Pathophysiology of Burn Injury

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1 Introduction

Advances in therapy strategies, due to improved understanding of resuscitation, enhanced wound coverage, better support of hypermetabolic response to injury, more appropriate infection control and improved treatment of inhalation injury, based on better understanding of the pathophysiologic responses after burn injury have further improved the clinical outcome of this unique patient population over the past years [1]. This chapter describes the present understanding of the pathophysiology of a burn injury including both the local and systemic responses, focusing on the many facets of organ and systemic effects directly resulting from hypovolemia and circulating mediators following burn trauma.

2 Local Changes

2.1 Temperature and Time Effect

Local changes appear in the tissue when the amount of absorbed heat exceeds the body system's compensatory mechanisms. On a molecular level, protein degradation begins at a temperature of 40 °C. This degradation leads to alterations in cell homeostasis. This is reversible if the temperature is lowered. Starting at 45 °C proteins are permanently denatured. This is reflected by local tissue necrosis. The speed with which permanent tissue damage can appear is dependent on time exposed and temperature (Table 1).

Table 1 Time and temperature exposure to cause a burn injury

45–51 °C	Within minutes
51 und 70 °C	Within seconds
Above 70 °C	Less than a second

The depth and severity of the burn are also determined by the ability of the contact material to transfer heat, a factor referred to as the specific heat. This is especially important in scald and contact burns. The knowledge about the material type allows for a more accurate estimate of tissue damage.

Definition: Burn depth is determined by the time of exposure, the temperature at which the burn occurred, and the caloric equivalent of the burn media.

Another determinant of the severity of burn is the location of the burn wound and the age of the burn patient. The thickness of the skin layers increases from the age of 5 up to the age of 50. In elderly patients, the thickness starts to decrease at the age of 65. The epidermis can vary by location from 0.03 up to 0.4 mm. Clinically, the severity of burn injury can be categorized by the differ-

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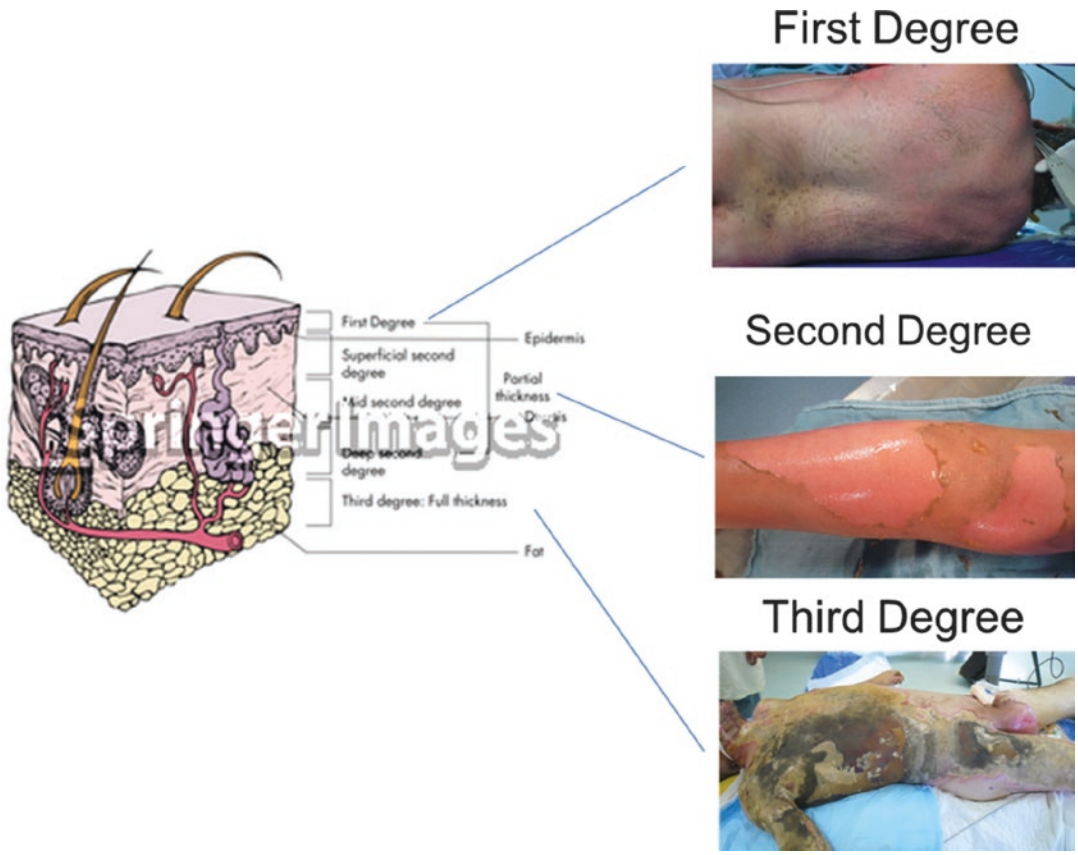

Fig. 1 Burn depth estimation based on appearance

ences in the tissue damage and is determined by the depth of the burn (Fig. 1).

1. **I degree: Superficial burn of the epidermis**
   First-degree burns are painful, erythematous, and blanch to the touch with an intact epidermal barrier. Examples include sunburn or a minor scald from a kitchen accident. These burns do not result in scarring, and treatment is aimed at comfort with the use of topical soothing salves with or without aloe and oral nonsteroidal anti-inflammatory agents.
2. **IIa degree: Burn including epidermis and superficial dermis**
3. **IIb degree: Burn including epidermis and deep dermis**
   Second-degree burns are divided into two types: superficial and deep. All second-degree burns have some degree of dermal damage, by definition, and the division is based on the depth of injury into the dermis. Superficial dermal burns are erythematous, painful, blanch to touch, and often blister. Examples include scald injuries from overheated bathtub water and flash flame burns. These wounds spontaneously re-epithelialize from retained epidermal structures in the rete ridges, hair follicles, and sweat glands in 1–2 weeks. After healing, these burns may have some slight skin discoloration over the long term. Deep dermal burns into the reticular dermis appear more pale and mottled, do not blanch to touch, but remain painful to pinprick. These burns heal in 2–5 weeks by re-epithelialization from hair follicles and sweat gland keratinocytes, often with severe scarring as a result of the loss of dermis.
4. **III degree: Burn including epidermis and dermis and subcuticular layer**
   Third-degree burns are full thickness through the epidermis and dermis and are characterized by a hard, leathery eschar that is

painless and black, white, or cherry red. No epidermal or dermal appendages remain; thus, these wounds must heal by re-epithelialization from the wound edges. Deep dermal and full-thickness burns require excision with skin grafting from the patient to heal the wounds in a timely fashion.

5. **IV degree: All dermal layers including fascia, muscles, and/or bones**

   Fourth-degree burns involve other organs beneath the skin, such as muscle, bone, and brain.

Currently, burn depth is most accurately assessed by judgment of experienced practitioners. Accurate depth determination is critical to wound healing as wounds that will heal with local treatment are treated differently than those requiring operative intervention. Examination of the entire wound by the physicians ultimately responsible for their management then is the gold standard used to guide further treatment decisions. New technologies, such as the multi-sensor laser Doppler flow meter, hold promise for quantitatively determining burn depth.

2.2 Etiology

The causes include injury from flame (fire), hot liquids (scald), contact with hot or cold objects, chemical exposure, and/or conduction of electricity. The first three induce cellular damage by the transfer of energy, which induces a coagulation necrosis. Chemical burns and electrical burns cause direct injury to cellular membranes in addition to the transfer of heat.

2.3 Pathophysiologic Changes

The area of cutaneous or superficial injury has been divided into three zones: zone of coagulation, zone of stasis, and zone of hyperemia. The necrotic area of burn where cells have been disrupted is termed the *zone of coagulation*. This tissue is irreversibly damaged at the time of injury.

The area immediately surrounding the necrotic zone has a moderate degree of insult with decreased tissue perfusion. This is termed the *zone of stasis* and, depending on the wound environment, can either survive or go on to coagulation necrosis. The zone of stasis is associated with vascular damage and vessel leakage [2, 3]. This area is of great importance as this area determines the injury depth of the burned skin. It is important to note that over-resuscitation and increased edema formation can increase the depth of burn and hence the zone of coagulation and fluids should not only be restricted to avoid pulmonary edema and abdominal compartment syndromes but also to minimize the progressive damage to the burned skin. Other means to attenuate the damage and prevent progression are antioxidants, bradykinin antagonists, and negative wound pressures also improve blood flow and affect the depth of injury [4–6]. Local endothelial interactions with neutrophils mediate some of the local inflammatory responses associated with the zone of stasis. Treatment directed at the control of local inflammation immediately after injury may spare the zone of stasis.

The last area is the *zone of hyperemia,* which is characterized by vasodilation from inflammation surrounding the burn wound. This region contains the clearly viable tissue from which the healing process begins and is generally not at risk for further necrosis.

2.4 Burn Size

Determination of burn size estimates the extent of injury. Burn size is generally assessed by the "rule of nines" (Fig. 2). In adults, each upper extremity and the head and neck are 9% of the TBSA, the lower extremities and the anterior and posterior trunk are 18% each, and the perineum and genitalia are assumed to be 1% of the TBSA. Another method of estimating smaller burns is to equate the area of the open hand (including the palm and the extended fingers) of the patient to be approximately 1% TBSA and then to transpose that measurement visually onto the wound for a determination of its size. This method is crucial when evaluating burns of mixed distribution. Children have a relatively larger portion of the body surface area in the head and

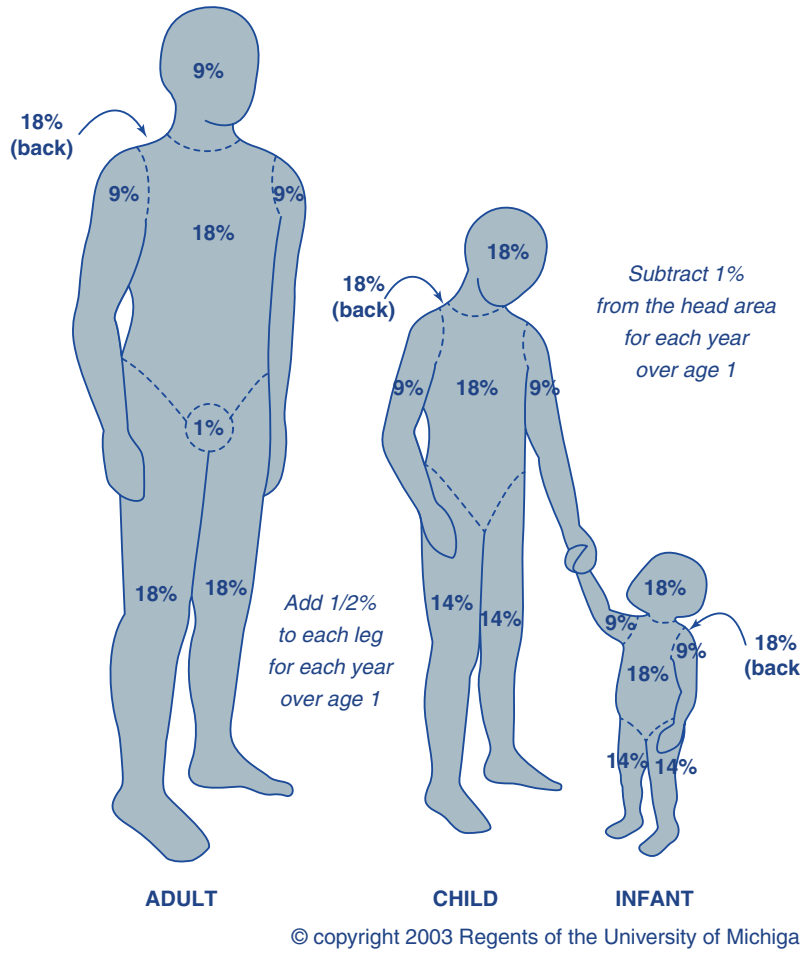

Fig. 2 Burn size estimation Lund Browder or rules of nines for adult patient and the Berkow formula for children

neck, which is compensated for by a relatively smaller surface area in the lower extremities. Infants have 21% of the TBSA in the head and neck and 13% in each leg, which incrementally approaches the adult proportions with increasing age. The Berkow formula is used to accurately determine burn size in children (Fig. 2).

3 Systemic Changes

3.1 Edema Formation

The release of cytokines and other inflammatory mediators at the site of injury has a systemic effect once the burn reaches 20–30% of total body surface area (TBSA) resulting in the severe and unique derangements of cardiovascular function called burn shock. Burn shock is a complex process of circulatory and microcirculatory dysfunction that is not easily or fully repaired by fluid resuscitation. Severe burn injury results in significant hypovolemic shock and substantial tissue trauma, both of which cause the formation and release of many local and systemic mediators [1, 7, 8]. Burn shock results from the interplay of hypovolemia and the release of multiple mediators of inflammation with effects on both the microcirculation and the function of the heart, large vessels, and lungs. Subsequently, burn shock continues as a significant pathophysiologic state, even if hypovolemia is corrected. Increases in pulmonary and systemic vascular resistance (SVR) and myocardial depression occur despite adequate preload and volume support [9–12]. Such cardiovascular dysfunctions can further

exacerbate the whole-body inflammatory response into a vicious cycle of accelerating organ dysfunction [1, 9–12].

Burn injury causes extravasation of plasma into the burn wound and the surrounding tissues. Extensive burn injuries are hypovolemic in nature and characterized by the hemodynamic changes similar to those that occur after hemorrhage, including decreased plasma volume, cardiac output, urine output, and an increased systemic vascular resistance with resultant reduced peripheral blood flow [1, 9–12]. However, as opposed to a fall in hematocrit with hemorrhagic hypovolemia due to transcapillary refill an increase in hematocrit and hemoglobin concentration will often appear even with adequate fluid resuscitation. As in the treatment of other forms of hypovolemic shock, the primary initial therapeutic goal is to quickly restore vascular volume and to preserve tissue perfusion in order to minimize tissue ischemia. In extensive burns (>20–30%TBSA), fluid resuscitation is complicated not only by the severe burn wound edema, but also by extravasated and sequestered fluid and protein in non-burned soft tissue. Large volumes of resuscitation solutions are required to maintain vascular volume during the first several hours after an extensive burn. Data suggests that despite fluid resuscitation normal blood volume is not restored until 24–48 h after large burns.

Edema develops when the rate by which fluid is filtered out of the microvessels exceeds the flow in the lymph vessels draining the same tissue mass. Edema formation often follows a biphasic pattern. An immediate and rapid increase in the water content of burn tissue is seen in the first hour after burn injury [13–15]. A second and more gradual increase in fluid flux of both the burned skin and non-burned soft tissue occurs during the first 12–24 h following burn trauma. The amount of edema formation in burned skin depends on the type and extent of injury and whether fluid resuscitation is provided as well as the type and volume of fluid administered. However, fluid resuscitation elevates blood flow and capillary pressure contributing to further fluid extravasation [14, 15]. Without sustained delivery of fluid into the circulation edema fluid is somewhat self-limited as plasma volume and capillary pressure decrease. The edema development in thermal injured skin is characterized by the extreme rapid onset of tissue water content, which can double within the first hour after burn [14, 15]. Leape and colleagues found a 70–80% water content increase in a full-thickness burn wound 30 min after burn injury with 90% of this change occurring in the first 5 min [16]. There was little increase in burn wound water content after the first hour in the non-resuscitated animals. In resuscitated animals or animals with small wounds, adequate tissue perfusion continues to "feed" the edema for several hours. Demling and others used dichromatic absorptionmetry to measure edema development during the first week after an experimental partial-thickness burn injury on one hind limb in sheep [14]. Even though edema was rapid with over 50% occurring in the first hour, maximum water content did not occur until 12–24 h after burn injury.

3.2 Hemodynamic and Cardiac Changes Post-Burn

The cause of reduced cardiac output (CO) during the resuscitative phase of burn injury has been the subject of considerable debate. There is an immediate depression of cardiac output before any detectable reduction in plasma volume [9, 10]. The rapidity of this response suggests a neurogenic response to receptors in the thermally injured skin or increased circulating vasoconstrictor mediators. Soon after injury, a developing hypovolemia and reduced venous return undeniably contribute to the reduced cardiac output. The subsequent persistence of reduced CO after apparently adequate fluid therapy, as evidenced by a reduction in heart rate and restoration of both arterial blood pressure and urinary output, has been attributed to circulating myocardial depressant factor(s), which possibly originates from the burn wound. Demling and colleagues showed a 15% reduction in CO despite an aggressive volume replacement protocol after a 40% scald burn in sheep [15]. However, there are also sustained increases in catecholamine secretion

and elevated systemic vascular resistance for up to 5 days after burn injury [12, 17]. We recently conducted two clinical studies measuring CO and SVR in severely burned patients and showed that CO fell shortly after injury and then returned toward normal; however, reduced CO did not parallel the blood volume deficit [9, 10]. We concluded that the depression of CO resulted not only from decreased blood volume and venous return, but also from an increased SVR. Thus, there are multiple factors that can significantly reduce CO after burn injury. However, resuscitated patients suffering major burn injury can also have supranormal CO from 2 to 6 days post-injury. This is secondary to the establishment of a hypermetabolic state [9, 10].

Immediately post-burn patients have low cardiac output characteristic of early shock [18] However, 3–4 days post-burn, cardiac outputs are greater than 1.5 times that of non-burned, healthy volunteers [9–11]. Heart rates of pediatric burn patients' approach 1.6 times that of non-burned, healthy volunteers. Post-burn, patients have increased cardiac work [19, 20]. Myocardial oxygen consumption surpasses that of marathon runners and is sustained well into rehabilitative period [19, 21].

Myocardial function can be compromised after burn injury due to overload of the right heart and direct depression of contractility. Increases in the afterload of both the left and right heart result from SVR and PVR elevations. The left ventricle compensates and CO can be maintained with increased afterload by augmented adrenergic stimulation and increased myocardial oxygen extraction. Burn injury greater than 30% TBSA can induce intrinsic contractile defects that cannot be corrected by early and adequate fluid resuscitation [22, 23]. Horton also showed more recently that also the left heart can suffer from contractile dysfunction in isolated, coronary perfused, guinea pig hearts harvested 24 h after burn injury [22]. This dysfunction was more pronounced in hearts from aged animals and was not reversed by resuscitation with isotonic fluid. It was largely reversed by treatment with 4 ml/kg of hypertonic saline dextran (HSD), but only if administered during the initial 4–6 h of resuscitation. The authors also effectively ameliorated the cardiac dysfunction of thermal injury with infusions of antioxidants, arginine, and calcium channel blockers [23]. Various other resuscitation and cardiac function studies emphasize the importance of early and adequate fluid therapy and suggest that functional myocardial depression after burn injury maybe alleviated in patients receiving early and adequate volume therapy.

A recent more study delineated the importance of intact cardiac function. The authors compared various burn sizes and the pathophysiologic differences between the burn sizes. They found that the patient with larger burns showed significant worse cardiac function which was the only significant difference in terms of organ function indicating that the heart plays an important role and that cardiac dysfunction is present in large burns and should be accounted for [24].

We therefore suggest to use Dobutamine for impaired cardiac function, beta blocker for tachycardia and catecholamine blockade, and adequate resuscitation and hemoglobin levels.

3.3 Hypermetabolic Response Post-Burn

Marked and sustained increases in catecholamine, glucocorticoid, glucagon, and dopamine secretion are thought to initiate the cascade of events leading to the acute hypermetabolic stress response with its ensuing catabolic state [25–34]. The cause of this complex response is not well understood. However, cytokines, endotoxin, reactive oxygen species, nitric oxide, and coagulation as well as complement cascades have also been implicated in regulating this response to burn injury [35]. Once these cascades are initiated, their mediators and by-products appear to stimulate the persistent and increased metabolic rate associated with altered glucose, protein, and lipid metabolism seen after severe burn injury [36]. Several studies have indicated that these metabolic phenomena post-burn occur in a timely manner, suggesting two distinct pattern of metabolic regulation following injury [37].

The first phase occurs within the first 48 h of injury and has classically been called the "ebb phase" [18, 37], characterized by decreases in cardiac output, oxygen consumption, and metabolic rate as well as impaired glucose tolerance associated with its hyperglycemic state. These metabolic variables gradually increase within the first 5 days post-injury to a plateau phase (called the "flow" phase), characteristically associated with hyperdynamic circulation and the above-mentioned hypermetabolic state. Insulin release during this time period was found to be twice that of controls in response to glucose load [38, 39] and plasma glucose levels are markedly elevated, indicating the development of an insulin resistance [40, 41]. Current understanding has been that these metabolic alterations resolve soon after complete wound closure. However, we found in recent studies that sustained hypermetabolic alterations post-burn, indicated by persistent elevations of total urine cortisol levels, serum cytokines, catecholamines, and basal energy requirements, were accompanied by impaired glucose metabolism and insulin sensitivity that persisted for up to 3 years after the initial burn injury [42].

3.3.1 Resting Energy Expenditure

For severely burned patients, the resting metabolic rate at thermal neutral temperature (30 °C) exceeds 140% of normal at admission, reduces to 130% once the wounds are fully healed, then to 120% at 6 months after injury, and 110% at 12–36 months post-burn [1, 25, 43, 44]. Increases in catabolism result in loss of total body protein, decreased immune defenses, and decreased wound healing [45].

3.3.2 Muscle Catabolism

Post-burn, muscle protein is degraded much faster than it is synthesized. Net protein loss leads to loss of lean body mass and severe muscle wasting leading to decreased strength and failure to fully rehabilitate [20, 45, 46]. Significant decreases in lean body mass related to chronic illness or hypermetabolism can have dire consequences.

- 10% loss of lean body mass is associated with immune dysfunction.
- 20% loss of lean body mass positively correlates with decreased wound healing.
- 30% loss of lean body mass leads to increased risk for pneumonia and pressure sores
- 40% loss of lean body mass can lead to death [47].

Uncomplicated severely burned patients can lose up to 25% of total body mass after acute burn injury [48] and protein degradation persists up to 2–3 years post severe burn injury resulting in significant negative whole-body and cross-leg nitrogen balance [20, 45, 49]. Protein catabolism has a positive correlation with increases in metabolic rates (Fig. 3) [45]. Severely burned patients have a daily nitrogen loss of 20–25 g/m^2 of burned skin [20, 45, 46]. At this rate, a lethal cachexia can be reached in less than 1 month. Burned pediatric patients' protein loss leads to significant developmental delay for up to 24–36 months post-injury [44].

Severe burn causes marked changes in body composition during acute hospitalization. Severely burned children lost about 2% of their body weight (−5% LBM, −3% BMC, and −2% BMD) from admission to discharge. Total fat and percent fat increased from admission to discharge by 3% and 7%, respectively.

Septic patients have a particularly profound increase in metabolic rates and protein catabolism up to 40% more compared to those with like-size burns that do not develop sepsis [45]. A vicious cycle develops, as patients that are catabolic are more susceptible to sepsis due to changes in immune function and immune response. Modulation of the hypermetabolic, hypercatabolic response, thus preventing secondary injury is paramount in the restoration of structure and function of severely burned patients.

3.3.3 Glucose and Lipid Metabolism

Elevated circulating levels of catecholamines, glucagon, cortisol after severe thermal injury stimulate free fatty acids and glycerol from fat, glucose production by the liver, and amino acids

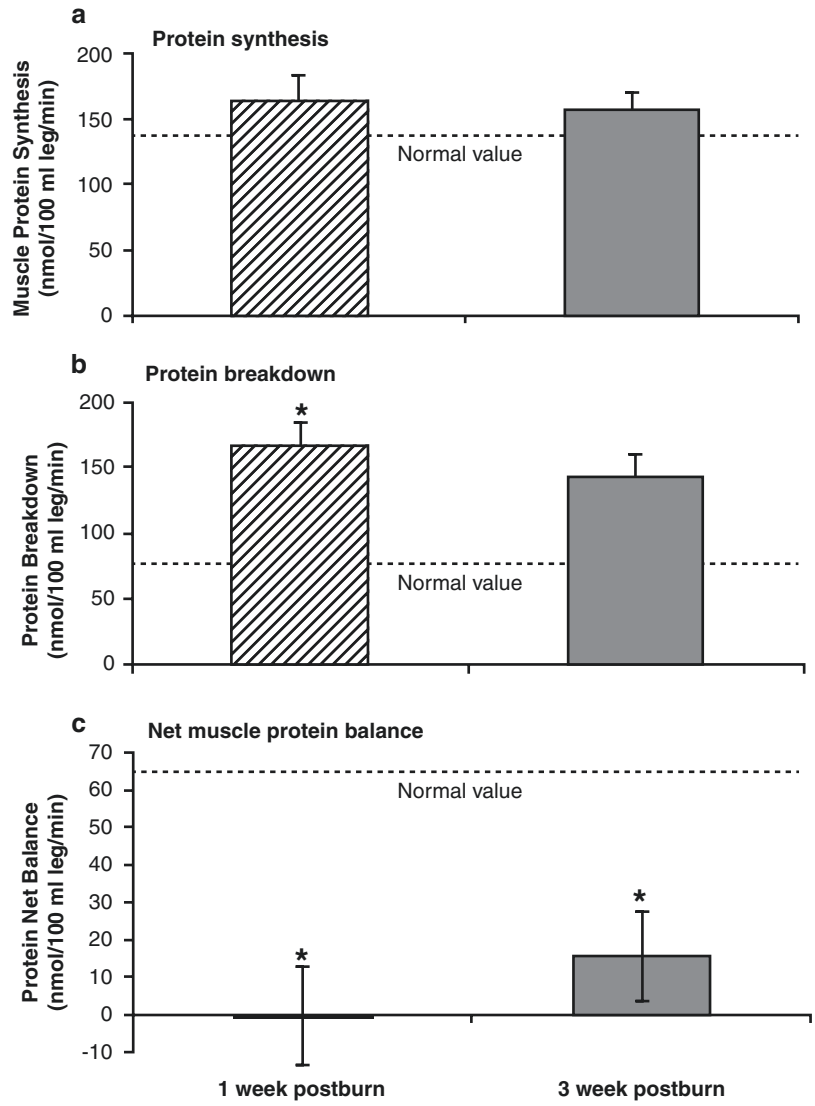

Fig. 3 Muscle protein synthesis, breakdown, and balance after burn injury. Burn causes substantial muscle protein breakdown with a minimal increase in synthesis leading to an overall substantial net protein balance

from muscle [37, 50, 51]. Specifically, glycolytic-gluconeogenic cycling is increased 250% during the post-burn hypermetabolic response coupled with an increase of 450% in triglyceride-fatty acid cycling [52]. These changes lead to increased lipolysis, fatty infiltration in various organs, hyperglycemia and impaired insulin sensitivity related to post-receptor insulin resistance and significant reductions in glucose clearance [17, 42, 53, 54].

In critical illness, metabolic alterations cause significant changes in energy substrate metabolism. In order to provide glucose, a major fuel source to vital organs, release of the above-mentioned stress mediators oppose the anabolic actions of insulin [55]. By enhancing adipose tissue lipolysis [51] and skeletal muscle proteolysis [56], they increase gluconeogenic substrates, including glycerol, alanine, and lactate, thus augmenting hepatic glucose production in burned patients [57–59]. Hyperglycemia fails to suppress hepatic glucose release during this time [60] and the suppressive effect of insulin on hepatic glucose release is attenuated, signifi-

cantly contributing to post-trauma hyperglycemia [61]. Catecholamine-mediated enhancement of hepatic glycogenolysis, as well as direct sympathetic stimulation of glycogen breakdown, can further aggravate the hyperglycemia in response to stress [57]. Catecholamines have also been shown to impair glucose disposal via alterations of the insulin signaling pathway and GLUT-4 translocation muscle and adipose tissue, resulting in peripheral insulin resistance [58, 62].

3.4 Renal System

Diminished blood volume and cardiac output result in decreased renal blood flow and glomerular filtration rate. Other stress-induced hormones and mediators such as angiotensin, aldosterone, and vasopressin further reduce renal blood flow immediately after the injury. These effects result in oliguria, which, if left untreated will cause acute tubular necrosis and renal failure. Twenty years ago, acute renal failure in burn injuries was almost always fatal. Today, newer techniques in dialysis became widely used to support the kidneys during recovery. The latest reports indicate an 88% mortality rate for severely burned adults and a 56% mortality rate for severely burned children in whom renal failure develops in the post-burn period [63, 64]. Early resuscitation decreases risks of renal failure and improves the associated morbidity and mortality [65].

If dialysis is needed, there are various approaches:

- Pediatric patients peritoneal dialysis (Tenckhoff catheter).
- Adult patients hemofiltration or hemodialysis.

We recommend using the dialysis form that is present in the individual setup.

The use of diuretics has been discussed controversially, but there seems to be strong support for the use of diuretics such as Lasix for patients being over-resuscitated, renal protection, or pulmonary edema.

3.5 Gastrointestinal System

The gastrointestinal response to burn is highlighted by mucosal atrophy, changes in digestive absorption, and increased intestinal permeability [66]. Atrophy of the small bowel mucosa occurs within 12 h of injury in proportion to the burn size and is related to increased epithelial cell death by apoptosis [66]. The cytoskeleton of the mucosal brush border undergoes atrophic changes associated with vesiculation of microvilli and disruption of the terminal web actin filaments. These findings were most pronounced 18 h after injury, which suggests that changes in the cytoskeleton, such as those associated with cell death by apoptosis, are processes involved in the changed gut mucosa [66]. Burn also causes reduced uptake of glucose and amino acids, decreased absorption of fatty acids, and reduction in brush border lipase activity. These changes peak in the first several hours after burn and return to normal at 48–72 h after injury, a timing that parallels mucosal atrophy.

Intestinal permeability to macromolecules, which are normally repelled by an intact mucosal barrier, increases after burn [67, 68]. Intestinal permeability to polyethylene glycol, lactulose, and mannitol increases after injury, correlating to the extent of the burn. Gut permeability increases even further when burn wounds become infected. A study using fluorescent dextrans showed that larger molecules appeared to cross the mucosa between the cells, whereas the smaller molecules traversed the mucosa through the epithelial cells, presumably by pinocytosis and vesiculation. Mucosal permeability also paralleled increases in gut epithelial apoptosis.

The best treatment to alleviate mucosal atrophy is early initiation of enteral nutrition, usually within 8–12 h post-burn. Glutamine and other antioxidants have been shown to improve enteral inflammatory driven pathways as well as gut function.

Despite the need for liver function and integrity the liver is profoundly affected post-burn and in our opinion a central contributor to post-burn morbidity and mortality [69–71]. The liver has

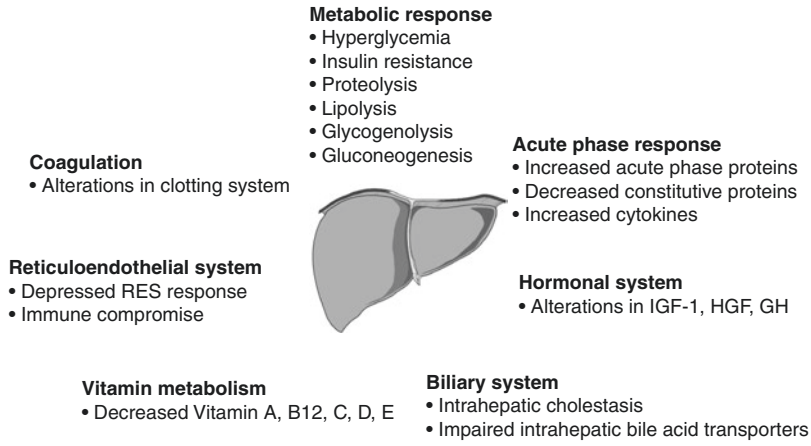

Fig. 4 Plethora of essential and physiologic functions of the liver under normal conditions and after burn

several myriad functions that are each essential for survival (Fig. 4):

All of these hepatic functions are affected by a thermal injury, and we have strong evidence that hepatic biomarkers predict and determine morbidity and mortality in severely burned patients. We, therefore, believe that the liver is central for post-burn outcome and we propose that attenuation of liver damage and restoration of liver function will improve morbidity and mortality of severely burned patients [69–71].

There is currently no treatment for hepatic dysfunction or failure post-burn. Animal and in vitro studies suggested a beneficial effect on hepatic apoptosis and function with the use of insulin and Propranolol.

3.6 Immune System

Burns cause a global depression in immune function, which is shown by prolonged allograft skin survival on burn wounds. Burned patients are then at great risk for a number of infectious complications, including bacterial wound infection, pneumonia, and fungal and viral infections. These susceptibilities and conditions are based on depressed cellular function in all parts of the immune system, including activation and activity of neutrophils, macrophages, T lymphocytes, and B lymphocytes. With burns of more than 20% TBSA, impairment of these immune functions is proportional to burn size.

Macrophage production after burn is diminished, which is related to the spontaneous elaboration of negative regulators of myeloid growth. This effect is enhanced by the presence of endotoxin and can be partially reversed with granulocyte colony-stimulating factor (G-CSF) treatment or inhibition of prostaglandin E_2. Investigators have shown that G-CSF levels actually increase after severe burn. However, bone marrow G-CSF receptor expression is decreased, which may in part account for the immunodeficiency seen in burns. Total neutrophil counts are initially increased after burn, a phenomenon that is related to a decrease in cell death by apoptosis. However, neutrophils that are present are dysfunctional in terms of diapedesis, chemotaxis, and phagocytosis. These effects are explained, in part, by a deficiency in CD11b/CD18 expression after inflammatory stimuli, decreased respiratory burst activity associated with a deficiency in p47-phox activity, and impaired actin mechanics related to neutrophil motile responses. After 48–72 h, neutrophil counts decrease somewhat like macrophages with similar causes.

T-helper cell function is depressed after a severe burn that is associated with polarization from the interleukin-2 and interferon-γ cytokine-based T-helper 1 (Th1) response toward the Th2 response. The Th2 response is characterized by the production of interleukin-4 and interleukin-10. The Th1 response is important in cell-mediated immune defense, whereas the Th2 response is important in antibody responses to

infection. As this polarization increases, so does the mortality rate. Burn also impairs cytotoxic T-lymphocyte activity as a function of burn size, thus increasing the risk of infection, particularly from fungi and viruses. Early burn wound excision improves cytotoxic T-cell activity.

4 Summary and Conclusion

Burn causes a distinct and complex responses that are delineated by time effects that are substantially change over time (Fig. 5). Thermal injury results in massive fluid shifts from the circulating plasma into the interstitial fluid space causing hypovolemia and swelling of the burned skin. When burn injury exceeds 20–30% TBSA, there is minimal edema generation in non-injured tissues and organs. The Starling forces change to favor fluid extravasation from blood to tissue. Rapid edema formation is predominating from the development of strongly negative interstitial fluid pressure (imbibition pressure) and to a lesser degree by an increase in microvascular pressure and permeability. Secondary to the thermal insult there is release of inflammatory mediators and stress hormones. Circulating mediators deleteriously increase microvascular permeability and alter cellular membrane function by which water and sodium enter cells. Circulating mediators also favor renal conservation of water and salt, impair cardiac contractility and cause vasoconstrictors, which further aggravates ischemia from combined hypovolemia and cardiac dysfunction. The end result of this complex chain of events is decreased intravascular volume, increased systemic vascular resistance, decreased cardiac output, end-organ ischemia, and metabolic acidosis. Early excision of the devitalized tissue appears to reduce the local and systemic effects of mediators released from burned tissue, thus reducing the progressive pathophysiologic derangements. Without early and full resuscitation therapy, these derangements can result in acute renal failure, vascular ischemia, cardiovascular collapse, and death. Edema in both the burn wound and particularly in the non-injured soft tissue is increased by resuscitation. Edema is a serious complication, which likely contributes to decreased tissue oxygen diffusion and further ischemic insult to already damaged cells with compromised blood flow increasing the risk of infection. Research should continue to focus on methods to ameliorate the severe edema and vasoconstriction that exacerbate tissue ischemia. The success of this research will require identification of key circulatory factors that alter capillary permeability, cause vasoconstriction, depolarize cellular membranes, and depress myocardial function. Hopefully, methods to prevent the release and to block the activity of specific mediators can be further developed in order to reduce the morbidity and mortality rates of burn shock. The profound and overall metabolic alterations post-burn associated with persistent changes in glucose metabolism and impaired

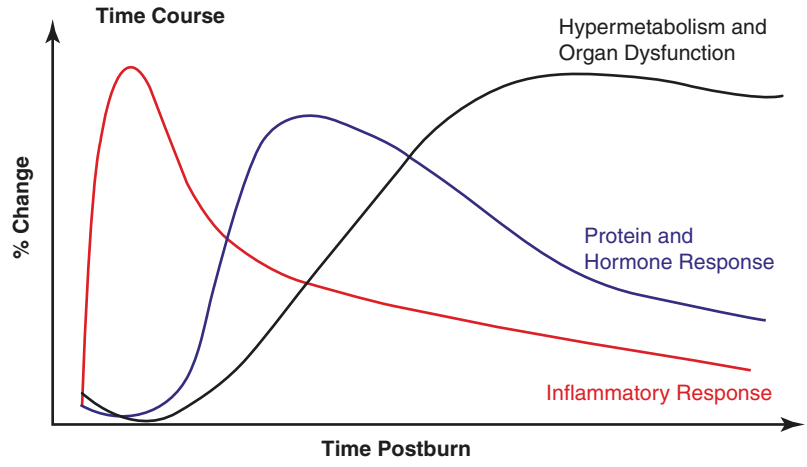

Fig. 5 Time course pattern of inflammatory response (red), protein and acute phase response (blue), and hypermetabolism and organ dysfunction (black). It is striking how long hypermetabolism and therefore catabolism and organ dysfunction persist

insulin sensitivity also significantly contribute to adverse outcome of this patient population and constitute another challenge for future therapeutic approaches of this unique patient population.

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