Endocrine, *vol. 7, no. 1, 57–60, August 1997* 0969-711X/97/7:57-60/$9.00

Sarcopenia and Hormonal Changes

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Introduction

Sarcopenia is a major determinant to age-related disabilities and is characterized by a decline in muscle mass, muscle weakness, and increased fatigability *(1)*. These changes, in combination with the declining endurance capacity of aging, results in the substantial physical disability of the elderly. The functional capacity of muscle depends upon both the quality and quantity of muscle protein, which accounts for approximately one-fifth of muscle weight. Besides the declining muscle mass, the decline in muscle quality is evident from the reduced muscle performance disproportionate to the loss of muscle mass *(2)*. The quality and quantity of muscle depends on the integrity of a continuous remodeling process that includes breakdown of old proteins and synthesis of new ones. The maintenance of muscle is determined by a delicate balance between these two processes, implying that a decline in muscle mass occurs when protein breakdown exceeds synthesis. Muscle strength depends not only on muscle mass but also on the ability of the tissue to generate adenosine triphosphate (ATP) from nutrient metabolism and the ability to hydrolyze ATP and make this chemical energy available for muscle contraction. The process also can be affected by abnormalities of the remodeling process of proteins (mostly enzymes) responsible for ATP production and hydrolysis. The pathophysiology of sarcopenia of aging is not known, but parallel decline of synthesis rates of muscle proteins and levels of various hormones with sarcopenia of aging and their interactions provide an alluring hypothesis.

Muscle Protein Dynamics

The biochemical basis for the declining muscle mass with normal aging is not well defined. Proteins, the major constituent of muscle (approx 20% of its wet weight) are crucial for all muscle functions. Therefore, a decline in muscle mass and function as observed in sarcopenia of normal aging indicate a reduction in muscle proteins. This decline in muscle mass occurs only when muscle protein synthesis is less than muscle protein breakdown. Although there is no conclusive evidence on protein breakdown in the elderly, recent reports suggest that the aging process is paralleled by a general decline in the capacity of muscle to synthesize proteins *(2–5)* and this decline occurs as early as middle age *(2,3)*.

Skeletal muscle protein is made up of several protein fractions, which in turn are made up of several individual proteins. These different protein fractions and individual proteins have specific functions and reportedly different synthesis rates *(2,4,6)* and changes occurring in a slow turning-over proteins (i.e., myosin) may be masked by the changes in a relatively fast turning-over protein fraction, i.e., mitochondrial protein. Therefore, a measure of synthesis rate of mixed muscle protein or myofibrillar protein fraction (representing average measures of several muscle proteins) is insufficient to understand the mechanism of sarcopenia.

Table 1 summarizes the results of various studies on the effect of age on muscle protein synthesis. Previous studies have reported the lower synthesis rate of both total mixed muscle *(5)* and myofibrillar *(4)* proteins in the elderly as compared to the young. Mixed muscle protein include several protein fractions, i.e., myofibrillar, sarcoplasmic, mitochondrial, and several other proteins. Myofibrillar protein represents several individual proteins such as myosin, actin, titin, tropomyosin, and C-protein. It is possible that a physiological intervention has a discordant effect on the synthesis rate of different protein fractions, as is evident from the results of resistance training reported by Yarasheski et al. *(5)* and Welle et al. *(7)*. It is also possible that some proteins (e.g., some mitochondrial protein) have a different response to an intervention or physiological changes (e.g., aging) than some other proteins (e.g., myosin or actin). Recent results from our laboratory have shown that the synthesis rates of specific protein fractions such as mitochondrial protein *(2)* and myosin heavy chain (MHC) *(3)* declined by middle age. However, sarcoplasmic protein (mainly involved in the anaerobic ATP utilization and many other enzyme actions) synthesis did not show any change with advancing age *(3)*. It has also been shown that

Received April 1, 1997; Accepted May 1,1997.

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Table 1
Muscle Protein Synthesis and Aging

	Young to middle	Middle to old	Young to old
Total mixed muscle protein (Yarashesky et al., ref. *5*)			↓ 38%
Myofibrillar protein (Welle et al., ref. *4*)			↓ 28%
Mitochondrial protein (Rooyackers et al., ref. *2*)	↓ 40%	↔	↓ 38%
Myosin heavy chain (Balagopal et al., ref. *3*)	↓ 31%	↓ 13%	↓ 41%
Sarcoplasmic protein (Balagopal et al., ref. *3*)	↔	↔	↔

aging is related to a decline in mitochondrial content (based on cytochrome C oxidase activity) in skeletal muscle *(2)*. Mitochondrial protein is mainly involved in the aerobic ATP production and MHC is responsible for the hydrolysis of ATP to ADP, which liberates mechanical energy for contractile function in the process. The decline in the mitochondrial protein synthesis rate likely explains the declining endurance capacity and increased fatigability in the elderly. But these do not entirely explain the age related decline in muscle mass. Although the above evidences provide direct support for the age-related mitochondrial damage, as initially proposed by Harman et al. *(8)*, other mechanisms for decreased synthesis of muscle protein are plausible. The hormonal changes occurring with aging may not affect only muscle protein dynamics but also its functions.

Hormones

A concomitant decrease in the efficacy of several endocrine systems with normal aging has been reported *(9)*. This includes declines in the levels of several hormones and tropic factors such as testosterone (T), estrogen, growth hormone (GH), insulin like growth factor-1 (IGF-1), and dehydroepinandrosterone (DHEA). It has been hypothesized that the reason for the reduction in the synthesis of proteins, muscle mass, and strength may be partly due to a decrease in the secretion of anabolic hormones such as GH, IGF-1, T, and DHEA. Recently, there has been considerable interest in the use of anabolic agents in the restoration of age-related impairment in muscle mass, strength, and protein synthesis because of the parallel decline in the levels of anabolic with sarcopenia.

Whereas insulin's action as an inhibitor of whole body and muscle protein breakdown has been well established *(10)*, GH, IGF-1, and T have been shown to stimulate muscle protein synthesis *(11–17)*. Although only insufficient information is available to draw conclusions on the effect of catabolic hormones and muscle protein metabolism, they may be involved in the increased muscle protein breakdown *(18)*. Cytokines may play a role in sarcopenia, although this has not been not established. The authors will confine their discussion to the anabolic hormones, GH, IDF-1, T, and DHEA.

A gradual decline in serum levels of total T has been reported with aging in men *(19)*. This decline is more pronounced for biologically active T because of age related increase of sex hormone-binding-globulin (SHBG). Also, there are several studies showing the anabolic effects of T under various conditions *(11,14,20)*. Recently, an increase in muscle strength and mixed muscle protein synthesis in elderly men with T administration (Fig. 1) has been reported *(16)*. However, decreases in T levels may have different effects on individual muscle proteins. The authors have recently reported (Fig. 2) that T treatment in hypogonadal men increases both mixed muscle protein and MHC synthesis rates along with substantial increases in muscle mass and decreases in fat mass *(11)*. There are several studies showing that T administration has no effect on VO_2 max and endurance performance *(21)*, whereas muscle protein synthesis increased *(14,16)*. This suggests that mitochondrial (mainly involved in aerobic energy utilization) or sarcoplasmic protein (involved in anaerobic energy) synthesis may not be stimulated by T administration. In a recent study, the authors found a strong correlation between MHC synthesis rate and free T levels in aging men and women *(3)*. This correlation and the augmentation of MHC synthesis with T treatment in hypogonadal men taken together suggest that the increase in mixed muscle protein synthesis with T administration is associated with increase in MHC synthesis rate.

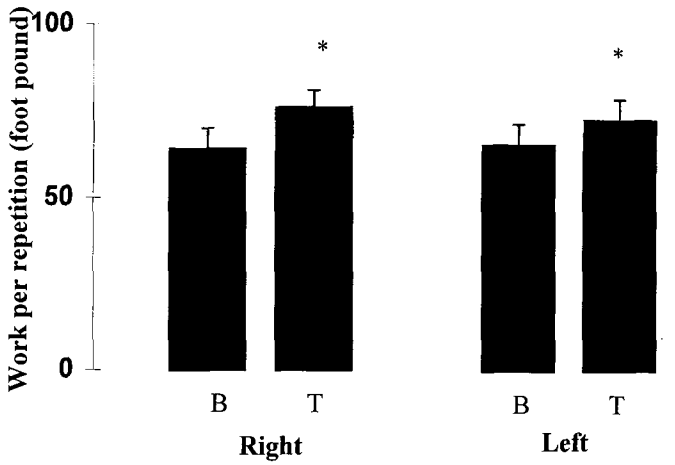

Fig. 1. Work per repetition for right and left legs, an estimation of muscle strength (quadriceps extension). B, Denotes before treatment and T denotes after testosterone treatment. Results are mean ± SE from six subjects. *Statistically significant increase. (Adapted with permission from ref 20.)

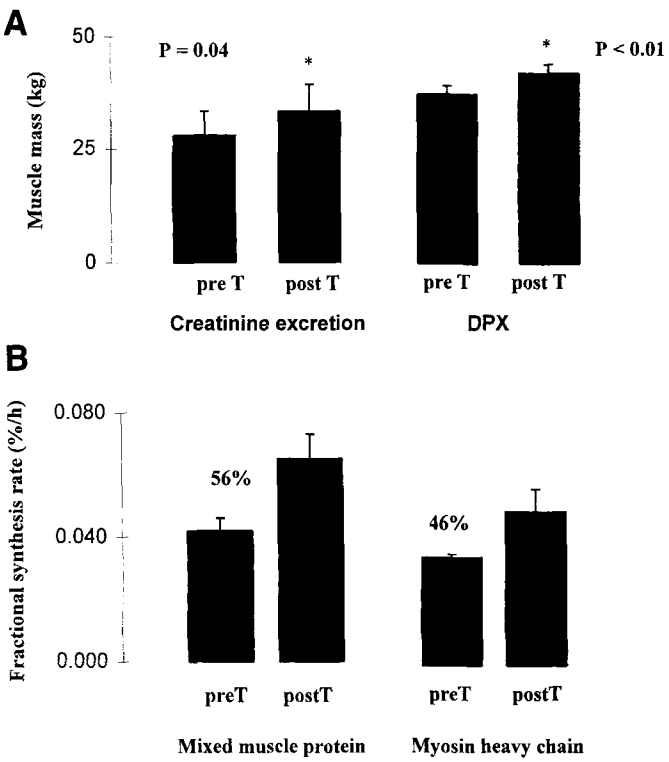

Fig. 2. Changes in muscle mass and skeletal muscle protein synthesis rate during replacement of T replacement in hypogonadal men. Before T treatment is denoted as "pre T" and that after treatment as "post T." (Adapted with permission from ref. *4*.) **(A)** Muscle mass calculated based on 24 h creatinine excretion and dual energy X-ray absorptiometry. Results are means ± SE from five subjects. *Denotes significant increase after T replacement. **(B)** Fractional muscle protein synthesis (%/h) for mixed muscle protein and MHC in hypogonadal men. There was a 56% increase in mixed muscle protein synthesis and a 46% increase in MHC synthesis rate with T replacement. Results are mean ± SE from five subjects.

Several studies have reported a decline in the plasma levels of GH and IGF-1 with age *(22)*. Although GH replacement has been shown to increase lean body mass in GH-deficient subjects *(15)*–thus reversing the process of muscle wasting–evidence to show that replacement GH therapy in healthy elderly individuals will prevent age related decline in muscle mass and strength is inconclusive *(23–25)*. In a recent study, even though a significant increase in muscle mass and a modest increase in strength were observed with growth hormone administration, there was no augmentation of myofibrillar protein synthesis *(24)*. However, in another study Butterfield et al. *(12)* reported an increase in mixed muscle protein synthesis with GH administration. In another study, GH administration had no additional benefits on muscle strength, muscle mass, and the mixed muscle protein synthesis rate in young and elderly subjects undergoing resistance training *(25)*. In the first two studies, there was an increase in muscle mass with GH administration and therefore the increased protein synthesis would presumably involve the myofibrillar component *(12,24)*. It is possible that only a small increase in muscle protein synthesis is required to show an increase in muscle mass with GH administration and this small increase may have occurred in a specific individual protein such as myosin. This small increase may have been offset by the changes in other myofibrillar proteins and therefore no increase in myofibrillar protein synthesis with GH administration *(24)*.

IGF-1, an indicator of GH activity levels, also decline with age and it has been shown that arterial infusion of IGF-1 stimulates protein synthesis *(26)*. A positive correlation of IGF-1 to myofibrillar protein synthesis *(27)* and MHC synthesis rates *(3)* suggest a role for IGF-1 in sarcopenia of aging. The short and long term effects of IGF-1 on synthesis of specific myofibrillar proteins in elderly people have not been reported.

Although a decline in DHEA levels has been widely reported in aging men and women, the underlying mechanism of DHEA's effects on muscle metabolism is not clear and replacement studies of DHEA have shown variable results *(17)*. It has been suggested that DHEA serves as a pro-hormone stimulating the action or release of other hormones. Studies done in humans indicate that DHEA administration increases circulating levels of total and biologically active IGF-1 levels as well as insulin sensitivity *(17)*. The effect of DHEA on sarcopenia of aging remains to be established.

Conclusion

Structural and functional changes that occur during aging are paralleled by changes in anabolic hormone levels. Although GH, T, and DHEA hormone replacement therapies have produced some tantalizing beneficial effects,

any rational basis for hormone therapy in the elderly population to reverse some of the age related changes require convincingly a greater benefit–risk ratio derived from long term controlled studies. There is increasing evidence that the activity of the GH/IGF system and of sex hormones may be closely interrelated. These interactions may play an important role in the elderly population. The potential importance of these hormonal interactions in relation to sarcopenia associated with aging is an intriguing possibility. Recent advances in the measurement of synthesis rates of mitochondrial protein fraction and MHC will help to expand our knowledge about the mechanism of sarcopenia with aging.

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