NUTRITIONAL AND PHARMACOLOGICAL MODULATION OF THE METABOLIC RESPONSE OF SEVERELY BURNED PATIENTS: REVIEW OF THE LITERATURE (part II)*

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SUMMARY. Severe burn patients are some of the most challenging critically ill patients, with an extreme state of physiological stress and an overwhelming systemic metabolic response. Increased energy expenditure to cope with this insult necessitates mobilization of large amounts of substrate from fat stores and active muscle for repair and fuel, leading to catabolism. The hypermetabolic response can last for as long as nine months to one year after injury and is associated with impaired wound healing, increased infection risks, erosion of lean body mass, hampered rehabilitation, and delayed reintegration of burn survivors into society. Reversal of the hypermetabolic response by manipulating the patient’s physiological and biochemical environment through the administration of specific nutrients, growth factors, or other agents, often in pharmacological doses, is emerging as an essential component of the state of the art in severe burn management. Early enteral nutritional support, control of hyperglycaemia, blockade of catecholamine response, and use of anabolic steroids have all been proposed to attenuate hypermetabolism or to blunt catabolism associated with severe burn injury. The present study is a literature review of the proposed nutritional and metabolic therapeutic measures in order to determine evidence-based best practice. Unfortunately, the present state of our knowledge does not allow the formulation of clear-cut guidelines. Only general trends can be outlined which will certainly have some practical applications but above all will dictate future research in the field.

Part II
Introduction

Part I of this review examined the energy and nutrient requirements of healthy and critically ill patients and the metabolic and hormonal changes following severe burn injury, as well as the assessment of energy and substrate requirements in such patients. Type (hypocaloric or hypercaloric), route, and timing of nutritional support were also reviewed. Part II of the review investigates the nutritional and metabolic therapeutic measures that can be undertaken to counter the effects of hypermetabolism in severely burned patients.

Insulin and hyperglycaemia control in severe burns

A high carbohydrate diet (3% fat, 82% carbohydrate, and 15% protein) stimulates protein synthesis, increases endogenous insulin production, and improves lean body mass accretion relative to an isocaloric-isoprotein but high-fat enteral diet 14 and may improve the net balance of skeletal muscle protein. 15 Enhanced insulin concentrations may explain the improvement observed in muscle protein synthesis with such high carbohydrate diets. 14,33 However, these diets may be associated with elevated glucose, which may be detrimental in critically ill patients. 98 In a study of 58 paediatric burn patients, there was a significant association between poor glucose control and complications such as increased bacteraemia, reduced skin graft take, and increased mortality. 99 Moreover, the metabolic link between hyperglycaemia and muscle loss following severe injury has been well established. 99 It has been shown also that hyperglycaemia, as well as accelerated muscle catabolism, adversely affects the immune response and survival. 100 Aggressive monitoring and treatment of hyperglycaemia are therefore highly recommended 1 and therapies that improve glucose tolerance may be of clinical value in ameliorating muscle catabolism in critically injured patients. 100

Since the recognition of the negative impact of hyperglycaemia on outcome, it has been argued that hypocaloric feeding, although there is no clear definition available, might facilitate glucose control, and it has been regularly proposed in the critically ill. The rationale behind the concept of hypocaloric feeding, found in the literature since the 1990s, is that an organism has some adaptation capacity and can reduce energy expenditure to some extent. Indeed, the normal response to injury includes a reduction of appetite. Nevertheless, the only randomized controlled study investigating iso- and hypocaloric parenteral nutrition did not confirm this potential benefit of glucose control. Moreover, although the evidence is strongly against prolonged hypocaloric feeding - that is, more than 96 h - the demonstration that limiting underfeeding improves outcome in the critically ill still awaits a prospective trial. Using an evidence-based approach, hypocaloric feeding in the critically ill cannot be supported.

On the other hand, tight glucose control in severe burn patients seems to be safe and associated with decreased risk of infection and improved survival. The treatment of hyperglycaemia generally includes exogenous insulin administration to reach euglycaemia. Continuous infusions of the anabolic peptide, insulin, in victims of major thermal injury prevent muscle catabolism and preserve lean body mass without increasing hepatic triglyceride production. These benefits appear to be due to decreased infections as well as to improved amino acid metabolism. Beneficial effects of insulin with regard to acute phase proteins and cytokine response have also been demonstrated. Insulin administration during the acute hospitalization of severely burned children significantly decreases hepatic acute phase proteins. Furthermore, insulin significantly decreases pro-inflammatory cytokines in severe trauma patients. Recently it was demonstrated that insulin administration in an experimental burn wound infection model had beneficial effects on the inflammatory response by decreasing the pro-inflammatory cytokines interleukin (IL) IL-5, IL-6, and keratinocyte-derived chemokine, and by increasing the beneficial mediator granulocyte colony stimulating factor. Several investigators, however, have asked the question whether the improvements were due to prevention of hyperglycaemia or to the pharmacological effects of insulin on pathways indirectly associated with glucose disposal. This question has not been answered to any real effect yet and will undoubtedly be the focus of future investigations. Irrespective, insulin infusions are suited to the closely monitored environment of the burn intensive care unit but are impractical in the rehabilitative outpatient setting.

Both insulin and metformin, an oral hypoglycaemic, have been shown to attenuate hyperglycaemia, reduce net muscle protein catabolism, and increase the rate of muscle protein synthesis following severe burn injury. Findings suggest that metformin and insulin may work also synergistically to further improve muscle protein kinetics. However, the anabolic effect on muscle protein of metformin is significant in contradistinction to the modest effect of insulin. Metformin use is associated with lower endogenous glucose production and glucose oxidation. When given with glucose, it improves glucose disposal and when given with additional insulin, it improves glucose uptake. The mechanisms involved include improved insulin sensitivity and thus greater insulin effects, rather than direct effects on glucose transporter-4 activity or effects on net protein synthesis.

Recently, the peroxisome proliferator-activated receptor-gamma agonists, known as thioglitazones, have been shown to have favourable effects on hyperglycaemia control. These agents have been used in patients with type II diabetes mellitus as insulin sensitizers. They are thought to be effective through suppression of peripheral lipolysis and redistribution of triglyceride stores to peripheral fat. It has also been shown that fenofibrate treatment decreases serum levels of glucose and improves insulin-stimulated glucose uptake. Nevertheless, more studies will be required before treatment with hypoglycaemic agents in addition to insulin can be widely adopted for severely burned patients.

Pharmacological modulation of the hormonal and endocrine response

Early wound excision and wound closure, coupled with aggressive enteral nutritional support with high-protein formulas, do not prevent post-resuscitation marked hypermetabolism burn physiology. It seems that post-burn hypermetabolism reversal cannot be fully achieved despite evidence-based improvements in surgical and nursing care. It requires apparently more than early enteral nutritional support. The realization that this physiology will continue for some months after wound closure and that there may be adverse consequences of inadequately supported catabolism in some patients has led to increasing interest in modifying the physiology, rather than simply supporting it.

Similarly to acute illness, burn injury is associated with increased levels of catecholamines, cortisol, and catabolic hormones augmenting REE and partly mediating the persistent hypermetabolic response. It is logical to assume that blockade of the catecholamine response or the use of anabolic steroids may attenuate hypermetabolism or blunt catabolism. New and innovative methods to modulate hormonal imbalances after burn injury have been the subject of intensive study. The most important agents investigated include: 1. anabolic hormones such as growth hormone, insulin, insulin-like growth factor (IGF-I), IGF-I and IGF-binding protein 3 (IGFBP-3) combinations, oxandrolone,
or testosterone; and 2. anticatabolic agents that include adrenergic antagonists (propranolol or metoprolol).14

Growth hormone
Pharmacological adjuncts are often utilized to convert catabolic patients to an anabolic state.16 The concept of anabolic steroids was brought to the forefront of the nutritional management of severely burned patients in the mid-1990s.18,110 While these patients may reach an anabolic state on their own, therapeutic interventions with soluble protein hormones and anabolic steroids can shorten the infirm period and improve recovery.18 Growth hormone was the first agent used clinically to ameliorate hypermetabolism after injury;16 however, enthusiasm for its use was severely diminished specifically after the increased mortality reported in critically ill adults.111 Likewise, recombinant human growth hormone has several adverse side effects, particularly in the acute care of severely burned patients,16 despite reported benefits following intramuscular administration on the hepatic acute phase response with increasing serum concentrations of its secondary mediator IGF-I, and despite improved muscle protein kinetics, muscular growth, and decreased donor site healing time.14,111-115 IGF-I, on the other hand, mediates the effects of growth hormone and can produce anabolism without the direct catabolic effects seen with growth hormone.14,16 IGF-I infusion to burn patients has been demonstrated to effectively improve protein metabolism in catabolic paediatric subjects and adults with significantly less hypoglycaemia than growth hormone itself. It attenuates muscle catabolism and improves gut mucosal integrity in children with serious burns. Immune function is effectively improved as well by attenuation of the type 1 and type 2 hepatic acute phase responses, increased serum concentrations of constitutive proteins, and vulnerability modulation of the hypercatabolic use of body protein.14,118-120 However, subjects treated with IGF-I may develop peripheral neuropathies, again quelling any enthusiasm for widespread use of this agent.16,121

Oxandrolone
Testosterone levels are extremely diminished after severe injury.16,122 Oxandrolone is an orally administered testosterone analogue, an anabolic hormone, and it has been used clinically to treat muscle wasting in various disease processes such as AIDS as also in convalescing burn patients to reverse skeletal muscle catabolism.2,16,18,106,123 In severely burned children, oxandrolone improves muscle protein metabolism through enhanced protein synthesis efficiency and increases anabolic gene expression in muscle.2,124 In adult burn patients, it significantly decreases weight loss and net nitrogen loss and effectively improves lean body mass, especially in emaciated subjects whose treatment has been delayed. It increases donor site wound healing and decreases hospital stay.2,14,18,110,123,126 Body weight and lean body mass can also be effectively restored in the post-burn recovery period with oxandrolone.127 Long-term administration of oxandrolone during rehabilitation in the outpatient setting is more favourably regarded for paediatric subjects than parental anabolic agents and safely improves lean body mass, bone mineral content, and bone mineral density in severely burned children.14,128 Significant increases in body mass have been observed over time at 6, 9, and 12 months, and in bone mineral content by 12 months after burn injury.14,129 Overall, it seems that oxandrolone may be beneficial in patients with large body surface area burns;1 however, it may enhance collagen deposition in acute respiratory distress, it may be associated with increased ventilatory days, and it may significantly increase hepatic transaminase.2 It must also be noted that although anabolic agents can increase lean body mass, exercise is essential to developing strength.14,129

Beta-adrenergic blockade
Immediately after major trauma or severe burns, there is a tenfold increase in plasma endogenous catecholamine concentrations, primary mediators of the hypermetabolic response, producing a hyperdynamic circulation, increasing basal energy expenditure, and promoting catabolism of skeletal-muscle proteins.14,130,131 Recently there has been an increased enthusiasm for the use of beta-blockers in the treatment of elective non-cardiac operations as well as in other trauma and surgical patients.132,133 Beta-adrenergic blockade of severely thermally injured subjects with propranolol (a non-selective beta-antagonist) can blunt the catecholamine effect by attenuating hypermetabolism, decreasing oxygen demand and REE, diminishing obligatory thermogenesis, and decreasing cardiac work, heart rate, and cardiac oxygen demand.14,42 Beta-blockers may also attenuate very effectively catecholamine-induced muscle catabolism and lipolysis,14,134,136 modify catecholamine-mediated defect in lymphocyte activation, and improve immune response with decreased infectious complications.137 Stable isootope and serial body composition studies have shown that propranolol reduces skeletal muscle wasting and increases lean body mass after major thermal injuries by enhancing intracellular recycling of free amino acids for protein synthesis.14 Moreover, long-term use of propranolol for acute care in burn patients, at a dose titrated to reduce heart rate by 20%, decreases peripheral lipolysis and reduces palmitate delivery and uptake by the liver, thus reducing liver fatty infiltration, which typically occurs in these patients.14 Administration of propranolol to burned children reduces the release of free fatty acids from adipose tissue and decreases hepatic triacylglycerol storage and fat accumulation.138,139 In a retrospective study of adult burn patients, use of beta-blockers was associated with a decrease in mortality, the wound infection rate, and wound healing time.140 Although
these data strongly support the use of beta-blockers in burn patients, there are no large randomized studies looking at mortality and wound healing. Nevertheless, many burn units use beta-blockers such as propranolol or metoprolol as the most effective catabolic treatment in burn patients.\(^2\)

RÉSUMÉ. Les grands brûlés constituent un groupe de patients critiquement malades difficiles à traiter et exposés à un stress physiologique extrême et à une réaction métabolique systémique dévastatrice. La quantité augmentée d’énergie qu’il faut utiliser pour affronter cette condition requiert la mobilisation de grandes quantités de substrat provenant des réserves de graisse et du muscle actif pour la réparation et pour carburant, ce qui mène au catabolisme. La réponse métabolique peut durer jusqu’à neuf mois et même un an après la brûlure, associée à un procès altéré de la guérison des lésions, des risques d’infection augmentés, l’érosion de la masse corporelle maigre, une rééducation gênée et un retard dans la réintégration dans la société des patients non décédés. L’inversion de la réponse hypermétabolique, moyennant la manipulation de l’état physiologique et biochimique du patient, obtenu grâce à l’administration de substances nutritives spécifiques, de facteurs de croissance et d’autres agents, souvent en doses pharmacologiques, commence à émerger comme composante essentielle de l’état de l’art pour ce qui concerne la gestion des brûlures sévères. Le support nutritif entéral précoce, le contrôle de l’hyperglycémie, le blocus de la réaction des catécholamines et l’emploi de stéroïdes anaboliques ont été proposés pour atténuer l’hypermétabolisme ou pour émousser le catabolisme associé aux brûlures sévères. Les Auteurs de la présente étude ont passé en revue la littérature relative pour ce qui concerne les mesures thérapeutiques nutritionnelles et métaboliques proposées dans le but de déterminer les pratiques meilleures sur la base de l’évidence. Malheureusement, l’état présent des connaissances ne permet pas la formulation de lignes directrices bien définies. Il est seulement possible d’indiquer à grands traits des tendances générales qui certainement auront des applications pratiques mais surtout dictent les recherches futures dans ce secteur.

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123