Altering Metabolism

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A significant proportion of the mortality and morbidity of severe burns is attributable to the ensuing hypermetabolic response. This response can last for as long as 1 year after injury and is associated with impaired wound healing, increased infection risks, erosion of lean body mass, hampered rehabilitation, and delayed reintegration of burn survivors into society. Pharmacologic and nonpharmacologic strategies may be used to reverse the catabolic effect of thermal injury. Nonpharmacologic strategies include early excision and wound closure of burn wound, aggressive treatment of sepsis, elevation of the environmental temperature to thermal neutrality (31.5 ± 0.7°C), high carbohydrate, high protein continuous enteral feeding, and early institution of resistive exercise programs. Pharmacologic modulators of the postburn hypermetabolic response may be achieved through the administration of recombinant human growth hormone, low-dose insulin infusion, use of the synthetic testosterone analog, oxandrolone, and beta blockade with propranolol. This review article discusses these modulators of postburn metabolism. (J Burn Care Rehabil 2005;26:194–199)

Severe thermal injury is followed by a severe systemic metabolic response that consists of an early "ebb" phase and a later "flow" phase. The "ebb" phase lasts for 2 to 3 days and is characterized by a decreased cardiac output and metabolic rate. The "flow" phase begins on day 5 after injury, lasts for at least 9 months, and is characterized by a hyperdynamic circulation and a elevated hypermetabolic rate.[1,2] The realization that this metabolic derangement will continue for months after wound closure has allowed researchers to develop various strategies abrogate the hypermetabolic response rather than simply offering supportive therapy to the individual.[3] This article outlines the deleterious effects of this hypermetabolic state and the therapeutic strategies that are being used to modulate it.

Postburn Hypermetabolic Response and Its Effects

Although the stress response after burn injury is similar to any major trauma, severe burns are characterized by a hypermetabolic response that is more severe and sustained than any other form of trauma. The resting metabolic rates in burn patients increase in a curvilinear fashion, ranging from near normal for burns less than 10% TBSA to twice that of normal in burns more than 40% TBSA. In patients with burn injuries greater than 40% TBSA, the resting metabolic rate at thermally neutral temperature (33°C) reaches 180% of the basal rate during acute admission, 150% at full healing of the burn wound, 140% at 6 months after the injury, 120% at 9 months after injury, and 110% after 12 months.[4]

Severe thermal injury is associated with a decreased oxygen consumption, glucose tolerance, and cardiac output during the early shock states. These metabolic variables gradually increase during the first 5 days after injury to a plateau that lasts through acute admission as long as 9 to 12 months after injury.[4] Enhanced oxygen consumption results from increased total energy expenditure in the major visceral organs and tissues, particularly the liver and skeletal muscle. Elevated energy expenditure closely matches increased substrate oxidation, which results from significant aberrations in the major ATP consumption pathways that control the increased protein turnover, enhanced gluconeogenesis, elevated urea production, and substrate cycling that occurs in severely burned patients. Approximately 60% to 70% of increased total energy expenditure results from ATP consumed by these processes, whereas 40% occurs from uncoupled reactions in cellular membranes and proton leakage in mitochondria.[5] Stable isotope tracer studies have demonstrated that significant in-

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creases occur in total rates of gluconeogenic and triglyceride–fatty acid cycling (250% and 450%, respectively). This futile substrate cycling contributes to increased thermogenesis, which in turn elevates core temperatures to 2°C greater than normal in these patients.[6]

Increased serum fasting glucose and insulin levels, reduced rates of glucose disappearance (insulin resistance), and an enhanced total glucose delivery to peripheral tissues occur during the "flow" phase of the early hypermetabolic response.[7] However, glucose oxidation remains limited. Furthermore, the greatly increased glucose flux is almost entirely directed to the burn wound, where glucose is consumed during anaerobic metabolism by fibroblasts, endothelial, and inflammatory cells.[8] Lactate, produced by anaerobic oxidation of glucose in the wound bed, is recycled to the liver to produce glucose via gluconeogenic pathways.[9] Three-carbon amino acids (mainly alanine), released as the result of continuing degradation of peripheral muscle, also are used as substrate for the increased gluconeogenic drive. As a result of these changes in metabolic pathways, lean muscle protein breakdown is amplified both in the acute and convalescent phases of response to burn injury.[10] This breakdown has been demonstrated with whole body and cross leg nitrogen balance studies in which pronounced negative nitrogen balances persisted for 6 and 9 months after injury.[11] This continuing degradation is disconcerting because animal research studies and isolated observations in starving human beings have demonstrated that loss of a quarter of total body nitrogen can be fatal. This limit can easily be reached in 3 to 4 weeks in untreated burned patients, in whom daily losses of 20 to 25 g/m^2/day occur if patients do not receive maximal nutritional support.[12] Nutritional support or hyperalimantation cannot in isolation reverse or prevent the persistent protein catabolism that results in loss of lean body mass and results in growth delay for as long as 2 years in severely thermally injured children.[13]

Altering Metabolism

The hypermetabolic response to thermal injury appears to have had a survival value considering its evolutionary retention across mammalian species. However, certain aspects of this physiology are maladaptive and can impair recovery. Muscle catabolism has become the principle target of efforts to modify hypermetabolic physiology, owing to its deleterious effects both during the acute and convalescent phase of burn recovery.[13] Treatment modalities can be pharmacologic and nonpharmacologic.

Nonpharmacologic Modalities

Early Excision and Closure. The greatest advancement in the treatment of patients with severe thermal injuries during the past two decades has been early excision and closure of the full-thickness burn wound. If a large burn wound (>50% TBSA) is totally excised and covered with autograft, cadaver skin, or both within 2 to 3 days of injury, the patient's metabolic rate will be 40% less than a comparable burn that is not covered until 1 week after injury.[11] Net protein loss measured by cross leg nitrogen studies doubled from 0.03 to 0.07 μmol of phenylalanine/min/100 ml of leg blood volume, when the burn wound was completely excised and resurfaced with in 72 hours of injury vs delayed primary reconstructions (10 to 21 days after injury).[14] Bacterial log counts in quantitative tissue cultures and the incidence of burn wound sepsis and pain are significantly reduced by early wound excision.[14–16] Biosynthetic skin substitutes and human cadaver skin are equally effective in immediate coverage of burn wounds as compared with autograft.[17–19]

Prompt Treatment of Sepsis. Systemic sepsis in burn patients is not easily defined because of severe derangement of serologic and physiologic variables normally used for diagnosis. An experienced clinician and scores modified from those of the American Academy of Chest Physicians and the Society of Critical Care Medicine Score are both required for diagnosis. Septic patients have an additional 40% increase in metabolic rate and protein catabolism relative to nonseptic burn patients of comparable size.[11] Hence, prevention of infection in burns patients is a critical step in reducing burn-related mortality and additional morbidity attributable to augmentation of the hypermetabolic response.[20]

Nutritional Support. Patients with 40% TBSA treated with vigorous oral alimentation alone can lose a quarter of their preadmission weight by 3 weeks after injury.[21] Continuous enteral or parental nutrition (delivering 25 kcal(0.105 MJ)/kg per day plus 40 kcal per % burn area per day in adults and 1800 kcal (7.56 MJ)/m^2 per day plus 2200 kcal/m^2 of burn area per day) can maintain total body weight in burn patients.[22–24] It also can partially abate the hypermetabolic response to burn.[25,26] Enteral nutrition maintains gastrointestinal motility, reducing translocation bacteremia and sepsis, and is preferable to parenteral feeding, which is reserved for patients with enteral feeding intolerance or prolonged ileus. Parenteral feeding also may be combined with maximally tolerated enteral nutrition to reach the targeted caloric delivery. However, caution must be exercised

because parenteral feeding has been associated with increased mortality, impaired liver function, and reduced immunocompetence. Delivery of nutrition in excess of 1.2 times resting energy expenditure (REE) maintains weight by merely increasing body fat rather than lean body mass.[27–30] Actual caloric requirements can be precisely estimated relative to actual measurements of REE that can be performed in burn intensive care unit using indirect calorimetry. Portable calorimeters that measure the actual oxygen consumption and carbon dioxide production allow REE to be calculated using the Harris-Benedict equation. Supplying nutrition at the rate of 1.4 times the REE (in kcal/m^2/day) can maintain body weight in the pediatric population.[31]

A high carbohydrate diet (3% fat, 82% carbohydrate, and 15% protein) stimulates protein synthesis, increases endogenous insulin production, and improves lean body mass accretion relative to an isocaloric–isoprotein but high-fat enteral diet.[32] Insulin concentrations also are enhanced with a high carbohydrate diet, which may explain the observed improvement in muscle protein synthesis. Adequate protein intake also is crucial to maintain lean body mass. Burn patients oxidize most amino acids at rates that are 50% higher than rates in healthy fasting individuals. Therefore, enhanced protein delivery at 1.5 to 2.0 g/kg/day is recommended for nutritional support of severely burned adults.[33]

Environmental Support. Burn patients can lose as much as 4000 ml/m^2 burned/day of body water through evaporative loss from extensive burn wounds that have not definitive healed.[34] The altered physiologic state resulting from the hypermetabolic response attempts to at least partly generate sufficient energy to offset heat losses associated with this inevitable water loss. The body attempts to raise skin and core temperatures to 2°C greater than normal. Raising the ambient temperature from 25 to 33°C can diminish the magnitude of this obligatory response from 2.0 to 1.4 resting energy expenditure in patients exceeding 40% TBSA. This simple environmental modulation is an important primary treatment goal that frequently is not realized.[35]

Exercise and Adjunctive Measures. A balanced physical therapy program is essential to restore metabolic variables and prevent burn-wound contracture. Progressive resistance exercises in convalescent burn patients can maintain and improve body mass, augment incorporation of amino acids into muscle proteins, and increase muscle strength and the ability to walk distances by approximately 50%.[36] It has been demonstrated that resistance exercising can be safely accomplished in pediatric burn patients without exercise-related hyperpyrexia as the result of an inability to dissipate the generated heat.[37,38]

Although the initial burn injury and sepsis-related complications principally determine the extent of the metabolic response in burn victims, obligatory activity, background and procedural related pain, and anxiety also greatly increase metabolic rates. Judicious maximal narcotics support, appropriate sedation, and supportive psychotherapy are mandatory to minimize their effects.[39]

Pharmacologic Modalities

The hypermetabolic response persists and cannot be fully reversed despite these evidence-based improvements in surgical and nursing care. Catabolic hormones, including catecholamines and cortisol, partly mediate this persistent response. Hence, new and innovative methods to modulate hormonal imbalances after burn injury have been the subject of intensive study. The most important agents include 1) anabolic hormones such as growth hormone (GH), insulin, insulin-like growth factor (IGF-I), IGF-I and IGF-binding protein 3 (IGFBP-3) combinations, oxandrolone, or testosterone; and 2) anticatabolic agents that include adrenergic antagonists (propranolol or metoprolol). These agents appear to be effective only for patients who are catabolic.

Anabolic Proteins. ***Recombinant Human Growth Hormone.*** Daily intramuscular administration of recombinant human growth hormone (rHGH) at doses of 0.2 mg/kg as a daily injection during acute burn care has favorably influenced the hepatic acute phase response,[40,41] increased serum concentrations of its secondary mediator IGF-I,[42] improved muscle protein kinetics, maintained muscular growth,[43,44] and decreased donor site healing time by 1.5 days.[45] These beneficial effects of rHGH are mediated by IGF-I and patients receiving treatment, demonstrated 100% increases in serum IGF-I and IGFBP-3 (the main serum binding-hormone of IGF-I) relative to healthy individuals.[46] However, recombinant HGH has several adverse side effects, particularly during acute care in burned patients, most notably hyperglycaemia[47] and an increased mortality rate in critically ill, nonburned adults.[48] An increase in mortality was not observed in severely burned children.[49]

Insulin-Like Growth Factor-I. Because IGF-I mediates the effects of GH, the infusion of equimolar doses of recombinant human IGF-1 and IGFBP-3 to burned patients has been demonstrated to effectively improve protein metabolism in catabolic pediatric subjects and adults with significantly less hypoglycemia than GH itself.[50,51] It attenuates muscle catabolism and improves gut mucosal integrity in children

with serious burns.[51] Immune function is effectively improved by attenuation of the type 1 and type 2 hepatic acute phase responses, increased serum concentrations of constitutive proteins, and vulnerary modulation of the hypercatabolic use of body protein.[51–54]

Insulin. Continuous infusions of the anabolic peptide, insulin, in victims of major thermal injury prevents muscle catabolism and preserves lean body mass without increasing hepatic triglyceride production.[55,56] Long-term insulin infusion is titrated to a serum concentration of 400 to 900mU/ml for 7 days, maintaining a euglycemia clamp with concomitant dextrose infusion. Lower dose infusions at 9 to 10 U/h, also promote substantial muscle anabolism without the need for additional large doses of carbohydrate.[57] Maintenance of euglycemia with insulin for nonburned patients in surgical critical care units substantially diminished infection and the mortality rate and is a critical hormonal manipulation in the acute setting.[58] Insulin infusions are suited to the closely monitored environment of the burn intensive care unit but are impractical in the rehabilitative outpatient setting.

Anabolic Steroids. ***Oxandrolone.*** Restoration of serum testosterone concentrations in previously healthy young burned males caused a 2-fold decrease in protein breakdown and a 2-fold improvement in protein synthetic inefficiency.[59] Although testosterone restoration is an effective therapeutic maneuver in both in male and female burn victims, a synthetic analog such as oxandrolone, which possesses only 5% of its virilizing androgenic effects, is preferable, particularly in women and prepubescent boys. Oxandrolone was found to improve net muscle protein synthesis in healthy young men[60] and was later found to effectively improve lean body mass in burned patients, especially emaciated subjects whose treatment had been delayed.[61,62] The effects were independent of age.[63] Treatment of acute pediatric burn patients with oral oxandrolone (0.1 mg/kg twice daily) enhances efficiency of protein synthesis and increases anabolic gene expression in muscle.[64,65] Long-term treatment with this oral anabolic during rehabilitation in the outpatient setting is more favorably regarded by pediatric subjects then parenteral anabolic agents. Oxandrolone successfully abates the effects of burn associated hypermetabolism on body tissues and significantly increases body mass over time, lean body mass at 6, 9, and 12 months after burn, and bone mineral content by 12 months after injury vs unburned controls.[66] Patients treated with oxandrolone show few complications relative to those treated with rHGH. However, it must be noted that although anabolic agents can increase lean body mass, exercise is essential to developing strength.[67]

Catecholamine Antagonists. Endogenous catecholamines have been implicated as primary mediators of the hypermetabolic response in major trauma and severe burns.[68] Immediately after injury, there is a 10-fold increase in plasma catecholamine concentrations. This increase produces a hyperdynamic circulation, increases basal energy expenditure, and promotes catabolism of skeletal-muscle proteins.[69] Blocking the effects of raised catecholamine levels has been demonstrated to be a very effective anticatabolic treatment in severe burns. Severely thermally injured subjects treated with beta-adrenergic blockade using propranolol have diminished obligatory thermogenesis, less tachycardia, and reduced cardiac work and resting energy expenditure.[70,71] Long-term use of propranolol during acute care in burn patients, at a dose titrated to reduce heart rate by 20%, was noted to diminish cardiac work load.[72] It also reduced fatty infiltration of the liver, which typically occurs in these patients as the result of enhanced peripheral lipolysis and altered substrate handling. Reduction of hepatic fat results from decreased peripheral lipolysis and reduced palmitate delivery and uptake by the liver,[73,74] producing smaller livers that adversely affect diaphragmatic function less frequently. Stable isotope and serial body composition studies have shown that propranolol reduces skeletal muscle wasting and increases lean body mass after a major thermal injuries by enhancing intracellular recycling of free amino acids for protein synthesis.[75–77] Exogenous continuous low-dose insulin infusion, beta blockade with propranolol, and the use of synthetic testosterone analogue oxandrolone are the most cost-effective and least-toxic therapies to date.

CONCLUSION

Patients with burns less than 40% TBSA are not catabolic unless they become septic. Those patients with burns greater than 40% are always catabolic, which will affect their metabolic derangements and persist for at least 1 year after injury in most body tissues. Burn-associated catabolism cannot be completely reversed but may be manipulated by nonpharmacologic and pharmacologic means. Early burn wound excision and complete wound closure, prevention of sepsis, maintenance of thermal neutrality for the patient by elevation of the ambient temperature, and graded resistance exercises during convalescence are simple, highly effective primary treatment goals. Anabolic and anticatabolic agents during acute care and rehabilitation greatly assist therapeutic minimization of loss of lean

body mass and linear growth delay and are effective in both septic and nonseptic burned patients.[78]

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