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The Hypermetabolic Response to Burn Injury and Interventions to Modify This Response

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SYNOPSIS

Severe burn injury is followed by a profound hypermetabolic response that persists up to 24 months after injury. It is mediated by up to 50-fold elevations in plasma catecholamines, cortisol and inflammatory cells that lead to whole body catabolism, elevated resting energy expenditures and multi-organ dysfunction. All of these metabolic and physiologic derangements prevent full rehabilitation and acclimatization of burn survivors back into society. Modulation of the response by early excision and grafting of burn wounds, thermoregulation, early and continuous enteral feeding with high protein–high carbohydrate feedings and pharmacologic treatments have markedly decreased morbidity.

Keywords

hypermetabolism; burns; beta-blockade; catabolism; catecholamines; wasting

INTRODUCTION

Severe thermal injury, defined as burns encompassing over 40% of a patient's total body surface area (TBSA), is followed by a pronounced hypermetabolic response which persists for up to one to two years post-burn (Figure 1) [1, 2]. The response is characterized by increased metabolic rates, multi-organ dysfunction, muscle protein degradation, blunted growth, insulin resistance, and increased risk for infection [1-5].

The initial stress response to severe injury, as originally described by Cuthbertson, features an “ebbed” phase with a decrease in tissue perfusion and a decrease in metabolic rate. In

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severe burns, this response lasts for the first two to three days post-burn. The subsequent “flow” phase is characterized by an increase in metabolism and hyperdynamic circulation. When left untreated, physiologic exhaustion ensues, and the injury becomes fatal [6-9].

Major progress has been made since the recognition of the hypermetabolic response. The aim of this review is to describe the magnitude of the metabolic and catabolic responses to major burn injury and to discuss the effects of various interventions to mitigate the hypermetabolic response. Numerous therapeutic strategies to modify this response have arisen in the past half century and include early excision and grafting, thermoregulation, early continuous enteral feeding with a high-carbohydrate high-protein diet, the use of anabolic agents growth hormone, insulin-like growth factor-1 (IGF-1), insulin-like growth factor binding protein-3 (IGFBP-3), insulin, oxandrolone, propranolol, and the use of therapeutic exercise. This overview outlines the destructive properties of the hypermetabolic response and the many strategies that have been implemented over the last decade to alter this response in an effort to improve burn care, quality of life and survival in burned patients.

The Hypermetabolic Response in Severe Burns

Mediators of the Hypermetabolic Response—Catecholamines and corticosteroids are the primary mediators of the hypermetabolic response following burns greater than 40% TBSA [10]. There is a 10- to 50-fold surge of plasma catecholamine and corticosteroid levels that last up to 9 months post-burn [11, 12]. Burn patients have increased resting energy expenditures, increased cardiac work, increased myocardial oxygen consumption, marked tachycardia, severe lipolysis, liver dysfunction, severe muscle catabolism, increased protein degradation, insulin resistance, and growth retardation [13-16].

Acute Phase Proteins (Cytokines and Hormonal Changes)—Cytokine levels peak immediately after burn, approaching normal levels only at 3-6 months post-burn [11]. Serum hormones, constitutive and acute phase proteins, are abnormal throughout acute hospital stay. Serum IGF-1, IGFBP-3, parathyroid hormone, and Osteocalcin drop immediately after the injury and remain decreased until 2 months post-burn compared to normal levels [11]. Sex hormones and endogenous growth hormone levels decrease around 3 weeks post-burn and remain low [11]. Larger burn injuries are characterized by more pronounced and persistent inflammatory responses indicated by higher concentrations of proinflammatory cytokines that promote more severe catabolism [17].

Changes in Resting Energy Expenditures—Past studies showed metabolic rates of burn patients’ approaching 180% of that of predicted based on the Harris-Benedict equation [18]. The resting metabolic rate of patients with large burns increases in a curvilinear fashion from close to normal predicted levels for TBSA < 10% to twice that of normal predicted levels at 40% TBSA and above. For severely burned patients, the resting metabolic rate at thermal neutral temperature (30°C) tops 140% of predicted basal rate on admission, reduces to 130% once the wounds are fully healed, then to 120% at 6 months after injury (Figure 2) [11]. Even 12 months post-burn, the resting energy expenditures for burn patients are 110%-120% of predicted, based on the Harris-Benedict equation [1]. Increases in catabolism result in loss of total body protein, decreased immune defenses, and decreased wound healing [1].

Multi-organ Dysfunction—Multi-organ dysfunction is a hallmark of the acute phase response post-burn [11]. Immediately post-burn patients may have low cardiac outputs, and contractility, characteristic of early shock [19]. However, three to four days post-burn, both cardiac outputs and heart rates are greater than 150% compared to non-burned [11, 15].

Post-burn, patients have increased cardiac work that lasts well into the rehabilitation phase [20, 21]. Myocardial oxygen consumption values are significantly increased well into the rehabilitation phase [20]. The liver increases in size by two weeks post-burn and remains increased at discharge by 200% [11].

Whole Body Catabolism—Post-burn, muscle protein is degraded much faster than it is synthesized [11, 15]. Net protein loss leads to loss of lean body mass and severe muscle wasting leading to decreased strength and failure to fully rehabilitate [1, 22]. Significant decreases in lean body mass related to chronic illness or hypermetabolism can have dire consequences. Immune dysfunction is associated with a 10% loss of total body mass. A 20% loss of total body mass positively correlates with decreased wound healing. A loss of 30% of total body mass leads to increased risk for pneumonia and pressure sores. In fact, a 40% loss of total body mass can lead to death [23]. Severely burned, catabolic patients can lose up to 25% of total body mass after acute burn injury [24]. Muscle wasting – which is the unintentional loss of 5-10% of total body muscle mass occurs when there is an imbalance of muscle protein degradation and synthesis [25]. Protein degradation persists up to 9 months post severe burn injury resulting in significant negative whole-body catabolism [21, 26, 27]. It is directly related to increases in metabolic rate (Figure 3) [26]. Severely burned patients have a daily nitrogen loss of 20-25 g per meter squared of burned skin [21, 28]. At this rate, a lethal limit can be reached in less than 30 days [28]. This protein catabolism leads to significant growth retardation for up to 24 months post injury [3].

Changes in Glucose Metabolism—Elevated circulating levels of catecholamines, glucagon, cortisol and gluconeogenic hormones in response to severe thermal injury propagate inefficient glucose production in the liver (Figure 4) [29]. Stable isotope data further indicate significant derangements in major adenosine triphosphate (ATP) consumption pathways including increased protein turnover, urea production and gluconeogenesis [5]. Glycolytic-gluconeogenetic cycling is increased 250% during the post-burn hypermetabolic response coupled with an increase of 450% in triglyceride-fatty acid cycling [5]. All of these changes cumulate into severe hyperglycemia and impaired insulin sensitivity related to post-receptor insulin resistance [5, 11]. Post-burn, there are significantly elevated levels of insulin, fasting glucose, and significant reductions in glucose clearance [4]. Although glucose oxidation is restricted, glucose delivery to peripheral tissues is increased up to 3-fold, leading to the elevated levels of fasting glucose. Increased glucose production is directed to the burn wound to support anaerobic metabolism of endothelial cells, fibroblasts, and inflammatory cells [30, 31]. Lactate, the end-product of anaerobic glucose oxidation is recycled to the liver to produce more glucose via gluconeogenic pathways [21]. Serum glucose and serum insulin remain significantly increased through the entire acute hospital stay [11]. Insulin resistance appears during the first week post-burn and persists at least until discharge [11].

Sepsis—Further perturbations, like sepsis increase resting energy expenditures and protein catabolism up to 40% compared to those with like-size burns that do not develop sepsis [1, 32]. Due to the changes that occur in the immune response in catabolic patients, they are more susceptible to sepsis, and thus at increased risk of further muscle and protein catabolism - propagating a vicious cycle. The emergence of multi-resistant organisms have led to increases in sepsis related infections and death overall [33, 34]. In combination, these responses lead to an increase in morbidity and mortality for burn victims. Thus, there is a dire need to enlist any therapeutic strategies to modulate the hypermetabolic, catabolic response after severe burn injury.

Modulation of the Hypermetabolic Response in Severe Burns

Early Excision and Grafting—The hypermetabolic response for a severely burned patient far surpasses any other disease state [35]. One of the most revolutionary improvements in burn care to attenuate the hypermetabolic response was the institution of early excision and grafting of the burn eschar post burn injury. For burns that encompass over 50% TBSA, there is a 40% decrease in metabolic rate for patients totally excised and covered within 3 days of injury compared to those patients, with like size burns, excised and covered one week after injury [26]. Early excision and grafting prevents further net protein loss and catabolism. Hart et al [36] showed that patients with early excision and grafting (within 72 hours of injury) compared to late (10 to 21 days post-burn) had a net protein loss (measured by stable isotope) of 0.03 μ mol compared to 0.07 μ mol of phenylalanine per minute per 100 ml of leg blood volume. In this same study, log bacterial counts in quantitative tissue cultures increased from 3 to 4.2 in early compared to late, respectively [36]. In fact, the incidence of sepsis also rose from 20% in the early group to 50% in the late group, with the only difference being the time to excision and grafting [26, 36]. By decreasing the incidence of sepsis, early excision and grafting further attenuates the hypermetabolic response by decreasing resting energy expenditures, and decreasing muscle protein catabolism [1, 33, 34].

Thermoregulation

Thermoregulation is the ability of the body to maintain core body temperature independent of environmental temperature and is mediated via metabolic activity and sweating [37]. The ability to regulate core body temperatures is lost in severely burned patients. The post-burn hypermetabolic response increases the metabolic rate to compensate for the profound water and heat loss severe burn patients suffer. Water loss approaches 4000 milliliters per meter squared burn area per day [38-41]. The body's natural response to this insult, partially mediated by increased ATP consumption and substrate oxidation, is to raise core and skin temperatures 2°C above normal compared to unburned patients [42]. This response is similar to the response seen during cold acclimatization. In fact, patients that do not mount this response are likely septic and or have exhausted physiologic capabilities to maintain needed body temperature [43]. In 1975, Wilmore et al [44] showed that the hypermetabolic response can be attenuated by increasing ambient temperatures to 33°C – a thermal neutral temperature. At this temperature, the energy required for vaporization will be derived from the environment rather than from the patient [44, 45]. By maintaining ambient temperatures between 28°C and 33°C, resting energy expenditures decrease from a magnitude of 2.0 to 1.4 in patients with severe burn injury [44, 45] This simple intervention, of increased ambient temperatures in operating rooms and patient rooms, decreased metabolic rates and thus protein and muscle catabolism, hence improving survival.

Nutrition

Aggressive, early enteral feeding improves outcomes in severely burned patients, in part, by mitigating the degree and extent of hypermetabolism [46, 47]. With oral alimentation alone, patients with 40% TBSA burns have lost up to a quarter of their preadmission weight by 21 days post injury [24]. Researchers have shown that only through aggressive nutritional replacement using 25 kcal/kg body weight and 40 kcal per percent TBSA burn per day, that body weight is barely maintained in burned adults [48, 49]. Hildreth et al [50] found that children require 1800 kcal per meter squared plus 2200 kcal per meter squared of burn area per day.

Enteral nutrition is preferable to parenteral nutrition [51]. Enteral nutrition reduces translocation bacteremia and sepsis, maintains gut motility, and preserves 'first pass' nutrient delivery to the liver [47]. Parenteral nutrition alone or even in combination with

enteral nutrition led to overfeeding, liver failure, impaired immune response and increased mortality [51-53]. Parenteral nutrition should be reserved for those with enteral feeding intolerance or prolonged ileus.

Hildreth et al have demonstrated that formulas used to predict caloric requirements from the 1970s and 1980s often provide 35% to 45% more calories than actually needed [48-50, 54]. By measuring resting energy expenditures, actual caloric requirements can be determined [55, 56]. Appropriate nutrient delivery can be accomplished by feeding 1.2 to 1.4 times measured resting energy expenditures. Resting energy expenditures can be safely and accurately measured by indirect calorimetry using bedside carts. Goran et al [55] found that feeding patients 1.2 times measured resting energy expenditures maintained body weight but resulted in 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 (measured by indirect calorimetry) the gains were in fat deposition, not lean body mass [56, 57]. Major complications can result by overfeeding severely burned patients. The overfeeding of carbohydrates results in elevated respiratory quotients, increased fat synthesis and increased elimination of carbon dioxide. Ventilated patients become more difficult to manage and wean from mechanical support [58]. The overfeeding of carbohydrate or fat can also lead to fat deposition in the liver [59]. Overfeeding can also lead to hyperglycemia, which is already present in the overwhelming majority of all critically ill patients. Hyperglycemia subsequently becomes harder to treat as both endogenous and exogenous insulin effects are countered by the surge of catabolic hormones [10, 60].

There is some evidence that increased protein replacement for severely burned patients may be beneficial [61, 62]. The purpose of protein replacement is to maintain or even increase lean body mass. Healthy individuals require 1 gm/kg body weight per day of protein intake [63, 64]. However, burn patients have protein requirements 50% greater than healthy individuals in a fasting state [61, 62, 65]. Thus, burn patients require a minimum of 1.5 to 2 gm/kg body weight per day of protein intake [66-68]. Any higher amount of supplementation may lead to increased urea production without improvements in lean body mass or muscle protein synthesis [69]. The nutritional needs of burn patients are profound due to the paucity of glycogen stores, increased protein and muscle catabolism and increased metabolic rates. Research has led to dramatic improvements in survival by improving protein net balance, and metabolic rates. Diets high in fat demonstrated elevated protein degradation and poor lean body mass gains in comparison to high-carbohydrate diets – consisting of 3% fat, 15% protein and 82% carbohydrate [70]. The high-carbohydrate diet increased protein synthesis, increased effective endogenous insulin production and improved lean body mass [15, 50, 54, 70].

Exercise

While the aforementioned techniques help abrogate the post-burn response during the acute phase, increased metabolic rates, and muscle catabolism last much longer than the acute hospitalization. Patients have elevated metabolic rates, and sustained muscle and protein catabolism longer than 12 months after the original insult [15, 29, 71]. Despite methods to abate the stress response, pediatric burn patients have continued growth retardation long into the rehabilitative phase [3]. Patients with severe burn injury have significant functional limitations as they progress through the rehabilitation phase. Exercise training is an essential adjunct to any and all metabolic treatments administered to the burn survivor. It increases lean body mass, improves strength, the ability to walk distances approximately 50%, and improves overall cardiopulmonary capacity [72, 73]. Further, we have reported that a 12-week resistance and aerobic exercise training program, added to standard of care, has been shown to profoundly improve muscle strength, lean body mass and power compared to standard of care alone [74, 75]. Thus, an exercise training program is essential to improve

body mass, decrease contractures, and optimize the metabolic improvements achieved through improved standard of care [72].

Modifying the Hormonal Response in Severe Burns

Non-pharmacological techniques are insufficient in abating the hypermetabolic response after severe burn injury. The hypermetabolic response is prolonged and persistent and its severity is directly related to the size of the original injury and the duration of time patients are exposed to elevated levels of catecholamines, cortisol, and glucagons [26]. These instigators perpetuate the profound changes in metabolic rates, growth and physiology seen in severely burned patients. Thus, pharmacologic agents which block or reverse mediators of the hypermetabolic response need to be enlisted to halt the hypercatabolic state.

Recombinant Human Growth Hormone (rhGH)

The underlying mechanisms responsible for severe muscle atrophy are not completely known. A significant reduction in IGF-1 has been linked to many catabolic disease processes [76] and endogenous IGF-1 levels are drastically reduced after a major burn injury. When administered intramuscularly to severely burned pediatric burn patients at a dose of 0.2 mg/kg per day, rhGH significantly improved outcomes. Endogenous levels of IGF-1 were significantly increased by discharge [77, 78]. Donor site healing times were decreased by 25% as were hospital length of stay, and total cost of care [77, 79, 80]. By two years post-burn, scarring had significantly improved compared to patients that did not receive rhGH [81].

rhGH significantly improved the hepatic acute phase response [82, 83]. It significantly decreased C reactive protein, serum TNF- α , interleukin-1 and serum amyloid-A [84]. It attenuates the immune response and increases albumin production in the liver [84, 85]. Recombinant growth hormone treatment enhanced T-helper-1 and reduced T-helper-2 cytokine production, lessening the immunosuppression that is potentially fatal in severely burned patients [86, 87]. There were significant improvements in weight gain, height velocities, lean body mass, bone mineral content and cardiac function, specifically ejection fraction even at a dose of 0.05 mg/kg per day [88, 89]. These effects were seen up to 36 months post injury [90, 91].

Although rhGH has been used safely in severely burned pediatric patients, it should be noted that treatment does not come without side effects. The most notable side effect was hyperglycemia [85, 92]. Although other researchers found in a double-blinded randomized controlled trial an increased mortality rate in non-burned critically ill adults, we found no differences in mortality for severely burned pediatric patients randomized to receive the drug [85, 93]. rhGH can be used safely in pediatric burn patients to attenuate the hypermetabolic response with close monitoring to prevent adverse outcomes.

Insulin-like Growth Factor-1 (IGF-1) and Insulin-like Growth Factor Binding Protein-3 (IGFB-3)

The primary mediator of the effects of rhGH is IGF-1. Infusion of IGF-1 alone led to significant improvements in protein metabolism, but also episodes of hypoglycemia [94]. In combination with equimolar doses of IGFBP-3, severely burned catabolic patients had improved protein synthesis with fewer episodes of hyperglycemia than the use of rhGH, and less hypoglycemia than the use of IGF-1 alone [94-96]. The fractional synthetic rate for muscle protein synthesis was improved by 2% per day compared to standard of care alone [95]. The combination improved gut mucosal integrity, immune function, in addition to decreasing muscle and protein catabolism [95, 97, 98]. Specifically, immune function was improved by the attenuation of the hepatic acute phase response, the increase of serum

constitutive proteins and decrease of the hypermetabolic, hypercatabolic utilization of whole-body protein [97, 98]. While the risk of side effects of hypoglycemia and peripheral neuropathies with the use of IGF-1 approached 25%, there were no documented side effects with the combination [95, 97, 98]. The combination of IGF-1 with IGFBP-3 offers great promise in ameliorating the hypermetabolic response in pediatric burn patients.

Oxandrolone

Hypoandrogenemia is a devastating consequence of the post-burn hypermetabolic, hypercatabolic response. Testicular steroid production is substantially decreased in severely burned male patients and is prolonged and persistent [99-101]. The elevated levels of cortisol coupled with the decreased levels of testosterone contribute greatly to the loss of lean body mass seen in male pediatric burn patients. Testosterone administration during a fasting state increases protein synthesis and ameliorate catabolism in normal subjects [102, 103]. It was also shown to ameliorates muscle protein loss after severe burn injury [99]. Despite its efficacy, however, weekly intramuscular administration of testosterone long term is fraught with both expense and difficulty with compliance. In addition, it is an androgenic steroid, minimizing its use in females. Oxandrolone, a synthetic analog, offers only 5% of the masculinizing effects of testosterone, and is safe for both genders. Oxandrolone improved net muscle protein synthesis and protein metabolism in severely burned patients when administered at a dose of 0.1 mg/kg twice daily [104, 105]. During the acute phase post-burn and up to one year of treatment, oxandrolone increases lean body mass and bone mineral content and increased muscle strength [104-108]. Acutely, it decreased length of stay by decreasing time between surgeries for patients randomized to receive oxandrolone plus standard of care [105]. It increased anabolic gene expression in muscle and enhanced the efficacy of net protein synthesis [106]. Significant improvements in lean body mass, protein synthesis, and overall growth in patients receiving oxandrolone, out-weigh the 1% risk of hirsutism, and hepatic dysfunction that can be seen with treatment [105-108].

Insulin

The increases in catecholamines, glucagon and glucocorticoid production post-burn lead to enhanced glycogenolysis and protein breakdown in both the liver and skeletal muscle [67]. Subsequently, there is an increase in triglycerides, urea and glucose production (gluconeogenesis) which consequently leads to hyperglycemia. Hyperglycemia in the severely burned patient leads to overwhelming muscle protein catabolism, reduced graft take and increased morbidity and mortality [109, 110]. van den Berghe et al [111] showed that intensive insulin therapy to achieve blood glucose levels between 80 and 110 mg/dl in the critically ill reduces morbidity and mortality. We have found that intensive insulin therapy stimulates muscle protein synthesis, and increases lean body mass without increasing hepatic triglyceride production in burn patients [112, 113]. Severely burned patients that received continuous infusions titrated to a plasma insulin concentration of 400 to 900 μ U/ml to maintain euglycemia for seven days had improved donor site wound healing [114]. Even by infusing insulin therapy to maintain blood glucose levels between 100 to 140 mg/dl significantly improved lean body mass, bone mineral density and decreased length of hospital stay in patients receiving a high carbohydrate, high-protein diet [115]. Judicious glucose control and insulin use is paramount in the clinical management of these patients as the risk for hypoglycemia approaches 20%. The potential mechanisms by which insulin exerts its anabolic effect is by increasing amino acid and glucose uptake into tissues by activating the sodium-dependent transport systems, regulation of proteolysis and initiation of protein translation [111]. There are currently no large prospective randomized-controlled trials to determine which blood glucose level is most appropriate for severely burned pediatric patients.

Fenofibrate

Post-burn hyperglycemia is associated with increased muscle protein catabolism, and increased morbidity and mortality [109]. In addition, mitochondrial oxidative function is impaired by up to 70% by the first 7 days after severe burn injury [116]. Many animal studies have showed improvements in mitochondrial function and glucose oxidation with use of fenofibrate – a peroxisome proliferator-activated receptor [alpha] agonist (PPAR) [117]. In humans, fenofibrate treatment significantly decreased plasma glucose levels without causing hypoglycemia [116]. It decreased hepatic gluconeogenesis, and improved mitochondrial oxidative capacity [116]. By 14 days of treatment, fenofibrate improved muscle and hepatic insulin resistance in pediatric burn patients without any notable side effects [116]. It is currently unknown whether fenofibrate affects the fractional synthetic rates of muscle protein synthesis in pediatric burned patients as it was not measured in this study.

Glucagon-like Peptide-1 (GLP-1) – (Exenatide)

Glucose modulation is a key regulatory component of the hypermetabolic response. If glucose is adequately controlled, severe muscle protein catabolism is halted and the inflammatory response after injury is blunted. Exenatide, an incretin (GLP-1) mimetic has been shown in clinical trials to improve glycemic control by glucose-dependent enhancement of insulin secretion, restoration of first-phase insulin secretion deficiency, suppression of elevated glucagon secretion to reduce postprandial hepatic gluconeogenesis, and by slowing the rate of gastric emptying to decrease blood glucose circulation [118, 119]. While Exenatide does not reverse insulin-resistance per se, its treatment improves the efficiency of insulin production in response to glucose levels. There is currently an ongoing trial looking at the effects of Exenatide on blood glucose levels of severely burned patients during the acute hospitalization (unpublished).

Beta-Antagonists

The 10- to 50-fold increase in catecholamine levels induce increased myocardial oxygen consumption, increased resting energy expenditures, and contribute greatly to the profound catabolism after severe burn injury [10, 11, 35]. Successful blockade of beta-adrenergic stimulation and the effects of elevated levels of catecholamines after severe injury decreases cardiac work, tachycardia, metabolic rates and thermogenesis [20, 120-122]. Beta-antagonist treatment reduces the rate of cardiac complications and decreases mortality after severe trauma [123]. Propranolol prevents increased peripheral lipolysis in thermally injured patients by impeding the activation of the Beta-2-adrenergic receptor [16, 121, 124]. It significantly decreases fatty infiltration of the liver compared to untreated severely burned children [125, 126]. In addition to inhibiting the release of free fatty acids from adipose tissue, propranolol decreases the rates of fatty acid oxidation and triacylglycerol secretion, and increases the efficiency of the liver to excrete fatty acids, thereby significantly reduces hepatic steatosis [125, 127, 128]. Propranolol increases lean body mass and decreases skeletal muscle wasting as proven by stable isotope and body composition studies [15]. Treatment, at a dose of 0.5 – 4 mg/kg/day to reduce heart rates 15-20% of admitting heart rates, did not effect inward transport of amino acids but did effectively increase the efficiency of muscle protein synthesis [15]. It enhances the availability of free amino acids for muscle protein synthesis [15, 127, 128]. Currently in the literature, there are no documented cases of bronchospasm, or cardiovascular collapse when propranolol is used in severely burned patients.

Ketoconazole

The hypercortisolemia post severe burn injury is immediate, prolonged and directly related to the size of injury [129, 130]. To decrease levels of cortisol, our institution administered ketoconazole. Ketoconazole is an imidazole antifungal agent that works principally by inhibition of cytochrome P450 14 α -demethylase (P45014DM) an enzyme that is in the sterol biosynthesis pathway that leads from lanosterol to ergosterol [131]. In essence, it inhibits the 11 β -hydroxylation and 18-hydroxylation reactions in the final steps during the synthesis of adrenocorticosteroids and functions as a glucocorticoid receptor antagonist [132-134]. When administered to severely burned patients, our institution has found a statistically significant decrease in urine cortisol levels (unpublished).

A Role for Combination Therapy

The anti-catabolic effect of propranolol and the potent anabolic effects of rhGH, or oxandrolone potentiate an ideal combination for attenuating the post-burn hypermetabolic response. While improving donor site healing, growth and the inflammatory cascade, rhGH treatment leads to hyperglycemia, increased free fatty acids and triglycerides. Propranolol treatment demonstrated improved fat metabolism and improvements in insulin sensitivity. In combination, there were significant improvements in metabolic rates, serum C-reactive protein, cortisone, liver function, lipid metabolism, and cytokine profiles compared to controls, without adverse side effects [135, 136]. There is currently an ongoing study looking at the potential synergistic benefits of oxandrolone and propranolol.

Conclusion

Severely burned, catabolic patients with 40% TBSA on average now have a 2% to 10% loss of total body mass, instead of 25% as was the case prior to the introduction of the metabolic interventions described in this article [11, 17]. The hypermetabolic stress response that causes severe catabolism, immune dysfunction and profound physiologic perturbations affects every patient with burns greater than 40% of their TBSA. This response is pervasive and prolonged and cannot be completely abolished despite pharmacologic and non-pharmacologic interventions (Figure 5 and Table 1). Alone, these interventions have helped improve morbidity and mortality, but it is the combination of non-pharmacologic and certain pharmacologic strategies that will continue to advance the standard of care of severely burned patients.

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1A

1B

Figure 1. Adolescent pediatric burn patient with a 90% TBSA flame burn at admission (1A) and at one year (1B).

Figure 2. Metabolic rates of severely burned (≥ 40% TBSA) compared to normal non-burned children (previously unpublished). * Denotes significance at a $p < 0.05$.

Figure 3.

Effect of Burn Size on Net Muscle Protein Balance Control. Plotted on the graph is average $\pm$ standard error of the mean (SEM). The x-axis has two points, burns less than 40% TBSA, and burns $\geq$ 40% TBSA. * Denotes significance at $p < 0.05$. Data was extrapolated from previously published data [17, 26]. The y-axis represents changes in net protein balance of muscle protein synthesis and breakdown induced by burn injury was measured by stable isotope studies using d5-phenylalanine infusion studies previously published [1, 11, 17, 26].

4A

4B

Figure 4.

Gross Pathology of Hepatomegaly (4A) and Fatty Liver Infiltration (4B) post-burn. These pictures were taken post-mortem during the autopsy of a severely burned male pediatric patient (40% TBSA). Figure 4A is the macroscopic gross pathology of hepatomegaly post-burn. Figure 4B demonstrates the profound fatty liver infiltration seen post-burn.

Figure 5.

Relative efficacy of the different anabolic agents to improve muscle protein synthesis compared to standard of care alone. Changes in net protein balance of muscle protein synthesis and breakdown induced by burn injury was measured by stable isotope studies using d5-phenylalanine infusion studies previously published [1, 11, 17, 26, 95, 137, 138]. * Denotes significance of $p < 0.05$. Graphs are averages $\pm$ SEM. White bars represent patients with burns 40% TBSA who received no anabolic agents. Black bars represent patients with burns 40% TBSA who were randomized to receive drug.

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
Fenofibrate	No Difference	No Difference	No Difference	No Difference	Improved	No Difference
GLP-1	Unknown	Unknown	Unknown	Unknown	Improved (Indirect)	Unknown
Propranolol	Improved	Improved	Improved	Improved	Improved	Improved
Ketoconazole	Unknown	Improved	Unknown	Unknown	Unknown	Unknown
rhGH + 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 [15, 20, 23, 45, 76, 80-82, 85-87, 90, 91, 94, 96-98, 104, 105, 107, 112, 116-118, 120, 121, 132-138].