Review

# Protein Nutrition, Exercise and Aging

**William J. Evans, PhD**

*Nutrition, Metabolism, and Exercise Laboratory, Donald W. Reynolds Center on Aging, Slot 806, University of Arkansas for Medical Sciences, Little Rock, Arkansas*

**Key words: aging, elderly, sarcopenia, muscle mass, diet, protein, strength conditioning**

Aging is associated with remarkable changes in body composition. Loss of skeletal muscle, a process called sarcopenia, is a prominent feature of these changes. In addition, gains in total body fat and visceral fat content continue into late life. The cause of sarcopenia is likely a result of a number of changes that also occur with aging. These include reduced levels of physical activity, changing endocrine function (reduced testosterone, growth hormone, and estrogen levels), insulin resistance, and increased dietary protein needs. Healthy free-living elderly men and women have been shown to accommodate to the Recommended Dietary Allowance (RDA) for protein of 0.8 $g \cdot kg^{-1} \cdot d^{-1}$ with a continued decrease in urinary nitrogen excretion and reduced muscle mass. While many elderly people consume adequate amounts of protein, many older people have a reduced appetite and consume less than the protein RDA, likely resulting in an accelerated rate of sarcopenia.

One important strategy that counters sarcopenia is strength conditioning. Strength conditioning will result in an increase in muscle size and this increase in size is largely the result of increased contractile proteins. The mechanisms by which the mechanical events stimulate an increase in RNA synthesis and subsequent protein synthesis are not well understood. Lifting weight requires that a muscle shorten as it produces force (concentric contraction). Lowering the weight, on the other hand, forces the muscle to lengthen as it produces force (eccentric contraction). These lengthening muscle contractions have been shown to produce ultrastructural damage (microscopic tears in contractile proteins muscle cells) that may stimulate increased muscle protein turnover. This muscle damage produces a cascade of metabolic events which is similar to an acute phase response and includes complement activation, mobilization of neutrophils, increased circulating an skeletal muscle interleukin-1, macrophage accumulation in muscle, and an increase in muscle protein synthesis and degradation. While endurance exercise increases the oxidation of essential amino acids and increases the requirement for dietary protein, resistance exercise results in a decrease in nitrogen excretion, lowering dietary protein needs. This increased efficiency of protein use may be important for wasting diseases such as HIV infection and cancer and particularly in elderly people suffering from sarcopenia. Research has indicated that increased dietary protein intake (up to 1.6 g protein $\cdot kg^{-1} \cdot d^{-1}$) may enhance the hypertrophic response to resistance exercise. It has also been demonstrated that in very old men and women the use of a protein-calorie supplement was associated with greater strength and muscle mass gains than did the use of placebo.

**Key teaching points:**

- Sarcopenia is the loss of skeletal muscle in the aging process.
- As the body ages, there is a natural loss of skeletal muscle and gains in total body fat and visceral fat.
- The elderly can benefit from aerobic conditioning and strength training, only strength training can stop or reverse sarcopenia.
- The current RDA of .8 grams/KG body weight per day is insufficient to meet the protein needs of most elderly people.
- Research shows that the use of a protein and calorie supplement was associated with greater strength and muscle mass gains than did the use of placebo.

Address reprint requests to: William J. Evans, Ph.D., Director, Nutrition, Metabolism, and Exercise Laboratory, Donald W. Reynolds Center on Aging, Slot 806, University of Arkansas for Medical Sciences, Little Rock, AR 72205. E-mail: evanswilliamj@uams.edu

Journal of the American College of Nutrition, Vol. 23, No. 6, 601S–609S (2004)
Published by the American College of Nutrition

# INTRODUCTION

Aging is associated with a remarkable number of changes in body composition and metabolism. Sarcopenia is a life-long process that likely begins in young adulthood [29,30]. This loss of skeletal muscle mass is also associated with increasing body fatness, decreased basal metabolic rate and daily energy needs [71], loss of bone mass, reduced strength and functional status. Nutrient requirements also may change with age. Recommendations for increased calcium, vitamin D, vitamin E intakes for elderly people have been made. Increased intake of specific nutrients is particularly difficult for elderly people in the face of reduced dietary energy needs. We [51] recently demonstrated that the currently accepted Atwater energy equivalents overestimate true energy needs in elderly people, suggesting either that the estimates are incorrect or that elderly people are not as efficient at energy absorption as young people. As discussed below, there is also strong evidence that the dietary protein needs of elderly people are greater than current recommendations (based on date primarily from young subjects) [8,11–13].

## Dietary Protein Needs of Elderly People

The current Recommended Dietary Allowance for protein to meet the needs of adults over the age of 19 years (unless pregnant or lactating) is 0.8 grams $\cdot$ kg$^{-1}$ $\cdot$ d$^{-1}$ [26]. This estimate should meet the needs of virtually all health people regardless of age of level of physical activity. However, the information concerning the dietary protein requirements of elderly people is limited. Campbell *et al.* [8,11] examined studies in the literature examining nitrogen-balance in elderly people and recalculated the balance data using currently accepted values for miscellaneous losses. The conclusion of this retrospective analysis and new balance data presented was that the current RDA is inadequate to meet the dietary protein needs of most elderly people. This conclusion was confirmed by our laboratory [13] in a study that examined the long-term consequences of consumption of the protein RDA. This study enrolled health, elderly men and women and provided the 0.8 g protein $\cdot$ kg$^{-1}$ $\cdot$ d$^{-1}$ over 14-week period in a metabolic ward. The subjects in this study demonstrated a classic accommodation response described by Waterlow [75] with a continued decrease in urinary nitrogen excretion over the 14-week period of the study. The accommodated tissue was skeletal muscle. Using computerized tomography, we demonstrated a significant reduction in the cross-sectional area of thigh muscle. Thus, these data suggest that the protein RDA for elderly people is not adequate, even while consuming a weight maintenance diet.

The etiology of this increased need for dietary protein is not well understood. While some have demonstrated that the rate muscle protein synthesis is reduced in elderly people [76], it appears that basal rate of muscle protein synthesis is not depressed in this population compared to that of young people [74]. There is evidence that post-prandial rise in amino acids results in a greater rise in muscle protein synthesis in young people compared to old. There is also a greater extraction of essential amino acid during the first pass through the liver, potentially diminishing the amount of amino acids presented to muscle. In addition, glucose intolerance may also play an important role in a reduced post-prandial increase in muscle protein synthesis in elderly people [73].

The fact that elderly people require more dietary protein than the RDA has important implications. Surveys of the nutrition status of older people have shown that a large number (up to 30%) consume the RDA or less each day. Inadequate intake of protein over a prolonged period of time results in a decrease in the rate of whole body protein turnover and an accelerated loss of muscle mass in elderly people [19,20]. Indeed, epidemiological evidence of increased dietary protein shows that elderly people who consume the RDA for protein are at greater risk of health problems than those older people who consume a greater amount of protein [72]. These investigators [72] suggested that "the mean protein requirement in elderly adults is greater than that established by the 1985 joint WHO/FAO/UNU expert committee." Dietary energy needs of elderly people are generally lower than those of young men and women [63]. This means that older people may need a greater amount of dietary protein as a percentage of their total energy intake. Because of their decreased energy requirements and decreased intake compared to young, elderly people should increase their intake of high quality but low fat protein, such as eggs, low fat meat and fish, and whey or casein.

These estimates of increased dietary protein needs of elderly people were made under eucaloric conditions. During periods of decreased energy intake, dietary protein needs increase. Certainly, strong consideration for increased intake of low fat, high quality protein should be made for those older people who voluntarily attempt to lose weight. In addition, appetite regulation has been demonstrated to be impaired in the elderly [62]. While energy intake increases in young people after a period of decreased energy intake, Roberts *et al.* [62] demonstrated that older people remain hypophagic after reduced energy intake and weight loss. This may help to explain why many older people experience involuntary weight loss with no increase in appetite. Indeed, use of protein/calorie supplements in very old men and women have not been shown to increased dietary energy intake or body weight [34]. In this population, dietary protein intake may be critical to the preservation of skeletal muscle mass.

## Strength Training

Progressive resistance exercise or strength training has been demonstrated to result in an increase in muscle size and strength. Strength conditioning or progressive resistance training is generally defined as training in which the resistance against which a muscle generates force is progressively increased over time. Progressive resistance training involves few

contractions against a heavy load. While endurance exercise has been the more traditional means of increasing cardiovascular fitness, the American College of Sports Medicine currently recommends strength or resistance training as an important component of an overall fitness program. This is particularly important in the elderly where loss of muscle mass and weakness are prominent deficits.

## Resistance Exercise and Muscle Damage

The metabolic and morphological adaptations resulting from resistance and endurance exercise are quite different. Muscle strength has been shown to increase in response to training between 60 and 100% of the 1 repetition maximum (1 RM) [54]. 1 RM is the maximum amount of weight that can be lifted with one contraction. Strength conditioning will result in an increase in muscle size and this increase in size is largely the result of increased contractile proteins. The mechanisms by which the mechanical events stimulate an increase in RNA synthesis and subsequent protein synthesis are not well understood. Lifting weight requires that a muscle shorten as it produces force (concentric contraction). Lowering the weight, on the other hand, forces the muscle to lengthen as it produces force (eccentric contraction). These lengthening muscle contractions have been shown to produce ultrastructural damage (microscopic tears in contractile proteins muscle cells) that may stimulate increased muscle protein turnover [31].

High intensity strength training has been shown to increase skeletal muscle mass despite resulting in increased myofibrillar proteolysis [40], suggesting a disproportionate increase in myofibrillar protein synthesis. Our laboratory has demonstrated that eccentric exercise (a large component of high intensity strength training) results in ultrastructural damage to skeletal muscle, which results in a prolonged increase in the rate of protein degradation. Our data also implicate the exercise-induced increase in skeletal muscle interleukin-1$\beta$ as a mediator of these changes. Interleukin-1$\beta$ is a peptide derived from mononuclear cells which has been implicated as the substance responsible for the so-called acute phase response to infection that includes fever, mobilization of neutrophils, redistribution of trace metals and increased skeletal muscle proteolysis. In addition, we have demonstrated that many of the components of this acute phase response to exercise are reduced in older compared to younger subjects. For example, we have shown that complement activation is similar between older and younger subjects, but neutrophil mobilization (presumably stimulated by complement) is greatly reduced or not apparent in old vs. young subjects. The release of creatine kinase from damaged muscle is also attenuated in older subjects compared to young. These age-related differences in the acute phase response to damaging exercise may result in an attenuated response in alterations in muscle protein metabolism and reduced amount of muscle hypertrophy in older compared to younger subjects.

Skeletal muscle undergoes well-established adaptations following repeated bouts of resistance exercise in animals and humans [5]. In particular muscle size and strength increase significantly following high-intensity resistance [22,40]. Contributing to these adaptations are temporary adjustments in whole body [67] and muscle protein synthesis [23,83] that exist for several days following acute exercise. While we have demonstrated that resistance training results in an increase in muscle size in older subjects, our results have been variable. While two studies demonstrated a significant increase in muscle size resulting from strength training [32,40], two other studies using the same intervention showed no change [10,33].

Exercises that involve eccentric (lengthening) contractions elicit the most rapid and largest improvements in muscle strength and size [24,25]. Seemingly events associated with muscle hypertrophy are more apparent following eccentric than concentric resistance exercise. For example, repeated eccentric contractions induce local accumulation of several peptide growth factors, including insulin like growth factor (IGF) [82], fibroblast growth factor (FGF) [81], and potentially platelet-derived growth factor (PDGF). All three growth factors stimulate satellite cell proliferation in vitro; processes which require an enhanced rate of protein synthesis. *In-vivo* effects of these growth factors on protein synthesis are scarce, but it has been shown that infusion of IGF-I increases whole-body protein synthesis in man [64].

Since a major source of these growth factors are macrophages [57], muscle hypertrophy may be linked with the body's inflammatory response to exercise-induced muscle injury [18,78]. Various indices of inflammation are apparent after damaging-type (eccentric) exercise, including leukocyte mobilization and infiltration, muscle proteolysis, complement activation and fever. Although eccentric exercise causes local inflammation [6,14–17,35] there is no *in-vivo* evidence that the inflammatory response induces protein synthesis and muscle hypertrophy.

We have recently demonstrated that a single bout of high intensity eccentric exercise performed by sedentary men resulted in a significant increase in skeletal muscle prostaglandin levels (PGE2 and PGF2$\alpha$) [69]. Previous studies have demonstrated that PGE2 and PGF2$\alpha$ have a [3,41,42]. Because cyclooxygenase inhibitors may effect the post-exercise rise in muscle prostaglandin, we examined the effect of two commonly consumed over-the-counter analgesics, ibuprofen and acetaminophen, on muscle protein metabolism following high intensity eccentric exercise. Twenty four men (age: 25 $\pm$ 3 yr, height: 180 $\pm$ 6 cm, weight: 81 $\pm$ 6 kg, body fat: 17 $\pm$ 8%) were randomly assigned to one of 3 groups that received either the maximal over-the-counter dose of ibuprofen (IBU; 1200 mg/d), acetaminophen (ACET; 4000 mg/d), or a placebo (PLA) following 10–14 sets of 10 repetitions at 120% of concentric 1 repetition maximum using the knee extensors. Post-exercise (24 h) skeletal muscle fractional synthesis rate (FSR, measured by incorporation of phenylalanine into muscle protein) was

increased 71 ± 20% ($p < 0.05$) in PLA (0.037 ± 0.009 %/h), and was unchanged ($p > 0.05$) in IBU (38 ± 22%; 0.015 ± 0.009%/h) and ACET (23 ± 26%; 0.006 ± 0.014%/h) [70]. Exercise induced a significant increase in skeletal muscle prostaglandin levels ($PGE_2$ & $PGF_{2\alpha}$) that was completely suppressed by ibuprofen and acetaminophen. These results suggest that both ibuprofen and acetaminophen suppress the protein metabolic response to eccentric exercise. These are the first data to demonstrate an anti-inflammatory effect of acetaminophen in skeletal muscle. Thus, these two analgesics may work through a common mechanism to influence protein metabolism in skeletal muscle. These data also indicate that the common practice of treating delayed onset muscle soreness that may result from exercise may have a strong effect on muscle hypertrophy by greatly decreasing the rate of protein synthesis.

## Effects of Resistance Exercise and Insulin on Protein Metabolism

Hormonal and nutritional factors, particularly the availability of insulin and amino acids, have important effects in the control of muscle protein synthesis [47,61]. For example, starvation reduces the rate of protein synthesis in skeletal muscle by more than 50% compared to the rate seen in fed animals. This inhibition of protein synthesis (also seen in muscle from diabetic animals) is a result of an impairment in the initiation phase of protein synthesis [47,61]. The mechanism through which insulin regulates protein synthesis initiation involves phosphorylation of the translational regulator eukaryotic initiation factor 4E (eIF-4E)-binding protein 1 (4E-PB1) [38]. Insulin-like growth factor 1 (IGF-I) results in the phosphorylation of 4E-BP1 and dissociation of the 4E-BP1 · eIF-4E complex in [43] cells in culture (muscle cells that are grown in a medium containing appropriate nutrients and growth factors). IGF-I has also been shown to stimulate protein synthesis in rats *in vivo* [45] and in muscle in perfused hindlimb preparations [46]. These studies also suggest that insulin plays a permissive role in the effect of IGF-I in stimulating muscle protein synthesis.

Studies of insulin secretion after resistance but not endurance exercise provide evidence for insulin's role in maintaining muscle mass. King *et al.* [48] and Dela *et al.* [27] showed that arginine-stimulated insulin secretion is decreased with endurance training. In contrast, acute resistance exercise in rats has been shown to increase insulin secretion [37]. As reviewed above, regular aerobic exercise is known to increase insulin sensitivity and glucose tolerance. In addition to its effects on insulin action, aerobic exercise training results in decreased insulin secretion [28]. Regularly performed endurance exercise in young men is associated with an insulin pulse profile in the resting fasted state characterized by less insulin secreted per burst but a similar number of bursts over a 90-min period. They suggested that training-induced elevations in target-tissue sensitivity to insulin reduce the requirement for pulsatile insulin secretion. This coordinated response keeps glucose concentrations constant. Dela *et al.* [27] demonstrated that aerobic exercise training decreases both arginine and glucose stimulated insulin secretion, indicating, they conclude, a profound $\beta$-cell adaptation.

A single bout of concentric exercise is a recognized enhancer of insulin action, while eccentric exercise transiently impairs whole body insulin action for at least 2 days after the bout [49]. We have demonstrated that eccentric exercise can result in a long-term delay in the rate of glycogen synthesis [59]. This decrease insulin action and delayed glycogen synthetic rate has been shown to result from decreased rate of glucose transport rather than decrease glycogen synthase activity [2]. This transient resistance to insulin and impaired resynthesis of glycogen can result in a systemic hyperinsulinemia that may result in an increase in the rate of muscle protein synthesis. Our laboratory [50] has demonstrated age-related differences in the insulin response to hyperglycemia following a single bout of eccentric exercise. Two days following upper and lower body eccentric exercise younger subjects demonstrated a pronounced pancreatic insulin response during a hyperglycemic clamp while this response was blunted in healthy elderly men.

The effects of resistance exercise on insulin availability appear to be opposite those of endurance exercise and thus stimulate net protein accretion. Insulin has been demonstrated to have profoundly anabolic effects on skeletal muscle. In the resting state, insulin has been demonstrated to decrease the rate of muscle protein degradation. Stable isotope amino acid studies in humans [21,68] clearly demonstrate that insulin inhibits whole body protein breakdown *in vivo* and stimulates muscle protein synthetic rate [4].

Insulin has been demonstrated to increase the rate of muscle protein synthesis in insulin deficient rats. However, in nondiabetic animals this effect was not seen. Fluckey *et al.* have argued [36,37] that insulin is not likely to stimulate muscle protein synthesis in quiescent muscle. We have demonstrated that an insulin infusion does not increase the rate of protein synthesis in non-exercised muscle. However, using a resistance exercise model, we have demonstrated that resistance exercise did not stimulate an increase in the rate of protein synthesis. It was only with the addition of insulin that an exercise induced increase in the rate of soleus and gastrocnemius protein synthesis was seen. This effect of insulin stimulation of the rate of protein synthesis was preserved with advancing age.

## Protein Requirements and Exercise

High intensity resistance training is clearly anabolic in both young and older individuals. Data from our laboratory [10] demonstrated a 10 to 15 percent decrease in N-excretion at the initiation of training that persists for 12 weeks. That is, progressive resistance training improved N-balance, thus older subjects performing resistance training have a lower mean

protein requirement than do sedentary subjects. This effect was seen at a protein intake of 0.8 and 1.6 g protein $\cdot$ kg$^{-1}$ $\cdot$ d$^{-1}$, indicating that the effect of resistance training on protein retention may not be related to dietary protein intake. These results are somewhat at variance to our previous research [56] demonstrating that regularly performed aerobic exercise causes an increase in the mean protein requirement of middle-aged and young endurance athletes (mean of 0.93 g $\cdot$ kg$^{-1}$ $\cdot$ d$^{-1}$). This difference likely results from increased oxidation of amino acids during aerobic exercise that may not be present during resistance training.

Strawford *et al.* [66] also demonstrated similar effects of resistance exercise training on nitrogen balance in patients with HIV-related weight loss. The investigators examined the effects of an anabolic steroid (oxandrolone, 20 mg/d and placebo) and high intensity resistance exercise training in 24 eugonadal men with HIV-associated weight loss (mean, 9% body weight loss). Both groups showed significant nitrogen retention and increases in LBM, weight, and strength. The mean gains were significantly greater in the oxandrolone group than in the placebo group in nitrogen balance, accrual of FFM, and strength. Results were similar whether or not patients were taking protease inhibitors. These results confirm the positive effects of resistance exercise on nitrogen retention and protein requirements.

These studies, taken as a whole demonstrate the powerful effects of resistance exercise training on protein nutriture. The anabolic effects have important implications in the treatment of many wasting diseases and conditions such as cancer, HIV infection, aging, chronic renal failure, and undernutrition seen in many very old men and women. By effectively lowering dietary protein needs, resistance exercise can limit further losses of skeletal muscle mass while simultaneously increase muscle strength and functional capacity.

## Resistance Exercise, Protein Intake, and Aging

A number of investigators have demonstrated that resistance exercise can result in a substantial increase in muscle size and strength in elderly people. However, it is clear that when the intensity of the exercise is low, only modest increases in strength are achieved by elderly subjects [1,53]. A number of studies have demonstrated that, given an adequate training stimulus, older men and women show similar or greater strength gains compared to young individuals as a result of resistance training.

Frontera *et al.* [39,40] showed that older men responded to a 12 week progressive resistance training program (80% of the 1 repetition maximum, 3 sets of 8 repetition of the knee extensor and flexors, 3 days per week) by more than doubling extensor strength and more than tripling of flexor strength. The increases in strength averaged approximately 5% per training session, similar to strength gains observed by younger men. Total muscle area estimated by computerized tomography (CT) increased by 11.4%. Biopsies of the vastus lateralis muscle revealed similar increases in type I fiber area (33.5%) and type II fiber area (27.6%). Daily excretion of urinary 3-methyl-L-histidine increased with training ($p < 0.05$) by an average of 40.8%, indicating that increased muscle size and strength resulting from PRT is associated with an increased rate of myofibrillar protein turnover. Half of the men who participated in this study were given a daily protein-calorie supplement (S) providing an extra 560 $\pm$ 16 kcal/d (16.6% as protein, 43.3% as carbohydrate, and 40.1% as fat) in addition to their normal *ad lib* diet. The rest of the subjects received no supplement (NS) and consumed an *ad lib* diet. By the twelfth week of the study, dietary energy (2960 $\pm$ 230 in S *vs.* 1620 $\pm$ 80 kcal in NS) and protein (118 $\pm$ 10 in S *vs.* 72 $\pm$ 11 g/d in NS) intake were significantly different between the S and NS groups. Composition of the midthigh was estimated by computerized tomography and showed that the S group had greater gains in muscle than did the NS men [55]. In addition, urinary creatinine excretion was greater at the end of the training in the S group when compared to that of the men in the NS group, indicating a greater muscle mass in the S group at the end of the 12 weeks of training. The change in energy and protein intake (beginning *vs.* 12 weeks) was correlated with the change in midthigh muscle area ($r = 0.69$, $p = 0.019$; $r = 0.63$, $p = 0.039$, respectively). There were no differences in the strength gains between the two groups. These data suggest that a change in total food intake, or perhaps, selected nutrients, in subjects beginning a strength-training program can affect muscle hypertrophy.

We applied this same training program to a group of frail, institutionalized elderly men and women (mean age 90 $\pm$ 3 years, range 87–96) [32]. After 8 weeks of training, the 10 subjects in this study increased muscle strength by almost 180% and muscle size by 11%. We also used [33] a similar intervention on frail nursing home residents and demonstrated not only increases in muscle strength and size, but increased gait speed, stair climbing power, and balance. In addition, spontaneous activity levels increased significantly while the activity of a non-exercised control group was unchanged. In this study the effects of a protein/calorie supplement combined with exercise was also examined. The supplement consisted of a 240-ml liquid supplying 360 kcal in the form of carbohydrate (60%), fat (23%), and soy-based protein (17%), and was designed to augment caloric intake by about 20%, and provide one third of the RDA for vitamins and minerals. The men and women who consumed the supplement and exercised gained weight compared to the three other groups examined (exercise/control, non-exercise supplemented, and non-exercise control). The non-exercising subjects who received the supplement reduced their habitual dietary energy intake so that total energy intake was unchanged. In other words, the supplement did not add to total energy intake, but rather substituted one source of energy (the supplement) for another (their meals). More recently (in the same study population), we [65] demonstrated

that the combined weight lifting and nutritional supplementation increased strength by 257 ± 62% ($p = 0.0001$) and type II fiber area by 10.1 ± 9.0% ($p = 0.033$), with a similar trend for type I fiber area (+12.8 ± 22.2%). Exercise was associated with a 2.5-fold increase in neonatal myosin (a form of myosin found in growing muscle) staining ($p = 0.0009$) and an increase of 491 ± 137% ($p < 0.0001$) in IGF-I staining. Ultrastructural damage increased by 141 ± 59% after exercise training ($p = 0.034$). Strength increases were largest in those with the greatest increases in myosin, IGF-I, damage, and caloric intake during the trial. Frail, very old, elders respond robustly to resistance training with musculoskeletal remodeling, and significant increases in muscle area are possible with resistance training in combination with adequate energy intakes. It should be pointed out that this was a very old, very frail population with diagnoses of multiple chronic diseases. The increase in overall levels of physical activity have been a common observation in our studies [33,39,58]. Since muscle weakness is a primary deficit in many older individuals, increased strength may stimulate more aerobic activities like walking and cycling.

We examined the influence of increased dietary protein on the hypertrophic response to resistance exercise in a group of healthy older people [10]. These men and women were randomly assigned to a RDA group consuming 0.8 or 1.6 g protein $\cdot$ kg$^{-1}$ $\cdot$ d$^{-1}$. All of the subjects in this study were asked to participate in a high intensity resistance exercise training program (3 d/wk, 80% 1 RM) for three months. The subjects who consumed the higher protein level tended to show a greater hypertrophic response to the training. More recently we compared the effects of a meat-free, lacto-ovo vegetarian diet *vs.* a diet with meat on gains in muscle size from resistance exercise [7]. This study demonstrated that those subjects who consumed meat (as part of normal dietary intake) gained more muscle than those who excluded meat did.

## Strength Training Effects in Older People

Strength training may increase balance through the improvement in strength of muscle involved in walking. Indeed ankle weakness has been demonstrated to be associated with increased risk of falling in nursing home patients [77]. However, balance training, which may demonstrate very little improvement in muscle strength, size, or cardiovascular changes has also been demonstrated to decrease the risk of falls in older people [80]. Tai Chi, a form of dynamic balance training that requires no new technology or equipment, has been demonstrated to reduce the risk of falling in older people by almost 50% [79]. As a component of the National Institute on Aging FICSIT trials (Frailty and Injuries: Cooperative Studies of Intervention Techniques), individuals aged 70+ were randomized to Tai Chi (TC), individualized balance training (BT), and exercise control education (ED) groups for 15 weeks [52]. In a follow-up assessment 4 months post-intervention, 130 subjects responded to exit interview questions asking about perceived benefits of participation. Both TC and BT subjects reported increased confidence in balance and movement, but only TC subjects reported that their daily activities and their overall life had been affected; many of these subjects had changed their normal physical activity to incorporate ongoing TC practice. The data suggest that when mental as well as physical control is perceived to be enhanced, with a generalized sense of improvement in overall well-being, older persons' motivation to continue exercising also increases. Province *et al.* [60] examined the overall effect of many different exercise interventions in the FICSIT trials on reducing falls. While each these separate interventions were not powered to make conclusions about their effects on the incidence of falls in and elderly population, they did conclude that "all training domains, taken together under the heading of "general exercise" showed and effect on falls, this probably demonstrates the "rising tide raises all boats" principle, in which training that targets one domain may improve performance somewhat in other domains as a consequence. If this is so, then the differences seen on fall risk due to the exact nature of the training may not be as critical compared with the differences in not training at all." The use of a community-based exercise program for frail older people was examined [44] in a group of predominantly sedentary women over age 70 with multiple chronic conditions. The program was conducted with peer leaders to facilitate its continuation after the research demonstration phase. In addition to positive health outcomes related to functional mobility, blood pressure maintenance, and overall well-being, this intervention was successful in sustaining active participation in regular physical activity through the use of peer leaders selected by the program participants.

In addition to its effect on increasing muscle mass and function, resistance training can also have an important effect on energy balance [9]. Men and women participating in a resistance training program of the upper and lower body muscles required approximately 15% more calories to maintain body weight after 12 weeks of training when compared to their pretraining energy requirements. This increase in energy needs came about as a result of an increased resting metabolic rate, the small energy cost of the exercise, and what was presumed to be an increase in activity levels. While endurance training has been demonstrated to be an important adjunct to weight loss programs in young men and women by increasing their daily energy expenditure, its utility in treating obesity in the elderly may not be great. This is because many sedentary older men and women do not spend many calories when they perform endurance exercise, due to their low fitness levels. Thirty to forty minutes of exercise may increase energy expenditure by only 100 to 200 kcals with very little residual effect on calorie expenditure. Aerobic exercise training will not preserve lean body mass to any great extent during weight loss. Because resistance training can preserve or even increase muscle mass

during weight loss, this type of exercise for those older men and women who must lose weight may be of genuine benefit.

In conclusion, progressive resistance exercise results in decreased nitrogen excretion and, thus, lower dietary protein needs. This has important implications for treatment of individuals with a wasting syndrome or cachexia, and particularly older men and women who experience involuntary weight loss. There is evidence that and increase in dietary protein intake will result in enhanced muscle hypertrophy when combined with high intensity resistance exercise training. Muscle strength training can be accomplished by virtually anyone. Many health care professionals have directed their patients away from strength training in the mistaken belief that it can cause undesirable elevations in blood pressure. With proper technique, the systolic pressure elevation during aerobic exercise is far greater than that seen during resistance training. Muscle strengthening exercises are rapidly becoming a critical component to cardiac rehabilitation programs as clinicians realize the need for strength as well as endurance for many activities of daily living. There is no other group in our society that can benefit more from regularly performed exercise, than the elderly. While both aerobic and strength conditioning are highly recommended, only strength training can stop or reverse sarcopenia. Increased muscle strength and mass in the elderly can be the first step towards a lifetime of increased physical activity and a realistic strategy for maintaining functional status and independence.

## REFERENCES


1. Aniansson A, Gustafsson E: Physical training in elderly men with special reference to quadriceps muscle strength and morphology. Clin Physiol 1:87–98, 1981.
2. Asp S, Richter EA: Decreased insulin action on muscle glucose transport after eccentric contractions in rats. J Appl Physiol 81: 1924–1928, 1996.
3. Baracos V, Rodemann HP, Dinarello CA, Goldberg AL: Stimulation of muscle protein degradation and prostaglandin E2 release by leukocytic pyrogen (interleukin-1). A mechanism for the increased degradation of muscle proteins during fever. N Engl J Med 308: 553–558, 1983.
4. Biolo G, Fleming RY, Wolfe RR: Physiologic hyperinsulinemia stimulates protein synthesis and enhances transport of selected amino acids in human skeletal muscle. J Clin Invest 95:811–819, 1995.
5. Booth FW, Thomason DB: Molecular and cellular adaptation of muscle in response to exercise: perspectives of various models. Physiol Rev 71:541–585, 1991.
6. Caiozzo VJ, Perrine JJ, Edgerton VR: Training-induced alterations of the in vivo force-velocity relationship of human muscle. J Appl Physiol: Respirat Environ Exercise Physiol 51:750–754, 1981.
7. Campbell WW, Barton Jr ML, Cyr-Campbell D, Davey SL, Beard JL, Parise G, Evans WJ: Effects of an omnivorous diet compared with a lactoovovegetarian diet on resistance-training-induced changes in body composition and skeletal muscle in older men. Am J Clin Nutr 70:1032–1039, 1999.
8. Campbell WW, Crim MC, Dallal GE, Young VR, Evans WJ: Increased protein requirements in the elderly: new data and retrospective reassessments. Am J Clin Nutr 60:167–175, 1994.
9. Campbell WW, Crim MC, Young VR, Evans WJ: Increased energy requirements and body composition changes with resistance training in older adults. Am J Clin Nutr 60:167–175, 1994.
10. Campbell WW, Crim MC, Young VR, Joseph LJ, Evans WJ: Effects of resistance training and dietary protein intake on protein metabolism in older adults. Am J Physiol 268:E1143–E1153, 1995.
11. Campbell WW, Evans WJ: Protein requirements of elderly people. Eur J Clin Nutr 50:S180–S185, 1996.
12. Campbell WW, Kruskall LJ, Evans WJ: Lower body versus whole body resistive exercise training and energy requirements of older men and women. Metabolism 51:989–997, 2002.
13. Campbell WW, Trappe TA, Wolfe RR, Evans WJ: The recommended dietary allowance for protein may not be adequate for older people to maintain skeletal muscle. J Gerontol A Biol Sci Med Sci 56:M373–M380, 2001.
14. Cannon JG, Fiatarone MA, Fielding RA, Evans WJ: Aging and stress-induced changes in complement activation and neutrophil mobilization. J Appl Physiol 76:167–175, 1994.
15. Cannon JG, Fielding RA, Fiatarone MA, Orencole SF, Dinarello CA, Evans WJ: Interleukin-1$\beta$ in human skeletal muscle following exercise. Am J Physiol 257:R451–R455, 1989.
16. Cannon JG, Meydani SN, Fielding RA, Fiatarone MA, Meydani M, Farhangmehr M, Orencole SF, Blumberg JB, Evans WJ: Acute phase response in exercise. II. Associations between vitamin E, cytokines, and muscle proteolysis. Am J Physiol 260:R1235–R1240, 1991.
17. Cannon JG, Orencole SF, Fielding RA, Meydani M, Meydani SN, Fiatarone MA, Blumberg JB, Evans WJ: Acute phase response in exercise: interaction of age and vitamin E on neutrophils and muscle enzyme release. Am J Physiol 259:R1214–R1219, 1990.
18. Carlson BM, Faulkner JA: The regeneration of skeletal muscle fibers following injury: a review. Med Sci Sports Exerc 15:187–198, 1983.
19. Castaneda C, Charnley JM, Evans WJ, Crim M: Elderly women accommodate to a low-protein diet with losses of body cell mass, muscle function, and immune response. Am J Clin Nutr 62:30–39, 1995.
20. Castaneda C, Dolnikowski GG, Dallal GE, Evans WJ, Crim MC: Protein turnover and energy metabolism of elderly women fed a low-protein diet. Am J Clin Nutr 62:40–48, 1995.
21. Castellino P, Luzi L, Simonson DC, Haymond M, DeFronzo RA: Effect of insulin and plasma amino acid concentrations on leucine metabolism in man. J Clin Invest 80:1784–1793, 1987.
22. Charette SL, McEvoy L, Pyka G, Snow-Harter C, Guido D, Wiswell RA, Marcus R: Muscle hypertrophy response to resistance training in older women. J Appl Physiol 70:1912–1916, 1991.
23. Chesley A, MacDougall JD, Tarnopolsky MA, Atkinson SA, Smith K: Changes in human muscle protein synthesis after resistance exercise. J Appl Physiol 73:1383–1388, 1992.
24. Colliander EB, Tesch PA: Effects of eccentric and concentric muscle actions in resistance training. Acta Physiol Scand 140:31–39, 1990.
25. Colliander EB, Tesch PA: Responses to eccentric and concentric

resistance training in females and males. Acta Physiol Scand 141:149–156, 1990.
26. Council NR: "Recommended Dietary Allowances." Washington D. C.: National Academy Press, 1989.
27. Dela F, Mikines KJ, Tronier BA, Galbo H: Diminished arginine-stimulated insulin secretion in trained men. J Appl Physiol 69:261–267, 1990.
28. Engdahl JH, Veldhuis JD, Farrell PA: Altered pulsatile insulin secretion associated with endurance training. J Appl Physiol 79: 1977–1985, 1995.
29. Evans W: Functional and metabolic consequences of sarcopenia. J Nutr 127:998S–1003S, 1997.
30. Evans W: What is sarcopenia? J Gerontol 50A(Special Issue):5–8, 1995.
31. Evans WJ, Cannon JG: The metabolic effects of exercise-induced muscle damage. In Holloszy JO (ed): "Exercise and Sport Sciences Reviews." Baltimore: Williams & Wilkins, pp 99–126, 1991.
32. Fiatarone MA, Marks EC, Ryan ND, Meredith CN, Lipsitz LA, Evans WJ: High-intensity strength training in nonagenarians. Effects on skeletal muscle. JAMA 263:3029–3034, 1990.
33. Fiatarone MA, O'Neill EF, Ryan ND, Clements KM, Solares GR, Nelson ME, Roberts SB, Kehayias JJ, Lipsitz LA, Evans WJ: Exercise training and nutritional supplementation for physical frailty in very elderly people. N Engl J Med 330:1769–1775, 1994.
34. Fiatarone Singh MA, Bernstein M, Ryan AD, O'Neill FF, Clements KM, Evans WJ: The effect of oral nutritional supplements on habitual dietary quality and quantity in frail elders. J Nutr Health Aging 4:5–12, 2000.
35. Fielding RA, Manfredi TJ, Ding W, Fiatarone MA, Evans WJ, Cannon JG: Acute phase response in exercise. III. Neutrophil and IL-1b accumulation in skeletal muscle. Am J Physiol 265:R166–R172, 1993.
36. Fluckey JD, Jefferson LS, Vary TC, Farrell PA: Augmented insulin action on rates of protein synthesis following resistance exercise in rats. Am J Physiol 270:E313–E319, 1996.
37. Fluckey JD, Kraemer WJ, Farrell PA: Pancreatic islet insulin secretion is increased after resistance exercise in rats. J Appl Physiol 79:1100–1105, 1995.
38. Flynn A, Proud CG: The role of eIF-4 in cell proliferation. Cancer Surv 27:293–310, 1996.
39. Frontera WR, Meredith CN, O'Reilly KP, Evans WJ: Strength training and determinants of VO2 max in older men. J Appl Physiol 68:329–333, 1990.
40. Frontera WR, Meredith CN, O'Reilly KP, Knuttgen HG, Evans WJ: Strength conditioning in older men: skeletal muscle hypertrophy and improved function. J Appl Physiol 64:1038–1044, 1988.
41. Goldberg AL, Baracos V, Rodemann, Waxman L, Dinarello C: Control of protein degradation in muscle by prostaglandins, Ca2+, and leukocytic program (interleukin 1). Fed Proc 43:1301–1306, 1984.
42. Goldberg AL, Kettelhut IC, Furuno K, Fagan JM, Baracos V: Activation of protein breakdown and prostaglandin E2 production in rat skeletal muscle in fever is signaled by a macrophage product distinct from interleukin 1 or other known monokines. J Clin Invest 81:1378–1383, 1988.
43. Graves LM, Bornfeldt KE, Argast GM, Krebs EG, Kong X, Lin TA, Lawrence JC: cAMP- and rapamycin-sensitive regulation of the association of eukaryotic initiation factor 4E and the translational regulator PHAS-I in aortic smooth muscle cells. Proc Natl Acad Sci USA 92:7222–7226, 1995.
44. Hickey T, Sharpe PA, Wolf FM, Robins LS, Wagner MB, Harik W: Exercise participation in a frail elderly population. J Health Care Poor Underserved 7:219–231, 1996.
45. Jacob R, Hu X, Niederstock D, Hasan S, NcNulty PH, Sherwin RS, Young LH: IGF-I stimulation of muscle protein synthesis in the awake rat: permissive role of insulin and amino acids. Am J Physiol 270:E60–E66, 1996.
46. Jurasinski CV, Vary TC: Insulin-like growth factor I accelerates protein synthesis in skeletal muscle during sepsis. Am J Physiol 269:E977–E981, 1995.
47. Kelly FJ, Jefferson LS: Control of peptide-chain initiation in rat skeletal muscle. Development of methods for preparation of native ribosomal subunits and analysis of the effect of insulin on formation of 40S initiation complexes. J Biol Chem 260:6677–6683, 1985.
48. King DD, Staten MA, Kohrt WM, Dsalsky GP, Elahi D, Holloszy JO: Insulin secretory capacity in endurance-trained and untrained young men. Am J Physiol 259:E155–E161, 1990.
49. Kirwan JP, Hickner RC, Yarasheski KE, Kohrt WM, Wiethop BV, Holloszy JO: Eccentric exercise induces transient insulin resistance in healthy individuals. J Appl Physiol 70:2197–2202, 1992.
50. Krishnan RK, Hernandez JM, Williamson DL, O'Gorman DJ, Evans WJ, Kirwan JP: Age-related differences in the pancreatic beta-cell response to hyperglycemia after eccentric exercise. Am J Physiol 275:E463–E470, 1998.
51. Kruskall LJ, Campbell WW, Evans WJ: The Atwater energy equivalents overestimate metabolizable energy intake in older humans: results from a 96-day strictly controlled feeding study. J Nutr 133:2581–2584, 2003.
52. Kutner NG, Barnhart H, Wolf SL, McNeely E, Xu T: Self-report benefits of Tai Chi practice by older adults. J Gerontol B Psychol Sci Soc Sci 52:P242–P246, 1997.
53. Larsson L: Physical training effects on muscle morphology in sedentary males as different ages. Med Sci Sports Exercise 14: 203–206, 1982.
54. McDonagh MJN, Davies CTM: Adaptive response of mammalian skeletal muscle to exercise with high loads. Eur J Appl Physiol 52:139–155, 1984.
55. Meredith CN, Frontera WR, Evans WJ: Body composition in elderly men: Effect of dietary modification during strength training. J Am Geriatr Soc 40:155–162, 1992.
56. Meredith CN, Zackin MJ, Frontera WR, Evans WJ: Dietary protein requirements and body protein metabolism in endurance-trained men. J Appl Physiol 66:2850–2856, 1989.
57. Nathan CF: Secretory products of macrophages. J Clin Invest 79:319–326, 1987.
58. Nelson ME, Fiatarone MA, Morganti CM, Trice I, Greenberg RA, Evans WJ: Effects of high-intensity strength training on multiple risk factors for osteoporotic fractures. JAMA 272:1909–1914, 1994.
59. O'Reilly KP, Warhol MJ, Fielding RA, Frontera WR, Meredith CN, Evans WJ: Eccentric exercise-induced muscle damage impairs muscle glycogen repletion. J Appl Physiol 63:252–256, 1987.
60. Province MA, Hadley CE, Hornbrook MC, Lipsitz LA, Miller JP, Mulrow CD, Ory MG, Sattin RW, Tinetti ME, Wolf SL: The

effects of exercise on falls in elderly patients: A preplanned meta-analysis of the FICSIT trials. JAMA 273:1341–1347, 1995.
61. Rannels DE, Pegg AE, Rannels SR, Jefferson LS: Effect of starvation on initiation of protein synthesis in skeletal muscle and heart. Am J Physiol E126–E133, 1978.
62. Roberts SB, Fuss P, Heyman MB, Evans WJ, Tsay R, Rasmussen H, Fiatarone M, Cortiella J, Dallal GE, Young VR: Impaired control of food intake and energy regulation in elderly men. JAMA 272:1601–1606, 1994.
63. Roberts SB, Young VR, Fuss P, Heyman MB, Fiatarone M, Dallal GE, Cortiella J, Evans WJ: What are the dietary energy needs of elderly adults? Int J Obes Related Metab Disord 16:969–976, 1992.
64. Russell-Jones DL, Umpleby AM, Hennessy TR, Bowes SB, Shojaee-Moradie F, Hopkins KD, Jackson NC, Kelly JM, Jones RH, Sonksen PH: Use of a leucine clamp to demonstrate that IGF-I actively stimulates protein synthesis in normal humans. Am J Physiol 267:E591–E598, 1994.
65. Singh MA, Ding W, Manfredi TJ, Solares GS, O'Neill EF, Clements KM, Ryan ND, Kehayias JJ, Fielding RA, Evans WJ: Insulin-like growth factor I in skeletal muscle after weight-lifting exercise in frail elders. Am J Physiol 277:E135–E143, 1999.
66. Strawford A, Barbieri T, Van Loan M, Parks E, Catlin D, Barton N, Neese R, Christiansen M, King J, Hellerstein MK: Resistance exercise and supraphysiologic androgen therapy in eugonadal men with HIV-related weight loss: a randomized controlled trial [see comments]. JAMA 281:1282–1290, 1999.
67. Tarnopolsky MA, Atkinson SA, MacDougall JD, Senor BB, Lemon PWR, Schwarcz H: Whole body leucine metabolism during and after resistance exercise in fed humans. Med Sci Sports Exerc 23:326–333, 1991.
68. Tessari P, Inchiostro S, Biolo G, Trevisan R, Fantin G, Marescotti MC, Lori E, Tiengo A, Crepaldi G: Differential effects of hyperinsulinemia and hyperaminoacidemia on leucine-carbon metabolism in vivo. J Clin Invest 79:1062–1069, 1987.
69. Trappe TA, Fluckey JD, White F, Lambert CP, Evans WJ: Skeletal muscle PGF(2)(alpha) and PGE(2) in response to eccentric resistance exercise: influence of ibuprofen acetaminophen. J Clin Endocrinol Metab 86:5067–5070, 2001.
70. Trappe TA, White F, Lambert CP, Cesar D, Hellerstein M, Evans WJ: Effect of ibuprofen and acetaminophen on postexercise muscle protein synthesis. Am J Physiol Endocrinol Metab 282:E551–E556, 2002.
71. Tzankoff SP, Norris AH: Longitudinal changes in basal metabolic rate in man. J Appl Physiol 33:536–539, 1978.
72. Vellas BJ, Hunt WC, Romero LJ, Koehler KM, Baumgartne RN, Garry PJ: Changes in nutritional status and patterns of morbidity among free-living elderly persons: a 10-year longitudinal study. Nutrition 13:515–519, 1997.
73. Volpi E, Mittendorfer B, Rasmussen BB, Wolfe RR: The response of muscle protein anabolism to combined hyperaminoacidemia and glucose-induced hyperinsulinemia is impaired in the elderly. J Clin Endocrinol Metab 85:4481–4490, 2000.
74. Volpi E, Sheffield-Moore M, Rasmussen BB, Wolfe RR: Basal muscle amino acid kinetics and protein synthesis in healthy young and older men. JAMA 286:1206–1212, 2001.
75. Waterlow JC: Observations on the mechanisms of adaptation to low protein intakes. Lancet 23:1901–1911, 1968.
76. Welle S, Thornton C, Statt M: Myofribrillar protein synthesis in young and old human subjects after three months of resistance training. Am J Physiol 268:E422–E427, 1995.
77. Whipple RH, Wolfson LI, Amerman PM: The relationship of knee and ankle weakness to falls in nursing home residents. J Am Geriatr Soc 35:13–20, 1987.
78. White CW, Ghezzi P, McMahon S, Dinarello CA, Repine JE: Cytokines increase rat lung antioxidant enzymes during exposure to hyperoxia. J Appl Physiol 66:1003–1007, 1989.
79. Wolf SL, Barnhart HX, Kutner NG, McNeely E, Coogler C, Xu T: Reducing frailty and falls in older persons: an investigation of Tai Chi and computerized balance training. Atlanta FICSIT Group. Frailty and Injuries: Cooperative Studies of Intervention Techniques [see comments]. J Am Geriatr Soc 44:489–497, 1996.
80. Wolfson L, Whipple R, Judge J, Amerman P, Derby C, King M: Training balance and strength in the elderly to improve function. J Am Geriatr Soc 41:341–343, 1993.
81. Yamada S, Buffinger N, Dimario J, Strohman RC: Fibroblast growth factor is stored in fiber extracellular matrix and plays a role in regulating muscle hypertrophy. Med Sci Sports Exerc 21:S173–S180, 1989.
82. Yan Z, Biggs RB, Booth WF: Insulin-like growth factor immunoreactivity increases in muscle after acute eccentric contractions. J Appl Physiol 74:410–414, 1993.
83. Yarasheski KE, Zachwieja JJ, Bier DM: Acute effects of resistance exercise on muscle protein synthesis rate in young and elderly men and women. Am J Physiol 265:E210–E214, 1993.

*Received June 30, 2004.*