MUSCLE WASTING AND PROTEIN METABOLISM

Carmen Castaneda, MD, Ph.D.[1]

[1] Jean Mayer USDA Human Nutrition Research Center on Aging at Tufts University, Boston, Massachusetts.

This work was funded in part by the U.S. Department of Agriculture, Agricultural Research Service, under agreement contract 58-1950-9-001. Any opinions, findings, conclusion, or recommendations expressed in this publication are those of the author(s) and do not necessarily reflect the view of the U.S. Department of Agriculture.

Address all correspondence and reprint requests to Carmen Castaneda, M.D., Ph.D., Jean Mayer USDA Human Nutrition Research Center on Aging at Tufts University, 711 Washington St., Boston MA 02111. Telephone number (617) 556-3081. Fax number (617) 556-3083. E-mail: ccastaneda@hnrc.tufts.edu

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 it is the case of 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-proteosome 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 (interlukin-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 adaptation 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 Disease

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 (interlukin-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. Interventions 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 which are intracellular proteins (Crim and Munro 1994; Young and Marchini 1990). The balance between synthesis and breakdown is such that any alteration in the supply (intake) or demand (utilization) could drastically altered cell function (Figure 1). Traditionally, protein nutritional status and homeostasis is determined by the nitrogen balance technique (National Research Council 1989). However, conventional measures of nitrogen balance along 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 and Marchini 1990). In its simplest form, accommodation to a low protein diet (providing between 0.4-0.6 g/kg/d) was tested in healthy elderly women consuming adequate energy intakes (Castaneda and others 1995a; Castaneda and others 1995b; Castaneda and others 2000), as well as in patients with chronic renal insufficiency prescribed moderately low protein diets (Castaneda and others 2001a). The results from these studies showed indeed that a marginal-to-low protein intake compromises body cell mass, 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 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 (Munro 1989; WHO/FAO/UNU 1985).

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). Since the contribution of endogenous amino acids to the pool is several-fold 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 allow to measure synthesis and breakdown in skeletal muscle more precisely. This is the case of measures of fractional synthetic rate (Nair and others 1988), protein synthesis using the three-compartment pool (Biolo and others 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 while body fat increases (Munro 1989; Young and others 1990). During severe malnutrition the loss in muscle mass ranges from 8 to 12% (Heymsfield and others 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, as 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. Since 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, reduced supply of amino acid 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 and others 1983; Cohn and others 1980; Womersley and others 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 muscle wasting characterized by a negative nitrogen balance and increased muscle protein degradation (Clague and others 1983; Rennie and Harrison 1984).

MUSCLE WASTING

Muscle wasting is defined as unintentional loss of body weight (5 to 10%) (Roubenoff and others 1997), do 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 and others 1983; Kehayias and others 1997), may be the best single measure closely linked to prognosis and survival (Keys and others 1950; Kotler and others 1996). 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 (interlukin-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-dependent 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 of the scope of this review and will be presented elsewhere.

Insulin Resistance. Insulin is an important regulator of protein synthesis (Kimball and others 1994) and proteolysis (Tessari and others 1987) in skeletal muscle. Insulin resistance or deficiency results in impaired muscle protein turnover (Garibotto and others 1994) and muscle wasting (Anderson 1991; Kaysen 1996). Poorly controlled diabetes is associated with severe muscle wasting (Gougeon and others 1997). Insulin's action on muscle appears to be primarily one of inhibiting protein degradation, while it has been difficult to demonstrate a sustained effect of insulin in increasing muscle protein synthesis (Charlton and others 1997; Nair and others 1995). Insulin resistance increases with age, fat mass, and physical inactivity (Cefalu 1998; Eriksson and others 1997; Muller and others 1996), all contributing factors for muscle loss.

Insulin-Like Growth Factor (IGF) 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 and others 1993). Because plasma IGF-I levels vary according to nutrient intake (Clemmons and others 1985a; Unterman and others 1985), IGF-I has been proposed as a biochemical marker in assessing early responses to dietary changes in protein and energy (Clemmons and others 1985b; 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 weeks (Castaneda and others 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 stimulus for protein degradation and muscle wasting, the most devastating complication of chronic uremia (Kopple and others 2000). It has been suggested that special attention to nutrient needs can help prevent the wasting syndrome of renal failure (Kopple and others 1989; Locatelli and others 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 since 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 and others 1996; Grinspoon and others 1997). In elderly men, low testosterone levels have been associated with reduced protein synthesis (Perrone and others 1995), loss of muscle mass and function (Baumgartner and others 1999). In hypogonadal men, replacement doses of

testosterone for 12 weeks increased muscle mass and strength (Morley and others 1993; Sih and others 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 (Florini and others 1991).

Growth hormone has been shown to increase protein synthesis and decrease protein oxidation rates (Jorgensen and others 1994). A study of recombinant human growth (rGH) supplementation in growth hormone deficient adults showed that non-oxidative leucine Rd (a measure of protein synthesis) increased while leucine oxidation decreased with rGH treatment (Russell-Jones and others 1993). Similarly, lean body mass, circulating IGF-I and insulin levels were significantly increased after 2 months 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 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-ß and IL-6, and tumor necrosis factor-a (TNF- a) on resting metabolic rate and protein metabolism have been observed in wasting and cachexia (Abad and others 2001; Dinarello 1999) resulting from immunodeficiency virus (HIV) infection and the acquired immunodeficiency syndrome (AIDS). Similarly a number of studies suggest that increased circulating levels of TNF-α (Nilsson 1998) as well as elevated skeletal muscle expression of TNF-α mRNA (Saghizadeh 1996), and increased plasma IL-6 are associated with insulin resistance and muscle wasting in diabetes (Fernandez-Real and others 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-α and IL-1-ß 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)-ß family (McPherron and Lawler 1997) implicated in the regulation of skeletal muscle growth (Grobet and others 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 correlate inversely with the fat-free mass-index (FFM/ht^2) (Gonzalez-Cadavid and others 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 suggest 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 where 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, utilization of 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 and others 1950; Winick 1979) 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) as 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 lessen 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 this 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 and others 1992). Resistance exercise training, in particular, has been shown to delay or reverse the loss of muscle mass and function (Campbell and others 1995; Fiatarone and others 1994). 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 that pharmacological treatment.

Studies examining the response of insulin deficient states in muscle mass and muscle function with exercise are very limited. Mandroukas et al (Mandroukas and others 1986) showed that patients with type 1 diabetes increased isokinetic torque and type IIa muscle fiber area after 20 weeks of endurance training. Durak et al (Durak 1990) found significant increases in strength in patients with type 1 diabetes undergoing resistance training for 10 weeks. More recently, a study of patients with type 2 diabetes enrolled in a progressive resistance training program for 16 week 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 two-fold increased in muscle IGF-I gene expression (Castaneda and others 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 weeks of resistance training patients with moderate chronic renal insufficiency not on dialysis successfully adapted to a low protein diet equivalent to 0.6 g/kg body weight/d. 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 and others 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 and others 1998). Nitrogen balance improved significantly from -0.6 ± 0.6 to $+2.6 \pm 0.6$ g N /d, while nitrogen flux, synthesis and breakdown rates were reduced by 18-23% 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 and others 1998). These results are similar to those observed by Nair et al (Nair and others 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 (Charlton and others 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. rGH treatment in chronic malnourished hemodialysis patients resulted in a 25% increase in phenylalanine disposal, an index of protein synthesis, while phenylalanine 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 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 and others 1997).

Anabolic Steroids. In AIDS wasting, endogenous secretion of testosterone is decreased by 30-50% 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 and others 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-1β and IL-6 (Pottratz and others 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 (3x/wk) vs. no training for 12 weeks, Grinspoon and collaborators (Grinspoon and others 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 and others 1998), and suggest that supervised resistance exercise effectively increases muscle mass to a similar degree to that of pharmacological treatment, 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-month 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 and others 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 resistance training on muscle mass and function as well as quality of life and morale.

SUMMARY AND IMPLICATIONS

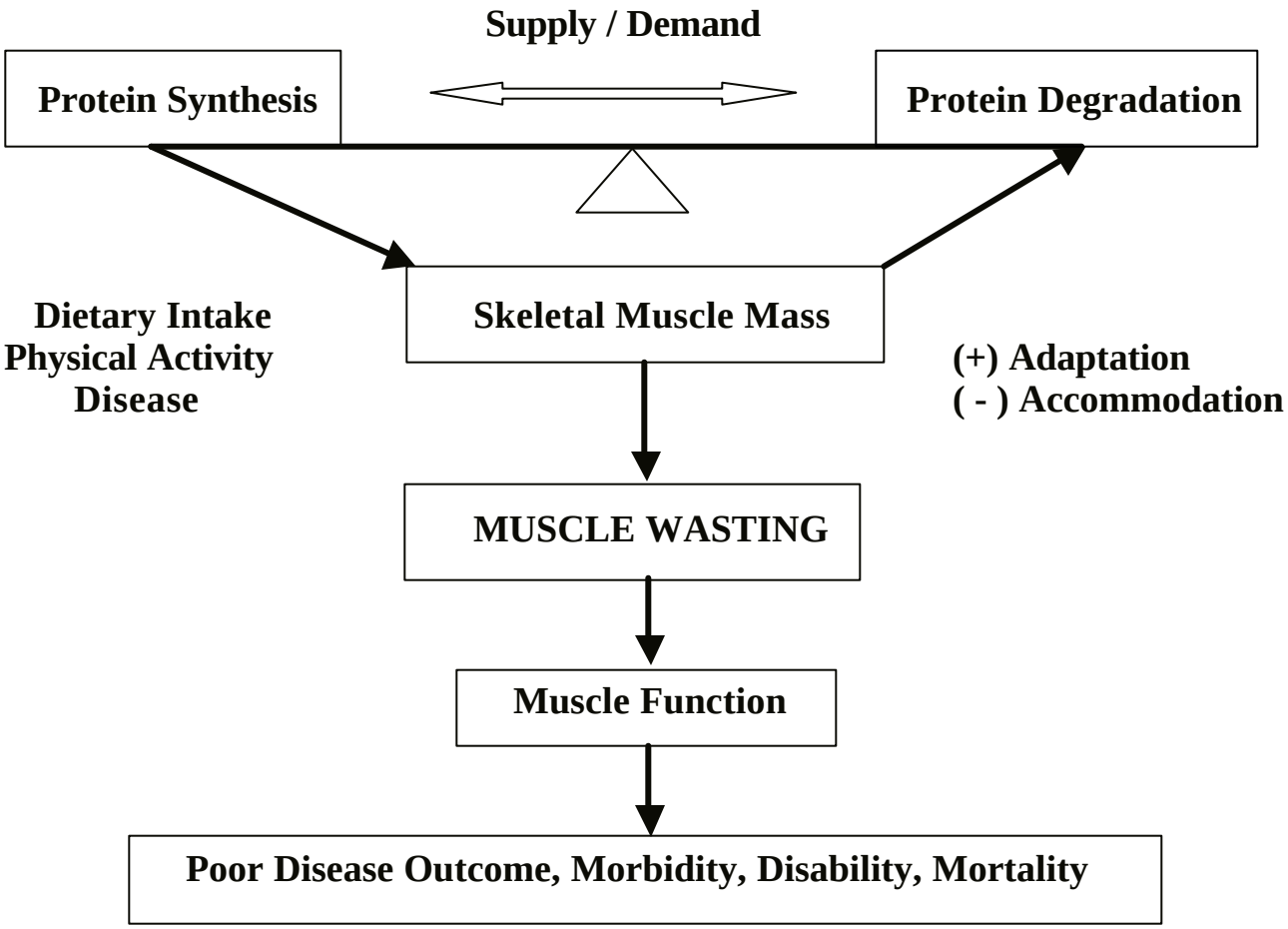
The balance between muscle protein synthesis and degradation determines the maintenance of muscle protein mass and ultimately function. The understanding of the role of different mediators of muscle wasting on protein metabolism is critical to achieve the goal of reducing the morbidity and mortality associated with many chronic diseases. The identification of nutritional and metabolic endpoints is needed to develop therapies and intervention strategies to reach these goals.

At the present, there is considerable interest in modulating protein metabolism with hormones and/or resistance training to enhance the effect of nutritional and clinical therapies in protein-wasting conditions. In most cases, nutritional support alone is insufficient to prevent the loss of protein from skeletal muscle. Further research is needed to elucidate some of 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 treatments modalities. In addition, the mechanisms of the catabolic response may be different in more advanced stages of a given disease, thus some interventions tested in a group of patients may not necessarily be safe and effective in another group, and thus merits additional research.

Table 1. Mediators of Muscle Wasting and End Points

CONDITION	POSSIBLE MEDIATORS
Anorexia and Starvation	Fasting – inadequate supply
Renal Disease	Metabolic acidosis
Diabetes	Insulin deficiency and/or resistance
	IGF-I resistance
	Increase TNF-a
	Increase counter-regulatory hormones
Sex and Growth Hormone Deficiency	IGF-I resistance
	Increase TNF-a and IL-6
HIV and AIDS	Increase myostatin
	Increase Il-6
	Increase leptin
Inflammation	Increase TNF-a and IL-1 ß
	Increase glucagon

Figure 1. Protein Metabolism and Muscle Wasting



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