Anabolic strategies in critical illness

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Critical illness precipitates a marked catabolic response, with protein wasting and loss of lean body mass. Prolongation of this response leads to impaired immunity, poor wound healing, loss of intestinal barrier function and muscle weakness, thereby increasing morbidity and perhaps mortality. Conventional nutritional support only partially ameliorates this process. Disappointingly, specific anabolic and anticatabolic strategies have so far met with only limited success, although recent findings, in particular studies demonstrating the potential value of aggressive insulin therapy and the administration of growth hormone secretagogues, have been encouraging.

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Abbreviations

GH	growth hormone
GHBP	growth hormone binding protein
GHRP	growth hormone releasing peptide
GnRH	gonadotrophin releasing hormone
ICU	intensive care unit
IGF-1	insulin-like growth factor-1
IGFBP	insulin-like growth factor binding protein
PRCT	prospective randomised controlled trial
rhGH	(recombinant human) growth hormone
TRH	thyrotrophin releasing hormone
TSH	thyroid stimulating hormone

Introduction – the metabolic response to critical illness

The metabolic response to critical illness is associated with global hypermetabolism, insulin resistance, alterations in substrate utilization and a negative nitrogen balance. Resting energy expenditure peaks in the second week of illness, increasing to as much as 60% greater than predicted normal values [1]. Although protein synthesis is increased (particularly in the liver [2] and immune system [3]), proteolysis is increased to a greater extent and more than 14% of total body protein can be lost over a 21-day period, the rate of loss being maximal during the first 10 days of critical illness [4]. These losses are far greater than can be accounted for by immobility alone. Initially protein loss is predominantly from skeletal muscle, later the viscera become the major site of proteolysis [5], although cardiac muscle is apparently spared [6].

These changes are triggered by a variety of complex mechanisms including the release of pro-inflammatory mediators and alterations in the neuroendocrine axes (Figure 1). Cytokines, including tumour necrosis factor, interleukin-1 and interleukin-6, influence skeletal muscle catabolism both directly, by modulating protein synthesis and degradation, and indirectly, through inhibition of the regulatory actions of anabolic hormones [7] and activation of the hypothalamic–pituitary–adrenal axis [8]. Global alterations in the function of the hypothalamic–pituitary axis affect the secretion of growth hormone, thyroid hormones, prolactin and gonadal steroids, whereas activation of the hypothalamic–pituitary–adrenal axis results in elevated catecholamine, glucocorticoid and mineralocorticoid levels [9••].

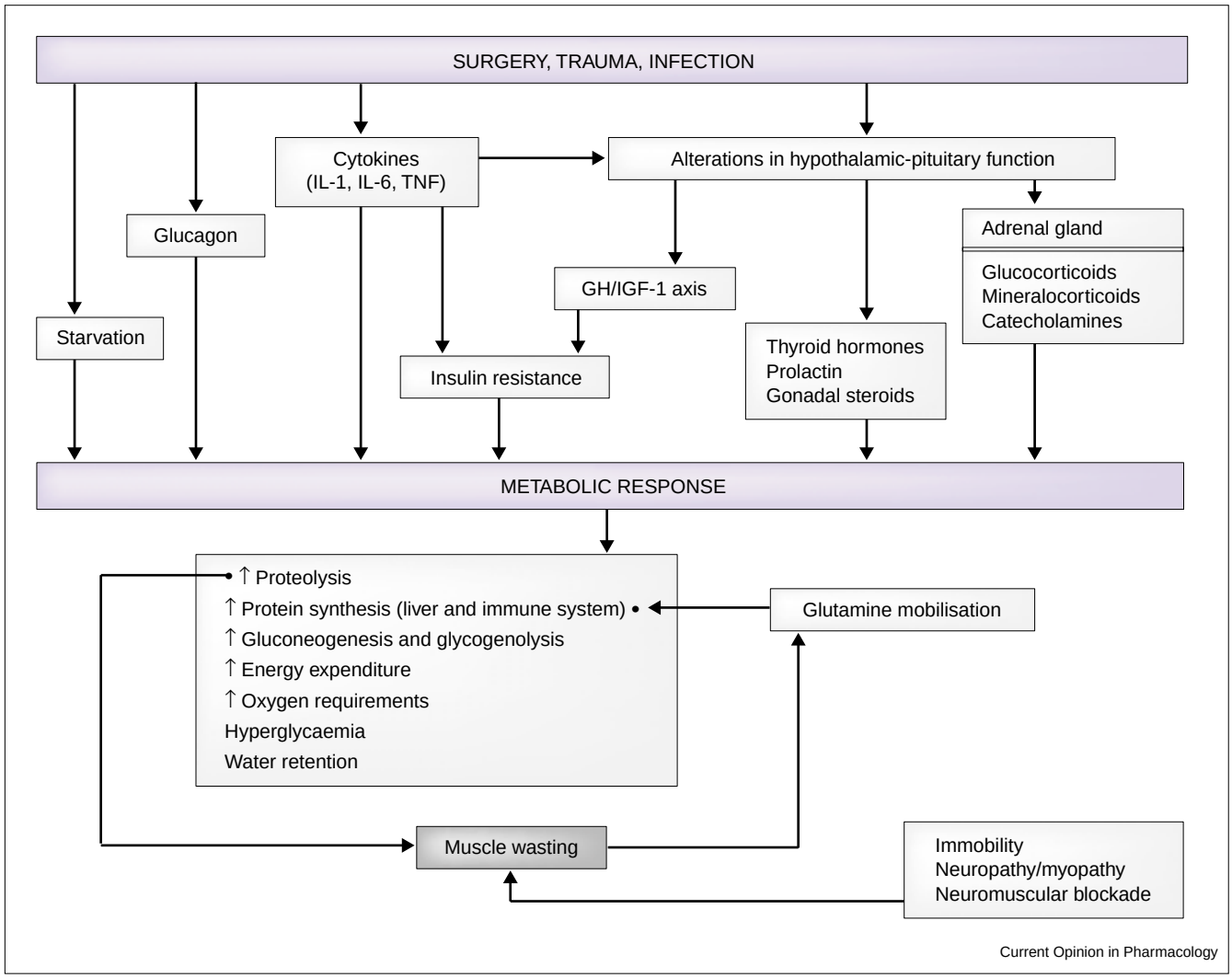
In the acute phase of critical illness at least some aspects of the catabolic response are likely to be beneficial; for example, increased availability of amino acids for gluconeogenesis, wound healing, increased immune cell replication and the synthesis of acute phase proteins in the liver. In the context of modern intensive care, however, where the most seriously ill and injured patients can often be supported throughout their illness, prolongation of the catabolic response has numerous detrimental effects (Box 1). These can include impaired wound healing and immune dysfunction, as well as skeletal muscle wasting and weakness resulting in difficulty weaning from mechanical ventilation and delayed mobilisation. The integrity of the intestinal mucosal barrier can also be compromised. Following recovery from the acute catabolic phase of illness, restoration of muscle mass is a lengthy process and rehabilitation can be prolonged.

For many years, therefore, investigators have attempted to develop treatment strategies that would limit the catabolic response to critical illness and enhance anabolic activity during recovery. Although laboratory investigations, studies in volunteers and clinical observational studies have often been encouraging, the few prospective randomised controlled trials (PRCTs) performed so far have been inconclusive, conflicting or disappointing. Clinicians are looking for interventions that not only produce theoretically beneficial biochemical, endocrine or metabolic changes but are also associated with measurable functional improvements, cost reductions and clinically relevant benefits. The latter should include reduced morbidity, more rapid mobilisation and weaning from mechanical ventilation, shorter length of stay (in the intensive care unit [ICU] or in hospital) and, most importantly, decreased mortality (Box 2). In this article, we review the strategies (largely nutritional and hormonal) that might have the potential to limit catabolic response to critical illness.

Nutritional support

Since an important function of the catabolic response to critical illness is to provide additional energy and substrates, the provision of sufficient calories and protein might be expected to limit catabolism. Unfortunately, even aggressive

Figure 1



Overview of the mechanisms and consequences of the metabolic response to critical illness.

nutritional support cannot prevent muscle protein catabolism [10] and increasing caloric intake by more than 20% above energy expenditure merely results in the accumulation of body fat [11]. Similarly, although provision of adequate protein content (1.5 g/kg lean body mass/day) in enteral nutrition can reduce protein loss, further increases in protein content fail to reduce proteolysis or increase muscle protein synthesis [12]. High carbohydrate enteral feeds appear to have a protein-sparing effect in comparison to high fat feeds with equivalent protein content [13]. Dietary fat might be best delivered in the form of an emulsion of structured triglycerides containing both medium- and long-chain fatty acids (rather than the conventional pure long chain triglyceride emulsion) since these preparations have been associated with improved nitrogen balance [14].

Glutamine

In health, glutamine is considered to be a non-essential amino acid. In the face of increased demand for fuel and precursors during the catabolic response, however, glutamine becomes an important substrate for protein synthesis, gluconeogenesis and the synthesis of glutathione (a free radical scavenger). It is also used directly as an energy source by the rapidly dividing cells of the immune system and intestinal mucosa. When given in small amounts, the majority of enterally administered glutamine is probably utilized by the gastrointestinal mucosa itself, whereas the immune system relies predominantly on endogenous sources of glutamine. Under conditions of stress, serum glutamine levels fall and large amounts of glutamine are mobilised from skeletal muscle, but release often fails to match demand [2]; therefore, immune function may be compromised and morbidity and mortality may be increased.

Most studies of glutamine supplementation of parenteral nutrition have been performed in less severely ill patients. In surgical patients given glutamine supplemented parenteral nutrition, nitrogen balance may be improved [15–17], the

Box 1. Deleterious effects of a prolonged catabolic response.

Impaired wound healing

Immune dysfunction

Integrity of intestinal mucosal barrier compromised

Skeletal muscle wasting and weakness
→Difficulty weaning from mechanical ventilation
→Delayed mobilisation
→Prolonged rehabilitation

Box 2. Potential clinical benefits of anabolic strategies in the critically ill.

Preservation of lean body mass
Improved muscle strength
Accelerated weaning from ventilator
Improved mobilisation
More rapid and complete rehabilitation
Enhanced wound healing
Enhanced immune function
Reduced incidence of sepsis
Reduced length of ICU and hospital stay
Reduced morbidity
Reduced mortality
Cost benefits

fall in skeletal muscle glutamine and protein synthesis may be attenuated [17], intestinal integrity may be maintained [15], immune function may be enhanced [16,18] and length of hospital stay may be reduced [15,16]. Intravenous administration of glutamine to enterally fed patients with severe burns also improves measures of nutrition and inflammation, and leads to a significant reduction in episodes of Gram-negative bacteraemia, perhaps indicating enhanced gut barrier function [19•].

The effects of glutamine supplementation of *parenteral* nutrition in heterogeneous groups of more seriously ill patients have, however, been more variable. A PRCT in 84 critically ill patients given parenteral nutrition when enteral nutrition failed or was contraindicated demonstrated that, when compared with an isonitrogenous, isoenergetic formula, glutamine supplementation significantly reduced mortality at six months, although there was no significant effect on ICU mortality [20]. Intensive care and total hospital costs were also reduced [20]. On the other hand, in a subsequent, larger study of 168 (mostly less seriously ill) patients receiving parenteral nutrition, glutamine supplementation failed to influence the incidence of infective complications, length of stay or mortality, either in the whole group or in the subgroup of 42 intensive care patients [21].

The value of glutamine supplementation of *enteral* nutrition in critically ill patients is even less certain. In trauma patients glutamine supplemented enteral feed reduced infectious complications, particularly Gram-negative bacteraemia [22], although in another study, nitrogen balance and protein turnover were not improved [23]. In recent years, there has been considerable interest in the potential benefits to critically ill patients of immunonutrition (i.e. the supplementation of enteral feed with specific nutrients, such as arginine, *glutamine*, nucleotides and omega-3 fatty acids, with the aim of modulating nutritional, immunological and inflammatory parameters) [24,25,26••]. In surgical patients it appears that immunonutrition including glutamine can reduce rates of infection and hospital stay [26••] but the benefits are less evident in more diverse groups of critically ill patients. Indeed, there is a possibility that mortality can be increased in some patient groups, perhaps because of adverse effects of immune stimulation [26••]. The importance of the inclusion of arginine (which has a mild anabolic effect) as a component of immunonutrition therapy has been emphasized [26••].

Insulin

The poor glycaemic control associated with the hypercatabolic response and insulin resistance is known to have several adverse effects including impaired immune function and compromised wound healing. In one observational study of critically ill burn patients, for example, hyperglycaemia was associated with an increased risk of bacteraemia, reduced skin graft take, and increased mortality [27].

In severely burned patients continuous infusion of insulin (at a rate equivalent to approximately 10 to 12 units per hour for a 70 kg patient) significantly increased skeletal muscle protein synthesis without influencing protein breakdown [28]. There was no change in amino acid uptake into skeletal muscle suggesting that the anabolic effects resulted from more efficient reutilization of amino acids generated by proteolysis [28]. Approximately half of the patients in this study required additional intravenous glucose to maintain normoglycaemia. These anabolic effects of insulin may be mediated by an increase in free insulin-like growth factor-1 (IGF-1), which increases glucose and amino acid uptake and reduces protein breakdown [29]. In critical illness (normally associated with reduced circulating IGF-1 levels [30,31]) insulin infusion may enhance the bioavailability of IGF-1 by inhibiting the production of IGF-binding protein-1 (IGFBP-1) and increasing IGFBP-3-proteolytic activity, which reduces the affinity of IGF-1 for IGFBP-3 [29].

In a recent, large PRCT intensive insulin therapy (blood glucose maintained between 4.4 and 6.1 mmol/l) was associated with an impressive reduction in morbidity and mortality in those with a prolonged ICU stay (longer than five days) [32••]. Intensive insulin treatment reduced the incidence of blood stream infections and critical illness polyneuropathy, as well as the need for prolonged ventilatory support and renal replacement therapy. Circulating levels of bilirubin and inflammatory markers were also

reduced [32••]. The precise mechanisms underlying these benefits are unclear, particularly because the effects of improved glycaemic control cannot be distinguished from the metabolic consequences of hyperinsulinaemia. Interpretation of the findings is also complicated by the unusually intensive nutritional support (albeit perhaps entirely appropriate) used in this study. Because further statistical analysis indicated that higher doses of insulin were associated with a worse outcome whereas lower blood glucose levels seemed to be related to an improved outcome, the authors believe that avoidance of hyperglycaemia is likely to be the more important mechanism [33]. Since the majority of the patients in this study were surgical (mainly post-cardiac surgery) the applicability of these findings to other groups of critically ill patients requires further investigation. Implementation of such aggressive insulin therapy in individual units will require the development of strict protocols and extensive education and training for staff, particularly in view of the significant risk of hypoglycaemia.

Growth hormone and insulin-like growth factor-1

In health, growth hormone (GH) secretion is pulsatile, with large nocturnal peaks superimposed upon a barely detectable baseline. This pattern of secretion is controlled by the balance between a hypothalamic releasing hormone (GHRH) and the inhibitory effects of somatostatin. In plasma, GH is bound to a high-affinity GH-binding protein (GHBP), which is identical to the extracellular domain of the GH receptor. The actions of GH are mediated both directly via peripheral GH receptors, and indirectly via the enhanced hepatic synthesis of IGF-1. It appears that the pulsatile GH profile is important for its peripheral metabolic functions, particularly the maintenance of IGF-1 levels [9••]. In the circulation, IGF-1 is bound to various IGF binding proteins, particularly the larger IGFBP-3 and its associated acid-labile subunit, which reduces the bioavailability of IGF-1 but prolongs its half-life in the circulation. Binding of IGF-1 to the smaller proteins (IGFBP-1, IGFBP-2 and IGFBP-6) may facilitate penetration into tissues [34].

In critical illness, basal circulating levels of GH are increased, normal pulsatility is lost [30] and there is a reduction in both the serum level of GHBP and peripheral GH receptor expression [9••]. These changes are associated with reduced serum concentrations of IGF-1 and its GH-dependent binding protein IGFBP-3 [31], whilst there is an increase in circulating levels of the smaller binding proteins [31,34]. It may be that the low IGF-1 levels result in a reduction in negative-feedback inhibition of pituitary GH secretion, which stimulates release of GH and permits the unopposed direct catabolic actions of GH (lipolysis, muscle wasting and insulin antagonism). This may be partially offset by an increase in the activity of IGFBP-3-protease, which reduces the affinity of IGF-1 for IGFBP-3, possibly increasing the bioavailability of IGF-1[31].

Over the past 20 years many relatively small studies have investigated the effect of recombinant human growth hormone (rhGH) in a wide range of patient groups including surgical, trauma, critically ill, respiratory and burns patients. Administration of GH has usually been associated with improvements in surrogate endpoints including increased circulating IGF-1 [35,36], improvements in nitrogen balance [36,37], attenuation of the fall in muscle glutamine [38], improved protein synthetic rates [36,38] and preservation of lean body mass [39]. Some studies have suggested that rhGH may possibly increase muscle strength [39], reduce weaning times [40], improve wound healing [35], reduce length of hospital stay [35] and even reduce mortality in burns patients [41], but convincing evidence of clinically important benefits in critically ill patients was lacking. Subsequently two parallel PRCTs investigated the effect of high dose rhGH in heterogeneous groups of critically ill adults enrolled after five to seven days of intensive care [42]. Despite increased blood levels of IGF-1 and improved nitrogen balance, GH administration was associated with a significantly higher mortality, prolonged weaning times and increased duration of ICU and hospital stay [42]. Several mechanisms may possibly explain this unexpected finding, including immune modulation, inhibition of glutamine mobilisation and the adverse effects of insulin resistance, perhaps compounded by an increased metabolic rate and inadequate nutritional support [43•]. Importantly, recent evidence suggests that the neuroendocrine response to critical illness is biphasic and that during the chronic phase there is complete loss of GH pulsatility and mean circulating levels are lower than during the acute phase [9••]. It seems that GH resistance may not be a feature of this chronic phase and under these circumstances administration of high doses of GH could be harmful.

Further investigations into the nature of the somatotropic disturbance in critical illness have revealed that administration of GH secretagogues during prolonged critical illness can stimulate GH secretion and restore pulsatility, excluding a pituitary cause of blunted GH secretion and suggesting that lack of hypothalamic GH secretagogues coupled with low availability of somatostatin (to suppress baseline secretion) is the most likely mechanism underlying the abnormal pattern of GH secretion [9••]. On the basis of these findings, an alternative, and perhaps more physiological, anabolic strategy aims to re-establish the pulsatile nature of pituitary secretion of GH and thyroid stimulating hormone (TSH) by continuous infusion of growth hormone-releasing peptide (GHRP) and thyrotrophin-releasing hormone (TRH). In patients already treated in the ICU for a minimum of two weeks, this approach restored pulsatile secretion of GH and TSH with associated increases in serum levels of IGF-1 and IGFBP-3 and reduced protein breakdown [44].

Administration of IGF-1 might provide the desired anabolic effects while avoiding some of the detrimental

Table 1

Proposed anabolic and anticatabolic strategies in critical illness.

Strategy	Current status
Nutritional support	Generally safe and partially effective. Cornerstone of treatment. Enteral route preferred.
Glutamine	
Parenteral	Possible benefit
Enteral	Uncertain value
Insulin	Controls blood sugar and has potentially beneficial anabolic effects. Reduced mortality in one PRCT.
Growth factors	
Growth hormone	Potentially detrimental
IGF-1	No proven benefit
Growth hormone and IGF-1	Potentially beneficial
Growth hormone secretagogues	Considerable potential for benefit
Gonadal steroids	Uncertain benefit
Adrenergic agents	
β_2-adrenoceptor agonists	Clinical trials needed
β-blockade	Potential value in some patient groups
Muscle stimulation	Potential to preserve strength in some muscle group
Environmental temperature	Potentially beneficial
Hyperventilation	Probably of limited clinical applicability
Afferent blockade	Potential for prophylaxis

effects of growth hormone. Studies of IGF-1 given alone have proved disappointing [45], perhaps because of inadequate or variable serum levels achieved after subcutaneous administration [46] or counter-regulatory changes in IGF-binding proteins [45]. On the other hand, when given in combination with IGFBP-3, IGF-1 increased muscle protein synthesis in severely burned adults, with no adverse affects on plasma glucose [47]. Alternatively a combination of IGF-1 and GH might facilitate the anabolic effects of both while maintaining more normal blood glucose concentrations [48]. When given in combination with glutamine-enriched parenteral nutrition, treatment with IGF-1 and GH significantly improved protein balance and had no adverse effects on glutamine metabolism [49•].

Gonadal steroids

In men with prolonged critical illness pulsatile secretion of luteinizing hormone is disturbed, with reduced serum concentrations associated with a fall in circulating levels of testosterone, another potent anabolic steroid [9••]. These changes can be only partially overcome by the intermittent administration of gonadotrophin-releasing hormone (GnRH), indicating combined hypothalamic–pituitary–gonadal dysfunction [50]. Co-administration of GHRP, TRH and GnRH reactivates the somatotropic, thyroid and gonadal axes with additional beneficial effects on markers of catabolism when compared to treatment with GHRP and TRH alone [51••].

A small study of six adult male patients approximately two weeks after burn injury demonstrated that testosterone administration could ameliorate muscle protein catabolism [52]. The testosterone analogue oxandrolone has minimal virilising activity and 10 times the anabolic activity of testosterone. In catabolic severely burned patients, oxandrolone increased protein synthesis by promoting more efficient re-utilization of amino acids [53] and markedly reduced nitrogen and weight loss while accelerating donor-site healing [54•]. A comparison of the effects of oxandrolone and GH in burn patients showed almost identical benefits [55]. GH did, however, further exacerbate the pre-existing hypermetabolism and was associated with an increased incidence of hyperglycaemia, a complication not seen with oxandrolone [55]. Testosterone analogues are less well studied in other patient groups, although oxandrolone has been shown to improve long-term survival in patients with alcoholic hepatitis [56]. On the other hand, a large study of oxandrolone administration to adults in the acute phase of illness following major trauma demonstrated no benefits in terms of nutritional or clinical outcomes [57].

Adrenergic agents

Through both hormonal and neurotransmitter actions mediated via β_2-adrenoceptor pathways, the sympathetic nervous system mediates anabolism in skeletal muscle, inhibiting protein degradation and increasing the rate of protein synthesis [58]. Clenbuterol, a β_2-adrenoceptor agonist, has been shown to attenuate the loss of muscle mass associated with disuse atrophy [59] and burn injury [60] in animals. Thus far there have been no clinical studies of the effects of β_2-adrenoceptor agonists on the catabolism associated with critical illness, but short-term administration of salbutamol can increase voluntary muscle strength in certain muscle groups of healthy volunteers [61].

Interestingly, it has also been hypothesized that non-selective β-adrenergic blockade might be beneficial in burns

patients by attenuating the catecholamine induced increase in energy expenditure and muscle catabolism. In a recent randomized trial carried out in 25 children with acute severe burns, oral propanolol, adjusted to decrease the resting heart rate by 20%, reduced resting energy expenditure, increased muscle protein balance and preserved lean body mass with no adverse effects [62•].

Other strategies

Muscle stimulation

Electrical stimulation can ameliorate the skeletal muscle protein loss and atrophy associated with immobility [63] and might reduce muscle wasting in critically ill patients [64]. Passive stretching of leg muscles in critically ill patients receiving neuromuscular blocking agents can preserve muscle architecture, reduce fibre atrophy and attenuate protein loss in comparison to the other untreated leg, although in this study it was not possible to assess the impact of this strategy on muscle strength [65].

Environmental temperature

Nursing post-operative patients at an elevated ambient temperature closer to their natural thermal neutrality (32°C compared to room temperature, 22°C) potentially reduces the need for heat production to regulate temperature and has been shown to reduce body protein catabolism and nitrogen excretion [66].

Hyperventilation

Protein synthesis is impaired in an acidic environment and enhanced under alkalotic conditions. Interestingly, in a small study of head injured patients, moderate hyperventilation (pCO_2 3.6 kPa; pH 7.50) resulted in significantly increased protein synthetic rate [67].

Afferent blockade

Measures to limit the stress response to surgery, including analgesia and neuronal blockade, might also attenuate the metabolic response.

Conclusions

Several anabolic strategies have been shown to have beneficial effects on clinically relevant outcome measures in certain patient subgroups, particularly surgical and burns patients (Table 1). The application of such strategies to diverse groups of more seriously ill patients, however, has failed to produce convincing evidence of benefit, emphasizing the complexity of the metabolic and endocrine response to critical illness and severe injury, as well as our limited understanding of the mechanisms involved. It remains unclear precisely which patients are most likely to benefit from such interventions and which elements of the catabolic response should be modified. Indeed, particularly in the acute phase of illness, complete abolition of the metabolic and hormonal response to stress might be undesirable and even detrimental. Additionally, the timing and duration of the intervention is likely to be crucial. Before anabolic strategies are introduced into clinical practice, it is essential that PRCTs with clinically relevant endpoints are performed to establish safety and efficacy in large numbers of the intended target population.

Importantly, the catabolic response and inadequate nutritional support are not the only causes of muscle wasting in critically ill patients and neither is loss of muscle mass the sole cause of muscle weakness [68•]. Functional denervation, resulting from immobility, critical illness polyneuropathy or the use of neuromuscular blocking drugs can cause muscle fibre atrophy, and various myopathic changes have been described. Also circulating cytokines can decrease the muscle resting membrane potential and reduce skeletal muscle contractility [69]. These and other factors may contribute to the failure of anabolic strategies alone to cause clinically detectable improvements.

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References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

1. Uehara M, Plank LD, Hill GL: Components of energy expenditure in patients with severe sepsis and major trauma: a basis for clinical care. *Crit Care Med* 1999, 27:1295-1302.

2. O'Leary MJ, Ferguson CN, Rennie MJ, Hinds CJ, Coakley JH, Preedy VR: Sequential changes in ***in vivo*** muscle and liver protein synthesis and plasma and tissue glutamine levels in sepsis in the rat. *Clin Sci (Lond)* 2001, 101:295-304.

3. Essen P, McNurlan MA, Gamrin L, Hunter K, Calder G, Garlick PJ, Wernerman J: Tissue protein synthesis rates in critically ill patients. *Crit Care Med* 1998, 26:92-100.

4. Plank LD, Hill GL: Similarity of changes in body composition in intensive care patients following severe sepsis or major blunt injury. *Ann NY Acad Sci* 2000, 904:592-602.

5. Plank LD, Connolly AB, Hill GL: Sequential changes in the metabolic response in severely septic patients during the first 23 days after the onset of peritonitis. *Ann Surg* 1998, 228:146-158.

6. Hill AA, Plank LD, Finn PJ, Whalley GA, Sharpe N, Clark MA, Hill GL: Massive nitrogen loss in critical surgical illness: effect on cardiac mass and function. *Ann Surg* 1997, 226:191-197.

7. Vary TC: Regulation of skeletal muscle protein turnover during sepsis. *Curr Opin Clin Nutr Metab Care* 1998, 1:217-224.

8. Navarra P, Tsagarakis S, Faria MS, Rees LH, Besser GM, Grossman AB: Interleukins-1 and -6 stimulate the release of corticotropin-releasing hormone-41 from rat hypothalamus ***in vitro*** via the eicosanoid cyclooxygenase pathway. *Endocrinology* 1991, 128:37-44.

9. •• Van den Berghe G: Novel insights into the neuroendocrinology of critical illness. *Eur J Endocrinol* 2000, 143:1-13.
An excellent review detailing current understanding of the neuroendocrine response to critical illness. Potential explanations are offered for the disappointing results of clinical trials of anabolic therapies, along with possible strategies for future development.

10. Streat SJ, Beddoe AH, Hill GL: Aggressive nutritional support does not prevent protein loss despite fat gain in septic intensive care patients. *J Trauma* 1987, 27:262-266.

11. Hart DW, Wolf SE, Herndon DN, Chinkes DL, Lal SO, Obeng MK, Beauford RB, Mlcak RP: Energy expenditure and caloric balance after burn: increased feeding leads to fat rather than lean mass accretion. *Ann Surg* 2002, 235:152-161.

12. Ishibashi N, Plank LD, Sando K, Hill GL: Optimal protein requirements during the first 2 weeks after the onset of critical illness. *Crit Care Med* 1998, 26:1529-1535.

13. Hart DW, Wolf SE, Zhang XJ, Chinkes DL, Buffalo MC, Matin SI, DebRoy MA, Wolfe RR, Herndon DN: Efficacy of a high-carbohydrate diet in catabolic illness. *Crit Care Med* 2001, 29:1318-1324.

14. Lindgren BF, Ruokonen E, Magnusson-Borg K, Takala J: Nitrogen sparing effect of structured triglycerides containing both medium- and long-chain fatty acids in critically ill patients; a double blind randomized controlled trial. *Clin Nutr* 2001, 20:43-48.

15. Jiang ZM, Cao JD, Zhu XG, Zhao WX, Yu JC, Ma EL, Wang XR, Zhu MW, Shu H, Liu YW: The impact of alanyl-glutamine on clinical safety, nitrogen balance, intestinal permeability, and clinical outcome in postoperative patients: a randomized, double-blind, controlled study of 120 patients. *JPEN J Parenter Enteral Nutr* 1999, 23:S62-S66.

16. Morlion BJ, Stehle P, Wachtler P, Siedhoff HP, Koller M, Konig W, Furst P, Puchstein C: Total parenteral nutrition with glutamine dipeptide after major abdominal surgery: a randomized, double-blind, controlled study. *Ann Surg* 1998, 227:302-308.

17. Hammarqvist F, Wernerman J, Ali R, von der DA, Vinnars E: Addition of glutamine to total parenteral nutrition after elective abdominal surgery spares free glutamine in muscle, counteracts the fall in muscle protein synthesis, and improves nitrogen balance. *Ann Surg* 1989, 209:455-461.

18. O'Riordain MG, Fearon KC, Ross JA, Rogers P, Falconer JS, Bartolo DC, Garden OJ, Carter DC: Glutamine-supplemented total parenteral nutrition enhances T-lymphocyte response in surgical patients undergoing colorectal resection. *Ann Surg* 1994, 220:212-221.

19. • Wischmeyer PE, Lynch J, Liedel J, Wolfson R, Riehm J, Gottlieb L, Kahana M: Glutamine administration reduces Gram-negative bacteremia in severely burned patients: a prospective, randomized, double-blind trial versus isonitrogenous control. *Crit Care Med* 2001, 29:2075-2080.

An innovative prospective randomised controlled trial demonstrating the efficacy of intravenous glutamine supplementation in improving nutritional status and reducing the incidence of Gram-negative bacteraemia in enterally fed burns patients. There was a non-significant trend towards reduced mortality and length of stay in intensive care unit.

20. Griffiths RD, Jones C, Palmer TE: Six-month outcome of critically ill patients given glutamine-supplemented parenteral nutrition. *Nutrition* 1997, 13:295-302.

21. Powell-Tuck J, Jamieson CP, Bettany GE, Obeid O, Fawcett HV, Archer C, Murphy DL: A double blind, randomised, controlled trial of glutamine supplementation in parenteral nutrition. *Gut* 1999, 45:82-88.

22. Houdijk AP, Rijnsburger ER, Jansen J, Wesdorp RI, Weiss JK, McCamish MA, Teerlink T, Meuwissen SG, Haarman HJ, Thijs LG, van Leeuwen PA: Randomised trial of glutamine-enriched enteral nutrition on infectious morbidity in patients with multiple trauma. *Lancet* 1998, 352:772-776.

23. Long CL, Nelson KM, DiRienzo DB, Weis JK, Stahl RD, Broussard TD, Theus WL, Clark JA, Pinson TW, Geiger JW: Glutamine supplementation of enteral nutrition: impact on whole body protein kinetics and glucose metabolism in critically ill patients. *JPEN J Parenter Enteral Nutr* 1995, 19:470-476.

24. Heys SD, Walker LG, Smith I, Eremin O: Enteral nutritional supplementation with key nutrients in patients with critical illness and cancer: a meta-analysis of randomized controlled clinical trials. *Ann Surg* 1999, 229:467-477.

25. Beale RJ, Bryg DJ, Bihari DJ: Immunonutrition in the critically ill: a systematic review of clinical outcome. *Crit Care Med* 1999, 27:2799-2805.

26. •• Heyland DK, Novak F, Drover JW, Jain M, Su X, Suchner U: Should immunonutrition become routine in critically ill patients? A systematic review of the evidence. *J Am Med Assoc* 2001, 286:944-953.

A systematic review of randomised clinical trials of enteral immunonutrition in surgical and critically ill patients, paying particular attention to those studies of high methodological quality. The differential effects of enteral immunonutrition in these two patient groups are emphasised, in particular the potentially detrimental effects of glutamine supplementation in the critically ill.

27. Gore DC, Chinkes D, Heggers J, Herndon DN, Wolf SE, Desai M: Association of hyperglycemia with increased mortality after severe burn injury. *J Trauma* 2001, 51:540-544.

28. Ferrando AA, Chinkes DL, Wolf SE, Matin S, Herndon DN, Wolfe RR: A submaximal dose of insulin promotes net skeletal muscle protein synthesis in patients with severe burns. *Ann Surg* 1999, 229:11-18.

29. Nygren J, Carlsson-Skwirut C, Brismar K, Thorell A, Ljungqvist O, Bang P: Insulin infusion increases levels of free IGF-I and IGFBP-3 proteolytic activity in patients after surgery. *Am J Physiol Endocrinol Metab* 2001, 281:E736-E741.

30. Ross R, Miell J, Freeman E, Jones J, Matthews D, Preece M, Buchanan C: Critically ill patients have high basal growth hormone levels with attenuated oscillatory activity associated with low levels of insulin-like growth factor-I. *Clin Endocrinol (Oxf)* 1991, 35:47-54.

31. Timmins AC, Cotterill AM, Hughes SC, Holly JM, Ross RJ, Blum W, Hinds CJ: Critical illness is associated with low circulating concentrations of insulin-like growth factors-I and -II, alterations in insulin-like growth factor binding proteins, and induction of an insulin-like growth factor binding protein 3 protease. *Crit Care Med* 1996, 24:1460-1466.

32. •• Van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M, Vlasselaers D, Ferdinande P, Lauwers P, Bouillon R: Intensive insulin therapy in critically ill patients. *N Engl J Med* 2001, 345:1359-1367.

A remarkable study of considerable clinical significance, showing reduced morbidity and mortality with stringent blood sugar control in surgical intensive care patients.

33. Van den Berghe G, Bouillon R, Lauwers P: Intensive insulin therapy in critically ill patients. [letter]. *N Engl J Med* 2002, 346:1587-1588.

34. Baxter RC: Changes in the IGF-IGFBP axis in critical illness. *Best Pract Res Clin Endocrinol Metab* 2001, 15:421-434.

35. Herndon DN, Barrow RE, Kunkel KR, Broemeling L, Rutan RL: Effects of recombinant human growth hormone on donor-site healing in severely burned children. *Ann Surg* 1990, 212:424-429.

36. Jeevanandam M, Holaday NJ, Petersen SR: Integrated nutritional, hormonal, and metabolic effects of recombinant human growth hormone (rhGH) supplementation in trauma patients. *Nutrition* 1996, 12:777-787.

37. Pape GS, Friedman M, Underwood LE, Clemmons DR: The effect of growth hormone on weight gain and pulmonary function in patients with chronic obstructive lung disease. *Chest* 1991, 99:1495-1500.

38. Gamrin L, Essen P, Hultman E, McNurlan MA, Garlick PJ, Wernerman J: Protein-sparing effect in skeletal muscle of growth hormone treatment in critically ill patients. *Ann Surg* 2000, 231:577-586.

39. Kissmeyer-Nielsen P, Jensen MB, Laurberg S: Perioperative growth hormone treatment and functional outcome after major abdominal surgery: a randomized, double-blind, controlled study. *Ann Surg* 1999, 229:298-302.

40. Knox JB, Wilmore DW, Demling RH, Sarraf P, Santos AA: Use of growth hormone for postoperative respiratory failure. *Am J Surg* 1996, 171:576-580.

41. Knox J, Demling R, Wilmore D, Sarraf P, Santos A: Increased survival after major thermal injury: the effect of growth hormone therapy in adults. *J Trauma* 1995, 39:526-530.

42. Takala J, Ruokonen E, Webster NR, Nielsen MS, Zandstra DF, Vundelinckx G, Hinds CJ: Increased mortality associated with growth hormone treatment in critically ill adults. *N Engl J Med* 1999, 341:785-792.

43. • Botfield C, Hinds CJ: Growth hormone in catabolic illness. *Curr Opin Clin Nutr Metab Care* 2000, 3:139-144.

A comprehensive review of the physiological and therapeutic role of growth hormone in catabolic illness.

44. Van den Berghe G, Wouters P, Weekers F, Mohan S, Baxter RC, Veldhuis JD, Bowers CY, Bouillon R: Reactivation of pituitary hormone release and metabolic improvement by infusion of growth hormone-releasing peptide and thyrotropin-releasing hormone in patients with protracted critical illness. *J Clin Endocrinol Metab* 1999, 84:1311-1323.

45. Goeters C, Mertes N, Tacke J, Bolder U, Kuhmann M, Lawin P, Lohlein D: Repeated administration of recombinant human insulin-like growth factor-I in patients after gastric surgery. Effect on metabolic and hormonal patterns. *Ann Surg* 1995, 222:646-653.

46. Yarwood GD, Ross RJ, Medbak S, Coakley J, Hinds CJ: Administration of human recombinant insulin-like growth factor-I in critically ill patients. *Crit Care Med* 1997, 25:1352-1361.

47. DebRoy MA, Wolf SE, Zhang XJ, Chinkes DL, Ferrando AA, Wolfe RR, Herndon DN: Anabolic effects of insulin-like growth factor in combination with insulin-like growth factor binding protein-3 in severely burned adults. *J Trauma* 1999, 47:904-910.

48. Kupfer SR, Underwood LE, Baxter RC, Clemmons DR: Enhancement of the anabolic effects of growth hormone and insulin-like growth factor I by use of both agents simultaneously. *J Clin Invest* 1993, 91:391-396.

49. • Umpleby AM, Carroll PV, Russell-Jones DL, Treacher DF, Jackson NC: Glutamine supplementation and GH/IGF-I treatment in critically ill patients: effects on glutamine metabolism and protein balance. *Nutrition* 2002, 18:127-129.
A study of the effects of glutamine, growth hormone (GH) and insulin-like growth factor-1 (IGF-1) in parenterally fed intensive care patients. Serum glutamine was increased with glutamine supplementation and protein balance was improved with combined GH + IGF-1 treatment, with no adverse effects on glutamine metabolism.

50. Van den Berghe G, Weekers F, Baxter RC, Wouters P, Iranmanesh A, Bouillon R, Veldhuis JD: Five-day pulsatile gonadotropin-releasing hormone administration unveils combined hypothalamic-pituitary-gonadal defects underlying profound hypoandrogenism in men with prolonged critical illness. *J Clin Endocrinol Metab* 2001, 86:3217-3226.

51. •• Van den Berghe GBR: The combined administration of GH releasing peptide-2 (GHRP-2), TRH and GnRH to men with prolonged critical illness evokes superior endocrine and metabolic effects compared to treatment with GHRP-2 alone. *Clin Endocrinol (Oxf)* 2002, 56:655-669.
A prospective randomised controlled trial comparing the effects of combined exogenous hypothalamic secretagogues on the growth hormone, thyroid stimulating hormone and luteinizing hormone axes. Only the co-administration of growth hormone releasing peptide-2, thyrotrophin releasing hormone and gonadotrophin releasing hormone reactivated all three axes and induced potentially beneficial effects on markers of inflammation and metabolism.

52. Ferrando AA, Sheffield-Moore M, Wolf SE, Herndon DN, Wolfe RR: Testosterone administration in severe burns ameliorates muscle catabolism. *Crit Care Med* 2001, 29:1936-1942.

53. Hart DW, Wolf SE, Ramzy PI, Chinkes DL, Beauford RB, Ferrando AA, Wolfe RR, Herndon DN: Anabolic effects of oxandrolone after severe burn. *Ann Surg* 2001, 233:556-564.

54. • Demling RH, Orgill DP: The anticatabolic and wound healing effects of the testosterone analog oxandrolone after severe burn injury. *J Crit Care* 2000, 15:12-17.
A prospective randomised controlled trial of oxandrolone in 20 adults in the acute catabolic phase following severe burn injury, demonstrating beneficial biochemical and clinical effects and no adverse sequelae.

55. Demling RH: Comparison of the anabolic effects and complications of human growth hormone and the testosterone analog, oxandrolone, after severe burn injury. *Burns* 1999, 25:215-221.

56. Mendenhall CL, Anderson S, Garcia-Pont P, Goldberg S, Kiernan T, Seeff LB, Sorrell M, Tamburro C, Weesner R, Zetterman R: Short-term and long-term survival in patients with alcoholic hepatitis treated with oxandrolone and prednisolone. *N Engl J Med* 1984, 311:1464-1470.

57. Gervasio JM, Dickerson RN, Swearingen J, Yates ME, Yuen C, Fabian TC, Croce MA, Brown RO: Oxandrolone in trauma patients. *Pharmacotherapy* 2000, 20:1328-1334.

58. Navegantes LCC, Migliorini RH, Kettelhut IC: Adrenergic control of protein metabolism in skeletal muscle. *Curr Opin Clin Nutr Metab Care* 2002, 5:281-286.

59. Herrera NM Jr, Zimmerman AN, Dykstra DD, Thompson LV: Clenbuterol in the prevention of muscle atrophy: a study of hindlimb-unweighted rats. *Arch Phys Med Rehabil* 2001, 82:930-934.

60. Martineau L, Little RA, Rothwell NJ, Fisher MI: Clenbuterol, a beta 2-adrenergic agonist, reverses muscle wasting due to scald injury in the rat. *Burns* 1993, 19:26-34.

61. Martineau L, Horan MA, Rothwell NJ, Little RA: Salbutamol, a beta 2-adrenoceptor agonist, increases skeletal muscle strength in young men. *Clin Sci (Lond)* 1992, 83:615-621.

62. • Herndon DN, Hart DW, Wolf SE, Chinkes DL, Wolfe RR: Reversal of catabolism by beta-blockade after severe burns. *N Engl J Med* 2001, 345:1223-1229.
A placebo-controlled trial of propanolol in children in the acute post-burn period demonstrating reduced energy expenditure and reversed muscle-protein catabolism.

63. Gibson JN, Smith K, Rennie MJ: Prevention of disuse muscle atrophy by means of electrical stimulation: maintenance of protein synthesis. *Lancet* 1988, 2:767-770.

64. Bouletreau P, Patricot MC, Saudin F, Guiraud M, Mathian B: Effects of intermittent electrical stimulations on muscle catabolism in intensive care patients. *JPEN J Parenter Enteral Nutr* 1987, 11:552-555.

65. Griffiths RD, Palmer TE, Helliwell T, MacLennan P, MacMillan RR: Effect of passive stretching on the wasting of muscle in the critically ill. *Nutrition* 1995, 11:428-432.

66. Ryan DW, Clague MB: Nitrogen sparing and the catabolic hormones in patients nursed at an elevated ambient temperature following major surgery. *Intensive Care Med* 1990, 16:287-290.

67. Vosswinkel JA, Brathwaite CE, Smith TR, Ferber JM, Casella G, Garlick PJ: Hyperventilation increases muscle protein synthesis in critically ill trauma patients. *J Surg Res* 2000, 91:61-64.

68. • Wagenmakers AJ: Muscle function in critically ill patients. *Clin Nutr* 2001, 20:451-454.
A thorough review of the pathophysiological mechanisms that lead to muscle wasting and weakness in critical illness.

69. Tracey KJ, Lowry SF, Beutler B, Cerami A, Albert JD, Shires GT: Cachectin/tumor necrosis factor mediates changes of skeletal muscle plasma membrane potential. *J Exp Med* 1986, 164:1368-1373.