Modulation of the Hypermetabolic Response to Trauma: Temperature, Nutrition, and Drugs

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Severe burn injury is associated with a profound hypermetabolic, hypercatabolic response proportional to the original size of the injury, which persists for 1 to 2 years postburn.[1,2] The response is characterized by supraphysiologic metabolic rates, hyperdynamic circulation, constitutive protein fat and bone catabolism, blunted growth, insulin resistance, and increased risk for infection[1–5] (Figs. 1 to 3).

Cuthbertson[6] originally described a stress response to fractures characterized by an "ebb" phase, with a decrease in tissue perfusion and a decrease in metabolism. This is followed by a "flow" phase—starting 3 to 5 days postinjury—which is characterized by an increase in metabolic rate and hyperdynamic circulation. If left untreated, physiologic exhaustion and death can result.[7–10] Severe burns exhibit the most dramatic hypermetabolic stress response of any injury.

This article reports our single institution's experience during the past decade, in >1,000 patients with burns of >40% of their total body surface area (TBSA), delineating the magnitude of the metabolic and catabolic responses to major burn injury. Serially performed randomized prospective clinical studies using common methods are described, demonstrating the efficacy of interventions to mitigate the hypermetabolic response: the effects of early excision and grafting, environmental thermoregulation, early continuous enteral feeding with a high-carbohydrate, high-protein diet, use of anabolic agents (growth hormone, insulin-like growth factor-1 [IGF-1], with insulin-like growth factor binding protein-3 [IGFBP-3], insulin, oxandrolone), the anticatabolic agent (propranolol), and use of therapeutic exercise are compared. This article describes the destructive aspects of the hypermetabolic response and strategies implemented during the last decade to modulate this response, which have improved burn care, survival, and quality of life in burn patients. It is hoped that these strategies might also be applicable to the larger populations of patients who have undergone other forms of injury, including large elective operations.

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Hypermetabolic response in severe burns

Catecholamines, corticosteroids, and inflammatory cytokines are primary mediators of the postburn hypermetabolic catabolic response.[11] A 10- to 20-fold elevation of plasma catecholamines and corticosteroid levels occur in major burns, which persist up to 9 months postinjury.[12,13] Burn patients have increased metabolic rates, increased cardiac work, increased myocardial oxygen consumption, marked tachycardia, severe lipolysis, liver dysfunction, muscle catabolism, increased protein degradation, insulin resistance, and growth retardation.[14–17] Cytokine levels peak immediately after burn, approaching normal levels only after 4 to 5 weeks postinjury. Constitutive and acute-phase proteins are altered beginning 1 week postburn, and remain abnormal throughout acute hospital stay. Serum IGF-I, IGFBP-3, parathyroid hormone, and Osteocalcin drop 10-fold immediately after the injury, and remain substantially decreased up to 2 to 6 months postburn, compared with normal levels.[12] Gender hormones and endogenous growth hormone levels decrease around 3 weeks postburn[12] (Fig. 1).

For severely burned patients, the resting metabolic rate at thermal neutral temperature (30°C–33°C) exceeds 140% of normal at admission, reduces to 130% once the wounds are fully healed, then to 120% at 6 months postinjury, and 110% at 12 months postburn.[1,12] Increases in catabolism result in loss of total body protein, decreased immune defenses, and decreased wound healing.[1]

Immediately postburn, patients have low cardiac output characteristic of early shock.[6] Three to four days postburn, cardiac outputs are > 1.5 times that of nonburned, healthy volunteers.[12] Heart rates of pediatric burn patients' approach 1.6 times that of nonburned, healthy volunteers.[16] Postburn, patients have increased cardiac work.[18,19] Myocardial oxygen consumption surpasses that of marathon runners and are sustained well into rehabilitation.[19]

There is profound hepatomegaly after injury. The liver increases its size by 225% of normal by 2 weeks postburn and remains enlarged at discharge by 200%.[12]

Postburn, muscle protein is degraded much faster than it is synthesized.[12,16] Net protein loss leads to loss of lean body mass and severe muscle wasting, leading to decreased strength and failure to fully rehabilitate.[1,20] Substantial decreases in lean body mass related to chronic illness or hypermetabolism can have dire consequences. A 10% loss of lean body mass is associated with immune dysfunction. A 20% loss of lean body mass positively correlates with decreased wound healing. A loss of 30% lean body mass leads to increased risk for pneumonia and pressure sores. A 40% loss of lean body mass has > 90% risk of death.[21] Uncomplicated severely burned patients can lose up to 25% of total body mass after acute burn injury.[22] Protein degradation persists up to 9 months after severe burn injury, resulting in considerable negative whole-body and cross-leg nitrogen balance[18,23,24] (Fig. 2). Protein catabolism is correlated to, and can be predicted by, increases in metabolic rates.[24] Severely burned patients have a daily nitrogen loss of 20 to 25 g/m^{2} burned skin.[18,25] At this rate, a lethal cachexia can be reached in <30 days.[25] Burned pediatric patients' protein loss leads to substantial growth retardation for up to 24 months after injury.[3]

Elevated circulating levels of catecholamines, glucagon, cortisol after severe thermal injury stimulate glucose production by the liver, amino acids from muscle, and free fatty acids and glycerol from fat[26] (Fig. 3). Glycolytic-gluconeogenic cycling is increased 250% during the post-burn hypermetabolic response, coupled with an increase of 450% in triglyceride fatty acid cycling.[5] These changes lead to hyperglycemia and impaired insulin sensitivity related to postreceptor insulin resistance, demonstrated by elevated levels of insulin, fasting glucose, and substantial reductions in glucose clearance.[4] Although glucose delivery to

peripheral tissues is increased up to threefold, glucose oxidation is restricted. Increased glucose production is directed, in part, to the burn wound to support the relatively inefficient anaerobic metabolism of fibroblasts, and endothelial and inflammatory cells.[27,28] The end-product of anaerobic glucose oxidation, ie, lactate, is recycled to the liver to produce more glucose through gluconeogenic pathways.[18] Serum glucose and serum insulin increase postburn and remain substantially increased through the acute hospital stay.[12] Insulin resistance appears during the first week postburn and persists considerably after discharge.[12]

Patients who become septic have a profound increase in metabolic rates and protein catabolism, up to 40% more compared with those with like-sized burns that do not develop sepsis.[1,29] A vicious cycle develops, as patients who are catabolic are more susceptible to sepsis because of changes in immune function and immune response. The emergence of multidrug-resistant organisms has led to increases in sepsis, catabolism, and mortality[30,31] (Fig. 4).

Modulation of hypermetabolic response in severe burns

Early excision and grafting

The hypermetabolic response of a severely burned patient far surpasses that of patients with any other disease state.[32] One of the most revolutionary improvements in burn care that has attenuated the hypermetabolic response is the excision and grafting of the burn eschar early after injury. For burns that encompass >50% TBSA, there is a 40% decrease in metabolic rate for patients totally excised and covered within 3 days of injury compared with those patients with like-sized burns, excised and covered 1 week after injury.[24] Additional benefits of early excision and grafting include less operative blood loss, fewer septic complications, decreased length of stay, and improved survival rates in children and young adults compared with patients treated with later excision.[33–36] Early excision and grafting decreases net protein loss and incidence of infections (Fig. 5).[37]

Immediate removal of burn eschar decreases release of inflammatory mediators. Substantial reductions in interleukin (IL)-6, IL-8, tumor necrosis factor– , and lipopolysaccharide have been seen in those patients after prompt excision and grafting of burn wounds.[38] Additional studies have shown a marked reduction in C-reactive protein, and C3 complement, along with reductions in IL-6 and serum tumor necrosis– factor, with early excision and grafting.[39] IL-6, in particular, has been implicated as a potential predictor of outcomes in severely burned patients.[24,40] Early excision and grafting remains a cornerstone in management of the hypermetabolic postburn response, decreasing infection rates, resting energy expenditures, and length of hospital stay.

Nutrition

Aggressive, early enteral feeding improves outcomes in the burned patient, by mitigating the degree and extent of catabolism.[41,42] With oral alimentation from hospital trays alone, patients with 40% TBSA burns have lost up to one-quarter of their preadmission weight by 21 days postinjury.[22] Only through aggressive, continuous parenteral or enteral, or both, nutrition with 25 kcal/kg body weight per day plus 40 kcal per percent TBSA burn per day, can body weight be maintained in adults.[43,44] Children require 1,800 kcal/m^2 plus 2,200 kcal/m^2 of burn area per day to maintain body weight.[45] Parenteral nutrition alone, or even in combination with enteral nutrition, led to overfeeding, liver failure, impaired immune response, increased infections, and mortality.[46–48] Enteral nutrition reduces translocation bacteremia and sepsis, maintains gut motility, and preserves "first-pass" nutrient delivery to the liver.[41] For burned patients, parenteral nutrition should be reserved for those with enteral feeding intolerance or prolonged ileus.

Milk, consisting of 44% fat, 42% carbohydrate and 14% protein, became standard of care for the pediatric burned patient.[16,49] Although well-tolerated, fat did not serve as the optimal energy source for these patients. There was continued protein degradation and lean body mass acquisition was less when compared with high-carbohydrate diets consisting of 3% fat, 15% protein, and 82% carbohydrate[16] (Fig. 5). The high-carbohydrate diet increased protein synthesis, increased endogenous insulin production, and improved lean body mass and muscle protein synthesis.[16]

By measuring resting energy expenditures with bedside carts, actual caloric requirements can be determined.[50,51] Appropriate nutrient delivery can be accomplished by feeding 1.2 to 1.4 times measured resting energy expenditures (in kcal/m^2 per day). Using stable isotopes we found that feeding pediatric burn patients 1.2 times measured resting energy expenditures resulted in a loss of 10% lean body mass.[50] In other studies of body composition over time in burned children, we found maintenance of body weight when feeding 1.4 times the resting energy expenditure, and increases in weight when feeding 1.6 times the resting energy expenditure. The latter gains in weight were a result of fat deposition, not lean body mass accretion.[51,52]

There is evidence that increased protein replacement for severely burned patients might be beneficial.[53,54] Healthy individuals require 1 g/kg body weight per day of protein intake.[55,56] Based on in vivo kinetics studies looking at oxidation rates of essential and nonessential amino acids, burn patients have 50% higher use rates than healthy individuals in the fasting state.[53,54,57] Burn patients require a minimum of 1.5 to 2 g/kg body weight per day protein intake.[58–60] Higher amounts of supplementation lead to increased urea production without improvements in lean body mass or muscle protein synthesis.[61]

Environmental thermoregulation

Postburn, the metabolic rate increases to compensate for profound water and heat losses. Water loss approaches 4,000 mL/m^2 burn area per day.[62–65] The body's natural response to this insult, partially mediated by increased ATP consumption and substrate oxidation, is to raise core and skin temperatures 2°C more than normal compared with unburned patients.[66] This response is similar to the response seen during cold acclimatization. In fact, patients that do not mount this response are likely septic and or have exhausted physiologic capabilities to maintain needed body temperature.[49] In 1975, Wilmore and colleagues[67] showed that we can profoundly attenuate the hypermetabolic response by increasing ambient temperatures to 33°C. At this temperature, the energy required for vaporization is derived from the environment rather than from the patient.[67,68] By increasing ambient temperatures from 20°C and 33°C, resting energy expenditures decrease from 2.0 to 1.4 times normal in patients with severe burn injury[67,68] (Fig. 5).

Hormonal response in severe burns

Elevated levels of catecholamines, cortisol, and glucagon mediate profound changes in metabolic rates, growth, and physiology seen in the pediatric burn patient population. We have studied the therapeutic use of recombinant human growth hormone (rhGH), insulin, IGF-1 and IGFB-3 in combination, testosterone, and oxandrolone as potential anabolic agents. To combat catecholamines, we have administered the adrenergic antagonist propranolol. Use of anabolic or anticatabolic agents in severely burned children, in addition to standard of care, has led to substantial decreases in protein catabolism.

Anabolic agents

rhGH

Blunted growth lasts at least 12 to 24 months postburn in severely burned pediatric patients.[3,69] Compared with age-matched controls, severely burned children have substantially reduced bone mineral density and mass, which persist indefinitely.[70] Bone loss is, in part, a result of bone-marrow suppression, calcium and magnesium homeostasis dysregulation, immobilization, hypoparathyroidism, and increased endogenous glucocorticoid production.[71–73] rhGH, when administered IM during acute hospitalization to patients with large burns at a dose of 0.2 mg/kg/d, significantly improved outcomes relative to blinded randomized control patients. Endogenous levels of IGF-1, which are drastically decreased in severely burned patients, were substantially increased by treatment.[74,75] Donor-site healing times were decreased by 25%, as were hospital lengths of stay.[75,76] Compared with patients who did not receive rhGH, scarring had improved considerably by 2 years postburn.[77] By decreasing donor-site healing times, rhGH decreased hospital length of stay and cost of care for patients who received the drug during the acute hospitalization.[78]

The rhGH substantially decreases the acute-phase response by decreasing C-reactive protein, serum tumor necrosis factor– , IL-1, and serum amyloid-A.[79]

In experimental models, growth hormone increases albumin production in the liver.[79,80] rhGH treatment enhances Thelper–1 and reduces T-helper–2 cytokine production, and positively modulates the humoral immune response.[81,82]

At a dose of 0.05 mg/kg/d, administered to children with burns >40% of the body for 1 year postburn, there were considerable improvements in weight gain, height velocities, lean body mass, bone mineral content, and cardiac function, specifically ejection fraction, relative to blinded controls.[69,83] These effects were seen up to 36 months postinjury[84,85]

It should be noted that rhGH treatment does not come without side effects. The most notable side effect in severely burned patients was hyperglycemia.[86] Although Takala and colleagues[87] found, in a double-blinded randomized controlled trial, an increased mortality rate in nonburned critically ill adults, we found no differences in mortality for severely burned pediatric patients randomized to receive the drug.[80] rhGH can be used safely in pediatric burn patients to attenuate the hypermetabolic response with close monitoring to treat sequelae of therapy.

IGF-1 and IGFBP-3

Effects of growth hormone are, in part, mediated by IGF-1. Infusion of IGF-1 alone led to dramatic improvements in protein metabolism, but also episodes of hypoglycemia.[88] In combination with equimolar doses of IGFBP-3 (the principal binding protein for IGF-1), severely burned catabolic patients had improved protein synthesis with fewer incidences of hyperglycemia than with use of rhGH, and fewer incidences of hypoglycemia than with use of IGF-1 alone.[88–90] The combination of IGF-1 and IGFBP-3 not only decreased muscle and protein catabolism in severely burned pediatric patients, but also improved gut mucosal integrity and immune function in experimental models.[90–92] In fact, the fractional synthetic rate for protein was stimulated by 2% per day for patients receiving the combination compared with standard of care.[90] IGF-1 with IGFBP-3 is potentially a good drug combination to ameliorate the hypermetabolic response in pediatric burn patients. This combination is being developed for clinical use as are other effective IGF-1 mimetic agents.

Insulin

Increases in catecholamine, glucagon, and glucocorticoid production postburn led to enhanced glycogenolysis and protein breakdown in both the liver and skeletal muscle.[59] There is an increase in triglycerides, glycerol, urea, and glucose production (gluconeogenesis), which leads to hyperglycemia. Hyperglycemia leads to reduced graft take and increased infections.[93,94] Van den Berghe and colleagues[95] showed that intensive insulin therapy to achieve blood glucose levels between 80 and 110 mg/dL in critically ill patients improves morbidity and mortality. We have found that intensive insulin therapy stimulates muscle protein synthesis and increases lean body mass without increasing hepatic triglyceride production in burn patients[96,97] (Fig. 6). Severely burned patients who received continuous infusions of insulin and glucose titrated to a plasma insulin concentration of 400 to 900 μu/mL to maintain euglycemia for 7 days had improved donor-site wound healing relative to untreated controls.[98]

Infusing insulin at a rate of 1.5 μu/kg/min to maintain blood glucose levels between 100 to 140 mg/dL—in burn patients fed 1,500 kcal/m^2 plus 1,500 kcal/m^2 burned per 24 hours of high-carbohydrate, high-protein enteral feedings (Vivonex TEN; Sandoz Nutritional Corp) —substantially improved lean body mass and bone mineral density, and decreased length of hospital stay.[99] Judicious control of the insulin infusion rates is paramount in the clinical management of these patients, as risk for hypoglycemia approaches 20%. There are currently no large prospective randomized controlled trials to determine which blood glucose level is most appropriate for severely burned patients.

Fenofibrate

Postburn hyperglycemia is associated with increased morbidity and mortality.[93] In addition, mitochondrial oxidative function is impaired by up to 70% at 1 week after severe burn injury.[100] Many animal studies have shown improvements in mitochondrial function and glucose oxidation with use of fenofibrate—a peroxisome proliferator– activated receptor [ ] agonist.[101] In a double-blind, prospective, placebo-controlled randomized trial, fenofibrate treatment significantly decreased plasma glucose levels without causing hypoglycemia.[100] It decreased hepatic gluconeogenesis and improved mitochondrial oxidative capacity.[100] Fenofibrate administration during 2 weeks improved muscle and hepatic insulin resistance in pediatric burn patients without any notable side effects, and it can be given orally.[100]

Oxandrolone

The hormonal milieu postburn is one of increased plasma catecholamines, increased cortisol and hypoandrogenemia. In severely burned male patients, testicular steroid production is substantially decreased, despite stable luteinizing hormone levels.[102,103] This state of testicular dysfunction can last months postburn.[103,104] Elevated levels of cortisol coupled with decreased levels of testosterone can contribute greatly to the loss of lean body mass seen in this patient population.[102] Testosterone administration has been shown to ameliorate catabolism in fasting by increasing protein synthesis in normal subjects.[105,106] It was also shown to ameliorate muscle protein loss after severe burn injury in male patients.[102] Despite its efficacy, weekly IM administration of testosterone longterm is fraught with both expense and difficulty with compliance. In addition, it is an androgenic steroid, contraindicated for use in female patients. Oxandrolone, a synthetic analogue, administered orally, offers only 5% of the masculinizing effects of testosterone and is safe for both genders. Oxandrolone, when administered at a dose of 0.1 mg/kg twice daily, improved net muscle protein synthesis and protein metabolism in severely burned patients[107,108] (Fig. 7). During the acute phase postburn and up to 1 year of treatment, oxandrolone increased lean body mass, bone mineral content, and muscle strength.[107–111] In addition, it decreased length of stay by decreasing time between operations for patients randomized to receive oxandrolone plus

standard of care.[108] Oxandrolone results in considerable improvements in lean body mass, protein synthesis, and overall growth in burn patients, mitigating the 1% risk of hirsutism, and hepatic dysfunction that can be seen with treatment.[108–111]

β-receptor-antagonists

The 10-fold increase in catecholamine levels in large burns induced increased myocardial oxygen consumption, increased resting energy expenditures, and contributed greatly to the profound catabolism the body experiences after severe burn injury.[11,32] One of the most effective anticatabolic strategies for the treatment of burns is to block the effects of elevated levels of plasma catecholamines. Catecholamines have been implicated in the tachycardia seen after major operations and -receptor-antagonist treatment reduced the rate of cardiac complications and decreased mortality.[112] In burns, -receptor-antagonist treatment reduced thermogenesis, marked tachycardia, and resting energy expenditures.[113,114] By reducing heart rates by 20%, there was a substantial decrease in cardiac work.[19] Catecholamines trigger increased peripheral lipolysis in thermally injured patients through activation of the 2-adernergic receptor.[17,113,115] Propranolol helps prevent this deleterious effect of catecholamines.[113] Propranolol treatment substantially decreased fatty infiltration of the liver compared with untreated severely burned children.[116,117] By inhibiting release of free fatty acids from adipose tissue, decreasing the rates of fatty acid oxidation and triacylglycerol secretion, and increasing the efficiency of the liver in excreting fatty acids, propranolol substantially reduces hepatic steatosis.[117–119] Propranolol increases lean body mass and decreases skeletal muscle wasting as proved by stable isotope and body composition studies.[16] It enhances the availability of free amino acids for muscle protein synthesis[16,118,119] (Fig. 8). It caused no substantial bronchospasm, or cardiovascular collapse in patients studied in randomized control trials to date.

A role for combination therapy

The anticatabolic effect of propranolol and the potent anabolic effects of rhGH might represent an ideal combination for attenuating the postburn hypermetabolic response. Although improving donor site healing, growth, and the inflammatory cascade, rhGH treatment leads to hyperglycemia and increased free fatty acids and triglycerides. Propranolol treatment demonstrated improved fat metabolism and improvements in insulin sensitivity and decreasing cardiac work. In combination, there were considerable improvements in metabolic rates, serum C-reactive protein, cortisol, liver function, lipid metabolism, and cytokine profiles compared with controls, without adverse side effects.[120,121] The combination of propranolol and oxandrolone is currently under trial.

Beyond acute hospitalization

The modulators mentioned previously that were used by our institution produce profound improvements in the hormonal, inflammatory, metabolic, and physiologic responses to severe burn injury during the acute hospitalization. Derangements seen in severely burned victims last well beyond acute hospitalization. Growth delay, hyperdynamic circulation, increased metabolic rates, and insulin resistance last at least 12 months after injury.[1,3,16,26,122] Muscle protein and bone catabolism contribute considerably to the cachexic state of our patients up to 2 years postinjury. Administration of oxandrolone beyond the acute hospitalization, for up to 1 year postinjury, led to dramatic improvements in lean body mass and bone mineral content— essentially reversing growth retardation.[111] Use of growth hormone, propranolol, and the combination of oxandrolone and propranolol longterm are currently being evaluated.

Exercise

Despite methods to abate the stress response, patients suffer growth retardation for years into the rehabilitative phase.[3] Patients with severe burn injury have substantial functional limitations as they progress through rehabilitation. Exercise training is an essential adjunct to any and all metabolic treatments administered to the burn survivor. It increases lean body mass, improves strength, ability to walk distances, and overall cardiopulmonary capacity.[123,124] We have reported that a 12-week resistance and aerobic exercise training program, added to standard of care after acute hospitalization, profoundly improves range of motion, muscle strength, lean body mass, and power compared with standard of care alone.[125,126] An exercise training program is essential to improve body mass, decrease joint contractures, and scarring.[123]

Complications and cost

Most catabolic burn patients respond positively to anabolic pharmacotherapy. Subgroup analyses revealed that patients who are not catabolic fail to respond to anabolic or anti-catabolic therapy. Response to anabolic drugs was greater in victims with >40% TBSA burned than in those with <40% TBSA. In ill, catabolic patients, the incidence of pharmacologic adverse reactions in our institution is low (Table 1). The pharmacologic strategies with the least documented complications in randomized controlled trials are propranolol and oxandrolone. These agents are the most cost-effective pharmacotherapy and drug regimen with the greatest experimental efficacy. Daily cost of these agents, extrapolated to the dose for a 70-kg person is provided in Table 2. Oxandrolone is 5% of the cost of recombinant growth hormone, and its efficacy has been documented by many investigative groups in a wide array of both healthy and ill, catabolic subjects. Based on our analysis of relative efficacy, cost, and documented adverse drug reactions (at our institution), we believe that oxandrolone and propranolol hold the greatest promise as pharmacotherapies for catabolic burn victims.

Relative efficacy

We have demonstrated the effectiveness of these pharmacologic agents in abating the hypermetabolic response, although they have different mechanisms of action. Using stable isotopes and body composition studies, we found substantial differences in outcomes with use of growth hormone, insulin, oxandrolone, propranolol, and combination therapy of growth hormone and propranolol, compared with placebo (Fig. 9). All pharmacologic treatments, specifically mentioned here, are superior to standard of care alone to curb the postburn hypermetabolic response. Currently, we recommend exercise, oxandrolone, and propranolol for the treatment of the severe hypermetabolic response in children and adults, and growth hormone for selected very large burns in pediatric patients.

The hypermetabolic, hypercatabolic response is prolonged and persistent beyond acute hospitalization. Neither nonpharmacologic nor pharmacologic strategies are sufficient to fully abate the response to severe burn injury. The therapeutic strategies described have contributed to improvements in morbidity and mortality. In 1942, the TBSA burned that killed 50% (lethal median dose) of the youngest (younger than 4 years) and oldest victims (older than 65 years) were 49% and 10%, respectively. Today, those numbers have improved to 98% and 35%, respectively[127,128] (Tables 3 to 4). Treated catabolic patients with 40% TBSA, on average, have a 2% to 10% loss of total body mass, down from 25% loss 20 years ago.[12,129] Modulation of the hypermetabolic response is paramount in the restoration of structure and function of severely burned patients. Certain pharmacologic strategies have superior experimental efficacy than others, but each addressed and reversed, in part, the maladaptive catabolic physiologic responses to severe burn injury. Combination

therapies can be superior to monotherapy interventions in attenuating the postburn response. Additional studies are necessary to determine the optimal treatment for the catabolic response in burns and to determine which of these therapies will be useful in the treatment of other injuries or elective operations.

Acknowledgments

Abbreviations and Acronyms

IGF-1	insulin-like growth factor-1
IGFBP-3	insulin-like growth factor binding protein-3
IL	interleukin
rhGH	recombinant human growth hormone
TBSA	total body surface area

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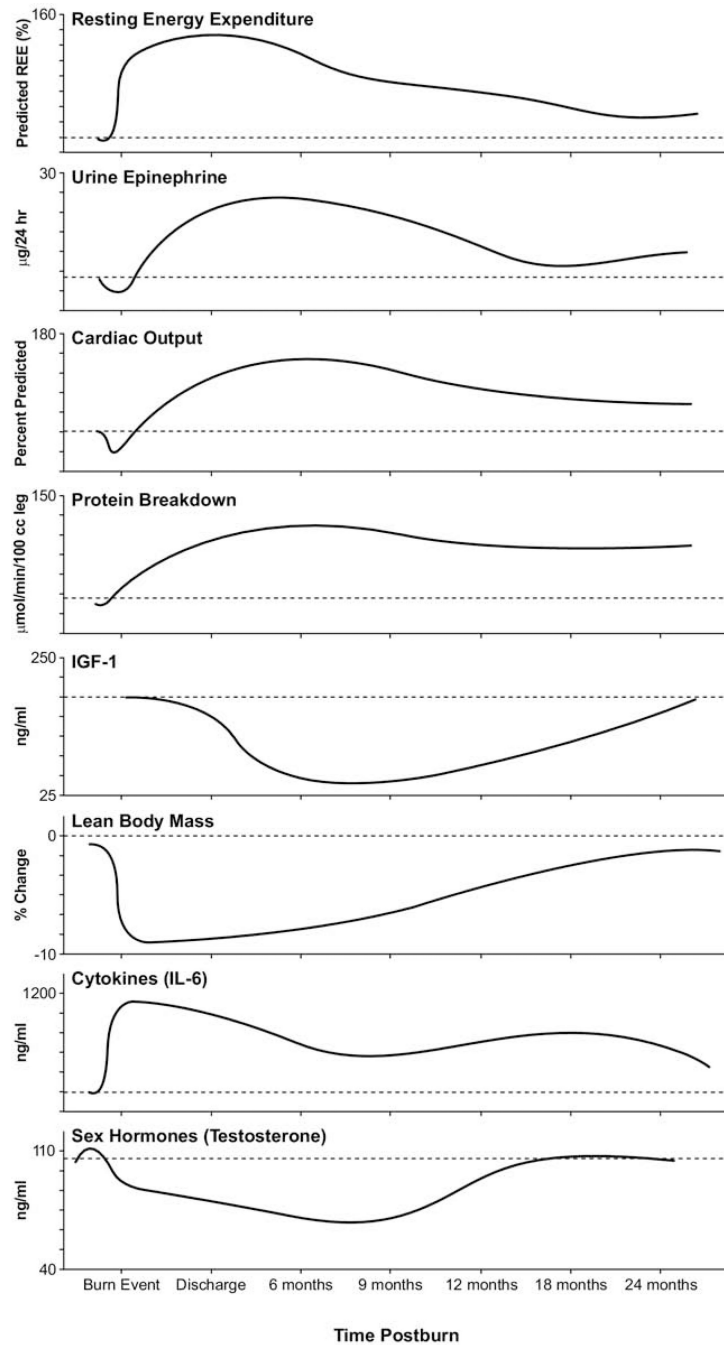
Figure 1.
Physiologic and metabolic changes post severe burn injury. Demonstrates changes in resting energy expenditure, stress hormones (epinephrine), cardiac function (cardiac output), gender hormones (testosterone), cytokines (interleukin-6) and changes in body composition (lean body mass). Data were summarized from published works from our institution.[1,12] Averages for burn patients are represented by solid curves. Values from nonburned, normal patients are represented by dashed lines (—).
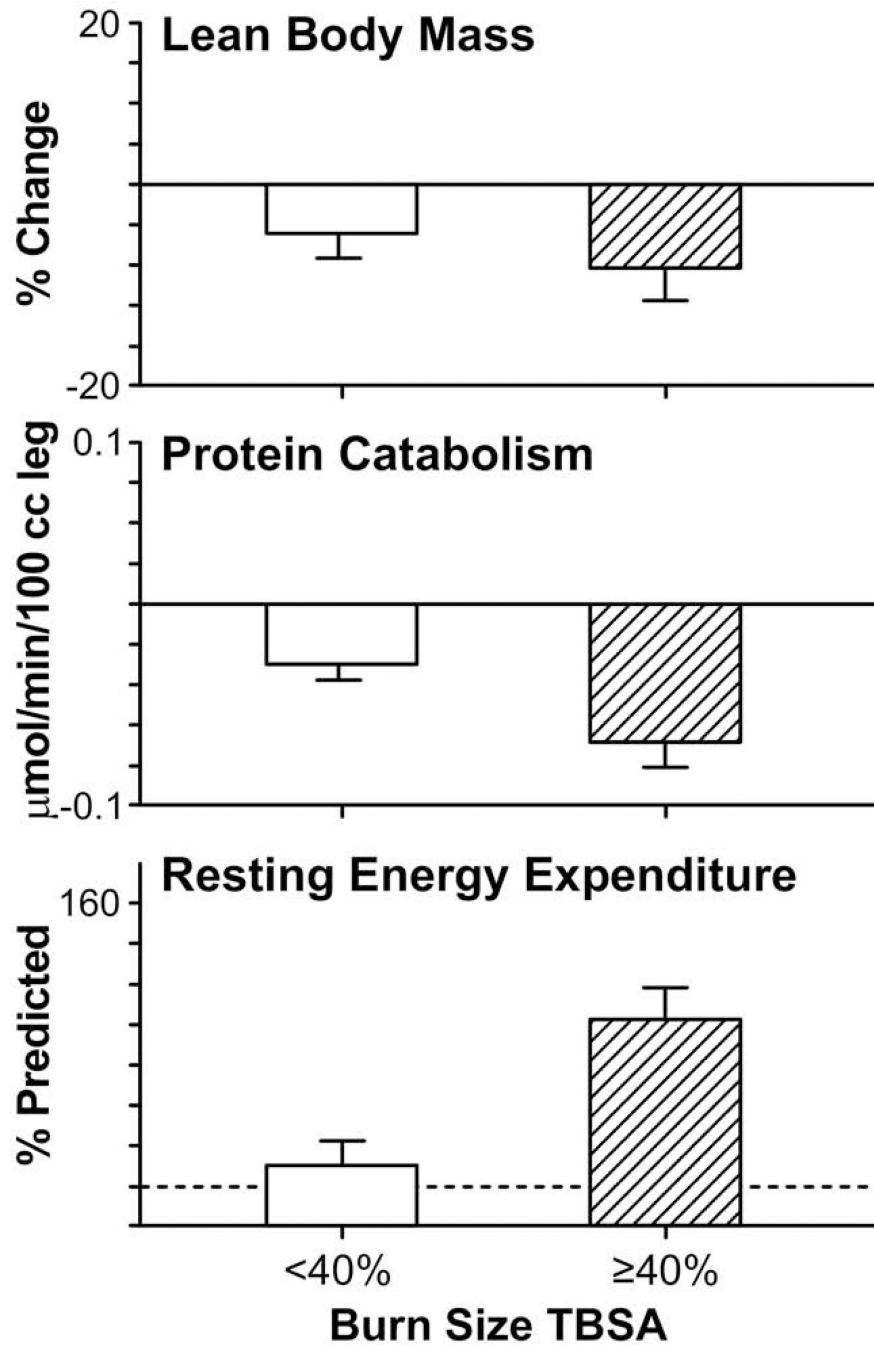
Figure 2.
Effect of burn size on body mass, resting energy expenditure, and protein degradation. Changes in net protein balance of muscle protein synthesis and breakdown induced by burn injury was measured by stable isotope studies using d5-phenyalanine infusion studies published previously.[1,12,24,129] Graphs are averages ± SEM. White bars represent patients with burns <40% total body surface area (TBSA). Striped bars represent patients with burns 40% TBSA. Values from nonburned, normal patients are represented by dashed lines (—).
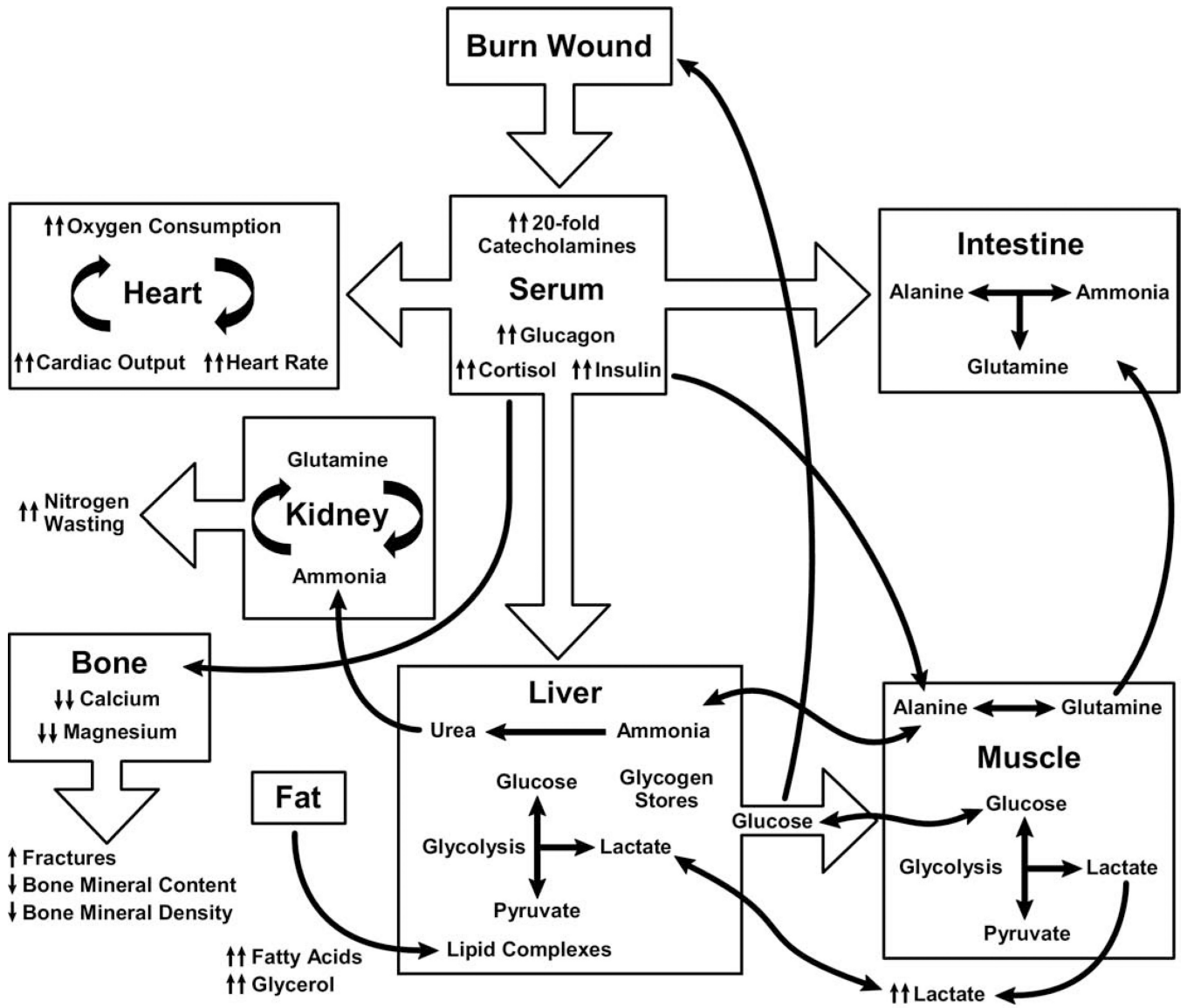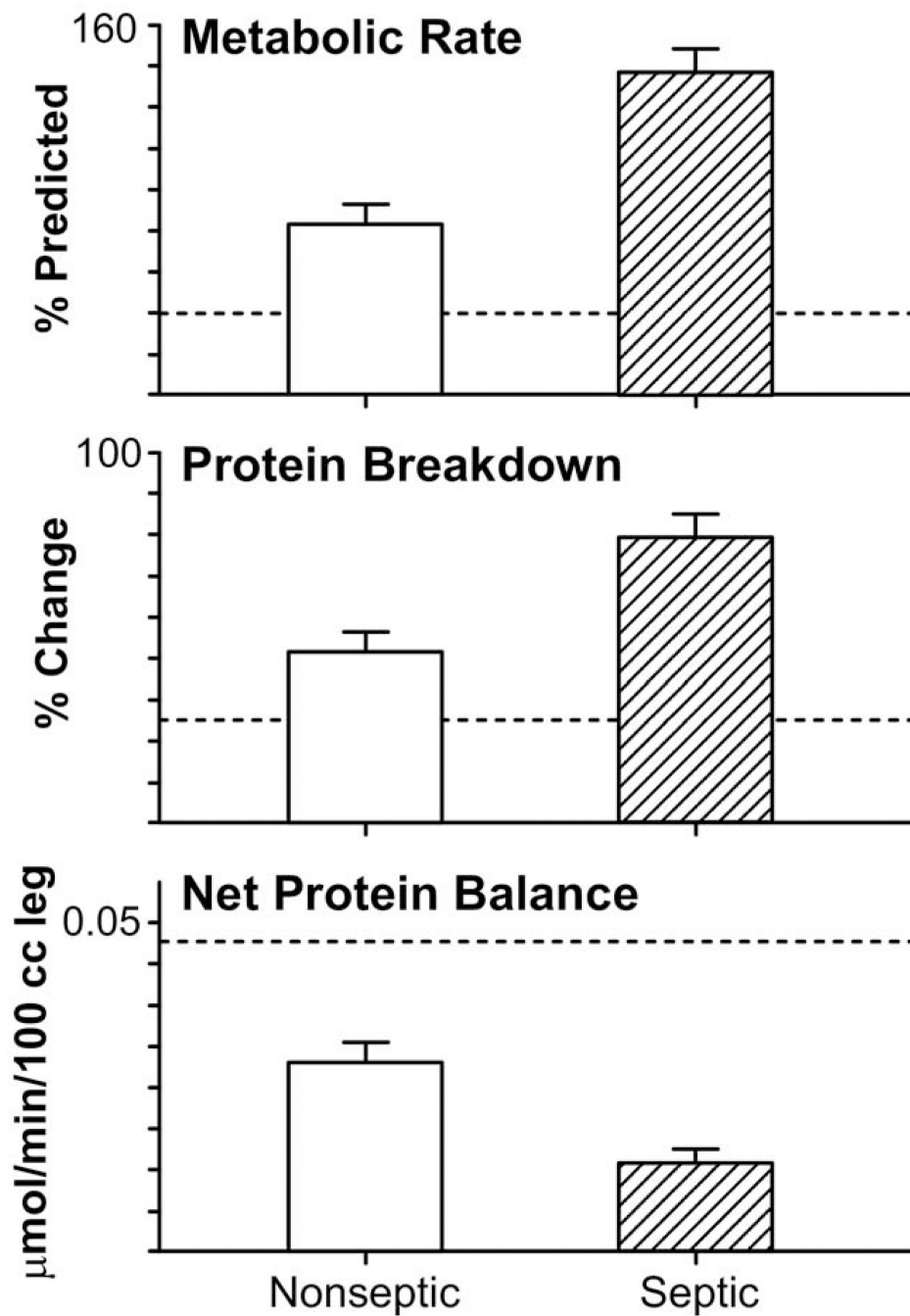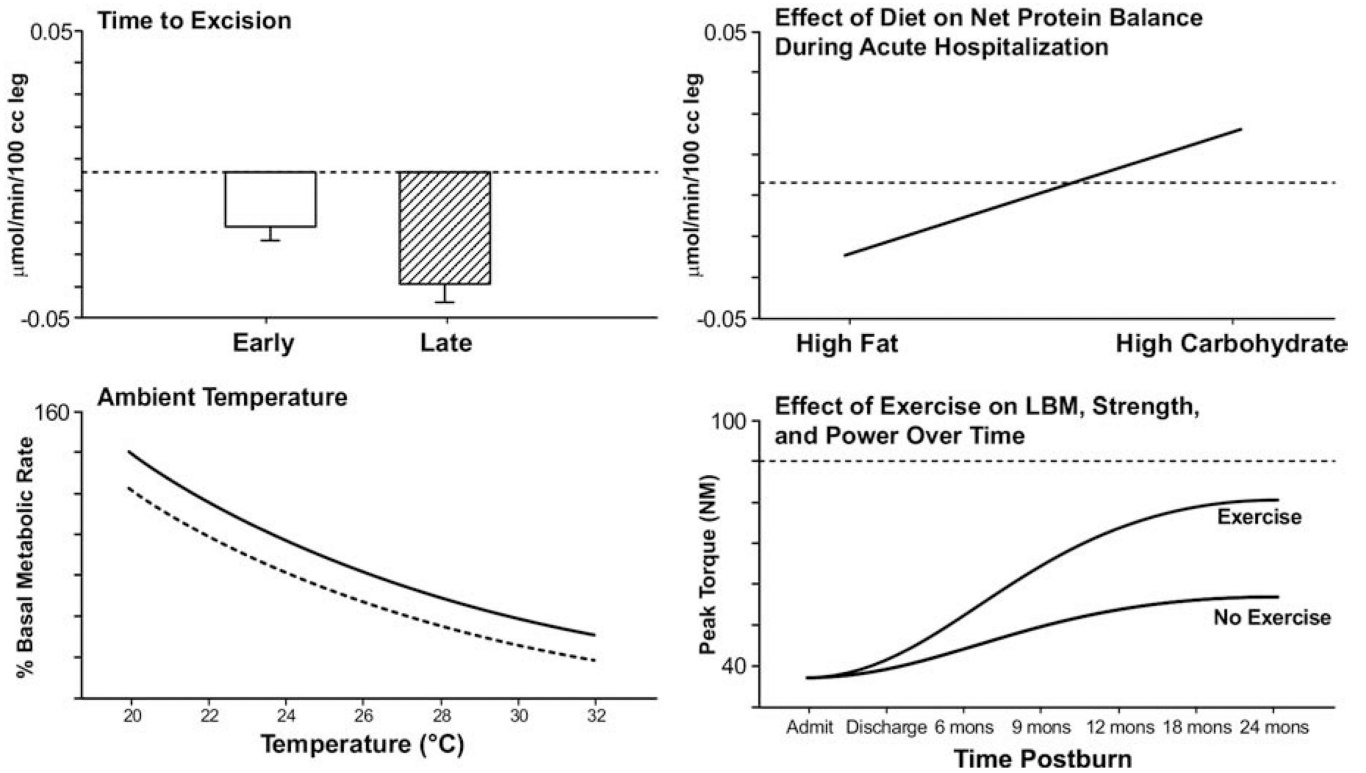
Figure 3.
Effects of metabolic dysfunction postburn.

Figure 4.
Effect of sepsis on resting energy expenditure, muscle protein breakdown, and fractional synthetic rate of muscle protein synthesis compared with like-sized burns. Changes in net protein balance of muscle protein synthesis and breakdown induced by burn injury was measured by stable isotope studies using d5-phenyalanine infusion studies published previously.[1,12,24,129] Graphs are averages ± SEM. White bars represent nonseptic patients with burns 40% total body surface area (TBSA). Striped bars represent septic patients with burns 40% TBSA. Values from nonburned, normal patients are represented by dashed lines (—).
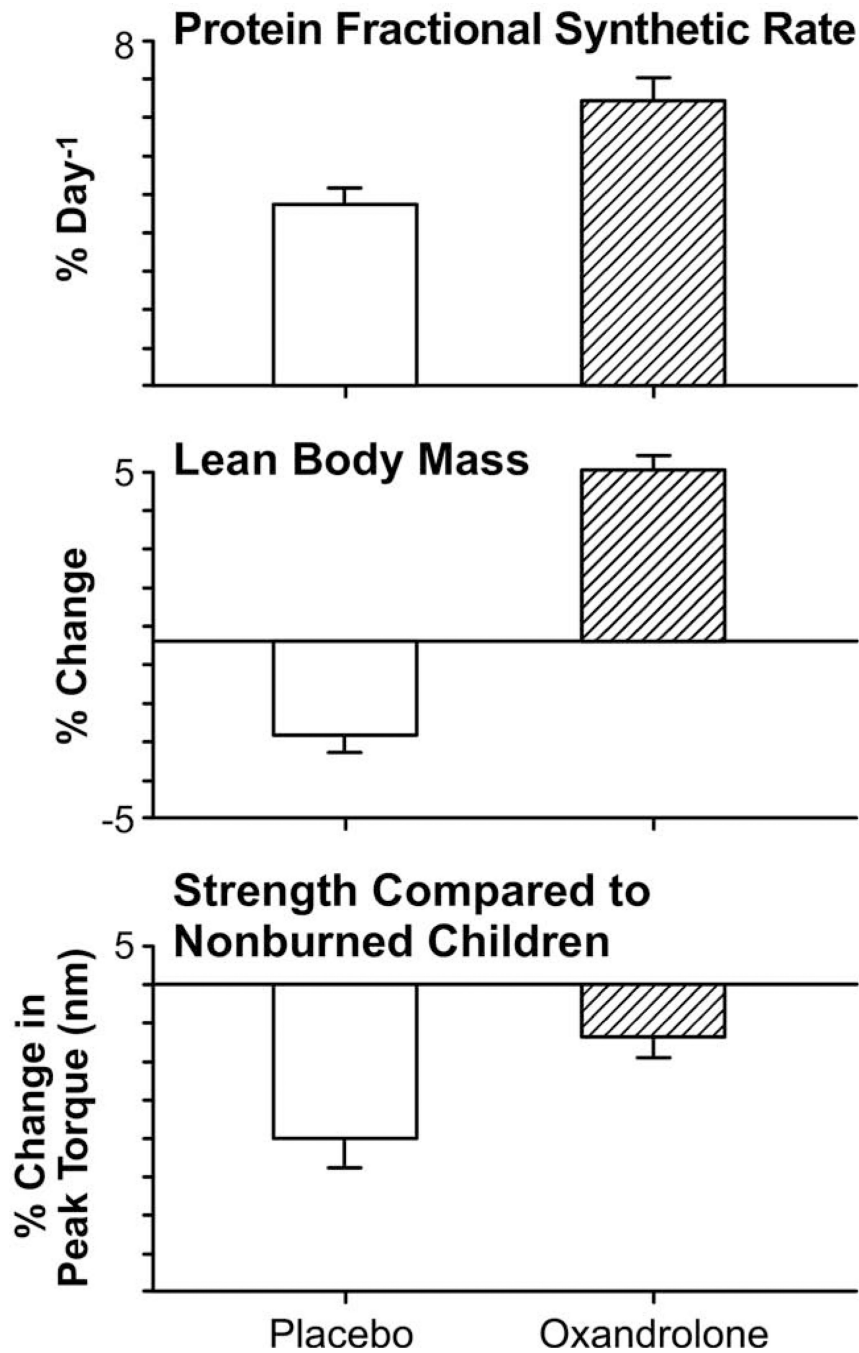
Figure 5.
Nonpharmacologic modulations of the hypermetabolic response postburn. Demonstrates effect of early excision and grafting, environmental thermoregulation, high-carbohydrate diet and exercise on physiologic derangements postburn.[12,24,68,130,131] Graphs are averages ± SEM. White bars represent patients with burns 40% total body surface area (TBSA) that had early excision. Striped bars represent patients with burns 40% TBSA that had late excision of burn eschar. Averages for burn patients are represented by solid curves. Values from non-burned, normal patients are represented by dashed lines (—).
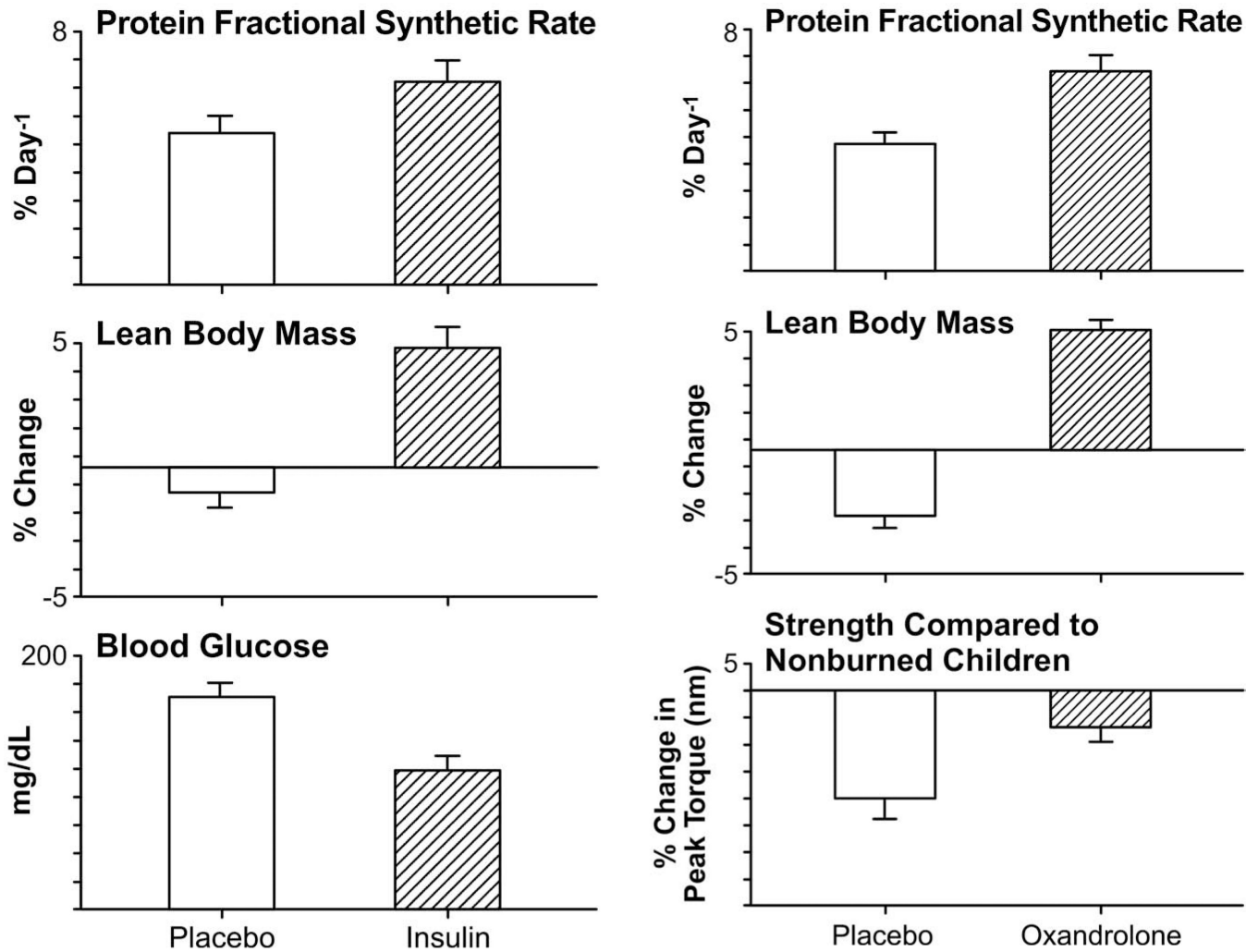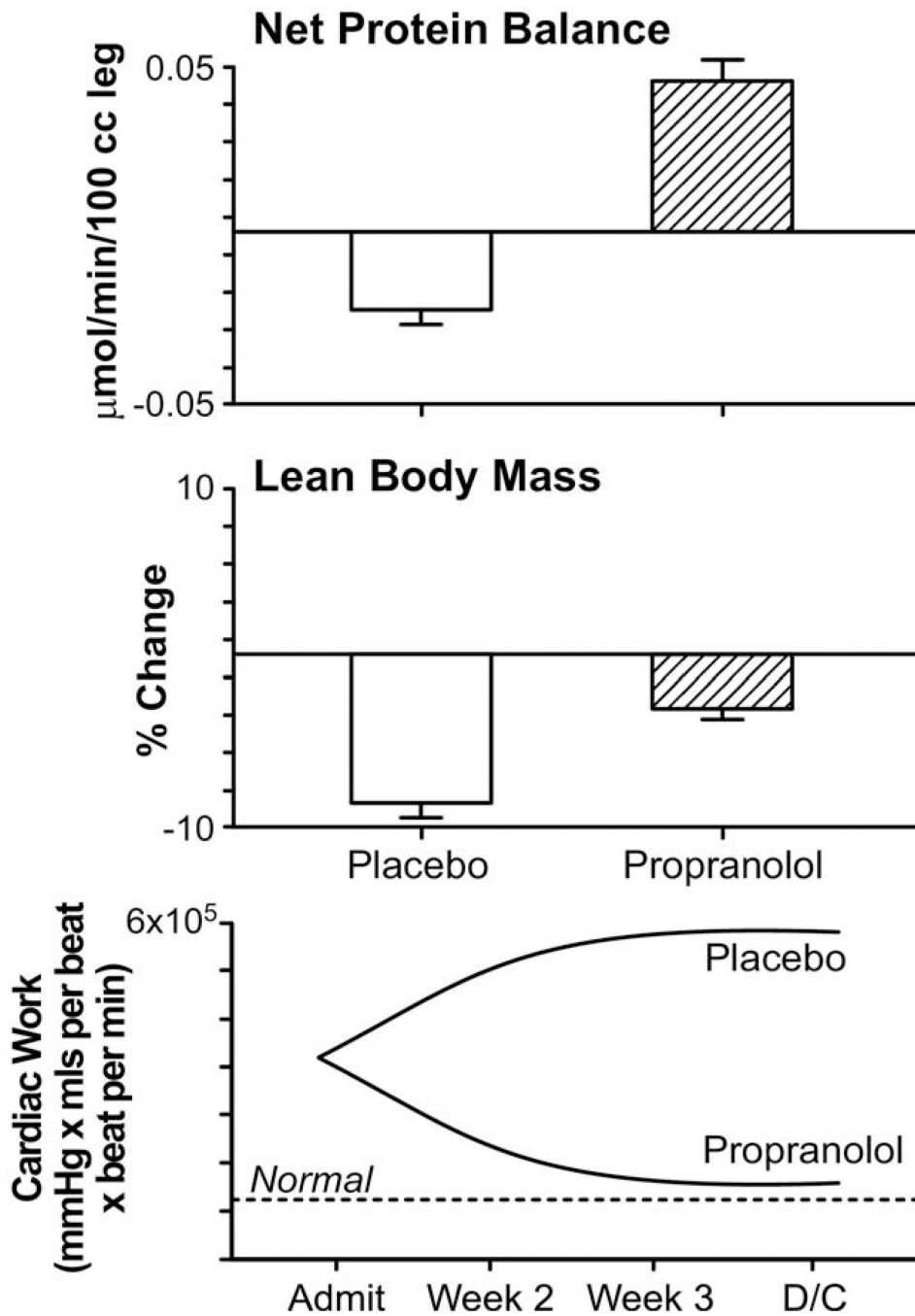
Figure 6.
Insulin. Effect of insulin therapy on the fractional synthetic rate of muscle protein synthesis, lean body mass, and average blood glucose levels.[96,99] Changes in net protein balance of muscle protein synthesis and breakdown induced by burn injury was measured by stable isotope studies using d5-phenyalanine infusion studies published previously.[90,132,133] Graphs are averages ± SEM. White bars represent patients with burns 40% total body surface area (TBSA) that received no anabolic agents or insulin. Striped bars represent patients with burns 40% TBSA who were randomized to receive insulin.
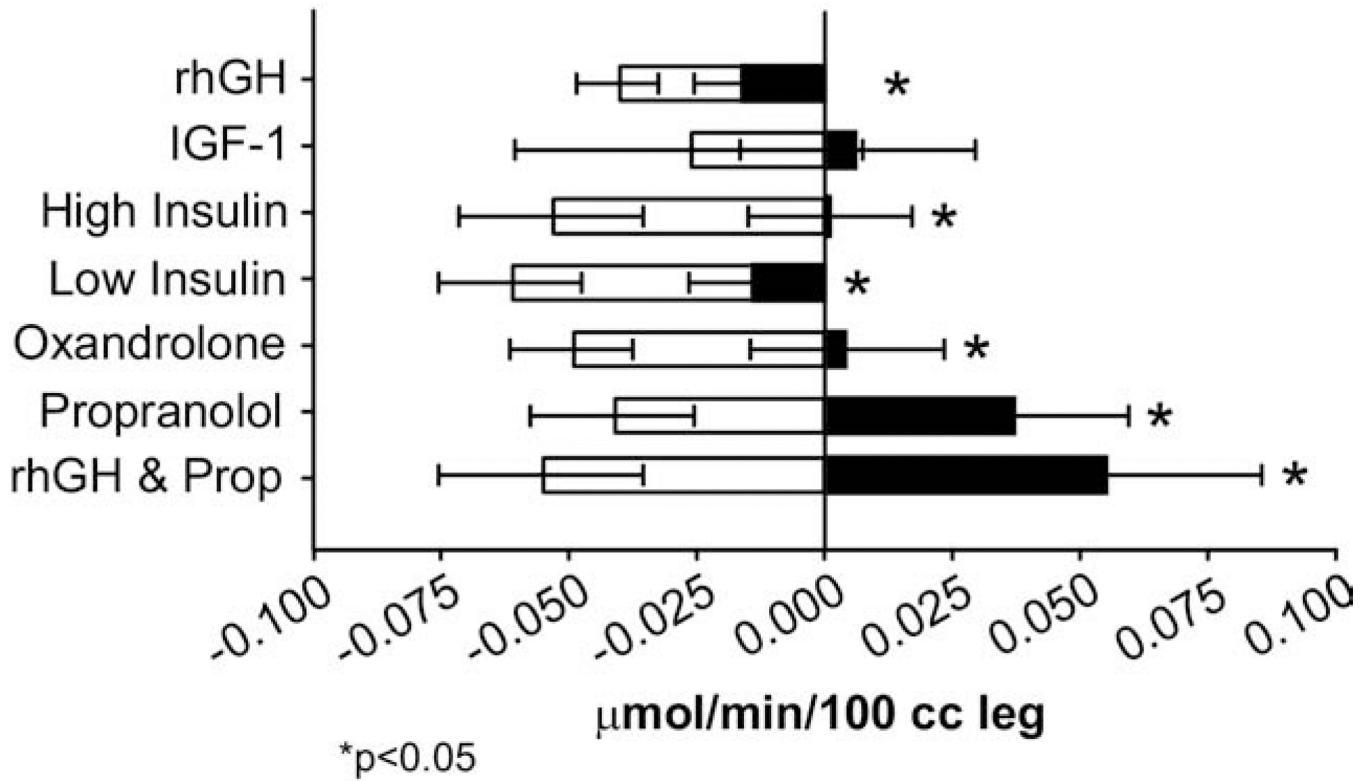
Figure 7.
Oxandrolone. Effect of oxandrolone treatment on the fractional synthetic rate of muscle protein synthesis, lean body mass, and strength.[107,108] Changes in net protein balance of muscle protein synthesis and breakdown induced by burn injury was measured by stable isotope studies using d5-phenyalanine infusion studies published previously.[1,24,107] Graphs are averages ± SEM. White bars represent patients with burns 40% total body surface area (TBSA) who received no anabolic agents. Striped bars represent patients with burns 40% TBSA that were randomized to receive oxandrolone.

Figure 8.
Propranolol. Effect of propranolol treatment on the fractional synthetic rate of muscle protein synthesis, lean body mass, and cardiac work.[16] Changes in net protein balance of muscle protein synthesis and breakdown induced by burn injury was measured by stable isotope studies using d5-phenyalanine infusion studies published previously.[1,16,24] Graphs are averages ± SEM. White bars represent patients with burns 40% total body surface area (TBSA) that received no anabolic agents. Striped bars represent patients with burns 40% TBSA that were randomized to receive propranolol. Values from nonburned, normal patients are represented by dashed lines (—).

Figure 9.
Relative efficacy of the different anabolic agents to improve muscle protein synthesis compared with standard of care alone. Changes in net protein balance of muscle protein synthesis and breakdown induced by burn injury was measured by stable isotope studies using d5-phenyalanine infusion studies published previously.[1,12,24,90,129,132,133] *p < 0.05. Graphs are averages ± SEM. White bars represent patients with burns 40% total body surface area (TBSA) that received no anabolic agents. Black bars represent patients with burns 40% TBSA that were randomized to receive drug.

Table 1

Potential Complications and Incidence in Pediatric Burns 40% Total Body Surface Area

Drug	Complications	Incidence (%)
rhGH	Hyperglycemia	50 [*]
	Growth arrest	0
IGF-1/IGFBP-3	Hypoglycemia	25 [*]
	Neuropathy	23
Insulin	Hypoglycemia	20 [*]
Oxandrolone	Hirsutism	1
	Hepatic dysfunction	1
Propranolol	Bronchospasm	0
	Cardiovascular collapse	0

[*] Dose-dependent.

IGF-1, insulin-like growth factor-1; IGFBP-3, with insulin-like growth factor binding protein-3; rhGH, recombinant human growth hormone.

Table 2

Approximate Cost of Daily Dose for 70-kg Patient

Drug	Dose	Cost per day ($)
rhGH	0.2 mg/kg/d	490
IGF-1/IGFBP-3	2 mg/kg/h	Off market
Insulin	1–5 U/h (IV)	3.47
Oxandrolone	15 mg/d	16.50
Propranolol	0.5–4 mg/kg/d	2.56

IGF-1, insulin-like growth factor-1; IGFBP-3, with insulin-like growth factor binding protein-3; rhGH, recombinant human growth hormone.

Table 3

Burn Mortality (LD$_{50}$) Percent Total Body Surface Area Lethal Burn

	n	Ages 0–14 y		Ages 15–44 y		Ages 45–64 y		Ages older than 65 y	
		% TBSA	n	% TBSA	n	% TBSA	n	% TBSA	n
1940–1950	2,807	49	1,336	46	967	27	330	10	144
1990–today	1,722	98	1,083	82	420	78	152	35	67

LD50, median dose that is lethal for 50% of those tested; TBSA, total body surface area.

Table 4

Mortality Rates for Pediatric Burn Patients in Our Institution from 1980 to 2007

	40–60% TBSA burn (%)	61–100% TBSA burn (%)
From 1980 to 1986 n = 1,524)	8	32
From 1987 to 2007 (n = 3,188)	4	18

TBSA, total body surface area.