6-2004

Anabolic agents: Adjuncts to nutrition support

Jane M. Gervasio
Butler University, jgervasi@butler.edu

Anabolic agents: Adjuncts to nutrition support

Jane Gervasio

Clarian Health at Methodist Hospital, Indianapolis, Indiana

Abstract

Anabolic agents as adjuncts to nutrition support therapy have been used to improve malnutrition and establish anabolism. Growth hormone, insulin-like growth factor, and anabolic steroids have been studied for their potential to reverse the catabolic process and promote anabolism. This paper reviews several anabolic agents and their possible role in nutrition support therapy.

The pursuit to halt or suppress the catabolic response to injury or disease has led to the investigation and administration of anabolic agents with specialized nutrition support. The catabolic response is multifactorial and enhances total body protein breakdown. Progressive loss of body protein leads to increased morbidity, impaired immune function, increased infection rates, impaired healing, and weakness; catabolic illnesses may eventually result in multiple-organ failure.[1]

Protein energy malnutrition is associated with increased morbidity and mortality and is still a common problem in hospitalized patients.[2] Nutrition support is administered to patients to decrease net protein loss. Quantities as high as 2 to 3 g/kg per day of protein have been used in attempts to produce an anabolic condition.[3] Although nutrition support has improved patient outcomes, it has failed to circumvent the catabolic response. Anabolic agents, in conjunction with nutrition support, have the potential to improve body composition by maintain- ing or enhancing lean body mass (LBM). Recombinant human growth hormone (HGH), insulin-like growth factor-1 (IGF-1) and anabolic steroids have been investigated as a means to increase protein synthesis and inhibit protein breakdown.

Growth Hormone

HGH is an amino acid polypeptide synthesized by the pituitary and secreted from the hypothalamus into the bloodstream. HGH is an anabolic agent that attenuates injury-induced catabolism, stimulates protein synthesis, reduces adipose tissue, improves humoral and cellular systemic host defenses, and increases muscle mass.[4,5] Growth hormone's effect on protein metabolism by increasing protein synthesis without affecting protein degradation has enticed researchers to investigate its potential use in trauma,[5,6] thermally injured,[4,7] postoperative,[8] septic,[9] and critically ill patients.[10,11]

Critical Care

Research with HGH in critically ill patients has evolved over 20 years. Early studies reported that HGH improved nitrogen retention and protein synthesis, decreased donor site healing time, and reduced postoperative fatigue.[4,9-11] Unfortunately, these early studies were small in number and clinical outcome data were not reported.

Much of the research with HGH has been in thermally injured and trauma patients to evaluate its ability to reverse severe catabolism resulting from the injury. Knox and colleagues[7] retrospectively reviewed 69 thermally injured patients and reported a decreased mortality rate in patients receiving HGH compared with a control group (11% vs 37%, $p < .03$, respectively).[7] Herndon et al,[12] in a prospective, double-blind, randomized study, enrolled 40 children between the ages of 2 and 18 years, with ≥40% total body surface area (TBSA) and ≥20% TBSA full-thickness flame or scald burns to receive placebo or 0.1 mg/kg per day HGH throughout hospital stay. After 24 patients were enrolled (12 patients receiving placebo and 12 patients receiving HGH), no differences were reported between rate of first donor-site healing, IGF-1 levels, or adverse events. The institutional review board mandated the study be redirected, and subsequently 16 patients were randomized to receive placebo or 0.2 mg/kg per day HGH. Patients receiving 0.2 mg/kg per day of HGH demonstrated significantly higher serum IGF-1 levels (4.8 ± 1.7 U/mL compared with control patients at 1.6 ± 0.4 U/mL; $p < .05$) and a significant decrease in donor-site healing times at first harvest compared with placebo (9.1 ± 0.4 days vs 7.4 ± 0.6 days, $p < .05$, respectively) and second harvest (9.0 ± 0.7 days vs 5.7 ± 0.3 days, $p < .05$ days, respectively). Length of hospital stay (length of hospital stay/% TBSA) was decreased from 0.80 ± 0.10 days per percentage of TBSA in the placebo group to 0.52 ± 0.04 days per percentage of TBSA burn in the 0.2 mg/kg per day treatment group ($p < .05$).[12]

Concern arose in November 1997 when the US Food and Drug Administration released a drug warning reporting a significantly higher mortality in critically ill patients receiving HGH. This drug warning was prompted by 2 parallel studies from Finland and Europe. Takala and colleagues[13] performed 2 prospective, multicenter, double-blind, randomized, placebo-controlled trials involving a total of 532 patients (247 Finnish patients and 285 European patients) who had been in an intensive care unit (ICU) for 5 to 7 days and were expected to remain in the ICU for at least 10 days. The patients were admitted to the ICU belonging to 1 of 4 diagnostic groups: cardiac surgery, abdominal surgery, multiple trauma, or acute respiratory failure. Exclusion criteria included patients with cancer, type 1 diabetes mellitus, chronic renal failure, burns, organ transplants, acute central nervous system damage, hepatic dysfunction, septic shock, or glucocorticoid therapy. Patients received either a daily dose of 0.10 ± 0.02 mg/kg HGH or placebo until discharged from the ICU or for a maximum of 21 days. The investigators reported that in both studies, the hospitalized mortality rate was higher in the patients who received HGH than in those who did not ($p < .001$). The mortality rate in the Finnish study was 39% in the HGH group as compared with 20% in the placebo group and in the European study, 44% in the HGH group compared with 18% in the placebo group. The relative risk of death for patients receiving HGH was 1.9 in the Finnish study (95% confidence interval, 1.3 to 2.9) and 2.4 in the European study (95% confidence interval, 1.6 to 3.5). Increased mortality associated with the

treatment group persisted when the data were analyzed according to diagnostic group, Acute Physiology and Chronic Health Evaluation (APACHE) II score, and age. Mortality rates were similar in men and women. The investigators also reported increased length of ICU and hospital days and increased days on mechanical ventilation among the survivors.

In the European study, most of the deaths occurred in the first 10 days of treatment, whereas in the Finnish study, half of the deaths occurred during the first 10 days of treatment and then the remainder occurred >3 weeks after enrollment. Main causes of death in both treatment groups were multiple-organ failure and septic shock or uncontrolled infections. The predominance of these causes of death was particularly marked in the patients receiving HGH.

The reason for the increased mortality is unclear but several hypotheses have been presented. Takala et al[13] postulated that with multiple-organ failure, septic shock, and uncontrolled infection as major causes of death in the study group, there was a modulation of immune function involved. HGH has been reported to augment or inhibit the production of reactive oxygen species and proinflammatory cytokines and reduce or increase the susceptibility to endotoxin or bacterial challenge in animals. This would suggest that HGH might be either beneficial or detrimental in a catabolic patient, depending on the underlying clinical condition.

Increased blood glucose concentrations are a common adverse effect with HGH. HGH-induced hyperglycemia could have resulted in an increase in infections and infectious complications. Takala et al[13] reported increased blood glucose concentrations in patients receiving HGH. The cause of hyperglycemia has been attributed to defective nonoxidative glucose disposal, an increase in splanchnic glucose release, and increased peripheral insulin resistance.[14] Hyperglycemia is associated with an increased risk of sepsis, and tightly controlled glucose concentrations have been reported to decrease morbidity and mortality in critically ill patients.[15] Insulin resistance induced by HGH could have deprived cells of glucose, leading to energy deficit,[13] or hyperglycemia from HGH could have increased the potential for infection and sepsis, leading to multiple organ dysfunction. Decreased mobilization of glutamine from muscle has also been speculated as a reason for the reported increased mortality.[13] Decreased mobilization would result in less glutamine available for leukocytes and enterocytes and for hepatic production of glutathione.[16]

Osterziel and colleagues[17] proposed a theory for increased multiple-organ failure in the patients receiving HGH. The authors suggest that growth signals to damaged cells may trigger cell death in some tissues. Administration of HGH increases concentrations of IGF-1.14 Serum growth hormone and IGF-1 concentrations have been associated with increased myocyte apoptosis in patients with acromegalic cardiomyopathy.[18] Stimulation of the growth hormone and IGF-1 receptor pathways could trigger apoptotic signals in compromised cells resulting in cellular death and ultimately, organ failure.

In an invited editorial by Demling,[19] major differences between the populations were identified as the potential reason for the increase in mortality seen in the study by Takala et al.[13] In that

study, the average age was 60 years and the majority of patients had respiratory failure (95%). Less than 10% were trauma patients. Earlier trials with HGH were usually in younger patients, and the majority of patients investigated were trauma, burn, and surgical patients. Demling proposed the increased mortality in the study by Takala et al[13] might have been caused by negative hypermetabolic and proinflammatory effects of HGH in the study populations.[19]

Growth hormone causes an initial energy deficit by directly increasing cellular metabolic rate and indirectly by increasing plasma catecholamine concentrations, which in turn increase energy demand. Demling[19] theorized that in patients in whom the systemic inflammatory response is activated, there is not a worsening energy deficit or further increased metabolic rate when HGH is added. The possibility of sudden energy deficit in the septic, trauma, or thermally injured patient is decreased because the systemic inflammatory response has been activated. But in patients in whom systemic inflammation is not a component of their disease process, increases in mortality may be the result of an energy deficit from HGH.[19]

Whether it is an energy deficit, a combination of factors, or an unidentified process, HGH should not be given to critically ill patients. Although thermally injured or trauma patients may be an exception, research with growth factors in critical care has been redirected from HGH to anabolic steroids. Oxandrolone and other anabolic steroids have become the more popular agents of research because of positive findings and less adverse effects.

Disease-Related Cachexia

Administration of HGH and other anabolic agents has been investigated for its effects on disease-related cachexia, including cachexia from human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) and cancer. Weight loss and protein malnutrition remain significant problems in these populations. Increases in morbidity and mortality are attributed to muscle wasting from the disease processes. Quality-of-life issues including a parallel decline in energy level, strength, and functional status associated with loss of LBM. Nutrition alone has not been sufficient to maintain body weight in the HIV/AIDS and cancer patient. Whether because of insufficient intake or malabsorption of nutrition, additional measures have been researched and implemented to help restore and maintain LBM.[20,21]

In a study by Mulligan et al,[22] 6 HIV-positive men with an average weight loss of 19% and 6 healthy, weight-stable HIV-negative controls were followed on a metabolic ward for 19 days and fed a constant diet at a level of energy intake to maintain body weight. After 7 days of a pretreatment period, patients were given 0.1 mg/kg per day HGH for 7 days. Both the HIV-positive and HIV-negative men maintained their weight during the pretreatment phase and progressively increased their weight during the treatment phase. Weight gain averaged 2.0 ± 0.3 kg and 1.6 ± 0.2 kg in the HIV-positive and HIV-negative subjects, respectively. Plasma concentrations of IGF-1 increased 3-fold in the HIV-negative subjects and only 2-fold in the HIV-positive subjects, but no significant differences were seen in nitrogen retention (4.0 ± 0.2 g/

day, HIV-positive and 4.0 ± 0.6 g/day, HIV-negative). These results demonstrated HIV-positive men were capable of responding to HGH in a manner similar to HIV-negative men.

Krentz et al[23] followed 4 patients with HIV-associated wasting and administered HGH for 3 months at a dosage of 5 mg every other day. Patients showed improved weight gain and LBM as measured by bioelectrical impedance analysis. Three patients receiving 2.5 mg every other day did not show any significant improvement in weight or LBM.

A larger, 3-month, randomized, double-blind, placebo-controlled multicenter study was conducted to determine if protein-anabolic effects of HGH could be sustained in a large group of patients with HIV-associated wasting.[24] A total of 178 patients with >10% weight loss or actual body weight <90% of ideal for body size were randomized to receive 0.1 mg/kg per day HGH (*n* = 90) or placebo (*n* = 88). At completion of the study, patients receiving HGH had sustained significant increases in weight and LBM and significantly decreased fat mass. Patients receiving a placebo did not have significant changes in weight, LBM, or fat.

Quality of life and energy level was also evaluated. After the 3-month period of receiving HGH, HIV-positive subjects showed an improvement in work output (graded treadmill testing). Volitional exhaustion increased significantly in the HGH group compared with placebo (13.2% vs 2.5%, respectively). Interestingly, quality of life, as assessed by an HIV-specific questionnaire, was not affected by HGH treatments, nor were significant differences reported in days of disability and use of ambulatory, hospital, or home care services.[24]

Limited research is available in cancer-related cachexia. Preliminary data from Wolf and colleagues[25] examined the effect of HGH and insulin administration on protein kinetics in cancer patients. Twenty-eight cancer patients received either 0.1 mg/kg per day HGH (*n* = 6), 0.2 mg/kg per day HGH (*n* = 6), or nothing (*n* = 16) for 3 days. Patients then underwent measurement of baseline protein kinetics followed by a 2-hour euglycemic insulin infusion (1 mU/kg per minute) and repeat kinetic measurements. Cancer patients receiving HGH and insulin had significantly improved whole-body protein net balance and skeletal muscle protein net balance.

In a similar study, Berman et al[26] investigated the impact of HGH alone and in combination with insulin. Patients with malignancies of the upper GI tract were prospectively randomized into 1 of 3 nutrition support groups after surgery: 10 patients received standard parenteral nutrition (PN), 10 received PN plus daily injections of HGH, and 10 received daily GH, systemic insulin, and PN. Standard PN per 24 hours was 2000 mL (500 mL of 20% lipid solution [Intralipid; Baxter, Deerfield, IL] plus 1500 mL amino acids and dextrose solution). HGH was dosed at 0.1 mg/kg per day and 1.4 units/kg regular human insulin were added to the PN. Patients receiving insulin in the PN also received a bolus of 400 mU/m2 of regular human insulin on day 1, before PN was initiated. Patients underwent a protein kinetic radiotracer study on the fifth day after surgery to determine whole body and skeletal muscle protein kinetics. Patient's receiving either HGH or HGH plus insulin showed improved skeletal muscle protein net balance and whole body protein

net balance compared with PN alone. No significant differences between HGH and HGH with insulin were noted.

A small, short-term study by Tayek and Brasel[27] failed to show improved anabolism in malnourished cancer patients receiving HGH. Ten cancer patients were given HGH injections for 3 days (0.125 mg/kg per day). Seven of the 10 patients who were at or above their ideal body weight showed improved nitrogen balances from baseline (-1.46 ± 0.99 vs 0.60 ± 1.03 g/day; $p < .01$). Unfortunately, severely malnourished patients (<90% of ideal body weight) did not show significant improvement in nitrogen retention.

Growth hormone administration in chronic dialysis patients causes increased weight gain and decreased blood urea nitrogen.[28,29] Unfortunately, long-term treatment with HGH in malnourished hemodialysis patients failed to show improvement in nutritional or anthropometric parameters.[30] Nineteen malnourished hemodialysis patients received HGH 0.125 IU/kg 3 times a week during the first 4 weeks and HGH 0.25 IU/kg 3 times a week thereafter for a total of 12 months. IGF-1 concentrations rose significantly from baseline over the first 3 months but declined thereafter. Total body fat declined at 3 and 9 months but LBM remained stable. Nutritional parameters (serum levels of albumin, prealbumin, transferrin) were not affected, nor was blood urea nitrogen.[31]

Intestinal Adaptation/Growth

Enteral nutrition support is critical for normal intestinal cell growth and function. Failure to stimulate intestinal mucosa and submucosa results in atrophy of the gut. Remaining mucosal cells exhibit cellular hyperplasia and increase net nutrient transport. This process is termed intestinal adaptation.[32]

Growth hormone and IGF-1 are 2 of several peptide growth factors required for normal intestinal growth and mucosal repair.[32] In patients in whom intestinal adaptation is insufficient, the addition of exogenous growth factors has been explored. Early research investigating the addition of HGH with or without additional glutamine to the patients with short bowel syndrome (SBS) showed improvements in weight gain, increased LBM, and decreased dependence on PN.[33-36]

Conversely, later research did not confirm these findings. In a 6-week, randomized, double-blind, placebo-controlled crossover study, Scolapio et al[37] compared the effects of high dose HGH (0.14 mg/kg per day), oral glutamine (0.63 g/kg per day), and a high-carbohydrate, low-fat diet on gut adaptation in 8 patients with SBS. Patients received 21 days of active treatment or placebo and then patients were crossed over. Results showed active treatment transiently increased body weight, significantly increased absorption of sodium and potassium, and decreased gastric emptying. No differences were seen with the assimilation of macronutrients, stool volumes, and morphometry of small bowel mucosa when the patient received active treatment or placebo.

Szkudlarek and colleagues[38] performed a similar study reporting the same results. In a randomized, double-blind, placebo-controlled, crossover study, 8 patients with SBS received high-dose HGH (0.12 mg/kg per day, mean) with oral (28 g/day, mean) and parenteral (5.2 g/day) glutamine for 28 days. Balance studies were performed at baseline and 5 days after the treatment was terminated. As with the study by Scolopio et al,[37] HGH with glutamine did not improve intestinal absorption compared with placebo.[38] Further analysis by the same investigators reported no changes in body weight or composition. And increases in LBM, comparing treatment and baseline periods, was not accompanied by an increase in 24-hour urinary creatinine excretion.[39]

Interestingly, Seguy et al[40] administered low-dose HGH (0.05 mg/kg per day) to 12 adult, PN-dependent patients with SBS in a randomized, double-blind, placebo-controlled, crossover study. Patients were on an unrestricted diet. Patients received HGH and placebo for a 3-week period separated by a 1-week washout period. Net intestinal absorption of macronutrients was assessed using a duplicated diet. Results showed a significant increase in intestinal absorption, body weight, LBM, D-xylose absorption, IGF-1 levels, and insulin-like growth factor binding protein when patients were treated with HGH. The authors concluded that low-dose HGH significantly improved intestinal absorption in PN-dependent SBS patients. Growth hormones role in intestinal adaptation is still controversial and further research in needed to determine its dose, duration, and appropriateness.

Insulin-like Growth Factor

Insulin-like growth factor is an amino acid, single-chained polypeptide synthesized primarily in the liver and under growth hormone control. Serum concentrations of IGF-1 usually parallel those of HGH. Insulin-like growth factor promotes growth function and has the ability to increase protein synthesis and decrease protein degradation. Unlike GH, IGF-1 does not induce insulin resistance; therefore, hyperglycemia is avoided. Unfortunately, because of IGF-1 effects on carbohydrate metabolism, hypoglycemia is frequently seen with IGF-1 administration.[41]

Critical Care

As with GH, administration of IGF-1 in the critical care population has been investigated as a means to diminish or block the catabolic process, especially in the trauma and thermally injured patient. In an earlier, randomized, control trial, Kudsk et al[42] studied the effects of IGF-1 and aggressive PN on CD4/CD8 ratios in head-injured patients. Fourteen patients admitted into a level 1 trauma center with a Glasgow Coma Scale score (GCS) of 4 to 10 within 6 hours of admission and requiring no major extracranial surgery (except isolated lower-extremity fracture fixation) were randomized to receive a continuous infusion of recombinant IGF-1 (0.01 mg/kg per hour) or saline. Both groups received PN advanced to a total protein intake of 2 g/kg per day and a maximum nonprotein caloric delivery of 40 kcal/kg per day. Patients receiving IGF-1 administration showed increased CD4/CD8 ratios and elevated IGF-1 levels. Infusion of IGF-1 and aggressive early IV nutrition in head-injured patients affected the immunologic response.

In a phase II, prospective, open-label, safety and efficacy trial, the effect of IGF-1 and aggressive nutrition support on the catabolic state and clinical outcome of head-injured patients was investigated.[43] Similar to the study by Kudsk and colleagues,[42] patients were randomized to receive a continuous infusion of IGF-1 (0.1 mg/kg per hour) beginning within 72 hours of injury and continuing for 14 days. Nutrition support was provided to a goal of 1.25 times the measured energy expenditure. PN was used until bowel sounds returned and gastric residual volumes were < 700 mL in 24 hours. Thirty-three patients enrolled in the study. The study demonstrated improvements in the IGF-1 treated patients including weight gain despite a significantly higher measured energy expenditure and lower calorie intake ($p = .02$), decreased nitrogen excretion, and improved nitrogen balances. Improvements were reported in GCS scores in those patients receiving IGF-1.

In an open-labeled, uncontrolled, prospective study, administration of a single dose of IGF-1 in patients with systemic inflammatory response syndrome was studied. Eight patients received subcutaneous administration of 40 μg/kg of IGF-1. Blood samples were taken 24 hours before and 48 hours after the IGF-1 dose. Results showed IGF-1 levels rose significantly above baseline, and peak concentrations were sustained 2 to 5 hours after treatment. No adverse effects were observed.[44]

Administration of IGF-1 has also been studied in thermally injured patients. Ten adult patients were studied consecutively after receiving saline (pre-treatment), and then IGF-1 combined with its principal binding protein IGF-1 binding protein-3 (IGFBP-3) for 5 days. Doses of IGF-1/IGFBP-3 were delivered as 1, 2, and 4 mg per day. As expected, IGF and IGFBP-3 concentrations increased but no incremental increases were discovered. No glucose abnormalities developed.[45]

Growth hormone and IGF-1 combination therapy used in healthy volunteers increase anabolic effects and decrease adverse events,[46,47] but the effects were not duplicated in HIV-wasting.[48] In a randomized, placebo-controlled trial of combination IGF-1 (5 mg subcutaneous twice daily) and low-dose HGH (0.34 mg subcutaneous twice daily), a total of 142 patients were randomized to receive either active treatment or placebo injections for 12 weeks. Eighty subjects completed the 12-week protocol. Weight gain at the end of 3 weeks of active treatment resulted in a significantly greater weight gain compared with controls, but this effect was not sustained by the end of the study. No significant differences were seen in isokinetic muscle strength, endurance testing, or quality of life. Growth hormone and IGF-1 treatment resulted in increased incidences of peripheral edema and fluid retention.[48]

Anabolic Steroids

Testosterone, the primary male hormone produced by the testicles, was first synthesized in a laboratory in 1935. Since then, testosterone and its primary derivative, the anabolic-androgenic steroids, have received worldwide recognition with mixed reviews. Athletes and bodybuilders have taken these drugs to increase muscle mass and to intensify training regimens. And although

recognized as “illegal” in competitive sports, anabolic steroids maintain a billion-dollar international black market.[49] In a more favorable light, testosterone and its analogs have been investigated in the malnourished and catabolic patient.

Testosterone is the body’s naturally occurring anabolic agent with androgenic activity. To mimic or enhance this testosterone effect, exogenous testosterone and testosterone analogs are given to increase LBM and muscle strength. Early research in trauma and surgical patients investigating injectable testosterone and testosterone analogs reported increased nitrogen retention and improved nitrogen balances.[50,51] Although positive findings were reported in these studies, clinicians were skeptical about the use of anabolic steroids, especially in women, because of the drugs androgenic complications (edema, lipid abnormalities, and virilizing effects). Additionally, with these early studies, clinical outcome data were not reported.[50,51] Hence, the use of injectable anabolic steroids was not overwhelmingly endorsed.

More recently developed anabolic agents, including oxandrolone, nandrolone, and oxymetholone, have offered a more favorable pharmacotherapeutic approach to catabolism because they have 5 to 10 times the anabolic activity of older anabolic steroids and have considerably less androgenic effects (Table 1). Oxandrolone and oxymetholone offer the advantage of oral administration. Later research has investigated the newer anabolic agents in various disease states and medical conditions.

Critical Care

Much of the critical care research with anabolic agents is in the thermally injured patient. Demling and colleagues[52] initially investigated the administration of an anabolic steroid, oxandrolone, combined with a high-protein diet (2 g/kg per day) in the recovery phase of thermally injured patients. Patients having sustained 30% to 50% deep TBSA burns were prospectively, randomized to receive a high-protein diet ±10 mg oxandrolone twice daily. Weight gain and muscle function restorations (muscle strength and endurance) were evaluated. Data were also compared with results from a retrospective group of burn patients also in the recovery phase receiving a high-protein diet of 1.3 to 1.4 g/kg per day. The investigators reported a significant increase in weight gain of 14.5 ± 2.5 pounds in the group of patients who received oxandrolone (n = 7) compared with the other 2 groups, 7.5 ± 1.7 pounds in the prospective group receiving 2 g protein per kg (n = 6) and 4.4 ± 0.8 pounds in the retrospective group receiving 1.3 to 1.4 g protein per kg (n = 10). In addition, muscle strength (weight machines, pulleys with

Table 1. Anabolic steriods

	Dosage	Androgenic effects	Anabolic effects	Orally available
Testosterone	100 mg/wk	++++	++	No
Nandrolone	50-200 mg × 1 Or in divided does over a 1- to 2-week period	++	++	No
Oxandrolone	20 mg/d to 80 mg/d	+	++++	Yes
Oxymetholone	10 mg/d to 150 mg/d	+	++++	Yes

*Dosages studied

weights, and dumbbells for both upper and lower body strengthening) and endurance (stationary bike riding, treadmill, and stair stepping) were assessed by a burn therapist and based on improvements observed over a 3-week course. Patients who exercised and received oxandrolone exceeded the therapist's expected outlined goals. Patients in the prospective study receiving only a high-protein diet reached 95% ± 9% of the outlined goals by 3 weeks, and the retrospective group reached 75% ± 12% of the outlined goals. The authors concluded that an anabolic steroid combined with increased protein intake significantly increased the rate of restoration of weight gain and improved physical therapy recovery.

Demling[53] followed his initial study by prospectively comparing oxandrolone and HGH in patients who sustained a severe burn injury. Criteria for entry into the study included deep burns over 50% TBSA, at least half requiring grafting, or deep burns over 25% TBSA with comorbid factors (eg, age over 60 years, malnutrition, or adult-onset diabetes). Patients were randomized to receive HGH at a dose of 0.1 mg/kg per day (n = 20) or oxandrolone 20 mg/day (n = 16), beginning between days 7 and 10 postburn and continuing until patients were sufficiently healed to be transferred to a rehabilitation center. Data were compared with data from burn patients not receiving either agent (n = 24). Results showed a net weight loss of 8 ± 2.1 kg in the control group compared with losses of 4 ± 1.8 kg with HGH and 3 ± 1.2 kg with oxandrolone. Net daily nitrogen loss was also significantly less in the patients receiving HGH and oxandrolone. A significant decrease in complete healing time of a standardized donor site from the control value of 14 ± 2 days to 10.3 ± 3 days for HGH and 10 ± 2 days for oxandrolone was also reported. Both anabolic agents significantly decreased weight and nitrogen loss and increased healing with nearly identical benefits. However, HGH did result in increased incidences of hyperglycemia, though therapy did not have to be discontinued. There was a significantly higher percentage of diabetic patients in the HGH and oxandrolone group than the control group. No side effects were noted with oxandrolone.[53]

Hart and colleagues[54] explored the hypothesis that oxandrolone might reverse muscle catabolism in cachectic, critically ill pediatric burn patients. Fourteen severely burned children were enrolled during a 5-month period in a prospective cohort study. All patients were admitted to the Shriners Burn Hospital for Children in Galveston, Texas, at least 1 week after injury. The authors noted a prolonged delay in the arrival of these patients to the burn unit for definitive care resulted in critically ill children with significant malnutrition. Enteral nutrition (Vivonex TEN; Sandoz Nutritional Corp, Minneapolis, MN) was initiated in all patients. Daily caloric intake was given at a rate calculated to deliver 1500 kcal/m^2 TBSA. Within 48 hours of admission, each patient underwent total burn wound excision and grafting. After the first surgical procedure, all patients were studied on postoperative day 5 to determine baseline protein metabolism. Net phenylalanine balance across the leg and the fractional synthetic rate of skeletal muscle protein were measured. When the donor sites healed in 6 to 10 days, patients again underwent another excision and grafting procedure. After the second surgical procedure, patients assigned to the treatment group received oxandrolone 0.1 mg/kg twice daily for 5 days. A second series of protein kinetic studies were performed on postoperative day 5 after the second surgical procedure to determine any differences with oxandrolone treatment or time between the drug and control

patients. The investigators reported muscle protein net balance decreased in the control group (-0.006 ± 0.021) and improved in the treatment group (0.064 ± 0.016; $p < .05$ vs time control). The improvement in the oxandrolone group was associated with increased protein synthesis efficiency. Muscle protein breakdown was unchanged.[54]

The investigators followed up with a study seeking to extend their findings to severely burned subjects who received early definitive treatment.[55] Using a similar design as their previous study, 32 severely burned children were enrolled in a prospective, randomized trial. No time lapse between injury and definitive care was present. As with the first study,[54] protein net balance did not improve in the placebo group, but a significant improvement was seen in the oxandrolone group. Body weights and fat-free mass significantly decreased in the placebo group. No significant differences were seen in incidences of sepsis and length of stay between the oxandrolone group and the placebo group.[55]

Demling and Orgill[56] investigated the effects oxandrolone when given to patients in the initial phase of their burn recovery. In a prospective, double-blind, placebo-controlled study, patients with 40% and 70% TBSA burns were randomized to receive oxandrolone 20 mg/day ($n = 11$) or a placebo ($n = 9$) initiated between days 2 and 3 postburn. Patients continued taking the anabolic agent or placebo until the degree of wound closure and recovery was sufficient to transfer to an acute rehabilitation unit. Enteral nutrition was the primary nutritional route. Protein was delivered at 2 g/kg/day to all patients. Net weight loss was 8 ± 3.1 kg in the placebo group compared with a loss of 3 ± 1.9 kg in the oxandrolone group ($p < .05$). Net daily nitrogen loss was significantly less in the treatment group (13 ± 4 g, placebo vs 4 ± 1.9 g, oxandrolone; $p < .05$) and healing time (13 ± 3 days, placebo vs 9 ± 2 days, oxandrolone; $p < .05$). Average length of stay before transfer to an acute burn rehabilitation center was 35 ± 9 days for the placebo group and 29 ± 8 days for the oxandrolone group. The investigators reported a valid comparison of length of stay could not be made between the placebo and oxandrolone because of small group size.[56]

Nutrition support and the administration of anabolic steroids have long been investigated in the surgical and trauma patient for the preservation of LBM. Early studies investigating the use of nandrolone and stanozolol reported improvements in nitrogen balance as a result of decreases in nitrogen excretion, but clinical outcome data were not studied.[50,51,57]

Gervasio and colleagues[58] investigated oxandrolone administration in multiple trauma patients. In a prospective, double-blind, placebo-controlled study, 60 trauma patients were randomized to receive oxandrolone 10 mg twice daily ($n = 30$) or placebo ($n = 30$) for a maximum of 28 days or until discharge if earlier. Patients received enteral nutrition within 48 hours of admission and oxandrolone/placebo treatment was started. The 2 groups were similar for demographics and enteral nutrition delivery. Measurement of total urinary nitrogen at study entry showed both groups to be highly catabolic (oxandrolone 17.2 ± 4.9, placebo 19.1 ± 10.8 g/day, NS). On days 7 and 10, urinary nitrogen increased in both groups, but there were no significant differences between groups. Nitrogen balance was negative throughout the study. Serum prealbumin

concentrations increased significantly from baseline but no significant difference was seen between the oxandrolone and placebo group. The groups did not differ significantly for length of stay (oxandrolone 30.8 ± 17.9 days, placebo 27.0 ± 25.7 days), ICU stay (oxandrolone 17.1 ± 7.8 days, placebo 15.5 ± 9.7 days) or frequency of pneumonia or sepsis (oxandrolone 48 episodes, placebo 43 episodes). The investigators concluded that oxandrolone does not have obvious benefit at this dose in nutritional and clinical outcomes during the first 28 days after multiple trauma.[58]

Disease-Related Cachexia

Loss of LBM and decreased energy are common complications of HIV infection, cancer cachexia, and respiratory disease (especially chronic obstructive pulmonary disease or chronic obstructive pulmonary disease [COPD]). Because of the catabolic processes of these diseases, nutrition support alone often fails to maintain LBM in these patients. Recognition of the diseases' catabolic processes and impending complications from malnutrition has prompted researchers to investigate the use of anabolic agents. Comparable with research in the critical care population, investigators have mainly focused on the newer anabolic agents because of their better anabolic and lower androgen profile.

Most disease-related cachexia research is found in the HIV/AIDS literature. Wasting with HIV is attributed to decreased nutrient intake, malabsorption, and abnormalities of metabolism and endocrinology associated with HIV infection. HIV-wasting is a major cause of morbidity and mortality. Oxandrolone was first evaluated for the treatment of AIDS-associated myopathy and wasting by Berger et al[59] In a multicenter, double-blind study, 63 HIV-seropositive men with >10% loss of body weight were randomized to receive either oxandrolone 5 mg/day, oxandrolone 15 mg/day, or placebo for 16 weeks. Patients were excluded for liver disease, a history of muscle disease, treatment with an appetite-stimulating agent within 8 weeks of enrollment, use of medications know to interact with anabolic steroid, coagulation disorders, history of drug abuse, eating disorders, alcoholism, significant psychiatric disorders, chronic diarrhea, and chronic fever. Body weight, neuromuscular evaluation, and measures of well-being were repeatedly assessed.

There were no major differences between the groups. All patients were male with a mean age of 40 years. Eighty-eight percent were Caucasians. Significantly more patients receiving oxandrolone 15 mg/day were taking hematopoietic and antidiarrheal medications and had a slightly lower mean weight at screening.

Over the 16-week treatment period, patients receiving oxandrolone 15 mg/day were able to gain weight. Patients receiving oxandrolone 5 mg/day maintained their weight, whereas patient receiving placebo lost weight. Significantly more patients receiving oxandrolone 15 mg/day reported increases in appetite and activity compared with placebo. Oxandrolone was well tolerated in all of the patients.[59]

Earthman et al[60] measured changes in body cell mass and quality of life in HIV-infected individuals receiving oxandrolone therapy. Twenty-five subjects (24 male, 1 female) between the ages of 27 and 56 years received oxandrolone 20 mg/day for 8 weeks. One subject's oxandrolone dosage was reduced to 10 mg/day after 4 weeks. Individuals had been HIV positive for an average of 7.2 ± 4.2 years. Fifteen subjects had an AIDS diagnosis and 12 subjects had lost at least 10% of the usual body weight in the previous 6 to 12 months. Ten subjects were diagnosed with an active opportunistic infection at the time of the study, and all but 3 subjects' infection was resolved by study conclusion. Dietary intake was recorded on 3 nonconsecutive days during the week before each testing visit. At the conclusion of the study, individuals receiving oxandrolone therapy in conjunction with antiretroviral therapy and nutrition management had a significant increase in body weight (2.6 ± 3.0 kg, $p < .001$) and body cell mass (3.7 ± 3.0 kg, $p < .001$) compared with baseline. Appetite improved ($p = .032$), and overall quality of life improved but did not reach statistical significance ($p = .056$).

The addition of oxandrolone to testosterone therapy in combination with resistance exercise has been studied. Twenty-four eugonadal men with HIV-associated weight loss received testosterone replacement (100 mg/week) to suppress endogenous testosterone production and ensure uniform basal testosterone concentrations. Subjects were then randomized to receive oxandrolone 20 mg/day or placebo in conjunction with resistance training. After 8 weeks, androgen status, LBM, nitrogen balance, body weight, and muscle strength were measured. Twenty-two individuals completed the study. Both groups demonstrated significant nitrogen retention and increases in LBM, weight, and strength compared with baseline, but the gains in the subjects receiving oxandrolone were significantly greater. The authors concluded that in eugonadal men with HIV-associated weight loss, oxandrolone plus a moderately supraphysiologic androgen regimen results in increased lean tissue accrual and strength compared with physiologic testosterone replacement alone.[61]

Anabolic steroids in combination with resistance training does appear to be more effective than pharmacotherapy alone. Asymptomatic HIV-positive men receiving nandrolone (600 mg/wk) for 12 weeks showed greater improvement in muscle quality (1-repetition maximum, 4.7% to 16% improvement) as compared with those men receiving nandrolone in combination with resistance training (1-repetition maximum, 51% to 63% increase).[62]

Oxymetholone has also been investigated for the treatment of HIV-wasting. In a double-blind, placebo-controlled trial, 89 HIV-positive eugonadal women and men were randomized to receive oxymetholone 100 mg/day, oxymetholone 150 mg/day, or placebo for 16 weeks. Both regimens of oxymetholone resulted in significantly improved weight gain and body cell mass and improved quality of life, appetite, and food intake and reduced weakness (by self-evaluation). Of great concern was the reported adverse event of liver-associated toxicity. Forty-three percent of patients in the oxymetholone 150 mg/day group, 25% of patients in the oxymetholone 100 mg/day group, and 8% in the placebo group had a >5 times baseline increase for alanine amino transferase, aspartate aminotransferase, and γ-glutamyltransferase.63

Research with anabolic steroids in other disease-related cachexia has been performed. Weight restoration, increases in LBM, and anthropometric measurements of arm and thigh circumference have been demonstrated with anabolic steroids in patients with COPD.[64-66] The administration of oxandrolone 20 mg/day for 30 days helped strengthen respiratory musculature in individuals with tetraplegia and ventilatory insufficiency.[67] Preliminary research investigating improvements in wound healing has been reported with oxandrolone.[68] Nandrolone decanoate implementation in patients receiving chronic dialysis improved LBM, increased dry weight, and improved visceral markers.[69-70]

Nandrolone decanoate was investigated as a pharmacotherapeutic agent to improve nutritional status in patients after esophageal resection for carcinoma. Forty patients were randomized to receive 50 mg nandrolone ($n = 19$) or placebo ($n = 21$) injections for 5 doses over 3 months. Treatment started 1 month after surgery. Measurements of body weight, midarm muscle circumference, and appetite were taken over a 6-month period. Nutrition interventions included dietary advice and esophageal dilatation if necessary. No statistical differences were reported with any measurable parameter between the steroid treatment group and the placebo group. The authors noted an increased dose schedule over a longer period of time might have produced a significant response.[71]

Higher doses of oxandrolone have also been investigated. Mendelhall and colleagues[72] evaluated the efficacy of oxandrolone 80 mg/day in combination with an enteral food supplement in 273 male patients with severe alcoholic hepatitis. Patients received 80 mg oxandrolone or placebo for 30 days followed by 60 days of reduced dose (40 mg) oxandrolone or placebo. On an intention-to-treat basis, only minimal changes in mortality were observed and no significant improvement was observed with severe malnutrition. Interestingly, in patients with moderate malnutrition, mortality at 1 month was less in patients receiving oxandrolone (9.4%) compared with patients receiving placebo (20.9%). The benefit was maintained between these groups at 6 months, with the oxandrolone group survival at 79.7% and placebo at 62.7% ($p < .05$). Significant improvements in both the severity of the liver injury ($p < .05$) and malnutrition ($p < .05$) were also reported.[72]

The investigators compared their results from a nearly identical population treated with oxandrolone but not given an enteral food supplement. Patients were stratified according to caloric intake, with adequate caloric intake defined as 2500 kcal/ day. No improvement in survival was seen in patients with severe malnutrition receiving oxandrolone, but the investigators did report that adequate caloric intake was associated with 19% mortality, whereas patients with inadequate intake exhibited 51% mortality ($p < .05$). Patients with moderate malnutrition meeting their defined caloric intake and receiving oxandrolone reported reduced 6-month mortality (4% oxandrolone vs 28% placebo). Patients with moderate malnutrition and inadequate caloric intake showed no decline in mortality (30% oxandrolone vs 33% placebo).[72]

The effect of anabolic steroids in differing patient populations continues to be researched. Age-related anorexia and patients with cardiomyopathies may benefit with the addition of an anabolic

steroid.[73,74] Although positive effects have been reported, the use of anabolic steroids in disease-related cachexia still needs to be investigated. Long-term safety from anabolic steroids in disease-related cachexia is unclear. Most clinical studies using anabolic steroids used short-term administration. No clinical study to date has reported safety data past 6 months. Anabolic steroid abuse has been associated with hepatic adenomas and psychotic symptoms.[75,76] Clinical research is still warranted, and long-term safety is needed.

Conclusion

Patients with malnutrition or severe catabolism are at risk for increased morbidity and mortality. The implementation of nutrition support has aided the clinician in improving patient care. When nutrition support is not enough, the administration of anabolic agents may be warranted. In patients with catabolic and disease-wasting medical conditions, anabolic agents including HGH, IGF-1, and anabolic steroids may improve nitrogen retention, increase energy and strength, and enhance quality of life. Conversely, in the wrong patient population, anabolic agents, particularly HGH, may be detrimental. Continued research investigating anabolic agents is necessary to help define appropriateness of the pharmacotherapy and improve the patient's clinical outcome.

References

1. Chang DW, DeSanti L, Demling RH. Anticatabolic and anabolic strategies in critical illness: A review of current treatment modalities. *Shock*. 1998; 10: 155-160. doi: http://dx.doi.org/10.1097/00024382-199809000-00001
2. Pennington CR. Disease and malnutrition in British hospitals. *Proc Nutr Soc*. 1997; 56: 393-407. doi: http://dx.doi.org/10.1079/PNS19970041
3. Shaw JHF, Wildbore M, Wolfe RR. Whole body protein kinetics in severely septic patients: The response to glucose and total parenteral nutrition (TPN). *Ann Surg*. 1987; 205: 388-394. doi: http://dx.doi.org/10.1097/00000658-198703000-00012
4. Herndon DN, Hawkins, HK, Nguyen TT, Pierre E, Cox R, Barrow RE. Characterization of growth hormone enhanced donor site healing in patients with large cutaneous burns. Ann Surg. 1995; 221: 649-659. doi: http://dx.doi.org/10.1097/00000658-199506000-00004
5. Vara-Thorbeck R, Ruiz-Requena E, Guerrero-Fernandez JA. Effects of human growth hormone on the catabolic state after surgical trauma. *Horm Res*. 1996;45:55–60. doi: http://dx.doi.org/10.1159/000184760
6. Jeevanandam M, Ali MR, Holaday NJ, et al. Adjuvant recombinant human growth hormone normalizes plasma amino acids in parenterally fed trauma patients. *JPEN*. 1995; 19: 137-144. doi: http://dx.doi.org/10.1177/0148607195019002137
7. Knox J, Demling R, Wilmore D, et al. Increased survival after major thermal injury: The effect of growth hormone therapy in adults. *J Trauma*. 1995; 39: 526-532. doi: http://dx.doi.org/10.1097/00005373-199509000-00021
8. Kissmeyer-Nielsen P, Jensen MB, Laurberg S. Perioperative growth hormone treatment and functional outcome after major abdominal surgery: A randomized, double-blind, controlled

study. *Ann Surg*. 1999; 229: 298-302. doi: http://dx.doi.org/10.1097/00000658-199902000-00020
9. Voerman HJ, van Schijndel RJM, Groeneveld ABJ, et al. Effects of recombinant human growth hormone in patients with severe sepsis. *Ann Surg*. 1992; 216: 648-655. doi: http://dx.doi.org/10.1097/00000658-199212000-00006
10. Gamrin L, Essen P, Hultman E, McNurlan MA, Garlick PJ, Wernerman J. Protein-sparing effect in skeletal muscle of growth hormone treatment in critically ill patients. *Ann Surg*. 2000; 231: 577-586. doi: http://dx.doi.org/10.1097/00000658-200004000-00018
11. Ziegler TR, Young LS, Ferrari-Baliviera E, Demling RH, Wilmore DW. Use of human growth hormone combined with nutritional support in a critical care unit. *JPEN*. 1990; 14: 574-581. doi: http://dx.doi.org/10.1177/0148607190014006574
12. Herndon DN, Barrow RE, Kunkel KR, Broemling L, Rutan RL. Effects of recombinant human growth hormone on donor-site healing in severely burned children. *Ann Surg*. 1990; 212: 424-473. doi: http://dx.doi.org/10.1097/00000658-199010000-00005
13. Takala J, Ruokonen E, Webster NR, et al. Increased mortality associated with growth hormone treatment in critically ill adults. *N Engl J Med*. 1999; 341: 785-792. doi: http://dx.doi.org/10.1056/NEJM199909093411102
14. Jeevanandam M, Holaday NJ, Peterson SR. Adjuvant recombinant human growth hormone does not augment endogenous glucose production in TPN-fed multiple trauma patients. *Metabolism*. 1996; 45: 450-456. doi: http://dx.doi.org/10.1016/S0026-0495(96)90218-8
15. van den Berghe G, Wauters P, Weekers F, et al. Intensive insulin therapy in the critically ill patients. *N Engl J Med*. 2001; 345: 1359-1367. doi: http://dx.doi.org/10.1056/NEJMoa011300
16. Biolo G, Iscra F, Toigo G, et al. Effects of growth hormone administration on skeletal muscle glutamine metabolism in severely traumatized patients: preliminary report. *Clin Nutr*. 1997; 16: 89-91. doi: http://dx.doi.org/10.1016/S0261-5614(97)80029-5
17. Osterziel KJ, Dietz R, Ranke MB. Increased mortality associated with growth hormone treatment in critically ill adults: author reply. *N Engl J Med*. 2000; 342: 134-135. doi: http://dx.doi.org/10.1056/NEJM200001133420214
18. O'Connor R. Survival factors and apoptosis. *Avd Biochem Eng Biotechnol*. 1998; 62: 137-166. PMID: 9755644
19. Demling R. Growth hormone therapy in critically ill patients. *N Engl J Med*. 1999; 341: 837-839. doi: http://dx.doi.org/10.1056/NEJM199909093411110
20. Grinspoon S, Mulligan K. Weight loss and wasting in patients infected with human immunodeficiency virus. *Clin Infect Dis*. 2003; 36: S69-S78. doi: http://dx.doi.org/10.1086/367561
21. Langer CJ, Hoffman JP, Ottery FD. Clinical significance of weight loss in cancer patients: Rationale for the use of anabolic agents in the treatment of cancer-related cachexia. *Nutrition*. 2001; 17: S1-S18. doi: http://dx.doi.org/10.1016/S0899-9007(01)80001-0
22. Mulligan K, Grunfeld C, Hellerstein MK, Neese RA, Schambelan M. Anabolic effects of recombinant human growth hormone in patients with wasting associated with human immunodeficiency virus infection. *J Clin Endocrinol Metab*. 1993; 77: 956-962. doi: http://dx.doi.org/10.1210/jc.77.4.956

23. Krentz AJ, Koster FT, Crist DM, et al. Anthropometric, metabolic, and immunological effects of recombinant human growth hormone in AIDS and AIDS-related complex. *J Acquir Immune Defic Syndr*. 1993; 5: 245-251. PMID: 8450399
24. Schambelan M, Mulligan K, Grunfeld C, et al. Recombinant human growth hormone in patients with HIV-associated wasting: A randomized, placebo-controlled trial. *Ann Intern Med.* 1996; 125: 873-882. doi: http://dx.doi.org/10.7326/0003-4819-125-11-199612010-00002
25. Wolf RF, Heslin MJ, Newman E, Pearlstone DB, Burt M, Brennan MF. Growth hormone and insulin reverse net whole body and skeletal muscle protein catabolism in cancer patients. *Ann Surg*. 1992; 216: 280-288. doi: http://dx.doi.org/10.1097/00000658-199209000-00007
26. Berman RS, Harrison LE, Pearlstone DB, Burt M, Brennan MF. Growth hormone, alone and in combination with insulin, increases whole body and skeletal muscle protein kinetics in cancer patients after surgery. *Ann Surg*. 1999; 229: 1-10. doi: http://dx.doi.org/10.1097/00000658-199901000-00001
27. Tayek JA, Brasel JA. Failure of anabolism in malnourished cancer patients receiving growth hormone: A clinical research center study. *J Clin Endocrinol Metab*. 1995; 80: 2082-2087. doi: http://dx.doi.org/10.1210/jc.80.7.2082
28. Ikizler AT, Wingard RL, Breyer JA, Schulman G, Parker RA, Hakim KM. Short-term effects of recombinant human growth hormone in CAPD patients. *Kidney Int*. 1994; 46: 1178-1183. doi: http://dx.doi.org/10.1038/ki.1994.382
29. Iglesias P, Diez JJ, Fernandez-Reyes MJ, et al. Recombinant human growth hormone therapy in malnourished dialysis patients: A randomized controlled study. *Am J Kidney Dis*. 1998; 32: 454-463. doi: http://dx.doi.org/10.1053/ajkd.1998.v32.pm9740162
30. Kotzmann H, Yilman N, Lercher P, et al. Differential effects of growth hormone therapy in malnourished hemodialysis patients. *Kidney Int*. 2001; 60: 1578-1585. doi: http://dx.doi.org/10.1046/j.1523-1755.2001.00971.x
31. Kotzmann H, Schmidt A, Lercher P, et al. One-year growth hormone therapy improves granulocyte function without major effects on nutritional and anthropometric parameters in malnourished hemodialysis patients. *Nephron Clin Pract*. 2003; 93: C75-C82. doi: http://dx.doi.org/10.1159/000068524
32. Ziegler TR, Estivariz CF, Jonas CR, Gu LH, Jones DP, Leader LM. Interactions between nutrients and peptide growth factors in intestinal growth, repair, and function. *JPEN*. 1999; 23: S174-S183. doi: http://dx.doi.org/10.1177/014860719902300602
33. Byrne TA, Persinger RL, Young LS, Ziegler TR, Wilmore DW. A new treatment for patients with short-bowel syndrome: Growth hormone, glutamine, and a modified diet. *Ann Surg*. 1995; 222: 243-254. doi: http://dx.doi.org/10.1097/00000658-199509000-00003
34. Byrne TA, Morrissey TB, Nattakom TV, Ziegler TR, Wilmore DW. Growth hormone, glutamine, and a modified diet enhanced nutrient absorption in patients with severe short bowel syndrome. *JPEN*. 1995; 19: 296-302. doi: http://dx.doi.org/10.1177/0148607195019004296
35. Wilmore DW, Lacey JM, Soultanakis RP, Bosch RL, Byrne TA. Factors predicting a successful outcome after pharmacologic bowel compensation. *Ann Surg*. 1997; 266: 288-292. doi: http://dx.doi.org/10.1097/00000658-199709000-00008

36. Ellegard L, Bosaeus I, Nordgren S. Low-dose recombinant human growth hormone increases body weight and lean body mass in patients with short bowel syndrome. *Ann Surg*. 1997; 225: 88-96. doi: http://dx.doi.org/10.1097/00000658-199701000-00010
37. Scolapio JS, Camilleri M, Fleming CR, et al. Effect of growth hormone, glutamine, and diet on adaptation in short-bowel syndrome: a randomized, controlled study. *Gastroenterology*. 1997; 113: 1074-1081. doi: http://dx.doi.org/10.1053/gast.1997.v113.pm9322500
38. Szkudlarek J, Jeppesen PB, Mortensen PB. Effect of high dose growth hormone with glutamine and no change in diet on intestinal absorption in short bowel patients: A randomised, double blind, crossover, placebo controlled study. *Gut*. 2000; 47: 199-205. doi: http://dx.doi.org/10.1136/gut.47.2.199
39. Jeppesen PB, Szkudlarek J, Hoy CE, Mortensen PB. Effect of high-dose growth hormone and glutamine on body composition, urine creatinine excretion, fatty acid absorption, and essential fatty acids status in short bowel patients: a randomized, double-blind, crossover, placebo-controlled study. *Scand J Gastroenterol*. 2001; 36: 48-54. doi: http://dx.doi.org/10.1080/00365520150218057
40. Seguy D, Vahedi K, Kapel N, Souberbielle JC, Messing B. Low-dose growth hormone in adult home parenteral nutrition-dependent short bowel syndrome patients: A positive study. *Gastroenterology.* 2000; 124: 293-302. doi: http://dx.doi.org/10.1053/gast.2003.50057
41. Kumpf VJ, Gervasio JM. Pharmacotherpeutics. In: Gottschlich MM, Fuhrman MP, Hammond KA, eds. *The Science and Practice of Nutrition Support: A Case-Based Core Curriculum.* Dubuque, Iowa: Kendall/Hunt Inc; 2001: 287-299.
42. Kudsk KA, Mowatt-Larssen C, Bukar J, et al. Effect of recombinant human insulin-like growth factor 1 and early TPN on immune depression following severe head injury. *Arch Surg.* 1994; 129: 66-70. doi: http://dx.doi.org/10.1001/archsurg.1994.01420250078010
43. Hatton J, Rapp RP, Kudsk KA, et al. Intravenous insulin-like growth factor-1 in moderate-to-severe head injury: A phase II safety and efficacy trial. *J Neurosurg.* 1997; 86: 779-786. doi: http://dx.doi.org/10.3171/jns.1997.86.5.0779
44. Yarwood GD, Ross RJ, Medbak S, Coakley J, Hinds CJ. Administration of human recombinant insulin-like growth factor-1 in critically ill patients. *Crit Care Med.* 1997; 25: 1352-1361. doi: http://dx.doi.org/10.1097/00003246-199708000-00023
45. Debroy MA, Wolf SE, Zhang XJ, et al. Anabolic effects of insulin-like growth factor in combination with insulin-like growth factor binding protein-3 in severely burned adults. *J Trauma.* 1999; 47: 904-910. doi: http://dx.doi.org/10.1097/00005373-199911000-00015
46. Kupfer SR, Underwood LE, Baxter RC, Clemmons DR. Enhancement of the anabolic effects of growth hormone and insulin-like growth factor 1 by use of both agents simultaneously. *J Clin Invest.* 1993; 91: 391-396. doi: http://dx.doi.org/10.1172/JCI116212
47. Jenkins RC, Ross RJ. Growth hormone therapy for protein catabolism. *QJM.* 1996; 89: 813-819. doi: http://dx.doi.org/10.1093/qjmed/89.11.813
48. Lee PD, Pivarnik JM, Bukar JG, et al. A randomized, placebo-controlled trial of combined insulin-like growth factor 1 and low dose growth hormone therapy for wasting associated with human immunodeficiency virus infection. *J Clin Endocrinol Metab.* 1996; 81: 2968-2975. doi: http://dx.doi.org/10.1210/jc.81.8.2968

49. Hoberman JM, Yesalis CE. The history of synthetic testosterone. *Sci Am.* 1995; 272: 76-81. doi: http://dx.doi.org/10.1038/scientificamerican0295-76
50. Hausmann DF, Nutz V, Rommelsheim K, Caspari R, Mosebach KO. Anabolic steroids in polytrauma patients. Influence on renal nitrogen and amino acid loses: A double-blind study. *JPEN.* 1990;14: 111-114. doi: http://dx.doi.org/10.1177/0148607190014002111
51. Mosebach KO, Hausmann DF, Caspari R, Stoekel H. Deca-Durabolin and parenteral nutrition in post-traumatic patients. *Acta Endocrinol Suppl.* 1985; 271: 60-69. PMID: 3934896
52. Demling RH, DeSanti L. Oxandrolone, an anabolic steroid, significantly increases the rate of weight gain in the recovery phase after major burns. *J Trauma.* 1997; 43: 47-50. doi: http://dx.doi.org/10.1097/00005373-199707000-00012
53. Demling RH. Comparison of the anabolic effects and complications of human growth hormone and the testosterone analog, oxandrolone, after severe burn injury. *Burns.* 1999; 25: 215-221. doi: http://dx.doi.org/10.1016/S0305-4179(98)00159-4
54. Hart DW, Wolf SE, Ramzy PI, et al. Anabolic effects of oxandrolone after severe burn. *Ann Surg.* 2001; 233: 55-64. doi: http://dx.doi.org/10.1097/00000658-200104000-00012
55. Wolf SE, Thomas SJ, Dasu MR, et al. Improved net protein balance, lean mass, and gene expression changes with oxandrolone treatment in the severely burned. *Ann Surg.* 2003; 237: 801-810. doi: http://dx.doi.org/10.1097/01.SLA.0000071562.12637.3E
56. Demling RH, Orgill DP. The anticatabolic and wound healing effects of the testosterone analog oxandrolone after severe burn injury. *J Crit Care.* 2000; 15: 12-17. doi: http://dx.doi.org/10.1053/jcrc.2000.0150012
57. Hansell DT, Davies JW, Shenkin A, Garden OJ, Burns HJ, Carter DC. The effects of an anabolic steroid and peripherally administered intravenous nutrition in the early postoperative period. *JPEN.* 1989; 13: 349-358. doi: http://dx.doi.org/10.1177/0148607189013004349
58. Gervasio JM, Dickerson RN, Swearingen J, et al. Oxandrolone in trauma patients. *Pharmacotherapy.* 2000; 20: 1328-1331. doi: http://dx.doi.org/10.1592/phco.20.17.1328.34889
59. Berger JR, Pall L, Hall CD, Simpson DM, Berry PS, Dudley R. Oxandrolone in AIDS-wasting myopathy. *AIDS.* 1996; 10: 1657-1662. doi: http://dx.doi.org/10.1097/00002030-199612000-00010
60. Earthman CP, Reid PM, Harper IT, Ravussin E, Howell WH. Body cell mass repletion and improved quality of life in HIV-infected individuals receiving oxandrolone. *JPEN.* 2002; 26: 357-365. doi: http://dx.doi.org/10.1177/0148607102026006357
61. Strawford A, Barbieri T, Van Loan M, et al. Resistance exercise and supraphysiologic androgen therapy in eugonadal men with HIV-related weight loss: A randomized controlled trial. *JAMA.* 1999; 281: 1282-1290. doi: http://dx.doi.org/10.1001/jama.281.14.1282
62. Schroeder ET, Terk M, Sattler FR. Androgen therapy improves muscle mass and strength but not muscle quality: Results from two studies. *Am J Physiol Endocrinol Metab.* 2003; 285: E15-E27. doi: http://dx.doi.org/10.1152/ajpendo.00032.2003

63. Hengge UR, Stocks K, Faulkner S, et al. Oxymetholone for the treatment of HIV-wasting: A double-blind, randomized, placebo-controlled phase III trial in eugonadal men and women. *HIV Clin Trials.* 2003; 4: 150-163. doi: http://dx.doi.org/10.1310/9V0C-YADY-UJNV-T2RT
64. Ferreira IM, Verreschi IT, Nery LE, et al. The influence of 6 months of oral anabolic steroids on body mass and respiratory muscles in undernourished COPD patients. *Chest.* 1998; 114: 19-28. doi: http://dx.doi.org/10.1378/chest.114.1.19
65. Schols AM, Soeters PB, Mostert R, Pluymers RJ, Wouters EF. Physiologic effects of nutritional support and anabolic steroids in patients with chronic obstructive pulmonary disease: A placebo-controlled randomized trial. *Am J Respir Crit Care Med.* 1995; 152: 1268-1274. doi: http://dx.doi.org/10.1164/ajrccm.152.4.7551381
66. Yeh SS, DeGuzman B, Kramer T. Reversal of COPD-associated weight loss using the anabolic agent oxandrolone. *Chest.* 2002; 122: 421-428. doi: http://dx.doi.org/10.1378/chest.122.2.421
67. Spungen AM, Grimm DR, Strakhan M, Pizzolato PM, Bauman WA. Treatment with an anabolic agent is associated with improvement in respiratory function in persons with tetraplegia: A pilot study. *Mt Sinai J Med.* 1999; 66: 201-205. PMID: 10377553
68. Demling R, DeSanti L. Closure of the "non-healing wound" corresponds with correction of weight loss using the anabolic agent oxandrolone. *Ostomy Wound Manage.* 1998; 44: 58-62. PMID: 9866597
69. Barton Pai A, Chretien C, Lau AH. The effects of nandrolone decanoate on nutritional parameters in hemodialysis patients. *Clin Nephrol.* 2002; 58: 38-46. PMID: 12141405
70. Johansen KL, Mulligan K, Schambelan M. Anabolic effects of nandrolone decanoate in patients receiving dialysis: A randomized controlled trial. *JAMA.* 1999; 281: 1275-1281. doi: http://dx.doi.org/10.1001/jama.281.14.1275
71. Darnton SJ, Zgainski B, Grenier I, et al. The use of an anabolic steroid (nandrolone decanoate) to improve nutritional status after esophageal resection for carcinoma. *Dis Esophagus.* 1999; 12: 283-288. doi: http://dx.doi.org/10.1046/j.1442-2050.1999.00074.x
72. Mendelhall CL, Moritz TE, Roselle GA, et al. A study of oral nutritional support with oxandrolone in malnourished patients with alcoholic hepatitis: Results of a Department of Veteran Affairs cooperative study. *Hepatology.* 1993; 17: 564-576. doi: http://dx.doi.org/10.1002/hep.1840170407
73. Morley JE. Orexigenic and anabolic agents. *Clin Geriatr Med.* 2002; 18: 853-866. doi: http://dx.doi.org/10.1016/S0749-0690(02)00036-8
74. Shapiro J, Christiana J, Frishman WH. Testosterone and other anabolic steroids as cardiovascular drugs. *Am J Ther.* 1999; 5: 167-174. doi: http://dx.doi.org/10.1097/00045391-199905000-00008
75. de Menis, Tramontin P, Conte N. Danazol and multiple hepatic adenomas: Peculiar clinical findings in an acromegalic patient. *Horm Metab Res.* 1999; 31: 476-477. doi: http://dx.doi.org/10.1055/s-2007-978778
76. Pope HG, Katz DL. Affective and psychotic symptoms associated with anabolic steroid use. *Am J Psychiatry.* 1988; 145: 487-490. PMID: 3279830