ORIGINAL ARTICLE

Modulation of Inflammatory and Catabolic Responses in Severely Burned Children by Early Burn Wound Excision in the First 24 Hours

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Hypothesis: Early burn wound excision modulates the hypermetabolic response in severe pediatric burn injuries.

Design: Before-after trial.

Setting: A 30-bed burn referral center in a private, university-affiliated hospital.

Methods: We studied 35 severely burned children who were divided into 2 groups. One group (n=20) was treated with early burn wound excision within 24 hours after the injury. The second group (n=15) was treated conservatively with silver sulfadiazine in other burn facilities for 5 days, and burn wounds were surgically excised when patients were admitted to our burn center on day 6 after the injury. Data compiled included oxygen consumption and acute-phase protein, interleukin 1β; interleukin 6, interleukin 10, tumor necrosis factor α, and anabolic hormone (growth hormone, insulinlike growth factor type 1) levels preoperatively and 24 hours and 5 days postoperatively.

Main Outcome Measures: Acute-phase and hypermetabolic responses.

Results: Early burn wound excision abrogated the hypermetabolic response in pediatric burn patients. Patients who underwent conservative treatment had a significantly more severe inflammatory and hypermetabolic response at the same time interval and significantly lower levels of anabolic hormones.

Conclusions: Early burn wound excision is a safe therapeutic approach that modulates the hypermetabolic response after burn injury. It was superior to the conservative treatment of silver sulfadiazine and delayed excision, and it should be considered when treating all severe full-thickness burns.

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SEVERE BURNS and major trauma are associated with an acute and persistent hypermetabolic response characterized by hyperdynamic circulation and increased circulating levels of catabolic hormones. Increases in catecholamine, glucagon, and cortisol levels raise energy requirements. The development of postinjury insulin resistance with alteration of glucose transport and futile cycling of triglycerides diverts amino acids to fuel production, resulting in muscle wasting and nitrogen imbalance.[1,2]

One of the main components of this response is the acute inflammatory response that is regularly seen in burn patients. There is an increase in acute-phase proteins soon after the onset of trauma that is usually mediated by proinflammatory cytokines with a concomitant depression of the anti-inflammatory component of this response.[3] Elevated levels of proinflammatory cytokines and acute-phase proteins have been associated with the induction of anorexia, weight loss, tissue wasting associated with malignancy, chronic diseases such as rheumatoid arthritis, sepsis-induced proteolysis, and multiple organ dysfunction syndrome.[4,5] In addition to this increase in catabolic hormone and acute-phase protein levels, a reduction in anabolic hormones, including growth hormone (GH) and insulinlike growth factor type 1 (IGF-1) is observed after a thermal injury.[6] Several studies of severely burned patients have shown that nutritional support and pharmacological intervention with anabolic agents, such as GH, insulin, and IGF-1 alone or combined with its principal binding protein, IGFBP-3, abrogate muscle wasting.[7-10] The treatment of burned children with recombinant human growth hormone showed an attenuation of elevated tumor necrosis factor α (TNF-α) levels, which

was consistent with the beneficial effect that GH has on the acute-phase response.[11]

Early burn wound excision is regarded as the main factor in the decline of invasive burn infection and improved survival.[12] Although early burn wound excision is widely accepted, there are still many who question its benefits. It has been suggested that the surgical trauma may increase the severity of the acute-phase response, which can damage other systems, such as the lungs, in a second-hit phenomenon.[13,14]

The real effect of immediate burn wound excision on acute-phase and metabolic responses is unclear. We hypothesize that immediate burn wound excision and grafting abrogates acute-phase and hypermetabolic responses after burn injury.

METHODS

PATIENTS

Early Excision Group

Twenty pediatric patients with severe burns were prospectively studied to determine the effects of early burn wound excision on the inflammatory and metabolic responses. Patients younger than 15 years with more than 40% of their total body surface area (TBSA) burned without evidence of organ failure were enrolled. Informed consent was obtained from all patients and/or their parents in accordance with the Institutional Review Board of the University of Texas Medical Branch at Galveston.

Resuscitation given immediately after the burn injury was guided by the Galveston formula of 5000 mL/m^2 of TBSA burned + 2000 mL/m^2 of TBSA lactated Ringer's solution given in increments during the first 24 hours. All patients underwent total burn wound excision on admission, and wounds were closed with available autograft and allograft skin. Donor sites were treated with fine mesh gauze impregnated with scarlet red. Sequential staged surgical procedures for repeated grafting were undertaken until the wounds were completely closed. All patients received nasoduodenal feedings with Vivonex TEN (Sandoz Nutrition, Minneapolis, Minn), an elemental formula containing 82.3% carbohydrate, 3% fat (linoleic acid), and 14.7% protein. Caloric intake was given at a rate calculated to deliver 1500 kcal/m^2 of TBSA burned + 1500 kcal/m^2 of TBSA. This feeding regimen was started at admission and continued at a constant rate until the wounds were 95% healed. No patients received recombinant human growth hormone, recombinant growth factors, anabolic agents, or propranolol hydrochloride during the study. Inhalation injury was diagnosed on admission by means of direct bronchoscopy.

After admission, patients were studied to determine cytokine production in serum and plasma, acute-phase protein levels, and metabolic rate. The same determinations in serum and plasma levels were made 24 hours and 5 days after the operation to determine the effect of early burn wound excision on the inflammatory and metabolic responses. Blood samples were collected to determine cytokine and hormone levels. Indirect calorimetry was performed to determine any changes in substrate utilization.

Control-Matched Group Comparison

To compare early burn wound excision with conservative treatment, a control group of 15 patients underwent topical treatment with 1% silver sulfadiazine at other institutions for 5 days before being transferred to our institution. Patient age, informed consent, and burn wound excision and closure on admission to our institution were the same as for the early excision group. Control patients were resuscitated accordingly to their individual needs and fed with Vivonex TEN throughout their stay with caloric intakes delivered at the same rate as for the experimental group. Patients in both groups were treated with the same therapeutic protocols.

On admission to our institution (day 5 postburn and day 5 of topical treatment), control patients were studied to determine cytokine production in serum and plasma, acute-phase protein levels, and metabolic rate. Blood samples were obtained to determine the inflammatory and metabolic responses and compare them with levels in the early excision group on postoperative day 5. None of the patients in the control group received anabolic agents during the study.

METHODS

Resting energy expenditure and respiratory quotient were calculated from oxygen and carbon dioxide concentrations in expired gases. A metabolic cart calorimeter (Sensormedics, Yorba Linda, Calif) and standard equations were used.

Levels of serum glucose, electrolytes, C-reactive protein, C3 complement, and α1-acid glycoprotein were determined using a nephelometer (Dade Behring Inc, Deerfield, Ill). Serum IGF-1, IGFBP-3, and GH levels were determined by radioimmunoassay (Nichols Institute Diagnostics, San Clemente, Calif).

Serum TNF-α levels were determined by an ultrasensitive human enzyme-linked immunosorbent assay (Endogen, Woburn, Mass). Standard curves for quantification of human TNF-α were linear from 0 to 1000 pg/mL on a logarithmic scale. Serum interleukin 1β (IL-1β), interleukin 6 (IL-6), and interleukin 10 (IL-10) levels were determined by enzyme-linked immunosorbent assay (Endogen). Standard curves for quantification of human IL-1β (0-400 pg/mL), IL-6 (0-3000 pg/mL), and IL-10 (0-600 pg/mL) were linear on a logarithmic scale.

STATISTICAL ANALYSIS

Comparisons of metabolic and cytokine data were made with a paired *t* test and repeated-measures analysis of variance. Comparisons between the early excision and control groups were made with an unpaired *t* test. Ordinal data were studied with the Fisher exact test. $P<.05$ was considered statistically significant. Data are presented as mean ± SEM.

RESULTS

EARLY EXCISION GROUP

Patient Demographics

The mean age of pediatric patients in the early excision group was 6.0 ± 0.8 years, and the mean burn size was 59% ± 4% of TBSA. Patient demographic characteristics are summarized in **Table 1**. No deaths occurred, and no patients presented with septic episodes during the study. Patients could be discharged home when all burn wounds were covered.

Caloric Intake and Indirect Calorimetry

There were no differences in the caloric intake of protein, carbohydrate, and fat before and after early excision and grafting. No differences could be demonstrated for oxy-

Table 1. Patient Demographics*

Demographic Characteristic	Early Excision Group (n = 20)	Topical (Control) Treatment Group (n = 15)
Age, y	6.0 ± 0.8	7.2 ± 1.3
Sex, M/F, % of patients	45/55	53/47
TBSA burned, %	59 ± 4	54 ± 3
TBSA full-thickness burns, %	55 ± 4	48 ± 6
Weight change, admission – discharge, %	–0.5 ± 1.5	–2.3 ± 2.5
Inhalation injury, % of patients	40	65
Length of hospital stay, d	39.5 ± 5	45 ± 6
Mortality, No. of patients	0	3

Abbreviation: TBSA, total body surface area.
*Data are presented as mean ± SEM unless otherwise indicated.

Table 2. Effects of Early Burn Wound Excision on Oxygen Consumption and Respiratory Quotient in 20 Patients

Metabolic Response	Mean ± SEM		
	Preoperatively	Postoperatively	5 d Postoperatively
Oxygen consumption, kcal/d	1630 ± 265	1625 ± 305	1645 ± 295
Respiratory quotient	1.00 ± 0.03	0.97 ± 0.02	0.98 ± 0.02

gen consumption or respiratory quotient (**Table 2**), which indicates that there were no significant changes in substrate utilization after excision and grafting.

Serum Glucose, Electrolyte, and Acute-Phase Protein Levels

No hyperglycemia, hypoglycemia, or electrolyte imbalances could be found during the study. Acute-phase protein levels did not change significantly during the first 24 hours after the operation. Serum levels of C-reactive protein significantly decreased 5 days after the operation ($P=.01$), whereas levels of the other acute-phase proteins showed a progressive decline (**Figure 1**).

Serum IGF-1, IGFBP-3, and GH Levels

There were no significant changes in serum concentrations of IGF-1, IGFBP-3, or GH throughout the study period (**Table 3**). Serum concentrations did increase slightly, but this change was not statistically significant.

Serum Cytokine Levels

There were no significant differences in serum levels of IL-1β, TNF-α, IL-6, and IL-10 before or 24 hours after the operation. Five days after the operation, however, all patients showed a significant decrease in proinflammatory cytokines levels, indicating a decrease in inflammatory status despite the surgical trauma ($P=.001$) (**Figure 2**). Levels of the anti-inflammatory cytokine IL-10 decreased slightly after the operation and returned to the preoperative level 5 days after the operation.

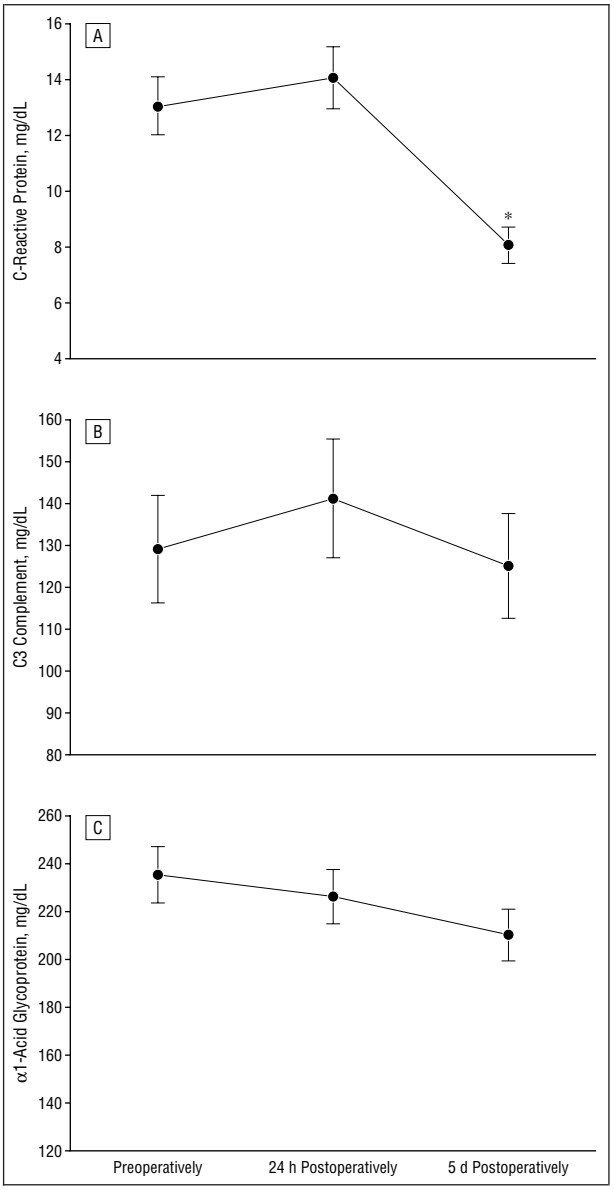

Figure 1. Serum levels of C-reactive protein (A), C3 complement (B), and α1-acid glycoprotein (C) progressively declined and did not increase after surgical excision of the burn wound, which shows that surgical intervention does not increase the inflammatory response of burn patients. Asterisk indicates $P=.01$ (repeated-measures analysis of variance) for 5 days postoperatively vs 24 hours postoperatively and preoperatively.

CONTROL-MATCHED GROUP COMPARISON

Demographic characteristics for the control group are shown in Table 1. There were no significant differences compared with the early excision group. Patients treated with 1% silver sulfadiazine for 5 days had levels of IGF-1 and GH that were significantly lower than those of patients treated with prompt surgical excision (**Table 4**). Furthermore, all cytokine and acute-phase protein levels were significantly higher than in the early excision group (**Figure 3** and **Figure 4**). Oxygen consumption and respiratory quotient were also significantly higher when compared with the early excision group ($P=.005$). Therefore, patients who underwent conservative treatment showed a more severe hypermetabolic response to

burn trauma than did patients treated with early surgical intervention. Three patients died in the control group (1 of sepsis and 2 of respiratory distress).

COMMENT

An acute hypermetabolic and inflammatory response is often observed following major illness or trauma, such as a severe burn. Increases in acute-phase protein, proinflammatory cytokine, and catabolic hormone levels raise energy requirements, resulting in muscle wasting, nitrogen imbalance, and futile substrate cycling of glucose and triglycerides. When this acute posttraumatic response is aggravated and prolonged, it results in multiple organ dysfunction syndrome and, eventually, death. The common denominators of the acute-phase response are the activation of the immune system, with overproduction of proinflammatory cytokines and depression of anti-inflammatory cytokines, and associated changes in neurological, metabolic, and endocrine functions irrespective of the diverse underlying pathologic conditions.[11,15] Most endocrine cells are directly affected by all cytokines that are released during the acute-phase response, and profound changes in the hormonal balance accompany this response.[16] This acute inflammatory response is associated with increased tissue needs for nutrients that are required for augmented demands related to increased substrate oxidation because of fever and to tissue remodeling and repair. Circulating cytokines contribute to this beneficial response by stimulating hormones and cellular processes that increase substrate uptake, mobilization, cellular transport, and metabolism. In contrast, prolonged elevation of cytokine levels may contribute to the development of insulin resistance and other catabolic responses mediated by abnormal release of hormones.[17] There is evidence that cytokines induce strong inhibitory hypothalamic signals for GH secretion. Interleukin 1β stimulates release of somatostatin, which in turn inhibits release of GH.[18] This stimulating effect on somatostatin is shared with TNF-α and IL-6, with a synergism between TNF-α and IL-1β.[19,20] At the level of the pituitary gland, IL-6 has been reported to have a positive effect, which may explain the elevated levels of GH in patients with inflammatory diseases or experimental endotoxemia.[21] However, in clinical experience, growth retardation usually follows prolonged periods of infection and inflammation, suggesting that the acute-phase response may cause resistance to GH and IGF-1.[22] Together with the former systemic response, the long-term paracrine effects

Table 3. Serum Concentrations of IGF-1, IGFBP-3, and GH Before and 5 Days After Early Burn Wound Excision in 20 Patients

	Mean ± SEM	
Hormones, µg/mL	Preoperatively	5 d Postoperatively
IGF-1	89 ± 8	109 ± 12
IGFBP-3	1.3 ± 0.2	1.4 ± 0.2
GH	3.2 ± 1.0	3.4 ± 0.5

Abbreviations: GH, growth hormone; IGF-1, insulinlike growth factor 1; IGFBP-3, insulinlike growth factor binding protein 3.

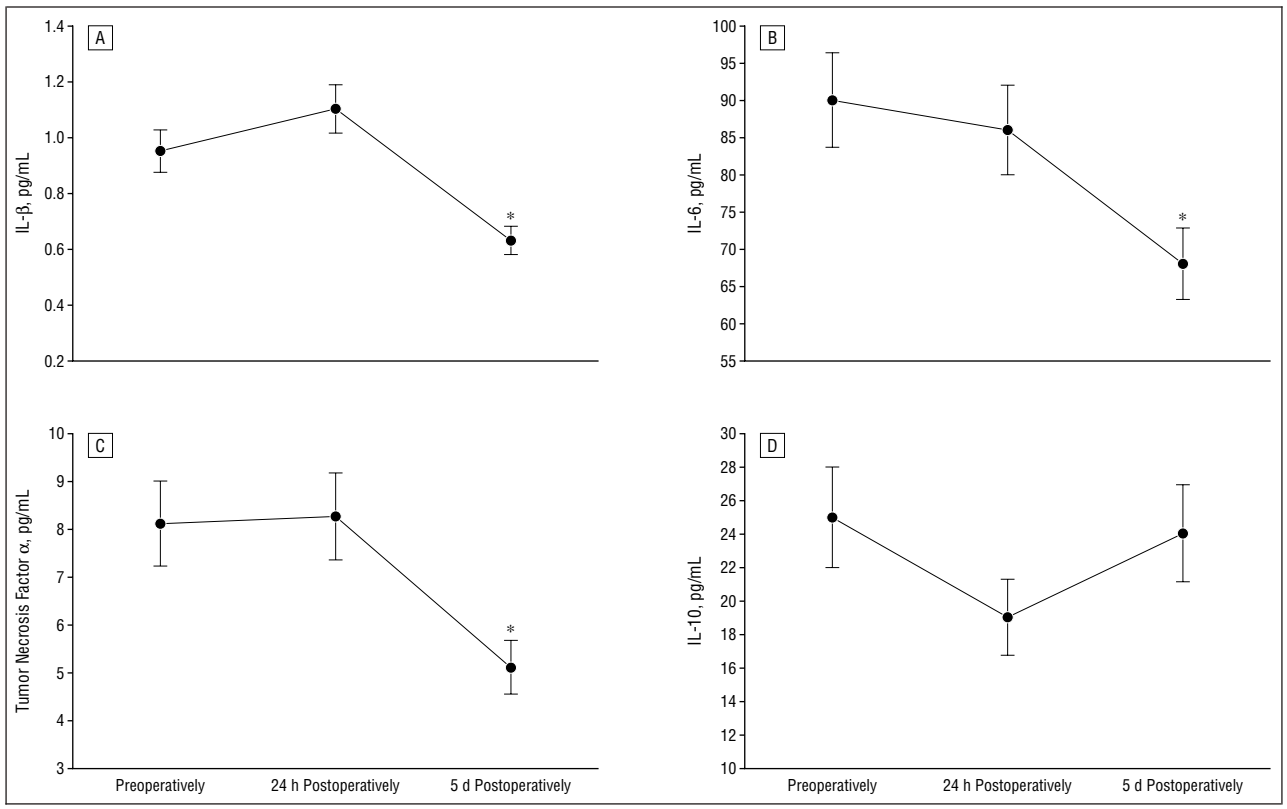

Figure 2. Serum levels of all proinflammatory cytokines, interleukin (IL) 1β (IL-β) (A), IL-6 (B), and tumor necrosis factor α (C), significantly decreased 5 days after burn wound excision. Levels of the anti-inflammatory cytokine IL-10 (D) decreased after the operation but returned to preoperative levels after 5 days. Asterisk indicates $P<.05$ (repeated-measures analysis of variance) for 5 days postoperatively vs 24 hours postoperatively and preoperatively.

Table 4. Comparison of Hormones Between the Early Excision Group and the Control Group

Hormones, µg/mL	Mean ± SEM: Early Excision Group, Day 5 (n = 20)	Mean ± SEM: Topical (Control) Treatment Group, Admission Day 6 (n = 15)
IGF-1	109 ± 12	77 ± 8*
IGFBP-3	1.4 ± 0.2	1.2 ± 0.3
GH	3.4 ± 0.5	2.8 ± 0.4*

Abbreviations: GH, growth hormone; IGF-1, insulinlike growth factor 1; IGFBP-3, insulinlike growth factor binding protein 3.
*$P<.05$; unpaired t test.

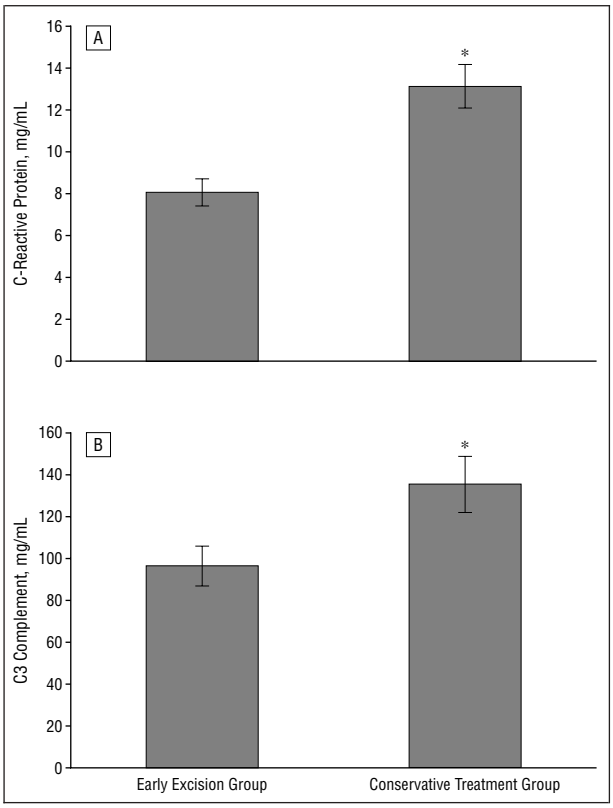

Figure 3. Patients treated conservatively had higher serum levels of C-reactive protein (A) and C3 complement (B) compared with patients in the early burn wound excision group on day 5 postoperatively. Asterisk indicates $P<.05$ (unpaired t test) for the early excision group vs the conservative treatment group.

of synergistically acting proinflammatory cytokines secreted in high local concentrations in tissues infiltrated by inflammatory cells may alter or inhibit the normal function of mesenchymal and endothelial cells and, in some cases, even cause cell destruction.

Different interventions and treatments have proved to be efficient in modulating acute-phase and hypermetabolic responses following burn injury. When room temperature is increased from 25°C to 33°C, the mean metabolic rate of patients with burns on more than 40% of TBSA significantly decreases.[23] Another intervention that has been universally accepted is nutritional modulation through enteral supplementation,[24] which, if applied as soon as possible, will help prevent weight loss. Lately, hormonal

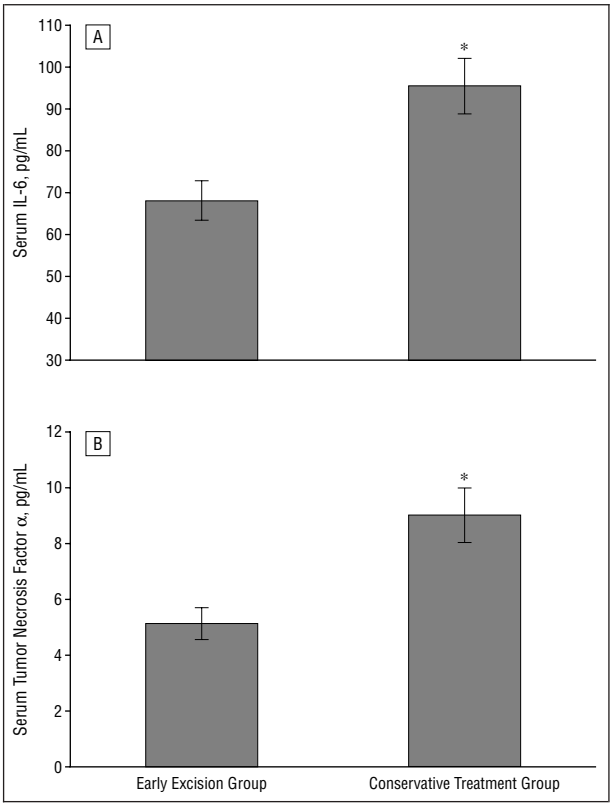

Figure 4. Serum levels of interleukin (IL) 6 (IL-6) (A) and tumor necrosis factor α (B) were higher in patients treated conservatively 5 days after the injury. Levels of IL-1β and IL-10 were similar in both patient groups. Asterisk indicates $P<.05$ (unpaired t test) for the early excision group vs the conservative treatment group.

modulation has opened a new door in the treatment of hypermetabolic and acute-phase responses. The administration of GH to burn patients produced beneficial metabolic effects and improved wound healing. In prospective randomized clinical trials, GH increased protein turnover, with synthesis exceeding breakdown,[8,25] and improved wound healing, with a significant acceleration of skin graft donor site wound healing.[26] Other anabolic agents that have been tested and proved effective, inducing fewer adverse effects, are IGF-1 with IGFBP-3 and oxandrolone.[10,27,28]

Although all former treatments effectively modulated inflammatory and hypermetabolic responses, the treatment that most has changed survival and outcome in burn injuries is surgery. Treatment of full-thickness burns by waiting for spontaneous separation and subsequent skin grafting is a prolonged process associated with much pain and suffering, severe metabolic derangements, multiple septic episodes, and lengthy hospitalization. Prompt wound closure has been shown repeatedly to improve survival,[29] decrease the length of the hospital stay, and curb metabolic expenditure for burn patients of all ages.[30,31] It is now unusual for a child to succumb to a burn injury of any size,[32] and older patients have also been shown to benefit from an early surgical approach.[33] The benefits of immediate burn wound excision were also proved in the present study. Children with burns who were treated with this approach showed a significantly decreased inflammatory response. Levels of all proinflammatory cytokines were lower after

excision of full-thickness burns, and acute-phase protein levels also showed progressive decline. On the other hand, levels of the anti-inflammatory cytokine IL-10 returned to preoperative levels (which were still below the reference range), and levels of anabolic hormones did not change. Changes in oxygen consumption were also minimal, which corroborated that early surgical intervention does not augment oxygen and caloric demands. All patients in the early excision group survived their injuries, and there were no adverse effects related to the operation. This was also our experience and others' in previous studies.[34,35] When patients treated with immediate burn wound excision were compared with patients who received topical treatment with silver sulfadiazine for the same period of time, the second group had significantly profound inflammatory and catabolic responses. Patients in the control group had significantly higher levels of acute-phase proteins and proinflammatory cytokines, whereas levels of IGF-1 were significantly lower. Conservative topical treatment of burn injuries is associated with significantly higher levels of burn contamination and infection,[31,36] which in turn raise the inflammatory response and caloric requirements. Early surgical intervention reduces the bacterial load in all burn wounds, and, as was proved in the present study, modulates the hypermetabolic response without collateral effects. Furthermore, 3 patients died in the control-matched group, whereas none died in the early excision group. Even though the difference was not statistically significant, probably owing to the small size of the groups, this difference illustrates another benefit of immediate surgical intervention. In previous studies of immediate surgical intervention, results showed that the surgical approach is very safe, shortening the length of hospital stays and decreasing complications without significant adverse effects.[34,37]

In summary, immediate burn wound excision is a safe therapeutic approach that is associated with minimal adverse effects.[31,34,38] It does not increase caloric demands and the postburn hypermetabolic response. Immediate excision of full-thickness burns modulates the inflammatory response, decreasing levels of acute-phase proteins and cytokines while preserving levels of anabolic peptides. Immediate surgical intervention was superior to conservative topical treatment and delayed excision, and immediate burn wound excision should be considered as the treatment of choice for full-thickness burns.

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