

# Muscle wasting and protein metabolism<sup>1</sup>

C. Castaneda<sup>2</sup>

Jean Mayer USDA Human Nutrition Research Center on Aging at Tufts University, Boston, MA 02111

**ABSTRACT:** Accelerated muscle proteolysis is the primary cause of muscle wasting in many catabolic diseases such as diabetes mellitus, renal and liver failure, HIV infection and AIDS, and cancer. In individuals with catabolic diseases, as is the case with fasting states (anorexia and starvation), protein breakdown increases while protein synthesis declines, resulting in negative muscle protein balance. The pathway responsible for accelerated proteolysis in catabolic conditions is the ubiquitin-proteasome-dependent system. Muscle proteolysis increases under conditions of acidosis, up-regulation of branched-chain ketoacid dehydrogenase, the

presence of catabolic hormones (glucocorticoids, thyrotoxic states), insulin resistance, and multiple cytokines (interleukin-1 and -6 and tumor necrosis factor). In contrast, factors that suppress muscle proteolysis and wasting, leading to a state of adaptation, include dietary protein deficiency with adequate energy intake, use of anabolic agents, and resistance exercise training. The understanding of the biochemical adaptations that reduce protein degradation and improve nitrogen balance are important for the development of effective therapies to combat muscle wasting and improve protein homeostasis with catabolic illnesses.

Key Words: Protein Turnover, Muscle Wasting, Nutritional Status, Chronic Infections

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## Introduction

Malnutrition and muscle wasting are common features of many catabolic chronic diseases associated with impaired protein homeostasis. Protein homeostasis takes place through a fine balance between the amino acid flow into the plasma pool coming from dietary intake (exogenous) and muscle protein degradation (endogenous) primarily, and the amino acid flow out of the pool to be used for synthesis and catabolism (transamination and oxidation). Thus, reutilization of amino acids constitutes a major factor of protein metabolism.

Protein and amino acids are not stored in the body, like fat and glucose are in adipocytes and as glycogen, respectively. The largest reservoir of protein, however, is skeletal muscle mass. Thus, muscle mass is the best indicator of protein homeostasis. Inadequate dietary intake of protein and energy due to anorexia or starvation, and the altered metabolic and physiologic processes resulting from increased catabolic stimuli and reduced anabolic stimuli, results in muscle wasting.

Muscle wasting is characterized by unintentional loss of body weight (5 to 10%) due to accelerated muscle protein degradation and reduced protein synthesis and represents a clinically significant complication of many chronic diseases.

The mechanisms of muscle wasting in different disease processes are poorly understood. Regardless of its cause, muscle wasting affects disease outcome, leading to weakness, disability, impaired quality of life, and increased hospitalization days. Muscle wasting is prevalent in disease states characterized by conditions such as metabolic acidosis, the presence of increased catabolic hormones (glucocorticoids, thyrotoxic states) or cytokines (interleukin-1 and -6 and tumor necrosis factor- $\alpha$ ), and insulin resistance.

Timely recognition of muscle wasting is critical if we are to intervene successfully while treating the underlying condition. Intervention strategies include nutritional support; hormonal treatment with insulin, growth hormone, and anabolic steroids; and resistance exercise training. This review will describe some of the mediators of and interventions for muscle wasting. It will emphasize the need for further research. Ultimately, the goal of this review is to point out the importance of early detection and intervention of chronic diseases leading to muscle wasting to prevent poor disease outcome, co-morbidity, and mortality.

## Protein Metabolism

In a normal 70-kg adult, about 280 g of protein is synthesized and degraded each day, the majority of

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<sup>2</sup>Correspondence: 711 Washington St. (phone: 617-556-3081; fax: 617-556-3083; E-mail: ccastaneda@hnrc.tufts.edu).

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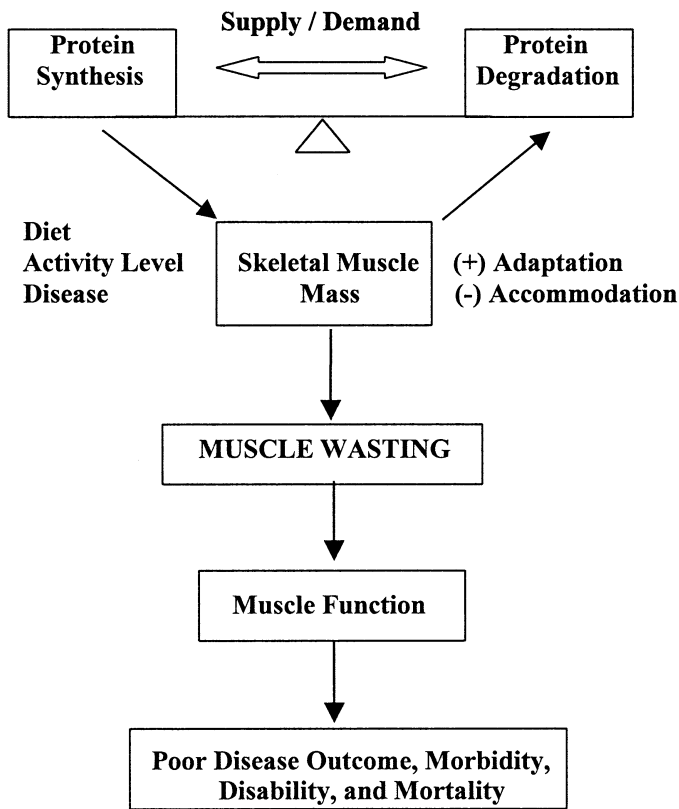


Figure 1. Role of protein metabolism in muscle wasting.

which are intracellular proteins (Young, 1990; Crim and Munro, 1994). The balance between synthesis and breakdown is such that any alteration in the supply (intake) or demand (utilization) could drastically alter cell function (Figure 1). Traditionally, protein nutritional status and homeostasis is determined by the nitrogen balance technique (NRC, 1989). However, conventional measures of nitrogen balance alone may not necessarily reflect the processes of adaptation or accommodation that take place in order to reach nitrogen equilibrium. Accommodation takes place when significant losses in important body tissues or functions occur as a result of an environmental, physical, or metabolic stress to maximize protein homeostasis and survival. In contrast, adaptation to such stress occurs while body tissues and functions are maintained (WHO/FAO/UNU, 1985; Young, 1990). In its simplest form, accommodation to a low-protein diet (providing between 0.4 and 0.6 g·kg<sup>-1</sup>·d<sup>-1</sup>) was tested in healthy elderly women consuming adequate energy intakes (Castaneda et al., 1995a,b, 2000), as well as in patients with chronic renal insufficiency prescribed moderately low-protein diets (Castaneda et al., 1995a). The results from these studies showed that a marginal-to-low protein intake compromises body cell mass and muscle size and function, despite a near-zero nitrogen equilibrium. This suggests that other measures of protein nutritional status may be better indicators of protein homeostasis and adequacy, particularly in the situation of accelerated protein degradation.

### Assessment of Protein Metabolism

**Nitrogen Balance.** Nitrogen balance is the most commonly used method to assess protein homeostasis (WHO/FAO/UNU, 1985). However, it is not a sensitive method to determine the continuous exchange of amino acids between tissues, which depends on the metabolic status of the organism (WHO/FAO/UNU, 1985; Munro, 1989).

**Amino Acid Kinetics and Protein Turnover.** Protein turnover is characterized by the dynamics of amino acids used for synthesis or degradation. In measuring protein turnover, the inward amino acid flow into the plasma pool comes from dietary intake (exogenous) and protein degradation (endogenous). These should balance with the outward flow of amino acids from the pool used for synthesis and catabolism (transamination and oxidation) (Crim and Munro, 1994). Because the contribution of endogenous amino acids to the pool is severalfold greater than the amino acid intake, reutilization of amino acids is a major contributing factor for protein metabolism.

Recently, more sophisticated measures of amino acid kinetics and protein turnover have allowed a more precise measurement of synthesis and breakdown in skeletal muscle. This is the case with measures of fractional synthetic rate (Nair et al., 1988), protein synthesis using the three-compartment pool (Biolo et al., 1995), and degradation using a single-pool model (Wolfe, 1992).

**Body Composition.** During the course of adult life, body protein in the form of lean tissue diminishes progressively and body fat increases (Munro, 1989; Young, 1990). During severe malnutrition the loss in muscle mass ranges from 8 to 12% (Heymsfield et al., 1982), and loss of about 40% of lean mass is fatal (Winick, 1979). The structural protein component of muscle is the main constituent of muscle mass that determines function and clinical outcome; it constitutes the main source of protein for antibody and enzyme production, wound healing, and immune response (Forbes, 1987). The loss of muscle protein is roughly proportional to the loss in muscle mass. Because protein is targeted to muscle and muscle mass represents the largest tissue in the body, protein nutrition plays a significant role in muscle metabolism. Thus, a reduced supply of amino acids from the diet or increased demand for amino acids from catabolic diseases will contribute to increased protein degradation from muscle, the largest reservoir of protein, to ensure bodily functions.

Body cell mass is the metabolically active body compartment constituted by muscle, viscera, brain, and the reproductive system where protein is targeted. Total-body potassium, 95% of which is intracellular, is more closely related to actively metabolizing nitrogen than total-body nitrogen (Cohn et al., 1980, 1983; Womersley et al., 1976) and thus may be a more appropriate reference value for estimating protein metabolism. The understanding of protein turnover and the role of muscle mass for protein homeostasis is important to explain

**Table 1.** Muscle wasting conditions and their postulated mediators

Condition	Possible mediators
Anorexia and starvation	Fasting, inadequate supply
Renal disease	Metabolic acidosis
Diabetes	Insulin deficiency and(or) resistance
	IGF-I resistance
	Increased TNF- $\alpha$
	Increase counter-regulatory hormones
Sex and growth hormone deficiency	IGF-I resistance
	Increased TNF- $\alpha$ and IL-6
HIV and AIDS	Increased myostatin
	Increased Il-6
	Increased leptin
Inflammation	Increased TNF- $\alpha$ and IL-1 $\beta$
	Increased glucagon

muscle wasting characterized by a negative nitrogen balance and increased muscle protein degradation (Clague et al., 1983; Rennie and Harrison, 1984).

### Muscle Wasting

Muscle wasting is defined as unintentional loss of body weight (5 to 10%) (Roubenoff et al., 1997) due to accelerated muscle proteolysis, resulting in loss of body cell mass. Body weight can be divided, at the simplest level, into mass and fat-free mass. Precise methods to evaluate loss of muscle mass are important to assess both baseline muscle mass and changes over time, particularly in the case of disease processes and interventions intended to reduce muscle wasting. Body cell mass estimated from total body potassium (Cohn et al., 1983; Kehayiaas et al., 1997) may be the best single measure closely linked to prognosis and survival (Keys et al., 1950; Kotler et al., 1989). The mechanisms of muscle wasting in different disease processes are poorly understood. However, regardless of its cause, muscle wasting affects disease outcome, leading to weakness, disability, impaired quality of life, increased hospitalization days, morbidity, and mortality.

#### *Mediators of Muscle Wasting*

At the whole-body level, the unexplained loss of body weight with wasting may be associated with low food intake, high levels of energy expenditure, or a combination of both. Starvation-induced malnutrition is the pure example of the detrimental effect of reduced amino acid supply and loss of muscle mass (Grant, 1983). Muscle wasting is accelerated in many disease states such as diabetes mellitus, renal and liver failure, HIV infection, and cancer. Muscle proteolysis increases under conditions of acidosis, up-regulation of branched-chain ketoacid dehydrogenase, the presence of catabolic hormones (glucocorticoids, thyrotoxic states) and catabolic cytokines (interleukin-1 and -6 and tumor necrosis factor), and insulin resistance (Table 1). Possible mechanisms of increased protein degradation include activation of the intracellular ubiquitin proteasome ATP-de-

pendent pathway (Mitch, 1996) and the decarboxylation of branched-chain amino acids (Gerber and Mitch, 1992), both resulting in increased protein catabolism and loss of lean body mass. Discussion of these mediators is outside the scope of this review and will be presented elsewhere.

*Insulin Resistance.* Insulin is an important regulator of protein synthesis (Kimball et al., 1994) and proteolysis (Tessari et al., 1987) in skeletal muscle. Insulin resistance or deficiency results in impaired muscle protein turnover (Garibotto et al., 1994) and muscle wasting (Kaysen, 1996). Poorly controlled diabetes is associated with severe muscle wasting (Gougeon et al., 1997). Insulin's action on muscle appears to be primarily one of inhibiting protein degradation, but it has been difficult to demonstrate a sustained effect of insulin in increasing muscle protein synthesis (Nair et al., 1995; Charlton et al., 1997). Insulin resistance increases with age, fat mass, and physical inactivity (Muller et al., 1996; Eriksson et al., 1997; Cafalu, 1998), all contributing factors for muscle loss.

*Insulin-Like Growth Factor I.* In skeletal muscle, circulating plasma IGF-I concentrations stimulate intracellular amino acid and glucose transport as well as protein synthesis while suppressing protein degradation (Musey et al., 1993). Plasma IGF-I levels vary according to nutrient intake (Clemmons et al., 1985b; Unterman et al., 1985). Insulin-like growth factor I has been proposed as a biochemical marker in assessing early responses to dietary changes in protein and energy (Clemmons et al., 1985a; Sullivan and Carter, 1994). We observed that a low-protein diet adequate in energy resulted in atrophy of type I muscle fibers associated with significant declines in plasma IGF-I levels in older women consuming a protein diet equivalent to one-half the protein Recommended Dietary Allowance (RDA) for 10 wk (Castaneda et al., 2000). The loss of high-turnover type I muscle fibers under conditions of dietary protein restriction suggests the need to increase protein degradation of these fibers to provide amino acid substrate for other essential functions.

*Metabolic Acidosis.* Metabolic acidosis in both pre-dialysis and dialysis patients constitutes a major stimu-

lus for protein degradation and muscle wasting, the most devastating complication of chronic uremia (Kopple et al., 2000). It has been suggested that special attention to nutrient needs can help prevent the wasting syndrome of renal failure (Kopple et al., 1989; Locatelli et al., 1991). Thus, the consumption of adequate amounts of protein to maintain nutritional status, reduce nitrogenous by-products leading to uremia, and preserve renal function is a challenge for medical care of renal patients.

Metabolic acidosis stimulates the intracellular ubiquitin proteasome ATP-dependent pathway, which catalyzes the breakdown of abnormal and short-lived proteins (Mitch, 1996). Acidosis enhances the decarboxylation of branched-chain amino acids (BCAA) and causes protein catabolism, suppresses albumin synthesis, promotes negative nitrogen balance, and induces protein degradation. The consequences may be severe because BCAA, particularly leucine, constitute the rate-limiting step for protein synthesis. The ketoacid of leucine,  $\alpha$ -ketoisocaproate (KIC), exhibits a nitrogen-sparing effect by inhibiting protein degradation (Gerber and Mitch, 1992). Thus, metabolic acidosis hinders adaptation to a low-protein diet, blocks the protein-sparing effect of KIC, and encourages the loss of muscle mass in renal patients.

*Hormones.* Both estrogen and testosterone have important anabolic effects on muscle, although the effect of estrogen may also be mediated through its conversion to testosterone (Grinspoon et al., 1996, 1997). In elderly men, low testosterone levels have been associated with reduced protein synthesis (Perrone et al., 1995) and loss of muscle mass and function (Baumgartner et al., 1999). In hypogonadal men, replacement doses of testosterone for 12 wk increased muscle mass and strength (Morley et al., 1993; Sih et al., 1997). The anabolic effects of testosterone therapy result from both systemic and local changes on protein metabolism that seem to be indirectly mediated by the regulatory effects of IGF-I in skeletal muscle.

Growth hormone has been shown to increase protein synthesis and decrease protein oxidation rates (Jorgensen et al., 1994). A study of recombinant human growth (rGH) supplementation in growth hormone-deficient adults showed that nonoxidative leucine Rd (a measure of protein synthesis) increased whereas leucine oxidation decreased with rGH treatment (Russell-Jones et al., 1993). Similarly, lean body mass and circulating IGF-I and insulin levels were significantly increased after 2 mo of treatment compared to placebo controls. These results suggest that growth and sex hormone actions on accretion of skeletal muscle are mediated by increases in protein synthesis rather than by reductions in protein degradation.

*Cytokines.* Cytokines, endogenous products of the immune system, are important mediators of some of the changes in protein metabolism and body composition (Roubenoff, 1993). The catabolic roles of interleukin (IL) I- $\beta$  and IL-6 and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ )

on resting metabolic rate and protein metabolism have been observed in wasting and cachexia (Dinarello, 1999; Abad et al., 2001) resulting from immunodeficiency virus (HIV) infection and the acquired immunodeficiency syndrome (AIDS). Similarly, a number of studies suggest that increased circulating levels of TNF- $\alpha$  (Nilsson, 1998) as well as elevated skeletal muscle expression of TNF- $\alpha$  mRNA (Saghizadeh, 1996) and increased plasma IL-6, are associated with insulin resistance and muscle wasting in diabetes (Fernandez-Real et al., 2001). In patients with rheumatoid arthritis the loss of body cell mass and function associated with increased resting energy expenditure has been directly associated with production of TNF- $\alpha$  and IL-1- $\beta$  by peripheral blood mononuclear cells (Roubenoff, 1993).

Other growth factors to consider include myostatin (growth differentiation factor 8, **GDF-8**) a member of the transforming growth factor (TGF)- $\beta$  family (McPherron et al., 1997) implicated in the regulation of skeletal muscle growth (Grobet et al., 1997). In HIV-infected men with wasting, serum and intramuscular myostatin-immunoreactive protein has been found to be significantly higher than that of healthy men and correlates inversely with the fat-free-mass index (FFM/ht<sup>2</sup>) (Gonzalez-Cadavid et al., 1998). The mechanisms by which myostatin may contribute to muscle wasting are not known. However, the presence of significant circulating levels of myostatin-immunoreactive protein suggests that receptors for this protein might exist in the muscle and other sites that are involved in the metabolic regulation of body composition.

*Anorexia and Starvation.* Protein and energy insufficiency are of concern primarily in circumstances in which needs are not being met due to lower intake (low income, anorexia, prescription) in combination with stress conditions due to surgery, hospitalization, and chronic diseases. In the case of protein deficiency, amino acids generated from endogenous tissue degradation, namely muscle, become the main source of amino acid supply for protein synthesis and the obligatory nitrogen losses (WHO/FAO/UNU, 1985). In prolonged starvation (Keys et al., 1950; Winick, 1979) a significant decrease in body weight is accompanied by reduced total protein concentrations. The sustained loss of body cell mass reaching about 60% of baseline is fatal (Winick, 1979), muscle protein synthesis is extremely dependent on external supplies of essential amino acids.

### *Interventions to Suppress Muscle Wasting*

Timely recognition of muscle wasting is critical if we are to intervene successfully while treating the underlying condition. Furthermore, the amelioration of nutritional problems related to wasting may prove to be one strategy for increasing quality of life, enhancing functional independence, and possibly lessening the burden of a specific disease.

*Nutritional Support.* Nutritional support is an extreme measure to provide exogenous substrate (amino

acids and energy) needed to promote nitrogen retention and net protein synthesis. For example, in the case of burn and trauma patients, there is an accelerated rate of protein degradation in response to the lack and impairment in amino acid transport into muscle associated with increased expression of catabolic cytokine expression in the short term and elevated stress hormones (i.e., glucagon, cortisol, and epinephrine) in the long term. In these cases, the enhanced outward flux of amino acids leads to reduced intracellular amino acid concentrations, which in turn stimulate more muscle degradation as a means to maintain normal amino acid concentrations (Wolfe, 1996).

*Physical Activity and Resistance Training.* Exercise and physical activity enhance protein utilization and contribute to the prevention of and recovery from wasting (Butterfield et al., 1992). Resistance exercise training, in particular, has been shown to delay or reverse the loss of muscle mass and function (Fiatarone et al., 1994; Campbell et al., 1995). The anabolic effects of resistance training on nitrogen retention and muscle mass are not observed with endurance exercise. Although the mechanisms whereby resistance training improves protein utilization are not well understood, several studies have shown that this exercise modality may in fact be more effective and safe in counteracting muscle wasting than pharmacological treatment.

Studies examining the response of insulin-deficient states in muscle mass and muscle function with exercise are very limited. Mandroukas et al. (1986) showed that patients with type 1 diabetes increased isokinetic torque and type IIa muscle fiber area after 20 wk of endurance training. Durak (1990) found significant increases in strength in patients with type 1 diabetes undergoing resistance training for 10 wk. More recently, a study of patients with type 2 diabetes enrolled in a progressive resistance training program for 16 wk showed positive results. Compared to controls, patients in the exercise group exhibited significant increases in glycemic control as measured by a reduction in glycosylated hemoglobin (17%) and plasma insulin levels (33%), accompanied by an absolute gain in lean body mass (1.5 kg), an increase in muscle strength (25%), and a twofold increase in muscle IGF-I gene expression (Castaneda et al., 2001b; Gordon, 2001). The change in muscle IGF-I was significantly associated with the change in muscle strength. These findings suggest that the anabolic effect of resistance training at the cellular level may be driven by improved insulin action and the compensatory actions of IGF-I in skeletal muscle.

Following 12 wk of resistance training, patients with moderate chronic renal insufficiency not on dialysis successfully adapted to a low-protein diet equivalent to  $0.6 \text{ g} \cdot \text{kg} \text{ body weight}^{-1} \cdot \text{d}^{-1}$ . Successful adaptation was evidenced by significant improvement in nitrogen retention, as shown by gains in total body potassium, hypertrophy of type I and II muscle fibers, increased plasma prealbumin levels, maintenance of body weight, and increased protein utilization, as measured by

higher leucine oxidation rates, compared to subjects consuming the low-protein diet alone. The anabolic effects of resistance training were observed despite subjects' age, uremia, self-reported low energy intakes, anemia, low aerobic capacity, and co-morbid diseases (Castaneda et al., 2001a).

These studies suggest that resistance training is an effective counter-measure to the negative effects of protein restriction, insulin resistance, and uremia on muscle mass accretion, protein utilization and nutritional status, and muscle function among these patients.

### *Anabolic Agents*

*Insulin.* Exogenous insulin was administered to a group of obese subjects with type 2 diabetes provided a weight-maintaining liquid formula containing 95 g protein/d for 15 d (treatment group) compared to controls (those not receiving exogenous insulin) (Gougeon et al., 1998). Nitrogen balance improved significantly from  $-0.6 \pm 0.6$  to  $+2.6 \pm 0.6 \text{ g N/d}$ , and nitrogen flux, synthesis, and breakdown rates were reduced by 18 to 23% in hyperglycemic subjects treated with insulin compared to controls. The combined treatment of exogenous insulin and generous protein intake help normalized whole-body protein kinetics and nitrogen balance in these patients (Gougeon et al., 1998). These results are similar to those observed by Nair et al. (1995) showing inhibition of protein degradation in type 1 diabetic patients during insulin repletion.

Although insulin's anti-catabolic effect on protein metabolism in type 1 diabetes has been shown to be related to inhibition of protein degradation, insulin's effect on muscle protein synthesis remains controversial. In a study by Charlton et al. (1997), fractional synthetic rate of myosin heavy chain in patients with type 1 diabetes (during both insulin treatment and acute insulin deprivation) was similar to that measured in healthy subjects. Myosin heavy chain was chosen because of its role as the major protein of the contractile apparatus of muscle, responsible for the conversion of chemical energy (adenosine triphosphate) to mechanical energy. However, these findings are not conclusive and more studies are needed to better understand the effects of exogenous insulin administration on protein metabolism at the cellular level.

*Growth Hormone.* Human recombinant growth hormone (rGH) treatment in chronically malnourished hemodialysis patients resulted in a 25% increase in phenylalanine disposal, an index of protein synthesis, whereas phenylalanine's rate of appearance, an index of protein degradation, was unchanged. Sixty-two percent of the variation in forearm net phenylalanine balance during treatment was accounted for by the changes in IGF-I and the IGF-binding protein (IGFBP)-1 levels. These findings suggest that the resistance to growth hormone occurring in malnourished end-stage renal patients may be overcome with pharmacologic doses of growth hormone (Garibotto et al.,

1997). However, the administration of rGH ( $0.10 \pm 0.02$  mg·kg body weight<sup>-1</sup>·d<sup>-1</sup>) vs a placebo in critically ill adults (who had been in an intensive care unit for 5 to 7 d and who were expected to require intensive care for at least 10 d) was evaluated in a randomized controlled study of 247 Finnish patients and 285 patients in other European countries. The patients received either rGH or placebo for a maximum of 21 d. The results from this study showed that in-hospital mortality rate was 40% higher in the patients who received growth hormone than in those randomized to the placebo (20%,  $P < 0.001$ ), suggesting an increased morbidity and mortality in patients with prolonged critical illness receiving high doses of rGH (Takala et al., 1999). This information underlines the need of further investigation in order to understand the risks associated with rGH administration in different populations.

**Anabolic Steroids.** In AIDS wasting, endogenous secretion of testosterone is decreased by 30 to 50% in men. Hypogonadal patients with AIDS wasting have been found to have reduced muscle mass and IGF-I levels and increased mean growth hormone levels compared to eugonadal controls (Grinspoon et al., 1996). Testosterone levels have been found to be positively associated with total body potassium, muscle mass, and functional capacity, suggesting that testosterone levels play an important role in the development of AIDS wasting. Furthermore, testosterone can inhibit the production of IL-1 $\beta$  and IL-6 (Pottratz et al., 1994), suggesting possible direct and indirect effects of this hormone in muscle.

In a study of testosterone supplementation to eugonadal men with AIDS wasting vs placebo and progressive resistance training (3 times per week) vs no training for 12 wk, Grinspoon et al. (2000) found significant hypertrophy of muscle cross-sectional area of the arm (142%) and leg (111%) with training compared to no training. Similar increases were observed for the arm (164%) and leg (210%) muscle fibers in response to testosterone therapy compared with placebo. These findings are similar to others (Roubenoff et al., 1998) and suggest that supervised resistance exercise and pharmacological treatment effectively increase muscle mass to a similar degree; however, exercise is associated with significant health benefits in quality of life that extend beyond those seen with hormone treatment.

Similarly, the effect of 6 mo of therapy with nandrolone decanoate was tested in end-stage renal patients. Nandrolone decanoate resulted in increased lean body mass and peak oxygen consumption and reduced walking and stair-climbing time compared to placebo controls (Johansen et al., 1999). Although the short-term effects of this pharmacological therapy were positive, the combination of such therapies with resistance training as a means to improve energy intake and reduce anorexia remains to be determined given the beneficial effects of resistance training on muscle mass and function as well as quality of life and morale.

## Implications

The balance between muscle protein synthesis and degradation determines muscle mass and function. Understanding the role of mediators of muscle wasting on nutritional and metabolic end points of protein homeostasis is critical to reducing morbidity and mortality associated with chronic diseases and to developing appropriate interventions. There is considerable interest in modulating protein metabolism with hormones and(or) resistance training in several protein-wasting conditions. Further research is needed to elucidate the molecular and cellular mechanisms that contribute to the maintenance of muscle mass, to understand the responsiveness of muscle to different treatment interventions, and to determine possible interactions between treatment modalities. In addition, catabolic response may differ by disease condition, such that some interventions tested in a group of patients may not necessarily be safe and effective in another group.

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