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Growth Factors in Clinical Practice

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Abstract. Growth factors enhance protein synthesis and thus reduce the catabolic response to injury. As a result of bioengineering and new manufacturing techniques several anabolic agents have become available for clinical use and have been evaluated in surgical patients with catabolic illness. Data support the anabolic effects of growth home in such patients, but its expense and possible deleterious effects during the acute phase of illness limit its use to selected patient groups. Insulin-like growth factor-1 has also been studied, but specific indications for its use have not been identified in catabolic patients. Testosterone and derivatives of this hormone exert anabolic effects, but few randomized trials include catabolic surgical patients, and higher doses of some derivative compounds are associated with hepatic dysfunction. Nonetheless, as we move into the future, studies will determine the specific doses for administration of these and other anabolic factors in specific patient groups. Anabolic therapy will shorten the length of therapy and improve the outcome in the future.

Growth factors participate in the regulation of cell proliferation, differentiation, and organ growth; and these factors should be thought of as the next major step forward to provide more efficient and effective nutritional support to the catabolic or wasted patient. These molecules can greatly enhance somatic growth [e.g., human growth hormone (GH) and insulin-like growth factor-1 (IGF-1)] or may target specific cells or organs and stimulate their proliferation [e.g., erythropoietin (EPO), granulocyte/macrophage colony-stimulating factor (GM-CSF) and hepatocyte growth factor (HGF)]. In addition, a variety of other substances are available that may stimulate or augment anabolism, including testosterone, anabolic steroids, and the amino acid glutamine (possibly the first growth factor to occur in evolution).

Myriad carefully performed laboratory and clinical studies have documented that somatic growth factors augment protein synthesis and enhance a positive nitrogen balance. That these substances also enhance human performance is demonstrated by the world class athletes and other sports competitors who practice "drug doping," a training approach that involves taking one or more of these agents to enhance skeletal muscle strength and improve performance to gain a competitive advantage. However, physicians have been reticent to utilize such anabolic agents in their catabolic or wasted patients.

The large-scale production of growth factors has made these agents available for study and use in the catabolic state. This paper reviews the therapeutic effects of these agents when used to combat catabolism in critically ill patients.

Why Is Anticatabolic/Anabolic Therapy Required?

Weight loss, associated with a substantial decrease in body fat and skeletal muscle mass characterizes the metabolic response to catabolic illness. These events are commonly observed in patients who have sustained extensive injury or severe infection. Similar responses have been described in individuals with other disorders, such as multiple organ system failure, chronic obstructive lung disease, acquired immunodeficiency syndrome (AIDS), and in individuals undergoing extensive chemotherapy and radiation treatment for cancer [1]. Adipose tissue represents a form of stored energy to be used as a fuel source during times of stress. In contrast, body protein is a critical component of the lean body mass and represents structural or functional tissue. *Loss of body protein is associated with loss of function.* Whereas functional changes may not be apparent in the short term (5–7 days in a well nourished individual), unchecked catabolism for more than 7 to 10 days results in increased morbidity and prolonged convalescence (Table 1). These protein catabolic responses impede the patient's ability to return to a healthy life.

The accelerated breakdown of body mass and loss of protein can be attenuated in critically ill patients by administration of adequate nutrients [2]. Along with adequate calories, the protein required to optimize nitrogen balance is approximately 1.5 to 2.0 g/kg/day. Although this amount does not achieve nitrogen balance, providing more protein (or protein equivalents) results in increased amino acid oxidation, heightened energy consumption, and excessive urea generation. Serial measurements of body composition and substrate-flux studies indicate that it is extremely difficult to maintain or optimally replete body protein during the catabolic state [3, 4]. Many factors contribute to the protein-catabolic response, including bed rest, sedation, mechanical ventilation and curarization, inotropic support, and inadequate exer-

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Table 1. Relation of catabolism to mortality.

Acute weight loss (%)	Clinical correlate	Approximate increased mortality (%)
10–15	Impaired immunity; increased infection	5
15–20	Decreased wound healing; failure to wean from a ventilator	15–30
30	Poor ambulation, bedridden pressure sores, high probability of pneumonia	50
40	Death, usually from pneumonia or infectious site; other	100

cise. Along with the production of cytokines, which enhance tissue breakdown, these factors are additive to a neuroendocrine environment that favors net protein catabolism. All of these factors commonly affect patients in most modern critical care units. Because present-day nutritional support does not prevent substantial loss of body protein during severe catabolic illness, anticatabolic therapy is required because body protein depletion is related to increased morbidity and mortality.

One approach to this problem is to block the mediators of catabolic events. These mediators can be grouped into three broad categories: hormones, cytokines, and lipid mediators. A simple cascade of events does not usually occur after major inflammatory stimuli; the response patterns depend on the stimulus, and release of multiple mediators is usually observed. Moreover, these three catabolic response systems are interconnected by amplification loops and negative and positive feedback signals. These responses have proven difficult to block or significantly attenuate as a strategy to decrease catabolism.

Another approach is to counterbalance the catabolic events with anabolic mediators. Thus physicians have administered such factors as GH, IGF-1, testosterone, and anabolic steroids in an attempt to attenuate the protein catabolic response to injury. The relevant data related to the administration of these agents are presented in this report.

Effects of GH

Growth hormone is a highly potient somatic growth factor secreted by the anterior pituitary gland. Its rate of secretion is high in growing children; then, from the third decade onward, plasma concentrations fall with age. GH stimulates bone growth, protein synthesis, and fat oxidation. It also causes insulin resistance and fluid and sodium retention. Administration of GH to normal or hypopituitary adults results in an increase in lean body mass and a decrease in adipose tissue. It was hoped that these characteristics could be utilized in catabolic surgical patients.

Initial studies evaluated the effect of GH on postoperative nitrogen balance. Ward et al. administered GH (0.3 U/kg/day or 0.12 mg/kg/day) or placebo to postoperative patients receiving approximately 400 calories from 5% dextrose solutions [5]. Nitrogen excretion over 6 days was reduced from 42.7 g to 24.0 g, and fat oxidation increased with GH treatment. There was also a rise in serum glucose, insulin, and IGF-1. A similar study was performed by Carli et al., who confirmed the GH effect of enhancing postoperative protein synthesis [6].

Manson and Wilmore demonstrated that positive nitrogen balance could be achieved in normal volunteers by providing adequate nitrogen but only 50% of the required energy [7]. This approach was applied by Jiang and associates, who studied a group of postoperative surgical patients following gastrectomy or colectomy [8]. The patients received parenteral nutrition containing 20 kcal/kg/day and 1 g protein/kg/day and were randomized in a blinded manner to receive placebo or GH (0.06 mg/kg/day or 0.15 U/kg/day). The GH subjects lost significantly less weight (1.3 vs. 3.3 kg); cumulative nitrogen loss over 8 days was only 7.1 g versus 32.6 g in the controls. Amino acid flux studies across the forearm demonstrate that GH-treated patients had increased uptake of amino acids into forearm skeletal muscle, whereas the control subjects released amino acids from their forearm. In the control patients, hand grip force decreased approximately 10% after operation, whereas the patients who received GH maintained their grip strength throughout the postoperative period.

GH after Accidental Injury and Burns

Early studies performed independently by Liljedahl et al. [9], Soroff et al. [10], and Wilmore et al. [11] established that improved nitrogen balance could be achieved in injured patients following GH administration. With the availability of recombinant GH, more extensive trials were performed, confirming these findings; the studies also suggested that GH might confirm benefits in patients by enhancing respiratory muscle strength and shortening convalescent recovery. It should be realized that these effects were achieved by administering reasonably large doses of GH (0.1–0.2 mg/kg/day) to injured patients, and they were accompanied by increased concentrations of IGF-1 and insulin with no significant effects on the elaboration of catabolic hormones such as glucocorticoids. In 1989 Shernan and associates [12] and Herndon et al. [13] reported that GH enhanced wound healing in adult and pediatric burn patients, respectively. The study in children is notable: young children (average age 9 years) with extensive burns (average 59% of total body surface) received GH (0.2 mg/kg/day) or placebo injections until their burns were healed or adequately skin grafted. The rate of wound healing was increased in the GH group by approximately 20%, which reduced the length of hospital stay by about 2 weeks. This and a subsequent study appear to document clear-cut efficacy of GH in injured patients with large, open wounds.

Concerns have recently been raised about the safety of GH in intensive care unit (ICU) patients. In two randomized placebo controlled trials in ICU patients an association was observed between GH administration and increased mortality [14]. These two large-scale studies examined the effect of GH in patients following open heart surgery, abdominal surgery, multiple trauma, or acute respiratory failure who had been in the ICU at least 5 days and were expected to stay at least another 5 days. The GH group received approximately 0.08 mg/kg/day adjusted for body weight. It appeared that there was little standardization of nutritional support or other drug use in this multicenter trial, but written reports are forthcoming. The deaths in the GH group occurred early after GH administration. Preliminary analysis demonstrated that there was a twofold increase in mortality in the GH group when compared with placebo, but the actual cause of the mortality is unknown at this time.

These results are surprising, as initial observations of critically ill adult patients receiving GH with respiratory failure [15] or

thermal injury [16] showed lower, not higher, mortality. However, these phase I studies allowed adjustment of the GH dose depending on the clinical condition of the patient. Another study that supported the safe use of GH in critically ill patients is a large double-blind randomized clinical trial in thermally injured children (n = 102) [17]. No increase in mortality with GH administration was observed, and a significant decrease in length of stay occurred in the GH-treated patients. If studies continue in ICU patients, the dose of GH used should probably be < 5 mg/day in adults, with provisions made for dose adjustment according to the clinical condition of the patient. Other investigations in less seriously ill patients, such as those convalescing after an operation, those with the short bowel syndrome, and individuals with human immunodeficiency virus (HIV) wasting syndromes demonstrate that these individuals appear to tolerate large doses of GH without detrimental effects.

IGF-1

Growth hormone stimulates production of a second hormone, IGF-1, which is primarily responsible for anabolic activity. This substance is similar to proinsulin and appears to mediate growth through its effects on protein synthesis, osteocyte activity, and mitogenic and insulin-like effects [18].

Synthesized in many tissues, IGF-1 is secreted into the bloodstream primarily by the liver. Its half-life is prolonged (unlike GH), and determination of the plasma concentration of IGF-1 has been utilized to reflect the anabolic or nutritional status.

The IGF-1 has six binding proteins (IGFBP 1–6) that are tissue-specific and regulated by the nutritional state and other factors. An important binding protein is IGFBP-3, which prolongs the half-life of IGF-1 and thus enhances its anabolic activity. Following injury and infection, proteases cleave IGF-1 from binding proteins and increase its disappearance from plasma, resulting in lower plasma levels and reduced anabolic efficacy of IGF-1. In addition to providing IGF-1, pharmaceutical firms have engineered IGF-1 bound to BP-3 and thus have enhanced the pharmaceutical potency of this anabolic molecule.

Animal and human studies have demonstrated the differences between and similarities of IGF-1 and GH, and some of these biochemical and physiologic effects are detailed in Table 2. From a practical point of view, IGF-1 is administered by injections given at least twice a day; alternatively, it can be given by intravenous infusion. (In contrast, GH is administered by subcutaneous injections given daily or every other day.) The dose-limiting complication of IGF-1 is hypoglycemia, and this side effect is related to its insulin-like activity. Because IGF-1 is a substance whose mode of action is via autocrine or paracrine effects, large parenteral doses are required to promote specific anabolic activity. Moreover, the tissue effects observed are not as generalized as those observed with GH administration (Table 2).

Given these limitations in IGF-1 administration and binding, only a few pilot studies have been performed with this substance. Cioffi and associates gave IGF-1 for 3 days to adult patients following burn injury [19]. They found a decrease in protein oxidation and promotion of glucose uptake. They also noted that energy expenditure remained unchanged. These findings suggested an anabolic effect of IGF-1 in this patient group.

Goeters et al administered IGF-1 to postoperative patients following gastric resections [20]. The patient received standard nutritional support via the intravenous route. IGF-1 failed to improve nitrogen balance, possibly because of the finding that serum concentrations of IGF-1 decreased with time. Two other studies in postoperative patients reported no effects on nitrogen balance with the administration of IGF-1 [21, 22].

Finally, Lieberman and associates give high dose and low dose IGF-1 to 10 patients with AIDS for 10 days [23]. Nitrogen balance was positive with both doses but was positive only 5 of the 10 days with low dose administration. Again, serum concentrations of IGF-1 gradually diminished with time.

Because negative feedback of IGF-1 alters GH and BP elaboration and interacts with insulin effects, it has been suggested that GH and IGF-1 should be co-administered. Thus, the hypoglycemic effects of IGF-1 would be offset by the tendency for GH to cause insulin resistance. GH would also enhance the elaboration of BPs. Studies in normal volunteers who were calorically restricted found more nitrogen retention and potassium conservation when the two substances were given as combination therapy than when either agent was administered alone [24]. Co-administration of IGF-1 and GH to patients with HIV wasting improved the gain in weight and lean body mass, and these changes were maintained at 12 weeks with both GH and IGF-1, compared to single-agent administration [25]. However, the combination failed to improve muscle strength, alter immunologic function, or improve quality of life. Therefore, the evidence does not favor wide-scale use of IGF-1 in catabolic or depleted patients. It is possible that the use of combination therapy (IGF-1 plus GH) or the IGF-1 BP-3 molecule may offer benefit in specific patient groups, but evidence to favor this approach is lacking at this time.

Table 2. Summary of the differences between insulin-like growth factor-1 (IGF-1) and growth hormone.

Parameter	Growth hormone	IGF-1
Salt and water retention	Increased	No effect
Calcium	Serum levels increased	No effect
Glucose concentration	Elevated	Lowered
Insulin	Enhanced secretion	Suppressed secretion
C-peptide	Elevated	Lowered
Glucagon	No effect	Lowered
Free fatty acids	Mobilizes free fatty acids	Inhibits lipolysis
Plasma amino acids	Maintained or increased	Decreased
Mode of action	Endocrine	Endocrine/autocrine/paracine
IGF BP-3	Increased production	Significant suppression
Protein	Stimulates synthesis	Primarily inhibits breakdown
Tissue growth	Balanced	Disproportionate effects on spleen, thymus, and kidney
Duration of effect	Sustained for weeks	Lost despite continued dose

Testosterone

A male hormone, testosterone has been utilized primarily as replacement therapy for males with hypogonadism. Under these conditions, protein synthesis is enhanced and lean body mass increases [26].

Because testosterone levels fall dramatically with critical illness, this substance has been considered by some as a potentially useful, inexpensive anabolic agent in catabolic patients. Few objective outcome data are available from studies in catabolic patients to support the use of testosterone therapy. Moreover, it is known that the incidence of bacteremia and possibly death from sepsis is higher in men than women [27], which is thought to be related to the endogenous hormonal environment related specifically to gender [28]. Therefore testosterone administration should be used with caution in catabolic patients until data from randomized trials are available to justify its use.

Testosterone Analogs

Analogs of testosterone have been developed that increase anabolic activity and decrease androgenic side effects. Several agents are available and have received Federal Drug Administration (FDA) approval for various indications. Oxandrin (Oxandrolone; Bio-Technology General Corp., Iselin, NJ, USA) is the only substance approved for restoration of body mass following a catabolic event (sepsis, operation, injury, AIDS). Studies have demonstrated that this agent enhances weight and muscle mass gain, and these effects are greater than with administration of optimal nutrition alone [29, 30]. Moreover, when this anabolic steroid was given with adequate nutrition to patients with alcoholic hepatitis, the mortality rate decreased from 28% to 5% [31]. The anabolic effects of oxandrin are dose-dependent, and alterations in liver function tests increase significantly with doses larger than 20 mg/day. Dose response data from a large trial in catabolic patients with HIV infection are unreported at this time, and the overall benefits of this drug in this patient group or in surgical patients are unknown. Contraindications are the presence of a carcinoma that may be sensitive to testosterone, such as cancer of the breast or prostate.

Résumé

Les facteurs de croissance stimulent la synthèse des protéines et ainsi réduisent la réponse catabolique aux agressions. Grâce aux progrès en bioengineering, et les techniques de fabrication, plusieurs agents anabolisants sont disponibles et ont été évalués en clinique chez des patients chirurgicaux en état catabolique. Les informations disponibles sont en faveur d'effets anabolisants de l'hormone de croissance chez ces patients, mais son utilisation est limitée par les coûts et les effets potentiellement délétères dans la phase aiguë de la maladie chez certains groupes de patients. On a également étudié le facteur de croissance insuline-like-1 mais les indications spécifiques de son utilisation n'ont pas encore été identifiées chez le patient en état catabolique. La testostérone et les dérivatifs de cette hormone exercent des effets anabolisants, mais on manque d'étude randomisée chez le patient chirurgical en catabolisme, et l'administration de plus fortes doses de certains de ces composés est associée à un dysfonctionnement hépatique. Néanmoins, au fur et à mesure du progrès, des études futures vont pouvoir déterminer la dose spécifique nécessaire de ce facteur et d'autres, chez des groupes spécifiques de patients. Une thérapie anabolisante pourrait raccourcir la durée d'une thérapeutique donnée et dans l'avenir, améliorer l'évolution.

Resumen

Los factores de crecimiento participan en la regulación de la proliferación celular, la diferenciación y el crecimiento de los órganos. Estos factores deben ser vistos como el paso siguiente de importancia mayor en la provisión de un soporte nutricional más eficiente y efectivo en pacientes catabólicos o severamente desnutridos. Estas moléculas tienen la capacidad de incrementar en forma notoria el crecimiento somático (son ejemplos de ellas las hormona de crecimiento humano, HC, y el factor de crecimiento similar a la insulina-l (FCI-l), o de actuar sobre las células u órganos específicos para estimular su proliferación [son ejemplos la eritropoyina (EPO), el factor estimulante de colonias de granulocitos macrófagos (FECGM) y el factor de crecimiento de hepatocitos (FCH)]. Además, se encuentra disponible una variedad de otras sustancias que pueden estimular o incrementar el anabolismo, entre ellas la testosterona, los esteroides anabólicos y el aminoácido glutamina (posiblemente el primer factor de crecimiento que apareció en la evolución). Una miríada de cuidadosos estudios de laboratorio y clínicos han documentado que los factores de crecimiento aumentan la síntesis proteica y mejoran el balance positivo de nitrógeno. Se ha demostrado que tales sustancias también mejoran el rendimiento físico, a juzgar por los atletas de talla mundial que practican "doping", lo cual implica tomar uno o más de estos agentes durante el entrenamiento con el objeto de estimular fortaleza muscular y mejorar el rendimiento. Sin embargo, los médicos se han mostrado reticentes en cuanto a utilizarlos en pacientes catabólicos o severamente desnutridos. La producción de factores de crecimiento en gran escala ha resultado en su disponibilidad para estudio y uso en condiciones catabólicas. Este artículo revisa los efectos terapéuticos del uso de tales agentes para combatir el catabolismo en los pacientes en estado crítico. Relation of catabolism to mortality. Summary of the differences between insulin-like growth factor-1 (IGF-1) and growth hormone.

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