STRATEGIES FOR ATTENUATING PROTEIN-CATABOLIC RESPONSES IN THE CRITICALLY ILL

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ABSTRACT

Specialized enteral and parenteral nutrition are now a standard components of care in critically ill patients. This adjunctive therapy corrects and prevents nutrient deficiencies, attenuates the loss of body protein, and improves clinical outcomes in malnourished patients. Several novel strategies designed to improve the metabolic and clinical effects of specialized nutrition are under vigorous clinical investigation.

These new approaches include increased emphasis on enteral feeding to maintain intestinal absorptive, immune, and barrier function; administration of
conditionally essential amino acids (glutamine, arginine); use of specialized lipid products and antioxidants; and administration of growth factors such as human growth hormone. Randomized, controlled clinical trials will define the clinical and metabolic efficacy and cost-effectiveness of these therapies in specialized nutrition support.

INTRODUCTION

Loss of body protein occurs during catabolic states such as infection and injury. Enhanced proteolysis may be due to increased rates of protein breakdown, reduced protein synthesis, or a combination of these two effects and is generally directly related to the degree of catabolic stress and quantity of nutrients in the diet. The mechanisms regulating erosion of body protein are complex, but they undoubtedly involve counterregulatory hormones (e.g. cortisol and catecholamines) and proinflammatory cytokines (e.g. tumor necrosis factor, or TNF, and interleukin-1). These signals interrelate with other mechanisms that favor net protein breakdown, including diminished nutrient intake, acidosis, and inactivity.

Because body protein represents both structural and functional components of the body, erosion of lean tissue is associated with diminished immune function, increased infection rates, delayed tissue repair, decreased wound healing, and diminished skeletal muscle function, which delays independence and self care (1, 2). Malnutrition and net loss of body proteins therefore contribute to increased morbidity and mortality, prolonged convalescence, and higher hospital costs. Over the past several decades, specialized enteral and parenteral nutrition have become routine in the clinical care of malnourished and critically ill patients. Provision of adequate calories, protein, and other essential nutrients (including vitamins and trace elements) is clearly beneficial in many clinical situations when adequate food intake is precluded and/or when nutrient losses are accelerated. Thus classical nutrient deficiencies in intensive care unit (ICU) patients with current forms of specialized nutrition are uncommon, and body protein loss is attenuated compared with responses of comparable patients receiving limited or no dietary intake (3).

Recent information has highlighted the potential complications and clinical limitations of adjunctive nutritional and metabolic support in attenuating body protein loss and improving overall clinical outcomes (4–6). An increasing number of therapeutic strategies are undergoing intensive clinical investigation in an attempt to improve the efficacy of nutrient support in the ICU setting and to enhance recovery and rehabilitation. This paper briefly reviews several of these promising therapies, which include administration of somatic growth factors, provision of tissue-specific or conditionally essential nutrients, use of biologic response modifiers, and combinations of these approaches.
CURRENT PRACTICES

*Objectives and Efficacy of Specialized Nutrition*

As outlined in recent guidelines published by the American Society for Parenteral and Enteral Nutrition, the major objectives of nutritional and metabolic support in critical care are to (a) detect and correct preexisting malnutrition; (b) prevent progressive protein-calorie malnutrition; (c) optimize the patient’s metabolic state (including fluid and electrolyte status); and (d) reduce morbidity and time to convalescence (7). However, despite routine use in critical care, the clinical efficacy of nutrition support has not been conclusively demonstrated by appropriately designed, prospective randomized trials. Moreover, current forms of nutrition support are relatively inefficient in stimulating protein synthesis or in reducing protein breakdown rates during critical illness and are unable to induce net protein anabolism or positive nitrogen balance (1–6). Losses of 4–8 g nitrogen/day (25–50 g protein/day) are not unusual in severely catabolic hospitalized patients despite aggressive feeding (3). In addition, body composition studies have shown that much of the observed weight gain associated with the provision of specialized nutrition represents a gain in total body fat and extracellular fluid (3, 4).

The relative ineffectiveness of current therapy in preventing acute proteolysis in the setting of severe injury or critical illness is probably multifactorial, i.e., related to a relative inability to effectively use exogenously supplied nutrients due to bed rest, organ dysfunction, the catabolic hormonal-cytokine environment and/or provision of imbalanced or deficient nutrient solutions (1, 3). However, during the convalescence phase after severe illness or in patients with mild catabolic stress, standard parenteral and enteral nutrition support stimulates protein synthesis and promotes nitrogen equilibrium or slight positive balance, particularly in patients with preexisting protein-energy malnutrition who are avid for protein retention.

Although increased flow of amino acids from skeletal muscle in catabolic stress may result in skeletal muscle weakness and diminished muscle function, acute proteolysis provides amino acid fuel and substrates for wound healing, visceral organ structural protein and acute-phase protein synthesis, gluconeogenesis, and immune cell support. Thus the proteolytic response represents an important adaptation during critical illness.

*Administration of Nutrition Support in Critical Illness*

**Complications of Therapy** Provision of carbohydrate, protein, and fat in excess of maintenance nutrient requirements (hyperalimentation) has been associated with metabolic complications in the ICU setting, including hyperglycemia, electrolyte disturbances (e.g., hypophosphatemia, hypomagnesemia),
fatty liver and liver function abnormalities, azotemia, and respiratory insufficiency due to excess CO₂ production (3, 7). These complications were much more common in the past when very large amounts of energy in the form of carbohydrate and lipid (> 40 kcal/kg per day) and high-protein diets (> 2.5 g/kg per day) were routinely prescribed.

An increased rate of infection is associated with parenteral feeding in normally nourished individuals (8–9). Additionally, parenteral nutrition (PN)–associated infections often involve sites distant from the intravenous catheter such as the lung, urinary tract, and wounds (8). Available data suggest that some component(s) of the nutrient solutions themselves, including potential immunosuppressive effects of current soybean or safflower oil–based lipid emulsions (9–10), the route of feeding (7), and/or provision of inadequate amounts of immune-stimulating nutrients (4) in standard formulations, plays a role in infection risk. Recent studies clearly show that enteral feeding with standard, commercially available tube-feeding solutions is associated with a much lower rate of infection in catabolic and surgical patients when compared with PN (9, 11). This beneficial effect of enteral feeding on infection rates may be due in part to (a) maintenence of intestinal morphologic barrier and immune function via stimulation of trophic intestinal hormones (e.g. gastrin, cholecystokinin, enteroglucagon, and insulin-like growth factors) or via provision of diets that are more complete or balanced relative to intravenous formulas; (b) reduced total caloric intake, usually provided when the enteral route is used exclusively; and (c) avoidance of intravenous hypertonic dextrose infusion and the associated infection risk with hyperglycemia or multiuse central venous catheters (4, 7, 11). Because infection induces further proteolysis and because malnutrition reduces immune defenses (thus creating a vicious cycle), strategies to reduce infection rates should thereby diminish protein losses and malnutrition.

GENERAL ADMINISTRATION GUIDELINES IN ICU PATIENTS The practice of providing nutritional support to critically ill patients has evolved in recent years. In general, the total doses of energy, protein, and fats commonly administered are lower than the amounts used from the 1970s to the early 1980s, and increasing emphasis is being placed on enteral feeding, provision of balanced nutrient mixtures, and administration of larger amounts of specific nutrients (e.g. glutamine, arginine, antioxidants, and specialized lipids, as outlined below). An experienced nutrition support consultative service, including physicians, dietitians, pharmacists, and nurses, is crucial to ensure appropriate nutritional and metabolic support in ICU patients (7). Numerous studies have demonstrated the efficacy of the nutrition support team in preventing feeding-associated complications, diminishing over- or underuse of specialized nutrient solutions, and reducing the cost of feeding (3, 7).
Current recommendations advocate enteral feeding whenever possible, even in small amounts. In contrast to the usual impressions at bedside, many studies indicate that enteral tube feeding is well tolerated in critically ill patients fed past the pylorus (7). If intravenous feeding is initiated, it should be discontinued as soon as the gut becomes functional, as determined by frequent assessment of gastric residual volumes, ileus, diarrhea, and other clinical parameters.

Normally, lactose-free, isotonic, nonelemental liquid diets should be administered in the ICU and supplemented by parenteral feeding until maintenance intake is achieved. Some patients may also tolerate oral food. The ICU dietitian is an invaluable resource for the provision of appropriate diets with supplements as needed. Numerous specialized, disease-specific liquid diet formulas are commercially available; these contain varying amounts of energy in the form of carbohydrate or lipid (including medium-chain triglycerides or fish oil), modified amino acid composition, and other differences in macro- or micronutrient content. In general, the clinical and metabolic efficacy of most of these diets has not been directly compared in controlled, blinded trials in similar groups of ICU patients; therefore, product choice is often based on cost considerations and clinical judgement (see section on use of specific nutrients).

To avoid complications associated with overfeeding, the current approach in most centers is to provide maintenance amounts of energy (∼25–40 kcal/kg per day, as required) and protein at doses of ∼1.5–2.0 g/kg per day in catabolic patients with normal renal function (3, 7). The protein dose should be lowered or raised to the target range as a function of the level and rate of change of azotemia and hyperbilirubinemia. This strategy takes into account the inability of many patients to efficiently utilize exogenous nutrients during severe catabolic illness, as well as the fact that most protein and lean tissue repletion occurs over a period of several weeks during convalescence, after the acute phase of injury or illness (when large amounts of body protein are rapidly lost). Branched-chain amino acid–enriched solutions have not been shown to improve clinical outcomes in critically ill patients (7); therefore, standard amino acid formulations should generally be used, pending the results of ongoing research as outlined below.

Enteral or parenteral feeding should be initiated at a caloric dose that provides ∼50% of energy requirements (determined by routine normograms based on age, sex, body surface area, and severity of illness or measured by indirect calorimetry). Energy intake may then be advanced slowly over several days to provide maintenance energy intake (i.e. to meet estimated or measured resting energy expenditure). Intravenous lipid emulsions are used only in patients requiring PN to provide essential fatty acids (1.0–1.5 liters of a 20% solution/week) and/or dietary calories at ∼20–30% of nonprotein energy.
intake, infused over a 24-h period. Dextrose should be administered at a dose providing $\sim 70$–$80\%$ of nonprotein energy, not to exceed 4–5 mg/kg per minute. Larger doses of dextrose are not efficiently oxidized for energy, resulting in hyperglycemia and excessive carbon dioxide production (3). The dextrose load should be reduced, and/or insulin should be provided in parenteral feeding (or as a separate insulin drip) to maintain blood glucose between 100 and 200 mg/dl.

Supplemental zinc (and possibly other trace elements such as selenium) should be given to patients with burns, large wounds, and/or significant gastrointestinal (GI) fluid losses. For example, $\sim 12$ mg of zinc are lost per liter of small bowel fluid lost. Although blinded, controlled trials in ICU patients have not been reported, many clinicians provide supplemental antioxidant nutrients (e.g. vitamins C and E, beta-carotene, glutamine) via the enteral route during severe catabolic stress. Plasma glucose, electrolytes (including magnesium), and triglycerides, as well as renal, hepatic, and pulmonary function in response to specialized feeding must be closely monitored and the nutrient mix adjusted as needed to avoid metabolic complications that may be associated with feeding. If the patient is extremely unstable, it is often prudent to lower the amount of parenteral and enteral diet or to simply administer intravenous dextrose with vitamins and minerals for a few days until organ function stabilizes.

NEW STRATEGIES FOR ATTENUATING PROTEIN-CATABOLIC RESPONSES

Administration of Growth Factors and Anabolic Hormones

Recombinant techniques have enabled large-scale production of peptide growth factors for clinical investigation and patient care. The most clinical information on adjunctive growth factor administration in ICU patients concerns the use of human growth hormone (GH) and insulin. Ongoing studies are also evaluating effects of recombinant insulin-like growth factor-I (IGF-I) administration. Additional studies have assessed protein-sparing effects of anabolic steroid hormones in the ICU setting.

GROWTH HORMONE  Pituitary GH administration in clinically stable non-GH-deficient patients has long been known to enhance retention of nitrogen, phosphorus, potassium, sodium, magnesium, and calcium (with a nitrogen-to-mineral retention ratio similar to that of skeletal muscle). GH also causes lipolysis, diminishes urea production, and increases plasma insulin levels (owing to insulin resistance in glucose homeostasis) (12). In several early studies, severely catabolic burn patients given adjunctive i.m. pituitary GH (5-10 mg/day s.c. or i.m.) consistently exhibited improved nitrogen and mineral
retention, increased appetite, and an antecdotal improvement in wound healing (13–15).

Recombinant GH as an adjunct to nutritional support has been extensively studied in clinically stable patients during the postoperative period (16, 17) and in malnourished patients with end-stage renal disease (18–19), chronic obstructive lung disease (20), AIDS (21) or GI diseases (e.g. inflammatory bowel disease, intestinal fistulas, chronic pancreatitis, and short bowel syndrome) (22–23).

In general, these studies in noncritically ill patients revealed a marked improvement in enteral and parenteral nutrient efficiency with recombinant GH, even when hypocaloric diets were provided (24). Significantly increased plasma insulin and IGF-I levels and corresponding positive nitrogen balance have been observed with s.c., i.m., or intravenous GH doses ranging from 0.06–0.18 mg/kg per day, compared with responses in controls receiving identical isonitrogenous, isocaloric diets. GH improved whole-body protein synthesis rates, reduced muscle amino acid efflux and urea generation, and enhanced whole-body retention of nitrogen, potassium, phosphorus, magnesium, and sodium in these individuals studied over a wide range of nutrient intakes and clinical conditions (16–24). In addition to improved metabolic effects, a recent large study in Spain of patients given GH after cholecystectomy or choledochoduodenostomy showed improved indices of immune function, reduced postoperative infection rates, and shortened hospital length of stay in GH-treated patients (17).

Limited data is available on direct improvements in skeletal muscle function with GH therapy in stable patients. In two studies, GH significantly improved skeletal muscle strength, as shown by maintained hand grip strength in the postoperative period (16), and respiratory muscle strength, as evidenced by greater inspiratory capacity in patients with chronic obstructive pulmonary disease (COPD) (20). In another study in stable patients with chronic lung disease, GH therapy improved nitrogen balance, but this result was not associated with improved indices of respiratory muscle strength (25). However, in GH-deficient adult patients treated with physiologic doses of GH or placebo for several months, physiologic replacement doses of GH improved indices of isometric exercise capacity (26).

Normal adult subjects subjected to skeletal muscle biopsy before and after a 6-h GH infusion (2 µg/kg per hour) demonstrated a 60% increase in postinfusion levels of myosin heavy-chain mRNA, indicating an improved capacity for synthesis of key proteins involved in skeletal muscle structure and/or function after acute GH administration (27). Other studies in normal adults demonstrated acute stimulation of protein synthesis in forearm muscle with short-term GH infusion. These changes occurred without measurable changes in muscle arterial or venous IGF-I concentrations, which suggests that GH may
play a direct role in this response, although tissue IGF-I levels were not measured (28). Furthermore, in a controlled study of stable postoperative patients, GH therapy reduced 3-methylhistidine urinary excretion. This finding implies that the rate of myofibrillar protein breakdown is diminished in this setting (16).

Several short-term studies evaluating short-term (three days to six weeks) adjunctive recombinant GH treatment in critically ill patients have been reported (29–37). In general, these studies document markedly improved net protein anabolism; enhanced nitrogen, potassium, and phosphorus retention; reduced urea generation; and/or stimulated wound healing with GH therapy at doses of 0.1–0.2 mg/kg per day (29–35). However, minimal protein-anabolic effects were seen in two studies using lower GH doses for short periods following sepsis or burn injury (36–37).

The metabolic and clinical effects of up to six weeks of recombinant GH therapy were studied in severely catabolic adult patients receiving conventional enteral and parenteral nutrition support following severe burn injury (~60% body surface area) or vehicular trauma (29). Daily s.c. recombinant GH (10 mg/day; dose range 0.096–0.172 mg/kg per day) was administered after an initial control week. In all patients, body protein, potassium, and phosphorus losses decreased markedly and rapidly with GH treatment (Figure 1). Marked protein-anabolic effects persisted throughout GH therapy, and nitrogen excretion and urea generation decreased by ~30% within the first few days of GH. Serum IGF-I levels rose approximately fivefold with GH, serum magnesium and alanine aminotransferase fell significantly, and serum calcium and triglycerides rose slightly but significantly with GH over time. Potassium, sodium, and phosphorus levels as well as other blood chemistries remained stable, despite mineral retention, suggesting mineral incorporation into cells with protein anabolism (29).

Additional studies in other groups of critically ill and septic patients have documented increased whole-body and limb protein synthetic rates, improved nitrogen balance, and increased fat oxidation rates with short-term GH administration compared with findings for clinically similar patients receiving placebo injections and comparable diets (30–35). The improvement of nitrogen balance with GH in these studies has ranged from ~2–5 g/day in comparison to nitrogen balance with comparable feeding without GH. This change represents a relative improvement in protein-rich tissue of 0.4–0.9 kg/week with GH therapy (22–24).

In a blinded, controlled trial in adult burn patients, two weeks of GH therapy (10 mg/day) attenuated expansion of the extracellular water (ECW) compartment and minimized loss of intracellular water (ICW). These effects were contrary to those observed in control patients, who experienced the expansion of ECW and contraction of ICW common in the critically ill (35).
Such observations suggest a possible effect of GH on cell membrane stability or permeability and are of particular importance given that the state of cellular hydration is a key independent variable controlling cellular protein turnover (38). Because ICW contraction appears to stimulate catabolic responses by reducing protein synthesis and increasing protein degradation rates in skeletal muscle (38), these effects may be minimized during GH treatment by inhibiting ICW loss (35). Further studies on this possible mechanism for GH anabolic effects are necessary.

Although many authors report anecdotal improvements in respiratory muscle strength, time to wean from the ventilator, and other indices of physical rehabilitation during GH therapy in critical illness, such endpoints have not been well characterized in the small patient groups reported on to date. Thus, whether GH improves skeletal muscle function in ICU patients is unclear at present. Several studies are currently underway to directly examine this critical issue.

Improved wound healing of skin graft donor sites with GH administration in burn patients was confirmed in two blinded, randomized trials (31–32). In one study of adults requiring skin grafting, a significant reduction in healing time of 2–4 days was noted with GH (10 mg/day) vs healing responses in matched patients receiving placebo injections (31). In the most dramatic study documenting improved clinical outcome with GH in ICU patients to date,
Herndon et al gave a s.c. GH dose of 0.1–0.2 mg/kg per day to severely burned children in a randomized, double blind trial (32). GH at the higher dose was associated with improved wound healing rates in all degrees of burn injury; at this GH dose, length of hospitalization was markedly decreased compared with that of matched placebo-treated control patients (32). Intermediate effects on wound healing and length-of-stay were observed in the low-dose group. Several patients receiving GH required insulin to control mild to moderate hyperglycemia (32).

The mechanisms of GH anabolic effects are undoubtedly multifactorial when combined with nutritional support. For example, consistent and marked elevations in circulating IGF-I occur with GH in these clinical settings and clearly play a role in tissue anabolic responses to GH. Interestingly, this IGF-I response is attenuated as injury severity increases in ICU patients (33). The IGF-I response is also directly related to nutritional status (39). Thus certain severely ill patients, e.g. those receiving low caloric or protein intakes, or patients with hepatic failure or multiple organ failure may not generate adequate IGF-I responses to induce significant anabolic effects. The stimulation of insulin release, production of endogenous fuel as free fatty acids (FFAs) via enhanced lipolysis, and regulation of circulating or tissue IGF–binding proteins (IGFBP) with GH treatment represent additional mechanisms of GH action that may influence protein-anabolic response during severe illness.

Although GH treatment has been well tolerated in the studies published to date in catabolic patients, these studies have generally not included patients with diabetes mellitus, severe fluid retention (e.g. congestive heart failure), or malignancies. GH causes hyperglycemia and insulin resistance, which may become severe in unselected patients with diabetes mellitus or underlying glucose intolerance. In addition, we have observed several cases of unexplained hypercalcemia in complicated, immobilized, critically ill patients with renal and other organ dysfunction temporally associated with GH therapy (29). GH may cause mild fluid and sodium retention and arthralgias or carpal tunnel syndrome in some individuals (22–24) and, as a growth factor, may theoretically stimulate neoplastic growth. Finally, several cases of benign intracranial hypertension (pseudotumor cerebri) were reported in patients receiving GH (or IGF-I) to enhance somatic growth (40). These and other unknown potential problems with even short-term use of GH in pharmacologic doses make it necessary to closely monitor and select all patients receiving this potent anabolic agent. Major metabolic and clinical effects of recombinant GH observed in malnourished and catabolic patients are summarized in Table 1. 

INSULIN-LIKE GROWTH FACTOR-I (IGF-I) A number of studies have evaluated the protein-anabolic effects of IGF-I (or somatomedin C) in humans without GH deficiency (41–45). IGF-I may be synthesized in most organs of the body, but
the liver is the primary site of production. GH is the primary regulator of IGF-I synthesis and release, although IGF-I production is also markedly influenced by nutritional status (39). IGF-I circulates in plasma largely bound to one of several IGFBPs, which are also synthesized in multiple tissues throughout the body. The six IGFBPs that have been characterized appear to variously potentiate or inhibit IGF-I action and may influence plasma and tissue IGF-I half-life and/or tissue distribution; however, the biological actions of the IGFBPs in catabolic patients and their regulation by GH, IGF-I, or nutrients in these states have not been widely studied.

When administered intravenously, IGF-I in healthy humans acutely lowered blood glucose by increasing peripheral glucose disposal and, to a lesser degree, by suppressing hepatic glucose production (41). FFA levels fell significantly with IGF-I infusion, indicating reduced lipolysis, while total branched-chain amino acid levels fell by ~50%, suggesting a possible protein-anabolic effect (41).

Clemmons et al documented that parenteral IGF-I could reverse the protein catabolic effects of hypocaloric oral diets, which provided 20 kcal/kg ideal body weight/day with adequate protein in healthy adults (42). Subjects were fed the hypocaloric diets for eight days prior to a six-day infusion of either recombinant IGF-I (12 µg/kg per hour over 16 h/day) or GH (0.05 mg/kg per day s.c.). IGF-I significantly attenuated nitrogen losses, a result similar to the protein-anabolic effect observed with GH. Several episodes of symptomatic hypoglycemia occurred with IGF-I infusion. In a subsequent study, these authors compared the protein-anabolic effects of combined six-day GH plus

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<td>Improved nitrogen retention, reduced urea generation</td>
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<td>Stimulated protein synthesis, increased protein breakdown and turnover</td>
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<td>Reduced amino acid efflux from muscle, maintained skeletal muscle intracellular glutamine levels</td>
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<td>Enhanced lipolysis</td>
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<td>Increased metabolic rate (15–25%)</td>
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<td>Enhanced retention of potassium, phosphorus, magnesium, and sodium</td>
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<td>Insulin resistance, increased plasma glucose, free fatty acids, calcium, and IGF-I</td>
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<td>Maintained extracellular and intracellular water compartments (in ICU patients)</td>
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<td>Improved wound healing</td>
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<td>Decreased infection rate, improved immune function</td>
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<td>Increased postoperative grip strength</td>
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<td>Variably increased respiratory muscle function in chronic obstructive lung disease</td>
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IGF-I infusion vs IGF-I infusion alone (43). Combined GH plus IGF-I therapy resulted in a markedly improved nitrogen balance over the baseline diet period compared with results with IGF-I alone. With IGF-I treatment, nitrogen balance improved from $-139 \pm 48$ to $-31 \pm 29$ mmol/day; however, with combined GH/IGF-I infusion, the subjects reverted to positive nitrogen balance from a pretreatment mean of $-140 \pm 50$ mmol/day to $+122 \pm 43$ mmol/day. Both therapies significantly reduced urea appearance, although combination therapy with GH plus IGF-I therapy was more potent in lowering blood urea nitrogen and in reducing urea and potassium excretion than IGF-I treatment alone. The GH/IGF-I treatment protocol also considerably reduced hypoglycemic episodes (43). In another study, normal volunteers were fed hypocaloric, adequate protein intravenous nutrition for 10 days prior to a 6-day infusion of saline or IGF-I at a dose of 25 µg/kg per hour (44). Subjects receiving IGF-I showed improved nitrogen balance and reduced amino acid efflux from skeletal muscle, without changes in fat oxidation (44).

Preliminary results of one study of IGF-I use in catabolic patients have been reported (45). Recombinant IGF-I (10 µg/kg per hour) or saline was infused for 14 days following severe head trauma in 24 adult patients. In saline-treated controls, daily nitrogen balance was negative ($-2.9$ g/day), falling to $-5.0$ g/day during the second week after injury. Nitrogen was significantly conserved during the first week postinjury in the IGF-I treated group ($+1.3$ g/day) as IGF-I levels rose considerably from 178 to 466 ng/ml. However, IGF-I levels fell to 220 ng/ml by day 14, despite continued IGF-I infusion, and the nitrogen-retaining effect of IGF-I was lost (45). Therefore, IGF-I therapy may be less efficacious than GH in promoting the sustained protein-anabolic response observed over several weeks in other groups of ICU patients (29, 35).

IGF-I may induce hypoglycemia, which is probably the major potential complication of this growth factor for patients requiring specialized enteral or parenteral nutrition. However, low-dose therapy, use in combination with dextrose-containing nutrient solutions, or use in combination with GH may minimize this risk. The safety and potential metabolic and clinical utility of this growth factor in humans requiring specialized feeding need to be further defined.

**INSULIN** Insulin is the major endogenous anabolic hormone in the body. Several studies have demonstrated reduced nitrogen loss with insulin administration in nondiabetic injured patients (46–49). Hinton et al (46) and Woolfson et al (47) documented marked reductions in protein breakdown rates and urea generation with administration of high doses of regular insulin at doses of 200–600 units/day or 2–20 units/h in the respective studies with hypertonic dextrose in burn and trauma patients (46–47). Reduced amino acid efflux from skeletal muscle was observed with insulin treatment in postoperative patients
Addition of insulin at a dose of 25 units/liter to PN in stable malnourished patients significantly improved lean body mass compared with PN alone, as determined by body composition analysis (49).

A number of studies suggest that insulin may reduce protein loss in some groups of catabolic patients. The limitations of this approach primarily relate to the risk of hypoglycemia; electrolyte imbalance as a result of shunting of potassium, phosphorus, and magnesium into cells; and fluid retention due to the sodium-retaining effect of this hormone.

ANABOLIC STEROIDS  Several investigators have reported on the use of anabolic steroid hormones (testosterone, testosterone derivatives) in surgical and other catabolic patients (50–52). These agents have consistently led to improved nitrogen balance, although the magnitude of this effect is minor. However, complications such as sodium and water retention, edema, lipid abnormalities, and unwanted virilizing effects may be observed with anabolic steroid administration (intravenous or oral), and cholestatic hepatitis may occur with oral administration; therefore, these hormones have not been routinely prescribed. Many malnourished, elderly men admitted to the hospital exhibit low circulating levels of testosterone. Further investigation of the short-term metabolic and clinical efficacy of parenteral testosterone administration in this patient group would be of interest.

USE OF SPECIFIC NUTRIENTS

Glutamine

Glutamine (GLN) is the most abundant free amino acid in the body (3). GLN is the major compound that facilitates interorgan transport of nitrogen in humans, particularly between skeletal muscle (the major site of GLN synthesis) and the splanchnic bed and kidney (the major sites of GLN uptake). GLN is physiologically important in several key metabolic processes, including nucleotide biosynthesis, skeletal muscle protein synthesis and breakdown, renal ammoniagenesis, and gluconeogenesis. GLN also serves as a major metabolic fuel in rapidly replicating cells such as the enterocyte (53).

Available data from both human and animal studies strongly support the concept that GLN may become conditionally essential in catabolic states. GLN requirements increase markedly during stress, as GLN-utilizing tissues and cells (e.g. intestinal mucosa, stimulated immune cells, wounds) consume increased amounts of this amino acid as GLN use exceeds endogenous GLN production from skeletal muscle. Thus a GLN-deficiency state may develop with the fall of GLN concentrations in intracellular muscle and plasma pools, as obligatory requirements are not satisfied by adequate provision of dietary
GLN. This conditional deficiency may manifest itself as altered structure and function of GLN-utilizing tissues and cells. Net catabolism of skeletal muscle (the major source of endogenous GLN) increases initially to provide greater quantities of GLN for the body. Considerable experimental and clinical evidence suggests that dietary supplementation of GLN during catabolic states may attenuate or reverse these sequelae (reviewed in Ref. 53).

L-glutamine is not present in most standard parenteral nutrient solutions because of its poor solubility and its tendency to degrade to ammonia and pyroglutamic acid with heat sterilization. However, these potential problems are obviated by use of cold sterilization methods and proper storage techniques (54). Glutamine dipeptides have recently been developed for parenteral use that also obviates these problems (53).

An increasing number of clinical studies [in postoperative, septic, or traumatized patients and in patients receiving bone marrow transplantation (BMT)] have demonstrated that GLN administration is safe and clinically efficacious. Table 2 lists beneficial effects observed in trials comparing results with specialized feedings enriched with L-GLN or GLN analogs [ornithine α-ketoglutarate (OAK) and α-ketoglutarate (AKG)] vs GLN-free or low GLN diets in nutrition support. In all clinical trials reported to date, GLN-enriched feeding resulted in reduced net body protein breakdown, as evidenced by improved nitrogen retention and enhanced protein synthesis compared with results with isonitrogenous, isocaloric control diets (53–63). In a recent trial in severely catabolic patients undergoing allogenic BMT, parenteral solutions providing 0.57 g L-GLN/kg per day (∼40 g/day) markedly attenuated nitrogen loss and 3-methylhistidine excretion during the acute post-BMT period compared with results from patients receiving standard, GLN-free PN (Figure 2) (57). Significantly reduced microbial colonization rates and a lower incidence of clinical infections were also observed during hospitalization with GLN.

Table 2 Beneficial effects of nutrition supplemented with L-GLN, GLN dipeptides or GLN analogs in the clinical setting

| Maintained plasma and skeletal muscle intracellular GLN levels after operation or trauma |
| Improved nitrogen balance and attenuated 3-methylhistidine excretion during catabolic stress |
| Enhanced skeletal muscle protein synthetic rates |
| Attenuated extracellular fluid expansion after BMT |
| Enhanced wound healing following burns (enteral ornithine-alpha-ketoglutarate) |
| Improved intestinal nutrient absorption in severe short bowel syndrome (combined with GH and fiber) |
| Reduced microbial colonization and clinical infection, and increased lymphocyte recovery after BMT |
| Shortened hospital length of stay after allogeneic or autologous BMT |

*Adapted from Ref. 53; BMT = bone marrow transplantation.*
supplementation. Furthermore, hospital stay was shortened by seven days, with a considerable reduction in hospital costs.

Another recent study in a different patient population confirmed this marked reduction in hospital stay with the use of specialized GLN-enriched PN after allogeneic and autologous BMT (61). Although the mechanism(s) resulting in improved clinical outcomes with GLN-supplemented nutrition is as yet unclear, it may relate to multiple factors induced by GLN nutrition, including reduced net proteolysis (53–57), maintenance of the gut mucosal barrier function (58), protection of antioxidant capacity (GLN is a major substrate for glutathione synthesis.) (59), normalization of body water compartments via attenuation of ECW expansion (60, 61), and/or enhanced lymphocyte recovery (63). Young and colleagues also demonstrated that intravenous GLN induces an improved state of well-being in catabolic patients, as determined in a double blind trial of BMT patients that evaluated patient-ad-

Figure 2  Daily nitrogen balance in two groups of adult patients receiving isonitrogenous, isocaloric PN between days 4 and 11 following allogeneic bone marrow transplantation. Nitrogen intake (mean ± SE) for the week is shown by the upper horizontal line, and nitrogen balance for each 24-h period is indicated by the black (negative balance) or stippled (positive balance) areas. Patients receiving standard feeding were given no glutamine, whereas the glutamine-supplemented group received 0.57 g glutamine/day. In the experimental diet, glutamine nitrogen replaced a proportion of nitrogen provided as nonessential amino acids; this diet also contained ~30% less total nitrogen in the form of essential amino acids compared with the control diet. Glutamine supplementation significantly attenuated nitrogen loss in these catabolic patients compared with those receiving standard nutritional support (P = 0.001 by ANOVA).
ministered mood-profiling instruments (62). These or other effects probably interrelate to induce the beneficial effects of GLN nutrition observed in patient subgroups to date. Additional studies evaluating the metabolic, molecular, and clinical mechanisms of GLN action in catabolic states will further define the potential benefit of this nutrient.

GLN administration has been well tolerated clinically, without appreciable generation of endproducts such as ammonia, glutamate, or pyroglutamic acid in plasma, despite the administration of relatively large amounts of GLN (20–40 g/day, based on dose-response studies in animals and humans). However, patients with severe renal or hepatic failure or central nervous system (CNS) dysfunction often do not efficiently metabolize or utilize large amino acid loads. GLN supplementation may be contraindicated in such clinical settings. Further study of the safety and clinical efficacy of this amino acid is needed. Ongoing studies of enteral and parenteral GLN-enriched nutrition provided as free L-GLN or GLN dipeptides or as OAK and AKG will further define the clinical efficacy of this amino acid in nutrition support. Nevertheless, based on the available data, GLN should be considered a potentially important dietary amino acid in a number of clinical settings (53).

Arginine

Several animal studies indicate that arginine has potent immunostimulatory effects when provided in amounts greater than normally present in the diet. Although data on the effects of arginine in humans are limited, a number of studies suggest that it may improve immune functions, particularly when provided with adequate nutritional support (64–65).

Barbul et al found that 30 g of arginine administered orally to normal volunteers resulted in a significant increase in peripheral blood lymphocyte blastogenic response to Con A and phytohaemagglutinin (PHA) (64). In the first study of immune effects of supplemental arginine in injured humans, Daly et al evaluated the immune and metabolic effects of L-arginine (25 g/day) or isonitrogenous L-glycine added to enteral feeding solutions postoperatively in 30 patients with GI malignancies requiring operation (65). Immune parameters were measured preoperatively and on days one, four, and seven postoperatively. The arginine-supplemented group exhibited increased plasma arginine levels but only slightly improved nitrogen balance; however, this group showed improved immune function by the end of the seven-day trial. Supplemental arginine significantly enhanced mean T-lymphocyte responses to mitogens PHA and Con-A vs controls on postoperative days four and seven. Arginine supplementation also increased the CD-4 phenotype on postoperative days one and seven but had no effect on other phenotype subsets, including total T cells, CD-8, and the CD-4 to CD-8 T-lymphocyte ratio. Arginine
increased IGF-I levels, and it is possible that this hormone (or GH) may mediate beneficial immune responses (17). No differences in infection rates were noted in this short-term trial (65).

**Combination Therapy of Growth Factors and Specific Nutrients**

One strategy to enhance the efficacy of metabolic support is to combine anabolic hormones with key nutrient substrates. We therefore studied the combined effects of GLN (0.45 g/kg per day by the intravenous or enteral route), parenteral GH (0.14 mg/kg per day), and a modified enteral diet in adult patients with GI failure vs individuals who received standard nutritional support (23).

After three weeks of therapy, the GH-GLN patients gained minimal body fat but significantly more lean body mass ($4.3 \pm 0.6$ kg vs $2.0 \pm 0.2$; $P < 0.03$) and protein ($1.4 \pm 0.3$ kg vs $0.9 \pm 0.1$; $P < 0.03$) than did individuals treated with standard therapy. The increase in lean tissue was not associated with an inappropriate expansion of extracellular water. In contrast, patients receiving standard therapy deposited a greater proportion of body weight as extracellular water and body fat (23).

In a subgroup of patients with short bowel syndrome, this combined therapy resulted in markedly improved intestinal absorption of nitrogen, calories, sodium, and water (66), implying that this treatment enhances bowel function, possibly through increased protein deposition. Further work is in progress to determine the nature of this additive or synergistic effect of combined therapy on nutrient absorption in patients with severe short bowel syndrome.

Several studies have demonstrated that GH attenuates or abolishes glutamine release from muscle and maintains free intracellular glutamine concentrations in skeletal muscle (16, 67). This finding is particularly important in light of data documenting metabolic and clinical efficacy of glutamine-enriched nutrition in catabolic patients (53–63) and provides an additional rationale for combined glutamine plus GH therapy as a means of maintaining intracellular glutamine concentrations in stressed patients. The effects of GH on glutamine metabolism may be one mechanism by which GH improves nitrogen balance and dietary protein use. Additional studies in rats show that combined IGF-I and GLN-enriched nutrition therapy has additive effects on intestinal protein content, plasma IGF-I levels, and plasma GLN levels after partial small bowel resection. This finding implies an important interaction between GLN and the GH–IGF-I action pathway (68).

**Use of Specific Lipid Products and Antioxidants**

Several new lipid products containing medium-chain triglycerides, fish oils, and structured lipids are undergoing clinical tests. Although some evidence suggests that these may have beneficial metabolic effects compared with com-
monly administered standard lipid products (9), only limited data on clinical outcomes are available. In general, effects on protein metabolism have not been impressive. Recent studies in postoperative patients have suggested that arginine (12.5 g/liter) added to enteral diets containing nucleotides and fish oil improves immune functions and possibly reduces infection rates compared with standard enteral diets that contain low amounts of arginine (1.6 g/liter) without RNA or fish oil (69–70). In one study, the arginine/RNA/fish oil–supplemented diet improved in vitro lymphocyte blastogenesis and appeared to reduce wound complications and hospital length of stay (69).

As noted above, investigators are evaluating the possible beneficial effects of antioxidant nutrients (e.g. vitamins C and E, beta-carotene, cysteine) in nutritional and metabolic support. Although numerous studies are in progress, no controlled clinical trial results demonstrating improved metabolic or clinical outcomes with use of antioxidant nutrients have yet been published.

**Biologic Response Modifiers**

Additional strategies to modify the biologic response to stress have been evaluated in humans in an attempt to reduce proteolysis and/or to improve clinical outcome. These include use of cyclooxygenase inhibitors such as ibuprofen, which reduces protein breakdown and the hormonal-cytokine stress response (71), as well as the administration of epidural anesthesia in critically ill patients, which reduces protein breakdown rates (72, 73). Specific blocking antibodies and other similar approaches designed to inhibit the effects of endogenous endotoxin and cytokines are currently under clinical investigation, but effects of these methods on protein metabolism in hospitalized patients have not been reported.

**SUMMARY**

Current nutritional and metabolic support modalities are clearly less effective in preventing body protein loss and improving clinical outcomes than previously believed. However, several promising new strategies are currently under investigation in the clinical setting. These strategies may reduce the

<table>
<thead>
<tr>
<th>Table 3 New strategies for nutritional/metabolic support in critical illness</th>
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<tr>
<td>Enteral feedings designed to maintain intestinal absorptive, immune, and barrier function</td>
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<tr>
<td>Administration of conditionally essential amino acids (e.g. glutamine, arginine)</td>
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<tr>
<td>Use of specialized lipid products (e.g. medium-chain trglycerides, fish oil)</td>
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<tr>
<td>Provision of antioxidants (e.g. vitamin E, vitamin C, cysteine)</td>
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<tr>
<td>Administration of growth factors (e.g. GH, IGF, EGF)</td>
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<tr>
<td>Combination approaches (e.g. GH + glutamine + dietary pectin)</td>
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protein-catabolic response to illness and injury and improve other important clinical outcomes (Table 3). In the future, increased amounts of certain nutrients (in particular glutamine, vitamins, and antioxidants) will likely be routinely administered in the care of patients with a variety of illnesses. In addition, use of peptide growth factors, modified lipids, and combinations of these approaches will probably prove beneficial in a number of clinical settings. Further clinical investigation will determine the safety, efficacy, and cost-effectiveness of these novel approaches.

**Literature Cited**

ZIEGLER, GATZEN & WILMORE

ATTENUATING CATABOLISM

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