Age-Related Sarcopenia in Humans Is Associated with Reduced Synthetic Rates of Specific Muscle Proteins\textsuperscript{1,2}

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ABSTRACT Sarcopenia of aging is not explained entirely on the basis of age-associated reduced physical activity. Progressive neuromuscular changes and diminishing anabolic hormone levels are thought to contribute to the pathogenesis of sarcopenia. Decline in muscle mass indicates a decline in muscle protein content. Recent studies demonstrated an age-related decline in synthesis rate of mixed muscle proteins, myosin heavy chain and mitochondrial protein. Reductions in myosin heavy chain and mitochondrial protein synthesis rates have been correlated with age-associated decrements in muscle strength and aerobic exercise tolerance, respectively. These changes have been reported as early as 50 y of age and are related to the decline in insulin-like growth factor (IGF)-I, testosterone and dehydroepiandrosterone (DHEA)-sulfate. The declining ability to remodel these important muscle proteins may therefore play a role in the development of muscle wasting, metabolic abnormalities and impaired physical functioning seen in old age. J. Nutr. 128: 351S–355S, 1998.

KEY WORDS: • muscle protein synthesis • anabolic hormones • muscle mass • humans

Normal aging in humans is associated with declines in skeletal muscle mass and strength and increased muscle fatigability (sarcopenia). These changes, together with the age-associated decline in whole-body exercise tolerance ($V_{O_{2max}}$), can substantially reduce the amount and intensity of physical activities performed by elderly (>60 y) men and women (Evans 1995). Moreover, the effects of reduced muscle mass and physical activity levels with advancing age substantially reduce daily energy expenditure among older people (Goran and Poehlman 1992). Decreased daily energy expenditure is thought to be involved in the age-associated accumulation of visceral and total body fat, which in turn is a risk factor for the development of type II diabetes (Holloszy and Kohrt 1995). These physical and metabolic impairments associated with sarcopenia are reducing the quality of life for a rapidly expanding older population (Dutta and Hadley 1995).

There is accumulating evidence that physically active older people maintain higher levels of muscle mass and function, and develop less central adiposity and insulin resistance with aging than their sedentary peers (Holloszy and Kohrt 1995, Tseng et al. 1995). However, even highly trained (10–20 y) older athletes do not maintain muscle function or body composition at the levels seen in physically active young subjects (Klitgaard et al. 1990). These findings suggest that there are some irreversible physiologic changes associated with aging per se that lead to sarcopenia in older humans. These age-dependent alterations are thought to result from diminished levels of anabolic hormones and progressive neuromuscular alterations (Lexell et al. 1988, Rudman et al. 1991). However, there is also a general decline in muscle protein turnover with advancing age (Nair 1995). This review describes the age-associated changes in human skeletal muscle mass and function, and the related alterations in synthesis rates of specific muscle proteins. The potential effects of anabolic hormone replacement on muscle mass, function and protein synthesis in the elderly are also discussed.

CHANGES IN SKELETAL MUSCLE MASS AND FUNCTION WITH AGING

Aging is associated with reductions in fat-free mass (FFM),\textsuperscript{4} total body potassium and urinary creatinine excretion, each indicative of a declining skeletal muscle mass (Fleg and Lakatta 1988, Flynn et al. 1992). The normal rate of muscle loss with advancing age is poorly defined, but there is a more rapid loss after 50 y of age. Women appear to lose less total muscle as they age than do men, but the relative (%) reductions in

\textsuperscript{1} Presented as part of the symposium “The Roles of Nutrition, Development and Hormone Sensitivity in the Regulation of Protein Metabolism” given at the Experimental Biology 97 meeting, April 7, 1997, New Orleans, LA. This symposium was sponsored by the American Society for Nutritional Sciences and supported in part by educational grants from Diagnostic Systems Laboratories, Inc., Mead Johnson Nutritional Group, Pig Improvement Company USA, Ross Products Division, Abbott Laboratories, Wyeth-Ayerst Laboratories and Zinpro. Guest editor for the symposium publication was Teresa A. Davis, Baylor College of Medicine, Houston, TX 77030.

\textsuperscript{2} Supported by Public Health Service grant RO1-AG-09531.

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\textsuperscript{4} Abbreviations used: DHEA, dehydroepiandrosterone; FFM, fat-free mass; GH, growth hormone; IGF, insulin-like growth factor.
Healthy men and women (estimated from Fleg and Lakatta 1988). The risk of falling.

The loss of skeletal muscle mass is substantial, amounting to 35–40% between 20 and 80 y of age (Evans 1995, Fleg and Lakatta 1988). Muscle loss also accounts for most of the loss of body protein with aging (Cohn et al. 1980). The muscle:body weight ratio declines progressively with age (Fig. 1). These losses of muscle mass and protein with advancing age do not typically result in weight loss because there is a corresponding accumulation of body fat.

The decline of muscle mass with aging results in large part from the loss of individual muscle fibers. Additionally, there seems to be a preferential atrophy of fast-twitch (type II) fibers. These changes have been shown by counting individual fibers in whole-muscle cross-sections from cadavers of various ages (Lexell et al. 1988). The proportions (%) of histochemical type I (slow-twitch) and type II fibers are relatively stable across age, suggesting that roughly equal numbers of slow- and fast-twitch fibers are lost. However, as a result of the greater atrophy and reduced reinnervation capacity of fast-twitch fibers in older muscle tissue, there is likely to be a proportionally greater loss of type II myosin from skeletal muscles with advancing age. These changes, together with increases in intramuscular fat and connective tissue (Frontera et al. 1991, Overend et al. 1992), reduce the contractile tissue volume (particularly type II myosin isoforms) available for the important locomotive and metabolic functions of skeletal muscle.

Summary of muscle functional changes with aging. Muscular strength is typically maintained at peak levels until the fifth or sixth decade, after which accelerated losses occur (Hurley 1995). The age-associated reduction of quadriceps muscle strength is such that the average 80-γ-old is at or near the minimum level of strength required to rise from a chair (Reynolds and Garrett 1989). Leg muscle strength also appears to be related to maximum (Conley et al. 1995) and sustainable (Ades et al. 1996) walking speeds in ambulatory older populations. Declines in maximal muscle strength could result from the loss of muscle mass, reductions in the intrinsic contractile properties (i.e., specific force) of the remaining fibers or to a reduced ability to activate the muscle maximally. In the proximal limb muscles of humans (i.e., knee/elbow flexors and extensors), a major cause of age-associated maximal strength losses appears to be the reduced cross-sectional area of the active muscle tissue (Conley et al. 1995, Evans 1995). This is shown for the quadriceps muscle group in Figure 2. However, this is in apparent contrast with studies of small muscle groups in humans (Kallman et al. 1990) and findings in old mice and rats, in which precise estimates of limb muscle specific force are reduced by as much as 20% (Brooks and Faulkner 1994). Additional studies are required to resolve this somewhat confusing area.

Aging also reduces the peak forces that can be generated by muscles at fast contraction speeds and the speed at which the activated muscles can relax (Overend et al. 1992). These physiologic changes, which are possibly related to shifts in myosin isoform composition, have important implications for peak and sustainable power output capacities of skeletal muscle. The importance of understanding the mechanisms underlying these particular muscle properties is supported by the close association between age-related reductions in lower extremity power output and functional abilities such as maximal walking speed and stair climbing ability (Hurley 1995). This reduced capacity for rapid force generation might also limit the ability to respond quickly to a loss of balance and increase the risk of falling.

AGING AND MUSCLE PROTEIN DYNAMICS

After excluding water, protein is the major component of skeletal muscle, accounting for ~20% of muscle weight. Therefore, changes in muscle mass should reflect an imbalance between removal of old and damaged muscle proteins (breakdown) and synthesis of new ones (Nair 1995). To understand the biochemical basis for sarcopenia, investigators have compared whole-body protein synthesis and breakdown rates in subjects of different ages. However, whole-body protein turnover measurements are inappropriate for determining small changes in muscle protein synthesis and breakdown because muscle contributes <30% to the whole-body protein turnover rate (Nair 1995). However, fractional synthesis rates of mixed or myofibrillar protein from muscle biopsy samples are reduced in older humans (Welle et al. 1993, Yarasheiski et al. 1993). Because there is no conclusive evidence of accelerated muscle protein breakdown in healthy older people (Nair 1995), these findings suggest that aging is associated with a reduced capacity of skeletal muscle to synthesize new proteins. This imbalance ultimately leads to reduced muscle mass and protein content.

The synthesis rate of mixed muscle protein represents an average value of all the individual proteins found within the muscle cell (mitochondrial, myofibrillar, sarcoplasmic and intracellular matrix proteins). These different protein fractions and their individual component proteins have specific functions and reportedly different synthesis rates (Balagopal et al. 1997). Therefore, a better understanding of the mechanisms leading to reduced muscle mass and function in old age is likely to be obtained by examining synthetic rates of these individual muscle proteins. This approach has been difficult in humans due to the need for large quantities of muscle. However, the techniques recently developed in our laboratory for purifying individual muscle proteins and measuring their isotopic enrichment have enabled such investigations to be initiated (Balagopal et al. 1997, Rooyackers et al. 1996). Preliminary studies have revealed that the synthesis rate of myosin heavy chain, a major structural protein that is responsible together with actin for ATP hydrolysis (ATPase activity), is significantly reduced in middle-aged (31%) and older (44%) men and women (Balagopal et al. 1997).

Protein turnover is not only critical for maintaining the integrity of structural and contractile proteins such as myosin, but is also necessary for maintaining other functional units such as enzymes. Rooyackers et al. (1996) recently reported a pronounced decline (40%) in mitochondrial protein synthesis.
rates of middle-aged (54 ± 1 y) subjects, but no further decrease in seven elderly (73 ± 2 y) subjects. This finding, which is shown in Figure 3, is intriguing because mitochondrial enzyme activities typically continue to decline beyond middle age. The reduced enzyme activities in old age could be explained by a reduced mitochondrial protein synthesis, possibly resulting from an increase in mitochondrial DNA mutations with aging. These findings are significant not only for age-related changes in muscular endurance and fatigability, but also for ATP requirements associated with the synthesis of other muscle proteins.

**HORMONAL CHANGES AND THEIR RELATIONSHIP TO SARCOPENIA**

Normal aging results in decreased circulating levels of several anabolic hormones that may contribute to the changes in muscle mass and function seen in older people (Tenover 1992). The major anabolic hormone changes that occur with advancing age are highlighted in Table 1.

Progressive declines in growth hormone (GH) secretion and plasma insulin-like growth factor (IGF)-I levels with advancing age have been suggested as possible mechanisms for the body composition changes with aging. In support of this hypothesis, Rudman et al. (1991) reported that older (>61 y) men who received GH injections for 18 months increased their FFM by 6% while decreasing fat mass by 15%. Direct evidence of muscle size increases with GH administration has been reported recently in two studies of healthy older men and women (Butterfield et al. 1997, Welle et al. 1996). However, the findings of these two studies differed with respect to muscle protein synthesis. Butterfield et al. (1997) reported a significant increase in mixed muscle protein synthesis with GH treatment, whereas Welle et al. (1996) failed to show an increase in myofibrillar protein synthesis. The exact reasons for this discrepancy are unclear. However, it is possible that GH-induced protein accretion occurs within specific proteins and may not be reflected in measurements of synthetic rates of mixed muscle proteins.

Thus, additional study of specific muscle proteins should prove helpful in determining the mechanistic role that diminished GH secretion plays in the body composition and functional changes that occur with advancing age.

Growth hormone exposure invariably leads to increases in the levels of IGF-I. IGF-I has anabolic properties and is reported to preferentially stimulate muscle protein synthesis (Fryburg et al. 1995) when administered locally. The mechanism and role of IGF-I (free vs. total) and the importance of individual binding proteins in sarcopenia remain to be established.

Although age-related osteoporosis and sarcopenia have been associated with a decline in testosterone levels in men, the effects of testosterone replacement on muscle mass, strength and metabolism in older men are poorly defined. For example, Tenover (1992) administered testosterone intramuscularly to older men age 57–76 y for 3 mo and demonstrated an increase in FFM, but no change in grip strength, whereas Morley et al. (1993) found exactly the opposite results in hypogonadal males. Urban et al. (1995) recently reported increased muscle strength and mixed muscle protein synthesis after testosterone administration in a small group of elderly men. Therefore, the effects of testosterone on age-related sarcopenia remain to be clearly defined. It is also unclear what effect testosterone replacement might have on prostate cancer risk.

The decline in dehydroepiandrosterone (DHEA) with aging coincides with the development of other age-related changes including sarcopenia and related metabolic disorders. Although several studies have failed to document physiologic effects in healthy young individuals, administration of DHEA seems to work more effectively in older men and women (Yen et al. 1995). In the studies on older subjects, DHEA administration increased DHEA blood levels and increased biologically active IGF-I (Yen et al. 1995), which has been shown to stimulate muscle protein synthesis in humans (Fryburg et al. 1995). However, the number of older subjects studied to date is rather small, and the mechanism underlying DHEA’s effects on muscle metabolism remains unclear.
Long-term controlled studies are lacking to determine the potential side effects vs. benefits of anabolic hormone administration in the elderly population. There is also a need to assess effects on synthesis rates of different muscle proteins (with different metabolic functions). It is not clear whether the increase in muscle mass by hormone supplementation is as efficient metabolically as muscle mass developed through exercise.

CONCLUSIONS

Age-related sarcopenia is a major public health problem in the rapidly expanding elderly population of our society. It is unclear if there are any reversible components in this aging problem. A better understanding of the biochemical basis and pathophysiology of sarcopenia is the crucial first step toward developing rational therapeutic or preventative measures to address this problem. Declining physical activities and lifestyles may play an important role in the pathogenesis of sarcopenia. Aging is also associated with declines in the levels and actions of many anabolic hormones and with reduced synthetic rates of key contractile (myosin heavy chain) and metabolic (mitochondrial) proteins. Future research is required to understand whether the replacement of hormones such as DHEA and testosterone will provide benefits that sufficiently exceed the potential risks. Such therapeutic trials should adopt a mechanistic approach, with careful attention focused on the benefit-risk ratio.

TABLE 1

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Relative change</th>
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<tr>
<td>Insulin Levels</td>
<td>↑ (+)</td>
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<tr>
<td>Sensitivity*</td>
<td>↓</td>
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<tr>
<td>IGF-1</td>
<td>↓</td>
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<tr>
<td>Growth hormone</td>
<td></td>
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<td>Testosterone (biologically active)</td>
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<td>DHEA-S</td>
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* May be related to fat distribution.
\(^1\) IGF, insulin growth factor; DHEA, dehydroepiandrosterone.

FIGURE 3  Age-associated changes in muscle mitochondrial oxidative capacity and fractional protein synthesis. Cytochrome c oxidase decreased progressively with age, whereas mitochondrial synthesis declined by middle age and showed no further decline in old age. Adapted from Rooyackers et al. (1996).

LITERATURE CITED

Kallman, D., Plato, C. & Tobin, J. (1990) The role of muscle loss in the age-


