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In-Brief

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Hypermetabolism remains a significant clinical problem after burn. Every organ system is transformed metabolically in response to an extensive burn. With long-term consequences including cardiac dysfunction, growth arrest for nearly a year after burn, and high incidence rates of depression, anxiety, and post-traumatic stress disorder (PTSD), the metabolic changes clearly have far reaching and long lasting detrimental effects.

After burn, the loss of the thermoregulatory epidermal/dermal layers prevent appropriate temperature homeostasis. Although heat loss and water losses occur from the patient's wounds, the majority of losses come from radiative loss. Evaporative losses can occur, which are about 4 times greater in second-degree burns than normal, and 3 times greater than normal in full thickness burns. Therefore, a burn patient may need an extra liter of water solely from the evaporative losses after burn, not including further losses from osmotic pull due to exudative losses in the wounds. So far gone is temperature homeostasis in burn that heat loss is transferred from typical heat-generating measures such as teeth-chattering and shivering to a thermogenic cellular heat generation, mostly due to aerobic uncoupling.

Mediators of burn are many, but certain culprits take center stage. After burn, glucocorticoids increase 3- to 10-fold and can remain elevated for more than 3 months after initial injury. Similar to Cushing's syndrome, these increases have detrimental effects to peripheral muscle fibers, leading to proteolysis and central adipose accumulation. Although

it is believed that many effects from burn are mediated by glucocorticoids, the blunting of the glucocorticoid receptors with ketoconazole has little to no effect in stopping this metabolic derangement.

Catecholamines are also increased 4- to 10-fold after burn and are elevated for a longer period of time, with epinephrine remaining elevated for 60 to 100 days after-burn and norepinephrine remaining elevated between 100 days and 2 years after-burn. Although glucocorticoids have a larger effect on glucose metabolism, catecholamines have a larger effect on fatty acid metabolism, causing lipolysis and triglyceride cycling, with the long-term effects of triglyceride deposition in the liver and increased plasma cholesterol levels.

Metabolic problems occur in all of glucose, fatty acid, and amino acid metabolic arenas. For glucose metabolism, the area of injury immediately stopped after burn and glucose uptake in those regions remain suppressed for approximately 24 hours. After this, the glucose uptake not only returns to normal, it soars to 3 to 4 times higher than in normal soft tissues. For whole body glucose metabolism, although cellular glucose uptake is significantly elevated after burn, there remains an increased cellular flux of glucose as well, due in part to a lack of responsiveness from beta cells in the pancreas (possibly due to IL-1β), but also decreases in post insulin-receptor cascades, leading to an overall insulin resistance and high glucose concentrations in the plasma. This insulin resistance can persist as long as 2 years after initial injury. Additionally, glucagon release, which is tightly linked to the sympathetic nervous system, is often increased after burn, leading to further hyperglycemia. Glucagon has also been shown to stimulate thermogenesis in brown adipocytes of rodents and to activate hormone-sensitive lipase for lipolysis to occur.

Glucagon, in addition to various other mediators, causes an increase in lipolysis, leading to increased free fatty acid and glycerol release into the bloodstream. Increased hepatic reesterification of these fatty acids with no net increase of beta-oxidation leads to a net accumulation of lipids, causing clinical hepatomegaly and steatosis. In addition to breakdown of white fat, burn also causes a browning of adipose tissue, which allows for increased thermogenesis and possibly heat production. This partially brown (beige) fat has increase UCP1 function and allows for uncoupling of the electron transport chain in the mitochondria of the adipocytes.

Lastly, due to the increased glucose requirements for tissue repair and immunologic response after burn, the amino acid stores of skeletal muscle begin to break down. The amino acids are then transported to the liver for gluconeogenesis and utilization of this energy for damaged tissues. This breakdown can occur long term with one study showing breakdown until 9 months after injury, leading to massive losses of lean body mass, specifically in the underutilized upper extremities. Losses can be between 7% and 17% of lean body mass in the extremities and are due to various factors including: increasing age, male sex, increasing height, increasing total body surface area (TBSA), increasing creatinine, increasing resting energy expenditure (REE), and (most importantly) a diagnosis of sepsis.

Improvement in the understanding of burn hypermetabolism and its consequences has allowed burn mortality to decrease drastically in the last half century. That being said, although mortality has improved, the other sequelae of burns, namely hypertrophic scarring, joint contractures, and psychological disorders, still plague the burn patient.

One of the more subtle treatments of burn injury, but possibly one of the most vital, is temperature regulation. As the thermoregulatory barriers are diminished after burn, maintaining the external environment at 30°C to 33°C may decrease patient's REE by up to 22%. This is considered an optimal range, since increasing from 32°C to 35°C has no further effect on REE. Temperature regulation becomes even more important during operative periods where anesthesia blunts any shivering or gross thermogenesis that patients may have had otherwise. We recommend maintaining operating room temperatures between 29°C and 32°C with thermostat regulation, heat lamps, or any other methods available in order to maintain core body temperature at 37.5°C.

The mobilization of nutrients to damaged tissues and the immune response after burn necessitates an increase in caloric intake to attempt to maintain homeostasis. Caloric needs not only increase by between 20% to 60% but increased caloric intake still may not be sufficient to prevent catabolism. Burn patients are unique in that high-carbohydrate diets are needed in order to blunt protein catabolism; diets high in carbohydrates and low in fat have been shown to decrease pneumonia incidence and slow muscle catabolism in burns with no effect on mortality. The current ESPEN guidelines recommend 55% to 60% from carbohydrates, 20% to 25% from proteins, and 20% to 25% from fats. Protein targets should be 1.5 to 2.5 g/kg/day in adults and 1.5–3.5 g/kg/day in children. Evidence in most other portions of the nutrition literature is not sufficient enough to recommend any additional supplements such as glutamine or vitamin A, C, D, or E, although some studies show benefit. For example, vitamin C has been shown to decrease the severity of infection, decrease fluid resuscitation, and improve immune function while vitamin E has been shown to improve wound healing and immune system capabilities. At our facility, we utilize the Galveston formula at 1500 kcal/m2 body surface area (BSA) baseline with an extra 1500 kcal/m2 total body surface area (TBSA) affected by burn, as well as frequent REE measurements by indirect calorimetry. 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). We also utilize daily goals for feeding instead of hourly rates, in order to prevent losses/stoppages due to operations. We supplement vitamin E at 10 IU/kg/day forpatients 0 to 18 years of age and 15 IU/kg/day for patients older than 18 years. For vitamin C, we supplement 250 mg PO daily for 0 to 11 years of age, and 500 mg for those older than 12 years of age. We also supplement zinc sulfate at 55 mg daily for 0 to 2 years of age, 110 mg for patients 3 to 11 years of age, and 220 mg for patients older than 12 years of age. Lastly, we give 1 mg folic acid 3 times weekly. Depending on the situation, multivitamins or additional micronutrients are given as needed only.

Early excision and grafting in larger burn wounds are vital for rapid improvement of the patient. Defined as wound excision within the first 24 to 48 hours, early excision has shown to decrease sepsis rates, improve mortality (in burns over 50% TBSA), and improve long-term net protein balance. By possibly leading to a faster metabolic recovery, early excision

and grafting may decrease the hypermetabolic state after burn and decrease the time allowed for opportunistic infections to occur. For second degree burns, occlusive dressings have also shown benefit. For example, Integra (Integra Lifesciences, Plainsboro Township, NJ) was shown to decrease REE and improved scarring compared to cadaveric grafting. Occlusive dressings may also be beneficial in that they save operative time, decrease procedural costs by half, and assist with thermoregulation. At our institution, if the burn wounds are contaminated, then homograft (cadaveric) is used. 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. Weekly operations as needed using 2:1 autografting are then done until wound closure. For second degree burns, we are now using Mepilex® (Mölnlycke Health Care, Gothenburg, Sweden) or similar occlusive dressings.

To attempt to minimize muscle catabolism, various 6 to 12 week exercise regimens, including aerobic and aerobic plus resistance, have been attempted. These 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) after burn. Although results vary widely between studies, exercise has been shown to decrease the need for repeat contracture release operations. The difficulty of exercise lies in graft fragility, wound healing, and pain, thus delaying initiation of exercise until damage to skeletal muscle fibers has already been done. Therefore, although we recommend a multi-modality approach for physical/occupational therapy and a 2 to 3-month exercise regimen after discharge, new methods to begin exercise even earlier such as very low load resistance training, may need to be researched in order to stop catabolism sooner or even to prevent it.

For most of the metabolic changes that occur after burn, there has been an attempt to diminish these changes by a pharmacologic agent. For glucose metabolism, insulin has taken a swing on the pendulum from mild to intensive glycemic control and has now swung back to a mild to moderate approach of maintaining glucose levels under 160 mg/dL. Because of the hypoglycemic events associated with insulin administration, other glucose control agents have been explored with promising early results. Metformin, for example, was shown to increase the muscle protein synthetic rate, improve glucose control, and have fewer hypoglycemic events than insulin. Fenofibrate has also been shown to improve insulin sensitivity by increasing cellular glucose uptake after 2 weeks of use with surprisingly little effect on triglyceride levels.

To assist in prevention of the catecholamine cascades, propranolol has also been attempted. With decreases in heart rate and no subsequent decreases in systolic or diastolic pressures at low doses, propranolol appears to create a more efficient cardiac pump after burn. Additionally, beta-blockade decreases peripheral lipolysis and hepatic fatty acid deposition. Additionally, it has been shown to decrease insulin resistance, although the effects on glucose metabolism appear to be more subtle than fatty acid metabolism. We currently use propranolol as a standard of care at our institution for pediatric patients with a targeted heart rate decrease of 15% of baseline after injury (24–48 hours). Doses are held if the patient shows any signs of hypotension, bradycardia, or bronchospasm, although these are rare from our experience. We cannot recommend the use of propranolol for adult burn patients at this time.

For protein metabolism, anabolic agents have been attempted to varying degrees. Since the major adverse effects of anabolic agents are often virilization, we use oxandrolone due to its low androgenic and high myogenic potential. Oxandrolone has been shown to assist in growth stunting in pediatric patients, reducing the number of patients who were 2 standard deviations below the mean from 48% to 7% one year after burn. Additionally, oxandrolone was shown to decrease length of stay by 6 days in a meta-analysis. 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; therefore, the proper dosing and timing of administration must be guaranteed in order to avoid long-term adverse effects. Similarly, recombinant growth hormone has been used to increase the insulin-like growth factor (IGF-1) and IGF binding protein-3 levels to normal levels after burn. Although it initially demonstrated benefit by improving wound healing, and decreasing septicemia, the price, hyperglycemia, and increased mortality in adults have plagued this agent. Overall, the minimization of burn hypermetabolism has taken great strides, and several pharmaceutical agents, dressings, and interventions are at the stage of decreasing hypermetabolism and improving outcomes. Much work still must be done in order to prevent or stop burn hypermetabolism before it begins instead of attempting to slow the flood.

Biography

Christian Sommerhalder, MD, MMS, is a Resident in General Surgery at the University of Texas Medical Branch in Galveston, Texas. He was formerly a post-doctoral fellow in the laboratory of Dr. Herndon at the Shriners Hospitals for Children in Galveston, Texas. He completed his bachelor’s degree in biology at the University of Texas at Dallas and graduated from medical school at Ross University.

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Andrew J. MUrton, PhD, is Assistant Professor in the Department of Surgery at the University of Texas Medical Branch in Galveston, texas. He received a bachelor’s degree in biochemistry and a PhD in skeletal muscle metabolism from the University of Nottingham. His research is focused on understanding the metabolic and molecular basis of muscle cachexia seen in response to critical illness, including severe burn trauma.

Celeste Finnerty, PhD, is Professor of Surgery at the University of Texas Medical Branch in Galveston, Texas and is the Associate Director of Research at the Shriners Hospitals for Children. She has mentored many burn research fellows.

David Herndon, MD, is formerly the Director of Research and Chief of Staff at Shriners Hospitals for Children in Galveston, Texas. He has served as the President of the International Society for Burn Injuries, American Burn Association, Society of University Surgeons, and the Singleton Surgical Society. He has received many awards in the burn field and has trained more than 170 post-doctoral fellows.