ORIGINAL ARTICLE

Extended Hypermetabolic Response of the Liver in Severely Burned Pediatric Patients

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Hypothesis: The acute phase response is a cascade of events contributing to hypermetabolism and substrate catabolism. It was believed to persist for only a short time after injury. There is now evidence that systemic catabolism and hypermetabolism associated with thermal injury persevere for a long time. We hypothesize that the proinflammatory hepatic acute phase response perseveres for an extended time and enhances hypermetabolism longer than previously believed.

Design: Prospective study.

Setting: Intensive Care Burn Unit, Shriners Hospital for Children.

Patients: Twenty-three children (aged 1-16 years) sustaining a severe thermal injury (≥40% total-body surface area) who remained in the intensive care unit longer than 30 days.

Main Outcome Measures: Patient demographics, nutritional support, incidence of sepsis, inhalation injury, mortality, and levels of serum constitutive proteins, type I and type II acute phase proteins, free fatty acids, proinflammatory cytokines, insulin-like growth factor (IGF) I, IGF binding protein-1, IGF binding protein-3, and hepatocyte growth factor.

Results: After thermal injury, constitutive hepatic protein levels decreased 2- to 3-fold 80 days after burn, whereas acute phase protein levels increased. Free fatty acid levels were increased 5 days after burn. Proinflammatory cytokine levels (interleukin [IL] 1, IL-6, IL-8, IL-10, and tumor necrosis factor) and IGF binding protein-1 levels were elevated for 40 days after burn, whereas serum IGF-I and IGF binding protein-3 levels were decreased. Hepatocyte growth factor levels were increased immediately after burn but rapidly returned to the normal range.

Conclusions: Despite adequate nutritional support, a severe thermal injury induces the proinflammatory acute phase response for a prolonged period. Thus, the liver with the hepatic acute phase response plays a more important role during catabolism after burn than previously believed. Pharmacologic agents that improve hepatic function may be an effective approach to attenuate hypermetabolism after trauma.

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THE PROINFLAMMATORY acute phase response is an orchestrated cascade of events in response to tissue injury, infection, or inflammation.[1-4] Characteristic of the acute phase response is up-regulation of acute phase proteins and a concomitant decrease in constitutive hepatic protein levels.[1-10] Mediators of the acute phase response are proinflammatory cytokines, such as interleukin (IL) 1β, IL-6, tumor necrosis factor α (TNF-α), IL-8, and IL-10.[1-3,11] The aim of the acute phase response is to restore homeostasis and organ equilibrium. A sustained or exaggerated acute phase response has been shown to be potentially life threatening, with the uncontrolled and prolonged action of proinflammatory cytokines and acute phase proteins being associated with hypermetabolism and catabolism, leading to the compromise of essential organs and thus to multiple-organ failure and increased morbidity and mortality.[12-18] Down-regulation of constitutive hepatic proteins may further augment these detrimental effects.[12-14] The metabolic rate in burns is extremely high; energy requirements are immense and are met by the mobilization of proteins and amino acids. Increased protein turnover, degradation, and negative nitrogen balance are all characteristic of this severe critical illness.[15,16] Consequently, the structure and function of essential organs, such as the liver, skeletal muscle, skin, immune system, and cellular membrane transport functions, are

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compromised.[17,18] Increased and prolonged action of the proinflammatory acute phase response enhances protein degradation and catabolism and may be associated with an increased incidence of multiple-organ system failure and ongoing sepsis.

In previous human and animal studies,[19,20] we showed that the hepatic acute phase response plays an important role immediately after burn trauma. The long-term role of the acute phase response after burn has not been defined. Recent studies,[21,22] however, have revealed that after a severe burn, resting energy expenditure and peripheral protein catabolism are increased for more than 9 months. These data led us to hypothesize that hypermetabolic mediators must be expressed over a longer period than expected, and the hepatic acute phase response perseveres for an extended period and thus mediates hypermetabolism and catabolism.[21,22] The purpose of this study is to determine whether a severe cutaneous thermal injury induces proinflammatory cytokine production, the hepatic acute phase response, and, thus, hypermetabolism in the short or long term.

METHODS

Thermally injured children with the following inclusion criteria were placed in a prospective study: 1 to 16 years of age, admitted within 3 days of injury to our institute (Shriners Hospital for Children, Galveston Burn Unit, Galveston), and burns covering 40% or more total-body surface area (TBSA) with a third-degree component of greater than 10% that required a minimum harvesting of 1 donor site for skin grafting. Patient demographics (age, date of burn and hospital admission, sex, burn size, and depth of burn) and concomitant injuries, such as inhalation injury, sepsis, morbidity, and mortality, were recorded. Sepsis was defined by a blood culture identifying the pathogen during hospitalization or at autopsy, in combination with leukocytosis or leukopenia, hyperthermia or hypothermia, and tachycardia.

Patients were resuscitated according to the Galveston formula with 5000 mL/m^2 TBSA burned + 2000 mL/m^2 TBSA lactated Ringer solution given in increments during the first 24 hours. Within 48 hours of hospital admission, all patients underwent total burn wound excision, and the wounds were covered with available autograft skin, with allograft used to cover any remaining open areas. After the first operative procedure, the donor site healed in 5 to 10 days, and patients were then taken back to the operating room. This procedure was repeated until all open wound areas were covered with autologous skin material.

The mean wound-healing time per percentage of third-degree burn is approximately 0.5 day. Because we wanted to know whether the hepatic acute phase response remains elevated after complete wound healing, and given a burn of 40% to 60% TBSA, we included patients who remained in the intensive care unit (ICU) for longer than 30 days. Blood samples were taken at the time of admission, on the first day after admission, then every fifth day up to 40 days, and then every 10 days until discharge or 80 days after burn. Almost all the patient data were available for measurement at each point.

NUTRITION

To exclude the effect of nutrition, we ensured that all patients underwent the same nutritional treatment according to a standardized protocol. The initial assessment for nutritional need is calculated by the Curreri formula, which is an accepted standard for estimating basal energy expenditure. This formula calls for 25 kcal/kg per day plus 40 kcal/% TBSA burned per day. It provides the needs plus the additional caloric needs of the burn wounds. In children, formulas based on body surface area are more appropriate because of greater body surface per kilogram. For children, we used the Galveston formulas: Galveston Infant, Galveston Revised, and Galveston Adolescent. The formula changes with age based on the body surface alterations that occur with growth. Generally, the intake is calculated as 1500 kcal/m^2 body surface plus 1500 kcal/m^2 burn area. The composition of the nutritional supplement is also important. The optimal dietary composition contains 1 to 2 g/kg per day of protein, which provides a calorie-nitrogen ratio of approximately 100:1 with the suggested caloric intakes. Nonprotein calories can be given either as carbohydrate or as fat, with clinical advantages for the carbohydrates.

The diet may be delivered in 2 forms, either enterally through enteric tubes or parenterally through intravenous catheters. Herndon et al[23] showed that total parenteral nutrition increased mortality by almost 50% compared with enteral nutrition. Therefore, we used enteral nutrition if possible in all our patients. Total parenteral nutrition was used only as a supplemental form of nutrition when calculated intake was not achieved, which never occurred.

ALBUMIN SUPPLEMENTATION REQUIREMENT

Serum albumin levels were measured daily at 4:30 AM. If serum albumin concentrations were less than 2.0 g/dL, albumin was supplemented based on age and body weight to maintain colloid osmotic pressure at 2.0 g/dL. Children younger than 2 years and less than 20 kg body weight received exogenous albumin, 6.25 g/d, over 6 hours; children aged 2 to 9 years weighing greater than 20 kg but less than 40 kg received 12.5 g/d over 6 hours; and children aged 10 to 18 years weighing greater than 40 kg received 25 g/d. Total amount of albumin infused, amount of albumin infused per day, and amount of albumin infused per square meter burned were calculated. Amount and distribution of caloric intake were determined for each patient.

SERUM CONSTITUTIVE HEPATIC PROTEINS, ACUTE PHASE PROTEINS, AND SERUM FATTY ACIDS

Levels of serum constitutive hepatic proteins, such as transferrin, prealbumin, and retinol binding protein; type I serum acute phase proteins, such as α_1-acid glycoprotein and C-reactive protein; type II serum acute phase proteins, such as α_2-macroglobulin, α_1-antitrypsin, haptoglobin, and free fatty acids; and triglyceride were measured using a nephelometer (Dade Behring, Deerfield, Ill) with N-antisera to different serum proteins (Behring Diagnostics Inc, Westwood, Mass).

SERUM CYTOKINES, IGF-I, IGFBP-1, AND IGFBP-3 AND PLASMA HGF

Serum TNF-α, IL-1β, IL-6, IL-8, and IL-10 levels were determined using a human enzyme-linked immunosorbent assay (Endogen Inc, Woburn, Mass, or Biosource International, Camarillo, Calif) on days 0 (admission), 10, 20, and 40 after burn. Serum insulin-like growth factor (IGF) I, IGF binding protein-1 (IGFBP-1), and IGF binding protein-3 (IGFBP-3) levels were determined using radioimmunoassay (Nichols Institute Diagnostics, San Clemente, Calif). The plasma hepatocyte growth factor (HGF) level was determined using an enzyme-linked immunosorbent assay for HGF (Institute of Immunology, Snow Brand Milk Products Co, Tokyo, Japan). The standard range was linear from 0 to 20 ng/mL.

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Table 1. Patient Demographics, Nutritional Intake, and Albumin Substitution Requirements of 23 Severely Burned Pediatric Patients*

Characteristic	Value
Age, y	5.7 ± 3.9
Sex, F/M, No.	11/12
TBSA, %	67 ± 14
Third-degree burn, %	59 ± 20
Length of ICU stay, d	63 ± 30
Ventilator use, d	8 ± 17
Inhalation injury, %	56
Incidence of sepsis, %	40
Onset of sepsis, d	31 ± 18
Time to 95% wound healed, d	42 ± 20
Mortality, %	13
Nutritional intake	
Caloric intake, % calculated	92 ± 7
Protein, % of total calories	79 ± 16
Fatty acids, % of total calories	19 ± 9
Albumin substitution requirement	
Total albumin, g	214 ± 200
Albumin per day, g	3.4 ± 2.3
Albumin, g/m^2 burn	273 ± 193

Abbreviations: ICU, intensive care unit; TBSA, total-body surface area.
*Data are given as mean ± SD except as indicated otherwise.

ETHICS AND STATISTICAL ANALYSIS

This study was reviewed and approved by the institutional review board of the University of Texas Medical Branch. Before the study, each participant, parent, or legal guardian signed a written informed consent form. Analysis of variance with post hoc Bonferroni correction, paired and unpaired Student *t* tests, χ^2 analysis, and Mann-Whitney tests were used where appropriate. Data are expressed as mean ± SEM. Significance was accepted at $P<.05$.

RESULTS

Twenty-three severely burned children were included in the study. Patient demographics are given in **Table 1**. Patients stayed in the ICU 63 ± 30 days and required 8 ± 17 days of mechanical ventilation support. Nine patients had sepsis, which was diagnosed 31 ± 18 days after burn. Overall mortality was 13% (3 of 23 patients). The deaths were late deaths, around the 60th day after burn.

NUTRITION AND ALBUMIN REQUIREMENT

Despite equal amounts of caloric intake and distribution of the calories, serum albumin substitution was required. The amount of albumin required for substitution, expressed as total albumin amount, albumin amount per day, or albumin amount per square meter of burned surface area, is given in Table 1.

SERUM CONSTITUTIVE HEPATIC PROTEINS, ACUTE PHASE PROTEINS, AND SERUM FATTY ACIDS

Levels of serum prealbumin, transferrin, and retinol binding protein, which are all constitutive hepatic proteins, declined below normal levels within 1 day after burn (**Figure 1**). Protein levels started to increase as early as 10 days after burn but remained low during the entire study. The decrease at 40 to 50 days after burn is most likely due to the onset of sepsis. Most important is the finding that 80 days after burn, the constitutive hepatic proteins prealbumin and transferrin did not reach normal levels ($P=.01$).

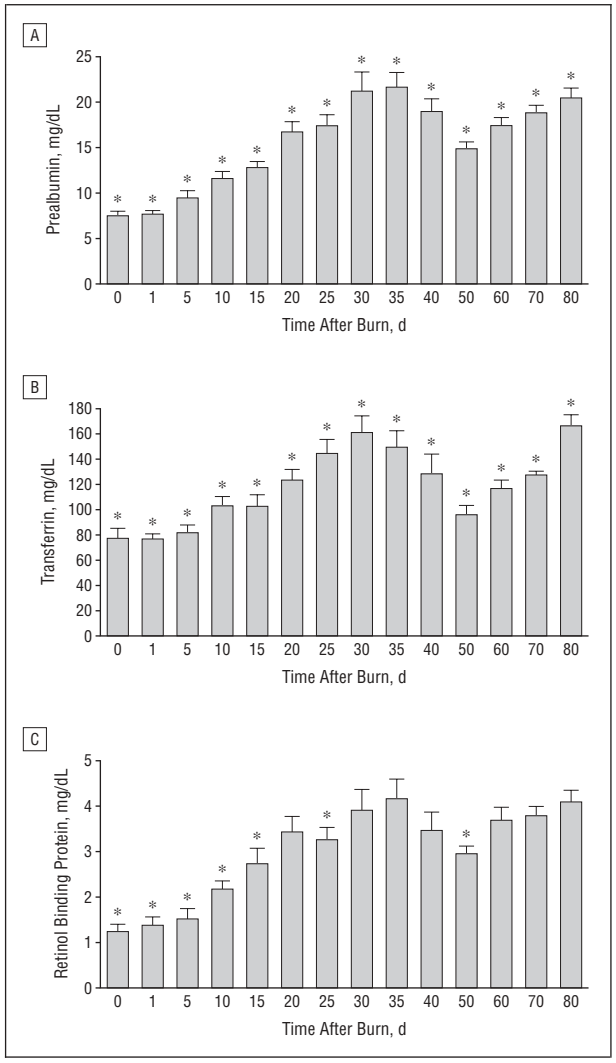

Figure 1. Mean constitutive hepatic protein concentrations after thermal injury. A, Serum prealbumin levels declined by 85% immediately after burn and had a slow recovery. Asterisks indicate significant difference between patients and age-matched controls: 35 ± 5 mg/dL ($P<.001$). B, Serum transferrin levels were decreased 3- to 4-fold compared with normal. Eighty days after burn, levels did not reach normal concentrations. Asterisks indicate significant difference between patients and age-matched controls: 310 ± 50 mg/dL ($P<.001$). C, Serum retinol binding protein levels were lowered by nearly 70% the first day after burn. Asterisks indicate significant difference between patients and age-matched controls: 5.0 ± 0.2 mg/dL ($P<.05$). Error bars represent standard error of the mean.

Levels of the serum type I acute phase proteins α_1-acid glycoprotein and C-reactive protein increased immediately after burn and continued to increase until days 15 and 20 after thermal injury (**Figure 2**A and B). The elevation around day 40 is again most likely due to the onset of sepsis. Although C-reactive protein approached normal levels 80 days after burn, α_1-acid glycoprotein levels remained elevated ($P=.02$).

Levels of the serum type II acute phase proteins haptoglobin and α_1-antitrypsin increased 2- to 5-fold above

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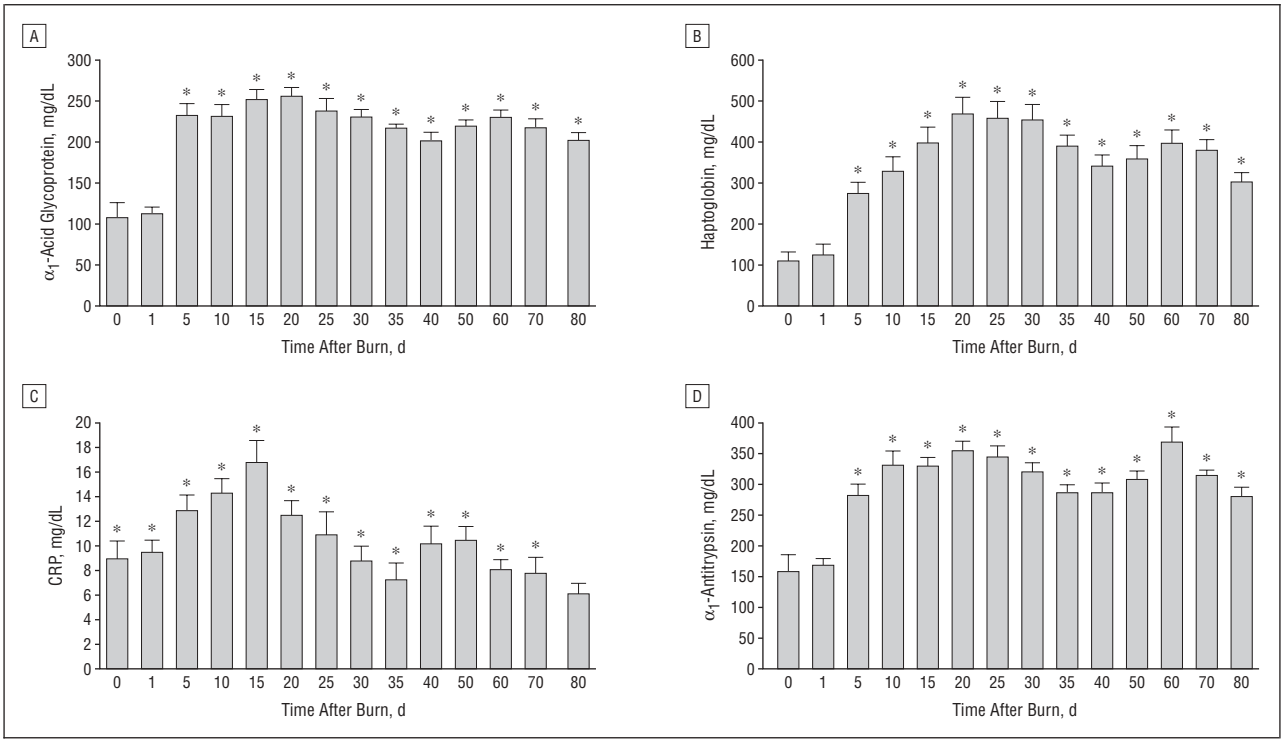

Figure 2. Mean type I (A and B) and type II (C and D) acute phase protein levels after thermal injury. A, Serum α_1-acid glycoprotein levels increased 10 days after burn and remained elevated throughout the study. B, Serum C-reactive protein (CRP) levels increased immediately after burn and peaked 15 days after burn. At the end of the study, CRP approached normal levels. C, Serum haptoglobin levels increased above normal within 10 days and remained elevated up to 80 days after burn. D, Serum α_1-antitrypsin levels increased above normal within 10 days and returned to normal at 40 and 80 days after burn. Asterisks indicate significant difference between patients and age-matched controls ($P<.001$). Error bars represent standard error of the mean.

normal after thermal injury within 5 to 15 days and started to decrease 25 to 30 days after injury (Figure 2C and D). Both acute phase protein levels remained increased during the full 80 days ($P=.02$). α_2-Macroglobulin remained at normal levels for 25 days and then demonstrated a slight increase, which was not statistically significantly different from control values.

Serum triglyceride levels increased above normal 10 days after burn and remained elevated until day 80 after burn ($P=.03$) (**Figure 3**A). In contrast to triglyceride levels, serum free fatty acid levels increased immediately after burn and then decreased to normal 5 days after burn (Figure 3B).

Striking was the finding that constitutive hepatic protein levels remained low and acute phase protein levels remained increased after 95% wound healing, which was approximately 40 days after the thermal injury.

SERUM CYTOKINES

All serum cytokine levels were elevated immediately after thermal injury. Serum TNF levels were significantly increased from day 0 to day 20 after burn, with a peak immediately after burn, and then showed a steady decline until TNF approached normal levels 40 days after burn (**Figure 4**A). Serum IL-1β levels showed a decrease from day 0 to day 20 after burn (Figure 4B). Levels of IL-1β remained at a plateau and were significantly elevated compared with normal levels during the entire 40 days after burn ($P=.05$). Serum IL-8 levels were nearly 100-fold increased compared with normal immediately after burn but decreased over time. However, IL-8 levels were still increased 40 days after the burn insult compared with normal ($P=.04$) (Figure 4C). Serum IL-6 levels were increased 0 and 10 days after thermal injury but decreased to normal 20 and 40 days after burn ($P=.02$) (Figure 4D). Serum IL-10 levels increased immediately after burn approximately 10-fold compared with normal, decreased, and then approached normal levels during the study (Figure 4E). Levels of IL-10 were significantly increased 40 days after burn compared with age-matched controls ($P=.02$) (Figure 4E).

PLASMA HGF

Plasma HGF levels increased immediately after burn and peaked 10 days after burn. Normal plasma HGF levels were reached 30 days after burn. However, levels increased again 60 days after injury and remained significantly elevated up to 70 days after burn ($P=.03$) (**Figure 5**).

SERUM IGF-I, IGFBP-1, AND IGFBP-3

Serum IGF-I levels decreased immediately after burn and remained low 40 days after thermal injury ($P<.05$) (**Table 2**). Levels of IGFBP-1 increased at days 0 and 10 after thermal injury and then approached normal levels. Serum IGFBP-3 levels, similar to IGF-I levels, decreased from the beginning of the injury throughout the entire study ($P=.01$).

COMMENT

It was believed that the hepatic acute phase response, which contributes to catabolism, persists only for a short

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time and then returns to normal. The metabolic rate in burns is extremely high; energy requirements are immense and are met by the mobilization of proteins and amino acids. Increased protein turnover, degradation, and negative nitrogen balance are characteristic of this severe critical illness.[15,16] Consequently, the structure and function of essential organs, such as skeletal muscle, skin, immune system, and cellular membrane transport functions, are compromised.[17,18] We showed that type I and type II acute phase protein levels were increased 2- to 3-fold above normal levels. Acute phase protein levels increased 5 to 10 days after the trauma and stayed elevated for 80 days after burn. All type I and type II acute phase protein levels showed, after a decrease, another increase around 50 days after burn. From our recordings, we associated that time point with the onset of sepsis, and this would explain why acute phase protein levels increased again. Most acute phase protein levels were still elevated 80 days after burn, indicating the perseverance of the hepatic acute phase response. Type II acute phase protein α_2-macroglobulin levels demonstrated a delayed and only slight increase above normal, and we, therefore, suggest that α_2-macroglobulin level may be not an adequate marker to determine the severity of the hepatic acute phase response after thermal injury.

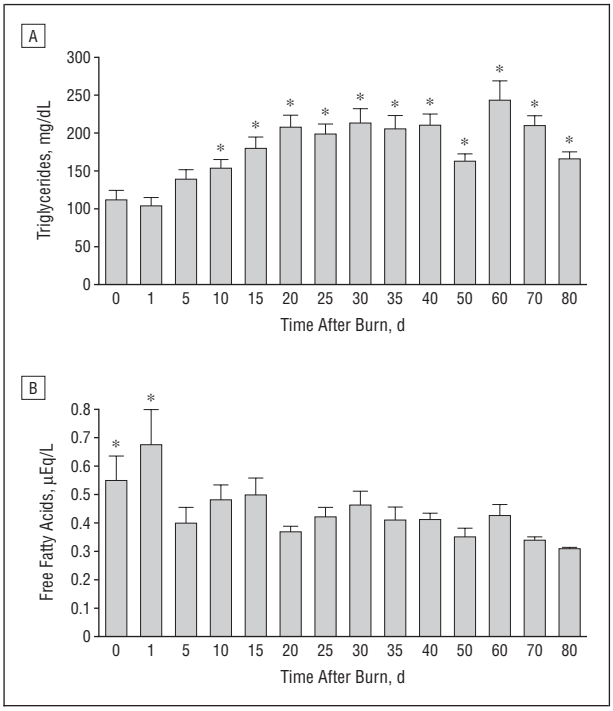

Figure 3. Mean serum triglyceride and free fatty acid concentrations in burned children. A, Serum triglyceride concentrations increased above normal 10 days after burn and approached normal concentrations 80 days after burn. Asterisks indicate significant difference between patients and age-matched controls: 110±13 mg/dL ($P<.001$). To convert triglycerides from milligrams per deciliter to millimoles per liter, multiply milligrams per deciliter by 0.0113. B, Serum free fatty acid levels were increased only immediately and 1 day after burn and then returned to normal values. Asterisks indicate significant difference between patients and age-matched controls: 0.3±0.05 µEq/L ($P<.05$). Error bars represent standard error of the mean.

Constitutive hepatic protein levels declined 3- to 4-fold below normal immediately after burn and remained low throughout the study. Because of adequate nutritional support (93% of the calculated rate), the decline in constitutive hepatic protein levels was most likely due to decreased hepatic synthesis and expression. Another marker for the hepatic impairment was the requirement for albumin substitution. During the ICU course, 214 g of albumin (3.4 g/d) was required for substitution to maintain serum albumin levels at 2.5 mg/dL. These data are in agreement with our animal studies,[8,19] but it was surprising that the decline in constitutive hepatic protein levels persisted after the burn wound was 95% healed and proinflammatory cytokine levels approached normal. Decreased albumin level is a well-documented response to acute injury and illness, and a consensus regarding albumin supplementation is not defined. Decreased albumin concentration is tolerated and not corrected with exogenous albumin therapy in other critically ill patients. Some studies[24] demonstrated increased morbidity with albumin supplementation, whereas other studies[9,10] demonstrated beneficial effects of albumin supplementation. At our institute (Shriners Hospital for Children), in severely burned children it is standard to substitute and supplement albumin according to the standard given previously herein. However, we also investigate other possibilities to increase endogenous albumin synthesis by the administration of anabolic growth factors, such as growth hormone, IGF-I, or insulin.

Proinflammatory cytokines are the mediators of the hepatic acute phase response.[1] In the present study, proinflammatory cytokine levels were statistically signifi-

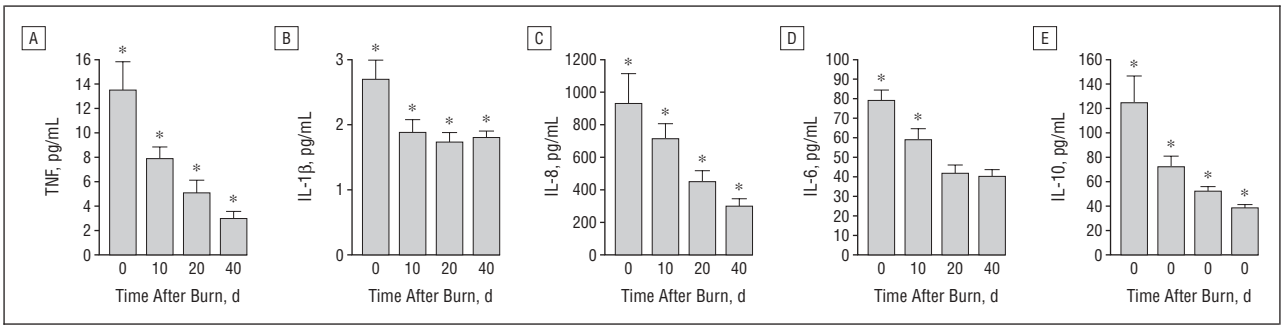

Figure 4. Mean serum cytokine levels after thermal injury. A, Serum tumor necrosis factor (TNF) levels increased immediately after burn and decreased at 40 days. B, Serum interleukin (IL) 1β levels decreased from day 0 to day 20 and demonstrated a slight increase at day 40, which was probably due to the onset of sepsis. Serum IL-1β never reached normal levels during the study. C, Serum IL-8 levels increased 100-fold after burn and decreased over time but remained elevated compared with normal IL-8 levels. D, Serum IL-6 levels increased 0 and 10 days after thermal injury but decreased to normal 20 and 40 days after burn. E, Serum IL-10 levels increased 10-fold immediately after burn, decreased, and then approached normal levels during the study. Asterisks indicate significant difference between patients and age-matched controls ($P<.001$). Error bars represent standard error of the mean.

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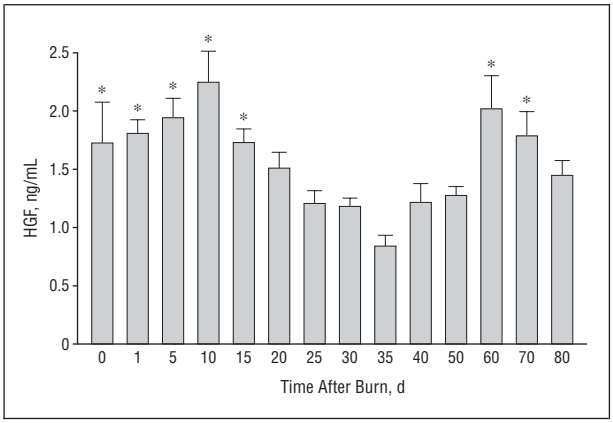

Figure 5. Mean plasma hepatocyte growth factor (HGF) concentrations after burn. Levels of HGF increased immediately after burn and at the onset of sepsis. Asterisks indicate significant difference between patients and age-matched controls: 0.5±0.2 ng/mL ($P<.001$). Error bars represent standard error of the mean.

Table 2. Serum IGF-I, IGFBP-1, and IGFBP-3 Concentrations*

	Days After Burn			
	0	10	20	40
IGF-I, μg/mL	92 ± 36†	84 ± 37†	115 ± 70†	147 ± 42†
IGFBP-1, μg/mL	170 ± 100†	150 ± 100	95 ± 80	89 ± 100
IGFBP-3, μg/mL	0.6 ± 0.2†	0.7 ± 0.2†	0.8 ± 0.2†	1.0 ± 0.4†

Abbreviations: IGF-I, insulin-like growth factor I; IGFBP-1, IGF binding protein-1; IGFBP-3, IGF binding protein-3.
*Data are given as mean ± SD.
†Significant difference between burned patients and age-matched controls: IGF-I: 365 ± 15 μg/mL; IGFBP-1: 115 ± 15 μg/mL; and IGFBP-3: 2.8 ± 0.9 μg/mL ($P<.001$ for all).

cantly increased for at least 40 days after thermal injury. Despite decreased cytokine levels, we found that constitutive hepatic protein levels were still decreased, whereas acute phase protein levels were still increased. This leads us to hypothesize that beside the cytokine-protein regulation loop, another regulative mechanism must be present, such as a protein-protein regulation loop. Despite the need of intact liver function for survival after trauma, a variable degree of liver injury is present, and it is usually related to the severity of the thermal injury. Fatty acid infiltration, a very common finding, are per se reversible, and their importance depends on the cause and severity of accumulation.[25] The mechanisms of fatty acid infiltration have been discussed in clinical studies,[26,27] where the authors speculated that a thermal injury increased peripheral lipolysis and, owing to a lack of transporter proteins (low-density and high-density lipoproteins), triglycerides accumulated in the liver. The clinical significance of fat accumulation has recently been shown by Barret et al.[28] In burned children who died, fatty liver infiltration was associated with increased bacterial translocation, liver failure, and endotoxemia.[28] Another mode of liver damage is due to increased hepatic edema formation, which leads to cell damage and the release of hepatic enzymes.[29] A third factor that causes liver damage is hepatocyte apoptosis.[29] Our group[29] has shown that a cutaneous thermal injury causes increased hepatocyte apoptosis. That liver damage is in fact present in our study is shown by increased HGF levels during the early postburn period and again at the onset of sepsis. Hepatocyte growth factor has been shown to accelerate hepatic regeneration and improve hepatic function in rats after trauma.[30] Within 30 to 60 minutes of injury, the plasma HGF level is elevated, presumably sending a strong mitogenic signal to the hepatocytes, which are already primed by IL-6, TNF, or insulin.[31] The rapid increase in the HGF concentration stimulates hepatocyte mitogenesis, motogenesis, and DNA synthesis.[31] Hepatocyte growth factor, however, is not the only factor enhancing and accelerating liver regeneration. Michalopoulos and DeFrances[31] delineated the importance of *IGF-I* and *IGFBP* genes during liver regeneration. The activation of transcription factors stimulates the expression of *IGF-I* and *IGFBP* genes, and *IGF-I* activates receptors and transcription factors.[32] Hepatocyte growth factor has been shown to induce the expression of early genes, such as *IGFBP-1*, which is believed to modulate the mitogenic effects of IGF-I on nonparenchymal liver cells.[31,33] Our group[19] recently showed that IGF-I improves liver homeostasis after thermal injury through increased hepatocyte proliferation and decreased apoptosis. Thus, HGF not only directly stimulate hepatocyte growth but also indirectly stimulate nonparenchymal liver cell growth through enhancement of the mitogenic effects of IGF-I. In this study, we showed that serum IGF-I and IGFBP-3 levels were decreased and IGFBP-1 levels were increased after burn. Thus, it is possible that the lack of IGF-I may prevent HGF from exerting its liver regenerative effect. The decreases in serum IGF-I and IGFBP-3 concentrations further indicate the persistence of hypermetabolism, as IGF-I and IGFBP-3 have been shown to be sensitive markers for the metabolic rate.[25]

In critically burned children, an ICU stay of 0.5 day per percentage of TBSA burn is necessary. We found in this study that healing time was indeed 0.5 day per percentage of TBSA burn, but the ICU stay was 1 day per percentage of TBSA burn. We do not know why these patients stayed in the ICU longer than other patients, as these patients were not more ill than others. Another issue that needs to be addressed is the effect of surgery, blood transfusion, and anesthesia on the hypermetabolic response. Studies[34] delineated the importance of transfusion and surgery on patient outcome. However, we did not determine the impact of surgery, blood transfusion, or anesthesia on the hepatic acute phase response as it was not part of the present study. We further hypothesize that the thermal injury was the most significant factor for induction of the acute phase response.

In the present study, we demonstrate the importance of the liver in the aftermath of a severe trauma. In contrast to recent knowledge, we demonstrate that the acute phase response persists for a long time, thus contributing to catabolism and, therefore, to the compromise of the structure and function of essential organs. Based on these data, we suggest that the liver plays a more important role during catabolism after burn than previously thought, thus allowing new therapeutic ap-

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proaches to improve patient survival after burn because new therapeutic agents modulating the hepatic acute phase response by restoring hepatic homeostasis, increasing constitutive hepatic protein levels, and decreasing acute phase protein and proinflammatory cytokine levels may improve not only hepatic function and structure but also hypermetabolism, catabolism, and, thus, clinical outcome after a severe thermal injury.

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