The Metabolic Stress Response to Burn Trauma: Current Understanding and Therapies

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Summary

Severe burns incur a profound stress response, which is unrivaled in terms of its magnitude and duration. Recent evidence suggests that the pathophysiological stress response to severe burns persists for several years post injury. Thus, there is a pressing need for novel strategies that mitigate this response and restore normal metabolic function in burn survivors.

This is the first installment of a three-part series exploring the stress response to severe burn trauma. In this article we aim to distill the current knowledge pertaining to the stress response to burn trauma, highlighting recent developments and important knowledge gaps that need to be pursued in order to develop novel therapeutic strategies which improve outcomes in burn survivors.

Introduction

Burns encompassing more that 20% of the total body surface area result in a prolonged pathophysiological stress response[1]. Recent work suggests that adrenergic and inflammatory

stress, hypermetabolism, metabolic dysfunction, and reduced lean body mass present for up to and beyond two years post injury[2]. Clearly, strategies which mitigate this stress response and promote recovery are needed to improve quality of life in burn survivors. In this article, we will review the literature pertaining to our current understanding of the pathophysiological stress response to burn trauma, and the leading therapies to mitigate this response. Focus will be placed on recent advances that have come to light in the last decade, while attempting to draw the readers attention to outstanding knowledge gaps. In particular, this manuscript will focus on three major metabolic consequences of severe burn trauma: hypermetabolism, muscle wasting, and stress induced diabetes.

The pathophysiological stress response to burn trauma

Severe burns: The most extreme form of trauma

Burn injury is frequently referred to as the most severe form of trauma/critical illness in terms of the debilitating stress response it incurs[3]. A comparison of genomic alterations in white blood cells (WBCs) following acute lipopolysaccharide (LPS) exposure, blunt trauma, and severe burns revealed that gene expression returned to normal within 24 hours of LPS exposure[4] and one month post-injury following blunt trauma[5]. In contrast, the WBC genome of burn patients remained altered for up to one year post burn (the furthest time point from injury studied)[6] (See Figure 1A). The duration of the genomic response to burns echoes that of the metabolic perturbations resulting from a burn trauma[7–9]. Metabolic rate has been shown to be ~40–80% above normal in the first few months post burn and remains elevated for up to one year post-injury[10]. While poly-trauma[11] and sepsis[12] both result in hypermetabolism, the degree of hypermetabolism is lesser than that of burns and resolves more promptly, (See Figure 1B), supporting the assertion that the stress response to severe burns is unrivaled in terms of its magnitude and persistence.

Hypermetabolism

Hypermetabolism (increased metabolic rate), is a hallmark of the stress response to burns[1]. Subsequently, delivering sufficient energy and nutrition to burn patients is not trivial, which may impede recovery[13]. Burn-induced hypermetabolism is associated with an increased substrate turnover[14], cachexia[15], and poor clinical outcomes[2]. Therefore, management of burn-induced hypermetabolism remains a clinical priority.

Hypermetabolism reflects an increase in whole body O_2 consumption above normative values. Typically, patients are considered hypermetabolic when their REE is 10% or more above normal. Recent reports suggest that in the acute phase post-injury, patients with >40% TBSA burns have an REE 40–80% above normal in the first month post-burn[10,16]. While this hypermetabolic response decays significantly in the first 6 months burn[10,17,18], studies suggest that patients with >40% TBSA burns are hypermetabolic for up to two years post-injury[10,17].

Several ATP-consuming reactions increase in response to burn injury. Increased ATP turnover to support protein synthesis accounts for ~20% of burn-induced hypermetabolism[19]. In addition, ATP production to support hepatic gluconeogenesis

accounts for ~10% of burn-induced hypermetabolism[19]. Further, cycling of glucose and fatty acids account for ~20% of the hypermetabolic response to severe burns[19]. Collectively, it is thought that ATP-consuming reactions account for 55–60% of the hypermetabolic response to burns[19].

Since ATP turnover does not fully explain burn-induced hypermetabolism means that mitochondrial O_2 consumption out-paces ATP production post-burn. Mechanistically, this suggests that the coupling of mitochondrial respiration to ADP phosphorylation is diminished post burn. Uncoupled mitochondrial respiration refers to proton conductance in the inner mitochondrial membranes which is independent of ATP synthase, resulting in heat production. While there are a number of trans-membrane proteins in the inner mitochondrial membrane that contribute to proton conductance, a class of carrier proteins named uncoupling proteins (UCP) are thought to be the principal mediators of mitochondrial thermogenesis.

While the uncoupling of oxidative phosphorylation has been postulated as a contributor to hypermetabolism in burn vicitms[1,19], empirical evidence supporting this theory has only recently been published. In 2015, the first report of UCP1 positive mitochondria within the subcutaneous adipose tissue of burn victims was published[20], a finding which has since been confirmed by others[21]. Following burn trauma, subcutaneous white adipose tissue (sWAT) has a greater abundance of UCP1 positive mitochondria[20]. Since these mitochondria are more uncoupled, sWAT becomes a more thermogenic tissue (Figure. 2A). Moreover, recent data suggests that humans, including burn patients, have functional brown adipose tissue, which upon activation by adrenergic stress significantly increases energy expenditure[22], further suggesting a role for UCP1 positive adipocytes in the hypermetabolic response to burns.

Skeletal muscle is densely populated with mitochondria, and is responsible for ~25% of resting metabolic rate in humans[23]. Interestingly, skeletal muscle O_2 consumption increases by about 50% in severely burned individuals[24]. While increased ATP production to support protein turnover will certainly contribute to this increase in muscle O_2 consumption[25,26], recent data also suggest that skeletal muscle mitochondria become uncoupled after burn injury[17,27] (Figure. 2B). While a mechanistic explanation for this response in muscle is still lacking, preliminary data suggests that transcription of the muscle UCP1 homologue UCP2 [28] may be involved in this response.

At a whole-body level, approximately 80% of mitochondrial respiration is coupled to ADP phosphorylation in healthy humans, with the remainder attributable to proton leaks (i.e., heat production)[23] (Figure 3A). In burn victims, hypermetabolism represents a significant component of total energy expenditure (TEE), where up to 45% of this hypermetabolic response is attributable to heat production (Figure 3A). Thus, while mitochondrial heat production accounts for ~20% of TEE in healthy humans, it may account for ~30% of TEE in burn patients (Figure 3B). In absolute terms, this means that in a healthy individual with a TEE of 2000 kcal/day, mitochondrial heat production accounts for ~400kcal/day (Figure 3C). In contrast, in a severely burned patient with a 50% increase in TEE (i.e., 2000 * 1.5 = 3000kcal/day), mitochondrial heat production may account for ~900kcal/day (Figure 3C).

The ~500-kcal/day increase in mitochondrial heat production described above represents a new target for strategies aimed at blunting burn-induced hypermetabolism. While increased ATP turnover reflects a necessary stress response to support recovery, mitochondrial thermogenesis may be the result of adrenergic stress and inability to conserve heat due to a compromised skin barrier. While such a response is likely important in maintaining core temperature, it represents a biochemical process that may be modulated to reduce hypermetabolism post burn. Given the role of adrenergic stress in the activation of UCPs, specific environmental and/or pharmacological approaches such as temperature control, wound management, and β-blockade may be targeted as a means to better control this response.

Burn Induced Muscle Cachexia

Chronic catabolism of skeletal muscle and the resultant muscle wasting is pathognomonic of severe burn trauma. This erosion of lean body mass can delay healing and significantly contribute to the long-term morbidity of burn survivors. Figure 4 shows images from a patient with a 95% TBSA burn at their hospital admission and at 3, 6, 12 and 24 months post-injury. Note the severe wasting evident at 3 months post-injury, particularly of the extremity musculature. In burns involving >30% of the TBSA, this cachectic state can persist for several years post injury. From a mechanistic standpoint, burn trauma results in concurrent increases in skeletal muscle protein synthesis (MPS) and breakdown (MPB) rates, but that MPB rates significantly surpass MPS rates, resulting in net losses of muscle proteins. It has recently been demonstrated that this dysregulation in skeletal muscle protein kinetics extends one year or more post-injury[26]. Consistent with this phenomenon, reduced lean body mass is observed in burn victims for two to three years post injury[2,29].

It has been postulated that in chronic disease states such as burn trauma, skeletal muscle acts as the bodies nitrogen depot. In this instance, amino acid efflux from skeletal muscle facilitates other metabolic functions in burn victims, such as the acute phase response, gluconeogenesis, and wound healing. Indeed by modeling blood flow and isotopically labelled amino acid fluxes in the blood, skeletal muscle and burn wounds, Gore and colleagues demonstrated that pronounced efflux of amino acids from skeletal muscle of burn victims was associated with marked deposition of amino acids in burn wounds[30] (Figure 5). While these data do not prove that skeletal muscle protein supports wound healing post burn, they do suggest that there is a redistribution of body nitrogen reserves after severe burn trauma. Moreover, at a whole body level, protein breakdown and synthesis are comparable in burned children[31], further suggesting that muscle protein may be redistributed rather that excreted in the severely burned patient. These observations underscore the importance of some aspects of the stress response to burns in facilitating healing. Thus, it would be facile to conclude that attenuation of all components of the stress response to burns would be beneficial. Specifically, blocking muscle protein catabolism pharmacologically may in fact delay wound healing. Therefore, supplementation of additional protein may be a safer approach that blunts muscle catabolism while still providing substrate for other key processes.

Stress Induced Diabetes in Burn Victims

Insulin resistance often accompanies the stress response to burn trauma. Indeed, burned children have impaired glucose tolerance acutely post-injury[32] and at discharge from hospital[33], as do burned adults[34]. Strikingly, like other components of the stress response to burn, reduced insulin sensitivity has been shown to persist for up to three years post injury[35]. Importantly, poor glucose control is associated with impaired wound healing and loss of skin grafts in burn victims[36], while also exacerbating skeletal muscle catabolism[37]. Furthermore, insulin resistance may have long-term implications for the metabolic health of burn patients, meaning strategies which restore insulin sensitivity and glucose control will likely hasten recovery and reduce future morbidity in burn survivors.

Poor glucose control can be brought about by a loss in hepatic (central) and skeletal muscle (peripheral) insulin sensitivity. More specifically, insulin exerts a diminished ability to suppress hepatic glucose output (central insulin resistance) and/or a diminished ability to stimulate glucose disposal into skeletal muscle (peripheral insulin resistance). In burned adults, the rate of glucose appearance from the liver is significantly (2-fold) than in healthy controls[14,38]. Moreover, unlike in healthy individuals, glucose infusion does not fully block hepatic glucose production in burn patients[38]. In addition to impaired central insulin resistance, insulin-stimulated glucose disposal in peripheral tissue such as skeletal muscle is also attenuated following severe burns[39]. Thus, it would appear that burn patients undergo a "double hit" where both central and peripheral insulin sensitivity are diminished post burn, resulting in poor glucose control.

Management of the Pathophysiological Stress Response to Burn Trauma

Environmental Management of Patients with Severe burns—Skin insulates the body, playing a central role in thermoregulation. Accordingly, destruction of this barrier means that burn survivors need to produce more heat to maintain thermal neutrality. Indeed, burn wound excision increases metabolic rate in patients not admitted to a specialist burn unit for ~30 days post burn, demonstrating the effect of losing a significant portion of one s skin on metabolic rate[40]. Increasing the ambient temperature in patient rooms and the use of occlusive wound dressing has long been known to blunt the hypermetabolic response to burns[41,42]. Prior to early wound excision and closure, the use of occlusive wound dressing, and modulation of the ambient temperature becoming standard care, severe burns (>50% TBSA) resulted in a 2- to 3-fold increase in metabolic rate[41]. More contemporary data suggest that metabolic is around 1.5-fold greater than normal after a major burn[2,17,27,32]. These data speak to the importance of wound management and ambient temperature in attenuating burn-induced hypermetabolism. However, in light of recent evidence indicating that mitochondrial thermogenesis remains a significant component of burn-induced hypermetabolism[17,20,21,27], there is likely still room for improvement, where new technologies for wound coverage such as synthetic skin products, drug therapies and environmental strategies should all be explored as a means to blunt hypermetabolism post burn injury.

The Importance of Early Wound Excision and Closure—Prompt excision and grafting of burn wounds is a cornerstone of burn care, which has been shown to reduce

sepsis[40] and mortality[43]. However, in the short-term, temporary use of cadaver skin and closure of burn wounds with expanded donor site skin may leave patients vulnerable to evaporative and conductive heat loss from burn and donor site wounds. Thus, novel skin substitutes which promote a more immediate restoration of a patent skin barrier may prevent heat loss from burn wounds, thereby blunting hypermetabolism. Integra (Integra LifeSciences, Plainsboro, NJ) is one such product which acts as a matrix that promotes rapid dermis formation. In children with massive full-thickness burns (>70% TBSA), randomized treatment with Integra resulted in a resolution of hypermetabolism from the 3rd week post-injury[44], supporting a putative role for skin substitutes in blunting hypermetabolism post burn. However, beyond this small pilot study[44], evidence supporting the efficacy of skin substitutes in blunting hypermetabolism in burn victims is lacking. Since the loss of an isolative skin barrier may be the primary cause of burn induced hypermetabolism, future research efforts should focus on developing new technologies which promote the prompt closure of wounds as a means to blunt the hypermetabolic response to burns.

Nutritional Management of Burn Victims

The nutritional management of burn survivors plays an important role in blunting acute muscle wasting, particularly when considering patients are hypermetabolic and have increased protein needs for wound healing. Similar to other forms of critical illness, the Society of Critical Care Medicine and the American Society of Parenteral and Enteral Nutrition recommend prompt and sufficient nutritional support for burn patients[45]. In particular, it is recommended that feeds be initiated within 4–6 hours of admission and energy intake be guided by energy expenditure estimated by indirect calorimetry[45]. Protein intakes are recommended to be in the range of 1.5 to 2 g/kg/day for burned adults[45]. More specifically, the European Society for Parental and Enteral Nutrition-endorsed recommendations for nutritional therapy of major burns emphasize the need for early enteral feeding and elevated protein provision ranging from 1.5–2 g/kg/day in adults to 3 g/kg/day in children[46].

What is clear from reviewing the literature is that there is a paucity of data concerning the role of nutritional support in burn victims. Studies performed in a small number of patients have shown that low fat (~3% of energy), high carbohydrate (~82% of energy) enteral formulas can blunt muscle wasting by ~40% when compared to formulas with more typical fat (~15% of energy) and carbohydrate (~70% of energy) compositions[47]. Moreover, in a cross-over study of six severely burned adults, a protein intake of 2.2 g/kg/day resulted in 25% more whole body protein synthesis when compared to a protein intake of 1.4 g/kg/day[48]. Furthermore, increasing protein intake from 1 to 3 g/kg/day is correlated with skin protein synthesis in burn patients[49]. Collectively, these data support the use of low fat and high protein nutritional formulas in supporting the stress response to burns. However, little progress has been made recently to further our understanding of the role nutrition plays in recovery from burns. As such, important questions regarding macronutrient composition of enteral formulas, feeding modalities, personalized feeding regimes, and long-term outpatient nutritional support remained unanswered. Future research and development of these areas will likely hasten recovery of burn survivors.

Pharmacological Modulation of the Stress Response to Burn Trauma

Propranolol—Catecholamines have long been known as a mediator of the stress response to burns. Indeed, Wilmore and colleagues elegantly demonstrated this over forty years ago, showing in a small cohort of burn patients that β-adrenergic receptor blockade bunted hypermetabolism[41]. These findings have since been reproduced in several studies, where the non-selective β-blocker propranolol lowers heart rate and metabolic rate in burn victims[50–52]. Interestingly, since hypermetabolism is now known to extend out to three years post injury[2,17], suggests that long-term β-blockade therapy may be warranted in burn survivors. Indeed, a recent placebo-controlled trial where propranolol was administered for one year post-injury revealed significantly lower heart rate and metabolic rate in burn victims receiving propranolol[53]. Thus, these data suggest that therapy with propranolol extended for 12 months post injury may be efficacious in mitigating the long-term hyperdynamic hypermetabolic response to severe burn trauma.

Hypermetabolism is accompanied by muscle wasting, at least in the acute period post burn trauma. Preliminary data support a role for propranolol in blunting skeletal muscle protein losses in burn victims[51]. More recently, it has been shown that long-term propranolol treatment (for one year post injury) promotes peripheral lean body mass accretion in the first six months after injury compared to placebo[53]. Thus, it would appear that the acute alterations in muscle protein turnover brought about by propranolol treatment translate to greater accrual of muscle protein with long-term treatment.

Propranolol is one of the most studied drugs in management of the stress response to burns. A recent systematic review and meta-analysis of 10 clinical trials concluded that propranolol was an efficacious and safe therapy for reducing metabolic rate in burn patients[54]. However, whether propranolol improves other outcomes post burn in both adult and pediatric populations requires further adequately powered multi-center clinical trials.

Recombinant Growth Hormone—A number of other pharmacological agents have been tested with an aim of blunting the stress response to burn trauma. One such agent, recombinant growth hormone (GH), has been studied for its reported benefits on wound protein metabolism and growth. In a number of small studies GH has been shown to stimulate burn wound and donor site wound healing in burn victims[55]. In a randomized clinical trial, GH therapy for one year resulted in reduced cardiac output and hypermetabolism in burn victims[56]. Whether reduced cardiac output fully explains this reduction in metabolic rate, or if accelerated wound closure contributed to this effect, remains unknown but is an interesting avenue for future studies to explore.

Long-term GH therapy has also been reported to have beneficial effects on recovery in pediatric burn survivors. Compared to placebo, one year of GH treatment resulted in greater body weight and lean body mass accretion in the first year post-injury in burned children[56]. Moreover, bone mineral content and height percentiles were greater at one and two years post burn in children treated with GH[56], suggesting that long term GH therapy supports anabolism and growth in burned children. More recently, GH (2 mg/week of sustained release GH) administered for 12-weeks has been shown to be safe and efficacious in terms

of restoring for lean body mass, aerobic fitness and muscle strength in severely burned adults[57].

While these preliminary results from small single-center studies are promising, the use of GH therapy in burns has been limited, likely due to two multi-center randomized controlled trials reporting that GH therapy increases morbidity and mortality in critically ill adults[58]. Thus, more research is needed to robustly test the efficacy and safety of GH therapy in patients recovering from severe burns, particularly in adult populations.

Testosterone Analogues

A number of small mechanistic studies support a role of testosterone[59] and its analogue oxandrolone[60,61] in blunting skeletal muscle protein catabolism in acutely injured burn patients. Recently, a five year follow-up of pediatric burn victims who were randomized to either placebo or oxandrolone for 12 months after injury demonstrated that from 2-years post burn, growth was accelerated in patients that received oxandrolone compared to placebo, evidenced by a greater accretion of lean body mass, bone mineral content and change in height percentiles[62]. More recently, it has been shown that two years of oxandrolone therapy was more efficacious than one year of therapy in terms of improving bone mineral content and density[63]. Collectively, these data suggest that oxandrolone therapy blunts acute muscle loss and promotes growth in children recovering from burns.

In addition to reported effects of protein turnover, body composition and growth, long-term (one year) treatment with oxandrolone blunted hypermetabolism in burned children in the first 6-months post-injury[62]. Reduced heart rate and cardiac output in oxandrolone treated patients may explain this response. While wound healing was not quantified in this study, it is plausible that oxandrolone therapy promotes faster wound healing, which may explain why oxandrolone treatment blunts metabolic rate in burn victims.

Collectively, small studies in adults and children suggest a role for testosterone analogues in blunting muscle wasting post burn, and a handful of single-center clinical trials support the efficacy and safety of long-term oxandrolone therapy in improving outcomes in severely burned children. Future studies including children and adults that focus on outcomes in both males and females are needed before therapy with testosterone analogues can be accepted as a frontline treatment for severe burns.

Current Strategies to Improve Glucose Control in Burn Victims—Hyperglycemia can readily be treated by the administration of insulin. This is also true of severely burned individuals, where in a randomized clinical trial intensive insulin therapy significantly improved glucose homeostasis compared to a control group[64]. Furthermore, in the aforementioned study improved glucose control with insulin therapy was associated with reduced dyslipidemia, increased insulin sensitivity, and better maintenance of body mass during the acute hospital course[64]. Indeed, both acute[65,66] and chronic[67,68] insulin administration is anabolic to skeletal muscle of burn victims, blunting muscle protein wasting post burn.

While tight glucose control through insulin therapy has been shown to reduce morbidity in burn survivors, this approach is not without its limitations. Indeed, the risk of hypoglycemic episodes associated with insulin therapy in critically ill patients has limited its widespread use in the ICU[69,70]. Thus, additional strategies which provide improved glucose control in burn survivors without the need for insulin administration are needed. Metformin is widely prescribed to treat type 2 diabetes mellitus by reducing hepatic glucose production and improving peripheral insulin sensitivity[71]. Metformin treatment is not associated with hypoglycemia, and thus may be a safe option to improve glucose control in burn victims. Indeed, preliminary data suggest that one week of metformin treatment in severely burned adults significantly reduced fasting glucose concentration when compared to a placebo group[72]. Metformin treatment also blunted hepatic glucose production while augmenting peripheral insulin sensitivity[72]. Furthermore, metformin treated patients required significantly less insulin during the study period than the placebo group[72]. More recently, a randomized phase II clinical trial reported that metformin treatment was as effective as insulin therapy in controlling blood glucose levels in severely burned adults[73]. Moreover, hypoglycemic episodes were significantly lower in metformin-treated patients[73].

Metformin therapy appears to increase both central and peripheral insulin sensitivity in burn victims, ultimately leading to better glucose control and a reduced reliance on insulin therapy. However, a potential caveat to metformin use is its association with lactic acidosis. The biguanide metformin and its predecessor phenformin inhibit mitochondrial NADH oxidase, causing upstream inhibition of oxidative pyruvate metabolism, resulting in lactate formation. However, at therapeutic doses metformin does not inhibit mitochondrial NADH oxidase in skeletal muscle of humans[74]. Further, a systematic review of the literature including data from 347 clinical trials found no evidence of fatal or non-fatal lactic acidosis with metformin treatment[75]. Indeed, in burn patients metformin treatment was not associated with lactic acidosis[72,73].

In addition to metformin, the peroxisome proliferator activated receptor alpha (PPAR-α) antagonist Fenofibrate has recently been trialed as a therapy to improve insulin sensitivity in burn victims. In a placebo controlled study, two weeks of Fenofibrate treatment significantly increased whole-body fat oxidation in burned children[76]. In a separate analysis of patients enrolled in the aforementioned clinical trial, fasting blood glucose was reduced while peripheral glucose disposal during a hyperinsulinemic euglycemic clamp was increased in Fenofibrate treated patients[39]. No changes in glucose metabolism were observed in the placebo group[39]. Furthermore, in these two studies[39,76], the authors reported that mitochondrial enzyme activity and respiratory function increased in skeletal muscle of Fenofibrate treated patients, whereas these parameters were either unchanged or declined in patients in the placebo group[39,76]. Thus, from this small clinical trial, data support a role for Fenofibrate in improving central and peripheral insulin sensitivity in severely burned children. However, larger clinical trials including both children and adults are needed to better understand the acute and chronic impact of Fenofibrate therapy in burn patients.

Exenatide, a synthetic analogue of the incretin hormone glucagon like peptide 1 (GLP-1), is released from the gut after feeding, and stimulates pancreatic insulin secretion[77]. GLP-1 agonists provide similar glucose control when compared to conventional insulin therapy[77],

but since GLP-1 has a half-life of ~ 2 min, the risk of excessive insulin secretion and hypoglycemia with GLP-1 receptor agonists such as Exenatide are low. In a small pilot study comparing intensive insulin therapy to Exenatide treatment in pediatric burn victims, patients randomized to Exenatide required less insulin to maintain a plasma glucose level of 80–140 mg/dl when compared to the intensive insulin group[78], suggesting that short acting GLP-1 analogues may be a safe means of improving glucose control and insulin sensitivity in burn patients.

There is promising preliminary data supporting a role for pharmacological strategies other than insulin therapy in improving insulin sensitivity and glucose control in burn victims. In particular, metformin appears to be an efficacious and safe strategy to improve glucose control in burn survivors. However, it should be noted that these clinical trials were performed in small cohorts of either burned adults or children over a short period of 1 to 2 weeks. Further large clinical trials are warranted to fully assess the efficacy and safety of these agents in the management of stress-induced diabetes in burn victims. Moreover, it has recently been reported that nurse-guided glucose control by insulin is a safe and efficacious means of preventing hyperglycemia in burned adults[79], suggesting that there may not be a need to abandon insulin treatment in burn patients completely.

Long-term Rehabilitation of Burn Survivors

Prolonged wasting of skeletal muscle and enforced immobilization leave burn victims cachectic and deconditioned[80]. Restoration of muscle mass and function is an essential component of rehabilitation of burn survivors. Rehabilitative exercise training (RET) has been demonstrated to be safe and efficacious in terms of restoring lean body mass, cardiorespiratory fitness, and muscle strength in burn survivors[81]. While most RET programs are initiated at 6 to 12 months post injury, new data show that RET commenced immediately upon discharge from hospital is efficacious in increasing muscle mass and strength as well as peak oxygen consumption when compared to more conservative occupational and physical therapy[82]. Furthermore, improvements in lean body mass in patients who performed RET were maintained even after cessation of the program. Thus, the question arises as to when is optimal to begin RET in burn victims? If feasible, perhaps exercise performed in-hospital may further hasten recovery and discharge from hospital. Further study of the important role of exercise, including timing in the implementation of training, the duration of RET programs, and the exercise modalities included in RET programs, is required to better meet this need of burn survivors. Moreover, despite a growing body of evidence supporting the efficacy of hospital[81] or community[83] based RET following burn trauma, prescription of RET is not common in most burn centers[84]. Thus, greater awareness of the utility of RET among caregivers and addressing the barriers preventing RET participation by burn survivors is needed to improve the holistic treatment of severe burn injuries.

Since a number of drugs and exercise all seem to promote the recovery of lean body mass and muscle function in burn survivors, it is intuitive to theorize that combined drug and exercise therapy may have a synergistic effect. Indeed, improvements in cardiorespiratory exercise capacity with RET training is augmented by propranolol therapy in burned

children[85]. Furthermore, RET combined with oxandrolone therapy has been shown to result in a doubling of muscle mass accretion during a 12-week recovery period when compared to RET or oxandrolone therapy alone[86]. Thus, it would appear the RET combined with drug therapy may result in greater improvements in body composition and functional capacity when compared to either intervention alone. Further studies investigating the effects of combined therapy with exercise and other drug and/or nutritional approaches would be helpful in optimizing the recovery of burn survivors.

Summary

There have been a number of significant advances in the last decade in our mechanistic understanding of the pathophysiological stress response to burns. New placebo-controlled trials support the safety and efficacy of drugs such as propranolol and oxandrolone in mitigating the stress response to burns, while new agents such as the insulin sensitizer s metformin and Fenofibrate may be realistic candidates for safe glucose control. Moreover, recent data has further underscored the utility of exercise training in restoring function in burn survivors. However, several important questions need to be answered in the near future if burn care is to continue to improve. In particular, the development of novel therapies and/or technologies to accelerate wound healing and blunt mitochondrial thermogenesis should be made a priority; as such therapies will likely mitigate the hypermetabolic catabolic response to severe burns. Further, while a number of interventions have been shown to blunt the stress response to burns and promote recovery after discharge from the hospital, whether combined nutrition, exercise and drug therapies have a more synergistic effect on morbidity remains largely unknown. Developing such combination therapies will likely represent a significant stride in reducing morbidity and mortality in burn victims.

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Key points

- Evidence has emerged in the last decade suggesting that the pathophysiological stress response to severe burns persists for several years post injury, meaning long-term therapeutic solutions are needed to fully rehabilitate burn survivors.

- Novel data suggests a role for mitochondrial thermogenesis in burn-induced hypermetabolism. Subsequently, renewed efforts to blunt adaptive thermogenesis in burn victims through environmental and pharmacological approaches are warranted.

- Skeletal muscle acts as a protein depot in burn victims, being redistributed after burn trauma. The provision of 2–3 g/kg/day of high quality protein may be needed to provide ample amino acids to blunt muscle catabolism.

- A growing body of evidence supports the safety and efficacy of rehabilitative exercise training (RET) in restoring body mass and function in burn survivors. RET needs to be installed as a cornerstone of the long-term treatment of burn survivors.

- Metabolic syndrome and stress-induced diabetes remain long-term complications of burn trauma that may have implications for future morbidity and mortality. Long-term therapy with glucose lowering compounds such as Metformin may be warranted in chronically hyperglycemic patients.
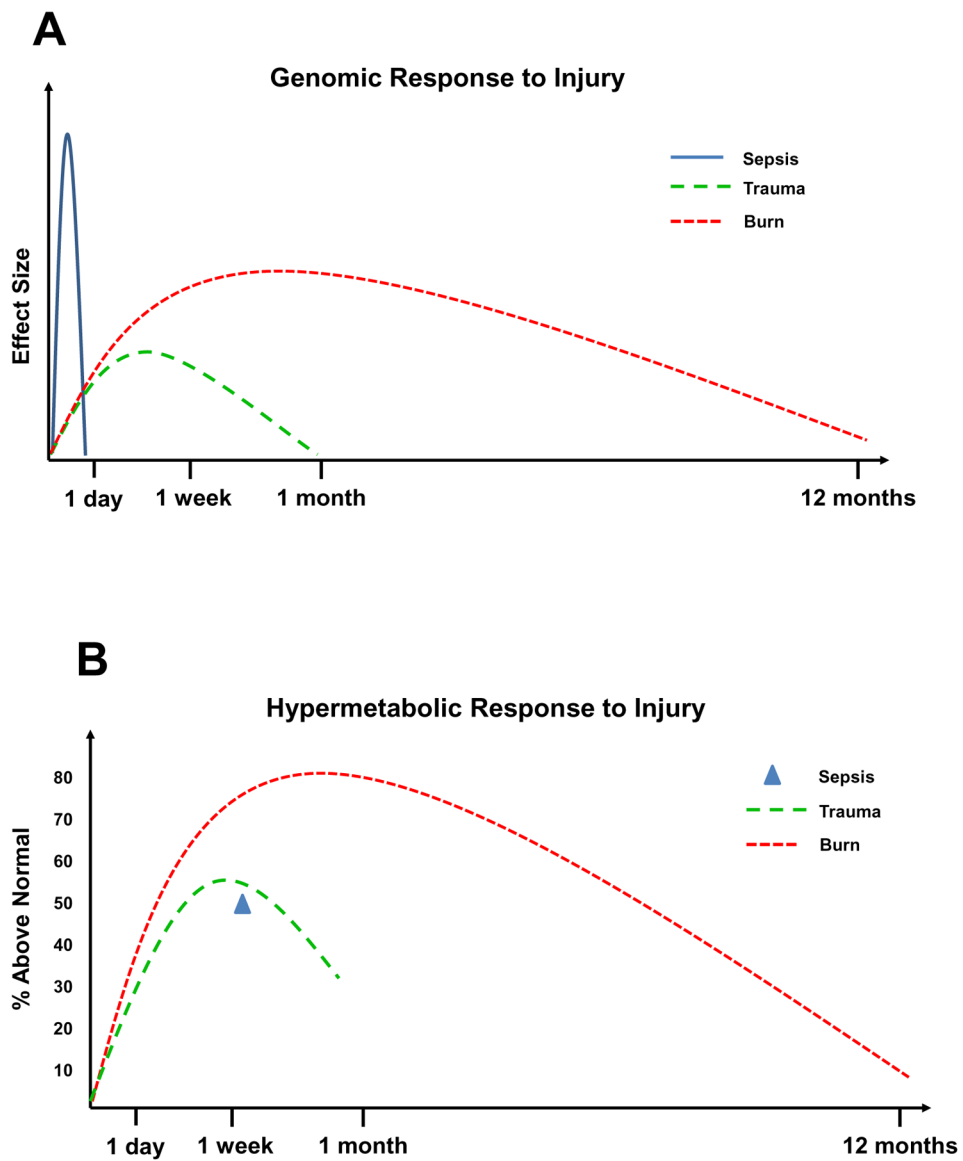
Figure 1.
Long-term stress response to injury. (A) The genomic response to injury in white blood cells in individuals who had undergone a lipopolysaccharide injection (sepsis), blunt trauma (trauma), or severe burns (burn) (adapted from reference 6). (B) Hypermetabolic response to injury in septic patients (sepsis), blunt trauma (trauma), or severe burns (burn) (adapted from references 10–12).
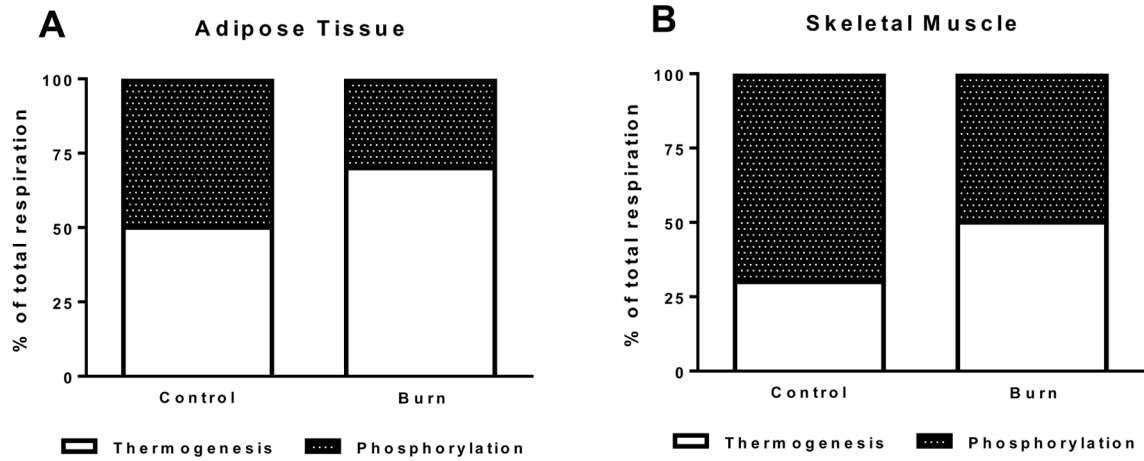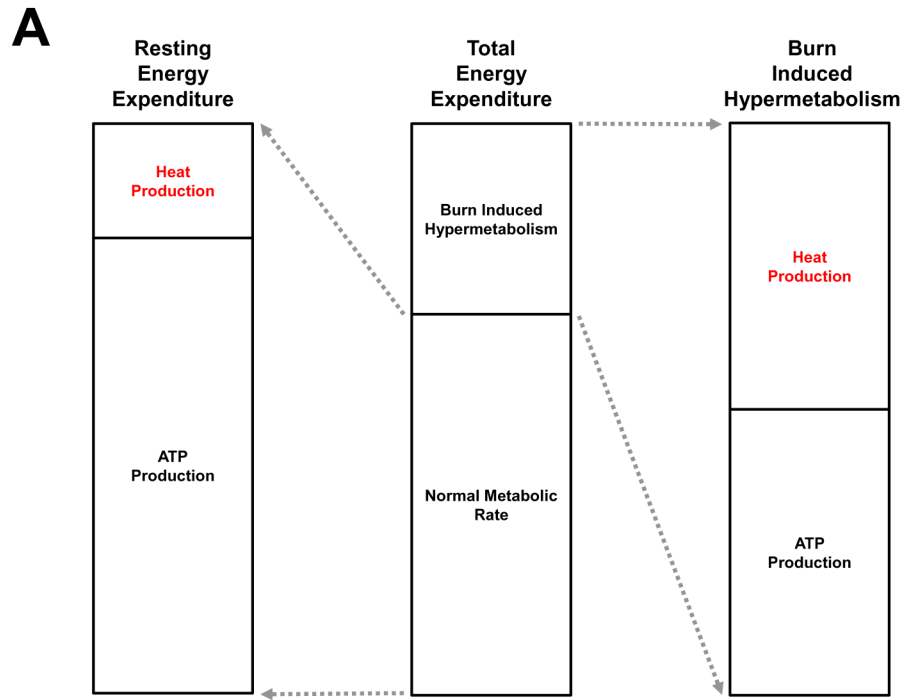
Figure 2.
(A) Altered mitochondrial function in adipose tissue of burn victims, where mitochondrial thermogenesis is increased after burn (adapted from reference 20). (B) Altered mitochondrial function in skeletal muscle of burn victims, where mitochondrial thermogenesis is increased after burn (adapted from reference 27).
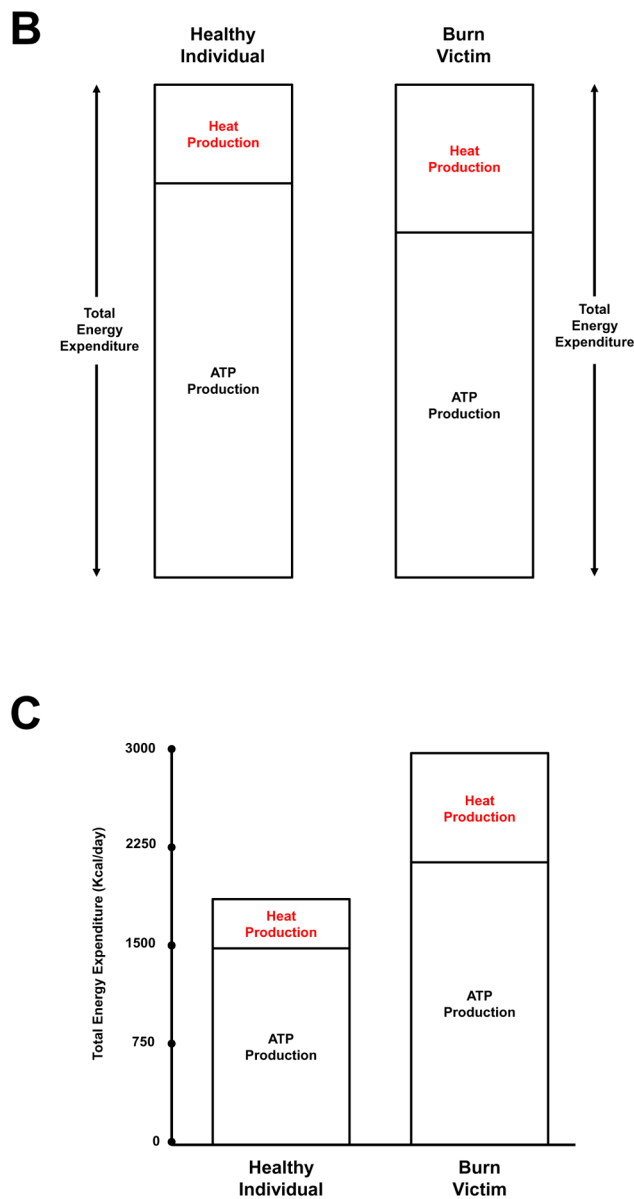
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Figure 3.
(A) Total energy expenditure (TEE) in a burn victim with a 50% increase in TEE. The proportion of normal metabolic rate attributable to ATP or heat production is adapted from reference 19. The proportion of burn induced hypermetabolism attributable to ATP or heat production is adapted from reference 19. (B) The proportion of TEE attributable to heat and ATP production in healthy individuals and burn victims based on data in Figure 3A. (C) Absolute kcal values for heat and ATP production in healthy individuals and burn victims based on data in Figure 3A.
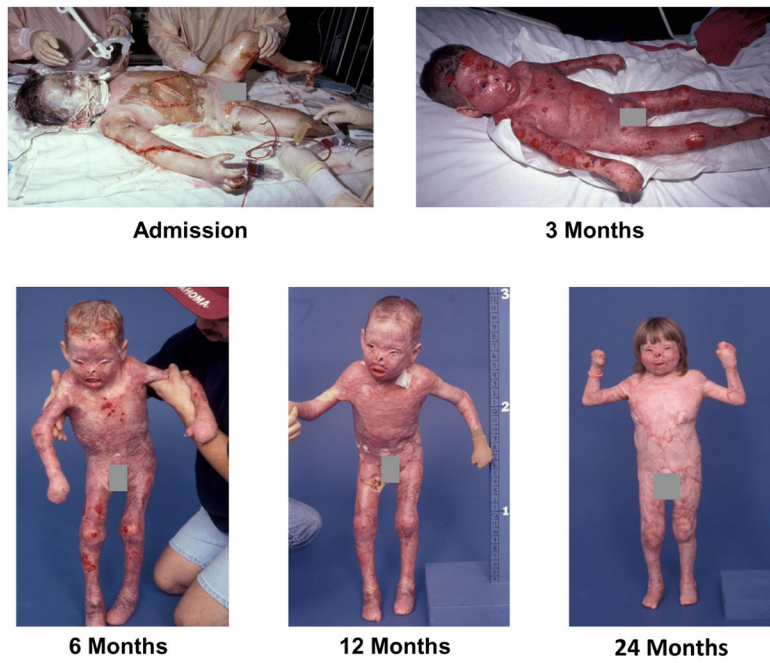
Figure 4.
Long-term catabolic stress response to massive burns. Images of a child with a 95% TBSA burn at their hospital admission and at 3, 6, 12 and 24 months post-injury.
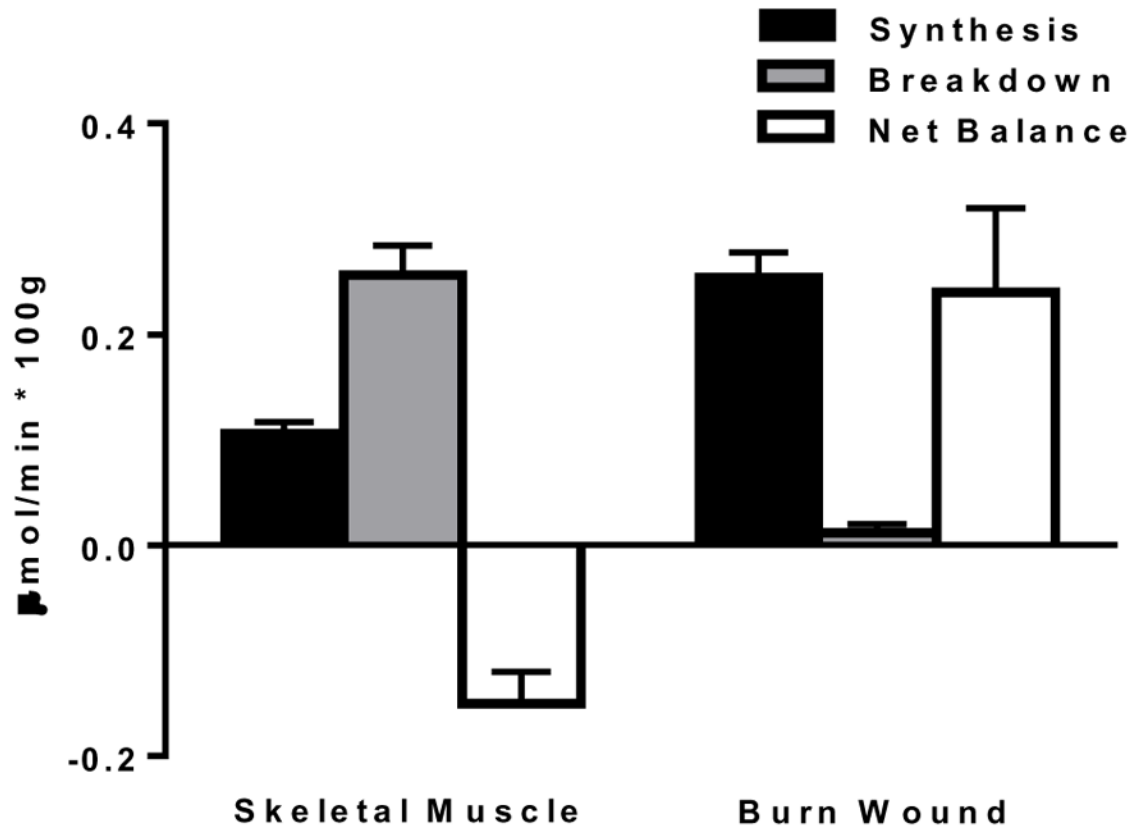
Figure 5.
Skeletal muscle and burn wound protein synthesis and breakdown rates in burn victims determine by isotopic dilution. Protein net balance is equal to protein breakdown subtracted from protein synthesis. Data are adapted from reference 30.