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BURNS: WHERE ARE WE STANDING WITH PROPRANOLOL, OXANDROLONE, rhGH, AND THE NEW INCRETIN ANALOGUES?

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Abstract

Purpose of review—The hypermetabolic response in critically ill patients is characterized by hyperdynamic circulatory, physiologic, catabolic and immune system responses. Failure to satisfy overwhelming energy and protein requirements after, and during critical illness, results in multiorgan dysfunction, increased susceptibility to infection, and death. Attenuation of the hypermetabolic response by various pharmacologic modalities is emerging as an essential component of the management of severe burn patients. This review focuses on the more recent advances in therapeutic strategies to attenuate the hypermetabolic response and its associated insulin resistance post-burn.

Recent findings—At present, beta-adrenergic blockade with propranolol represents probably the most efficacious anti-catabolic therapy in the treatment of burns. Other pharmacological strategies include growth hormone, insulin-like growth factor, oxandrolone and intensive insulin therapy.

Summary—Novel approaches to the management of critical illness by judicious glucose control and the use of pharmacologic modulators to the hypercatabolic response to critical illness have emerged. Investigation of alternative strategies, including the use of metformin, glucagon-like-peptide-1 and the PPAR- γ agonists are under current investigation.

Keywords

Nutrition; glucose; propranolol; critical illness

INTRODUCTION

Critical illness or injury is associated with a profound metabolic and catabolic response which persists long after the initial insult [1]. The response is characterized by supraphysiologic metabolic rates, hyperdynamic circulation, constitutive muscle and bone

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catabolism, growth retardation, insulin resistance, and increased risk for infection [2]. Immediately after stress or injury there is a decrease in metabolism and tissue perfusion – an “ebb” phase [2]. This is quickly followed by a period of increased metabolic rates and hyperdynamic circulation – a “flow” phase. If untreated, physiologic exhaustion ensues, and the insult becomes fatal [2-4]. This period is characterized by profoundly accelerated glycolysis, lipolysis, proteolysis, insulin resistance, liver dysfunction, and decreases of lean body mass and total body mass. A 10% loss of total body mass leads to immune dysfunction; 20% leads to decreased wound healing; 30% leads to severe infections; and a 40% loss leads to death [5].

Inflammatory cytokine levels, serum hormone, acute protein and constitutive proteins are altered upon onset of any acute critical illness and remain abnormal throughout the convalescent period. Resting metabolic rates of patients with critical illnesses or injuries increase in a curvilinear fashion: from close to normal predicted levels to twice that of normal predicted levels for patients with significant comorbidities and sepsis. However, it remains uncertain when exactly these measurements return to normal levels.

Muscle protein is degraded much faster than it is synthesized [2,6]. Net protein loss leads to loss of lean body mass and severe muscle wasting significantly contributing to decreased strength and failure to fully rehabilitate [7]. Persisting protein degradation results in significant negative whole-body and cross-leg nitrogen balance [7,8]. Protein catabolism is directly related to increases in metabolic rate [7].

Elevated circulating levels of catecholamines, glucagon, cortisol and gluconeogenic hormones in response to critical illness stimulate inefficient glucose production in the liver [2,5]. Stable isotope data from critically ill thermally injured patients indicate significant derangements in major adenosine tri-phosphate (ATP) consumption pathways including increased protein turnover, urea production and gluconeogenesis. Glycolytic-gluconeogenic cycling is increased coupled with an increase of 450% in triglyceride-fatty acid cycling [2,5]. Collectively, these changes lead to increased glycogenolysis, gluconeogenesis, and increased circulation of glucogenic precursors. This leads to hyperglycemia and impaired insulin sensitivity related to post-receptor insulin resistance [9,10*]. The end-product of anaerobic glucose oxidation – lactate – is recycled to the liver to produce more glucose via gluconeogenic pathways [8]. Serum glucose and serum insulin remain significantly increased through the convalescent period [2] and characteristics of insulin resistance persist for up to 3 years post-burn [10*]. Large amounts of glucose, as a source of energy, are required to decrease severe protein catabolism [9,10*]. Catabolic hormones counteract the anabolic effect of insulin resulting in significant lipolysis, proteolysis, and hyperglycemia [9,10*]. To meet the remaining metabolic and energy requirements, proteins and lipids are rapidly but inefficiently utilized after critical illness [9,10*]. Skeletal muscle becomes the major obligatory fuel. Classically, in starvation, the metabolic rate falls, and fat becomes the major source for fuel. During critical illness, however, there is the eventual and persistent increase in metabolic rate and the body fails to utilize fat as an energy source. Lipids have limited “protein-sparing” effect, leading to substantial muscle protein catabolism [2]. The hypermetabolic, hypercatabolic response mandates aggressive nutritional replacement to meet these metabolic requirements.

Perturbations, such as sepsis increase metabolic rates and protein catabolism compared to those with like-size injuries or insults that do not develop sepsis [7,11]. A vicious cycle exists, as patients that are catabolic are more susceptible to sepsis due to changes in immune function and immune response. The emergence of multi-resistant organisms have led to increases in sepsis-related infections and death overall [4,12].

The Hormonal Response to Injury

Elevated levels of catecholamines, cortisol, and glucagon perpetuate the profound changes in metabolic rates, growth and physiology seen after severe injury and critical illness. Many groups have studied the effects of recombinant human growth hormone (rhGH), insulin, insulin-like growth factor (IGF)-1 and IGF-binding protein-3 (IGFBP-3) – in combination – testosterone and oxandrolone as potential anabolic agents. To counter elevated levels of catecholamines, groups have administered the adrenergic antagonist, propranolol. The use of anabolic or anti-catabolic agents in the critically ill, in addition to standard of care, has led to significant decreases in protein catabolism.

Recombinant Human Growth Hormone

Recombinant human growth hormone (rhGH) significantly improved in weight gain, height velocities, lean body mass, bone mineral content and cardiac function [13]. Daily intramuscular administration of rhGH at doses of 0.2 mg/kg as a daily injection during acute burn care has favorably influenced the hepatic acute phase response [5,14], increased serum concentrations of its secondary mediator IGF-1 [5], improved muscle protein kinetics, maintained muscular growth [13], decreased donor site healing time by 1.5 days [5], improved resting energy expenditure and decreased cardiac output [13]. These beneficial effects of rhGH are mediated by IGF-1 and patients receiving treatment, demonstrated 100% increases in serum IGF-1 and IGFBP-3 relative to healthy individuals [5]. However, in a prospective, multicenter, double-blind, randomized, placebo-controlled trial involving 247 patients and 285 critically ill non-burned patients Takala and others found that high doses of rhGH (0.10 ± 0.02 mg/kg BW) were associated with increased morbidity and mortality [5,13]. Others demonstrated growth hormone treatment to be associated with hyperglycemia and insulin resistance. However, neither short-term nor long-term administration of rhGH was associated with an increase in mortality in severely burned children [13].

IGF-1 with IGFBP-3

Because IGF-1 mediates the effects of growth hormone, the infusion of equimolar doses of recombinant human IGF-1 and IGFBP-3 to burned patients has been demonstrated to effectively improve protein metabolism in catabolic pediatric subjects and adults with significantly less hypoglycemia than rhGH itself [5,15,16]. It attenuates muscle catabolism and improves gut mucosal integrity in children with serious burns [5,16]. Immune function is effectively improved by attenuation of the type 1 and type 2 hepatic acute phase responses, increased serum concentrations of constitutive proteins, and vulnerary modulation of the hypercatabolic use of body protein [16,17]. However, studies by Langouche and Van den Berghe [18] indicate that the use of IGF-1 alone is not effective in critically ill patients without burns.

Oxandrolone

Treatment with anabolic agents such as oxandrolone, a testosterone analog which possesses only 5% of its virilizing androgenic effects, improves muscle protein catabolism via enhanced protein synthesis efficiency, reduces weight loss and increases donor site wound healing [19]. In a prospective randomized study Wolf and colleagues [20] demonstrated that administration of 10 mg of oxandrolone every 12 h decreased hospital stay. In a large prospective, double-blind, randomized single-center study, oxandrolone given at a dose of 0.1 mg/kg every 12 h shortened length of acute hospital stay, maintained lean body mass and improved body composition and hepatic protein synthesis [19]. Long-term treatment with this oral anabolic during rehabilitation in the outpatient setting is more favorably regarded by pediatric subjects than parenteral anabolic agents. Oxandrolone successfully abates the effects of burn-associated hypermetabolism on body tissues and significantly increases body

mass over time, lean body mass at 6, 9, and 12 months after burn, and bone mineral content by 12 months after injury vs. unburned controls [21]. Patients treated with oxandrolone show few complications relative to those treated with rhGH. However, it must be noted that although anabolic agents can increase lean body mass, exercise is essential to developing strength [22].

Propranolol

Propranolol treatment reduced thermogenesis, marked tachycardia, and resting energy expenditures [5,6,23*]. By reducing heart rates by 20%, there was a significant decrease in cardiac work [6,23*]. Propranolol helps prevent peripheral lipolysis by blocking the activation of the beta-2-adrenergic receptor (stimulated by catecholamines) [2,5,6]. Propranolol treatment significantly decreased fatty infiltration of the liver [24]. Propranolol also increases lean body mass and decreases skeletal muscle wasting as proven by stable isotope and body composition studies [6]. The underlying mechanism of action of propranolol is still unclear; however, its effect appears to occur due to an increased protein synthesis in the face of a persistent protein breakdown and reduced peripheral lipolysis [25]. Recent data suggest that administration of propranolol given at 4 mg/kg BW/q24 also markedly decreased the amount of insulin necessary to decrease elevated glucose level post-burn [23*]. Propranolol may thus constitute a promising approach to overcome post-burn insulin resistance.

Insulin

Insulin represents probably one of the most extensively studied therapeutic agents, and novel therapeutic applications are constantly being found. Besides its ability to decrease blood glucose via mediating peripheral glucose uptake into skeletal muscle and adipose tissue and suppressing hepatic gluconeogenesis, insulin is known to increase DNA replication and protein synthesis via control of amino acid uptake, increase fatty acid synthesis and decreased proteinolysis [26]. The latter makes insulin particularly attractive for the treatment of hyperglycemia in severely burned patients because insulin given during acute hospitalization has been shown to improve muscle protein synthesis, accelerate donor site healing time, and attenuate lean body mass loss and the acute phase response [9,27,28]. In addition to its anabolic actions, insulin was shown to exert totally unexpected anti-inflammatory effects potentially neutralizing the proinflammatory actions of glucose [9,28]. These results suggest a dual benefit of insulin administration: reduction of proinflammatory effects of glucose by restoration of euglycemia and a proposed additional insulin-mediated anti-inflammatory effect [29]. Van den Berghe and colleagues [31] confirmed the beneficial effects of insulin in a large recent milestone study. Insulin administered to maintain glucose at levels below 110 mg/dl decreased mortality, incidence of infections, sepsis and sepsis-associated multiorgan failure in surgically critically ill patients [30]. They also found intensive insulin therapy to significantly reduce newly acquired kidney injury, accelerating weaning from mechanical ventilation and accelerating discharge from the ICU and the hospital. The authors further showed that insulin given during the acute phase not only improved acute hospital outcomes but also improved long-term rehabilitation and social reintegration of critically ill patients over a period of 1 year, indicating the advantage of insulin therapy [32,33]. However, since strict blood glucose control in order to maintain normoglycemia was required to obtain the most clinical benefit, a dialogue has emerged between those who believe that tight glucose control is beneficial for patient outcome and others who fear that high doses of insulin may lead to increased risks for hypoglycemic events and its associated consequences in these patients [30]. In fact, a recent multi-center trial in Europe [Efficacy of Volume Substitution and Insulin Therapy in Severe Sepsis (VISEP)] investigated the effects of insulin administration on morbidity and mortality in patients with severe infections and sepsis [34]. The authors found that insulin administration

did not affect mortality but the rate of severe hypoglycemia was 4-fold higher in patients receiving intensive insulin therapy when compared to the conventional therapy group [34]. Another large multi-center study examined the use of a continuous hyperinsulinemic-euglycemic clamp throughout ICU stay and found a dramatic increase in serious hypoglycemic episodes [35]. The ideal target glucose range therefore has not been found and several groups are currently undertaking clinical trials in order to define ideal glucose levels for the treatment of ICU and burned patients: a study by Finney and colleagues [36] suggests glucose levels of 140 mg/dl and below, while the Surviving Sepsis Campaign recommend to maintain glucose levels below 150 mg/dl [37]. However, maintaining a continuous hyperinsulinemic-euglycemic clamp in burn patients is particularly difficult since these patients are being continuously fed large caloric loads via enteral feeding tubes in an attempt to maintain euglycemia. Because burn patients require weekly operations and daily dressing changes, enteral nutrition needs occasionally to be stopped, which may lead to disruption of gastrointestinal motility and increased risk of hypoglycemia [8].

Metformin

Metformin (Glucophage), a biguanide, has been suggested as an alternative means to correct hyperglycemia in severely injured patients [38]. By inhibiting gluconeogenesis and augmenting peripheral insulin sensitivity, metformin directly counters the two main metabolic processes which underlie injury-induced hyperglycemia [39]. In addition, metformin has also been rarely associated with hypoglycemic events, thus possibly eliminating this concern associated with the use of exogenous insulin [40]. In a small randomized study reported by Gore and colleagues [38] metformin reduced plasma glucose concentration, decreased endogenous glucose production and accelerated glucose clearance in severely burned. A follow-up study looking at the effects of metformin on muscle protein synthesis confirmed these observations and demonstrated an increased fractional synthetic rate of muscle protein and improvement in net muscle protein balance in metformin-treated patients [39]. Metformin may thus, analogous to insulin, have efficacy in critically injured patients as both, an anti-hyperglycemic and muscle protein anabolic agent. Despite the advantages and potential therapeutic uses, treatment with metformin, or other biguanides, has been associated with lactic acidosis [40]. To avoid metformin-associated lactic acidosis, the use of this medication is contra-indicated in certain diseases or illnesses in which there is a potential for impaired lactate elimination (hepatic or renal failure) or tissue hypoxia – and should be used with caution in subacute burn patients.

GLP-1 and PPAR- γ Agonists

Other ongoing trials in order to decrease post-burn hyperglycemia include the use of glucagon-like-peptide (GLP)-1 and PPAR- γ agonists (e.g., pioglitazone, thiazolidinediones) or the combination of various anti-diabetic drugs. PPAR- γ agonists, such as fenofibrate, have been shown to improve insulin sensitivity in patients with diabetes. Cree and colleagues [41] found in a double-blind, prospective, placebo-controlled, randomized trial that fenofibrate treatment significantly decreased plasma glucose concentrations by improving insulin sensitivity and mitochondrial glucose oxidation. Fenofibrate also led to significantly increased tyrosine phosphorylation of the insulin receptor (IR) and IRS-1 in muscle tissue after hyperinsulinemic-euglycemic clamp when compared to placebo-treated patients, indicating improved insulin receptor signaling [41]. Exogenous GLP-1 decreases blood glucose by suppressing glucagon, stimulating insulin and slowing gastric emptying. Because the former effects are glucose dependent, the use of GLP-1 is not associated with hypoglycemia. Deane and colleagues [42] demonstrated in a recent study including seven mechanically ventilated critically ill patients, not previously known to have diabetes, that acute, exogenous GLP-1 infusion markedly attenuates the glycemic response to enteral nutrition in the critically ill, suggesting that GLP-1 and/or its analogs may have the potential

to manage hyperglycemia in critically ill patients. In an open-label study of 24 severely burned pediatric patients, exenatide, an exogenous GLP-1 analog, significantly reduced the amount of exogenous insulin needed to control hyperglycemia (to maintain plasma glucose levels between 80 and 140 mg/dl) in the acute setting [43]. Although these studies are promising as novel approaches to attenuating hyperglycemia in the acute setting, larger, randomized controlled trials are needed to truly assess the utility in critically ill patients.

Conclusion

Critically ill patients have profound metabolic alterations associated with persistent changes in glucose metabolism and impaired insulin sensitivity significantly contribute to adverse outcome of this patient population. At present, beta-adrenergic blockade with propranolol represents probably the most efficacious anti-catabolic therapy in the treatment of burns. Other pharmacological strategies that have been successfully utilized in order to attenuate the hypermetabolic response include growth hormone, insulin-like growth factor and oxandrolone. (Table 1 and Fig. 1) [44-48]. Maintaining blood glucose at levels below 110 mg/dl using intensive insulin therapy has been shown to reduce mortality and morbidity in critically ill patients; however, associated hypoglycemic events have led to the investigation of alternative strategies, including the use of metformin and the PPAR- γ agonist fenofibrate. Nevertheless, further studies are warranted to determine ideal glucose ranges and the safety and the appropriate use of the above-mentioned drugs in critically ill, severely burned patients.

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Figure 1.

Relative efficacy of the different anabolic agents to improve muscle protein synthesis compared to standard of care alone in severely burned pediatric patients. Changes in net protein balance of muscle protein synthesis and breakdown induced by burn injury were measured by stable isotope studies using d5-phenylalanine infusion studies previously published. *Denotes significance of $p < 0.05$. Graphs are averages $\pm$ SEM. White bars represent patients with burns $\geq 40\%$ TBSA that received no anabolic agents. Black bars represent patients with burns of at least 40% TBSA that were randomized to receive drug. IGF-1=insulin-like growth factor-1; rhGH=recombinant human growth hormone. (Reproduced with permission from [5]).

Table 1
Summary of the main effects of various pharmacologic interventions to alter the hypermetabolic response to burn injury.

Drug	Inflammatory Response	Stress Hormones	Body Composition	Net Protein Balance	Insulin Resistance/Glucose Metabolism	Cardiac Work
rhGH	Improved	No Difference	Improved	No Difference	Hyperglycemia	No Difference
IGF-1	Improved	No Difference	Improved	Improved	Improved	No Difference
Oxandrolone	Improved	No Difference	Improved	Improved	No Difference	No Difference
Insulin	Improved	No Difference	Improved	Improved	Improved	No Difference
Fenofibrate	No Difference	No Difference	No Difference	No Difference	Improved	No Difference
GLP-1	Unknown	Unknown	Unknown	Unknown	Improved (Indirect)	Unknown
Propranolol	Improved	Improved	Improved	Improved	Improved	Improved
Ketoconazole	Unknown	Improved	Unknown	Unknown	Unknown	Unknown
rhGH + Propranolol	Improved	Improved	Improved	Improved	Improved	Improved
Oxandrolone + Propranolol	Improved (Preliminary)	Improved (Preliminary)	Improved (Preliminary)	Improved (Preliminary)	Improved (Preliminary)	Improved (Preliminary)

The data summarized in the table is extrapolated from previously published data [6,13,15,17,19,25,41,44-47].

GLP-1=glucagon-like peptide-1; IGF-1=insulin-like growth factor-1; rhGH=recombinant human growth hormone. Reproduced with permission from [48].