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Regulation of muscle disuse atrophy by energy and protein intake in humans. Insights from bed rest studies

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Abstract

Physical inactivity and muscle atrophy are characteristic features of many chronic disease states. Maintenance of neutral energy balance plays a pivotal role in counteracting inactivity-mediated decreases in muscle mass. Both overfeeding and underfeeding are associated with accelerated muscle loss. Inactivity is per se a low-grade pro-inflammatory condition and negatively interacts with excess energy intake to increase oxidative stress and muscle catabolism. Underfeeding and malnutrition are also frequently observed in patients with appetite abnormalities and anorexia. Inactivity at negative energy balance accelerates muscle leucine oxidation and protein catabolism. With regard to protein/amino acid intake, essential amino acid supplementation contributes to counteracting skeletal and myocardial muscle atrophy during inactivity. The rapidly digested whey protein was more efficient than the slowly digested casein in increasing postprandial protein anabolism during inactivity.

Key Words: inactivity, energy balance, whey protein, chronic disease, inflammation

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Chronic diseases states are inevitably associated with decreased physical activity and muscle atrophy [12] leading to weakness, decreased bone density, falls and fractures, loss of independence, increased social needs, decreased quality of life, physical disability and increased all-cause morbidity and mortality (Fig. 1). Metabolic abnormalities also include decreased basal metabolic rate, energy requirement and glutamine production as well as insulin resistance and immune impairment [1,25]. In disease states, stress mediators and inactivity negatively interact to accelerate muscle atrophy [15]. Exercise training, when appropriate, plays a key role in counteracting muscle atrophy [10]. Nonetheless, we have recently provided evidence suggesting that nutritional interventions can substantially contribute to delaying inactivity-mediated muscle atrophy [1-5,9,13] (Fig. 1).

Inactivity is a low-grade inflammatory state

It is well known that physical activity influences the inflammatory response. Acute strenuous exercise activates systemic inflammation [18]. After a marathon race, cytokine activation is similar to that observed in medium-severity infection. Overtraining is associated to inflammation and decreased immune defenses [18]. In contrast to acute exercise, long-term exercise training down-regulates inflammation leading to decreased cardiovascular risk [21]. Population-based studies indicate that sedentary lifestyle is associated to systemic inflammation and increased cardiovascular risk. We have recently investigated the effects of two weeks of experimental bed rest in healthy volunteers on activation of inflammatory mediators [9]. Inactivity was associated to unbalanced production of pro-inflammatory and anti-inflammatory cytokines leading to increased production of the acute phase reactants C-reactive protein and long pentraxin-3 [9].

Overfeeding

In western countries, about half of dialysis patients are overweight (i.e., body mass index >25 kg/m2) [17] and have altered body composition due to increased fat-to-lean mass ratio [16]. In these patients, energy requirement is decreased due to muscle atrophy and inactivity leading to positive energy balance. An association between immobility and fat accumulation is often observed in neurological and orthopedic patients; while physiological aging is also associated to inactivity and changes in body composition. Adipose tissue produces and releases pro-inflammatory mediators, such as cytokines and leptin, potentially contributing to muscle protein catabolism. We have recently demonstrated in healthy volunteers that overfeeding and fat deposition during experimental bed

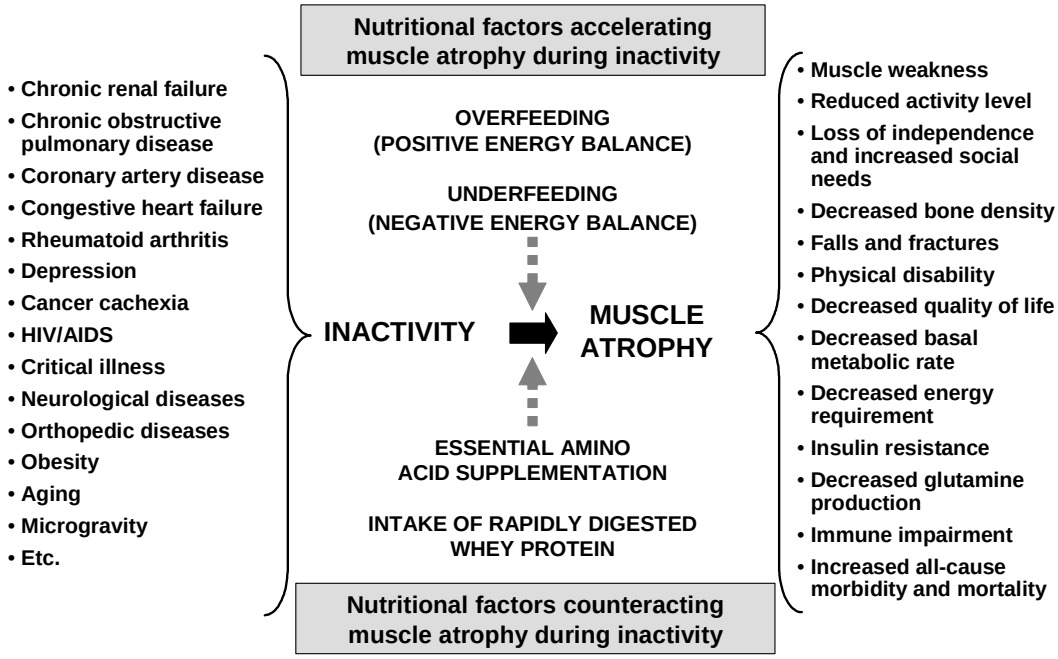

Fig. 1 *Causes and consequences of inactivity-mediated muscle atrophy. Influence of nutritional factors [Ref. 1-5,9,13]*

rest was associated to accelerated muscle atrophy and activation of systemic inflammation and oxidative stress [3]. The results contribute to understanding the association of fat accumulation and muscle atrophy observed in the so-called "sarcopenic obesity" [16]. We suggest that muscle mass in obesity may decrease rapidly when the level of physical activity is not adequate. Overfeeding and fat deposition can aggravate inactivity-induced muscle oxidative stress that has been recognized as a key mechanism of atrophy [22].

Underfeeding

Underfeeding and malnutrition are also frequently observed in patients with appetite abnormalities and anorexia. Causes of anorexia are often multifactorial. Increased cytokine production, gastrointestinal alterations, poor mood and decreased physical activity can decrease appetite in patients with chronic renal failure or other chronic diseases. In these patients, fat mass decreases progressively in parallel to muscle mass, leading to severe wasting and cachexia. Physical activity is also decreased. We have assessed the interaction between moderate energy restriction and inactivity in healthy volunteers [5]. Lean body mass atrophy was greater when bed resting subjects received a low-calorie diet. The mechanism did not involve inflammation because energy restriction prevented inactivity-induced activation of pro-inflammatory mediators [9].

Protein intake

Protein intake and amino acid availability are the key regulators of muscle protein synthesis. Amino acid administration acutely stimulates muscle protein synthesis and such effect is greatly enhanced when resistance or aerobic exercise is performed [6]. The anabolic effect of amino acid administration is quantitatively much greater than the effects of insulin and glucose administration both in the resting state and after exercise [7]. While endurance exercise increases the oxidation of essential amino acids and increases the requirement for dietary protein [26], resistance exercise results in a decrease in nitrogen excretion, lowering dietary protein needs [20]. In patients with chronic renal failure, resistance training was effective against the catabolism of lean body mass exacerbated by low-protein diets prescribed to delay disease progression [10]. In contrast to exercise, the anabolic efficiency of amino acid administration is decreased during inactivity. We have compared the ability of an amino acid load to stimulate whole body protein synthesis in healthy volunteers at the end of 2-week periods of experimental bed rest or normal physical activity [4]. Bed rest impaired by about 20% the amino acid anabolic efficiency in the post-prandial state. In addition, the rate of protein turnover in the fasting state was decreased both at muscle and whole body levels during bed rest [4, 14]. When minimal (i.e., 0.6 g protein/kg/day) and adequate (i.e., 1.0 g protein/kg/day) protein intake levels were compared during bed rest, results indicated that dietary protein restriction led to 23% suppression of whole body protein turnover in the fasting state [24]. In the attempt to counteract decreased anabolic efficiency of dietary proteins, we increased protein intake levels from 1 to

about 1.5 g protein/kg/day during 2 months bed rest in healthy women. Myocardial mass was better maintained in the high-protein diet group [13]. In another study, about 50 g of essential amino acids were provided daily to healthy male volunteers during 4-wk bed rest [19]. Lean leg mass was maintained throughout bed rest while strength loss was less pronounced in the supplemented than in the control group [19]. Despite a beneficial effects on skeletal muscle, amino acid supplementation increased acid production and calcium excretion leading to bone resorption and decreased total bone mineral content at the end of bed rest [28]. Alkalinizing agents may improve mineral balance and bone metabolism in bed resting subjects receiving high protein diet or amino acid supplementation [23].

The concept of nutritional protein quality includes ability to provide specific amino acid patterns and digestibility. The major milk proteins are casein and whey. These two proteins differ in amino acid composition and digestion rate. Whey is a fast-digesting protein and casein is a slow-digesting protein. Whey also has higher levels of leucine and cysteine. Leucine interacts with the insulin signaling pathway to stimulate downstream signal control of protein synthesis. Cysteine is rate limiting for synthesis of glutathione, the main intracellular antioxidant system. Casein is an excellent source of all the essential amino acids in balanced proportion relatively to individual requirements in healthy subjects. Whey ingestion was better than casein in promoting protein anabolism in the elderly [11] and in bed resting young subjects [2]. In contrast, in physically-active young men at rest or after resistance exercise whey was not superior to casein [8,27]. These results indicate that the relative ability of whey and casein to stimulate protein anabolism is dependent on physical activity level being inactivity closely related to the ageing process. Different mechanisms could be responsible for a greater whey anabolic efficiency during inactivity. First, a slow rate of amino acid absorption from casein may be rate limiting for protein synthesis stimulation during inactivity, whereas a higher and short-term elevation of aminoacidemia after whey ingestion could normalize inactivity-induced inhibition of protein anabolism [4]. Second, increased leucine availability after whey ingestion could enhance intracellular signaling of muscle protein synthesis stimulation. Finally, whey-mediated increased cysteine availability could activate the glutathione system thereby improving muscle redox balance and decreasing catabolism [22].

Conclusions

Maintenance of neutral energy balance plays a pivotal role in counteracting muscle atrophy during physical inactivity. Both overfeeding and underfeeding are associated with accelerated muscle loss. Achieving energy balance is a difficult task in disease states associated to inactivity. Interventions may include appetite stimulation and nutritional supplementation in underfed patients with systemic inflammation and anorexia. Energy intake should be closely monitored in those patients characterized by decreased energy expenditure due to immobility and muscle atrophy. Daily protein intake should not be lower that 1 g protein/kg body weight. The rapidly digested whey protein may be more efficient than the slowly digested casein in increasing postprandial net protein synthesis.

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References

[1] Agostini F, Heer M, Guarnieri G, Biolo G. Physical inactivity decreases whole body glutamine turnover independently from changes in proteolysis. J Physiol 2008 586:4775-4781.

[2] Antonione R, Caliandro E, Zorat F, Guarnieri G, Heer M, Biolo G. Whey protein ingestion enhances postprandial anabolism during short-term bed rest in young men. J Nutr. 2008; 138:2212-2216.

[3] Biolo G, Agostini F, Simunic B, Sturma M, Torelli L, Preiser JC, Deby-Dupont G, Magni P, Strollo F, di Prampero P, Guarnieri G, Mekjavic IB, Pisot R, Narici, MV. Positive energy balance is associated to accelerated muscle atrophy and increased erythrocyte glutathione turnover during 5 wk of bed rest. Am J Clin Nutr 2008; 88:950-958.

[4] Biolo G, Ciocchi B, Lebenstedt M, Barazzoni R, Zanetti M, Platen P, Heer M, Guarnieri, G. Short-term bed rest impairs amino acid-induced protein anabolism in humans. J Physiol 2004; 558:381-388.

[5] Biolo G, Ciocchi B, Stulle M, Bosutti A, Barazzoni R, Zanetti M, Antonione R, Lebenstedt M, Platen P, Heer M, Guarnieri G. Calorie restriction accelerates the catabolism of lean body mass during 2 wk of bed rest. Am J Clin Nutr 2007; 86:366-372.

[6] Biolo G, Tipton KD, Klein S, Wolfe, R.R. An abundant supply of amino acids enhances the metabolic effect of exercise on muscle protein. Am J Physiol 1997; 273:E122-129.

[7] Biolo G, Williams BD, Fleming RY, Wolfe RR.

Insulin action on muscle protein kinetics and amino acid transport during recovery after resistance exercise. Diabetes 1999; 48:949-957.

[8] Boirie Y, Dangin M, Gachon P, Vasson MP, Maubois JL, Beaufrère B. Slow and fast dietary proteins differently modulate postprandial protein accretion. Proc Natl Acad Sci 1997; 94:14930-14935.

[9] Bosutti A, Malaponte G, Zanetti M, Castellino P, Heer M, Guarnieri G, Biolo G. Calorie restriction modulates inactivity-induced changes in the inflammatory markers C-reactive protein and pentraxin-3. J Clin Endocrinol Metab 2008; 93:3226-3229.

[10] Castaneda C, Gordon PL, Uhlin KL, Levey,AS, Kehayias JJ, Dwyer JT, Fielding RA, Roubenoff R, Singh MF. Resistance training to counteract the catabolism of a low-protein diet in patients with chronic renal insufficiency. A randomized, controlled trial. Ann Intern Med 2001; 135:965-976.

[11] Dangin M, Guillet, C., Garcia-Rodenas, C., Gachon, P., Bouteloup-Demange, C., Reiffers-Magnani, K., Fauquant, J., Ballèvre, O., and Beaufrère, B.. The rate of protein digestion affects protein gain differently during aging in humans. J Physiol 2003; 549:635-644.

[12] de Boer MD, Seynnes OR, di Prampero PE, Pisot R, Mekjavić IB, Biolo G, Narici MV. Effect of 5 weeks horizontal bed rest on human muscle thickness and architecture of weight bearing and non-weight bearing muscles. Eur J Appl Physiol 2008; 104:401-407.

[13] Dorfman TA, Levine BD, Tillery T, Peshock RM, Hastings JL, Schneider SM, Macias BR, Biolo G, Hargens AR. Cardiac atrophy in women following bed rest. J Appl Physiol 2007; 103:108-116.

[14] Ferrando AA, Lane HW, Stuart CA, Davis-Street J, Wolfe RR. Prolonged bed rest decreases skeletal muscle and whole body protein synthesis. Am J Physiol 1996; 270:E627-633.

[15] Ferrando AA, Stuart CA, Sheffield-Moore M, Wolfe RR. Inactivity amplifies the catabolic response of skeletal muscle to cortisol. J Clin Endocrinol Metab 1999; 84:3515-3521.

[16] Honda H, Qureshi AR, Axelsson J, Heimburger O, Suliman ME, Barany P, Stenvinkel P, Lindholm, B. Obese sarcopenia in patients with end-stage renal disease is associated with inflammation and increased mortality. Am J Clin Nutr 2007; 86:633-638.

[17] Johansen KL, Kutner NG, Young B, Chertow GM. Association of body size with health status in patients beginning dialysis. Am J Clin Nutr 2006; 83:543-549.

[18] Lakier Smith L. Overtraining, excessive exercise, and altered immunity: is this a T helper-1 versus T helper-2 lymphocyte response? Sports Med 2003; 33:347-364.

[19] Paddon-Jones D, Sheffield-Moore M, Urban RJ, Sanford AP, Aarsland A, Wolfe RR, Ferrando AA. Essential amino acid and carbohydrate supplementation ameliorates muscle protein loss in humans during 28 days bed rest. J Clin Endocrinol Metab 2004; 89:4351-4358.

[20] Phillips SM. Protein requirements and supplementation in strength sports. Nutrition 2004; 20:689-695.

[21] Plaisance EP, Grandjean PW. Physical activity and high-sensitivity C-reactive protein. Sports Med 2006; 36:443-458.

[22] Powers SK, Kavazis AN, McClung JM. Oxidative stress and disuse muscle atrophy. J Appl Physiol 2007; 102:2389-2397.

[23] Sebastian A, Harris ST, Ottaway JH, Todd KM, Morris RC Jr. Improved mineral balance and skeletal metabolism in postmenopausal women treated with potassium bicarbonate. N Engl J Med 1994; 330:1776-1781.

[24] Stuart CA, Shangraw RE, Peters EJ, Wolfe RR. Effect of dietary protein on bed-rest-related changes in whole-body-protein synthesis. Am J Clin Nutr 1990; 52:509-514.

[25] Stuart CA, Shangraw RE, Prince MJ, Peters EJ, Wolfe RR. Bed-rest-induced insulin resistance occurs primarily in muscle. Metabolism 1988; 37:802-806.

[26] Tarnopolsky M. Protein requirements for endurance athletes. Nutrition 2004; 20:662-668.

[27] Tipton KD, Elliott TA, Cree MG, Wolf SE, Sanford, AP, Wolfe RR. Ingestion of casein and whey proteins result in muscle anabolism after resistance exercise. Med Sci Sports Exerc 2004; 36:2073-2081.

[28] Zwart SR, Davis-Street JE, Paddon-Jones D, Ferrando AA, Wolfe R, Smith, S.M. Amino acid supplementation alters bone metabolism during simulated weightlessness. J Appl Physiol 2005; 99:134-140.