Introduction

The number of burn injury victims in the United States is estimated to be 1.2 million per year, with an annual incidence of 2 million fire accidents reported. Among these injuries, 75% are considered mild, treated on an outpatient basis, while on average 50,000 burn patients require admission to a hospital or major burn center.

Despite a considerable decrease in the incidence of burns in the developed world, they remain one of the commonest forms of injury, accounting for a significant proportion of trauma cases in hospital emergencies worldwide, and they continue to cause devastating morbidity and mortality.

The distressing consequences of burns have been recognized by the medical community, and significant amounts of resources and research have been dedicated to successfully improving these dismal statistics. Recent reports revealed a 50% decline in burn-related deaths and hospital admissions in the USA over the last 20 years. This is attributable to the effective prevention strategies that have been introduced to the practice, limiting burn-associated morbidities as well as reducing the number and severity of burns.

Local changes

Burn injury triggers coagulative necrosis of the different...
layers of the skin as well as the underlying tissues. The gravity of the damage is determined by the energy carried by the causative agent, the spell of exposure, in addition to the temperature to which the skin is exposed.

Thermal injuries are categorized based on their etiology and depth of injury. Causative agents include fire, scald and contact with hot/cold objects. They contribute to coagulative necrosis by inducing tissue damage through transfer of energy. Other causative agents include exposure to chemicals and conduction of electricity. In addition to transfer of heat, chemical and electrical burns also induce direct damage to cellular membranes. Thanks to its major function as a reliable barrier reducing heat transfer to underlying tissues, the skin usually restricts the propagation of damage into the deep layers; however, injury of underlying tissues still occurs secondary to local tissue responses. In principle, three zones can be identified at the site of cutaneous injuries:

1. Zone of coagulation: this zone confines the area of necrosis. It is characterized by irreversibly damaged tissues at the time of injury.
2. Zone of stasis: lying adjacent to the zone of coagulation, this area is subject to a moderate degree of damage associated with vascular leakage, elevated concentrations of vasoconstrictors as well as local inflammatory reactions resulting in compromised tissue perfusion. Depending on the wound environment, this zone can either survive or proceed into necrosis.
3. Zone of hyperemia: secondary to inflammation-induced vasodilation, this zone is characterized by increased blood supply with healthy tissues under no major jeopardy for demise.

**Systemic changes**

Burns exceeding 30% of total body surface area (TBSA) result in considerable hypovolemia coupled with formation and release of inflammatory mediators with subsequent systemic effect, namely a distinctive cardiovascular dysfunction known as burn shock. Burn shock is a complex process of circulatory and microcirculatory impairment as well as edema generation in both traumatized and non-traumatized tissues. Even with timely and adequate fluid support, this pathophysiologic state remains incompletely reversible. In fact, burn shock involves an anomalous condition of inadequate tissue perfusion with resultant insufficient oxygen and nutrient delivery as well as failure to remove waste products from tissues. Despite proper fluid resuscitation and adequate preload, pulmonary and systemic vascular resistances are increased and myocardial depression follows. This, in turn, will stimulate further exacerbation of the inflammatory response and contribute to the risk of organ failure.

A typical immediate response after a thermal insult is plasma extravasation followed by a sequence of hemodynamic events. The most common hemodynamic changes include diminished plasma volume, cardiac output and urine output as well as increased systemic vascular resistance (SVR) with resultant reduced peripheral blood flow. Unlike in hemorrhage, burn insults are associated with an increase in hemoglobin and hematocrit.

Edema formation is another characteristic reaction of burn injuries. As the ratio of fluid filtered out of microvessels to fluid entering them becomes more than 1, edema is developed. The process of edema formation is biphasic. Initiated in the first hour following burn trauma, the primary phase witnesses an abrupt increase in the water content of traumatized tissues. The second phase involves a more gradual increase in fluid flux of both burned and intact skin and soft tissues 12-24 hours post-burn.

Of significant importance is the rapidity of tissue water content increase. Double the original volume is usually reached during the first hour, with 90% of this change observed in the initial few minutes. Whether fluid resuscitation is provided or not determines the amount of edema development. Following burn-induced plasma extravasation, additional extravasation occurs following resuscitation since fluid support increases blood flow and capillary pressure. On the other hand, the edema remains self-limited when no fluid is administered. In addition to the trauma type and extent, type and amount of administered fluid also play a key role in determining the volume of edema.

Thermal insults additionally have a major impact on cellular membranes. Cellular transmembrane potentials in skeletal muscles distant to the site of injury are subject to a systemic decrease when the burn size exceeds 30% of TBSA. Furthermore, it has been proven that both directly and indirectly traumatized cells experience tissue edema following cell membrane alterations and increased sodium and potassium fluxes. Cellular membranes in injured and intact skeletal muscles demonstrate partial depolarization of membrane potential from -90mV to -70mV and -80mV. As soon as the decrease in membrane potentials is initiated, water and sodium contents within cells increase. Those alterations are also seen in cases of hemorrhagic shock. Reports of similar changes encountered in cardiac, hepatic and endothelial cells have been published. The driving forces responsible for membrane depolarization have been a subject of debate. Some authors attribute membrane depolarization to a decrease in ATP and reduced ATPase activity. Others postulated increased sodium conductance in membranes and enhanced sodium-hydrogen antiport activity as the etiologies behind membrane depolarization. Several studies have been conducted aiming at identifying the factors responsible for the cellular edema seen in burn shock. It has been postulated that membrane depolarization could be attributed to the presence of unidentified complex circulating shock factor(s). This hypothesis has been supported by the failure of resuscitative measurements to fully restore membrane potential and intracellular sodium concentration to normal levels. By concluding that burn-associated tissue edema is not solely caused by hypovolemia, burn shock, thereby, should not be considered just as another form of hemorrhage.

Immense energy needs is a typical finding in victims of burns. Measured by resting energy expenditure, the metabolic rate reaches astronomical levels depending on the size of burn. The resting metabolic rates in mild burns (less than 10% TBSA) are quantified to be near normal levels. These rates rapidly increase to 2-fold of the basal rate in burns exceeding 40% of TBSA during acute admission. Following this curvilinear-fashioned increase, resting metabolic rate in severely burned patients starts to decrease progressively to reach 150% of the basal rate at the time of burn wound healing. Resting metabolic rates at 6, 9 and 12 months post trauma are calculated to be 140%, 120% and 110% of the basal rate respectively.

The hypermetabolic response has deleterious effects and
devastating sequelae at cellular and systemic level, as well as socio-economic consequences for the victim. The structure and function of essential organs (heart, liver, skeletal muscle, skin), the immune system and the cellular membrane transport system are compromised while wound healing is impaired, infection risk is increased, rehabilitation is hampered and reintegration of survivors back into society is delayed. Persistent hyperglycemia is explained by a significant and persistent rise in secretions of catecholamine, cortisol, glucagon and dopamine. Several factors have been identified to regulate metabolic response and alter glucose metabolism for up to 3 years after the initial insult. The list of these mediators includes interleukins (IL) 1 and 6, platelet-activating factor (PAF), tissue necrosis factor (TNF), reactive oxygen species (ROS) and complement cascades. These metabolic regulations have been found to occur in 2 phases: early and late. The ‘Ebb’ phase starts immediately following thermal injury. It lasts for three days with a characteristic hypermetabolic state associated with hypodynamic circulation, decreased oxygen consumption and hyper-glycemia. These variables later start to progressively increase until reaching the ‘Flow’ phase. This hypermetabolic phase lasts for up to 1 year.

In response to burn injury, alterations in metabolic pathways and pro-inflammatory cytokines promote the shift of muscle protein metabolism into a faster rate of degradation than synthesis. Significant net protein loss becomes evident in the form of negative whole-body and cross-leg nitrogen balance. Accelerated protein degradation contributes to a remarkable decrease in lean body mass (LBM) and muscle wasting associated with a decrease in strength and delay in rehabilitation. Several dysfunctions and impairments follow depending on the magnitude of LBM loss. While alterations in the immune system, increase in rate of infection and delay in wound healing are correlated with a 20% loss of LBM, inhibited cough reflexes, prolonged mechanical ventilatory requirements as well as increased risk for pneumonia and pressure ulcers are seen in patients who lose 30% of their lean body mass. When loss reaches 40%, the mortality rate varies between 50-100%.

Energy substrate metabolism is also modified as a result of the metabolic changes seen in severe burns. Glucose is consumed through anaerobic pathways with resultant high lactate production. Patients with severe burns experience increased glucose production, particularly from alanine. Amino acids become the main fuel for glucose generation through gluconeogenesis, leaving very few of them involved in their original function as building blocks of body protein. Nitrogen excretion, primarily in urea, increases and the body becomes short of protein storage. An important finding observed in patients with severe burns is the development of insulin-resistance. Despite a 2-fold increase in insulin levels, plasma glucose levels remain significantly elevated, reaching up to 180mg/dL. Persistent hyperglycemia is explained by an increase in gluconeogenic substrates, attenuation of the suppressive effect of insulin on hepatic glucose release, enhanced hepatic glycogenolysis, and impaired glucose disposal. Gluc- erol, alanine and lactate are gluconeogenic substrates that are increased in burns secondary to enhanced adipose tissue lipolysis and skeletal muscle proteolysis. Glycogenolysis enhancement, in burns, is secondary to the direct effect of sympathetic stimulation as well as catecholamine.

Cardiac function is subject to several modifications starting at the time of injury. Before any plasma volume reduction is detected, receptors on thermally affected skin induce a neurogenic response initiating a rapid cardiac output depression. This is associated with an initial reduction followed by a remarkable increase in cardiac index starting on the third day. Other common findings include long-term increase in cardiac work, myocardial oxygen consumption and heart rate, which remain elevated during the recovery period. As cardiac stress becomes massive, myocardial depression ensues. Fluid resuscitation usually fails to resume normal cardiac output. This persistent depression is justified by hypovolemia, high SVR, low venous return, and the effects of myocardial depressed substance.

The renal system is also affected following alterations in the cardiovascular system. Renal blood flow and glomerular filtration rate (GFR) are reduced secondary to hypovolemia, diminished cardiac output, and the effects of angiotensin, vasopressin and aldosterone. These alterations are usually translated in the form of oliguria as an early sign of renal compromise. Failure to promptly and adequately manage these cases may lead to acute tubular necrosis (ATN), renal failure and mortality.

As thermal trauma seldom spares the hepatic function, a severe burn affects expression of acute phase proteins. Both serum complement C3 and α2- macroglobulin levels experience an initial fall followed by a gradual rise over time. Substantial depletion of constitutive hepatic proteins is also prominent secondary to decreased production or accelerated consumption or loss. In addition, alterations in serum levels of triglycerides and free fatty acids are highlighted, both of which are significantly increased secondary to a decrease in fat transporter proteins rendering the liver susceptible for fatty infiltration and hepatomegaly with resultant increased risk of sepsis and burn mortality.

The effects of burns on the gastrointestinal system should not be underestimated, as demonstrated by mucosal atrophy, reduced absorptive capacity, and increased surface permeability. In proportion to burn size, apoptotic epithelial cell death occurs, stimulating bowel mucosa degeneration. Mucosal atrophy subsequently leads to several defects in the absorptive function of the digestive system, notably the uptake of glucose, amino acids as well as fatty acids. Brush border lipase activity is also disturbed. Increase in bowel permeability to macro-molecules is also noted following alterations in intestinal blood supply.

Endocrine response is among the systemic reactions exhibited by severely injured burn patients. Characterized by significant alterations in the hypothalamic-anterior-pituitary-peripheral-hormone axes, this response follows a biphasic pattern. Target-organ resistance is considered to be responsible for the low levels of effector hormones seen in the acute phase. In the long-term phase, on the other hand, decreased levels of target organ hormones are due to suppression at the level of the hypothalamus. Among the hormones actively involved at the onset of injury are catecholamine, glucagon and cortisol, collectively labelled as stress hormones. These hormones display an exponential increase in their levels, sometimes reaching 10-fold their normal values. The significance of such an upsurge resides in its influence on the cardiovascular system and the resultant fluid shifts that follow these changes. The stress hormones are thereby considered as the initiators of the hyper-
metabolic-catabolic and proteolytic-response. Subsequent to the initial stress-related hormonal response, alterations occur at several points in the hypothalamic-pituitary-organ axes. Growth Hormone – Insulin-Like Growth Factor-1 (GH-IGF-1) axis is considered as one of the essential axes to be affected in severe burns. Of significant importance is the fact that IGF-1 and Insulin-Like Growth Factor Binding Protein-3 (IGFBP-3) were found to be much more affected when compared to GH.\textsuperscript{92,93,94,95} During the acute post-burn phase, decrease in Thyroid Stimulating Hormone (TSH), Triiodothyronine (T\textsubscript{3}), Thyroxine (T\textsubscript{4}), Testosterone, Osteocalcin and Parathyroid Hormone (PTH) are also not uncommon.

Regarding the effects of burn on the male reproductive system, thermal insults commonly affect the histology of seminiferous epithelium with germ cell atrophy being the most typical change encountered followed by sloughing.\textsuperscript{96} The etiologies of germ cell apoptosis and alterations in spermatogenesis are multifactorial: scrotal temperature, hormonal reduction, systemic trauma and oxidative stress following under-perfusion.\textsuperscript{97,98,99,100} Depletion of testosterone concentrations in blood is occasionally attributed to the presence of testicular toxins. Reversing the deleterious effects of these toxicants can be achieved by the administration of free radical scavengers: i.e. ascorbic acid, which also reduces resuscitative fluid needs and complications.\textsuperscript{101,102}

Immunologically speaking, thermal insults exert a considerable effect, in terms of global depression, on the immune system, notably cellular immune responsiveness. The immunodeficiency seen in burn patients is thought to be due to attenuated expression of bone marrow Granulocyte Colony Stimulating Factor (G-CSF) receptors rather than decreased G-CSF levels.\textsuperscript{103} Although the loss of skin and the mechanical barrier it provides contributes to infection in burn patients, it has long been established that impaired immune mechanisms are key factors in post-burn bacterial, viral and fungal infections. Such vulnerabilities are attributed to qualitative and quantitative compromises in all components of the immune system.

**Burn metabolism management strategies**

To date, not a single therapeutic modality has been successful in completely reversing the complex reactions induced by a burn injury; nevertheless, several non-pharmacological and pharmacological strategies have been found to effectively modulate burn-associated metabolism.

So far, early excision and closure of the burn wound have been described as the greatest advancement in the management of patients with severe thermal injuries. In fact, this strategy remains the single most important management modality to decrease the rate of complications associated with severe burn injuries. Patients undergoing total excision and wound coverage with autograft and/or cadaveric skin within the initial 72 hours following severe thermal injury (50\% TBSA) have metabolic rates 40\% less than those with similar burn severity that are not excised and covered within a week.\textsuperscript{61} Furthermore, immediate excision and resurfacing have been found to offer additional advantages in terms of net protein loss, infection/sepsis rate and pain compared to delayed primary reconstructions.\textsuperscript{104,105,106} Compared to autografts, biosynthetic skin substitutes and human cadaver skin have demonstrated equal effectiveness in early reconstructions.\textsuperscript{107,108,109}

Since sepsis plays a major role in boosting burn-associated mortality and morbidity related to hypermetabolic response, every effort should be made to control the rate of sepsis by taking the appropriate measurements to prevent infection in burn patients.\textsuperscript{110}

Adequate nutrition and proper feeding are of utmost importance in the recovery process of burn patients. Unlike oral nutrition alone, continuous enteral usually succeeds in preserving total body weight and decreases hypermetabolic response in burn patients.\textsuperscript{111,112,113,114,115,116} Enteral feeding remains the gold standard nutrition for burn patients. It preserves gastrointestinal motility and reduces microorganisms’ translocation and sepsis. Should the patient have absolute contraindications for enteral feeding such as prolonged ileus and enteral nutrition intolerance or in cases where enteral feeding alone is not reaching the target caloric delivery, parenteral feeding can be considered. It is crucial that parenteral nutrition is avoided as much as possible due its reported adverse effects, namely immunosuppression, liver function impairment as well as increased mortality.\textsuperscript{117,118,119} Concerning the diet profile that best fits burn patients, several considerations should be taken into account that aim at maintaining lean body mass. Considering the high rates of amino acid oxidation in burn patients, protein synthesis can be stimulated and lean body mass can be maintained with a high protein, high carbohydrate diet which also increases endogenous insulin production.\textsuperscript{120}

Another conservative management action that helps diminish resting energy expenditure in patients with more than 40\% TBSA burn is raising the room temperature. This simple step elevates the patient’s core temperature, subsequently reducing body water evaporative loss.\textsuperscript{121}

Burn wound contracture is an inevitable sequel that remains with the patient throughout life if not treated properly. Its prevention, however, remains the most adequate management modality. This can be achieved with early, progressive physical therapy with specific regimens designed to improve body mass and muscle strength.\textsuperscript{122}

In an attempt to modulate burn-induced hormonal disequilibrium, several pharmacological therapeutic strategies have already been established. These can be classified into anabolic agents and anti-catabolic agents. The anabolic hormones include GH, insulin, IGF-1, oxandrolone and testosterone. The most important anti-catabolic agent remains pranproanolol, an adrenergic antagonist.

Recombinant human growth hormone (rhGH) has proved to modulate responses initiated by the burn in various ways. It reduces the hepatic acute phase response by increasing constitutive hepatic proteins, decreasing acute phase proteins and modulating cytokine expression.\textsuperscript{123,124} It also decreases donor site healing time,\textsuperscript{125} improves muscle protein kinetics, maintains muscular growth,\textsuperscript{126,127} stimulates protein synthesis and attenuates nitrogen loss after injury.\textsuperscript{128} However, treatment with rhGH has been associated with increased mortality rate in adult patients, thus restricting its administration.\textsuperscript{121}

On the other hand, it has been demonstrated that recombinant human IGF-1 and IGFBP-3 effectively improve muscle protein synthesis in catabolic patients with significantly less adverse effects compared to GH.\textsuperscript{128,129} These agents further enhance intestinal mucosal integrity in the severely burned pediatric population,\textsuperscript{130} attenuate muscle catabolism, and improve hepatic acute phase, the inflammatory response as well as the immune response. As the clinical use of GH is restricted, it appears that recombinant human insulin-like growth factor-1
resting energy expenditure, tachycardia and cardiac work.\textsuperscript{80,139} As a synthetic testosterone analogue, it restores serum testosterone levels with a resultant surge in anabolic gene expression in muscles as well as a decrease in protein breakdown.\textsuperscript{133,134,135} Oxandrolone was demonstrated to abate obligatory thermogenesis, introduced to the burn injury management protocol. Propranolol was also found to be influential in increasing lean body mass and decreasing urinary nitrogen loss and whole-body urea production. Moreover, reduced insulin resistance, peripheral lipolysis, hepatic acute phase response, fatty infiltration of the liver and skeletal muscle wasting were additional advantages offered by beta-adrenergic blockers.\textsuperscript{57,140,141}

With the destructive effects induced by elevated body concentrations of catecholamine, anti-catabolic agents have been introduced to the burn injury management protocol. Propranolol was demonstrated to abate obligatory thermogenesis, restoring energy expenditure, tachycardia and cardiac work.\textsuperscript{80,139} It was also found to be influential in increasing lean body mass and decreasing urinary nitrogen loss and whole-body urea production. Moreover, reduced insulin resistance, peripheral lipolysis, hepatic acute phase response, fatty infiltration of the liver and skeletal muscle wasting were additional advantages offered by beta-adrenergic blockers.\textsuperscript{57,140,141}

Conclusions

In response to thermal insult, the human body reacts in an immediate and complex manner by releasing stress hormones and inflammatory mediators that subsequently induce vasoconstriction, increase vascular permeability, reduce diuresis, alter cellular membrane function and impair cardiac contractility. Depending on the burn size, the outcomes of these responses include, but are not limited to, decreased intravascular volume, increased systemic vascular resistance, decreased cardiac output, end-organ ischemia and metabolic acidosis. This can further lead to systemic deterioration, multi-organ failure and death when early appropriate resuscitation is not provided.

Burn-associated catabolism cannot be completely reversed but may be manipulated by non-pharmacologic and pharmacologic means. Early burn wound excision and complete wound closure, prevention of sepsis, maintenance of the patient’s thermal neutrality, and graded resistance exercises during recovery are simple, safe, reliable and successful primary treatment strategies. Anabolic and anti-catabolic agents greatly reduce lean body mass loss and linear growth delay. Continuous administration of low-dose insulin, beta-blockers (propranolol), and synthetic testosterone analogue (oxandrolone) are still the safest and most cost-effective therapeutic modalities to date.

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