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Current Problems in Burn Hypermetabolism

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Introduction:

Hypermetabolism remains a significant clinical problem after burn. Every organ system is transformed metabolically in response to severe burn trauma. With long-term consequences including cardiac dysfunction in as many as 60% long term,¹ growth arrest for nearly a year after burn in children,² and high incidence rates of depression, anxiety, and posttraumatic stress disorder(PTSD),³ the metabolic changes after burn clearly have far reaching and long lasting detrimental effects.

The history and recognition of burn (and traumatic) hypermetabolism has an extensive history, with the principal changes beginning in the 1930s. Cuthbertson and colleagues monitored metabolism via nitrogen balances in healthy humans, patients with fractures, and patients with sepsis. Their preliminary studies revealed that increased nitrogen losses and temperature changes between the groups were not simply localized to the exact source of infection/trauma but involved a systemic response.^{4, 5} This concept of a systemic hypermetabolic response to trauma was extended to burns in the 1940s with various authors. Cope and colleagues monitored various aspects of burn hypermetabolism including oxygen consumption and thyroid function, while Truman Blocker monitored muscle protein breakdown using radiolabeled albumin.^{6, 7} Francis D. Moore and others then furthered the

understanding of burn hypermetabolism in the early 1940s by further quantifying the causes of hypermetabolism, including sources of nitrogen and exudative ion losses.^{8, 9} Subsequently, Dr. Moore began using patient weights to guide fluid resuscitation and feeding, noting that weight loss signified a dire situation in trauma and burn patients, in part reflecting severe electrolyte and nutritional deficiencies.¹⁰ Based on their research, resuscitative protocols for severely burned individuals emerged.⁹ In the 1960s and 1970s, research continued to define key mediators of the systemic responses to trauma and burns. Moore and colleagues observed endocrine alterations in response to trauma, including elevated cortisol and catecholamine levels and decreased growth hormone levels.¹⁰⁻¹² These contributions spawned further investigation in the field of burn hypermetabolism that would eventually provide a better understanding of this stress response while leading to therapeutic strategies that improve survival of patients with severe burns.

The initial response to burns has 2 specific phases. An initial “ebb” phase during the first 1 to 3 days after-burn is characterized by a decrease in tissue perfusion and temporary decrease in metabolic rate similar to a short lived “fight or flight” response, possibly to preserve vital organ functions and central blood flow. Thereafter, a the hypermetabolic “flow” phase is initiated (Fig. 1), characterized by increased perfusion of superficial tissues, increased adrenergic stress, increased glucocorticoid levels, and increased levels of inflammatory cytokines. These alterations in hormone and cytokine levels drive many energy dependent biochemical processes in response to severe burn trauma, collectively resulting in a hypermetabolic response that necessitates a drastic increase in the caloric needs of severely burned individuals.^{13, 14} Therefore, the hypermetabolic response can be defined as an increase in the whole body oxygen consumption and resting metabolic rate. This response is created by various modifications in protein turnover, hepatic acute phase response, mitochondrial uncoupling, and various other metabolic pathway modifications, and has now been shown to last up to 2 years after-burn (Table 1).¹⁵

In regard to treating burn hypermetabolism, therapies targeting catecholamines, glucocorticoids, and other specific mediators have decreased morbidity and mortality and improved quality of life in patients with severe burns. However, current treatment paradigms are still unable to fully prevent the hypermetabolic response to burn trauma, suggesting that there is room for improvement in terms of patient care. Multi-pronged approaches targeting numerous biochemical processes are likely needed to promote recovery from severe burns.

Mediators of Burn Hypermetabolism

Thermoregulation

Since burned patients lose their principal thermoregulatory barrier, they have a diminished capacity to maintain temperature homeostasis. Accordingly, patients with severe burns require a warmer ambient temperature to maintain thermoneutrality. The difficulty comes in deciding what environmental temperature the patient should be maintained in during hospital stay, quantifying the evaporative losses for resuscitation, and otherwise minimizing the hypermetabolic response associated with evaporative losses.

Many studies have shown that both evaporative heat and water losses occur from burn wounds, although the majority of heat loss remains due to radiative heat losses.^{16, 17} In a recent study, Busche and colleagues showed that evaporative water losses were 4 times greater in partial thickness (second degree) burns and 3 times higher in full thickness burns (third degree) when compared to normal skin. Although this may be counterintuitive initially, the leathery consistency of third-degree burns may reduce evaporative losses. It was also noted that graft donor sites are equal to partial thickness burns in evaporative water losses.¹⁸ Applying this clinically, a burned adult patient with the average adult body surface area of 1.73 m² would need 0.7 extra liters of fluid per day for full thickness and 0.9 liters of extra fluid for partial thickness burns (assuming 50% TBSA burn) due to evaporative losses alone. It is important to note that these fluid losses are not without corresponding electrolyte and exudative losses, which further the need for more replacement fluids. Losses in nitrogen, sodium, and potassium have been noted in the evaporative exudate from burn and amount to a significant (25-30% of total nitrogen, 95% of total sodium, and 20% of total potassium) portion of electrolyte losses in burn patients.⁸ Therefore, these electrolyte losses should be replaced as clinically needed, and monitored at least daily (more so than in typical trauma patients) to prevent rapid declines in levels.

Humans have a hypothalamic region that controls physiological heat-generating measures, such as shivering, teeth chattering, vasoconstriction in the periphery, and biochemical reactions at a cellular level that constitute non-shivering thermogenesis. The temperature at which a thermogenic cellular response is initiated is referred to as the critical temperature. Critical temperature and the length of time needed to reach it may vary from patient to patient. However, as burn severity increases, the critical temperature decreases. Therefore in severely burned patients, cellular heat production begins at higher ambient temperatures (earlier) than in normal patients.⁵ By minimizing heat losses via mechanisms described later, the hypermetabolic state can be managed to a degree, thus improving patient coagulation, morbidity, and mortality.

Glucocorticoids

Cortisol levels increase 3- to 10-fold after burn and remain elevated for at least 3 months after injury.^{15, 19, 20} Increased cortisol levels have been implicated as a potential mediator of the metabolic stress response to burns. Brillion and colleagues showed that hydrocortisone infusions increased whole body muscle protein breakdown in humans by anywhere from 5% to 20% (for leucine and phenylalanine release).²¹ Hypercortisolemia can lead to both central and peripheral insulin resistance at the level of both adipose tissue and skeletal muscle. For example, glucocorticoids increase the release of neuropeptide Y, which further increases hepatic insulin resistance in burn and trauma states.²² Since both insulin resistance and hypercortisolemia cause muscle proteolysis, cortisol may contribute both directly and indirectly to muscle wasting in response to burns. Cortisol has also been linked to peripheral adipose depot depletion and central adipose tissue accumulation, although the mechanism has not clearly been elicited.^{23, 24} Similar to the metabolic complications accompanying Cushing's disease, such as altered lipid storage, diabetes, and peripheral muscle wasting, elevated glucocorticoid levels in burns may contribute to the increased central adiposity and peripheral muscle wasting seen after injury.²⁵

One clinical trial in burns showed that blunting glucocorticoid receptors with ketoconazole had only mild effects on hypermetabolism.²⁰ This may in part be due to the fact that the levels seen in trauma or burns are not quite as high as the levels elicited in experiments and Cushing's disease, or may be due to a suboptimal effect of ketoconazole on inhibiting cortisol synthesis. Therefore, although increased glucocorticoids after burn mediate key metabolic processes, altering glucocorticoid levels/signaling alone may not be an effective strategy in managing the hypermetabolic response to burn.

Catecholamines

Catecholamines are thought to be a major driver of burn-induced hypermetabolism. Increased by approximately 4- to 10-fold after injury in patients with major burns (~60% TBSA burned), catecholamines can remain elevated for more than 1 year after-burn.^{15, 26} Specifically, in children with massive burns, norepinephrine remains elevated for 100 days to 2 years after injury while epinephrine is significantly elevated for 60 to 100 days after injury.^{19, 26} Given the plethora of regulatory roles catecholamines play in metabolism, prolonged elevations in circulating catecholamine levels can cause significant metabolic dysfunction in humans.²⁷ That being said, acute increases in catecholamine levels after trauma are likely necessary for survival, suggesting that a degree of adrenergic stress after burn may in fact be useful.²⁸⁻³⁰ For instance, in a cohort of burn patients, non-survivors had significantly lower levels of catecholamines than survivors,²⁷ underscoring the importance of an adrenal response in the recovery of critically ill patients. However, detriment is seen when catecholamines are chronically elevated, leading to excess stress on the cellular level.

In regards to metabolic dysfunction after burn, catecholamines have been shown to have a pronounced effect on fatty acid metabolism. Indeed, burns result in increased adipose tissue lipolysis and triglyceride-fatty acid cycling, which can be reduced in burned individuals with the infusion of a beta-blocker.^{31, 32} Additionally, catecholamines drive increased lactate and amino acid efflux from muscles for energy utilization,^{33, 34} although the role catecholamines play in glucose and protein metabolism in response to burns is less well defined.

Glucose metabolism:

Although proper glucose control is lost in response to burns, with a number of tissues exhibiting insulin resistance, increased whole body glucose turnover is a hallmark of the metabolic stress response to burns. This likely reflects increased energy demand to support healing. Skin and soft tissue glucose uptake at the area of the burn drops immediately after injury and remains depressed even 24 hours after the burn. Thereafter, wound glucose uptake rebounds and by 3 weeks after injury is 3 to 4 times higher than that seen in normal skin. Similarly, after an initial drop, glucose uptake increases to around twice the normal rate in non-burned skin.³⁵ Although counterintuitive in the context of insulin resistance, increased cellular uptake of glucose in response to burns likely reflects greater whole body glucose flux in the context of burn-induced hypermetabolism. Thus, in burned individuals, while insulin sensitive tissues like muscle may need more insulin to clear the same amount of glucose, overall glucose uptake is significantly elevated in response to burns due to high gradients across membranes. In the context of burns, it is also possible that chronic

glycogenolysis and glycolysis play a role in driving non-insulin stimulated serum glucose concentrations.

Insulin resistance is a key factor in these outcomes of burn glucose metabolism. Clinically, hyperglycemia secondary to insulin resistance has been linked to poor wound healing, increased skin graft loss, increased muscle protein catabolism, increased infections, and greater mortality in severely burned patients.^{36, 37} Increased blood insulin concentrations persist for a year and a half after burn whereas the resistance to this insulin persists for up to 3 years after burn.¹⁵

In response to burn, both glucagon and insulin concentrations in the blood are increased.³¹ Glucagon is secreted by pancreatic alpha cells and is responsible for maintaining euglycemia in the post-absorptive state by breaking down liver glycogen stores and stimulating hepatic gluconeogenesis. In the long term (greater than 24 hours), proteins and triglycerides also mobilize from muscle and adipose tissue in order to provide precursors for further gluconeogenesis. Glucagon is tightly linked to the sympathetic nervous system through feedback cycles and causes an overall nutrient mobilization.³⁸ Glucagon is also known to activate lipolysis through hormone-sensitive lipase and to stimulate muscle amino acid mobilization.³⁹ This mechanism may be particularly pertinent in the context of burns, where the caloric needs are greatly increased. Although the effects of glucagon on thermogenesis in humans remain unclear, glucagon has been shown to stimulate thermogenesis in the brown adipocytes of rodents.⁴⁰ In regards to hepatic metabolism, glucagon in part leads to large increases in glycogen cleavage via glycogenolysis contributing to increased rates of hepatic glucose output.^{38, 41} In summary, Although glucagon does not directly increase energy expenditure on its own, it does lead to substrate mobilization and substrate cycling which in turn increases the caloric demand.

Blood insulin concentration is also chronically elevated after burn. Secreted by the beta islet cells of the pancreas in response to increased glucose concentrations, insulin is typically thought to have the opposite metabolic effects of glucagon. Specifically, insulin normally lowers glucagon levels via inhibition of alpha cells, thus attenuating gluconeogenesis (although this effect is blunted in burn).³⁸ Moreover, insulin blocks hepatic glucose release while stimulating glucose uptake into muscle, ultimately lowering glucose levels in the blood. Lastly, in contrast to glucagon, insulin is anti-lipolytic, preventing the breakdown of adipose tissue triglycerides. In response to burn trauma, insulin levels are elevated, but hyperglycemia still exists.

There are hypothesized reasons for both insulin resistance and submaximal insulin levels. One theory is that inflammatory cytokines/hormones such as IL-1 β cause damage to beta cells, thus blunting maximal insulin output by the pancreas. So, for any given stimulation after burn or sepsis, beta islet cells would secrete less insulin than expected due to decreased response from and decreased numbers of beta islet cells, even though overall measured insulin levels are still increased.⁴²

Another theory, and the most prominent one, is that insulin resistance is mostly due to a post-insulin receptor deficit.⁴³⁻⁴⁵ In other words, the cells are unable to mount an

appropriate response to insulin receptor binding. For example, Black and colleagues exhibited that healthy individuals had a glucose uptake of 14.3 mg/kg/min whereas burn patients had only a 9.17 mg/kg/min uptake thus quantifying peripheral (muscle and adipose) insulin resistance.⁴⁶ In a separate study, Chen and colleagues reported that insulin levels rose 3-fold while plasma glucose levels increased approximately 1.5-fold following burns.⁴⁷ This study devised an insulin sensitivity score, which showed that the sensitivity to a given insulin amount decreased by one half in burned patients, worsening even further with sepsis.^{47, 48} Along with peripheral tissues, after burns the liver itself is highly resistant to insulin, which explains increased glycogenolysis and gluconeogenesis even in the presence of higher insulin levels.³¹ Realistically, the insulin resistance is due to a culmination of different causes.

Fatty acid metabolism

In a similar fashion, fatty acid turnover is also increased in response to burns. In general, lipoprotein lipase from the endothelial cells breaks micelles down into free fatty acids that can then enter various tissues and cells. Adipose tissue will store the majority of these as triglycerides but other organs store small amounts intracellularly which can be used for beta-oxidation and the tricarboxylic acid (TCA) cycle for ATP generation (in the case of burns this can also be used for heat generation).⁴⁹

In response to burn, chronic adipose tissue lipolysis leads to greater fatty acid and glycerol release into the blood stream.⁵⁰ In turn, deposition of lipid moieties derived from adipose tissue lipolysis in the liver is thought to drive the hepatomegaly seen after burn. In response to burns, the liver increases the rate of re-esterification of these free fatty acids into triglycerides while the rate of oxidation remains unchanged, leading to the net accumulation of lipids, and clinical hepatomegaly (Fig. 2).⁵¹ Investigations at autopsy suggest that liver weights of burned patients are approximately double that of normal age and sex matched patients.⁵² Furthermore, clinically approximately 60% of children and nearly all adults who passed away from their injury had developed hepatic steatosis.⁵³⁻⁵⁵

In addition to the breakdown of peripheral white adipose tissue, the process of browning of white adipose tissue has recently arisen in burns. Brown adipose tissue is in part responsible for non-shivering thermogenesis, where the presence of a mitochondrial uncoupling protein (UCP1) allows fuel oxidation in brown fat mitochondria to directly generate heat. In burn patients, it was noted that the adrenergic response leads to the development of brown like adipocytes within subcutaneous white adipose tissue.^{56, 57} In humans, the “brown fat” is white adipose tissue whose phenotype has shifted along the spectrum towards brown fat, also known as “beige fat”. These brown-like, or beige, fat cells are reduced in size, enriched with mitochondria, and express increased levels of UCP1 protein.⁵⁶ In addition to browning of white fat, animal data and a recent report in burned patients suggest recruitment and activation of previously inactivated, bona fide brown fat.⁵⁸

Amino Acid Metabolism

The vast majority of the body's protein stores reside in skeletal muscle. Thus, in response to massive increases in protein requirements that cannot be met readily by dietary protein

intake alone, breakdown of muscle occurs to further increase circulating amino acid availability. After burn, muscle protein degradation occurs at a faster rate than synthesis of new muscle proteins, leading to a chronic net efflux of nitrogen and amino acids from skeletal muscle and ultimately muscle cachexia. Using stable isotopes of various amino acids, our group traced leg muscle protein metabolism in healthy and severely burned adults. We found that the rate of muscle protein synthesis was elevated 1.5-fold in fasting burned patients. However, the rate of protein breakdown was elevated 1.8-fold in these patients as compared to controls in the fed state.³⁵ This discord in protein synthesis and breakdown in the muscle of these patients underlies the marked catabolic response to burns. Along with protein breakdown, increased outward transport of amino acids from muscle occurs, in order to provide amino acids for wound healing and hepatic gluconeogenesis.³⁵ Attempts to diminish muscle protein breakdown by exogenous amino acid administration failed to stop the loss of muscle protein content; therefore, these cycles are not necessarily due to a lack of dietary proteins.⁵⁹ Both catecholamines and glucocorticoids have been implemented as causative factors for the increased protein breakdown seen in muscle post burn.

Clinically, muscle catabolism after burn leads to catastrophic decreases in long-term exercise tolerance and gross muscle atrophy.⁶⁰⁻⁶³ In 2000, Hart and colleagues demonstrated using stable isotopes that patients exhibit elevated protein breakdown until 9 months after burn, as well as a lack of response to protein nutrition.^{59, 64} This correlates well with decreases in lean body mass on dual-energy x-ray absorptiometry (DEXA) scans with as much as 17% lean body mass loss in upper extremities and 7% in the lower extremities between admission and discharge from the intensive care unit (ICU).²⁵ Therefore, even after the burn is healed, the increased protein breakdown remains, most likely due to continued hormonal imbalances. Specific risk factors for this protein catabolism include increasing age, male sex, increasing height, increasing TBSA burned, increasing creatinine, and increasing REE. The most important risk factor, though, is a diagnosis of sepsis.⁶²

I. Metabolic modulation and treatment after burn:

Due to extensive research in the latter half of the 1900s, our understanding of the metabolic stress response to burns has greatly improved. This new knowledge has led to several new treatment strategies that have had a significant impact on burn mortality (Table 2), which details improvements in burn mortality over the last 70 years by comparing our current mortality prediction model to previous ones, demonstrating improvements in burn care symbolized by improved mortality rates at all ages.⁶⁵ These improvements in mortality include various improvements in early excision, nutrition, fluid resuscitation, and infectious control methods.

Despite huge improvements in burn mortality in the last half century, there is still need for new treatment strategies aimed at lessening the deleterious impact of the metabolic stress response, hastening recovery, and improving the long-term quality of life in burn survivors. Indeed, since mortality has improved drastically, physicians and researchers are now able to focus on long-term patient outcomes, such as the patient's perception of scars, and other parameters of well-being. Hypertrophic scarring, psychological disorders, and joint contracture still plague burned patients long after discharge from the hospital.

Temperature/Evaporative control

Hypothermic body temperatures have been linked to poor coagulation and high caloric utilization in burn patients. Thus, one easily controllable aspect of burn care is the ambient room temperature, which can have a significant impact on the caloric needs of the patient. This has been studied in rodents and in humans where significant improvements in hypermetabolism, decreased catabolism, and wound healing are observed when animals and patients are kept at 30°C to 33°C after burn when compared to those kept at 20°C to 25°C after injury. For example, Kelemen and colleagues showed in human patients with 50% TBSA burns that decreasing ambient temperatures from 32°C to 22°C increased patients' REE by approximately 22%.⁶⁶ It is important to note that increasing the ambient temperature from 32°C to 35°C did not further blunt hypermetabolism, suggesting that a temperature range of 30°C to 32°C may be an optimal ambient temperature for burned patients (especially considering that staff become uncomfortable at higher temperatures).⁶⁶ These ambient changes become more important as the TBSA of burns increases, with beneficial effects from treatment beginning somewhere around 20% TBSA. In cohesion with this, the REE increases with increasing TBSA of burns (Fig. 3).^{18,17} Anesthesia during operations additionally prevents the normal thermogenesis generated by the patient, and therefore temperature regulation during operative periods is vital.⁶⁷

In our facility, we maintain the operating temperatures at 85°F to 90°F (29-32°C) via heat lamps and thermostat regulation in order to prevent hypothermia during excision. If these commodities are not available, we recommend (at minimum) forced air patient warming with portable heat lamps, or the best possible attempt to maintain core temperature. Although no specific core temperature guidelines have been set, attempting to maintain core temperature above approximately 37.5°C is prudent.⁶⁸ In our ICU we also maintain ambient temperature between 28°C and 30°C in patient rooms and common areas with additional overhead heaters in each room if needed.

Nutrition

Nutrition is another key component for survival after severe burns, allowing for improved outcomes by partially offsetting the deleterious impact of long-term hypermetabolism while providing substrates for wound healing. The vast mobilization of nutrients to superficial tissues at the burn sites and internal organs necessitate an increase in caloric intake to maintain homeostasis. Caloric needs of burned patients can be increased anywhere from 20% to 60% based on the patient's status and whether or not sepsis is confounding the burn.⁶⁹ Unfortunately, increasing caloric intake alone is not always sufficient to prevent catabolism in burns, demonstrated by continued catabolism even in the face of adequate or even excessive caloric intake.

Diets deriving a significant (approximately 80%) proportion of their total calories from carbohydrates appear to have a beneficial effect on muscle protein catabolism as compared to those with more moderate carbohydrate and higher fat or protein contents.^{70, 71} Further, a systematic review also concluded that high-carbohydrate low-fat diets decrease the incidence of pneumonia and blunt muscle catabolism in burned patients, but did not affect mortality.⁷²

Dietary fats, while essential for many key biochemical processes, may have detrimental effects after burn if supplied at moderate to high levels (i.e., more than 15% to 20% of total calories). This is likely due to the lipolytic response to burns, where the circulation is already flooded with fatty acids from adipose tissue lipolysis, driving hepatic VLDL secretion and triglyceride accumulation. In a Cochrane Review, low-fat and high-carbohydrate diets demonstrated less insulin requirements in addition to decreased pneumonia incidence in burned adult patients.⁷³ The current European Society for Clinical Nutrition and Metabolism (ESPEN) recommendation in burns is a high-carbohydrate and low-fat diet defined as 55% carbohydrates with less than 25% of caloric intake from fats (and 20-25% from proteins).^{74, 75}

Protein requirements in response to burn trauma are massively elevated. Increased wound protein synthesis and increased production of acute phase proteins drive this response. Indeed, it has been suggested that catabolism of muscle protein provides amino acids to support healing after burn. Accordingly, there may be an opportunity to intervene where increased dietary protein can support healing after injury and help attenuate muscle catabolism. Enteral formulas are recommended to have approximately 20% of their calories derived from protein that amounts to 1.5-2.5 g/kg/day in adults and 1.5-3.5 g/kg/day in children.^{70, 74} Specific amino acid supplementation has also been attempted but with limited effect. For example, direct alanine supplementation appears to cause an increase in protein/nitrogen losses as well as increased nitric oxide levels.⁷⁰ Glutamine has also been controversial. Several multi-centered and international studies have shown no benefit or even harm with glutamine supplementation, while a Cochrane review by Tan and colleagues in 2014 demonstrated both mortality and length of stay benefit overall.⁷⁶⁻⁷⁸ Theories on why glutamine may be beneficial include improved glutathione synthesis, improved gut integrity, and increased tissue uptake of branched chain amino acids.⁷⁰ It is currently recommended in trauma that if glutamine is to be supplemented, it should be given at 0.3-0.5 g/kg, although at our facility we do not supplement regularly.⁷⁵

The levels of various vitamins and antioxidants are also diminished after-burn, including but not limited to vitamins A, C, D, and E. Vitamins C and E both are greatly decreased after burn and attention has recently been turned to administering high levels of these antioxidants individually or in combination, with mixed results in the intensive care realm. Dosages recommended for vitamin E are anywhere from 150 IU/day for ages 2 to 5 years to 1200 IU/day for adults (range based on age and varies depending on study as no formal recommendations have been made),⁷⁹ and for vitamin C is 250 mg twice daily for children and 500 mg twice daily for adults in one study.⁸⁰ Vitamin C has been shown to decrease severity of infection,⁸¹ decrease fluid resuscitation and fluid overload, and improve immune function.⁸²⁻⁸⁴ Vitamin E also acts as an antioxidant, possibly improving inhalation injury outcomes,⁸⁰ improving wound healing, and improving immune system capabilities,⁸⁵⁻⁸⁷ although the human literature is scarce and the results are mixed between studies.⁷⁹ For example, vitamin E is often quoted to be detrimental to wound strength but at the same time increases the speed of wound healing. It has been shown that the majority of vitamins are back to normal levels within weeks (as opposed to months or years) and, therefore, we recommend supplementation during the acute hospital stay only.

Other trace minerals are usually supplemented based on their necessity for wound healing or due to losses at the burn. For example, zinc and copper are often supplemented in burn units, as they are vital to wound healing processes. Zinc can assist with wound healing by acting as a co-factor for collagen synthesis as well as improving immune system response. The losses of zinc occur in high levels through exudate as well as urine after-burn injury.⁸⁸ Copper, another depleted trace element, is often transferred into the liver after injury due to its antioxidant properties; therefore, the collagen cross-linking function for wound healing is left lagging. Copper is usually supplemented only in cohesion with other antioxidants, but is still vital for adequate wound healing. Iron, manganese, and selenium have all been found to be low after burns as well, although true selenium deficiency is rare.⁸⁰ Various mixtures of vitamins and trace minerals have also been used with varying benefit in several studies but no multi-center trials have been done.⁸⁹⁻⁹²

With all of the types of supplementation, one would assume that the catabolism of burns would be drastically decreased, but muscle catabolism, growth stunting, and hormonal alterations/imbances still occur. Given that tissue breakdown persists even with supplementation, it seems that a mixture of decreased uptake and inefficient usages are responsible. In addition, much of the catabolism is not necessarily from a lack of nutrition, but more from a lack of functional movement and exercise during extended periods of stay in the hospital.

In our facility we use Vivonex TEN[®] elemental formula with a protein content of 14%, carbohydrate content of 83%, and fat content of 3% (Nestle Health Sciences, Vevey, Switzerland). Our caloric intake is initially based on the Galveston formula at 1500 kcal/m² BSA baseline with an extra 1500 kcal/m² TBSA burned, and subsequently on clinical and anthropometric parameters as well as REE by indirect calorimetry. Daily (or near daily) weights are taken on our patients in order to estimate gains or losses while taking into account diuresis and various other clinical variables. Another important aspect to feeding is reaching caloric goals by minimizing interruptions of feeds. As an example, we most often use a post-pyloric position for enteral feeds, and therefore continue feeds throughout operation. This allows minimization of the “catch up” period after operation.

We supplement vitamin E at 10 IU/kg/day for patients 0-18 years of age and 15 IU/kg/day for those older than 18 years of age. For vitamin C, we supplement 250 mg PO daily for patients 0-11 years of age, and 500 mg for those who are 12 years of age or older. We also supplement zinc sulfate at 55 mg daily for patients 0-2 years of age, 110 mg for those 3-11 years of age, and 220 mg for those who are 12 years of age or older. Lastly, we give 1 mg folic acid 3 times weekly. Depending on the situation, multivitamins or additional micronutrients are given as needed.

Early total excision and grafting

Early excision of burn wounds is defined as the excision of full thickness burn wounds within 24 to 48 hours of injury. This is often not feasible and therefore can be defined as excision of burn as early as possible based on the individual situation. Although Ambrose Pare first mentioned early excision of burn wounds in the early 1900s, the concept did not truly take hold until the 1970s and 1980s when studies began reporting significant

advantages to early wound excision including decreased mortality and decreased muscle catabolism.^{93, 94} Our group showed significant improvements in mortality in early excision versus conservative treatment in patients with large burns (more than 50% of the TBSA). Hart and colleagues also showed that sepsis 5 days post excision was significantly higher in delayed/conservative treatment patients as compared to early excision patients.^{95, 96} These studies, as of yet, were not able to show that early excision and grafting decreases energy expenditure, and if anything may initially increase energy expenditure. That being said, early excision leads to improved long-term net protein balance.⁹⁶ One potential explanation is that there may be an earlier increase in energy expenditure with early excision/grafting but early healing as well, leading to faster resolution of the hypermetabolic state, allowing for a shorter catabolic period. This, in theory, would lead to less muscle loss and potentially improved recovery. Lastly, it is important to note that one of the major benefits of early excision and grafting is that excision and grafting occurs (if feasible for the patient) all in one operation as opposed to several shorter procedures. Decreasing the number of operations allows for decreased blood loss, hypothermia, and stress from anesthetic agents. With the resources and medical technologies of today, total excision in a single operation is not only feasible but also beneficial to patients.

Sepsis is a major complication in burned patients. Based on studies it appears as though taking the nidus of infection away by early excision and grafting helps minimize the chances of burn wound infection.⁹⁶⁻⁹⁸ It was shown based on quantitative cultures with thresholds of bacterial count 10×10^5 , that early excision had lower bacterial colonization of the eschar and of the excised wound bed as well as decreased overall rates of infection during hospitalization.⁹⁸

It has been noted that early excision has a large modification in the cellular inflammatory pathways intracellularly and extracellularly during burn. Horton and colleagues demonstrated large decreases in IL-1, IL-6, IL-10, and TNF- α in cardiac myocytes after 20% and 30% burns after early excision (30 minutes after burn) vs. no excision in a rat model. They also showed a significant improvement in myocardial contractility and relaxation with early excision of the wounds.⁹⁹

In addition to excision and grafting, occlusive dressings have been shown to be beneficial to patients with high and low TBSA burns, especially for second-degree burns.¹⁰⁰ For example Integra (Integra Lifesciences, Plainsboro Township, NJ), a 2-layer collagen and polysiloxane polymer dressing, has been shown to decrease REE and improve scarring when compared to allograft (cadaveric graft) in patients with greater than 50% TBSA burns.¹⁰⁰ Biobrane, a silicon film with interwoven nylon fabric, was similarly shown to be as effective as allograft in healing time, dressing changes, and autograft take.¹⁰¹ Physicians around the world are optimistic in the efficacy of these and other skin substitute dressings, and usage in questionnaires of burn surgeons is as high as 96% in some form or fashion.¹⁰² This may be in part because their use can often save time, and can decrease procedural costs by almost half.^{103, 104} Occlusive dressings also assist in thermoregulation after burn. Using topical dressings in comparison to exposed patients (control group) with no dressings, Caldwell and colleagues established that the dry heat loss was reduced by approximately 33%, the evaporative losses were decreased by 10%; the heat production needed by the patient was

decreased by 18%.¹⁰⁵ Although these losses were still higher than non-burned expected values, the occlusive dressing did assist in decreasing heat loss overall.

In our institution, based on the situation, we attempt excision and grafting within 24 hours of arrival to the ICU. If the burn wounds are contaminated, then homograft (cadaveric) is used from a local skin bank. If the wounds have low contamination, then autograft is used primarily. If the burn is large, we use 4:1 autografting with a 2:1 homograft overlay. We subsequently operate weekly, as needed, using 2:1 autografting, which leads to a predicted hospital stay of half a day per percent burn. For second degree burns, we previously used Biobrane and are now using Mepilex® (Mölnlycke Health Care, Gothenburg, Sweden) as well as prospectively experimenting with Permeaderm® (Permeaderm, Carlsbad, California).

Exercise: Although maintenance of muscle through exercise during and after a patient's ICU stay seems like the best logical intervention to restore lean body mass and function, exercise therapy has received relatively little attention in burns. Early exercise is recommended in the critical care setting, but in burn patients early exercise is often difficult to implement due to fragile skin grafts, pain with range of motion, and debilitating weakness.

Various types of in-hospital 6-12-week exercise regimens, including aerobic and aerobic plus resistance, have been shown to improve various parameters of cardio-respiratory fitness in adults (although not significant in meta-analysis) and children (significant in meta-analysis).¹⁰⁶ Exercise also induced body mass changes improving both trunk and leg lean body masses but not for the arms.²⁵ Furthermore, exercise has been shown to significantly decrease the need for repeat contracture release operations in all ages, although the impact on actual range of motion remains unclear.¹⁰⁷ The majority of exercise programs range from 6 to 12 weeks, but one study examined the difference between a 6- vs. 12-week duration and found the 6-week regimen to be just as beneficial as the 12-week.¹⁰⁸ In addition to in hospital rehabilitative exercise, community based exercise outside of the hospital with instructional videos and personal trainers has proven to be as beneficial as in hospital regimented exercise programs in one study using subjective questionnaires. In fact, the community-based exercise patients reported better social outcomes including pain, emotional, and family cohesion topics.¹⁰⁹

As stated previously, the primary challenges of using exercise in these patients are pain and fragility of grafting, leading to delays in implementation during acute hospital stay. Patients are either unwilling or unable to move sufficiently at any given time during their hospital stay, therefore, minimal exercise is accomplished. Sitting up in bed, standing, and walking are typical exercises done in our hospital due to these limitations and, therefore, atrophy often sets in before conventional exercise can be attempted. By the time the patient is able to tolerate an outpatient exercise regimen, the damage from immobility in the form of muscle breakdown and contractures have already occurred.

New methods will need to be found to maintain muscle composition early on including inpatient exercise regimens and exercise immediately after discharge. Currently, we are using newer methods such as virtual reality during tub room (dressing change and wound

washing) treatments, as well as for rehabilitation.¹¹⁰ This allows the patient some distraction from the pain of washing or exercise, allowing for improved participation and effort.¹¹¹ Additionally, we are attempting low-load resistance training in the ICU in order to begin the rehabilitation process sooner post burn. Currently, though, we begin early ambulation on the fourth day after operation when possible. For patients with 30% TBSA burn, patients are offered exercise regimens for 2-3 months post-discharge. The regimens consist of aerobic exercise 5 days a week at 75% VO₂ max, with additional isometric resistance training 3 times a week.

Pharmacologic agents

Insulin

Although insulin therapy has been used for decades in diabetic patients, intensive insulin therapy (IIT) in the ICU is a newer concept. IIT involves maintaining blood glucose concentrations to near fasting levels (90-120 mg/dL) as opposed to 160-180 mg/dL as typically seen in burn patients. Although we know that improving glucose control is beneficial in burn patients, maintaining euglycemia in critically ill patients through IIT while avoiding episodes of hypoglycemia is not trivial. Studies examining this issue set out to determine whether IIT was beneficial to patients in the ICU and whether it increased hypoglycemic episodes.

In a meta-analysis of studies focused on burn patients, it was evident that although IIT reduced the incidence of hyperglycemia, IIT also increased the incidence of hypoglycemia. In a trial of non-burned adults in the ICU, IIT increased mortality (NICE trial).¹¹² In contrast, in the context of burns, IIT was shown to improve mortality in children, with no effect on mortality in adults.¹¹³ In both adult and pediatric patients, no significant differences were noted in the length of stay with IIT. Although IIT was not found to be detrimental in the context of burns, as a consequence of the increased mortality seen with IIT in non-burned ICU populations, the use of IIT for tight glucose control has generally fallen out of favor in the United States.

Interestingly, insulin therapy (not IIT) has been shown to prevent proteolysis in both normal patients and trauma patients, and has demonstrated increases in lean body mass in burns.¹¹⁴ Furthermore, bone mineral density was also improved with insulin therapy, although total body weight after burn showed no overall improvement. Lastly, insulin was found to decrease the hepatomegaly associated with severe burn, decrease liver enzymes, and decrease inflammatory cytokines associated with these injuries.³⁶ Overall, insulin therapy seems to be safe as well as effective in terms of glucose control and restoring body composition in patients with burns.¹¹³

Metformin, Exenatide, and Fenofibrate

Data concerning the safety profile of insulin use to control glucose in the ICU has led researchers to explore other agents to manage hyperglycemia with fewer incidents of hypoglycemia. Burn patients specifically are prone to hypoglycemia with cases occurring fairly suddenly in association with ileus at our institution. These agents have been pursued

as alternatives to insulin therapy in the hope of causing fewer hypoglycemic episodes. Even with the relative paucity of information, there are some promising preliminary reports. For example, metformin has been shown to be beneficial in decreasing blood glucose concentration in both fed and fasted burn patients, while also decreasing the length of stay for patients.^{115, 116} Seven days of metformin administration demonstrated increased muscle protein synthetic rate from control group where insulin (3-hour insulin clamp) did not significantly increase synthesis. Muscle protein synthetic rate also increased synergistically when metformin and Insulin were combined. On the other hand, no differences were noted in the muscle energy availability (by ATP concentrations), or serum insulin levels from control.¹¹⁵ Metformin appears mostly to decrease hepatic gluconeogenesis while increasing peripheral glucose utilization, with a larger effect on hepatic gluconeogenesis.¹¹⁶ In terms of hypoglycemic events, Jeschke and colleagues demonstrated a 15% incidence with insulin treatment targeting a blood glucose concentration of 130 to 140 mg/dL vs. 6% incidence with metformin administered 500 to 1000 mg twice daily.¹¹⁷

In addition to a potential benefit of metformin in controlling burn-induced hyperglycemia, a small study has shown that GLP1 analogue exenatide, an insulin secretagogue, may be as beneficial as insulin in controlling blood glucose levels in burned children. Indeed, exenatide decreased the necessity of exogenous insulin to control blood glucose in burned children but hypoglycemic events were not significantly reduced, albeit the patient group was small.¹¹⁸

Treatment with Fenofibrate, a peroxisome proliferator activated receptor α (PPAR- α) agonist, may also improve insulin sensitivity in burned children. Cree and colleagues showed that whole body glucose uptake was increased compared to a placebo in patients receiving fenofibrate for 2 weeks.¹¹⁹ Interestingly, there were increases in whole-body fatty acid oxidation as one would expect, but this study was unable to find any significant changes in muscle triglycerides or liver triglycerides with treatment.¹²⁰ Therefore, although the fatty acid oxidation was increased, the serum and intracellular triglyceride levels remain unchanged and so the benefit of fenofibrate in burns for decreasing free fatty acid and triglyceride levels may be limited. The combined use of a beta-blocker and fenofibrate may be an exciting avenue to pursue in terms of reducing muscle and liver lipid delivery while concurrently driving fatty acid oxidation. Currently due to lack of evidence we do not recommend metformin, exenatide, or fenofibrate due to the paucity of data and lack of multi-centered trials and, therefore, we continue to use insulin sliding scales or insulin drips for targets of 140 to 220 mg/dL, starting treatment for glucose concentrations above 180 mg/dL.

Propranolol

Since catecholamines are one of the major mediators of burn hypermetabolism, beta blockade has been studied extensively as a means to quench the adrenergic stress accompanying a large burn. The major therapeutic effects of propranolol after burn are decreased heart rate, rate pressure product (systolic blood pressure X heart rate), and cardiac work. These changes were not accompanied by decreases in systolic or diastolic blood pressure, and, therefore, it appears that in burn patients it makes a more efficient cardiac pump. It does appear that the body begins to compensate to these adjustments as the

propranolol dose needed to maintain a similar (15%) decrease in heart was higher after 10 days.^{121, 122}

By preventing downstream reactions to adrenergic surge, propranolol decreased rates of glycerol and free fatty acid appearance, but did not have an apparent effect on gluconeogenic-glycolytic cycling or on total glucose production.³¹ This response appears to be mediated via antagonism of β_2 adrenoreceptors, since the β_1 selective blocker metoprolol had no effect on lipolysis.¹²³ Beta-blockade also decreased hepatic fatty acid deposition there by decreasing hepatomegaly and steatosis, which is in agreement with observations that catecholamines appear to influence fatty acid cycling more so than glucose metabolism in burned patients. That being said, in a meta-analysis, propranolol administration was shown to decrease insulin resistance, highlighting that gluconeogenic blunting by beta-blockade occurs, just at a lesser extent than lipolysis.¹²⁴ In regards to protein metabolism, propranolol has shown to improve leg nitrogen balance,¹²⁵ although whether this response is mediated by a direct effect on muscle tissue or via indirect effects (e.g., propranolol effect on blood flow) remains unknown. Lastly, no studies to date have shown a mortality benefit to propranolol administration in burn patients.^{124, 126} It is important to note that the majority of patients in propranolol studies are pediatric patients and safety and efficacy in adult patients remains to be confirmed. With regard to cost, propranolol is very cheap and is a feasible option even in third world countries.

In our institution, we currently use propranolol as standard of care in the pediatric population, with a target decrease in heart rate of 15% to 20%, and a dosing range of 1.0 mg/kg/day based on benefits described by our group and others of bringing heart rate near normal for age. These doses are held if the patient shows signs of hypotension, bradycardia, bronchospasm, and other similar circumstances in which propranolol maybe be detrimental, and resumed as soon as this circumstance has resolved. Currently, we cannot recommend propranolol in adults, and multi-centered trials are currently undergoing attempts to show benefit or harm in this population.

Ketoconazole

Ketoconazole, an anti-fungal, has been shown to antagonize glucocorticoid receptors and decrease cortisol synthesis in healthy individuals and those with Cushing disease.¹²⁷ Logically, then, blunting the glucocorticoid response in burns may be beneficial in burn patients. In one pediatric burns study, there were no improvements in cytokines, length of stay, infection rates, protein catabolism, or catecholamine levels.²⁰ In a separate study of burned adults, ketoconazole showed net increases in muscle protein synthesis.¹²⁸ These mixed results in the literature pertaining to the efficacy of ketoconazole may be due to the fact that urinary cortisol levels did not completely reach non-burn levels. Therefore, a larger effect may be seen with a more specific glucocorticoid receptor antagonist or even in a larger study.²⁰

Anabolic steroids

Circulating androgen levels are decreased after-burn (beginning at 3-4 weeks) while glucocorticoids are increased.¹²⁹ Additionally, anabolic agents displace cortisol from

glucocorticoid receptors in vitro.^{130, 131} Because of this, anabolic agents may show promise in terms of mitigating the metabolic stress response to burns by decreasing cortisol binding and thus preventing muscle catabolism (via insulin like growth factor 1). Oxandrolone has been used more often than any other anabolic agent in burns due to its safety profile. The beneficial effects of oxandrolone in burned children appear to be mediated through increased protein anabolism in muscle.¹³² Clinically, oxandrolone therapy showed significant improvements in growth stunting; this was demonstrated by decreasing the percentage of patients who were 2 standard deviations below the mean height for age, from 48% to 7% at 1-year follow-up after burn.¹³³ It is important to note that the majority of changes in mass were through increases in lean body mass as opposed to adipose tissue, so the impact of oxandrolone on body composition after burn is likely a functional one.^{133, 134} Muscle strength measurements support this idea, where muscle strength was increased in children receiving oxandrolone compared to those who did not.¹³³ Lastly, a meta-analysis concluded that oxandrolone treatment significantly decreased the length of stay by 6 days in burned patients.¹³⁴ Anabolic agents show promise in terms of blunting the acute metabolic response to burns as well as promoting long-term recovery, but multi-centered long-term studies are required to adequately assess the efficacy and safety of oxandrolone as an adjunct therapy for burns. Specifically, detrimental cardiac effects have been seen with these agents when abused and therefore the proper dosing and timing of administration must be guaranteed in order to avoid this and other complications noted in studies outside of the burn field.

Currently, we believe that larger multi-center trials are needed to show true benefits of using oxandrolone after burn. At our facility for research we use 0.1 mg/kg for oxandrolone in pediatric patients and have noted few side effects (which included 2 cases of clitoromegaly) with otherwise good results.

Human Growth Hormone

Recombinant growth hormone has also been used as an anabolic agent. Insulin like growth factor (IGF-1) and IGF binding protein-3 are decreased significantly after-burn and in one study remained low all the way out to 9 months before returning to normal.^{15, 135} Similar to the other anabolic agents used, growth hormone has some adverse effects with the most prominent being a doubling of the incidence of hyperglycemia.¹³⁶ Growth hormone has also shown promise in terms of wounds and donor sites healing, decreased mortality, decreased septicemia, and decreased length of stay in a Cochrane review.¹³⁶ One of the major limiting factors in the usage of growth hormone is pricing. Whereas oxandrolone is approximately \$360 for 60 pills, human growth hormone prices can reach up to \$1,000 per injection.¹³⁷

Currently, we no longer use growth hormone in adults, due to the fact that growth hormone has been shown to increase mortality in critical care studies. Therefore, our current studies are now focused on pediatric patients only.

Conclusion

Overall, the minimization of burn hypermetabolism has taken great strides, and several pharmaceutical agents, dressings, and interventions are at the stage of decreasing hypermetabolism. As with most of medicine, there has yet to be a magic bullet to solve the

problem of hypermetabolism, and there very well may never be. For now, the current agents must be run through multi-center trials in order to ensure long-term safety, and to decide where their efficacy is best served, and specifically which age groups can benefit the most. The ideal solution to hypermetabolism would be an early intervention that prevents the initial neurologic cascade, something that “masks” the fact that the body is injured without decreasing the ability of the immune system to combat subsequent infections. The current problems lie in minimizing the detrimental effects of hypermetabolism and catabolism, while improving the ability of the immune system to react without harm to self. As technologies continue to advance, and studies continue to fine tune efficacies and safety of various interventions, the hypermetabolic state will be further minimized.

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Figure 1:

Simulation of the overall timeline of the hypermetabolic response, with the ebb phase occurring in the first 1-3 days, and the flow phase occurring subsequently, and resolution (depending on which hormone/aspect is examined) occurring at some point during the next 2 years.

Figure 2:
Abdominal X-ray demonstrates severe hepatomegaly 60 days after burn in a pediatric patient with 90% total burn surface area.

Figure 3: Variation in metabolic rate (REE measured by indirect calorimetry) at room temperature (22°C) by percentage of total body surface area burned.⁶⁶ (Adapted from: Kelemen JJ, 3rd, Cioffi WG, Jr., Mason AD, Jr., Mozingo DW, McManus WF, Pruitt BA, Jr. Effect of ambient temperature on metabolic rate after thermal injury. *Ann Surg.* 1996;223(4):406-412).

Table 1:

The metabolic response in specific aspects of burn hypermetabolism significantly elevated from control over time.¹⁵

Aspect of Burn Hypermetabolism	Duration of Significant Elevation
Catecholamines	2-6 Months
Cortisol	36 months
IL-5, IL-6, IL-8, TNF	6-9 months
IL-7, IL-10, MIP-1b MCP-1	36 months
Resting Energy Expenditure	18 months
Glucose	6-9 months
Insulin	36 months – Lag phase of 6-9 months
C-Peptide	36 months
IGF-1, and IGF binding protein-3	2 months - Depression

Table 2:

Historical comparison of percent total body surface area (TBSA) burn resulting in 50% mortality (Lethal Area₅₀).⁶⁵

Year	First Author (Country)	Patient Age (Years)							
		0-14		15-44		45-64		65	
		N	%	N	%	N	%	N	%
1949	Bull (UK)	342	51	311	43	95	23	46	9
1954	Bull (UK)	1,366	49	967	46	330	27	144	10
1956	Schwarz (US)	-	-	480	65	-	-	-	-
1957	Barnes (US)	217	39	221	65	219	39	128	26
1964	Pruitt (US)	238	49	806	56	56	29	-	-
1971	Bull (UK)	962	64	565	56	246	40	149	17
1980	Cuerri (US)	232	63	413	63	178	38	114	23
1987	Herndon (US)	875	95	612	76	132	46	52	19
2018	Herndon (US)	5,524	98%	3,154	95%	1,267	70%	439	40%

(With permission from Capek KD, Sousse LE, Hundeshagen G, et al. Contemporary burn survival. *J Am Coll Surg* 2018;226(4):453-463).