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] Myo-

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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

cardial 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 postburn 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

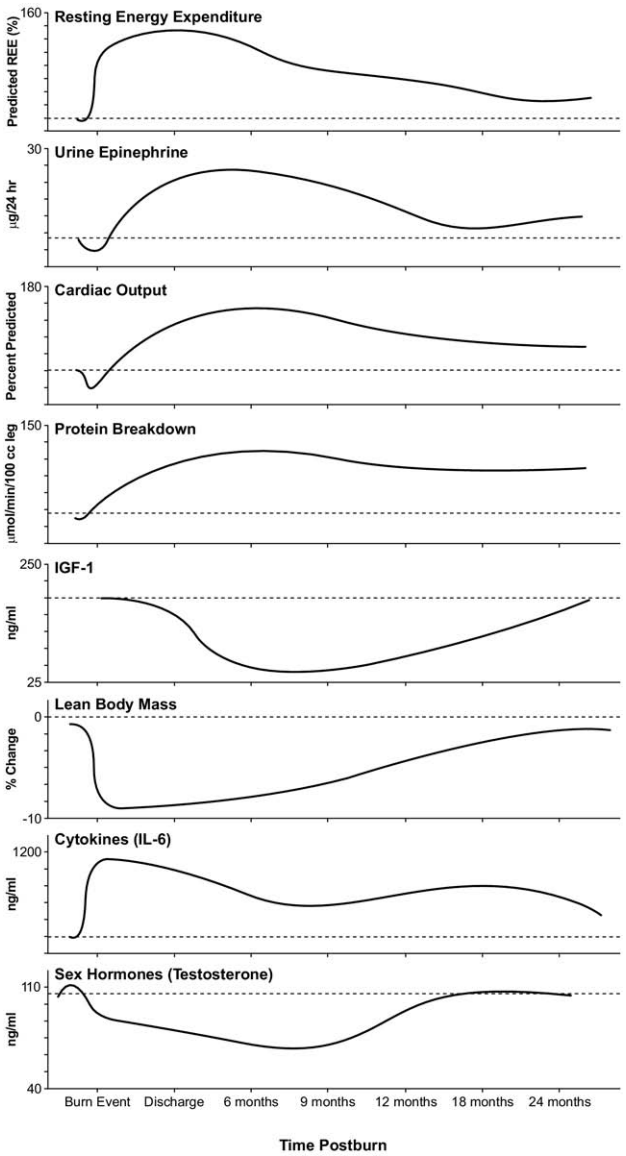

Figure 1. Physiologic and metabolic changes post severe burn injury. Demonstrates changes in resting energy expenditure, stress hormones (epinephrine), cardiac function (cardiac output), gender hormones (testosterone), cytokines (interleukin-6) and changes in body composition (lean body mass). Data were 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 (—).