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WHAT, HOW, AND HOW MUCH SHOULD BURN PATIENTS BE FED?

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SYNOPSIS

The hypermetabolic response to severe burn injury is characterized by hyperdynamic circulation, profound metabolic, physiologic, catabolic and immune system derangements. Failure to satisfy overwhelming energy and protein requirements after, and during severe burn injury, results in multi-organ dysfunction, increased susceptibility to infection, and death. Attenuation of the hypermetabolic response by various pharmacologic modalities is emerging as an essential component of the management of severe burn patients. This review focuses on the more recent advances in therapeutic strategies to attenuate the hypermetabolic response and its post-burn associated insulin resistance. Modulation of the response by early excision and grafting of burn wounds, environmental thermoregulation, early and continuous enteral feeding with high protein-high carbohydrate feedings and pharmacologic treatments that stimulate anabolism and oppose catabolism have markedly decreased morbidity in the acute phase post severe burn injury.

Keywords

Hypermetabolic Response; Burn Injury; Trauma; Nutrition

INTRODUCTION

Severe burn injury represents a significant problem worldwide. More than 1 million burn injuries occur annually in the United States. Although most of these burn injuries are minor, approximately 10% of burn patients require admission to a hospital or major burn center for appropriate treatment every year¹. Recent reports revealed a 50% decline in burn-related deaths and hospital admissions in the USA over the last 20 years, mainly due to effective prevention strategies, decreasing the number and severity of burns^{2, 3}. Advances in therapeutic strategies, including advances in resuscitation, wound coverage, better support of hypermetabolic response to injury, more appropriate infection control and improved treatment of inhalation injury, have further improved the clinical outcome of this unique

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patient population over the past years. However, severe burns remain a devastating injury affecting nearly every organ system and leading to significant morbidity and mortality⁴.

METABOLIC CHANGES FOLLOWING SEVERE BURN INJURY

Severe burns covering more than 40% total body surface area (TBSA) are typically followed by a period of stress, inflammation and hypermetabolism, characterized by a hyperdynamic circulatory response with increased body temperature, glycolysis, proteolysis, lipolysis and futile substrate cycling.⁵⁻⁷ These responses are present in all trauma, surgical, or critically ill patients, but the severity, length and magnitude is unique for burn patients^{4, 8}. Marked and sustained increases in catecholamine, glucocorticoid, glucagon and dopamine secretion are thought to initiate the cascade of events leading to the acute hypermetabolic response with its ensuing catabolic state^{5, 9-16}. The response is characterized by supraphysiologic metabolic rates, constitutive muscle and bone catabolism, growth retardation, insulin resistance, and increased risk for infection^{5-7, 17, 18}. If untreated, physiologic exhaustion ensues, and the insult becomes fatal¹⁹⁻²². This period is characterized by profoundly accelerated glycolysis, lipolysis, proteolysis, insulin resistance, liver dysfunction, and decreases of lean body mass and total body mass²³⁻²⁹. A ten percent loss of total body mass leads to immune dysfunction; 20% leads to decreased wound healing; 30% leads to severe infections; and a 40% loss leads to death³⁰. Severely burned, catabolic patients can lose up to 25% of total body mass after acute severe burn injury²⁵.

The cause of this complex response is not well understood. However, it is hypothesized that interleukins 1 and 6, platelet-activating factor, tumor necrosis factor (TNF), endotoxin, neutrophil-adherence complexes, reactive oxygen species, nitric oxide and coagulation as well as complement cascades have also been implicated in regulating this response to burn injury³¹. Once these cascades are initiated, their mediators and by-products appear to stimulate the persistent and increased metabolic rate associated with altered glucose metabolism seen after severe burn injury³². The primary mediators of this response after severe burn injury are catecholamines, corticosteroids, and inflammatory cytokines³³. There is a 10 to 50-fold elevation of plasma catecholamines and corticosteroid levels that last up to 12 months post-burn^{34, 35}. Inflammatory cytokine levels, serum hormones, acute proteins and constitutive proteins are altered immediately post-burn and remain abnormal throughout the acute hospitalization up to 2 months post-burn compared with normal levels³⁴.

Several studies have indicated that these metabolic phenomena post-burn occur in a timely manner, suggesting two distinct patterns of metabolic regulation following injury³⁶. The first phase occurs within the first 48 hours of injury and has classically been called the “ebb phase,”^{36, 37} characterized by decreases in cardiac output, oxygen consumption, and metabolic rate as well as impaired glucose tolerance associated with its hyperglycemic state. These metabolic variables gradually increase within the first five days post-injury to a plateau phase (called the “flow” phase), characteristically associated with hyperdynamic circulation and the above mentioned hypermetabolic state.

Multi-organ dysfunction is the hallmark of the acute phase response post-burn⁸. Immediately post-burn, patients may have low cardiac values characteristic of early shock³⁸. However, by four days post-burn, at the onset of shock, they have cardiac outputs greater than 150% compared with non-burned, healthy volunteers³⁴. Heart rates of our patients approach 160% compared with non-burned, healthy patients²⁸. Post-burn, patients have increased cardiac work that lasts well into the rehabilitation phase^{4, 39}. Myocardial oxygen consumption values far surpass values of marathon runners and are sustained well into the rehabilitation phase^{39, 40}. Profound hepatomegaly occurs after burn injury. The liver

increases its size by 225% by two weeks post-burn and remains increased at discharge by 200%³⁴.

Insulin release during this time period was found to be twice that of controls in response to glucose load^{41, 42} and plasma glucose levels are markedly elevated, indicating the development of an insulin-resistance^{42, 43}. Current understanding has been that these metabolic alterations resolve soon after complete wound closure. However, recent studies found that the hypermetabolic response to burn injury may last for more than 12 months after the initial event^{5, 9, 16, 44}. We found in a recent study that sustained hypermetabolic alterations post-burn, indicated by persistent elevations of total urine cortisol levels, serum cytokines, catecholamines and basal energy requirements, were accompanied by impaired glucose metabolism and insulin sensitivity that persisted for up to three years after the initial burn injury⁴⁵.

Glucose metabolism in severely burned patients is dramatically deranged. In order to provide glucose, a major fuel source to vital organs, release of the above mentioned stress mediators oppose the anabolic actions of insulin⁴⁶. By enhancing adipose tissue lipolysis⁴⁷ and skeletal muscle proteolysis⁴⁸, they increase gluconeogenic substrates, including glycerol, alanine and lactate, thus augmenting hepatic glucose production in burned patients⁴⁹⁻⁵¹. In healthy subjects glucose metabolism is tightly regulated, and under normal circumstances, a postprandial increase in blood glucose concentration stimulates release of insulin from pancreatic β -cells. Insulin mediates peripheral glucose uptake into skeletal muscle and adipose tissue and suppresses hepatic gluconeogenesis, thereby maintaining blood glucose homeostasis^{49, 50}. In severe burns, however, metabolic alterations can cause significant changes in energy substrate metabolism. Hyperglycemia fails to suppress hepatic glucose release during this time,⁵² and the suppressive effect of insulin on hepatic glucose release is attenuated, significantly contributing to post-trauma hyperglycemia⁵³. Catecholamine-mediated enhancement of hepatic glycogenolysis, as well as direct sympathetic stimulation of glycogen breakdown, can further aggravate the hyperglycemia in response to stress⁴⁹. Catecholamines have also been shown to impair glucose disposal via alterations of the insulin signaling pathway and GLUT-4 translocation in muscle and adipose tissue, resulting in peripheral insulin resistance^{50, 54}. Researchers have shown an impaired activation of Insulin Receptor Substrate-1 at its tyrosine binding site and an inhibition of AKT in muscle biopsies of children at seven days post-burn⁵³. There is a link between impaired liver and muscle mitochondrial oxidative function, altered rates of lipolysis, and impaired insulin signaling post-burn, attenuating the suppressive actions of insulin both on hepatic glucose production and on the stimulation of muscle glucose uptake^{42, 47, 52, 53}. Another counter-regulatory hormone of interest during stress of the critically ill is glucagon. Glucagon, like epinephrine, leads to increased glucose production through both gluconeogenesis and glycogenolysis⁵⁵. The action of glucagon alone is not maintained over time; however, its action on gluconeogenesis is sustained in an additive manner by the presence of epinephrine, cortisol, and growth hormone^{46, 55}. Similarly, epinephrine and glucagon have an additive effect on glycogenolysis⁵⁵. Pro-inflammatory cytokines contribute indirectly to post-burn hyperglycemia by enhancing the release of the aforementioned stress hormones⁵⁶⁻⁵⁸. Other groups showed that inflammatory cytokines, including tumor necrosis factor (TNF), interleukin (IL) -6 and monocyte chemotactic protein (MCP) -1 also act via direct effects on the insulin signal transduction pathway through modification of signaling properties of insulin receptor substrates, contributing to post-burn hyperglycemia via liver and skeletal muscle insulin resistance⁵⁹⁻⁶¹. Alterations in metabolic pathways as well as pro-inflammatory cytokines, such as TNF, have also been implicated in significantly contributing to lean muscle protein breakdown, both during the acute and convalescent phases in response to burn injury^{62, 63}. In contrast to starvation, in which

lipolysis and ketosis provide energy and protect muscle reserves, burn injury considerably reduces the ability of the body to utilize fat as an energy source.

Skeletal muscle is thus the major source of fuel in the burned patient, which leads to marked wasting of lean body mass (LBM) within days after injury^{4, 64}. This muscle 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 injury⁶⁵. Since skeletal muscle has been shown to be responsible for up to 80% of whole body insulin-stimulated glucose uptake, decreases in muscle mass may significantly contribute to this persistent insulin resistance post-burn⁶⁶. The correlation between hyperglycemia and muscle protein catabolism has been also supported by Flakoll and others⁶⁷, in which an isotopic tracer of leucine was utilized to index whole-body protein flux in normal volunteers. The group showed a significant increase in proteolysis rates occurring without any alteration in either leucine oxidation or non-oxidative disposal (an estimate of protein synthesis), suggesting that hyperglycemia induced increased protein breakdown. Flakoll and others⁶⁷ further demonstrated that elevations of plasma glucose levels resulted in a marked stimulation of whole body proteolysis during hyperinsulinemia. Net loss of protein leads to loss of lean body mass, and severe muscle wasting leads to decreased strength and failure to rehabilitate fully. The resultant muscle weakness was further shown to prolong mechanical ventilatory requirements, and delay mobilization in protein-malnourished patients, thus markedly contributing to the incidence of mortality in these patients⁶⁸. This loss of protein is directly related to increases in metabolic rate and may persist up to 9 months after critical burn injury, often resulting in significantly negative whole-body and cross-leg nitrogen balances. Severely burned patients have a nitrogen loss of 20–25 g/m²TBSA/day, and if unattended, lethal cachexia becomes imminent in less than 30 days. Persistent protein catabolism may also account for the delay in growth frequently observed in our pediatric patient population for up to 2 years post-burn¹⁷.

Perturbations, such as sepsis, increase metabolic rates and protein catabolism up to 40% compared with patients with like-size burns that do not develop sepsis^{5, 69}. A vicious cycle ensues, as patients that are catabolic are more susceptible to sepsis due to changes in immune function and immune response. The emergence of multi-resistant organisms have led to increases in sepsis related infections and death overall^{70–72}. Inflammatory cells, in response to burn wounds and burn wound infections metabolize glucose anaerobically to pyruvate and lactate⁷³. These are returned to the liver for gluconeogenesis which produces recycled energy for use by leukocytes and fibroblasts in the burn wound^{74, 75}.

In past years, therapeutic approaches therefore, have, mainly focused on reversing the hypermetabolic response, with its ensuing catabolic state post-burn, using a large number of different strategies.

Nutritional Support of the Severely Burned Patient

The hypermetabolic response for a severely burned patient far surpasses that in any other disease state¹⁴. Determinants of successful initial burn treatment include early aggressive resuscitation (including nutrition), control of infection, and early closure of the burn wound. Aggressive, early enteral feeding improves outcomes in the burned patient by mitigating the degree and extent of catabolism^{76,77}. Attempting to overcompensate by providing excess calories and/or protein is ineffective and likely to increase such complications as hyperglycemia, carbon dioxide retention (CO₂), and azotemia⁶⁴. Thus, the primary goal of nutritional support in burn patients is to satisfy acute, burn-specific requirements, and not to overfeed.

Patients with 40% TBSA treated with vigorous oral alimentation alone can lose a quarter of their preadmission weight by 3 weeks after injury²⁵. Attempts to feed severely burned patients orally failed due to altered mental status, inhalation injuries that compromised pulmonary function, gastrointestinal dysfunction, and/or feeding intolerance²⁵. The amount of nutrition necessary to provide adequate support and prevent severe catabolism was intolerable for these patients. Inanition proved fatal as severely burned victims succumbed to severe systemic infections and respiratory failure^{25, 78}. Thus, the primary goal of nutritional support, is to address the ever-evolving metabolic needs in severely burned patients. Nutrition should be tailored to promote wound healing, to increase resistance to infection, and to prevent persistent loss of muscle protein. During the acute hospitalization of severely burned patients, attempts to optimize nutrition are countered by immobility and evolving catabolic responses to injury; attempts to achieve a positive nitrogen balance are repeatedly thwarted.

Total parenteral nutrition (TPN) for the nutrition and rehabilitation of severely burned patients surfaced in the 1970's^{79, 80}. TPN allows for the provision of elemental components that do not require digestion or a functioning alimentary tract. Dextrose is the main calorie source in TPN, and protein is supplied as crystalline amino acid solutions. Lipid emulsions can comprise a significant proportion of the calories in TPN. Use of TPN has now been largely replaced by enteral nutrition (EN) in burn patients.

Adults can maintain body weight after severe burn injury only with aggressive, continuous nutrition of 25 kilocalories per kilogram body weight per day plus 40 kilocalories per percent total body surface area burn per day^{81,82}. Children require 1,800 kilocalories per square meter of body surface plus 2,200 kilocalories per square meter of burn area per day to maintain body weight⁸³. The mechanism by which patients are fed affects outcomes. Research shows that parenteral nutrition alone or even in combination with enteral nutrition could lead to overfeeding, liver failure, impaired immune response and increased mortality by 3-fold⁸⁴⁻⁸⁶. Enteral nutrition reduces translocation bacteremia and sepsis, maintains gut motility, and preserves 'first pass' nutrient delivery to the liver⁷⁶. For these patients, parenteral nutrition should be reserved primarily for those who have enteral feeding intolerance or prolonged ileus.

Timing of Nutrition

Advances in burn care have altered the magnitude of the post-burn hypermetabolic response, but not the nature of the response⁶⁴. A major determinant of outcome for severe burn patients is time to treatment. Any delays in resuscitation lead to poorer outcomes⁸⁷. In the acute phase, in the unfed patient, there is significant gut mucosal damage and increased bacterial translocation that collectively lead to decreased nutrient absorption^{88, 89}. Therefore, optimal nutritional support for the severely burned patient is best accomplished by early initiation of enteral nutrition. Moreover, multiple studies demonstrate that early institution of enteral feeding can significantly modulate the hypermetabolic response to severe burn^{76, 77}. Laboratory studies showed significant decreases in metabolic rates by two weeks post-burn in animals enterally fed continuously by two hours post-burn compared with animals fed 3 days post-burn, indicating the benefits of early initiation⁷⁶. Significant modulation of catecholamine levels and support of gut mucosal integrity have been shown with early enteral nutrition⁹⁰. In human studies, early continuous enteral nutrition delivered calculated caloric requirements (resting energy expenditure) by post-burn day three, nearly prevented the hypermetabolic response, and significantly decreased circulating levels of catecholamines, cortisol and glucagon^{90, 91}. Early enteral feeding preserved gut mucosal integrity, motility and intestinal blood flow⁷⁶. Intestinal hypoperfusion or ileus, secondary to delays in resuscitation can be reversed by reperfusion or adequate resuscitation. Post-burn ileus spares the small bowel and primarily affects the stomach and colon⁹². Patients with

severe burn injury can be safely enterally fed in the duodenum or jejunum 6 hours post-burn, whether or not they have total gastroduodenal function⁹³. Nasojejunal, or nasoduodenal feeding should be initiated as soon as possible to facilitate the full resuscitation of the severely burned patient.

The Nutritional Requirements

Actual caloric requirements can be accurately determined by measuring resting energy expenditures with bedside carts.^{94,95} Preservation of lean body mass should be a nutritional goal for severe burn victims, as a major consequence of the hypermetabolic response is severe total body catabolism. Appropriate nutrient delivery can be accomplished by feeding 1.2 to 1.4 times the measured resting energy expenditures (in kilocalories per square meter per day). Goran et al⁹⁴ found that by feeding patients 1.2 times the measured resting energy expenditures, body weight may be maintained, but with a loss of 10% of lean body mass. While others found an increase in body weight by feeding 1.4 times the resting energy expenditure, the gains, however, were in fat deposition, not lean body mass^{95, 96}.

The major energy source for burn patients should be carbohydrates which serve as fuel for wound healing, provide glucose for metabolic pathways, and spare the amino acids needed for catabolic burn patients. It is estimated that critically ill, burned patients have caloric requirements that far exceed the body's ability to use glucose, which is approximately 7 grams per kilogram per day (gm/kg/day) (2,240 kcal for an 80 kilogram man)⁹⁷. Providing a limited amount of dietary fat reduced requirements for carbohydrates and can improve glucose tolerance significantly.

The hypermetabolic, catabolic response to severe burns suppresses lipolysis and limits the extent to which lipids can be utilized for energy. Thus, fat should comprise no more than about 30% of non-protein calories, or about 1 gm/kg/day of intravenous lipids in TPN⁹⁸. Thirty percent may be overwhelming in burned patients. In an animal model, immune function was further compromised with diets containing more than even 15% lipids, advocating the use of low-fat diets in severely burned patients^{99, 100}. The composition of administered fat is more important than the quantity. Most common lipid sources contain omega-6 free fatty acids (ω -6 FFA's) such as linoleic acid which are metabolized through synthesis of arachidonic acid, a precursor of pro-inflammatory cytokines such as Prostaglandin E2. Omega-3 fatty acids (ω -3 FFA's) are metabolized without provoking pro-inflammatory compounds. Diets high in ω -3 FFA's have been associated with an improved inflammatory response, improved outcomes, and reduced incidences of hyperglycemia^{101, 102}.

Proteolysis is another hallmark of the hypermetabolic response after severe burn injury. Protein catabolism in burn patients can exceed 150 grams/day, or almost a half-pound of skeletal muscle⁶⁴. Increased protein catabolism leads to decreased wound healing, immunoincompetence, and loss of lean body mass⁶⁴. There is some evidence that increased protein replacement for severely burned patients may be beneficial^{103,104}. Healthy individuals require 1 gram per kilogram body weight per day of protein intake^{105,106}. However, based on *in vivo* kinetics studies measuring oxidation rates of essential and non-essential amino acids, burn patients have 50% higher utilization rates than healthy individuals in the fasting state^{103,107, 104}. Thus, burn patients require a minimum of 1.5 to 2 grams per kilogram body weight per day protein intake^{16, 64, 108}. Any higher amount of supplementation in burned children, however, leads to increased urea production without improvements in lean body mass or muscle protein synthesis¹⁰⁹.

Amino acids have a key role in recovery following injury. Alanine and glutamine (GLU) are important transport amino acids, created in skeletal muscle to supply energy to the liver and

to aid in wound healing¹¹⁰. GLU serves as a primary fuel for enterocytes and lymphocytes, and aids in maintaining small bowel integrity, preserving gut-associated immune function, and limiting intestinal permeability following acute injury^{111, 112}. GLU is rapidly depleted from both serum and muscle following severe burn injury, limiting visceral protein synthesis, and underscoring the importance of glutamine replacement after severe burn injury^{110, 113}. When GLU was given at 25 gm/kg/day, severely burned patients had a decrease in incidence of infections, improved visceral protein levels, decreased length of stay, and reduced mortality^{114–116}. Replacement of branched-chain amino acids led to improvements in nitrogen balance, but no effect on survival¹¹⁷.

Vitamins and other micronutrients are also profoundly affected by the hypermetabolic – catabolic response post-burn¹¹⁸ (Table 1)^{119,120,166}. Decreased levels of Vitamins A, C, and D, iron, zinc, and selenium have been implicated in decreased wound healing and immune dysfunction post severe burn injury^{118, 121}. Vitamin A replacement is important for wound healing and epithelial growth^{120, 122}. Vitamin C is paramount for synthesis and the cross-linking of collagen post-burn, and burn patients often require up to 20 times the recommended daily allowance^{120, 121}. Vitamin D is essential in the prevention of further bone catabolism post-burn¹²¹. Iron is an important cofactor in oxygen-carrying proteins⁶⁴. Zinc supplementation contributes to improvements in wound healing, DNA replication, and lymphocyte function¹²³. Selenium replacement improves cell-mediated immunity¹²⁴. Collectively, replacement of these micronutrients has contributed to the improvement in morbidity of severely burned patients.

Milk, traditionally an isocaloric-isoprotein, but high fat diet, consisting of 44% fat, 42% carbohydrate and 14% protein, became standard of care for the pediatric burned patient^{125, 126}. Although it was well-tolerated, fat did not serve as the optimal energy source for these patients. There was continued protein degradation, and lean body mass gains paled in comparison with high carbohydrate diets – consisting of 3% fat, 15% protein and 82% carbohydrate¹²⁶. The high carbohydrate diet increased protein synthesis, increased effective endogenous insulin production, and improved lean body mass. Increased endogenous insulin levels, stimulated by high carbohydrate delivery, may have contributed to improved muscle protein synthesis¹²⁶. Parenteral formulas which are traditionally 70% dextrose, 15% amino acids and 20% lipids, can be manipulated and adjusted to meet patients' caloric needs. However, TPN is associated with increased pro-inflammatory cytokines, increased pulmonary dysfunction, and increased mortality^{84, 85, 127, 128}. Thus, all TPN formulas containing currently available fat emulsions should be reserved for patients that cannot tolerate EN.

Overfeeding

The overfeeding of severely burned patients can lead to major complications. Overfeeding with carbohydrates results in elevated respiratory quotients, increased fat synthesis, and increased CO₂ elimination. Ventilated patients become more difficult to manage and to wean from support¹²⁹. Excess carbohydrate or fat can also lead to fat deposition in the liver¹³⁰. Excess protein replacement leads to elevations in blood urea nitrogen (BUN), which could lead to acute renal failure, increased propensity to sepsis, and death¹³⁰. Overfeeding can lead to hyperglycemia, which is already present in up to 90% of all critically ill patients – leading to increased morbidity and mortality¹³¹. This iatrogenic hyperglycemia is even harder to treat as both endogenous and exogenous insulin effects are often countered by the surge of catabolic hormones^{33, 132}. These complications are not specific to parenteral or enteral feedings, but are manifestations of attempts to over-compensate for the tremendous losses suffered by severely burned patients.

Positive changes in body weight are among the best predictors of overall nutritional status. Significant weight loss, particularly rapid and unplanned, is a predictor of mortality¹³³. However, it should be noted that resuscitation and maintenance fluid increases may mask ongoing loss of lean body mass so that patients can suffer significant inanition and still weigh more than they did at the time of admission. In addition, fluid shifts associated with infections, ventilator support, hypoproteinemia, and elevations in aldosterone and antidiuretic hormone lead to wide fluctuations in weight that have little to do with nutritional status¹³⁴. Judicious monitoring of long-term trends is paramount in the clinical management of severely burned patients.

Determination of nitrogen balance, serum proteins, and abnormalities of immune function will also aid the assessment of nutritional supplementation post-burn^{121, 135, 136}. While no single laboratory test is fully reliable in nutritional monitoring, regular metabolic assessment is paramount in the ever-evolving physiologic response post-burn.

The Hormonal Response in Severe Burns

Elevated levels of catecholamines, cortisol, and glucagon perpetuate the profound changes in metabolic rates, growth, and physiology observed in the burn patient population. Anabolic agents such as recombinant human growth hormone (rhGH), insulin, insulin-like growth factor (IGF-1), and insulin-like growth factor binding protein-3 (IGFB-3) in combination with testosterone and oxandrolone have been shown to abate post-burn metabolism. To counter elevated levels of catecholamines, the adrenergic antagonist, propranolol, has been used with profound results. Other glucose modulators, besides insulin, have also been shown to attenuate post-burn metabolic derangements. The use of anabolic or anti-catabolic agents in severely burned children, in addition to standard of care, have led to significant decreases in protein catabolism.

PHARMACOLOGIC MODALITIES

Recombinant human Growth hormone

Intramuscular administration of recombinant human growth hormone (rhGH) at doses of 0.2 mg/kg as a daily injection during the acute burn phase favorably influenced the hepatic acute phase response^{137, 138}, increased serum concentrations of its secondary mediator IGF-I¹³⁹, improved muscle protein kinetics, maintained muscular growth^{140, 141}, decreased donor site healing time by 1.5 days¹⁴², improved resting energy expenditure, and attenuated hyperdynamic circulation¹⁴³. These beneficial effects of rhGH are mediated by insulin-like growth factor (IGF) -I, and patients receiving treatment demonstrated 100% increases in serum IGFI and IGF-binding protein (IGFBP) -3 relative to healthy individuals^{144, 145}. However, in a prospective, multicenter, double-blind, randomized, placebo-controlled trial involving 247 patients and 285 critically ill non-burned patients, Takala and others found that high doses of rhGH (0.10 +/- 0.02 mg/kg BW) were associated with increased morbidity and mortality¹⁴⁵. Others demonstrated growth hormone treatment to be associated with hyperglycemia and insulin resistance^{146, 147}. However, neither short nor long-term administration of rhGH was associated with an increase in mortality in severely burned children^{143, 148}.

Insulin-like Growth Factor

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 be effective in improving protein metabolism in catabolic pediatric subjects and adults with significantly less hypoglycemia than rhGH alone^{149, 150}. It attenuates muscle catabolism and improves gut mucosal integrity in children with severe burns¹⁵⁰. 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 use of body protein resulting from hypercatabolism^{150–153}. However, studies by van den Berghe and colleagues¹⁵⁴ indicate that the use of IGF-1 alone is not effective in non-burned critically ill patients.

Oxandrolone

Treatment with anabolic agents such as oxandrolone, a testosterone analog which possesses only 5% of its virilizing androgenic effects, improves muscle protein catabolism via enhanced protein synthesis efficiency¹⁵⁵, reduces weight loss, and increases donor site wound healing¹⁵⁶. In a large prospective, double-blinded, randomized single-center study, oxandrolone given at a dose of 0.1 mg/kg every 12 hours shortened length of acute hospital stay, maintained LBM, and improved body composition and hepatic protein synthesis¹⁵⁷. These effects were independent of age¹⁵⁸. Long-term treatment with this oral anabolic during rehabilitation in the outpatient setting is more favorably regarded by pediatric subjects than parenteral anabolic agents. Oxandrolone use in children successfully abates the effects of burn associated hypermetabolism on body tissues and significantly improves body mass over time, increasing lean body mass at 6, 9, and 12 months after burn, and bone mineral content by 12 months after injury in comparison with unburned controls¹⁵⁹. Patients treated with oxandrolone experience 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 strength¹⁶⁰.

Propranolol

Beta-adrenergic blockade with propranolol probably represents the most efficacious anti-catabolic therapy in the treatment of burns.⁸ Long-term use of propranolol during acute care in burn patients, at a dose titrated to reduce heart rate by 15 to 20%, was noted to diminish cardiac work³⁹. It also reduced fatty infiltration of the liver, which typically occurs in these patients as the result of enhanced peripheral lipolysis and altered substrate disposition. Reduction of hepatic fat results from decreased peripheral lipolysis and reduced palmitate delivery and uptake by the liver^{161, 162}, resulting in smaller livers and avoiding the hepatomegaly that frequently adversely affects diaphragmatic function.. Stable isotope serial body composition studies showed that administration of propranolol reduces skeletal muscle wasting and increases lean body mass post-burn^{28, 163}. The underlying mechanism of action of propranolol is still unclear, however, its effects appear to occur due to increased protein synthesis in the presence of persistent protein breakdown and reduced peripheral lipolysis¹⁶⁴. Recent data suggest that administration of propranolol at 4 mg/kg BW/q24 also markedly decreased the amount of insulin necessary to reduce elevated blood glucose levels post-burn.⁴⁰ Propranolol may thus constitute a promising approach to overcoming post-burn insulin resistance.

ATTENUATION OF HYPERGLYCEMIA POST-BURN

Insulin

Insulin probably represents one of the most extensively studied therapeutic agents and novel therapeutic applications are continually being explored. Insulin decreases blood glucose levels by mediating increased peripheral glucose uptake by skeletal muscle and adipose tissue, and suppressing hepatic gluconeogenesis. It also increases DNA replication and protein synthesis via control of amino acid uptake, increases fatty acid synthesis and decreases proteolysis¹⁶⁵. The latter action makes insulin particularly attractive for the treatment of hyperglycemia in severely burned patients since insulin given during acute hospitalization has been shown to improve muscle protein synthesis, accelerate donor site

healing, and attenuate lean body mass loss and the acute phase response^{166–173}. In addition to its anabolic actions, insulin was shown to exert totally unexpected anti-inflammatory effects, potentially neutralizing the pro-inflammatory actions of glucose^{170, 171, 174}. These results suggest a dual benefit of insulin administration: reduction of pro-inflammatory effects of glucose by restoration of euglycemia, and a possible additional insulin-mediated anti-inflammatory effect¹⁷⁵. Van den Berghe and colleagues confirmed the beneficial effects of insulin in a large recent milestone study. Insulin administered to maintain glucose at levels below 110 mg/dl decreased mortality, incidence of infections, sepsis, and sepsis-associated multi-organ failure in critically ill surgical patients¹³¹. Intensive insulin therapy also significantly reduces newly acquired kidney injury, accelerating weaning from mechanical ventilation and accelerating discharge from the ICU and the hospital¹⁷⁶. The ideal target blood glucose range for the severely burned patient has not been identified unequivocally, and several groups are currently undertaking clinical trials in order to define ideal blood glucose levels for the treatment of ICU and burned patients: A study by Finney and colleagues suggests maintaining blood glucose levels of 140 mg/dl and below¹⁷⁷, while the Surviving Sepsis Campaign recommends maintenance of blood glucose levels below 150 mg/dl¹⁷⁸. However, maintaining a continuous hyperinsulinemic, euglycemic clamp in burn patients is particularly difficult since these patients are being continuously fed large caloric loads via enteral feeding tubes. Since burn patients require weekly operations and daily dressing changes, enteral nutrition occasionally needs to be stopped, which may lead to disruption of gastrointestinal motility and increased risk of hypoglycemia⁴.

Metformin

Metformin (Glucophage), a biguanide, has recently been suggested as an alternative means to correct hyperglycemia in severely injured patients¹⁷⁹. By inhibiting gluconeogenesis and augmenting peripheral insulin sensitivity, metformin directly counters the two main metabolic processes which underlie injury-induced hyperglycemia^{180–182}. In addition, metformin has only rarely been associated with hypoglycemic events, thus possibly minimizing this concern which is associated with the use of exogenous insulin¹⁸³. In a small randomized study reported by Gore and colleagues, metformin reduced plasma glucose concentration, decreased endogenous glucose production, and accelerated glucose clearance in severely burned patients¹⁷⁹. A follow-up study evaluating the effects of metformin on muscle protein synthesis, confirmed these observations and demonstrated an increased fractional synthetic rate of muscle protein and improvement in net muscle protein balance in metformin treated patients¹⁸². Thus, metformin, analogous to insulin, may have efficacy in critically injured patients as both an antihyperglycemic and a muscle protein anabolic agent. On the other hand despite the advantages and potential therapeutic uses, treatment with metformin, or other biguanides, has been associated with lactic acidosis^{183, 184}. To avoid metformin-associated lactic acidosis, the use of this medication is contraindicated in certain diseases or illnesses in which there is a potential for impaired lactate elimination (hepatic or renal failure) or tissue hypoxia – and it should be used with caution in acute burn patients.

Novel therapeutic options

Other ongoing trials, with the goal of decreasing post-burn hyperglycemia, include the use of Glucagon-Like-Peptide (GLP)-1 and PPAR- γ agonists (e.g., pioglitazone, thiazolidinediones) or the combination of various anti-diabetic drugs. PPAR- γ agonists, such as fenofibrate, have been shown to improve insulin sensitivity in patients with diabetes. Cree and colleagues found in a recent double-blind, prospective, placebo-controlled, randomized trial that fenofibrate treatment significantly decreased plasma glucose concentrations by improving insulin sensitivity and mitochondrial glucose oxidation⁵³. Fenofibrate also led to significantly increased tyrosine phosphorylation of the insulin receptor (IR) and IRS-1 in

muscle tissue after a hyperinsulinemic-euglycemic clamp when compared with placebo treated patients, indicating improved insulin receptor signaling⁵³.

SUMMARY AND CONCLUSION

Severely burned patients have profound nutritional requirements secondary to the prolonged post-burn hypermetabolic, hypercatabolic response. Enteral nutritional support should be initiated early to optimize total burn care and decrease long-term morbidity. Neither non-pharmacologic nor pharmacologic strategies are sufficient to abate completely the catabolic response to severe burn injury. All therapeutic strategies have contributed to some extent to the improvements in morbidity and mortality (Table 1). Early enteral nutrition has contributed to the significant decline in lean body mass loss of severely catabolic patients^{34, 44}. Modulation of the hypermetabolic response is paramount in the optimal restoration of structure and function of severely burned patients and remains an elusive completely fulfilled goal despite the significant advances made in this area in the past few decades.

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References

1. Nguyen TT, Gilpin DA, Meyer NA, et al. Current treatment of severely burned patients. *Ann Surg.* Jan; 1996 223(1):14–25. [PubMed: 8554414]
2. Brigham PA, McLoughlin E. Burn incidence and medical care use in the United States: estimates, trends, and data sources. *J Burn Care Rehabil.* Mar–Apr; 1996 17(2):95–107. [PubMed: 8675512]
3. Wolf, S. Critical Care in the Severely burned: organ support and management of complications. In: Herndon, DN., editor. *Total Burn Care*. 3rd ed.. Vol. Vol 2007. Saunders Elsevier; London:
4. Herndon DN, Tompkins RG. Support of the metabolic response to burn injury. *Lancet.* Jun 5; 2004 363(9424):1895–1902. [PubMed: 15183630]
5. Hart DW, Wolf SE, Mlcak R, et al. Persistence of muscle catabolism after severe burn. *Surgery.* Aug; 2000 128(2):312–319. [PubMed: 10923010]
6. Reiss E, Pearson E, Artz CP. The metabolic response to burns. *J Clin Invest.* Jan; 1956 35(1):62–77. [PubMed: 13278402]
7. Yu YM, Tompkins RG, Ryan CM, Young VR. The metabolic basis of the increase of the increase in energy expenditure in severely burned patients. *JPEN J Parenter Enteral Nutr.* May–Jun; 1999 23(3):160–168. [PubMed: 10338224]
8. Williams FN, Jeschke MG, Chinkes DL, et al. Modulation of the hypermetabolic response to trauma: temperature, nutrition, and drugs. *J Am Coll Surg.* Apr; 2009 208(4):489–502. [PubMed: 19476781]
9. Mlcak RP, Jeschke MG, Barrow RE, et al. The influence of age and gender on resting energy expenditure in severely burned children. *Ann Surg.* Jul; 2006 244(1):121–130. [PubMed: 16794397]
10. Przkora R, Barrow RE, Jeschke MG, et al. Body composition changes with time in pediatric burn patients. *J Trauma.* May; 2006 60(5):968–971. [PubMed: 16688056]
11. Dolecek R. Endocrine changes after burn trauma--a review. *Keio J Med.* Sep; 1989 38(3):262–276. [PubMed: 2511373]
12. Jeffries MK, Vance ML. Growth hormone and cortisol secretion in patients with burn injury. *J Burn Care Rehabil.* Jul–Aug; 1992 13(4):391–395. [PubMed: 1429807]
13. Klein GL, Bi LX, Sherrard DJ, et al. Evidence supporting a role of glucocorticoids in short-term bone loss in burned children. *Osteoporos Int.* Jun; 2004 15(6):468–474. [PubMed: 15205718]

14. Goodall M, Stone C, Haynes BW Jr. Urinary output of adrenaline and noradrenaline in severe thermal burns. *Ann Surg.* Apr; 1957 145(4):479–487. [PubMed: 13412024]
15. Coombes EJ, Batstone GF. Urine cortisol levels after burn injury. *Burns Incl Therm Inj.* May; 1982 8(5):333–337. [PubMed: 7093798]
16. Norbury, WB.; Herndon, DN. Modulation of the hypermetabolic response after burn injury. In: Herndon, DN., editor. *Total Burn Care*. 3rd ed.. Saunders & Elsevier; New York: 2007. p. 420-433.
17. Rutan RL, Herndon DN. Growth delay in postburn pediatric patients. *Arch Surg.* Mar; 1990 125(3):392–395. [PubMed: 2306187]
18. Wilmore DW, Mason AD Jr, Pruitt BA Jr. Insulin response to glucose in hypermetabolic burn patients. *Ann Surg.* Mar; 1976 183(3):314–320. [PubMed: 1259488]
19. Goldstein DS, Kopin IJ. Evolution of concepts of stress. *Stress.* Jun; 2007 10(2):109–120. [PubMed: 17514579]
20. Selye H. Stress and the general adaptation syndrome. *Br Med J.* Jun 17; 1950 1(4667):1383–1392. [PubMed: 15426759]
21. Selye H. An extra-adrenal action of adrenotropic hormone. *Nature.* Jul 28; 1951 168(4265):149–150. [PubMed: 14875028]
22. Selye H, Fortier C. Adaptive reaction to stress. *Psychosom Med.* May–Jun; 1950 12(3):149–157. [PubMed: 15430520]
23. Herndon D. Mediators of Metabolism. *Journal of Trauma-Injury Infection and Critical Care.* 1981; 21:701–705.
24. Lee JO, Herndon DN. Modulation of the post-burn hypermetabolic state. *Nestle Nutr Workshop Ser Clin Perform Programme.* 2003; 8:39–49. discussion 49–56.
25. Newsome TW, Mason AD Jr, Pruitt BA Jr. Weight loss following thermal injury. *Ann Surg.* Aug; 1973 178(2):215–217. [PubMed: 4198796]
26. Barrow RE, Hawkins HK, Aarsland A, et al. Identification of factors contributing to hepatomegaly in severely burned children. *Shock.* Dec; 2005 24(6):523–528. [PubMed: 16317382]
27. Barrow RE, Wolfe RR, Dasu MR, et al. The use of beta-adrenergic blockade in preventing trauma-induced hepatomegaly. *Ann Surg.* Jan; 2006 243(1):115–120. [PubMed: 16371745]
28. Herndon DN, Hart DW, Wolf SE, et al. Reversal of catabolism by beta-blockade after severe burns. *N Engl J Med.* Oct 25; 2001 345(17):1223–1229. [PubMed: 11680441]
29. Wolfe RR, Herndon DN, Peters EJ, et al. Regulation of lipolysis in severely burned children. *Ann Surg.* Aug; 1987 206(2):214–221. [PubMed: 3606248]
30. Chang DW, DeSanti L, Demling RH. Anticatabolic and anabolic strategies in critical illness: A review of current treatment modalities. *Shock.* Sep; 1998 10(3):155–160. [PubMed: 9744642]
31. Sheridan RL. A great constitutional disturbance. *N Engl J Med.* Oct 25; 2001 345(17):1271–1272. [PubMed: 11680449]
32. Pereira C, Murphy K, Jeschke M, et al. Post burn muscle wasting and the effects of treatments. *Int J Biochem Cell Biol.* Oct; 2005 37(10):1948–1961. [PubMed: 16109499]
33. Wilmore DW, Long JM, Mason AD Jr, et al. Catecholamines: mediator of the hypermetabolic response to thermal injury. *Ann Surg.* Oct; 1974 180(4):653–669. [PubMed: 4412350]
34. Jeschke MG, Chinkes DL, Finnerty CC, et al. Pathophysiologic response to severe burn injury. *Ann Surg.* Sep; 2008 248(3):387–401. [PubMed: 18791359]
35. Wilmore DW, Aulick LH. Metabolic changes in burned patients. *Surg Clin North Am.* Dec; 1978 58(6):1173–1187. [PubMed: 32634]
36. Wolfe RR. Review: acute versus chronic response to burn injury. *Circ Shock.* 1981; 8(1):105–115. [PubMed: 7016359]
37. Cuthbertson DP, Angeles Valero Zanuy MA, Leon Sanz ML. Post-shock metabolic response. 1942. *Nutr Hosp.* Sep–Oct; 2001 16(5):175–182.
38. Cuthbertson D. Post-shock metabolic response. *Lancet.* 1942; 1:433–436.
39. Baron PW, Barrow RE, Pierre EJ, et al. Prolonged use of propranolol safely decreases cardiac work in burned children. *J Burn Care Rehabil.* May–Jun; 1997 18(3):223–227. [PubMed: 9169945]

40. Williams FN, Herndon DN, Kulp GA, et al. Propranolol decreases cardiac work in a dose-dependent manner in severely burned children. *Surgery*. Jun 30.2010
41. Galster AD, Bier DM, Cryer PE, et al. Plasma palmitate turnover in subjects with thermal injury. *J Trauma*. Nov; 1984 24(11):938–945. [PubMed: 6389897]
42. Cree MG, Aarsland A, Herndon DN, et al. Role of fat metabolism in burn trauma-induced skeletal muscle insulin resistance. *Crit Care Med*. Sep; 2007 35(9 Suppl):S476–483. [PubMed: 17713396]
43. Childs C, Heath DF, Little RA, et al. Glucose metabolism in children during the first day after burn injury. *Arch Emerg Med*. Sep; 1990 7(3):135–147. [PubMed: 2152453]
44. Jeschke MG, Mlcak RP, Finnerty CC, et al. Burn size determines the inflammatory and hypermetabolic response. *Crit Care*. 2007; 11(4):R90. [PubMed: 17716366]
45. Gauglitz GG, Herndon DN, Kulp GA, et al. Abnormal insulin sensitivity persists up to three years in pediatric patients post-burn. *J Clin Endocrinol Metab*. May; 2009 94(5):1656–1664. [PubMed: 19240154]
46. Khani S, Tayek JA. Cortisol increases gluconeogenesis in humans: its role in the metabolic syndrome. *Clin Sci (Lond)*. Dec; 2001 101(6):739–747. [PubMed: 11724664]
47. Wolfe RR, Herndon DN, Jahoor F, et al. Effect of severe burn injury on substrate cycling by glucose and fatty acids. *N Engl J Med*. Aug 13; 1987 317(7):403–408. [PubMed: 3614284]
48. Gore DC, Jahoor F, Wolfe RR, et al. Acute response of human muscle protein to catabolic hormones. *Ann Surg*. Nov; 1993 218(5):679–684. [PubMed: 8239784]
49. Robinson LE, van Soeren MH. Insulin resistance and hyperglycemia in critical illness: role of insulin in glycemic control. *AACN Clin Issues*. Jan–Mar; 2004 15(1):45–62. [PubMed: 14767364]
50. Gearhart MM, Parbhoo SK. Hyperglycemia in the critically ill patient. *AACN Clin Issues*. Jan–Mar; 2006 17(1):50–55. [PubMed: 16462409]
51. Carlson GL. Insulin resistance and glucose-induced thermogenesis in critical illness. *Proc Nutr Soc*. Aug; 2001 60(3):381–388. [PubMed: 11681813]
52. Wolfe RR, Durkot MJ, Allsop JR, et al. Glucose metabolism in severely burned patients. *Metabolism*. Oct; 1979 28(10):1031–1039. [PubMed: 491960]
53. Cree MG, Zwetsloot JJ, Herndon DN, et al. Insulin sensitivity and mitochondrial function are improved in children with burn injury during a randomized controlled trial of fenofibrate. *Ann Surg*. Feb; 2007 245(2):214–221. [PubMed: 17245174]
54. Hunt DG, Ivy JL. Epinephrine inhibits insulin-stimulated muscle glucose transport. *J Appl Physiol*. Nov; 2002 93(5):1638–1643. [PubMed: 12381748]
55. Gustavson SM, Chu CA, Nishizawa M, et al. Interaction of glucagon and epinephrine in the control of hepatic glucose production in the conscious dog. *Am J Physiol Endocrinol Metab*. Apr; 2003 284(4):E695–707. [PubMed: 12626324]
56. Mastorakos G, Chrousos GP, Weber JS. Recombinant interleukin-6 activates the hypothalamic-pituitary-adrenal axis in humans. *J Clin Endocrinol Metab*. Dec; 1993 77(6):1690–1694. [PubMed: 8263159]
57. Lang CH, Dobrescu C, Bagby GJ. Tumor necrosis factor impairs insulin action on peripheral glucose disposal and hepatic glucose output. *Endocrinology*. Jan; 1992 130(1):43–52. [PubMed: 1727716]
58. Akita S, Akino K, Ren SG, et al. Elevated circulating leukemia inhibitory factor in patients with extensive burns. *J Burn Care Res*. Mar–Apr; 2006 27(2):221–225. [PubMed: 16566572]
59. Fan J, Li YH, Wojnar MM, et al. Endotoxin-induced alterations in insulin-stimulated phosphorylation of insulin receptor, IRS-1, and MAP kinase in skeletal muscle. *Shock*. Sep; 1996 6(3):164–170. [PubMed: 8885080]
60. del Aguila LF, Claffey KP, Kirwan JP. TNF-alpha impairs insulin signaling and insulin stimulation of glucose uptake in C2C12 muscle cells. *Am J Physiol*. May; 1999 276(5 Pt 1):E849–855. [PubMed: 10329978]
61. Sell H, Dietze-Schroeder D, Kaiser U, et al. Monocyte chemotactic protein-1 is a potential player in the negative cross-talk between adipose tissue and skeletal muscle. *Endocrinology*. May; 2006 147(5):2458–2467. [PubMed: 16439461]

62. Baracos V, Rodemann HP, Dinarello CA, et al. Stimulation of muscle protein degradation and prostaglandin E2 release by leukocytic pyrogen (interleukin-1). A mechanism for the increased degradation of muscle proteins during fever. *N Engl J Med*. Mar 10; 1983 308(10):553–558. [PubMed: 6402699]
63. Jahoor F, Desai M, Herndon DN, et al. Dynamics of the protein metabolic response to burn injury. *Metabolism*. Apr; 1988 37(4):330–337. [PubMed: 3282147]
64. Saffle JR.; Graves, C. Nutritional support of the burned patient. In: Herndon, DN., editor. *Total Burn Care*. 3rd ed.. Saunders Elsevier; London: 2007. p. 398–419.
65. Hart DW, Wolf SE, Chinkes DL, et al. Determinants of skeletal muscle catabolism after severe burn. *Ann Surg*. Oct; 2000 232(4):455–465. [PubMed: 10998644]
66. DeFronzo RA, Jacot E, Jequier E, et al. The effect of insulin on the disposal of intravenous glucose. Results from indirect calorimetry and hepatic and femoral venous catheterization. *Diabetes*. Dec; 1981 30(12):1000–1007. [PubMed: 7030826]
67. Flakoll PJ, Hill JO, Abumrad NN. Acute hyperglycemia enhances proteolysis in normal man. *Am J Physiol*. Nov; 1993 265(5 Pt 1):E715–721. [PubMed: 8238497]
68. Arora NS, Rochester DF. Respiratory muscle strength and maximal voluntary ventilation in undernourished patients. *Am Rev Respir Dis*. Jul; 1982 126(1):5–8. [PubMed: 7091909]
69. Greenhalgh DG, Saffle JR, Holmes JH, et al. American Burn Association consensus conference to define sepsis and infection in burns. *J Burn Care Res*. Nov–Dec; 2007 28(6):776–790. [PubMed: 17925660]
70. Murray CK, Loo FL, Hospenthal DR, et al. Incidence of systemic fungal infection and related mortality following severe burns. *Burns*. Dec; 2008 34(8):1108–1112. [PubMed: 18691821]
71. Pruitt BA Jr. McManus AT, Kim SH, et al. Burn wound infections: current status. *World J Surg*. Feb; 1998 22(2):135–145. [PubMed: 9451928]
72. Williams FN, Herndon DN, Hawkins HK, et al. The leading causes of death after burn injury in a single pediatric burn center. *Crit Care*. 2009; 13(6):R183. [PubMed: 19919684]
73. Im MJ, Hoopes JE. Energy metabolism in healing skin wounds. *J Surg Res*. Oct; 1970 10(10):459–464. [PubMed: 5476457]
74. Falcone PA, Caldwell MD. Wound metabolism. *Clin Plast Surg*. Jul; 1990 17(3):443–456. [PubMed: 2199136]
75. Wilmore DW, Aulick LH, Mason AD, et al. Influence of the burn wound on local and systemic responses to injury. *Ann Surg*. Oct; 1977 186(4):444–458. [PubMed: 907389]
76. Mochizuki H, Trocki O, Dominioni L, et al. Mechanism of prevention of postburn hypermetabolism and catabolism by early enteral feeding. *Ann Surg*. Sep; 1984 200(3):297–310. [PubMed: 6431918]
77. Dominioni L, Trocki O, Fang CH, et al. Enteral feeding in burn hypermetabolism: nutritional and metabolic effects of different levels of calorie and protein intake. *JPEN J Parenter Enteral Nutr*. May–Jun; 1985 9(3):269–279. [PubMed: 3159914]
78. Wilmore DW. Nutrition and metabolism following thermal injury. *Clin Plast Surg*. Oct; 1974 1(4):603–619. [PubMed: 4154156]
79. Ireton-Jones CS, Gottschlich MM. The evolution of nutrition support in burns. *J Burn Care Rehabil*. Mar–Apr; 1993 14(2 Pt 2):272–280. [PubMed: 8491752]
80. Popp MB, Law EJ, MacMillian BG. Parenteral nutrition in the burned child: a study of twenty-six patients. *Ann Surg*. Feb; 1974 179(2):219–225. [PubMed: 4204269]
81. Curreri PW, Richmond D, Marvin J, et al. Dietary requirements of patients with major burns. *J Am Diet Assoc*. Oct; 1974 65(4):415–417. [PubMed: 4213656]
82. Wilmore DW, Curreri PW, Spitzer KW, et al. Supranormal dietary intake in thermally injured hypermetabolic patients. *Surg Gynecol Obstet*. May; 1971 132(5):881–886. [PubMed: 4995336]
83. Hildreth MA, Herndon DN, Desai MH, et al. Reassessing caloric requirements in pediatric burn patients. *J Burn Care Rehabil*. Nov–Dec; 1988 9(6):616–618. [PubMed: 3146576]
84. Herndon DN, Barrow RE, Stein M, et al. Increased mortality with intravenous supplemental feeding in severely burned patients. *J Burn Care Rehabil*. Jul–Aug; 1989 10(4):309–313. [PubMed: 2507548]

85. Herndon DN, Stein MD, Rutan TC, et al. Failure of TPN supplementation to improve liver function, immunity, and mortality in thermally injured patients. *J Trauma*. Feb; 1987 27(2):195–204. [PubMed: 3102754]
86. Jeejeebhoy KN. Total parenteral nutrition: potion or poison? *Am J Clin Nutr*. Aug; 2001 74(2): 160–163. [PubMed: 11470715]
87. Wolf SE, Rose JK, Desai MH, Mileski JP, Barrow RE, Herndon DN. Mortality determinants in massive pediatric burns. An analysis of 103 children with > or = 80% TBSA burns (> or = 70% full-thickness). *Ann Surg*. May; 1997 225(5):554–565. discussion 565–559. [PubMed: 9193183]
88. Deitch EA. Intestinal permeability is increased in burn patients shortly after injury. *Surgery*. Apr; 1990 107(4):411–416. [PubMed: 2108508]
89. van Elburg RM, Uil JJ, de Monchy JG, et al. Intestinal permeability in pediatric gastroenterology. *Scand J Gastroenterol Suppl*. 1992; 194:19–24. [PubMed: 1298042]
90. Mochizuki H, Trocki O, Dominioni L, et al. Reduction of postburn hypermetabolism by early enteral feeding. *Curr Surg*. Mar-Apr; 1985 42(2):121–125. [PubMed: 3922681]
91. McDonald WS, Sharp CW Jr, Deitch EA. Immediate enteral feeding in burn patients is safe and effective. *Ann Surg*. Feb; 1991 213(2):177–183. [PubMed: 1899551]
92. Tinckler LF. Surgery and Intestinal Motility. *Br J Surg*. Feb.1965 52:140–150. [PubMed: 14255984]
93. Moss G. Maintenance of gastrointestinal function after bowel surgery and immediate enteral full nutrition. II. Clinical experience, with objective demonstration of intestinal absorption and motility. *JPEN J Parenter Enteral Nutr*. May-Jun; 1981 5(3):215–220. [PubMed: 6788969]
94. Goran MI, Peters EJ, Herndon DN, et al. Total energy expenditure in burned children using the doubly labeled water technique. *Am J Physiol*. Oct; 1990 259(4 Pt 1):E576–585. [PubMed: 2171351]
95. Gore DC, Rutan RL, Hildreth M, et al. Comparison of resting energy expenditures and caloric intake in children with severe burns. *J Burn Care Rehabil*. Sep-Oct; 1990 11(5):400–404. [PubMed: 2246309]
96. Hart DW, Wolf SE, Herndon DN, et al. Energy expenditure and caloric balance after burn: increased feeding leads to fat rather than lean mass accretion. *Ann Surg*. Jan; 2002 235(1):152–161. [PubMed: 11753055]
97. Wolfe RR, Allsop JR, Burke JF. Glucose metabolism in man: responses to intravenous glucose infusion. *Metabolism*. Mar; 1979 28(3):210–220. [PubMed: 763155]
98. Demling RH, Seigne P. Metabolic management of patients with severe burns. *World J Surg*. Jun; 2000 24(6):673–680. [PubMed: 10773119]
99. Mochizuki H, Trocki O, Dominioni L, et al. Optimal lipid content for enteral diets following thermal injury. *JPEN J Parenter Enteral Nutr*. Nov-Dec; 1984 8(6):638–646. [PubMed: 6441004]
100. Garrel DR, Razi M, Lariviere F, et al. Improved clinical status and length of care with low-fat nutrition support in burn patients. *JPEN J Parenter Enteral Nutr*. Nov-Dec; 1995 19(6):482–491. [PubMed: 8748363]
101. Alexander JW, Saito H, Trocki O, et al. The importance of lipid type in the diet after burn injury. *Ann Surg*. Jul; 1986 204(1):1–8. [PubMed: 3015058]
102. Huschak G, Zur Nieden K, Hoell T, et al. Olive oil based nutrition in multiple trauma patients: a pilot study. *Intensive Care Med*. Sep; 2005 31(9):1202–1208. [PubMed: 16132897]
103. Wolfe RR, Goodenough RD, Burke JF, et al. Response of protein and urea kinetics in burn patients to different levels of protein intake. *Ann Surg*. Feb; 1983 197(2):163–171. [PubMed: 6824370]
104. Yu YM, Young VR, Castillo L, et al. Plasma arginine and leucine kinetics and urea production rates in burn patients. *Metabolism*. May; 1995 44(5):659–666. [PubMed: 7752916]
105. Melville S, McNurlan MA, McHardy KC, et al. The role of degradation in the acute control of protein balance in adult man: failure of feeding to stimulate protein synthesis as assessed by L-[1-¹³C]leucin infusion. *Metabolism*. Mar; 1989 38(3):248–255. [PubMed: 2493121]
106. Hoerr RA, Matthews DE, Bier DM, et al. Effects of protein restriction and acute refeeding on leucine and lysine kinetics in young men. *Am J Physiol*. Apr; 1993 264(4 Pt 1):E567–575. [PubMed: 8476035]

107. Yu YM, Ryan CM, Burke JF, et al. Relations among arginine, citrulline, ornithine, and leucine kinetics in adult burn patients. *Am J Clin Nutr.* Nov; 1995 62(5):960–968. [PubMed: 7572742]
108. Matthews DE, Marano MA, Campbell RG. Splanchnic bed utilization of leucine and phenylalanine in humans. *Am J Physiol.* Jan; 1993 264(1 Pt 1):E109–118. [PubMed: 8430779]
109. Patterson BW, Nguyen T, Pierre E, et al. Urea and protein metabolism in burned children: effect of dietary protein intake. *Metabolism.* May; 1997 46(5):573–578. [PubMed: 9160826]
110. Soeters PB, van de Poll MC, van Gemert WG, et al. Amino acid adequacy in pathophysiological states. *J Nutr.* Jun; 2004 134(6 Suppl):1575S–1582S. [PubMed: 15173433]
111. De-Souza DA, Greene LJ. Intestinal permeability and systemic infections in critically ill patients: effect of glutamine. *Crit Care Med.* May; 2005 33(5):1125–1135. [PubMed: 15891348]
112. Souba WW. Glutamine: a key substrate for the splanchnic bed. *Annu Rev Nutr.* 1991; 11:285–308. [PubMed: 1892702]
113. Gore DC, Jahoor F. Glutamine kinetics in burn patients. Comparison with hormonally induced stress in volunteers. *Arch Surg.* Dec; 1994 129(12):1318–1323. [PubMed: 7986163]
114. Garrel D. The effect of supplemental enteral glutamine on plasma levels, gut function, and outcome in severe burns. *JPEN J Parenter Enteral Nutr.* Mar-Apr.2004 28(2):123. author reply 123. [PubMed: 15080608]
115. Wischmeyer PE, Lynch J, Liedel J, et al. Glutamine administration reduces Gram-negative bacteremia in severely burned patients: a prospective, randomized, double-blind trial versus isonitrogenous control. *Crit Care Med.* Nov; 2001 29(11):2075–2080. [PubMed: 11700398]
116. Zhou YP, Jiang ZM, Sun YH, et al. The effect of supplemental enteral glutamine on plasma levels, gut function, and outcome in severe burns: a randomized, double-blind, controlled clinical trial. *JPEN J Parenter Enteral Nutr.* Jul-Aug; 2003 27(4):241–245. [PubMed: 12903886]
117. Cerra FB, Mazuski JE, Chute E, et al. Branched chain metabolic support. A prospective, randomized, double-blind trial in surgical stress. *Ann Surg.* Mar; 1984 199(3):286–291. [PubMed: 6422868]
118. Gamliel Z, DeBiasse MA, Demling RH. Essential microminerals and their response to burn injury. *J Burn Care Rehabil.* May-Jun; 1996 17(3):264–272. [PubMed: 8736375]
119. Dietary Reference Intakes, Food and Nutrition Board, Institute of Medicine. National Academy Press; 1997. 1998, 2002
120. Mayes T, Gottschlich MM, Warden GD. Clinical nutrition protocols for continuous quality improvements in the outcomes of patients with burns. *J Burn Care Rehabil.* Jul-Aug; 1997 18(4):365–368. discussion 364. [PubMed: 9261706]
121. Gottschlich MM, Mayes T, Khoury J, Warden GD. Hypovitaminosis D in acutely injured pediatric burn patients. *J Am Diet Assoc.* Jun; 2004 104(6):931–941. quiz 1031. [PubMed: 15175591]
122. Rock CL, Dechert RE, Khilnani R, et al. Carotenoids and antioxidant vitamins in patients after burn injury. *J Burn Care Rehabil.* May-Jun; 1997 18(3):269–278. discussion 268. [PubMed: 9169953]
123. Selmanpakoglu AN, Cetin C, Sayal A, et al. Trace element (Al, Se, Zn, Cu) levels in serum, urine and tissues of burn patients. *Burns.* Apr; 1994 20(2):99–103. [PubMed: 8198733]
124. Hunt DR, Lane HW, Beesinger D, et al. Selenium depletion in burn patients. *JPEN J Parenter Enteral Nutr.* Nov-Dec; 1984 8(6):695–699. [PubMed: 6441013]
125. Lee, Jea. The Pediatric Burned Patient. In: Herndon, DN., editor. *Total Burn Care.* 3 ed.. Saunders Elsevier; Philadelphia: 2007. p. 485-493.
126. Hart DW, Wolf SE, Zhang XJ, et al. Efficacy of a high-carbohydrate diet in catabolic illness. *Crit Care Med.* Jul; 2001 29(7):1318–1324. [PubMed: 11445678]
127. Battistella FD, Widergren JT, Anderson JT, et al. A prospective, randomized trial of intravenous fat emulsion administration in trauma victims requiring total parenteral nutrition. *J Trauma.* Jul; 1997 43(1):52–58. discussion 58–60. [PubMed: 9253908]
128. Fong YM, Marano MA, Barber A, et al. Total parenteral nutrition and bowel rest modify the metabolic response to endotoxin in humans. *Ann Surg.* Oct; 1989 210(4):449–456. discussion 456–447. [PubMed: 2508583]

129. Askanazi J, Rosenbaum SH, Hyman AI, et al. Respiratory changes induced by the large glucose loads of total parenteral nutrition. *JAMA*. Apr 11; 1980 243(14):1444–1447. [PubMed: 6767043]
130. Klein CJ, Stanek GS, Wiles CE 3rd. Overfeeding macronutrients to critically ill adults: metabolic complications. *J Am Diet Assoc*. Jul; 1998 98(7):795–806. [PubMed: 9664922]
131. van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in the critically ill patients. *N Engl J Med*. Nov 8; 2001 345(19):1359–1367. [PubMed: 11794168]
132. Turina M, Fry DE, Polk HC Jr. Acute hyperglycemia and the innate immune system: clinical, cellular, and molecular aspects. *Crit Care Med*. Jul; 2005 33(7):1624–1633. [PubMed: 16003073]
133. Shopbell, JHB.; Shrouts, E. Nutrition screening and assessment. In: Gottschlich, MM., editor. *A Case-based Core Curriculum*. Society of Parenteral and Enteral Nutrition; Silver Spring: 2001.
134. Zdolsek HJ, Lindahl OA, Angquist KA, et al. Non-invasive assessment of intercompartmental fluid shifts in burn victims. *Burns*. May; 1998 24(3):233–240. [PubMed: 9677026]
135. Graves C, Saffle J, Morris S. Comparison of urine urea nitrogen collection times in critically ill patients. *Nutr Clin Pract*. Apr; 2005 20(2):271–275. [PubMed: 16207662]
136. Rettmer RL, Williamson JC, Labbe RF, et al. Laboratory monitoring of nutritional status in burn patients. *Clin Chem*. Mar; 1992 38(3):334–337. [PubMed: 1547547]
137. Jeschke MG, Herndon DN, Wolf SE, et al. Recombinant human growth hormone alters acute phase reactant proteins, cytokine expression, and liver morphology in burned rats. *J Surg Res*. May 15; 1999 83(2):122–129. [PubMed: 10329105]
138. Wu X, Herndon DN, Wolf SE. Growth hormone down-regulation of Interleukin-1beta and Interleukin-6 induced acute phase protein gene expression is associated with increased gene expression of suppressor of cytokine signal-3. *Shock*. Apr; 2003 19(4):314–320. [PubMed: 12688541]
139. Jeschke MG, Chrysopoulou MT, Herndon DN, et al. Increased expression of insulin-like growth factor-I in serum and liver after recombinant human growth hormone administration in thermally injured rats. *J Surg Res*. Jul; 1999 85(1):171–177. [PubMed: 10383855]
140. Aili Low JF, Barrow RE, Mittendorfer B, et al. The effect of short-term growth hormone treatment on growth and energy expenditure in burned children. *Burns*. Aug; 2001 27(5):447–452. [PubMed: 11451596]
141. Hart DW, Herndon DN, Klein G, et al. Attenuation of posttraumatic muscle catabolism and osteopenia by long-term growth hormone therapy. *Ann Surg*. Jun; 2001 233(6):827–834. [PubMed: 11371741]
142. Herndon DN, Barrow RE, Kunkel KR, et al. Effects of recombinant human growth hormone on donor-site healing in severely burned children. *Ann Surg*. Oct; 1990 212(4):424–429. discussion 430–421. [PubMed: 2121109]
143. Branski LK, Herndon DN, Barrow RE, et al. Randomized Controlled Trial to Determine the Efficacy of Long-Term Growth Hormone Treatment in Severely Burned Children. *Ann Surg*. Sep 2.2009
144. Klein GL, Wolf SE, Langman CB, et al. Effects of therapy with recombinant human growth hormone on insulin-like growth factor system components and serum levels of biochemical markers of bone formation in children after severe burn injury. *J Clin Endocrinol Metab*. Jan; 1998 83(1):21–24. [PubMed: 9435411]
145. Takala J, Ruokonen E, Webster NR, et al. Increased mortality associated with growth hormone treatment in critically ill adults. *N Engl J Med*. Sep 9; 1999 341(11):785–792. [PubMed: 10477776]
146. Demling RH. Comparison of the anabolic effects and complications of human growth hormone and the testosterone analog, oxandrolone, after severe burn injury. *Burns*. May; 1999 25(3):215–221. [PubMed: 10323605]
147. Gore DC, Honeycutt D, Jahoor F, et al. Effect of exogenous growth hormone on glucose utilization in burn patients. *J Surg Res*. Dec; 1991 51(6):518–523. [PubMed: 1943090]
148. Ramirez RJ, Wolf SE, Barrow RE, et al. Growth hormone treatment in pediatric burns: a safe therapeutic approach. *Ann Surg*. Oct; 1998 228(4):439–448. [PubMed: 9790334]
149. Moller S, Jensen M, Svensson P, Skakkebaek NE. Insulin-like growth factor 1 (IGF-1) in burn patients. *Burns*. Aug; 1991 17(4):279–281. [PubMed: 1930660]

150. Herndon DN, Ramzy PI, DeBRoy MA, et al. Muscle protein catabolism after severe burn: effects of IGF-1/IGFBP-3 treatment. *Ann Surg.* May; 1999 229(5):713–720. discussion 720–712. [PubMed: 10235530]
151. Spies M, Wolf SE, Barrow RE, et al. Modulation of types I and II acute phase reactants with insulin-like growth factor-1/binding protein-3 complex in severely burned children. *Crit Care Med.* Jan; 2002 30(1):83–88. [PubMed: 11902293]
152. Jeschke MG, Herndon DN, Barrow RE. Insulin-like growth factor I in combination with insulin-like growth factor binding protein 3 affects the hepatic acute phase response and hepatic morphology in thermally injured rats. *Ann Surg.* Mar; 2000 231(3):408–416. [PubMed: 10714634]
153. Cioffi WG, Gore DC, Rue LW 3rd, et al. Insulin-like growth factor-1 lowers protein oxidation in patients with thermal injury. *Ann Surg.* Sep; 1994 220(3):310–316. discussion 316–319. [PubMed: 8092898]
154. Langouche L, Van den Berghe G. Glucose metabolism and insulin therapy. *Crit Care Clin.* Jan; 2006 22(1):119–129. vii. [PubMed: 16399023]
155. Hart DW, Wolf SE, Ramzy PI, et al. Anabolic effects of oxandrolone after severe burn. *Ann Surg.* Apr; 2001 233(4):556–564. [PubMed: 11303139]
156. Demling RH, Orgill DP. The anticatabolic and wound healing effects of the testosterone analog oxandrolone after severe burn injury. *J Crit Care.* Mar; 2000 15(1):12–17. [PubMed: 10757193]
157. Jeschke MG, Finnerty CC, Suman OE, et al. The effect of oxandrolone on the endocrinologic, inflammatory, and hypermetabolic responses during the acute phase postburn. *Ann Surg.* Sep; 2007 246(3):351–360. discussion 360–352. [PubMed: 17717439]
158. Demling RH, DeSanti L. The rate of restoration of body weight after burn injury, using the anabolic agent oxandrolone, is not age dependent. *Burns.* Feb; 2001 27(1):46–51. [PubMed: 11164665]
159. Murphy KD, Thomas S, Mlcak RP, et al. Effects of long-term oxandrolone administration in severely burned children. *Surgery.* Aug; 2004 136(2):219–224. [PubMed: 15300183]
160. Suman OE, Thomas SJ, Wilkins JP, et al. Effect of exogenous growth hormone and exercise on lean mass and muscle function in children with burns. *J Appl Physiol.* Jun; 2003 94(6):2273–2281. [PubMed: 12588788]
161. Barret JP, Jeschke MG, Herndon DN. Fatty infiltration of the liver in severely burned pediatric patients: autopsy findings and clinical implications. *J Trauma.* Oct; 2001 51(4):736–739. [PubMed: 11586168]
162. Aarsland A, Chinkes D, Wolfe RR, et al. Beta-blockade lowers peripheral lipolysis in burn patients receiving growth hormone. Rate of hepatic very low density lipoprotein triglyceride secretion remains unchanged. *Ann Surg.* Jun; 1996 223(6):777–787. discussion 787–779. [PubMed: 8645051]
163. Gore DC, Honeycutt D, Jahoor F, et al. Propranolol diminishes extremity blood flow in burned patients. *Ann Surg.* Jun; 1991 213(6):568–574. [PubMed: 2039287]
164. Pereira CT, Jeschke MG, Herndon DN. Beta-blockade in burns. *Novartis Found Symp.* 2007; 280:238–251. [PubMed: 17380798]
165. Pidcoke HF, Wade CE, Wolf SE. Insulin and the burned patient. *Crit Care Med.* Sep; 2007 35(9 Suppl):S524–530. [PubMed: 17713403]
166. Ferrando AA, Chinkes DL, Wolf SE, et al. A submaximal dose of insulin promotes net skeletal muscle protein synthesis in patients with severe burns. *Ann Surg.* Jan; 1999 229(1):11–18. [PubMed: 9923795]
167. Pierre EJ, Barrow RE, Hawkins HK, et al. Effects of insulin on wound healing. *J Trauma.* 1998; 44(2):342–345. [PubMed: 9498508]
168. Thomas SJ, Morimoto K, Herndon DN, et al. The effect of prolonged euglycemic hyperinsulinemia on lean body mass after severe burn. *Surgery.* 2002; 132(2):341–347. [PubMed: 12219032]
169. Zhang XJ, Chinkes DL, Wolf SE, et al. Insulin but not growth hormone stimulates protein anabolism in skin wound and muscle. *Am J Physiol.* 1999; 276(4 Pt 1):E712–E720. [PubMed: 10198308]

170. Jeschke MG, Klein D, Herndon DN. Insulin treatment improves the systemic inflammatory reaction to severe trauma. *Ann Surg.* Apr; 2004 239(4):553–560. [PubMed: 15024317]
171. Jeschke MG, Klein D, Bolder U, et al. Insulin attenuates the systemic inflammatory response in endotoxemic rats. *Endocrinology.* Sep; 2004 145(9):4084–4093. [PubMed: 15192048]
172. Jeschke MG, Rensing H, Klein D, et al. Insulin prevents liver damage and preserves liver function in lipopolysaccharide-induced endotoxemic rats. *J Hepatol.* Jun; 2005 42(6):870–879. [PubMed: 15885358]
173. Klein D, Schubert T, Horsch RE, et al. Insulin treatment improves hepatic morphology and function through modulation of hepatic signals after severe trauma. *Ann Surg.* Aug; 2004 240(2):340–349. [PubMed: 15273560]
174. Gauglitz GG, Toliver-Kinsky TE, Williams FN, et al. Insulin increases resistance to burn wound infection-associated sepsis. *Crit Care Med.* Jan; 2010 38(1):202–208. [PubMed: 19770742]
175. Dandona P, Chaudhuri A, Mohanty P, et al. Anti-inflammatory effects of insulin. *Curr Opin Clin Nutr Metab Care.* Jul; 2007 10(4):511–517. [PubMed: 17563472]
176. Van den Berghe G, Wilmer A, Hermans G, et al. Intensive insulin therapy in the medical ICU. *N Engl J Med.* Feb 2; 2006 354(5):449–461. [PubMed: 16452557]
177. Finney SJ, Zekveld C, Elia A, et al. Glucose control and mortality in critically ill patients. *JAMA.* Oct 15; 2003 290(15):2041–2047. [PubMed: 14559958]
178. Dellinger RP, Levy MM, Carlet JM, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. *Crit Care Med.* Jan; 2008 36(1):296–327. [PubMed: 18158437]
179. Gore DC, Wolf SE, Herndon DN, et al. Metformin blunts stress-induced hyperglycemia after thermal injury. *J Trauma.* Mar; 2003 54(3):555–561. [PubMed: 12634538]
180. DeFronzo RA, Goodman AM. Efficacy of metformin in patients with non-insulin-dependent diabetes mellitus. The Multicenter Metformin Study Group. *N Engl J Med.* Aug 31; 1995 333(9):541–549. [PubMed: 7623902]
181. Stumvoll M, Nurjhan N, Perriello G, et al. Metabolic effects of metformin in non-insulin-dependent diabetes mellitus. *N Engl J Med.* Aug 31; 1995 333(9):550–554. [PubMed: 7623903]
182. Gore DC, Herndon DN, Wolfe RR. Comparison of peripheral metabolic effects of insulin and metformin following severe burn injury. *J Trauma.* Aug; 2005 59(2):316–323. [PubMed: 16294070]
183. Bailey CJ, Turner RC. Metformin. *N Engl J Med.* Feb 29; 1996 334(9):574–579. [PubMed: 8569826]
184. Luft D, Schmulling RM, Eggstein M. Lactic acidosis in biguanide-treated diabetics: a review of 330 cases. *Diabetologia.* Feb; 1978 14(2):75–87. [PubMed: 344119]
185. Heszele MFC, Price SR. Insulin-like growth factor I: The yin and yang of muscle atrophy. *Endocrinology.* Nov; 2004 145(11):4803–4805. [PubMed: 15489312]
186. Barret JP, Dziewulski P, Jeschke MG, et al. Effects of recombinant human growth hormone on the development of burn scarring. *Plastic and Reconstructive Surgery.* Sep; 1999 104(3):726–729. [PubMed: 10456525]
187. Takagi K, Suzuki F, Barrow RE, et al. Recombinant human growth hormone modulates Th1 and Th2 cytokine response in burned mice. *Annals of Surgery.* Jul; 1998 228(1):106–111. [PubMed: 9671074]
188. Takagi K, Suzuki F, Barrow RE, et al. Growth hormone improves immune function and survival in burned mice infected with Herpes simplex virus type? *Journal of Surgical Research.* Apr; 1997 69(1):166–170. [PubMed: 9202664]
189. Low JFA, Herndon DN, Barrow RE. Effect of growth hormone on growth delay in burned children: a 3-year follow-up study. *Lancet.* Nov 20; 1999 354(9192):1789–1789. [PubMed: 10577644]
190. Demling RH, DeSanti L. Oxandrolone, an anabolic steroid, significantly increases the rate of weight gain in the recovery phase after major burns. *Journal of Trauma-Injury Infection and Critical Care.* Jul; 1997 43(1):47–51.

191. Aarsland A, Chinkes DL, Sakurai Y, et al. Insulin therapy in burn patients does not contribute to hepatic triglyceride production. *Journal of Clinical Investigation*. May 15; 1998 101(10):2233–2239. [PubMed: 9593779]
192. Minnich A, Tian N, Byan L, Bilder G. A potent PPAR alpha agonist stimulates mitochondrial fatty acid beta-oxidation in liver and skeletal muscle. *American Journal of Physiology-Endocrinology and Metabolism*. Feb; 2001 280(2):E270–E279. [PubMed: 11158930]
193. Schnabel D, Grasmann C, Staab D, et al. A multicenter, randomized, double-blind, placebo-controlled trial to evaluate the metabolic and respiratory effects of growth hormone in children with cystic fibrosis. *Pediatrics*. Jun; 2007 119(6):E1230–E1238. [PubMed: 17545356]
194. Herndon DN, Barrow RE, Rutan TC, et al. Effect of Propranolol Administration on Hemodynamic and Metabolic Responses of Burned Pediatric-Patients. *Annals of Surgery*. Oct; 1988 208(4):484–492. [PubMed: 3052328]
195. Engelhardt D, Dorr G, Jaspers C, et al. Ketoconazole Blocks Cortisol Secretion in Man by Inhibition of Adrenal 11-Beta-Hydroxylase. *Klinische Wochenschrift*. 1985; 63(13):607–612. [PubMed: 2993735]
196. Engelhardt D, Mann K, Hormann R, Braun S, Karl HJ. Ketoconazole Inhibits Cortisol Secretion of an Adrenal Adenoma In vivo and In vitro. *Klinische Wochenschrift*. 1983; 61(7):373–375. [PubMed: 6306332]
197. Loose DS, Stover EP, Feldman D. Ketoconazole Binds to Glucocorticoid Receptors and Exhibits Glucocorticoid Antagonist Activity in Cultured-Cells. *Journal of Clinical Investigation*. 1983; 72(1):404–408. [PubMed: 6135709]
198. Hart DW, Wolf SE, Chinkes DL, et al. beta-blockade and growth hormone after burn. *Annals of Surgery*. Oct; 2002 236(4):450–457. [PubMed: 12368673]
199. Jeschke MG, Finnerty CC, Kulp GA, et al. Combination of recombinant human growth hormone and propranolol decreases hypermetabolism and inflammation in severely burned children. *Pediatric Critical Care Medicine*. Mar; 2008 9(2):209–216. [PubMed: 18477935]
200. Debroy MA, Wolf SE, Zhang XJ, et al. Anabolic effects of insulin-like growth factor in combination with insulin-like growth factor binding protein-3 in severely burned adults. *Journal of Trauma-Injury Infection and Critical Care*. Nov; 1999 47(5):904–910.
201. Williams FN, Herndon DN, Jeschke MG. The Hypermetabolic Response to Burn Injury and Interventions to Modify this Response. *Clinics in Plastic Surgery*. Oct; 2009 36(4):583–596. [PubMed: 19793553]

Table 1

Summary of the main effects of various pharmacologic interventions to alter the hypermetabolic response to burn injury.

Drug	Inflammatory Response	Stress Hormones	Body Composition	Net Protein Balance	Insulin Resistance	Hyperdynamic Circulation
rhGH	Improved	No Difference	Improved	No Difference	Hyperglycemia	No Difference
IGF1	Improved	No Difference	Improved	Improved	Improved	No Difference
Oxandrolone	Improved	No Difference	Improved	Improved	No Difference	No Difference
Insulin	Improved	No Difference	Improved	Improved	Improved	No Difference
Propranolol	Improved	Improved	Improved	Improved	Improved	Improved
Oxandrolone + Propranolol	Improved (Preliminary)	Improved (Preliminary)	Improved (Preliminary)	Improved (Preliminary)	Improved (Preliminary)	Improved (Preliminary)

The data summarized in the table is extrapolated from previously published data^{23, 28, 30, 53, 137, 140, 142, 148, 149, 151, 152, 155, 157, 166, 185-200} and has been previously published in Williams FN, Herndon DN, Jeschke MG. The Hypermetabolic Response to Burn Injury and Interventions to Modify this Response. *Clinics in Plastic Surgery*. Oct 2009;36(4):583-596, with permission.