Muscle Protein Metabolism and the Sarcopenia of Aging

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Loss of muscle mass, strength, and oxidative capacity accompanies normal aging in humans. The mechanisms responsible for these changes remain to be clearly defined. Muscle protein mass and function depend on protein turnover. Synthesis rate of the major muscle contractile protein, myosin heavy chain (MHC), and transcript levels of fast MHC isoforms decrease in association with strength reductions, while mitochondrial protein synthesis rate declines in parallel with activities of mitochondrial enzymes and maximal oxidative capacity (VO\textsubscript{2max}). Resistance exercise training increases the synthesis rate of MHC and transcript levels of the slow MHC isoform in older humans, along with increasing muscle strength. The relationship between the synthesis of muscle proteins, and muscle size and function, with aging and exercise training are discussed in this review.

Innovations in technology, medicine, and nutrition have contributed to a doubling of the average human life span in the last century. Life expectancy in the U.S. is now 73 and 79 years for men and women, respectively, and is projected to reach 80 (men) and 84 (women) years by 2050 (31). Despite living longer, the quality of life tends to decline with age due the onset of many age-related pathologies such as cardiovascular disease, bone fractures, diabetes, immobility, and dementia. Physical and metabolic deterioration can be partly ascribed to the age-related loss of skeletal muscle mass and function, or “sarcopenia of aging.” The size and strength of skeletal muscles are critical determinants for the level of physical functioning (movement, stability, daily living skills; 24). Aside from locomotion, skeletal muscles are also major metabolic organs, with major roles in glucose, fatty acid, and amino acid metabolism.

The goal of this review is to briefly summarize what is currently known about the loss of muscle mass, strength, and oxidative function with aging in humans. Emphasis is given to what is known about muscle protein metabolism and how it relates to sarcopenia. The effect of exercise training on protein metabolism and muscle function is also considered as an intervention to offset the effects of aging. Physical exercise is the only non-pharmacological treatment for sarcopenia. The effectiveness of hormone replacement has recently been reviewed elsewhere (6).
Loss of Muscle Mass and Strength With Aging

There is clear evidence that aging is associated with a loss of fat-free body mass, particularly muscle mass (18, 19, 22). In young healthy subjects, muscle comprises nearly 60% of the fat-free mass and over half of the total body protein, but in elderly subjects muscle accounts for only 45% of fat-free mass and less than half of body protein, as a result of muscle loss (22). The detectability of sarcopenia may vary with the methods used. Proctor et al. (22) demonstrated that muscle mass, calculated from urinary creatinine excretion, declined about 7% per decade from young (~24 years) to middle (48 years) to old age (70 years), but this change was underestimated by dual-energy X-ray absorptiometry because of changes in body water content.

Muscle strength is closely associated with muscle size, so aging is accompanied by reduced muscle strength in both the legs (2, 15, 18, 19, 32) and arms (2, 15, 19). The loss of muscle strength contributes to the eventual inability of elderly individuals to carry out tasks of daily living and is associated with increased risk of falls and fractures (24). In both the arms (15, 19) and legs (15, 18), strength loss often is shown to exceed the loss of muscle size, resulting in lower specific force capacity (force generated per unit of muscle mass). In some studies, though,

![Figure 1](image_url)

**Figure 1** — Changes in leg muscle strength and muscle quality with aging. Absolute strength (upper panel) was lower in middle (52 years), and old (72 years) men and women versus young (24 years). After normalization for whole body muscle mass, as determined from urinary creatinine excretion, there was still a decrease in muscle quality with aging in men but not in women (lower panel). *Less than young; †Less than middle; §Less than men of the same age, p < .05. Adopted from (2).
normalization of muscle strength for muscle size has eliminated the strength deficit in aged muscles (11, 32). Some of these discrepancies may be due to differences in the muscle groups examined, the physical activity history of the subjects, the methods of testing, or other factors. There may also be gender differences in the age-effect on muscle quality, as shown in Figure 1. When leg extensor strength was normalized for metabolically active, whole-body muscle tissue (based on 24-hour urinary creatinine excretion while on a meat-free diet), an age-related decline in muscle quality was evident in men but not in women. In contrast, studies of isolated single muscle fibers suggest that contractile speed and force declines with aging in both men and women (11, 16). These measurements are made independent of the nervous system, hormones, and prevailing metabolite concentrations, and therefore suggest that the function of proteins in the contractile apparatus is somehow altered during aging.

The mass and function of muscle proteins depend on protein turnover. Net anabolism or catabolism of a tissue is determined from the balance between the rates of protein synthesis and protein breakdown. Protein turnover is also important for maintaining cellular integrity and function by continuously replacing damaged proteins with newly synthesized proteins. Changes in muscle size and strength may be due in part to lower protein turnover in aging muscles. The synthetic rate of mixed muscle proteins (MMP), an average of all muscle proteins, is lower in older (age 65–84 years) than younger (20–35 years) subjects (2, 12, 39, 40). Likewise, synthesis rates of the mixed myofibrillar component of muscle, containing mostly contractile proteins (35), as well as a key individual contractile protein, myosin heavy chain (MHC; 2, 12), are significantly lower in older subjects. Of note is that synthesis rate of MHC, but not MMP, is positively correlated with muscle mass and strength (2). This observation is not surprising, since measurements of MMP synthesis include many proteins that may not contribute directly to muscle strength or may not be affected by aging. In the study by Balagopal et al. (2), for example, synthesis rates of sarcoplasmic proteins in muscle were unchanged or slightly higher in older subjects. Results from a small number of subjects suggests that synthesis rate of another contractile protein, actin, is also unaltered with aging (12). Recent work

![Figure 2 — Changes in mRNA levels of myosin heavy chain (MHC) isoforms in human muscle with aging. Transcript levels were measured by Real-Time PCR and expressed in arbitrary units (A.U.) after normalization to 28S RNA. Y, M, O are young, middle, and old subjects, respectively (subjects are the same as in Figure 1.) *Less than young; †Less than middle, p < .05. Adopted from (3).](image-url)
indicates that aging is associated with a decrease in transcript abundance of MHC isoforms IIa and IIx (Figure 2A; 3). These changes may explain the decrease in MHC synthesis (2) as well as the preferential atrophy of type II muscle fibers reported to occur with aging (17).

It is difficult to determine how much of the reduction in muscle size and strength is due to physical inactivity versus aging per se. It is clear that maintaining a pattern of regular vigorous exercise into old age is helpful for maintaining muscle mass and strength (15). Perhaps more important from the treatment perspective are the numerous demonstrations that resistance training can be successfully performed even by frail elderly people and that such a program can result in gains in strength, muscle mass, and daily function (2, 12, 28, 38). The stimulation of protein synthesis is thought to contribute to these positive changes. Welie et al. (37) found that myofibrillar protein synthesis rates were increased in older subjects after 1 week of resistance training. Surprisingly, though, these investigators did not detect an increase following 3 months of training (36). In contrast, Yarasheski and colleagues...
showed that resistance training programs lasting 2–12 weeks result in higher synthesis rates of MMP in both young and old subjects. They also demonstrated that 2 weeks of vigorous training produced an approximate doubling in the synthesis rate of myosin heavy chain in both young and old participants (12). The discrepancies between these studies may be related to the various mixed muscle protein components that were measured. MHC synthesis is also increased by 3 months of resistance training in both middle-aged and older men and women (3; Figure 3A). This training program also resulted in increased mRNA levels of the slow (type I) MHC isoform, with concomitant decreases in the fast MHC isoforms IIa and IIx (Figure 3B). This raises the possibility that protein expression of the different isoforms may also be altered, but the effect of resistance exercise on protein synthesis rates of individual MHC isoforms has not been reported. The increase in contractile protein turnover due to resistance exercise may contribute to increased muscle quality (27). The recent finding that resistance training can increase the power of contraction in both type I and type II muscle fibers in older men is consistent with this possibility (28).

**Muscle Oxidative Capacity**

Maximal aerobic capacity (VO$_{2 \text{max}}$) during cycling or treadmill exercise declines with aging, even in highly trained athletes (21, 25, 26, 29). Reductions in muscle mass and muscle blood supply contribute to the decline in VO$_{2 \text{max}}$ (23, 26), but there is also evidence indicating that oxidative capacity of muscle is reduced with aging. Mitochondrial volume density, respiration capacity, and oxidative enzyme activities have been reported to be reduced in aging leg muscles (8, 13, 20, 25, 30). Age-related impairments in mitochondrial metabolism have also been detected in vivo with magnetic resonance spectroscopic techniques (7, 10).

There are, however, reports in which these same variables were unaffected by aging (5, 13, 14). Subject selection may have much to do with the discrepant results
among studies, since physical activity patterns of the subjects may not have been considered or described in sufficient detail (7, 10). Other studies may be confounded by the use of muscle samples from trauma or orthopedic surgery patients (5, 30). The choice of muscles examined is also important as illustrated by the study of Houmard et al. (13) in which citrate synthase activity declined significantly with age in the gastrocnemius but not in the vastus lateralis. There were no changes in muscle fiber type in either muscle, so whether these results reflect different responses to aging per se, or arise from different patterns of muscle use remains to be determined.

The reduction in muscle oxidative function appears related to a lower rate of remodeling of mitochondrial proteins. Rooyackers et al. (25) have demonstrated that the synthesis rate of mitochondrial proteins is reduced with aging in sedentary individuals. The decline in mitochondrial protein synthesis was evident by middle age (~53 years) and was closely related to reductions in mitochondrial enzyme activities and $\text{VO}_{2\text{max}}$.

The mechanisms underlying the reduction in mitochondrial protein synthesis are not completely understood. Oxidative damage to mitochondrial DNA (mtDNA) and proteins increases with aging in post-mitotic tissues, including muscle, and this has been proposed to be potentially limiting for mitochondrial protein expression and function (20, 33). Oxidative damage could explain the recent observation that mtDNA abundance is reduced in hindlimb muscles of aging rats (4; Figure 4). Among the 37 proteins encoded by mtDNA are 13 peptides required for assembly of the electron transport chain. Although the reduced number of mtDNA templates could limit gene expression, abundance of mitochondrially-encoded mRNAs (cytochrome c oxidase subunits I and III) was not reduced to the same extent as mtDNA in muscles of old rats (4). This raises the possibility that either the transcription rate or mRNA stability is increased in aging rat muscle, perhaps as a compensatory mechanism. Levels of mtDNA in aging human muscle have not been reported. However, the abundance of several gene transcripts encoding mitochondrial proteins was recently shown to be reduced in vastus lateralis muscle of old men (66–77 years) compared to young (21–24 years) men (34). Thus, lower gene expression could be one of the causes underlying the reduction in mitochondrial protein synthesis rate in aging humans.

Just as resistance training can effectively improve muscle size and strength, aging muscle retains the ability to respond to aerobic exercise by increasing oxidative capacity. $\text{VO}_{2\text{max}}$ and mitochondrial enzyme activities are increased following endurance training programs in older adults (9). Mitochondrial protein synthesis and gene transcript levels may also be increased by aerobic exercise, but these parameters have yet to be reported in human studies. The benefits of aerobic training include increased endurance, insulin sensitivity, and cardiovascular health and reduced adiposity (1). However, aerobic exercise is not sufficient to prevent loss of muscle strength and size (1, 15), so current recommendations are for older adults to engage in both aerobic and resistance types of exercise to improve overall health (1).

**Conclusion**

There is growing evidence that reduced synthesis rates of specific muscle proteins like myosin heavy chain or mitochondrial proteins contribute to the age-related declines in muscle size and function. Resistance training performed by older adults results in increased synthesis of myosin heavy chain, which may contribute to
improvements in muscle strength. The effects of endurance training on the synthesis rates of specific muscle proteins in older individuals has not been reported. Additionally, more information is needed on how muscle protein synthesis is regulated by transcription and translation in the context of aging and exercise.

References


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