Published in final edited form as:
Expert Opin Pharmacother. 2012 December ; 13(17): 2485–2494. doi:10.1517/14656566.2012.738195.

Burns: an update on current pharmacotherapy

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Abstract

Introduction—The world-wide occurrence of burn injuries remains high despite efforts to reduce injury incidence through public awareness campaigns and improvements in living conditions. In 2004, almost 11 million people experienced burns severe enough to warrant medical treatment. Advances over the past several decades in aggressive resuscitation, nutrition, excision, and grafting have reduced morbidity and mortality. Incorporation of pharmacotherapeutics into treatment regimens may further reduce complications of severe burn injuries.

Areas covered—Severe burn injuries, as well as other forms of stress and trauma, trigger a hypermetabolic response that, if left untreated, impedes recovery. In the past two decades, use of anabolic agents, beta adrenergic receptor antagonists, and anti-hyperglycemic agents has successfully counteracted post-burn morbidities including catabolism, the catecholamine-mediated response, and insulin resistance. Here we review the most up-to-date information on currently used pharmacotherapies in the treatment of these sequelae of severe burns and the insights that have expanded our understanding of the pathophysiology of severe burns.

Expert opinion—Existing drugs offer promising advances in the care of burn injuries. Continued gains in our understanding of the molecular mechanisms driving the hypermetabolic response will enable the application of additional existing drugs to be broadened to further attenuate the hypermetabolic response.

Keywords

burns; pharmacotherapy; hypermetabolic response; oxandrolone; growth hormone; propranolol; ketoconazole

1. Introduction

1.1 Burns: A global public health problem

Injuries caused by severe burn injuries result in significant disability and death [1]. In 2004, 11 million severely burned people sought medical attention globally. Burn injury ranks fourth among all injuries, following vehicle accidents, falls, and violence. A significant

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Declaration of Interest
The authors declare no conflict of interest.

number of people sustain burn injuries, with incidence rates higher than those for HIV infections and tuberculosis combined. The post-burn sequelae account for a large portion of disabilities in low-to-middle income countries [1].

Recent advances in clinical care have reduced morbidity and mortality. From 1981 to 1998, the age-adjusted death rate associated with burns decreased by over 50% in the U.S [2]. Although a decline in mortality has occurred due to advances in clinical care, low-to medium-income countries bear the main burden of burn injuries. This is probably attributable to socioeconomic factors, outdoor fires for cooking, poorly grounded electrical lines, crowding, and inconsistent access to quality acute care. The majority (90%) of burn deaths occur in lower-middle or low income countries, 7% in high-middle, and 3% in high income countries [2]. In all countries, disparities exist in the treatment of burns in children, the elderly, and racial and ethnic minorities.

1.2 The pathophysiology of severe burns

Severe burn injuries, which cover more than 30% of the total body surface area (TBSA), cause an inflammatory and subsequent hypermetabolic response that starts immediately post burn and persists for at least 3 years [3–5]. This response has two aspects— the “ebb” and “flow” phases. The “ebb” phase, occurring within the first 48 hours after injury, is associated with decreased cardiac output and metabolism. The chronic “flow” phase then ensues with development of a hyperdynamic circulation and increased metabolic rate [6]. Hyperglycemia occurs due to increased glucose synthesis, increased glucose flow to inflamed tissues, and development of peripheral insulin resistance. The hypermetabolic response is thought to be due to post-burn elevation of endogenous catecholamines and cortisol. In a large single-center study evaluating the extent and magnitude of the catecholamine surge following severe burn in pediatric patients, Kulp *et al.* showed that catecholamine levels are consistently and significantly elevated in burn patients and that levels increase with burn size [7, 8]. Epinephrine returns to normal levels within 2 months of burn injury, while norepinephrine remains elevated for 18 months [3]. Cortisol, however, remains persistently elevated for 3 years post burn. Supraphysiologic levels of stress hormones contribute to the long-lasting tachycardia, catabolism, and immune suppression that characterize the hypermetabolic response.

Hypermetabolism can be quantitated by analyzing resting energy expenditure (REE), consumption of oxygen and glucose, and CO_2 production. REE remains elevated at 130–140% of the predicted value for 3 years after burn injury [3]. This hypermetabolic response is associated with a hyperdynamic circulation, hyperthermia, and skeletal muscle and fat breakdown [9–12]. During this time, the metabolic and energy requirements are vast, necessitating recruitment of proteins and amino acids to sustain healing and recovery. This, in turn, increases protein turnover and produces a negative nitrogen balance. The accompanying reductions in lean body mass (LBM) and bone density produce weakness and impair wound healing. The loss of LBM can further drive detrimental responses in burned patients. Chang *et al.* demonstrated that impaired immunity occurs when 10% of LBM is lost. Thirty percent mortality occurs as a result of decreased wound healing with 20% loss of LBM. Thirty percent loss of LBM leads to bed sores, pneumonia, and 50% mortality. Death uniformly occurs when 40% of LBM is lost [13]. Although the hypermetabolic response undoubtedly evolved to aid survival from burns, this physiologic response also has maladaptive consequences that can negatively affect survival and hinder recovery [14]. As a consequence, the rehabilitation and reintegration of severely burned victims into society are hampered.

Over the past several decades, increasing knowledge of burn pathophysiology has led to advances in burn care, both in inpatient and outpatient settings. This has led to an overall

reduction in morbidity and mortality in patients admitted to tertiary referral care centers [15]. In addition to improvements in resuscitation, early enteral nutrition, early excision and coverage of burn wounds, and the development of new topical and systemic agents, the implementation of existing drugs to reduce aspects of the pathophysiologic response to burn has contributed to this overall improvement in burn care.

Here we review therapeutic interventions with beta blockade to prevent the detrimental effects of the post-burn catecholamine surge, anti-hyperglycemia therapies to reduce blood glucose and improve insulin sensitivity, ketoconazole to block cortisol, and anabolic agents (testosterone, oxandrolone, recombinant human growth hormone, and insulin-like growth factor-1 and its binding protein 3) to improve muscle mass. Insights gained from these studies have improved the care of severely burned patients. Continued pursuit of pharmacotherapies for use in burn patients will yield the next major advancements in burn care.

2. Current therapies administered to counteract specific aspects of the post-burn pathophysiologic response

2.1 Propranolol

The burn-induced stress response stimulates secretion of endogenous catecholamines, which are thought to be the primary mediators of hypermetabolism after severe burns [12]. This elevation of catecholamines induces a hyperdynamic circulation, augments energy expenditure, and promotes protein catabolism in skeletal muscle. Drugs that block this catecholamine surge have been shown to be effective at countering catecholamine-induced sequelae after severe burns [16]. Propranolol, a non-specific beta 1, beta 2 adrenergic receptor antagonist that has been studied extensively, holds promise for reduction of the post-burn hypermetabolic response.

Initial studies of beta adrenergic blockade with infusion of 2 mg/kg/day propranolol for 5 days showed that this short duration of therapy diminishes tachycardia and reduces cardiac work without affecting the REE [17, 18]. Catecholamines induce myocardial oxygen consumption. Accordingly, administering low doses of propranolol (0.5–1.0 mg/kg) to severely burned patients reduces myocardial oxygen requirements without adversely affecting oxygen delivery. When titrated at a dose to reduce heart rate by 10–20% of baseline for more than 10 days, propranolol continues to safely reduce cardiac work load in severely burned children [19]. Randomized-controlled trials suggest that propranolol works in a dose-dependent manner in severely burned patients. Patients initially treated with 1 mg/kg/day propranolol to reduce the heart rate to 15% of the admission heart rate required a dose escalation to ~4 mg/kg/day within 10 days to sustain the goal heart rate and treatment benefits of decreased cardiac work [20]. Interim analysis of a large randomized-control trial at our institution to assess the efficacy and safety of long-term propranolol use in severely burned pediatric patients has revealed that a decrease in heart rate of 15% below admission heart rate and a subsequent decrease in cardiac work is maintained with an average dose of 4 mg/kg/day, when given every 6 h or once daily as an extended-release formulation for 12 months [21]. Increased episodes of hypotension were not seen in the propranolol group at this dose when compared to the placebo, confirming the long-term safety of this drug. Furthermore, this study found that despite treatment, tachycardia and cardiac work were still significantly elevated from normal [21]. Given the safety of propranolol at 4 mg/kg/day, increasing the dose to further decrease cardiac work could be considered in severely burned patients.

In burn patients, peripheral lipolysis is increased through the activation of beta 2 adrenergic receptors by catecholamines [17, 18, 22]. This results in substantial fatty infiltration of the

liver. By way of beta 2 adrenergic blockade, propranolol inhibits liberation of free fatty acids from adipose tissue, increases the efficiency of the liver in excreting fatty acids, and in turn decreases burn-induced hepatic steatosis [22–24]. The majority of patients administered propranolol to decrease the heart rate 12–15% experience decreased liver size. Plasma triglycerides are also significantly lower in these patients. Long-term administration of propranolol at 4 mg/kg/day is associated with maintenance of peripheral fat mass (and consequently no change occurs in central fat mass), while non-treated patients have a 23% increase in central fat mass with concurrent reduction in peripheral fat mass 12 months post burn despite similar nutritional intake [21].

In addition to decreasing tachycardia, cardiac work, REE, and hepatic steatosis in severely burned patients, beta blockade with propranolol reduces breakdown of peripheral muscle and increases protein synthesis. In a randomized controlled trial, children with burns over 40% of the TBSA receiving an average daily dose of propranolol of 2–6 mg/kg/day had a net muscle protein balance increase of 82% above baseline compared to a decrease of 27% in the non-treatment group [24]. Recently, Olah *et al.* demonstrated that Poly (ADP-ribose) polymerase (PARP) activation, which promotes cellular necrosis during critical illness, occurs in skeletal muscle following severe burn injury. Peak activation occurred at 13–18 days post injury and persisted into the later disease phase. PARP activation was lower in patients who received propranolol at 4 mg/kg/day than in control patients [25]. This study suggests that propranolol may increase net protein balance and decrease overall lean mass catabolism by preventing skeletal muscle necrosis after severe burn injury.

Studies evaluating reduction of cardiac work with administration of propranolol have also revealed that smaller amounts of insulin are needed to reduce elevated glucose levels after burn in propranolol-treated patients [19]. Recent studies using rat models of burn injury have provided insights into the mechanism underlying the effects of propranolol on insulin resistance. The hepatic endoplasmic reticulum (ER) stress response is induced with severe burn injury, resulting in activation of c-Jun N-terminal kinase, which negatively regulates insulin signaling as well as suppression of insulin receptor signaling leading to insulin resistance [26]. Administration of propranolol at 5 mg/kg/day orally immediately post burn attenuates the ER stress response and increases insulin sensitivity [27]. Further studies are needed to evaluate this promising approach to overcoming post-burn insulin resistance.

Murine studies suggest that non-selective beta blockade with propranolol during episodes of septicemia are detrimental and increase mortality [28]. However, this was not evident in large prospective, intent-to-treat clinical studies. In 2007, Jeschke *et al.* found that propranolol attenuated the hypermetabolic response, as indicated by a significant decrease in REE during acute hospitalization, without increasing the incidence of infection and sepsis [29].

The role of propranolol in the treatment of burn injuries goes beyond modulating metabolism. Both local and systemic administration of propranolol have been shown to enhance wound healing and decrease the surface area requiring skin grafting [30, 31]. With reduced mortality from the acute injury, the emphasis of burn care has shifted to improving morbidity and optimizing rehabilitation. Given that approximately one-third of burn victims suffer from acute and posttraumatic stress disorder, the use of psychotropic agents in the burn population is common. The use of propranolol as a potential pyschotropic agent is being explored [32, 33].

2.2 Insulin

Hyperglycemia is a prominent component of the post-burn hypermetabolic response [34]. Stress-induced hyperglycemia is also noted after other major trauma and results from

increased hepatic gluconeogenesis and insulin resistance in skeletal muscle [34]. Elevated plasma glucose levels have been shown to suppress immune function by altering macrophage cytokine production. This, in turn, decreases lymphocyte proliferation and suppresses bactericidal activity in leukocytes [32–34], possibly contributing to post-burn immune depression. Immune function is further affected by elevated glucose levels, which lead to immunoglobulin glycosylation when glucose levels are >220 mg/dL, reducing opsonic activity [35]. Van den Berghe and colleagues showed that, in the critically ill, survival and morbidity improve when blood glucose levels are maintained at ≤110g/dL [36–38]. Glucose control is also associated with improved wound healing [39].

Given that infection is a leading cause of mortality in severely burned patients and that wound healing is vital for recovery, burn victims are especially vulnerable to the consequences of hyperglycemia. In 58 severely burned pediatric patients, Gore *et al.* found that patients with hyperglycemia had worse skin graft take and were more likely to be bacteremic [40]. Complementary to this finding, intensive insulin treatment has been shown to increase donor site wound protein synthesis in burned patients, further supporting the notion that improved serum glucose has a positive effect on wound healing [41]. Gore *et al.* also found that persistent hyperglycemia is associated with increased mortality [40]. In burn patients, glycemic control is associated with lower death rates. By post-burn day 3, patients who have not achieved a mean glucose concentration of ≤150 mg/dl for a minimum of two consecutive days had an increased risk of mortality. This finding was independent of age, burn size, and number of infections [42].

In addition to providing the benefits of normoglycemia and wound healing, continuous infusions of this anabolic peptide in severe burn patients prevent breakdown of muscle protein and maintain lean mass [43, 44]. Low infusion doses of 9–10 U/h improve muscle anabolism in the absence of large carbohydrate loads [43]. Burn patients receiving insulin infusions (1.5 U/kg/min to maintain 100–140 mg/dL blood glucose) and a high carbohydrate/protein diet (1,500 kcal/m^2 + 1,500 kcal/m^2 burned every 14 hours) exhibit improvements in LBM, bone mineral density, and length of hospitalization [45]. The exact mechanism underlying the ability of insulin to induce this anabolic state is unclear; however, administration of insulin to severely burned children does reduce pro-inflammatory cytokines and proteins and elevates constitutive hepatic proteins. This suggests that insulin attenuates the inflammatory response independent of its effect on serum glucose levels [46]. Furthermore, studies in rat cardiomyocytes have shown that insulin decreases inflammatory cytokine expression and apoptosis by inhibiting p38 mitogen-activated protein kinase, which is upregulated after thermal injury [47]. This blockade of a stress-signaling pathway known to be activated by cytokines may also mediate the beneficial effects of insulin in other tissues. Intensive insulin treatment to maintain blood glucose between 80 and 110 mg/dL during the acute hospitalization period results in further benefits to severely burned children [48], including significantly decreased infectious episodes, sepsis, organ dysfunction, and insulin resistance, and it improves mitochondrial oxidative capacity [49]. The recent use of computerized insulin infusion programs in surgical intensive care units has been found to be both an effective and safe method of administering insulin [50]. However, because of the risk of hypoglycemia, infusions of insulin do require close monitoring and are of no use in the outpatient setting [16].

2.3 Anti-hyperglycemic therapeutics: Fenofibrate, metformin, GLP-1 agonists, and SS31

Metformin (glucophage), a biguanide, has been widely used to correct hyperglycemia in diabetic patients and is currently an alternative drug for treatment of injury-induced hyperglycemia. Metformin targets the metabolic process underlying hyperglycemia in critical illness, inhibiting gluconeogenesis and augmenting insulin sensitivity in the periphery [51]. In addition to reducing hyperglycemia, metformin speeds muscle protein

formation and increases the net protein balance in muscle [52]. Metformin appears to have effects analogous to insulin in critically injured patients and is a promising alternative given its safety record in the outpatient setting. Although lactic acidosis has been reported with administration of metformin and other biguanides, this side effect has not been reported in preliminary trials of this drug in severely burned patients. However, patients should be monitored for this development as recommended. Thus, the biguanide drugs should be used with caution as a replacement therapy for insulin.

Mitochondrial oxidative function in skeletal muscle appears to be impaired in patients with insulin resistance, such as type 2 diabetics [53]. Furthermore, severe burn injury also causes mitochondrial dysfunction, which may contribute to insulin resistance after burns [54]. In a randomized control trial of fenofibrate, a peroxisome proliferator-activated receptor alpha agonist, significant reduction of plasma glucose was achieved without inducing hypoglycemia. Administration of this drug to burned children for 2 weeks reduces insulin resistance [55]. Fenofibrate not only ameliorates hyperglycemia and insulin resistance, but also improves wound healing in severely burned patients. Clinical trials evaluating the effects of long-term use in burn patients are now underway [56].

Other approaches to targeting mitochondrial dysfunction targets include the use of SS31, an antioxidant peptide. Studies in thermally injured mice have shown promising improvements in insulin resistance with the use of SS31 [57]. These studies suggest that SS31 may be of benefit in the treatment of post-burn insulin resistance.

Other ongoing approaches to reduce hyperglycemia after burn injury include the use of glucagon-like-peptide (GLP)-1 agonists. GLP-1 suppresses glucagon, stimulates insulin secretion, and therefore, decreases serum blood glucose. A recent study by Deane and coworkers revealed that, in the critically ill, administration of GLP-1 infusions markedly attenuates the glycemic response seen with enteral nutrition [58]. A study of 24 severely burned children showed that, in the acute setting, hyperglycemia could be controlled with a smaller amount of insulin when patients were given a GLP-1 analog [59].

2.4 Ketoconazole

In a prospective randomized trial, the administration of ketoconazole successfully blocked cortisol production but did not affect whole-body catabolism in severely burned patients. Additionally, no alterations were reported in the post-burn inflammatory response, REE, hormones, acute-phase proteins, or sex steroids. These results suggest that hypercortisolemia may not play an important role in the post-burn hypermetabolic catabolic response as once believed [60].

2.5 Testosterone and oxandrolone

Testosterone production is greatly decreased after severe burn injury. In a large prospective trial, serum testosterone levels were reported to be elevated 8–10 days post burn and gradually fall below baseline levels on day 60 [3]. Levels remain below normal for up to 3 years post injury [3]. Testosterone administration makes the use of intracellular amino acids that are derived from protein catabolism more efficient and leads to an overall increase in protein synthesis [61]. Restoring serum testosterone in severely burned males significantly decreases breakdown of muscle and improves protein synthesis [62].

Oxandrolone, an analogue of testosterone that has lower androgenicity and is well absorbed when administered orally, is a more favorable option, particularly for women and prepubescent boys. In skeletal muscle, oxandrolone binds to intracellular androgen receptors. The androgen receptor-oxandrolone complex then moves to the cell nucleus and binds to DNA, stimulating protein synthesis and anabolism [63]. During amino acid

infusions, the use of oxandrolone significantly speeds protein catabolism without affecting the rate of protein break down when compared to a no-oxandrolone group, thereby leading to a higher net protein balance [64]. Oxandrolone has been used in acute and rehabilitating adult burn patients with promising results with regard to weight gain, net protein synthesis in the muscle, and LBM [65, 66]. When treated orally with 0.1 mg/kg oxandrolone twice daily, acute pediatric burn patients exhibit enhanced protein anabolism and upregulation of anabolic genes in the muscle [67, 68]. Oxandrolone affects LBM and bone mineral density not only in the acute setting, but also up to 12 months post burn [68]. More recently, in a single-centered randomized clinical trial, Porro *et al.* demonstrated that oxandrolone, when given at 0.1 mg/kg twice a day for one year post burn, provides benefits that persist for up to 5 years post burn with few deleterious side effects [69]. Increases in LBM and bone mineral content persist for 3–5 years post therapy.

2.6 Recombinant human growth hormone, insulin-like growth factor-1 (IGF-1), and IGF-1 binding protein 3

The GH-IGF-1 axis is a key endocrine axis affected by severe injury and critical illness [70]. Both GH and IGF-1 are significantly reduced following severe burn injury and remain at subnormal levels even 3 years post injury [3]. Studies of the administration of recombinant human growth hormone (*rh*GH) to improve growth and build muscle following burn injury have demonstrated that rhGH ameliorates immune function, wound healing, the hypermetabolic response to major stress, and protein synthesis after burn [71–75]. The benefits of *rh*GH administration continue for up to 1 year after discontinuation of the drug [72, 76]. Patients treated with long-term rhGH experienced greater weight and height gains, improved LBM, and higher bone mineral content. Several doses (0.05, 0.1, and 0.2 mg/kg/day) have been tested in the pediatric burn population, with improvements associated with each dose. The combination of a 12-week resistive and aerobic exercise program with the administration of rhGH (0.05 mg/kg/day) provided an increase in muscle strength and aerobic capacity that was greater than that seen in the non-exercise group, but the gains were comparable to the exercise alone group. However, a prospective, randomized study revealed that *rh*GH increases mortality in critically ill adults [77]. Furthermore, *rh*GH has been noted to cause hyperglycemia in severely burned patients when administered at 0.2 mg/kg/day; lower doses of 0.05mg/kg/day did not lead to hyperglycemia.

The effects of growth hormone (GH) are partly mediated by insulin-like growth factor (IGF-1). Infusions with IGF-1 alone have also been shown to improve protein metabolism. However, hypoglycemic episodes have been reported with IGF-1 alone [78, 79]. IGF-1 appears to inhibit stress-induced muscle proteolysis, explaining the improved protein metabolism seen clinically [80]. Concomitant use of IGF-1 and insulin-like growth factor binding protein 3 (IGFBP-3) attenuates the inflammatory response in severely burned patients. It also appears to elevate constitutive hepatic proteins and reduce IL-1b, TNF-alpha, and acute-phase proteins [81]. When combined with equal doses of IGFBP-3, IGF-1 infusions result in less hyperglycemia than IGF-1 in combination with *rh*GH and less hypoglycemia than with IGF-1 alone. Improved protein synthesis in severely burned patients continues to be observed [82].

In a randomized prospective trial comparing the effects of human growth hormone (hGH) and oxandrolone on metabolism and wound healing after severe burn injury, these drugs were found to have a comparable ability to speed wound healing and diminish weight and nitrogen loss. However, hGH resulted in higher rates of hyperglycemia and REE than oxandrolone [83].

More recent studies have shown that concomitant use of *rh*GH and propranolol attenuates hypermetabolism, reduces peripheral lipolysis, and decreases inflammation, and it does not produce the problematic effects of using *rh*GH alone [78, 84].

3. Conclusion

In spite of the improvements seen in burn care over the last several years, burn injury is still a clinical challenge and continues to be a global public health problem. Mortality has specifically decreased in specialized burn care units practicing aggressive resuscitation, early enteral nutrition, early excision and coverage of wounds, and use of potent antibiotics. With improved survival, the focus of care has shifted to optimizing recovery and rehabilitation. If left untreated, the hypermetabolic response that occurs in severe burns can have detrimental effects on recovery and rehabilitation. Alternative uses and combinations of existing agents that counteract specific aspects of the post-burn pathophysiologic response are promising (Table 1).

4. Expert opinion

Improved clinical care has led to reductions in mortality; 32% of patients with >60% TBSA burns died in 1980–1986, with this mortality rate being reduced to 18% in 1987–2011. With recent elucidation of the pathophysiology of severe burn injury, the ability to conduct both clinical and translational research to attenuate specific aspects of burn complications has been greatly enhanced.

Particular aspects of the hypermetabolic response—the catecholamine surge, hyper-inflammation, insulin resistance, catabolism, and hyperglycemia—may be attenuated using drugs developed to treat these conditions in other populations. The drugs discussed here have mainly been used for investigational purposes in severely burned patients and are not yet standard-of-care therapies despite clear potential clinical benefit. Oxandrolone is the closest of these therapies to becoming a standard-of-care therapy in severely burned patients. It is easy to administer, has few side effects, and when coupled with an aerobic exercise regimen, can improve LBM with long-lasting benefits [69]. The widespread use of oxandrolone in burned patients has been brought about by the positive results from clinical trials discussed in this article. However, further multi-center investigations are needed to understand the molecular mechanisms underlying the possible efficacious effects of this drug. Future studies should include long-term follow-up (>5 years) studies to determine whether the benefit related to LBM persists. As an aerobic exercise program clearly augments the beneficial effects of this drug, clinicians may want to incorporate an exercise program into patients' management plans.

The use of propranolol to reduce complications related to the catecholamine surge and the subsequent increase in cardiac work holds the potential to vastly improve burn patient outcomes. At the very least, a reduction in heart rate and anxiety improves how the patient feels. We recommend propranolol, as opposed to other beta blockers or newer generation anti-hypertension drugs, because of beta 2 adrenoreceptor-mediated effects on fat metabolism. Concerns still exist regarding the safety of this drug in critically ill patients. That is, blunting the post-burn stress response may interrupt a necessary adaptive mechanism for survival. Despite several studies showing that propranolol reduces mortality in other patient populations, the results of the Perioperative Ischemic Evaluation Study (POISE) trial necessitate that the safety and efficacy of this therapy be thoroughly investigated in severely burned patients [85]. In a randomized controlled trial of metoprolol administered to cardiac patients undergoing non-cardiac surgery, a significant increase in mortality was found in the treatment group. Increased mortality has not been found in our

single-center studies of propranolol. Current single- and multi-center trials will reveal whether the use of propranolol is safe and efficacious in severely burned patients.

Attenuation of hyperglycemia to reduce blood glucose to <110mg/dL improves outcomes in critically ill patients and in burn patients. Although administration of an intensive insulin protocol has anti-catabolic and anti-inflammatory results, the difficulty in maintaining continuous monitoring and feeding to avoid hypoglycemic episodes in the critical care setting reduces the enthusiasm of most clinical teams for using this agent in the acute unit or even after discharge. Other drugs proven to be effective for maintaining normoglycemia are still in the early stages of use in this patient population; however, preliminary studies are promising.

Growth hormone has fallen out of favor due to expense and due to concerns regarding safety that surfaced following a European trial showing increased mortality in critically ill patients [86]. In severely burned children, only beneficial effects were noted [75]. Recent studies in non-burned patients have ignited a controversy regarding whether an association exists between GH use and later development of cancers [87, 88]. To date, follow-up studies in patients administered growth hormone to improve muscle synthesis and growth have not found adverse events associated with the use of rhGH.

Combination therapies that take advantage of drugs with complementary modes of action have largely been unexplored. However, we briefly reviewed several of the studies that have been beneficial, and this area shows promise. Future multi-centered studies focusing on counteracting multiple aspects of the post-burn hypermetabolic response may yield further advances in patient care.

The use of anabolic and anti-catabolic agents has allowed attenuation of the hypermetabolic response to burn injury and improved patient outcomes. With an ever increasing understanding of molecular mechanisms underlying this response, additional drug targets may be identified to improve patient care even further. Further research in the field of burn care is warranted, as many unanswered questions remain.

Acknowledgments

We would like to acknowledge support from grants from the National Institute for Disabilities and Rehabilitation Research (H133A070026), the National Institutes of Health (P50-GM60338, R01-GM56687-11S1, and T32-GM8256), and Shriners Hospitals for Children (71001, 71008, and 84080). CCF is an ITS Career Development Scholar supported, in part, by NIH KL2RR029875 and NIH UL1RR029876.

Grant Information:

This review was supported by grants from the National Institute on Disability and Rehabilitation Research (H133A070026, H133A70019), the National Institutes of Health (P50-GM06338, R01-HD049471, T32-GM8256), and Shriners Hospitals for Children (71008, 71001, 84080). CCF is an ITS Career Development Scholar supported, in part, by NIH KL2RR029875 and NIH UL1RR029876. Portions of the studies described here are registered at clinicaltrials.gov, NCT00675714.

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Article Highlights

- The hypermetabolic response to severe burn injury has deleterious consequences including catabolism, inflammation, insulin resistance, supraphysiologic levels of catecholamines, and associated sequelae.
- Modulators of the hypermetabolic response that improve acute outcomes now appear to have long-term benefits in burn patients.
- Beta blockade with propranolol has been used to attenuate catecholamine-mediated responses to burn.
- Burn-induced insulin resistance can be reduced with insulin, fenofibrate, metformin, or GLP-1.
- Anti-catabolic agents such as testosterone, oxandrolone, rhGH, IGF-1, and IGF-1/BP3 can be used to improve muscle mass.
- Large multi-center studies are needed to bring these therapies into standard-of-care treatment regimens
- Further research is needed to broaden the application of existing drugs to burn care.

Expert Opin Pharmacother. Author manuscript; available in PMC 2013 February 19.

Table 1

Summary of hypermetabolic response modulators

Drug	Inflammatory response	Cardiac work	Hepatic steatosis	Protein balance	Insulin resistance/hyperglycemia	Wound healing
Propranolol	Decreased	Decreased	Decreased	Improved	Reduced	Improved
Insulin	Decreased	No change	Decreased	Improved	Reduced	Improved
Testosterone	Unknown	Unknown	Unknown	Improved	Unknown	Unknown
Oxandrolone	Decreased	Improved	No change	Improved	No change	Improved
rhGH	Decreased	No change	Unknown	Improved	Increased	Improved
IGF/IGFBP-3	Decreased	No change	Unknown	Improved	Reduced	Improved
Fenofibrate	No change	No change	Unknown	No change	Reduced	Improved
Metformin	Unknown	Unknown	Unknown	Improved	Reduced	Unknown
GLP-1	Unknown	Unknown	Unknown	Unknown	Reduced	Unknown
Ketoconazole	No change	No change	No change	Unknown	Unknown	Unknown