

# Therapeutic Approaches to Combatting Hypermetabolism in Severe Burn Injuries

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## Abstract

The complex pathophysiologic response of hypermetabolism plays a central role for the acute and long term outcomes in severely burned patients. Burns encompassing greater than 20% total body surface area (TBSA) are characterized by stress, insulin resistance, hyperglycemia, lipolysis and catabolism. The objective of this review is to discuss landmark studies in the field of hypermetabolism post-burn with regards to the current best practice for efficacious burn care and to investigate the pros and cons of those treatments. Different modalities were identified from the literature to ameliorate the hypermetabolic condition. These include early excision and closure of the burn wounds, external thermoregulation, adequate nutritional supplementation, exercise and the utilization of various pharmacologic treatments. Furthermore, we included future avenues of research with regards to treating the complex condition of hypermetabolism and determining how we can create personalized treatments for the unique set of hypermetabolic conditions presented in each patient.

**Keywords:** Burns; Hypermetabolism; Non-pharmacological; Pharmacological

**Received:** November 18, 2015, **Accepted:** November 28, 2015, **Published:** December 05, 2015 †Authors contributed Equally

## Introduction

Every year, patients with burn injuries account for approximately 500,000 hospital emergency department visits in the United States [1]. While most burn injuries are minor, 40,000 hospitalizations related to severe burn injuries occur annually [1]. Severe burn injuries result in metabolic inflammatory alterations that are similar to those presented by other major trauma patients. However the severity, length, and magnitude of these changes are most profound and prolonged in patients with burn injuries [2-4]. In fact, insulin resistant, hyperglycemic, hypermetabolic state of burn injury patients was found to persist for up to three years [5]. The complex condition of hypermetabolism plays a critical role in the healing and long-term outcomes to severe burn injury in a patient. Burns which encompass greater than 20% total body surface area (TBSA) are characterized by pathophysiological stress, insulin resistance, hyperglycemia and catabolism due to factors such as enhanced glycolysis, proteolysis, lipolysis and wasted substrate cycling [3, 6, 7]. As a result, the clinical complications following severe burn injury are unique and complex [8] and patients require an elaborate and carefully executed treatment plan to combat the challenges they face.

There are 2 distinct phases in the post-burn hypermetabolic

response that correspond to the phases of the severe injury induced stress response that was first described by Cuthbertson [9]. These phases of the hypermetabolic response are thought to be initiated by the rise in the levels of catecholamines, corticosteroids, and inflammatory cytokines that occurs following burn injury [4, 10-12]. The first phase, described as the ebb phase, occurs within the 48-72 hours of thermal injury. During this phase patients exhibit decreased cardiac output, oxygen consumption, metabolic rate, and are both hyperglycemic and glucose intolerant. The flow phase is the second of the two phases and occurs within the first 5 days post burn injury. This phase is characterized by insulin resistance, lipolysis, proteolysis, increases in body temperature, and a pronounced hypermetabolic state [9, 10]. This hypermetabolic state is reflected in the rise of the basal metabolic rate to 140% of normal at admission. While complete wound healing reduces the basal metabolic rate to 130% of normal, the hypermetabolic state still persists at 110-120% of normal basal metabolic rate 3 years post burn [6, 10]. An increase in ATP consumption accounts for 57% of the increase in energy expenditure experienced by burn patients [3], while the rest may be attributed to increased substrate oxidation [13], and increased

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**Citation:** Bakhtyar N, Sivayoganathan T, Jeschke MG. Therapeutic Approaches to Combatting Hypermetabolism in Severe Burn Injuries. J Intensive & Crit Care 2015, 1:1.

mitochondrial uncoupling and thermogenesis [14]. Consequently, carbohydrate, protein, and fat stores are mobilized to satisfy these prolonged heightened energy demands, thus resulting in hyperglycemia and whole body catabolism. This review will first provide an overview of the hallmarks of hypermetabolism in burn patients and then describe the non-pharmacological and pharmacological interventions used to treat this response. Finally, this review will summarize the therapeutic approaches to combat hypermetabolism post burn, and discuss future avenues of research (Figure 1).

## Hypermetabolism Post Burn

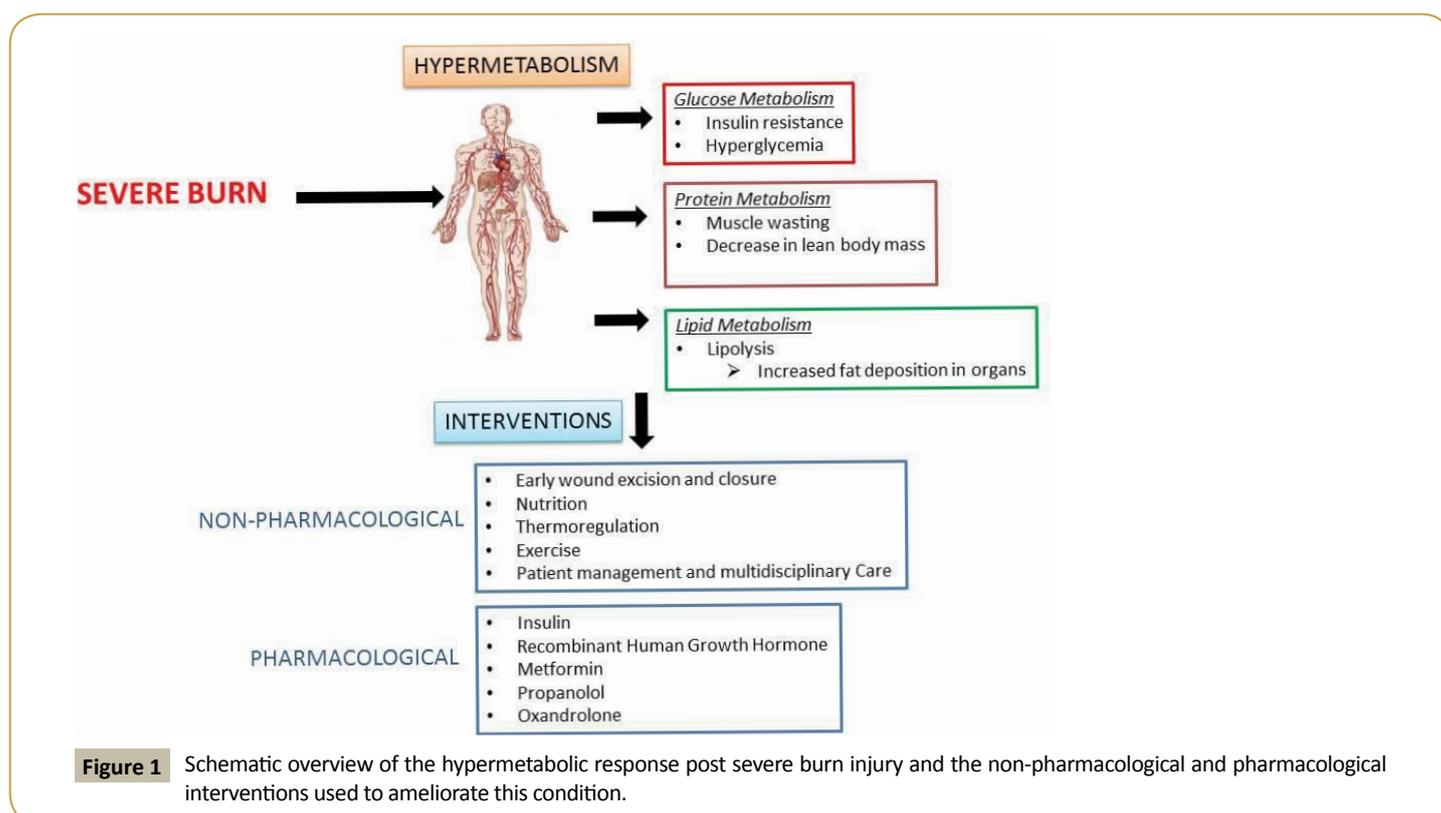
### Glucose metabolism

There are many pathways affected in the hypermetabolic state, but one that dramatically affects burn outcomes is glucose metabolism and its ensuing insulin resistance and hyperglycemia [15, 16]. Impaired glucose uptake and increased hepatic glucose production result in hyperglycemia during the early phases of the hypermetabolic response to severe burn injury [17, 18]. Glycogen stores are quickly diminished since glycogen is constantly broken down to liberate glucose, resulting in high levels of circulating glucose [19, 20]. In addition, hepatic gluconeogenesis increases glucose output which contributes to the hyperglycemic state [10, 21]. The increase in glucose production is the response to battle the elevated energy demands post burn injury, and to maintain whole body homeostasis. However, previous studies have shown that hyperglycemia in patients with burn injuries is linked to impaired wound healing, increased incidence of infection and sepsis, increased whole body catabolism and hypermetabolism, and increased incidence of pneumonia [15, 16, 22-25].

Accordingly, glucose control improves post-burn organ function, morbidity and mortality [22, 24, 25]. Insulin resistance develops post-burn as shown by the persistence of hyperglycemia in patients with burn injury despite insulin levels being twice as much as those found in controls [26]. In fact, insulin resistance has been found to remain in patients up to 3 years post-burn [5]. The regulation of insulin resistance has been associated with interleukins 1 and 6, tumor necrosis factor, endotoxin, neutrophil adherence complexes, nitric oxide, reactive oxygen species, platelet-activating factor, coagulation and complement cascades, but to date, no single factor could be identified as inducing this response [27].

### Protein metabolism

The post-burn hypermetabolic response results in the degradation of protein of the whole body, and proteins and amino acids in skeletal muscle become a major source of fuel to provide sufficient energy. As a result, burn injury results in protein catabolism rates to surpass 150 g/d [7, 28] and oxidization of amino acids to increase by 50% in comparison to healthy individuals [28-30]. Consequently, muscle wasting and a decrease in lean body mass (LBM), up to 25% loss of LBM in uncomplicated burns, are hallmarks of burn injuries [10]. This muscle weakness not only worsens mortality but also impedes rehabilitation and impairs cough reflexes, extending required ventilation time, and preventing mobilization of these patients [31]. In addition, decreases in LBM leads to a progressively worse clinical outcome and raises the probability of mortality. For example a 10% loss of LBM results in immune dysfunction, 20% loss of LBM impairs wound healing with 30% mortality, 30% loss of LBM increases the incidence of pneumonia with 50% mortality, and a 40%



**Figure 1** Schematic overview of the hypermetabolic response post severe burn injury and the non-pharmacological and pharmacological interventions used to ameliorate this condition.

LBM loss translates into 100 % mortality [32]. Moreover, muscle wasting may contribute to the development and persistence of insulin resistance post-burn since 70-80% of whole body insulin-stimulated glucose uptake occurs in skeletal muscle [33].

### Lipid Metabolism

Fat stores are mobilized following burn injury in order to satisfy the high energy demands that result from the hypermetabolic state [19, 34]. Burn injury promotes lipolysis, the process by which hydrolysis reactions breakdown triglycerides into free fatty acids (FFAs) and glycerol molecules [19, 34]. These substrates are then used as fuel by most tissues in the body through beta-oxidation, gluconeogenesis, and glycolysis. Unfortunately FFA levels overwhelm the mitochondria's ability to metabolize the substrate; this in turn leads to increased fat deposition in the organs. Lipolysis results in increased fatty infiltration of various organs which has been associated with a poorer patient outcome. Fatty liver in particular is common among burn patients and is associated with increased incidence of infection and sepsis [35]. Furthermore, Kraft et al showed that that elevated triglyceride levels post-burn were associated with reduced organ function, impairments to glucose metabolism and worse patient outcomes [19]. This is in agreement with previous studies demonstrating that fat accumulation impedes glucose metabolism [36] and studies showing that FFAs contribute to insulin resistance by preventing glucose uptake [37]. These studies highlight the importance of further research into the specific mechanisms by which lipids induce insulin resistance and promote hypermetabolism. Sidossis et al. demonstrate that the subcutaneous white adipose tissue of pediatric burn patients under prolonged stress, greater than 2 weeks, adopts a more thermogenic phenotype that is similar to that of brown adipose tissue and was associated with an increase in whole body metabolic rate [38]. The rise in catecholamine levels post-burn has been suggested to be the mediator of the observed increase in the lipolysis response and the appearance of beige adipose tissue [13, 38, 39]. In 2015, our lab published in Cell Reports that burn induces a transition in the phenotype of the subcutaneous fat from white to beige. The associated features were UCP1 expression which is a marker of fat browning. There was a drastic increase (~7-fold) in the expression UCP1 in fat that was excised during the patient's last surgery (10 days to 3 weeks post-burn). This upregulation was not detected on fat collected during the first surgery (0-3 days post-burn). UCP1 expression was elevated in the subcutaneous fat, especially in the smaller adipocytes. Another associated feature of beige fat is increased mitochondrial mass. We detected that adipocytes in the fat collected from burned patients during their last surgery were enriched in mitochondria. We then showed that there is a significant positive correlation between IL-6 and measured resting energy expenditure in burned patients [40]. Therefore, subcutaneous fat remodeling and browning illustrates an underlying mechanism that helps explain the elevated energy expenditure observed in burn-induced hypermetabolism. Thus, further research into the browning of white adipose tissue following burn injury and the potential cytokines involved could lead us to elucidate the role and impact this process has in the hypermetabolic response and how we can block this process. Thus, further research into the browning of white adipose tissue

following burn injury is required to elucidate the role and impact this process has in the hypermetabolic response.

Thus, there is a critical need to establish the best practice for burn care in order to ameliorate the enhanced and prolonged effects of glucose, protein and lipid metabolism of the hypermetabolic state post-burn injury.

## Non-Pharmacological Interventions

### Early wound excision and closure

Early excision and closure of the wound post burn injury is the most significant single treatment to alleviate the hypermetabolic response as the institution of this practice in burn care considerably attenuates the hypermetabolic response [6] and improves the mortality rates [4, 40]. Excision and closure of burn wounds surpassing 50% TBSA within the first three days of injury resulted in a 40% decrease in the resting energy expenditure in comparison with patients with similar burns whose wounds were excised and closed one week after injury [6]. Furthermore, early wound excision and closure has been shown to attenuate protein catabolism as wound excision and closure within 10-21 days in comparison to three days post burn injury resulted in an increase in net protein loss from 0.03  $\mu\text{mol}$  to 0.07  $\mu\text{mol}$  of phenylalanine per minute per 100 ml of leg blood volume respectively [41]. This was also accompanied by an increase in log counts of bacteria in quantitative cultures of 3 to 4.2 and an increased incidence of sepsis from 20% to 50% [6, 41]. This is in agreement with other studies suggesting that early excision and closure of burn wounds attenuates the resting energy expenditure and protein catabolism by reducing the incidence of sepsis [42-44]. However, excision and grafting alone cannot revise the hypermetabolic state.

### Nutrition

Nutritional supplementation is an essential component of treatment for burn patients as it attenuates the hypermetabolic response by exogenously providing the required energy supply and substrates. Feeding via enteral nutrition as early as possible after burn is paramount. However, overfeeding must be avoided as excess nutrition in the form of carbohydrates and fat can result in hyperglycemia and in fat infiltration of organs [11, 35, 45]. Carbohydrate supplementation is necessary in preventing reductions in lean body mass by sparing protein from oxidation, and by providing the energy required for sufficient wound healing. Consequently, 55-60% of nutritional intake should be supplied in the form of carbohydrates without surpassing 5 mg/kg/min in adults and children [13, 28]. This recommendation accounts for the minimum baseline adult carbohydrate requirement of 2 g/kg/d, [28] and the maximum glucose absorption rate which is 7 g/kg/d [28]. While protein recommendations for healthy individuals are estimated at 0.8-1 g/kg/d, protein catabolism, protein oxidation, and consequently the loss of lean body mass experienced by burn patients necessitate higher protein intakes for this population. The required protein intake for burned pediatric patients is 1.5-2 g/kg/d and 2.5-4.0 g/kg/d for adult patients [28, 30]. However, overfeeding of protein should be avoided as it has been demonstrated that there is no benefit of supplementation with protein in excess of the recommended 1.5-2 g/kg/d [46]. In

comparison to protein catabolism, the extent of lipid catabolism following burn injury is not significant. Furthermore, only 30% of the liberated free fatty acids undergoes substrate oxidation while the remaining 70% undergoes reesterification into triglycerides [47]. In addition, excessive fat supplementation not only promotes fat infiltration but also promotes immunosuppression [48]. Consequently, the Ross Tilley Burn Center recommends that burn patients receive less than 25% of non-protein calories in the form of fat. [28, 30, 49].

### Thermoregulation

The water loss and subsequent heat loss that is generated when the skin barrier is compromised by burn injury contributes to the hypermetabolic state [50]. It is also resetting the hypothalamus. Patients with burn injuries compensate for the 4000 mL/m<sup>2</sup> of water that is lost per day [51-54] by raising core and skin temperatures by 2°C more than normal compared with unburned patients. This is accomplished by increasing the resting energy expenditure and basal metabolic rates via increased ATP consumption, increased substrate oxidation, and increased mitochondrial thermogenesis [3, 13, 14]. Wilmore et al [55] demonstrated that increasing ambient temperatures to from 25 to 33°C decreased resting energy expenditures from a magnitude of 2.0 to 1.4 in patients with severe burn injury. Increasing the ambient temperature to 33°C allows for the patient to derive the energy required for vaporization from the environment rather than from their own metabolic and thermoregulatory processes [55, 56].

### Exercise

Although there is evidence demonstrating that exercise improves the clinical outcome of patients who have experienced major trauma [57], exercise is not commonly incorporated into rehabilitation programs for this patient population [58]. Exercise intervention should be considered because of its effects on normalizing metabolism through effects which include promoting an anti-inflammatory cytokine profile [59] and by improving insulin sensitivity and glucose uptake [60]. This is further supported by studies that exercise enhances glucose control, insulin sensitivity, body composition, cardiorespiratory fitness, lipid status, and blood pressure in diabetic patients [61-65]. The incorporation of exercise into the regimens of convalescent burn patients is crucial, as burn patients who undergo progressive resistance exercises and aerobic exercises in addition to standard of care experience improved muscle strength and endurance, increased lean body mass, increased power, and enhanced assimilation of amino acids into muscle proteins in comparison to patients who have only received standard of care [66-68]. Exercise has also been shown to have synergistic effects on lean body mass and strength when coupled with specific pharmacological agents. In particular, resistance exercise in combination with propranolol was shown to have an additive effect on the VO<sub>2</sub> peak of pediatric patients with burn injuries [69]. This might be explained by exercise enhancing propranolol's positive effects lean body mass and O<sub>2</sub> extraction [69, 70]. Similarly, oxandrolone and exercise have also been shown to have synergistic effects in preventing deficits in the lean body mass of pediatric burn patients [71].

Increases in adenosine triphosphatase (ATP)-dependent processes such as cardiac contractility, protein synthesis, and substrate cycling significantly contribute to elevated metabolic rate in burn patients [3, 27, 34]. This suggests that O<sub>2</sub> consumption out-paces ATP production post-burn injury. Since a majority of the oxygen consumption and 90% of ATP production in respiring cells occur inside the mitochondria [72], metabolism may be normalized by interventions restoring mitochondrial function. Porter et al have shown in a cohort of adults with large burns that skeletal muscle mitochondrial function is altered, where the coupling of oxygen consumption to ATP production is diminished [14], suggesting that skeletal muscle mitochondrial thermogenesis increases in burn patients. In a 2015 study by Porter et al, they showed that muscle mitochondrial respiratory capacity remains significantly lower in burn patients for 1-year post injury. Mitochondrial coupling control is also diminished for up to 2 years post injury in burn patients, resulting in greater mitochondrial thermogenesis [73]. Porter et al showed that resistance exercise training significantly improved mitochondrial respiration coupled to ATP production [74]. Therefore, exercise post burn could potentially normalize mitochondria and maintain cellular ATP levels to meet the metabolic demands post burn while attenuating the skeletal muscle thermogenesis and the associated hypermetabolism.

### Severe Burns in Elderly

Population aging coupled with an increased susceptibility to burn injury in the elderly has created the demand for burn care practices to change in order to accommodate elderly burn patients [76]. Over the last decades, morbidity and mortality in the Lethal Dose 50 (LD50) burn size in patients over age 65 has remained the same. Our lab investigated the underlying reasons behind such poor outcomes in elderly burn patients and compared them to adult burn patients. Our results illustrate that adult burn patients are more hypermetabolic in the first week after burn but then steadily decrease their metabolic needs. Elderly patients however, have an inverse metabolic response where they are less hypermetabolic during the post burn phase but steadily increased their metabolic needs at > 4 weeks post-burn, elderly patients also had a significantly increased resting energy expenditure compared to adults [77]. The increased metabolic requirements in the elderly was accompanied by hyperglycemia and hyperlipidemia. OGTT revealed that elderly and adult burn patients share the insulin resistant phenotype. However, metabolic profiling revealed a unique loss in the pancreatic function of elderly burn patients that was accompanied by a substantial impairment of insulin production by the beta-cells of the pancreas. Abnormal beta-cell function resulted in a 17% increase in glucose. Furthermore, by dividing patients into adult and elderly, we found that elderly have significantly increased lipolysis expressed as increased free fatty acids when compared to adults. We further performed a qualitative and quantitative analysis of free fatty acid species in the serum of adult and elderly burned patients approximately 10 days post-injury. We found that Docopentanoic, Cis-7-Hexadecenoic, Myristic, Palmitoleic, Stearic and Vaccenic acids were significantly increased in elderly when compared to adults as well as control non-burned patients. Therefore, the sum of these fatty acids indicated that the levels of circulating fatty acids was greatly elevated in elderly patients

compared to adults burned and control [77]. The fatty acids profile in elderly burned population indicate that lowering lipolysis and circulating non-esterified fatty acids may be a beneficial strategy to diminish the consequences of thermal injury in the elderly population. Furthermore, reestablishing the balance in the fatty acid population with nutritional intervention aiming at lowering the percentage of saturated fatty acids and mono unsaturated fatty acids while increasing poly unsaturated fatty acids, may provide additional benefits to severely burned elderly patients [77]. Thus, elderly burn patients have a dramatically different physiological response to burns as compared to adults and this requires a multi-modal approach to improve the outcomes of severely burned elderly patients.

### Patient management and the multidisciplinary care approach

The complex care required for a hypermetabolic patient post burn injury needs to be well coordinated and managed in a collaborative team approach. Ciccone et al, have shown through Project Leonardo that when the combined efforts and networking of all the people involved in patient care create a strong collaborative "health team" approach, there is noticeable improvement in the clinical parameters of the patients enrolled who achieved improved control of their disease [75]. Additionally, the communication and collaboration between health care staff and patients is essential to promote patient empowerment and can achieve better compliance with care recommendations [75]. The Chronic Care Model developed by Wagner et al, and the Innovative Care for Chronic Conditions, suggest that ideal care for chronic conditions is attained when health care providers interact with informed patients [76, 77]. Providing the necessary self-management education, assistance in implementing lifestyle changes that are specific to each individual, and close monitoring of the patient's conditions by both the patient and health care staff can improve health outcomes and promote appropriate resource utilization [75]. Patient self-management is critical to the clinical outcome of chronic disease [78]. Therefore, this collaborative team approach can be applied to the multidisciplinary and complex burn team in the amelioration of hypermetabolic conditions in patients post severe burn. This approach is aimed to improve patient outcomes and reduce morbidity and mortality.

## Pharmacological Interventions

### Insulin

Hyperglycemia and insulin resistance leads to morbidity and mortality in severely burned patients and therefore glycemic control is critically important. Insulin acts to control glucose, as an anabolic agent and an anti-apoptotic agent that is routinely used to treat hyperglycemia after injury [79]. Studies conducted by Van den Berghe et al reported improved survival and decreased morbidity in critically ill patients by maintaining blood glucose levels at or less than 110 mg/dL through the use of intensive insulin regimens [80, 81]. Their results also show a reduction in the incidence of infections, sepsis, and sepsis-associated multi organ failure in surgical patients, lower kidney injury, and faster weaning from mechanical ventilation and discharge from the ICU

[80-82]. After these studies, tight glycemic control has become a standard of care in critical illness.

Insulin has a plethora of effects in addition to increasing cellular uptake of glucose, which makes insulin a very attractive agent [83]. Insulin has been reported to improve wound matrix formation, as well as inhibiting the production of proinflammatory mediators such as nuclear factor kappa B and I kappa B and IL-5 and IL-6 [83-86]. Insulin has been shown to decrease donor site healing time due to the acceleration in the differentiation of the junctional mechanism necessary for dermal-epidermal adhesion, insulin also increase the levels of laminin and type IV collagen in the wound [85].

The survival of critically ill patients is inversely correlated with loss of lean body mass [87]. Moreover, the atrophy of ventilatory muscles, particularly in patients requiring ventilators, is an important problem. The principal defect appears to be an accelerated rate of protein breakdown, along with an insufficient increase in the rate of protein synthesis to fully restore protein balance [88]. Studies have demonstrated that insulin therapy can lead to altered protein kinetics in skeletal muscle and curtail muscle catabolism and improve protein synthesis [85, 87, 89]. This in turn, leads to a reduction in the loss of lean body mass.

Regardless of the beneficial effects of insulin treatment for burn patients, there are increasing concerns about whether Insulin induces hypoglycemic events [90]. For example in follow up studies by Van den Berghe, the intensive insulin therapy had no beneficial effect on survival rates. Furthermore, such therapy was associated with an increase in hypoglycemic events. A study by Brunkhorst et al conducted on 537 patients showed that after 28 days of treatment with intensive insulin therapy or conventional insulin therapy there was no significant difference between the two groups in the rate of death or the mean score for organ failure. The rate of severe hypoglycemia (glucose level,  $\leq 40$  mg per deciliter [2.2 mmol per liter]) was higher in the intensive-therapy group than in the conventional-therapy group (17.0% vs. 4.1%), as was the rate of serious adverse events (10.9% vs. 5.2%) [91]. Our lab has conducted a study to determine the ideal glucose target in severely burned children. It was found that 130 mg/dl is the best glucose target because of the glucose levels being  $<150$  to  $160$  mg/dl but preventing hypoglycemia. Following the recommendations from the critical care literature and other patient populations, it appears that a glucose range of 90 to 140 mg/dl seems ideal for treating burn patients [90]. Moreover, the current surviving sepsis guidelines are calling for glucose  $<180$  mg/dl [92].

Therefore, insulin has many beneficial effects such as glucose control, improving wound healing and acting as an anabolic agent however the dangers of hypoglycemia do need to be considered.

### Recombinant human growth hormone

Literature demonstrates that as the catabolic state in hypermetabolism continues, weight loss, lean muscle mass loss, weakening of the immune system and subsequently poor or delayed wound healing, and prolonged recovery times result [88, 93-95]. In severely burned children, this response is often illustrated by a short and long term decrease in physical

growth and development [96]. Growth hormone, as a pituitary product, improves nitrogen balance and decrease weight loss in hypermetabolic patients following thermal injury [97, 98]. Liljedahl et al. and Wilmore et al. showed that growth hormone caused a considerable improvement in nitrogen and potassium balance in the postburn period with no significant side effects [98, 99]. In addition growth hormone has been shown to increase circulating IGF-1 levels, cell mass, and linear growth in growth hormone-deficient children [100]. Initially growth hormone was collected post mortem from human pituitary tissue however now it has been replaced by genetically engineered recombinant human growth hormone [99, 101]. Recombinant human growth hormone (rHGH) is known to be a potent anabolic agent [102]. After severe burn, rHGH decreases whole body catabolism, improves muscle protein synthesis, accelerates wound healing, improves immune function, reduce prolonged hyperactivity of the hepatic acute phase response, and promotes linear growth [103-106].

The anabolic effects of rHGH are thought to be mediated by IGF-1 because growth hormone treatment has been demonstrated to increase their circulating levels. IGF-I has been shown to enhance cell recovery, wound healing, peripheral muscle protein synthesis, and gut and immune function after burn injury [107-109]. A study by Herndon et al on children between the ages 2-18 with 40% total body surface area (TBSA) and 20% or more TBSA full-thickness flame or scald burns, received placebo or 0.1 mg/kg/day recombinant human growth hormone (rHGH) until the first donor site healed or received 0.2 mg/kg/day rHGH or placebo from admission throughout hospitalization. Patients that received 0.2 mg/kg/day rHGH had significantly higher serum IGF-1 levels at  $4.8 \pm 1.7$  U/mL compared to placebos at  $1.6 \pm 0.4$  U/mL and a significant decrease in donor-site healing times compared to placebo. Length of hospital stay was decreased in the 0.2 mg/kg/day treatment group in comparison to the placebo group. This translated, for the average 60% TBSA burned patient, to a decrease in length of stay from 46 to 32 days [105].

The hepatic acute phase response can be influenced positively by a daily intramuscular injection of rHGH at doses of 0.2 mg/kg during acute burn it also increases serum concentrations of its mediator IGF-1, and decreased donor site healing time by 1.5 days [110, 111]. However, a major paper by Roukonen and Takala found that high doses of rHGH ( $0.10 \pm 0.02$  mg/kg BW) were associated with increased morbidity and mortality in critically ill patients and there was no use in infection and sepsis [112]. Others demonstrated growth hormone treatment to be associated with adverse side effects such as hyperglycemia and insulin resistance [110, 113]. To verify these results, Jeschke et al investigated whether rHGH delivery to patients increase and prolong acute phase response and increase mortality. They looked at the interaction of rHGH and the liver on acute phase proteins, constitutive hepatic proteins, cytokines, and IGF-I in severely burned children. It has been reported that the synthesis of certain proteins during acute phase response can be utilized as a marker to predict morbidity and mortality. Jeschke et al establish that burned children receiving rHGM had increased serum IGF-I and IGFBP-3; the treatment group required significantly less albumin substitution to maintain normal levels compared with placebo

[114]. Those receiving rHGH demonstrated a decrease in serum C-reactive protein and serum amyloid-A and an increase in serum retinol-binding protein compared with placebo. rHGH decreased acute phase proteins serum tumor necrosis factor-[alpha] and interleukin (IL)-1beta. Free fatty acids were elevated in burned children who received rHGH. Jeschke lab's data indicate that given that the acute phase response contributes to mortality after trauma, rHGH administration appears not to increase mortality in severely burned children since rHGH does not increase or prolong the acute phase response. In contrast, rHGH might have clinical advantages in terms of clinical outcome because of a decreased acute phase response [114].

### Metformin

Metformin has been added as an alternative to insulin in correcting the postburn hyperglycemic state in the clinic [115]. Metformin is reported to inhibit gluconeogenesis and augment peripheral insulin sensitivity therefore it directly counters the two main metabolic processes which underlie injury-induced hyperglycemia [92, 116, 117]. In addition, metformin has been rarely associated with hypoglycemic events, thus potentially eliminating the concern accompanying the use of exogenous insulin. Metformin also enhances the uptake and oxidation of glucose by adipose tissue as well as lipogenesis [118]. In a study by Gore et al; metformin was administered to patients with a TBSA >60%. Their results show that after 8 days of metformin or placebo treatment, when fasting, metformin treatment group had significantly reduced rate of endogenous glucose production and glucose oxidation as compared to the placebo group. After intravenous glucose administration, the metformin group had significantly elevated glucose clearance, attenuating hyperglycemia. Also during hyperinsulinemia, glucose uptake was significantly increased in the metformin patients, as well this group of patients had a significantly higher plasma insulin concentration [115]. A later study by Gore et al validated the effect of metformin on muscle protein synthesis; their results demonstrate an increased fractional synthetic rate of muscle protein and improvement in net muscle protein balance in metformin treated patients [116]. Hence an improved anabolic effect on muscle protein was displayed and therefore Metformin may have efficacy in critically injured patients as both, an antihyperglycemic and muscle protein anabolic agent.

However, caution should be taken when using metformin as a therapeutic agent. Metformin (and other biguanides) are associated with lactic acidosis [119, 120]. When interpreting the increases in blood lactate levels one should take into account the fact that obesity and diabetes slightly raise blood lactate concentrations [121]. The increased blood lactate concentrations are potentially caused by metformin-induced conversion of glucose to lactate by the intestinal mucosa [122]. When the liver is ineffective and cannot clear lactate, more lactate gains entry into the systemic circulation. In burn patients there are very few reports that indicate that metformin is associated with lactic acidosis post-burn when given after complete resuscitation.

### Propranolol

The hypermetabolic response in severely burned patients in

associated with increase in catecholamines 10-20 fold. This increases myocardial oxygen consumption, increased resting energy expenditures, and contribute greatly to the profound catabolism after severe burn injury [123, 124]. It has been suggested that blocking  $\beta$ -adrenergic stimulation after severe burns decreases supraphysiologic thermogenesis, tachycardia, cardiac work, resting energy expenditure [125]. Propranolol is an important  $\beta$ -adrenergic receptor blocker. Studies by Herndon et al has shown that beta-blockage reduced the heart rates and resting energy expenditure in the propranolol group, as compared with the base-line values and compared to the control group. In the propranolol treatment patients, the net muscle-protein balance was elevated by 82% above baseline values. Their results therefore show that in pediatric patients with burns, treatment with propranolol during hospitalization reduces hypermetabolism and reverses muscle-protein catabolism [125].

Catecholamine-mediate hypermetabolism, lipolysis, and fatty liver are critical features of the stress induced response to severe burns [35, 106, 123, 126-128]. The pathological signs are deposition of fat in the liver as well as increased liver size, which could range from 2- to 3-fold [126, 129]. Fatty liver may be due to an enhanced rate of peripheral lipolysis associated with a lack of increased fat oxidation [34]. The increase in basal lipolysis in burn patients is caused by excessive catecholamine production, which can be reduced by beta-adrenergic blockade with propranolol [34, 94]. Propranolol prevents increased peripheral lipolysis in thermally injured patients by hampering the activation of the Beta-2-adrenergic receptor [88, 130]. A study by Wolfe et al showed that beta-blockade using Propranolol caused a prompt lessening in the plasma concentration of glycerol (released due to lipolysis). The rate of appearance of free fatty acids also fell after beta-blockade, from a mean basal value of  $13.3 \pm 3.1$  mol/kg/min to a low of  $7.44 \pm 2.33$  mol/kg/min at 40 minutes after propranolol. In all cases after beta-blockade, the potential energy available in the form of plasma free fatty acids was lowered more than was the overall rate of energy expenditure [88, 130]. Since hepatic fatty acid uptake is associated to plasma free fatty acid availability, Barrow et al has shown that propranolol diminishes net fat accumulation in the liver through the reduction in hepatic free fatty uptake while maintaining VLDL-TG secretion and also without affecting fat oxidation. Barrow's data supports the hypothesis that  $\beta$ -adrenergic blockade can reduce delivery of fatty acids to the liver and hepatic congestion usually found in severely burned children by preventing lipolysis and reducing hepatic blood flow [131].

### Oxandrolone

The hypermetabolic response to burn injury results in the development of hypoandrogenemia. Despite stable luteinizing hormone levels, male burn patients have been shown to suffer from a prolonged and significant reduction in testicular steroid production [132-134]. This is of significance because the hypoandrogenemia and the elevated catecholamine and cortisol levels post-burn injury promotes the loss of lean body mass experienced by burn patients [134]. Consequently, treatment with oxandrolone, a synthetic analog to testosterone, should be considered to combat the effects of protein catabolism. In

comparison to testosterone, oxandrolone produces only 5% of the masculinizing effects of testosterone, is safe to use in both males and females, is not hepatotoxic and is cleared by the kidneys, has received approval and has been effectively used in treating chronic wasting syndromes, including burn trauma [135]. Burn patients receiving oxandrolone intervention experience reduced muscle wasting due to an increase in protein synthesis [136], diminished weight loss, and increased donor site wound healing [137]. Jeschke et al have also shown that oxandrolone treatment reduces hepatic protein synthesis, maintains lean body mass, and results in shorter acute hospital stay [7]. Moreover, it has been demonstrated that oxandrolone intervention improved morbidity and mortality regardless of age [138-140]. Not only has oxandrolone been shown to be beneficial in short term interventions for burn patients, but long term treatment with oxandrolone has been shown to improve lean body mass, bone mineral content, and attenuate the hypermetabolic state 12 months post burn injury [71, 141]. However oxandrolone may cause hepatic damage [142], impair recovery by promoting collagen deposition and fibrosis, and extend the requirement of mechanical ventilation. Consequently, treatment with oxandrolone necessitates careful consideration of the potential side effects burn patients may face.

### Conclusion and Future Directions

A severe burn is a devastating injury that affects almost every organ system, leading to morbidity and mortality, and is accompanied by a hallmark hypermetabolic response which persists for 1 to 2 years after the initial burn injury [44, 143]. Prolonged hypermetabolism is detrimental and is characterized by multi-organ dysfunction, muscle protein breakdown, blunted growth, insulin resistance and a higher risk of infection [44, 143]. Treating post burn hypermetabolism is of high importance for both the acute stage and rehabilitative stage of the patient. Furthermore, the elderly population is a vulnerable group that requires a multi-modal approach to improve the outcomes since they display a hypermetabolic response which differs from that of adult burn patients. Early excision and closure of the burn wound post burn injury is extremely important in alleviating the hypermetabolic response and improving mortality and morbidity [4, 6, 40]. Nutrition is crucial in supplying the energy supply required for wound recovery, and for the attenuation of hypermetabolism and protein catabolism. Despite being commonly overlooked, increasing ambient temperatures reduces resting energy expenditure and attenuates the effects of the hypermetabolic response [55, 56]. Exercise is important to consider in rehabilitation regimens to improve lean body mass, muscle strength and general patient outcome [66-68]. Non-pharmacological therapies by themselves are often times not enough to alleviate the hypermetabolic condition and pharmacological interventions are necessary.

Several options are available such as insulin, recombinant growth hormone, metformin and propranolol and oxandrolone. They all have their merits but one must consider not only the benefits of the pharmacological drug but also the adverse events and if those adverse events will worsen the hypermetabolic state or the duration of healing. Combination therapies are also proving

to be quite promising in optimizing desired results and reducing the adverse effects. For example, since rHGH has the deleterious side effect of increasing hyperglycemia and increasing free fatty acids; we studied rHGH and propranolol to determine if this combination of drugs can be used without deleterious side effects. Our results demonstrate that the combination of rHGH plus propranolol exerted positive effects on the inflammatory and the hypermetabolic response without causing the adverse effects associated with rHGH administration alone [10]. Future directions also look towards identifying biomarkers of the hypermetabolic state to predict patient outcomes and mortality. These biomarkers could also be used to design a treatment plan which would be tailored to the individual patient based on their biomarker profile this would lead to aggressive treatments when necessary, greater patient monitoring and improved survival and recovery. In 2014 we conducted a prospective cohort study on 230

severely burned children with 30%>TBSA to evaluate biomarkers. Their results illustrated that survivors and non-survivors display significant differences in critical markers of inflammation and metabolism at each time point. Non-survivors had significantly higher serum levels of IL-6, IL-8, granulocyte colony-stimulating factor, monocyte chemoattractant protein-1, c-reactive protein, glucose, insulin, blood urea nitrogen, creatinine, and bilirubin [144]. Furthermore, non-survivors had a huge increase in hypermetabolic response that was associated with increases in organ dysfunction and sepsis in comparison to the survivors [144]. Further research initiatives in the field of hypermetabolism post severe burn injury is warranted to find the optimal combination of pharmacological treatments, non pharmacological care and potential biomarkers to establish a highly personalized treatment plan for burn patients which reduce mortality, improve healing time and in turn lead to a high quality of life for such patients.



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