrin, and retinol-binding protein markedly decreased 4–8-fold almost immediately postburn and levels remained low up to 60 days postburn (Figure 4F–H). Serum apolipoprotein A1 significantly decreased postburn while apolipoprotein B showed an increase after an initial decrease (Figure 4I–J). Serum-free fatty acids and triglycerides significantly increased 2–4 fold postburn (Figure 4K–L).

Non-fasted serum glucose increased markedly during the acute phase postburn to 170–180 mg/dl along with increased levels of endogenous insulin implying that insulin resistance is present causing increased insulin associated with hyperglycemia (Figure 5, n=180–212).

Serum hormone levels showed a marked alteration postburn (n=100–175). Serum insulin-like growth factor-I (IGF-I) decreased markedly immediately after burn and remained significantly decreased throughout acute hospitalization (Figure 6A). Similar to IGF-I, serum insulin-like growth factor binding protein-3 (IGFBP-3) decreased almost immediately postburn and remained low through acute hospitalization (Figure 6B). Serum GH did not decrease immediately postburn-like IGF-I and IGFBP-3. Serum GH started to decrease 8–10 days postburn and showed a steady decline through acute hospitalization (Figure 6C).

Serum T4 decreased 2–3-fold immediately postburn (Figure 6D). Serum T4, however, increased through acute hospitalization and approached normal levels at discharge (Figure 6D). Free thyroid index (FTI) showed a significant decrease for 14 days postburn and then returned to normal levels (Figure 6E).

Serum cortisol significantly increased immediately postburn and remained elevated for 3 weeks returning to normal levels (Figure 6F). Urine-free cortisol increased 5–7-fold during the acute stay, but decreased over time (Figure 6G). Serum osteocalcin and iPTH were drastically decreased (5–7-fold) immediately after burn and showed almost no increase over time (Figure 6H and I). Serum β-estradiol, testosterone, and progesterone showed very different patterns postburn. While β-estradiol decreased immediately postburn with an increase over time (Figure 6J), testosterone was normal during the early postburn phase, but showed marked decreases beginning 4 weeks postburn (Figure 6K). Progesterone demonstrated a very different pattern. Progesterone was increased at various time points when compared with normal levels (Figure 6L).

Serum creatinine and creatinine clearance were not significantly different during the acute postburn response when compared to normal values (data not shown).

We found that all of the 17 serum cytokines measured are significantly altered and these perturbations are possibly clinically relevant (n=100–150). Dramatic changes were observed for serum G-CSF, IL-6, IL-8, MCP-1, and MIP-1β (Figure 7A). These cytokines demonstrated up to a 100–200-fold increase when compared to normal levels. All 17 cytokines are depicted over time, but also in a heat map, which illustrates the marked changes in the serum (Figure 7B).

Cardiac and liver changes

Analysis of cardiac output, predicted cardiac output, heart rate, predicted heart rate, cardiac index, and central venous pressure (CVP) showed alterations postburn. Cardiac output and predicted cardiac output was increased immediately postburn (up to 160% of predicted) and significantly decreased until discharge (Figure 8, n=212). Heart rate and predicted heart rate were also significantly increased (up to 160% predicted) postburn and remained elevated at discharge (Figure 8, n=212). Central venous pressure was not significantly altered postburn. Cardiac index was increased immediately postburn and significantly decreased from admit to discharge (Figure 8, n=212).

Immediately after burn, liver size markedly increased and remained elevated when patients were discharged from the hospital/ICU (Figure 9, n=178).

Physical function

Both groups, burned and non-burned children, were similar in age and gender distribution. Peak torque (PT) was significantly lower in burned children (48±36 Newton-meters) when compared to non-burned control children (91±40 Newton-meters), $p<0.05$. Similarly, peak cardiopulmonary capacity was significantly lower in burned children (27.0±6.8 mL oxygen/kg/min) when compared to non-burned control children (34.9±8.4 mL oxygen/kg/min), $p<0.05$.

DISCUSSION

Despite advances made in burn care over the last decade, burn injury remains a major clinical challenge and is associated with severe disabilities and impairment of the burn victim.[4] Burn over 30–40% of the body induces an inflammatory and hypermetabolic response that persists for 2 years after the initial insult.[1, 2] The metabolic demands and energy requirements are immense and are met by the mobilization of proteins and amino acids.[25] Increased protein turnover, degradation, and negative nitrogen balance are characteristics of this severe critical illness.[25] As a consequence, the structure and function of essential organs such as skeletal muscle, skin, immune system, and cellular membrane transport functions are compromised.[26, 27] Chang et al.[28] delineated in their study that a 10% loss of LBM leads to an impairment of immune function, 20% loss of LBM decreased wound healing with 30% mortality, 30% loss of LBM to pneumonia and pressure sores with 50% mortality, and if 40% of LBM is lost, death will occur in 100%. Despite the identification and delineation of parts of the postburn response, no prospective large clinical study has ever fully characterized the major components during the acute phase postburn. The purpose of the present study was to determine the pathophysiologic response postburn in terms of hypermetabolism, inflammation, hormonal and body composition changes, organ function and muscle protein synthesis in a large prospective clinical trial to enable developments of future interventions and treatment options.

The patients in this study were severely burned children with an average age of 8 years and two-thirds were males. The mortality was low (8%), indicating that mortality in severely burned children has, in fact, drastically decreased over the last decades and does not

represent a valid outcome determinant for clinical studies in this patient population.[29] More striking was the effect of severe burn on metabolic and physiologic markers. Hypermetabolism measured by resting energy expenditure was markedly elevated to 130–140% predicted and remained elevated for the entire study period. The physiologic consequences of hypermetabolism are protein catabolism, loss of body weight, LBM, BMC, and BMD. This tremendous loss in essential body structures is not limited to acute hospitalization. We have shown that loss of proteins, muscle, and bone persists up to 2 years postburn affecting patients' lives remarkably.[1, 2] We, therefore, suggest that it is beneficial to attenuate the hypermetabolic response immediately postburn and subsequently preserve protein and amino acid stores. Agents known to affect postburn hypermetabolism and catabolism are insulin, IGF-I, oxandrolone, GH, and propranolol.[4, 18, 30–33] As GH increases mortality in critically ill adults[34] and IGF-I is at the moment limited in its availability, we recommend the use of insulin, oxandrolone, or propranolol to attenuate hypermetabolism and catabolism.

In this large prospective trial, we found that a severe burn affects expression of acute phase proteins. Serum complement C3 decreased initially but then increased over time, as did α2-macroglobulin. These two proteins appear to act as slow-acting acute phase proteins, whereas haptoglobin, α1-acid glycoprotein, and CRP act as more rapid acute phase proteins. Constitutive hepatic proteins, on the other hand, are significantly decreased throughout hospital stay. This decrease could be due to decreased production, increased consumption or increased loss due to capillary leakage. These proteins are markers for general homeostasis indicating the severity and intensity of the postburn dysbalance. We found that apolipoprotein A1 is significantly decreased, while apolipoprotein B is initially decreased but increases at later time points. The exact role of these 2 proteins during the postburn response needs to be determined in order to evaluate their potential as targets for therapeutic interventions.

Of greater interest is the change in serum triglycerides and free fatty acids, both of which are significantly increased through almost the entire acute hospital stay. Fat transporter proteins are decreased postburn while triglycerides and free fatty acids are increased which could explain the fatty infiltration of the liver and other organs postburn. We have shown that hepatomegaly with fatty infiltration is associated with increased incidence of sepsis and mortality implying the importance of organ integrity and function.[35] A therapeutic approach to decrease lipolysis and fatty infiltration and reverse the acute phase response may thus improve morbidity and mortality.[36] We have recently shown that propranolol administration attenuates lipolysis and the hepatic acute phase response. Beta blockade decreases urinary nitrogen loss, peripheral lipolysis, whole-body urea production[37], and resting energy expenditure.[31] Propranolol also decreases hepatic fat storage by limiting fatty acid delivery in severely burned pediatric patients.[36] In addition, we showed that propranolol decreased peripheral lipolysis and improved insulin responsiveness.[38] Recently, we further showed that propranolol has a profound effect on fat infiltration of the liver by reversing hepatomegaly.[36]

A striking finding of the current study was the change in the hormonal axis. In general, critical illness is characterized by marked alterations in the hypothalamic-anterior-pituitary-peripheral-hormone axes, the severity of which is associated with a high risk of morbidity and mortality.[12] We looked at several hormonal axes, such as the GH-IGF-I-IGFBP-3-axis, FTI-T4-axis, cortisone-cortisol-axis, insulin-glucose-axis, PTH-Osteocalcin axis, and sex hormones (testosterone, β-estradiol, progesterone). One of the most important endocrine axis after a severe injury and in the critically ill is the GH-IGF-I axis. Recombinant human growth hormone (*rhGH*) has been shown to enhance immune function,[39, 40] wound healing[41] and to diminish the hypermetabolic response after major surgery, trauma, sepsis or

a thermal injury.[42–44] *rhGH* stimulates protein synthesis and attenuates the nitrogen loss after injury and improves clinical outcomes.[45] As animal and *in vitro* studies have shown, *rhGH* modulates the hepatic acute phase response by increasing constitutive hepatic proteins, decreasing acute phase proteins, modulating cytokine expression, and increasing IGF-I concentrations.[46, 47] However, in a prospective, randomized, double-blind study in European ICU's, it has been demonstrated that *rhGH* treatment increased mortality among adult trauma patients when compared to placebo (42% vs. 18%).[34] Thus, GH administration is restricted and the indication for its administration is limited. In addition, by analyzing our data, it appears that GH administration may not be the best therapeutic agent for critically ill or burned patients. In the present study, we showed that IGF-I and IGFBP-3 are much more affected when compared to GH.[9, 10, 48, 49] As the clinical use of GH is restricted, it appears that IGF-I may be a better drug compared to GH to effectively attenuate the postburn. In fact, we conducted an animal and a clinical study in which we showed that IGF-I, in combination with its principle binding protein, improved muscle protein synthesis, hepatic acute phase and inflammatory response, and immune system.[30, 32, 50] However, we suggest that it would be necessary to test IGF-I in a large multicenter trial to determine whether IGF-I would be a beneficial treatment option in severely burned patients.

The other hormonal axis that may play an important role is the thyroid hormone axis. Van den Berghe and colleagues[51] showed in patients who died after intensive care, not only did the hypothalamus-pituitary-thyroid axis undergo marked changes, but that also tissue-specific mechanisms are involved in the reduced supply of bioactive thyroid hormone in critical illness. We showed in the present study that T4 significantly decreased by 2-folds immediately postburn. Free thyroxine index also significantly decreased but reached normal levels 2 weeks postburn. The questions whether thyroid hormones should be replaced or not is difficult to answer and is controversially discussed.[52–54] As T4 and FTI levels did not change in the magnitude as other hormones measured, we suggest that a replacement with thyroid hormones is not warranted at this time and that T4 and FTI should be considered as a marker for the systemic homeostasis post stress.

Catecholamines and stress hormones such as cortisol drive the hypermetabolic response to burn injury.[5, 7, 55, 56] In the present study, we found that a severe burn injury increases serum and urine cortisol. Urine cortisol increased 5–8-fold and remained elevated throughout the entire acute hospital stay. Stress hormones such as glucocorticoids have been described as one of the major hormones responsible for proteolysis and catabolism.[57–60] Glucocorticoid levels are markedly increased postburn, and therefore, a hypothetical approach to attenuate protein breakdown and hypermetabolism would be to block cortisol production. We are currently conducting a prospective randomized controlled trial to block cortisol production using ketoconazole.

Glucose kinetics in severely burned patients is almost always abnormal. Glucose utilization in burned patients is through inefficient anaerobic mechanisms as characterized by increased lactate production accounting for increased glucose consumption.[5, 7, 61, 62] Glucose production, particularly from alanine, is elevated in almost all patients with severe burn.[25] The increased gluconeogenesis from amino acids renders these amino acids unavailable for re-incorporation into body protein. Nitrogen is excreted, primarily in urea, thus contributing to the progressive depletion of body protein stores. In the present study, we showed that plasma insulin levels are significantly increased over 4–5 weeks postburn. This confirms data from other groups who showed that a severe burn causes increased insulin levels.[63, 64] Increased insulin levels do not result in decreased glucose levels. In contrast, we showed that serum glucose is significantly increased for 4–5 weeks postburn. The fact that the basal rate of glucose production is elevated despite elevated plasma, insulin levels indicates hepatic insulin resistance, since under normal conditions elevated serum insulin would lower

the rate of glucose production.[61, 65, 66] We would like to point out that our values are not fasted values as most of our patients receive continuous feeding via a duodenal tube and we almost never stop feedings. Hyperglycemia is associated with increased mortality in critically ill patients[67, 68] and worsens the outcome in severely burned patients.[69–71] In a recent study, we determined serum insulin and glucose levels in severely burned patients with different burn sizes. We found that insulin levels were significantly increased in the >80% TBSA burn group and lower in the smaller burn groups. This indicates that with the increased severity of the burn injury, insulin resistance increases and more insulin needs to be synthesized to maintain normoglycemia. It further indicates the necessity to attenuate hyperglycemia in order to improve outcome and survival. Agents to decrease glucose and improve insulin sensitivity encompass insulin, metformin, and fenofibrate.[63, 69, 72–75]

Another striking finding was that osteocalcin and parathyroid hormone were drastically decreased immediately after burn and remained decreased during the acute phase postburn. Klein and colleagues[76–82] published extensively on bone metabolism postburn. They showed that burned children have decreased BMC and BMD. Using labeled tetracycline, they determined bone turnover rates and found that burned patients have almost no bone formation and synthesis.[76–82] We did not determine bone turnover rates in this study, however, the biochemical markers that we determined indicate that bone metabolism is dysfunctional very early postburn indicating another target for therapeutic intervention. In a recent study, pamidronate[81] was shown to improve bone metabolism during the acute phase and long-term phase postburn. Another possible treatment approach would be sex hormone substitution. Estrogens have been shown to improve bone mineralization and metabolism.[83] Chaudry and colleagues have found that estrogens have a positive effect on inflammation and hypermetabolism and improve survival in a trauma hemorrhage model.[84–87] In the present study, we found that estrogen was significantly decreased immediately after the injury but increased during hospital stay, while testosterone decreased and progesterone increased over time. Therefore, it would be interesting to investigate the effects of estrogen on the postburn response. While the effect of estrogens after burn has not been investigated, the effects of testosterone on postburn muscle metabolism were studied.[88] Testosterone improved muscle catabolism but is associated with side-effects.[89, 90] Therefore, we and others determined the effects of oxandrolone, a synthetic testosterone analogue on the postburn response, and found that oxandrolone increased LBM and shortened acute hospitalization.[18, 91, 92]

We suggest that changes in protein expression are driven by the inflammatory response.[3, 20] Cytokines and pro-inflammatory mediators are known via cellular mediators to block and therefore decrease endogenous anabolic agents.[93, 94] Immediately postburn, there are marked changes in the cytokine expression profile. Out of 17 cytokines, 16 drastically increased, most significantly IL-6, IL-8, MCP-1, MIP-1β, and G-CSF. Even so called anti-inflammatory cytokines increased significantly postburn. Only IL-5 was in the normal range postburn and decreased over time. IL-5 is a TH-2 cytokine produced by T helper-2 cells and mast cells. It stimulates B cell growth and increases immunoglobulin secretion, and is also a key mediator in eosinophil activation. Unlike other members of this cytokine family (IL-3 and GM-CSF) this glycoprotein is a homodimer and is also expressed by eosinophils. Postburn immune exhaustion and compromise is present, and therefore, decreased IL-5 may be an important factor for this exhaustion.

Other intriguing findings of this study were changes in cardiac function. Burn patients with burns over 40% of their TBSA demonstrated an increased cardiac output and cardiac index accompanied by a massive tachycardia with 160–170% predicted heart rate. CO, CI and heart rate remained high at ICU discharge at around 130–150% predicted. We now have evidence that the heart rate remains elevated up to 2 years postburn. Increased cardiac stress

postburn is associated with myocardial depression.[95–97] The hypothesis that cardiac stress and myocardial dysfunction may be one of the main contributors to mortality in large burns was confirmed in a recent retrospective autopsy study,[98] as well as clinical study,[19] implying the therapeutic need to improve cardiac stress and function. That this finding is not specific to our center is shown by the WHO report, in which the WHO delineates highest mortality rates in children <4 years and adults >65 years.[99] Propranolol decreases cardiac work and improves oxygen delivery to the heart representing a therapeutic approach to improve cardiac morbidity.[31, 100]

That all these biomedical markers are related to real physical changes is demonstrated by the markedly compromised physical function in regards to muscle strength and cardiopulmonary capacity. An increase in both would go a long way in improving a burned child's capability to return to normal activities of daily living, in addition to improving quality of life. In fact, our group has an exercise program implemented at discharge as part of the outpatient rehabilitation and its effects are currently being evaluated. However, we have reported that an exercise program implemented at the 6-month postburn time point significantly improves physical function.[22–24]

We would like emphasize that the present cohort study is heterogeneous because we included, in our cohort study, male and female patients with the latter containing both pre- and post-menarche patients, patients with and without inhalation injury, patients with and without infection/sepsis, patients with and without multi-organ failure, and patients who died and did not die. We did not eliminate patients with inhalation injury, sepsis, and multiple organ failure and death to smoothen out the trajectory of change of the variables measured because we wanted to achieve a large patient cohort to perform robust statistics. We propose that the development of trajectories or patterns of these detrimental outcomes will be the focus of future studies. Another concern could be the fact that the time to admission after injury averaged 6.7 days, which means that the population of study patients was biased towards survival since the mortality rate of extensively burned patients decreases across time and plateaus after the tenth post-burn day. We, however, suggest that we did not bias our study population because we attempted to get patients as soon as possible to our center. Transfer of patients from Central and South America shortened over the past years to times comparable within the United States and the majority of our patients now arrive at our center within the first 72 hours postburn.

Based on our findings, we suggest that a burn injury involving more than 30–40% of the total body surface causes marked and prolonged inflammation, marked increases in hypermetabolism, catabolism, cardiac dysfunction, hormonal changes, and subsequently prolonged morbidity and mortality in 10% of this patient population. We suggest that these events occur in a timely manner. Treatment should focus on several aspects of the pathophysiologic events postburn, such as anti-inflammation, attenuate hypermetabolism and improve glucose metabolism, immune system and cardiac function.

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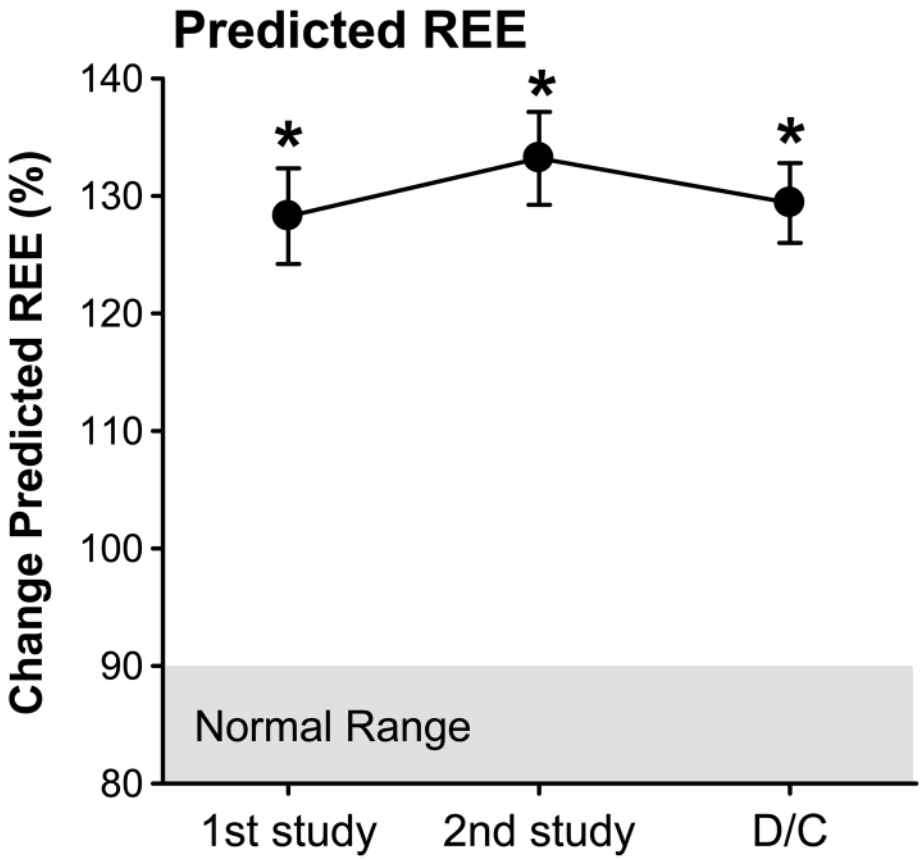

Figure 1.
Percent predicted REE. Predicted REE increased immediately postburn, peaked at 2 weeks postburn and remained significantly elevated at hospital discharge indicating marked hypermetabolism. * Significant difference between burned children vs. normal range, $p<0.05$.

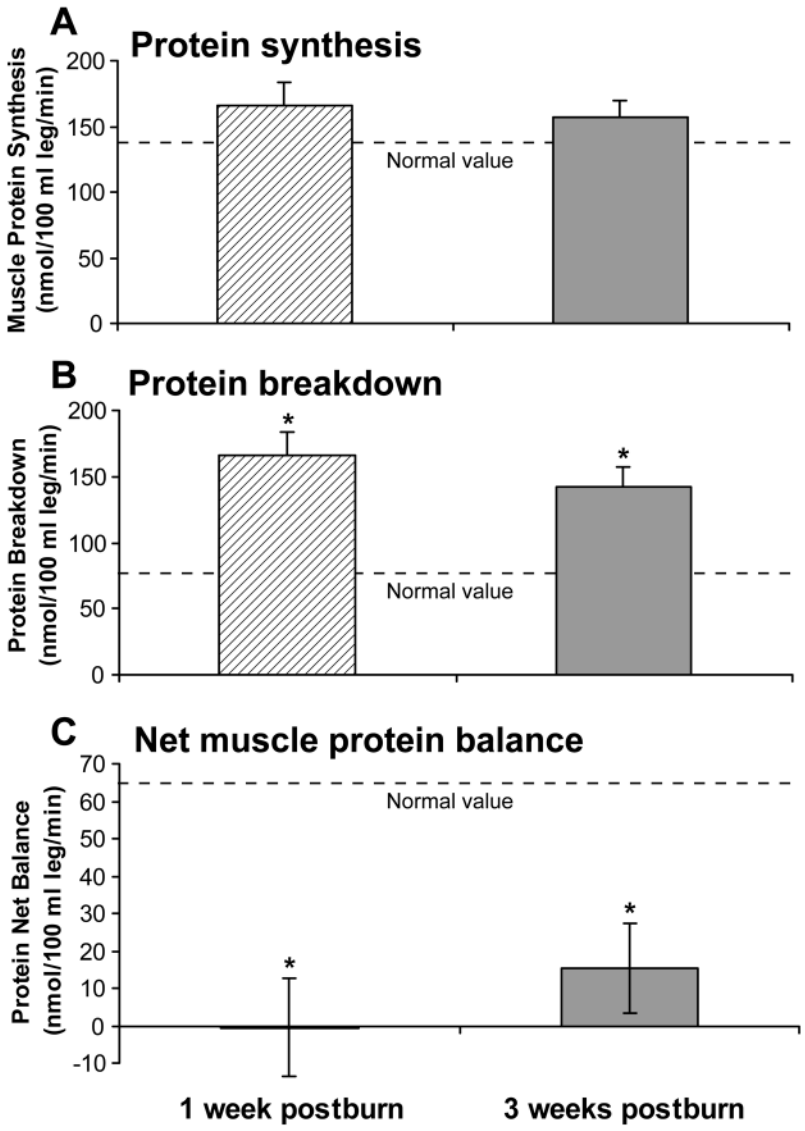

Figure 2.

Stable isotope infusions were used to determine muscle protein net balance in a subgroup of 59 burned patients and 5 unburned young adults. Peripheral muscle protein synthesis was not altered at week 1 and week 3 when compared to unburned young adults (A). Protein breakdown however was increased 3–4 fold at 1 and 3 weeks postburn (B) leading to a negative protein net balance (C).

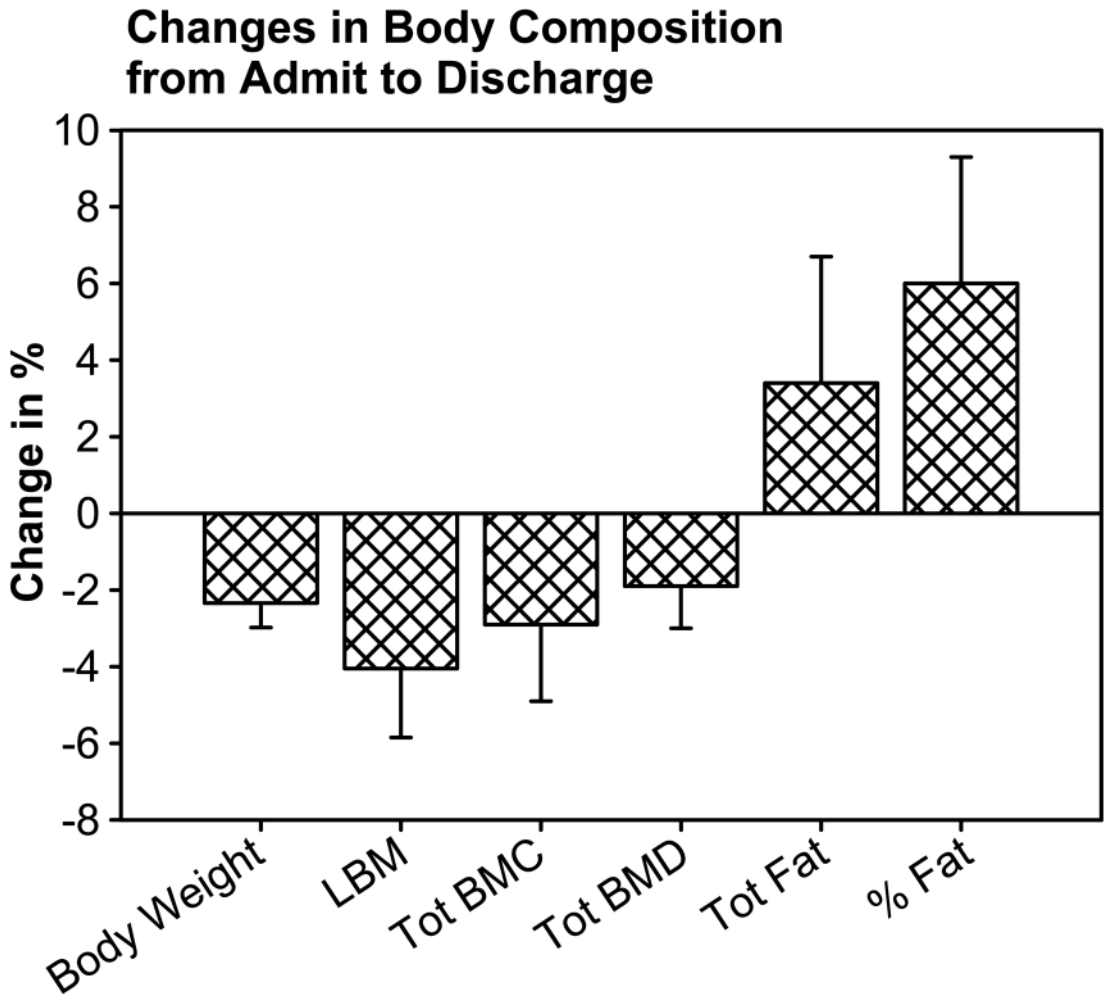

Figure 3.
Severe burn causes marked changes in body composition during acute hospitalization (n=105). Severely burned children lost about 2% of their body weight, which is 5% lean body mass, 3% bone mineral content, 2% bone mineral density from admission to discharge. Total fat and percent fat increased from admission to discharge by 3% and 7%, respectively.

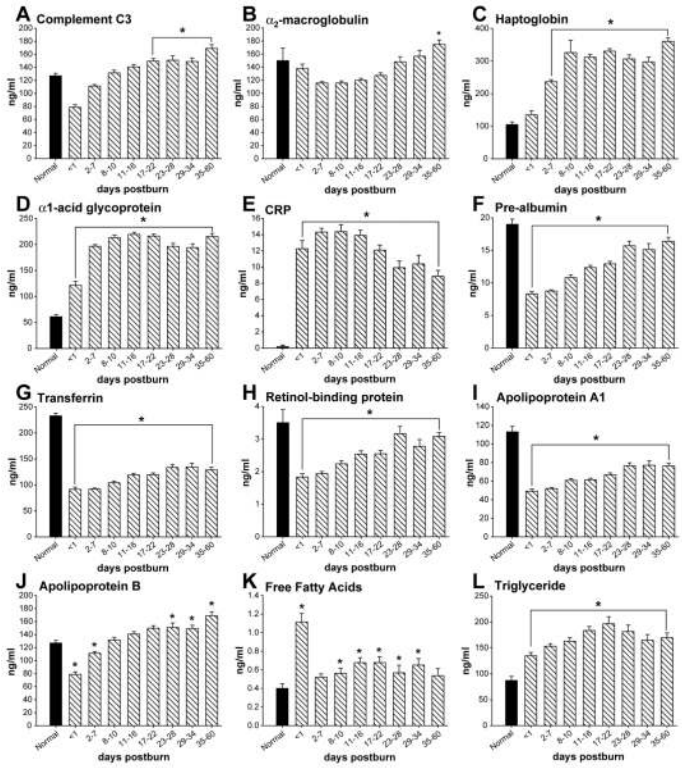

Figure 4.

Serum complement C3 (A), α2-macroglobulin (B), haptoglobin (C), α1-acidglycoprotein (D), and CRP (E) were significantly increased postburn. Serum constitutive hepatic proteins pre-albumin (F), transferrin (G), retinol binding protein (H) markedly decreased immediately postburn and levels remained low up to 60 days postburn. Serum apolipoprotein A1 (I) significantly decreased postburn while apolipoprotein B (J) showed an increase. Serum free fatty acids (K) and triglycerides (L) significantly increased postburn. * Significant difference between burn vs. normal ranges, $p<0.05$.

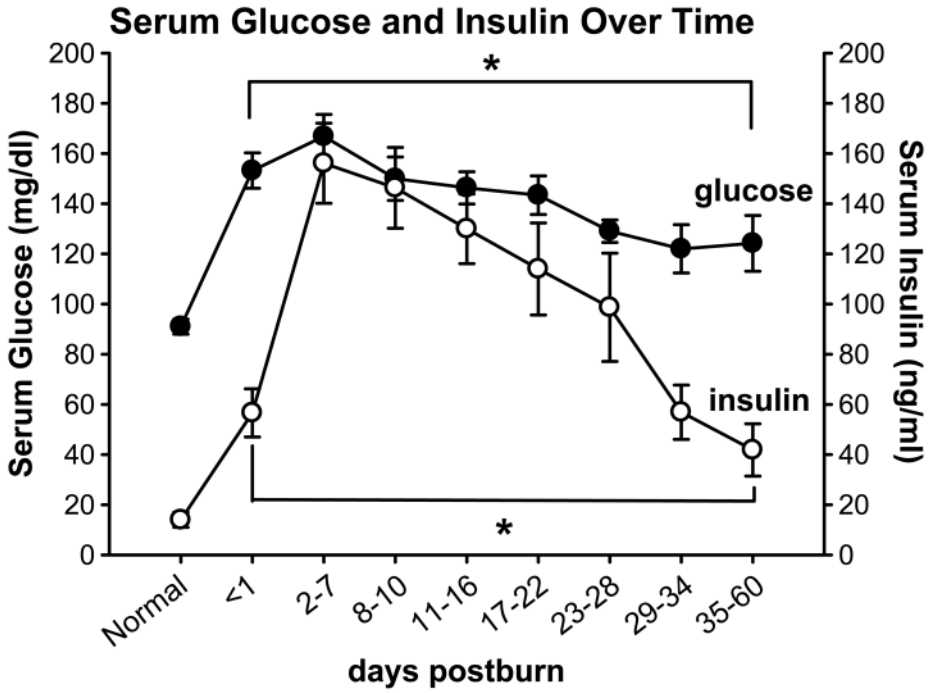

Figure 5.
Serum glucose increased during the acute phase postburn along with increased levels of endogenous insulin implying the presence of insulin resistance. * Significant difference between burned children vs. normal range, $p<0.05$.

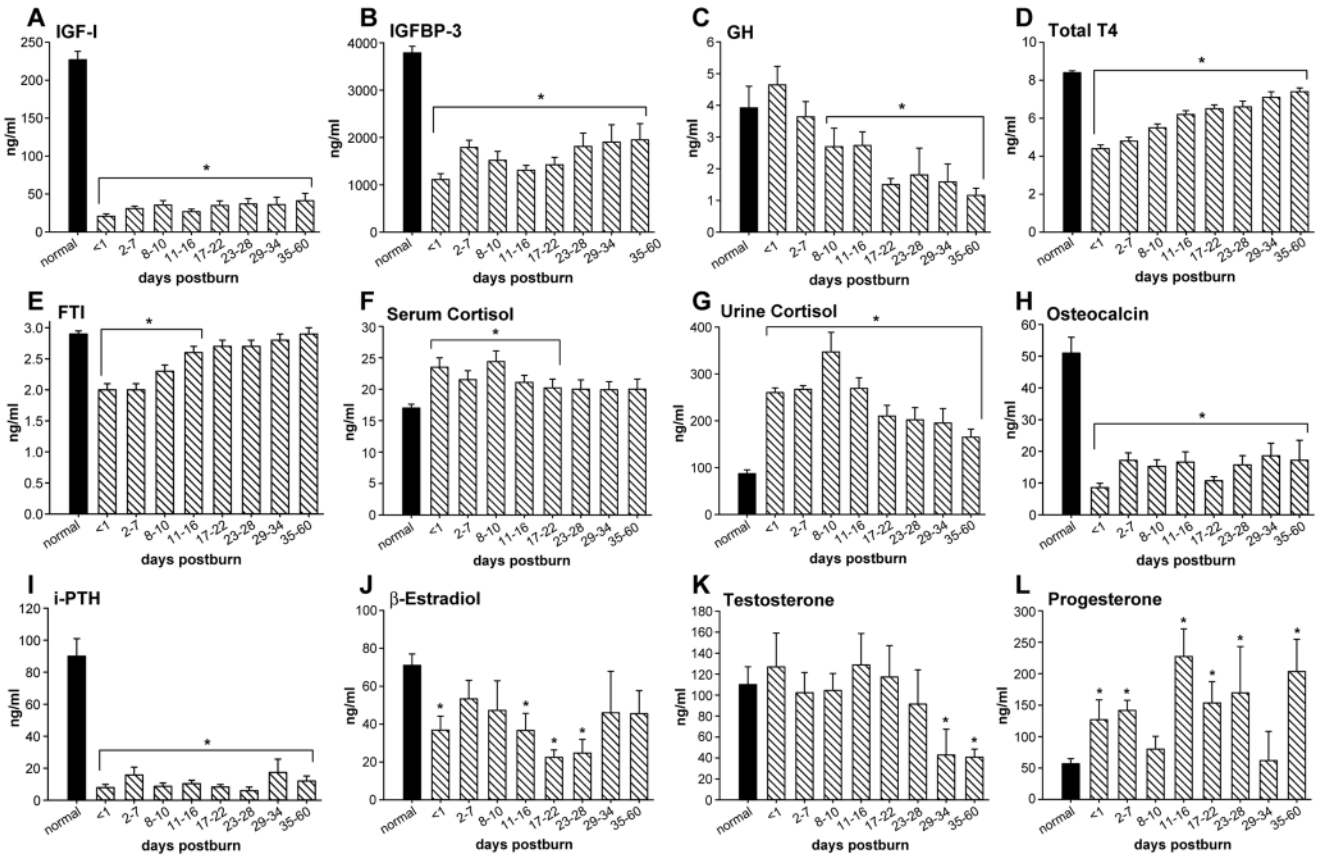

Figure 6.

Serum hormone levels. Serum IGF-I and IGFBP-3 (A–B) decreased markedly immediately after burn and remained significantly decreased throughout acute hospitalization. Serum GH (C) started to decrease 8–10 days postburn and showed a steady decline through acute hospitalization. Serum T4 (D) decreased immediately postburn but increased through acute hospitalization. Free thyroid index (FTI, E) showed a significant decrease for 14 days postburn and then returned to normal levels with no apparent difference. Serum cortisol (F) significantly increased immediately postburn and remained elevated for 3 weeks returning to normal levels. Urine cortisol (G) increased 5–7 folds during the acute stay but decreased over time. Serum osteocalcin (H) and iPTH (I) were drastically decreased (5–7 folds) immediately after burn and showed almost no increase over time. Serum β-estradiol (J) decreased immediately postburn but increased over time; testosterone (K) was normal during the early postburn phase, but showed marked decreases beginning 4 weeks postburn. Progesterone (L) was increased at various time points when compared with normal. * Significant difference between normal vs. burn, $p<0.05$.

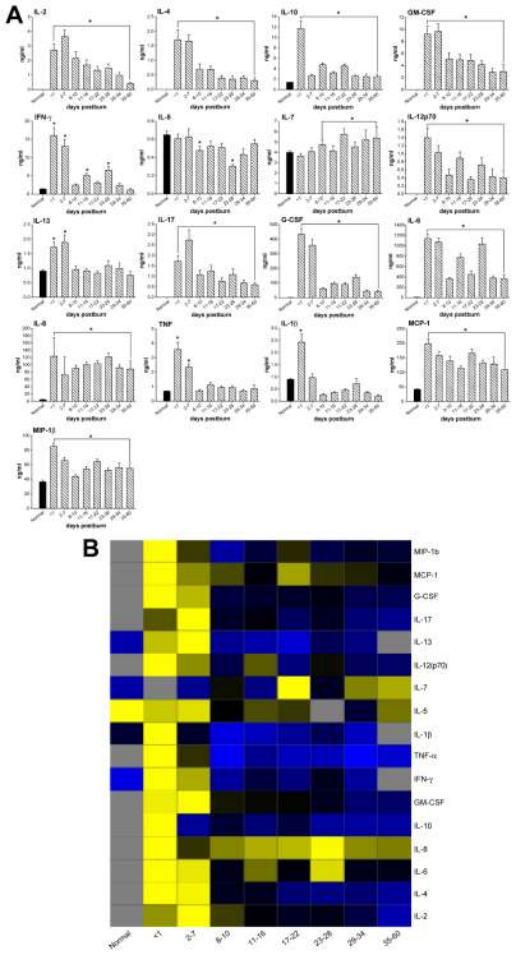

Figure 7.

All of the 17 serum cytokines measured were significantly altered (A) and these perturbations are possibly clinically relevantly. Dramatic changes were observed for serum G-CSF, IL-6, IL-8, MCP-1, and MIP-1β. * Significant difference between burn vs. normal ranges, $p<0.05$. Heat map (B) comparing normal (non-injured, non-burned children), and burned children controls at each time point <1 days postburn, (2–7 days postburn, 8–10 days postburn, 11–16 days postburn, 17–22 days postburn, 23–28 days postburn, 29–34 days postburn, and 35–60 days postburn. Values are $\log_{10}$ (average cytokine concentration, pg/ml); the color range for each cytokine is based on the detected values with blue indicating lower levels, yellow indicating highest levels, and black in the middle. Gray squares indicate that no expression was detected.

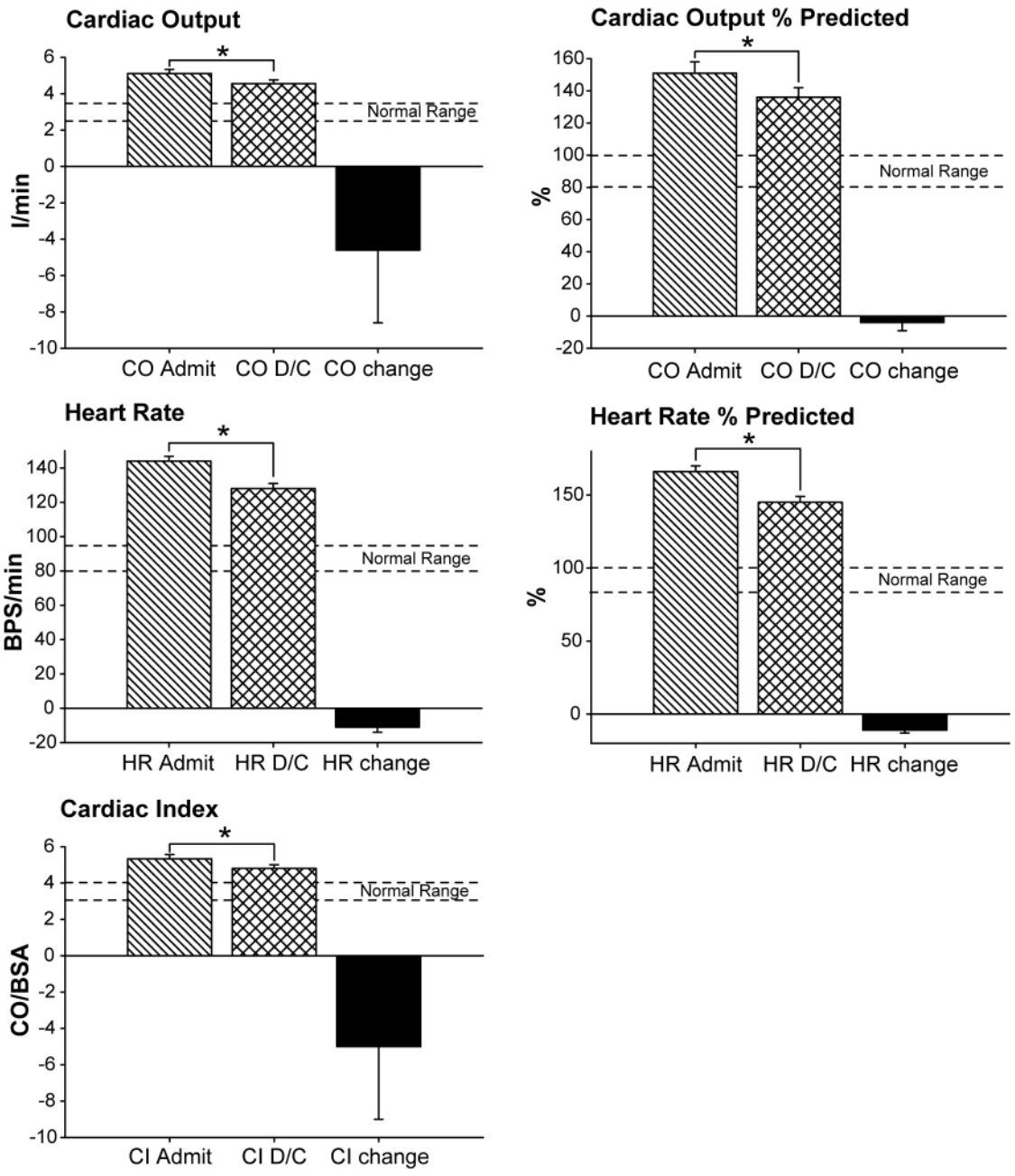

Figure 8.

Cardiac output and predicted cardiac output was increased immediately postburn (up to 160% of predicted) and significantly decreased until discharge. Heart rate and predicted heart rate were also significantly increased postburn and remained elevated at discharge. Cardiac index was increased immediately postburn and significantly decreased from admission to discharge. * Significant difference between admission and discharge, $p<0.05$.

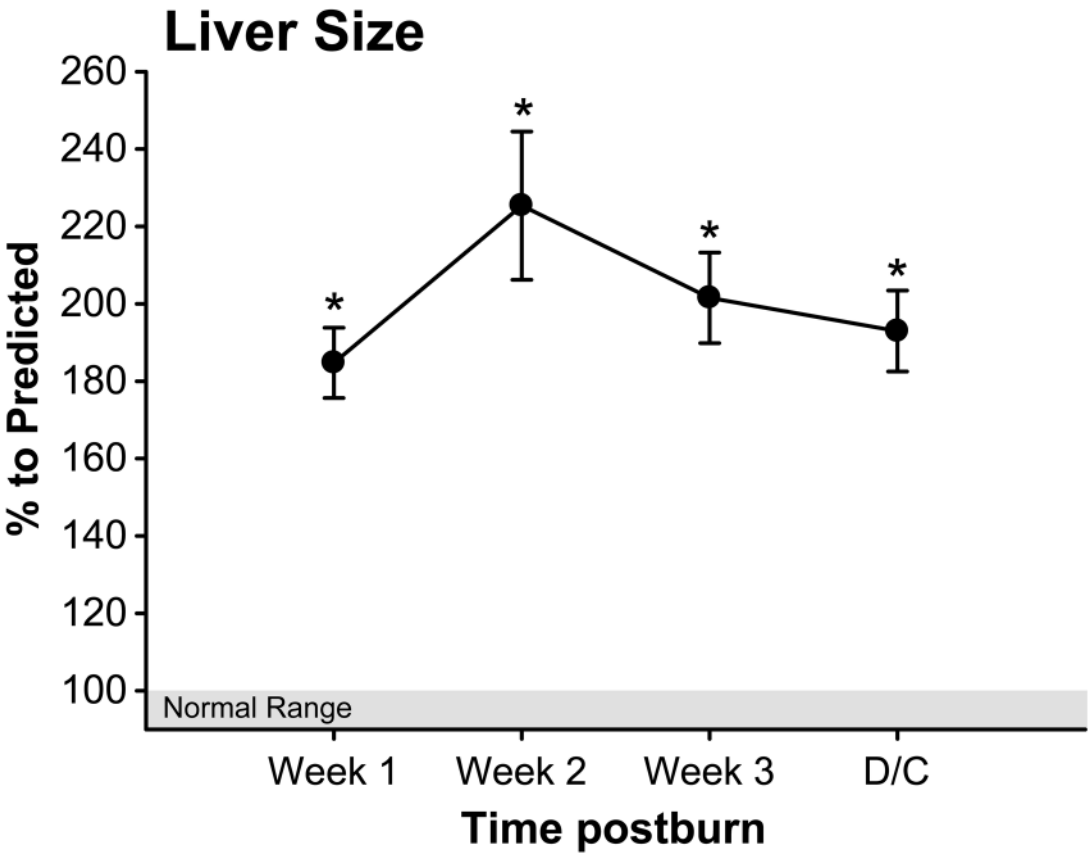

Figure 9.
Immediately after burn, liver size doubled and at week 2, postburn was 220% of predicted liver size. Liver size remained elevated when patients were discharged from the ICU. * Significant difference between burn vs. normal range, $p<0.05$.

Table 1

Patient demographics.

	>30% TBSA N=242
Age (yrs)	8.0±0.2
Gender (F/M)	97/145
Time to admission (days)	6.7±0.7
LOS (days)	31±0.7
TBSA (%)	56±0.3
3rd degree (%)	43±0.3
Los/% TBSA (days/%)	0.55±0.2
OR's (n)	4.3±0.12
Time between operations (days)	8±0.3
Inhalation Injury (%)	32
Wound Infections (n)	2.5±0.2
Sepsis (%)	18
Multi Organ Failure (%)	21
Mortality (%)	8

TBSA = total body surface area. Data presented as means±SEM or percentages.