Update on clinical trials of growth factors and anabolic steroids in cachexia and wasting\(^1\textsuperscript{-}4\)

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**ABSTRACT**

This article and others that focused on the clinical features, mechanisms, and epidemiology of skeletal muscle loss and wasting in chronic diseases, which include chronic kidney disease, cancer, and AIDS, were presented at a symposium entitled "Cachexia and Wasting: Recent Breakthroughs in Understanding and Opportunities for Intervention," held at Experimental Biology 2009. The clinical and anabolic efficacy of specific growth factors and anabolic steroids (eg, growth hormone, testosterone, megestrol acetate) in malnutrition and other catabolic states has been the subject of considerable research during the past several decades. Research on the effects of these agents in cachexia or wasting conditions, characterized by progressive loss of skeletal muscle and adipose tissue, focused on patients with AIDS in the early 1990s, when the devastating effects of the loss of body weight, lean body mass, and adipose tissue were recognized as contributors to these patients' mortality. These same agents have also been studied as methods to attenuate the catabolic responses observed in cancer-induced cachexia and in wasting induced by chronic obstructive pulmonary disease, congestive heart failure, renal failure, and other conditions. This article provides an updated review of recent clinical trials that specifically examined the potential therapeutic roles of growth hormone, testosterone, oxandrolone, and megestrol acetate and emerging data on the orexigenic peptide ghrelin, in human cachexia and wasting. Am J Clin Nutr 2010;91(suppl):1143S–7S.

**INTRODUCTION**

Cachexia, or wasting, is the progressive loss of skeletal muscle and adipose tissue associated with fatigue and weakness commonly observed in multiple disease states, which include cancer, AIDS, chronic obstructive pulmonary disease (COPD), congestive heart failure (CHF), and chronic renal failure (1–5). Body tissue wasting in cachexic patients is likely multifactorial and is potentially due to a number of complex factors, which include anorexia and early satiety, blunted muscle protein synthesis, increased muscle protein breakdown, enhanced lipolysis, and an increase in local and systemic inflammatory mediators, which include proinflammatory cytokines [eg, interleukins such as interleukin (IL)-6 and IL-8 and tumor necrosis factor-\(\alpha\) (1, 2, 6)]. Other potential mediators include the relative deficiency of, or resistance to, endogenous anabolic hormones [eg, testosterone, insulin-like growth factor 1 (IGF-1)] and elevated concentrations of glucocorticoids and myostatin (1, 2, 4). Potential molecular mechanisms are covered elsewhere in this supplement.

Cachexia is associated with increased death and morbidities, which include skeletal muscle weakness and impaired muscle work capacity, prolonged convalescence, and increased risk of infection (2, 4, 5, 7). In 2006, it was estimated that \(\approx\) 5 million people with these conditions in the United States were cachectic because of cancer and other major causes (2). At the 2006 Cachexia Consensus Conference, cachexia was defined as "a complex metabolic syndrome associated with underlying illness and characterized by loss of muscle with or without loss of fat mass" (7). The purpose of this article is to provide an update on the metabolic and clinical efficacy of a specific growth factor [growth hormone (GH)], anabolic steroids (testosterone, oxandrolone and derivatives, megestrol acetate), and the orexigenic peptide ghrelin and ghrelin agonists in human states of cachexia and wasting.

**GROWTH HORMONE**

GH is a peptide hormone that is released from the anterior pituitary gland and is regulated by the hypothalamus. GH primarily exerts somatic anabolic effects by stimulating production of IGF-1 by the liver and other tissues; IGF-1 concentrations, in turn, are regulated by nutritional status and food intake (1, 8). IGF-1 stimulates protein synthesis, myoblast differentiation, and muscle growth, whereas it suppresses protein oxidation and proteolysis and enhances lipolysis (8). Recombinant GH has consistently induced anabolic effects in patients with malnutrition and in other catabolic states (9–13). Recombinant GH is currently approved by the US Food and Drug Administration for use in HIV/AIDS wasting, parenteral nutrition-dependent short bowel syndrome, and pediatric chronic kidney disease, and in adult and pediatric GH-deficiency states. Side effects of this agent

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include dose-related paresthesias and arthralgias, insulin resistance, sodium retention, and peripheral edema (9–12).

**GH in cachexia induced by pulmonary and cardiac disease**

In a pilot study of malnourished patients with COPD by et al (13), subcutaneous injections of recombinant GH (0.05 mg/kg daily) caused substantial weight gain and improved nitrogen balance during the first week of GH treatment. Maximal inspiratory pressure improved by 27 ± 8% after GH treatment (P < 0.02) (13). Burdet et al (14) studied 16 malnourished adults with COPD who received placebo or 0.06 mg GH · kg⁻¹ · day⁻¹. After 3 wk, lean body mass (LBM) was significantly higher in the GH group (±2.3 ± 1.6 kg compared with 1.1 ± 0.9 kg; P < 0.05). However, changes in maximal respiratory pressures, grip strength, maximal exercise capacity, and subjective well-being were similar in the 2 groups (14).

Cachexia occurs in ≈20% of patients with CHF (4, 5). In addition, patients with CHF and cachexia have a death rate that has been estimated to be as high as 50% over a period of 18 mo (4, 5, 15). Acquired GH resistance appears to occur in these individuals (4, 5, 16). In several small randomized trials, GH treatment failed to improve the clinical status of CHF patients (17–19). In one trial, a significant increase in left-ventricular mass in patients with dilated cardiomyopathy occurred with GH, without an improvement in clinical status (18). However, a recent randomized, single-blind, controlled trial evaluated GH therapy in the 56 of 158 patients with CHF (New York Heart Association class II to IV) with positive stimulation test criteria for GH deficiency. Those in the GH group (n = 28) received GH at replacement doses (20). GH therapy improved quality of life (QOL) scores and increased peak oxygen uptake, exercise duration, flow-mediated vasodilation, and left ventricular ejection fraction in the active treatment group. No significant changes from baseline occurred in the controls (20).

**GH in HIV/AIDS-associated wasting**

Similar to CHF, elevated concentrations of GH and decreased concentrations of IGF-1 are observed in HIV-associated wasting, which implies GH resistance. In several randomized, placebo-controlled studies in cachectic patients with HIV, recombinant human GH has significantly improved both LBM and total body weight over 12 wk when compared with placebo, and has been associated with significant improvements in physical endurance and QOL, as shown in supplementary Table 1, which can be found under "Supplemental data" in the online issue (21). In the first major trial of GH in HIV/AIDS wasting (performed in the pre-highly active antiretroviral therapy era), Schambelan et al (22) administered 0.1 mg · kg⁻¹ · day⁻¹ GH (n = 90) or placebo (n = 88) SC for 12 wk in 178 patients with HIV-associated wasting. GH treatment resulted in a significant increase in body weight (+1.6 kg) and LBM by dual-energy X-ray absorptiometry (DXA) (+3.0 kg), coupled with a lipolytic effect (−1.7 kg fat mass) (22). Graded treadmill testing showed a significant increase in work output with GH (+13.2 compared with 2.5%, respectively; P = 0.039), but no differences in QOL indexes occurred between groups. GH treatment was generally well tolerated (22). These authors subsequently observed that GH caused a significant increase from baseline in resting energy expenditure (+232 ± 69 kcal/d; P = 0.020) and lipid oxidation (+3.1 ± 1.0 kcal · kg LBM⁻¹ · day⁻¹; P = 0.016) and a significant decrease in protein oxidation (−1.3 ± 1.0 kcal · kg LBM⁻¹ · day⁻¹; P = 0.027) (23).

In a pilot, randomized, double-blind, placebo-controlled trial of GH in acute wasting, HIV-infected subjects with newly diagnosed opportunistic infections were given antimicrobial therapy; high-calorie nutritional supplements, and either GH (6 mg/d subcutaneously) or placebo (24). Patients in the GH group showed a significant increase in body weight and LBM and a significant decrease in fat mass and the rate of protein breakdown in the 14-d trial (24) (see Table 1 under "Supplemental data" in the online issue).

With regard to functional outcomes, in a small trial in patients with HIV-associated wasting by Esposito et al (25), GH (6 mg/d subcutaneously × 12 wk) induced accrual of LBM and improved body weight in association with an improvement in peripheral muscle oxygen extraction use during exercise. In a crossover study in 27 patients with HIV-associated wasting, these authors observed that the same dose of GH induced a significant increase in LBM in association with significantly improved pulmonary function (ventilatory threshold) and exercise capacity (6-min-walk test work) (26). In the largest trial to date of GH therapy in HIV/AIDS wasting, Moyle et al (27) studied 555 patients with HIV infection and a 10% body weight loss, body mass index (BMI; in kg/m²) <20 or body weight <90% of ideal. A total of 166 patients received daily GH (0.1 mg · kg⁻¹ · day⁻¹) to a maximum of 6 mg/d), 190 patients received the same GH dose every other day, and 199 patients received placebo treatment. GH therapy resulted in a dose-related and significant improvement in LBM and body weight; both GH regimens also significantly improved work output, as measured by cycle ergometry, and QOL, as measured by the Bristol-Meyers Anorexia/Cachexia Recovery Instrument score (27). Adverse events related to fluid retention and hyperglycemia were more common in the daily, compared with the every other day, GH regimen and no changes in HIV viral load or CD4 count occurred between the placebo or GH groups (27). To date, no randomized trials of GH therapy as an agent to treat cancer cachexia have been published.

An issue with trials of GH therapy is that signs and symptoms of fluid retention and the arthralgias that may occur with the higher GH doses in some individuals may present a challenge in terms of the performance of truly blinded investigations. Improvements in lean tissue measured by DXA may also be influenced by GH-induced fluid retention in that an excess of body water may be measured in the fat-free mass compartment (10).

**Ghrelin and Ghrelin Agonists**

Ghrelin is a peptide hormone produced by the stomach and also by a variety of other tissues that is secreted predominantly by the stomach in response to fasting (28, 29). Ghrelin binds to the GH secretagogue-1a receptor in the arcuate nucleus of the hypothalamus to stimulate the release of GH from the anterior pituitary. Ghrelin also increases hypothalamic expression of the orexigenic neuropeptides agouti-related peptide and neuropeptide Y; intravenous infusion of ghrelin to replicate postprandial blood concentrations increases the sensation of hunger and ad libitum food intake (28, 29). The sum effect of ghrelin is an
increase in appetite and food intake, which, when coupled with ghrelin-mediated antiinflammatory activity, have led to the current interest in the use of this agent in human cachexia. Several experimental studies in animal models (28, 29) and a few clinical trials of ghrelin (or ghrelin agonists) have shown modestly promising results of these agents as potential therapies for cachexia (30–35).

To date, only a few pilot human trials of synthetic ghrelin or ghrelin agonist therapy in cancer cachexia have been published. Neary et al (30) studied 7 cancer patients with impaired appetite administered a single dose of synthetic human ghrelin (5 pmol ⋅ kg⁻¹ ⋅ min⁻¹ × 90 min) or placebo in a randomized crossover design. A significant mean increase (+31%) in the consumption of calories from an ad libitum buffet meal offered immediately after ghrelin infusion was documented (30). Strasser et al (31) studied adults with multiple cancer types and cachexia who received either 2 (n = 9) or 8 μg human ghrelin/kg (n = 9) as a 60-min infusion before lunch on 2 study days, 7 d apart, in a randomized, placebo-controlled, double-blind, double crossover trial. Ad libitum meal food intake tended to improve during ghrelin administration but this was not statistically significant. No adverse effects of ghrelin were observed (30, 31).

In a randomized, double-blind, crossover study, Wynne et al (32) gave 9 patients with dialysis-dependent chronic kidney disease and protein-energy malnutrition a single SC dose of ghrelin or placebo, followed by provision of a buffet meal. Administration of ghrelin resulted in a marked increase in ad libitum meal energy intake (204% of placebo), and energy intake remained 57% higher in the ghrelin period than in the placebo period (P < 0.01) (32). Nagaya et al (33) gave human ghrelin (2 μg/kg twice daily intravenously) for 3 wk to cachectic patients with COPD in an open-label study. After ghrelin therapy, significant increases from baseline measures were observed for body weight (+1 kg or +2%), LBM (+0.7 kg or +1.8%), food intake (+9%), hand grip strength, maximal inspiratory pressure, and Karnofsky performance score (+17 points) (33). In another unblinded protocol, this investigative group administered human synthetic ghrelin (2 μg/kg twice daily intravenously) to 10 patients with CHF for 3 wk (34). Ghrelin increased LBM measured by DXA (from 38.3 ± 2.1 to 39.1 ± 2.1 kg; P < 0.05) and significantly improved hand-grip strength, left ventricular ejection fraction, workload, and peak oxygen consumption during cycle ergometry exercise; these parameters remained unchanged in 8 patients who did not receive ghrelin (34).

Very limited data on the effects of ghrelin receptor agonists are published. In a pilot, randomized, double-blind, placebo-controlled, dose-escalation phase I study, Garcia and Polvino (35) studied an orally available ghrelin mimetic in healthy volunteers. Results showed that the agonist produced a dose-related increase in body weight without dose-limiting adverse effects. These authors recently published data from a double-blind, randomized, placebo-controlled study that evaluated the short-term effects of this agent (anamorelin) (36). Anamorelin was well tolerated, significantly increased blood GH concentrations at all doses, and sustained increases in blood IGF-1 concentrations compared with placebo after 5–6 d of treatment. Significant dose-related increases in body weight occurred that were directly correlated with changes in IGF-1 concentrations (36). In a pilot double-blind trial in cachectic patients with multiple cancer types, oral anamorelin (50 mg/d for 12 wk) significantly increased LBM by 1.3% compared with placebo and was well tolerated (37). The chief concern about the use of ghrelin or agonists is that it may stimulate tumor growth in cancer patients. More trials are needed to assess the safety and efficacy of these agents as potential therapies for cachexia.

MEGESTROL ACETATE

Megestrol acetate is a synthetic derivative of progesterone that has long been approved by the US Food and Drug Administration for cancer-associated anorexia/cachexia and, since 1993, for the treatment of anorexia, cachexia, or unexplained weight loss in patients with AIDS (1, 3, 38). The precise mechanism of action of megestrol acetate is unknown. A variety of human studies show that various doses of megestrol stimulate appetite and increase weight gain and this agent is routinely used in cancer patients for this purpose; unfortunately, body composition studies show that the weight gain is predominantly caused by an increase in fat mass, whereas performance status and QOL were generally not influenced by this treatment (1, 38–40).

A 2005 Cochrane Database Review included 30 trials (n = 4123 patients) to evaluate the efficacy, effectiveness, and safety of megestrol acetate in anorexia-cachexia syndrome in patients with cancer, AIDS, and other underlying pathologies (40). Twenty-one trials compared megestrol acetate at different doses with placebo; 4 compared different doses of megestrol acetate with other drugs; 2 compared megestrol acetate with other drugs and placebo; and 3 compared different doses of megestrol acetate. For all patient conditions, meta-analysis showed a benefit of megestrol acetate with regard to appetite improvement and body weight gain in cancer patients, but no conclusion about QOL changes could be drawn (40). There was insufficient information to define the optimal dose of megestrol acetate. The small number of patients studied to date, methodologic problems, and reporting issues precluded the authors from a recommendation for use of megestrol acetate in AIDS patients or in wasting associated with other underlying pathologies (40).

Side effects of megestrol acetate include thromboembolism at high doses, transient adrenal insufficiency, hypogonadism, edema, and central nervous system effects (eg, confusion, headache, dizziness) in some patients (3, 41, 42). The relatively recent understanding that megestrol acetate increases body fat mass, but generally not LBM, coupled with emerging known side effects of this agent, has tempered the routine use of this drug in many clinical centers (3).

ANABOLIC STEROIDS

Testosterone or testosterone derivatives are steroid hormones that exert their effect through binding to cytosolic receptors, which leads to an increase in protein synthesis and muscle mass (43). Recently, studies have emerged of testosterone and derivatives in other conditions in which malnutrition is present (44, 45). Studies on the use of these anabolic agents in cachexia patients have been limited largely to patients with COPD and HIV/AIDS, where positive effects on body weight, LBM, and some functional parameters have been documented (46–51). Testosterone (typically administered as testosterone cypionate or enanthate intramuscularly and more recently dermally by skin patches) has long been approved for use in hypogonadal states in
men. Oxandrolone, a modified testosterone derivative with minimal androgenic effects, has been approved for several decades as an oral anabolic agent for both men and women with weight loss associated with surgery, infection, and other catabolic conditions (45). Nandrolone decanoate was approved to stimulate red blood cell production in patients with renal failure, is an anabolic steroid commonly abused by athletes, and has been studied in several trials in patients with cachexia and wasting. Side effects of these agents have included elevated transaminase concentrations (especially with nandrolone); decreased high-density lipoprotein concentrations; interaction with oral anticoagulants, oral hypoglycemics, and adrenal steroids to require dose modification of these agents; and hypogonadism (manifested by decreased systemic testosterone concentrations).

A long experience with testosterone use makes this hormone a therapeutic candidate for use in cachectic patients. The limited number of trials that have investigated the anabolic effect of testosterone in cachetic states demonstrate a generally favorable effect of this agent to enhance body weight, LBM, and muscle strength with an acceptable safety profile (46–49).

Oxandrolone has an excellent safety profile, is orally administered (approved dosing concentration: 5–20 mg/d), has less potential for hepatic toxicity and virilizing effects than other androgens and, thus, is well tolerated in women (45). A variety of studies have shown that oxandrolone has potent anabolic effects in conditions associated with cachexia and wasting (50–53). Several placebo-controlled trials have suggested that nandrolone decanoate has anabolic effects in patients with HIV- or COPD-associated wasting (54, 55). Anabolic steroids have the potential to cause fluid retention in some individuals, which leads to the same issues with blinding and LBM estimates by DXA as noted for GH above.

In summary, relatively robust data are published on the metabolic and functional efficacy of GH in HIV/AIDS wasting and of testosterone in AIDS wasting and several other cachexia-associated states as agents to enhance body weight, LBM, and muscle strength and, in some cases, QOL. Additional data are clearly needed on the potential efficacy of ghrelin and ghrelin mimetics. These and a number of other promising new agents are currently under development (3). They include the above-mentioned agents, selective androgen receptor modulators, which appear to have anabolic effects in animal models and are under phase I studies in humans (56), and combined treatment, which data suggest may be superior to single agents (3). There is a general need for additional data to define the clinical and long-term efficacy of all the agents highlighted in this article. This need can only be addressed by future appropriately powered, rigorous phase III trials.

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REFERENCES
27. Moyle GJ, Daar ES, Gertner JM, et al. Growth hormone improves lean body mass, physical performance, and quality of life in subjects with


