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Overview

Muscle loss in aging population

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Abstract

Sarcopenia is a generic term for the loss of skeletal muscle mass, quality and performance associated with normal aging that can lead to frailty in the elderly. It cannot be considered a disease or a condition that has a clear diagnostic marker. However, the clearly is a decline in the average muscle mass and performance associated with senescence. Because of the great increase in the proportion of the population living long enough that frailty becomes a significant problem, there is much interest in achieving a better scientific understanding of sarcopenia. The ageing of the European population is a major public health problem for most of the industrialized western countries, and represents both a social and an economic burden for the European population.

INTRODUCTION

Skeletal muscle is a dynamical tissue. Because of its ability to shorten and produce force, we are able to breathe or walk, and perform all the activities required in daily lives. Muscle fibers are structures capable of altering their phenotype under various conditions such as increased or decreased neuromuscular activity, mechanical loading or unloading, altered hormonal profiles and aging. Muscle atrophy is a typical age related phenomenon, but is highly variable from one individual to another and between different muscles *(1,2)*.In humans the age related changes are greater in the lower extremities than in the upper extremities *(1,2)*. Muscle atrophy during aging has been postulated to be due to a decrease in fiber number or size, or both, and muscle atrophy in ageing is a multifactoral process *(3)*.

Effects on muscle fiber number and size

Skeletal muscle cross-sectional area decreases with age *(4)*. This phenomenon can be result of a reduction in fiber size, fiber number, or combination of these two situations. Most researchers who have investigated sarcopenia have used either imaging techniques or muscle biopsies that have been performed in a cross-sectional area *(4)*. Any fiber loss can only be compensated for by hypertrophy of the remaining fibers. New fibers are not normally produced, and if they are it is probably only to a very limited extent. One of the key studies in humans is that of Lexell et al *(4)* involving examination of cross-sections of the quadriceps muscle taken at autopsy from males aged from 15 to 80 years of age. Fiber number was found to decline by 39%, which approximately paralleled the loss of muscle force. Interestingly, the decline seemed to be progressive, and commencing at about the age of 30. A loss of muscle fibers is consistent with other human based investigations,

including the rectus abdominis muscle *(5)*. Conversely, much of the more recent animal-based data indicates no loss of fibers with age. This is the case for soleus and EDL muscles for rats between 9 and 30 months of age *(6)*. Consistent with such results was the finding of Holloszy et al.*(3)* in the rat plantaris that the reduction in the muscle mass was consistent with a reduction in cross--sectional area of the fibers, suggesting that there was no change in fiber number. It has also been suggested that there is a relative loss of type II (fast-twitch) fibers in advanced age. The results from the human and animal-based studies are equivocal. In general the human data indicate that there is a loss of muscle fibers; conversely the rodent data suggest there is no loss of muscle fibers. It has to be acknowledged that the rodent data were obtained from simple fusiform hindlimb muscles, whereas the human data were obtained from more complex pennate muscles. Despite this, several reviews maintain that there is a loss of fibers with age *(7)*.

All studies, whether in humans or animals, and for all muscles studied, have shown a reduction in muscle fiber size – as a reduction in cross-section area with increasing age. The only differences seem to be in the degree of reduction in the different muscle fiber types. Grimby et al. *(8)*, for example, found a selective reduction in cross--sectional area of type II fibers in vastus lateralis muscles of humans above 70 years of age, with only slight reductions prior to the age of 60–70 years. Coggan et al. *(9)* also found no reduction in cross-sectional area of type I (slow-twitch) fibers but a 13–30% reduction in type II fibers in the aged gastrocnemius muscle. Comparable changes have been observed in animal studies. Alnaqeeb and Goldspink *(10)* found a significant decline in the cross-sectional area of type II fibers in soleus between rats aged 10 months and 24 months, but no reduction in size of type I fibers. In the rat plantaris muscles the cross--sectional area of type II fibers declined 37% and the type I fibers by only 21% between the ages of 9–10 months and 28–30 months *(3)*. It is perhaps not surprising that most reduction in fiber cross-sectional area is seen in type II fibers, particularly the IIB fibers (fast-twitch, predominantly glycolytic and readily fatigable). Order of recruitment of motor units*(11)* and therefore muscle fibers dictates that type I fibers will remain in relatively regular use, even in aged subjects, whereas the type II fibers and particularly the IIB fibers will rarely be recruited and therefore subject to disuse atrophy.

Effect on motor unit characteristics

The neuromuscular junction is link between the motoneuron and the muscle. The arrival of an action potential at the nerve terminal almost invariably results in an action potential in the muscle fiber. Consequently, any change in the security of synaptic transmission at the neuromuscular junction may profoundly affect the extent to which individual muscle fibers are recruited for normal function. Results of both animal and human studies indicate that there is remodeling and fragmentation of the neuromuscular junction with age, which suggest a progressive degeneration of the neuromuscular junction. Considerable fragmentation in the distribution of acetylcholine receptors *(12)* and in acethylcholinesterase staining has been demonstrated, and also an increase in the incidence of branches or boutons that are spatially separate or only connected by fine nerve filaments, suggesting fragmentation of the terminal *(13)*. An increase innerve terminals innervated by two or more axon branches was found in rats from the age of 21 months to 26 months. Specifically, in soleus muscle there was an increase from an already high 30% of terminals to 37,5% of terminals at 26 months of age. A gradual and progressive loss of synaptic contact was found in rat soleus and diaphragm muscles aged 21 months, with entire neuromuscular junctions being lost *(14)*. A comparison of the morphology of gastrocnemius neuromuscular junctions of old (27 months old) with young (6 month old) mice showed that 85%of neuromuscular junctions in young mice could be considered normal; however, this was reduced to 40% in the old mice *(15)*. The results suggest a significant age related deterioration in the structure and functional capacity of the neuromuscular junctions, involving outright failure or loss of the neuromuscular junctions.

The concept of the motor unit was defined by Liddell and Sherrington *(16)* and consists of the motoneuron and all the muscle fibers innervated by that motoneuron. Essentially, if a motoneuron is lost, a motor unit is lost. The consensus view from both animal and human studies is that motor units are lost with age. Early studies of Gutmann and Hanzlikova *(17)* demonstrated a significant loss of motor units in aged rats. More recently, with the use of morphometric and physiological techniques, Edstrom and Larsson *(18)* found that the average number of motor units in soleus muscle declined from 49 in 3 to 6 month old rats to 29 in 20 to 24 month old rats. This is a reduction of about 40 percent. Also was found a reduction in motor unit number in the medial gastrocnemius muscle from an average 93 to 66. Consistent with these results, the number of motoneurons in a particular motoneuron pool, identified by retrograde labeling with horseradish peroxidase was found to decline with age *(19)*. Hashizume and Kanda *(20)* found a significant decrease in the number of medial gastrocnemius motoneurons from average of 132 in middle aged rats to 121 in aged rats (27 months). Interestingly, there was no change in the number of motoneurons supplying the ulnar nerve in the rat forelimb. In addition the mean soma size of both motoneuron pools was reduced with age. In addition to the overall loss of motoneurons, there appears to be preferential loss of the larger motoneurons *(19)*. More specifically, in rat hindlimb muscles, the number of IIB muscle fibers was reduced at 14 months without reduction in numbers of type I and type IIA fibers, whereas by the age of 27 to 31 months the type IIA and IIB fibers had started to decline along with a preferential loss of the largest motoneurons with lowest oxidative capacity *(21)*. This would also be consistent with the preferential loss of type IIB muscle fibers, given that in general the largest

motoneurons innervate the type II fibers, particularly the type IIB. Human studies indicate a similar pattern of motoneuron loss. Tomlinson and Irving *(22)* determined the number of motoneurons in the lumbosacral region of the spinal cord from subjects aged 13 to 95 years. There appeared to be little change up to the age of 60 years, but from that age the number of motoneurons declined linearly, such that subjects in their nineties had about 70% the number of motoneurons of subjects up to 60 years of age. Both human and animal studies have demonstrated a significant loss of motor units with age, and this loss occurs predominantly after the age of 60 in humans. Although this is certainly true for those more distal muscles that have been investigated, the extent to which more proximal muscles exhibit this loss is less certain. In young animals and humans when motoneurons are lost through injury or disease, the remaining motoneurons will sprout and reinnervate the denervated fibers. This is a powerful compensatory mechanism, and motor unit innervation ratios may increase five to tenfold *(23)*.

Morphological changes in the anterior horn of the spinal cord, as well as those in the peripheral axon in older humans and animals, can be accountable for the old age muscle atrophy as well *(24)*. The morphological finding supporting these investigations, i.e. the atrophy of motor neurons in the spinal cord of older humans, is that some types of muscle fibers tend to cluster, and do not show the mosaic distribution observed in younger people. This is actually the process of denervation with subsequent reinervation by the neighboring axon, whose motor neuron has not been affected by atrophy, thus producing clusters of one type fibers in older people *(25)*. Investigations based on quantitative electromyography revealed a reduction in the number of functional motor units in aging human skeletal muscles *(26)*. This loss being more prominent in larger and faster motor units, i.e. type 2 motor units *(9)*. These investigations point to an increase in the size of the remaining motor units. Furthermore, morphological investigations have shown that the number of motor neurons in the lumbo-sacral cord is reduced after sixty years of life; in some cases this number accounts for as little as 50% of the number found in young people *(27)*. Other age related changes in motor unit characteristics have been identified. There appears to be a slowing of contractile characteristics, although whether this is due to changes in contractile properties of both fast and slow units or whether it is due to a preferential loss of fast type units remains unclear.

Effect on satellite cells

Skeletal muscles grow or become repaired upon injury. This ability is principally dependent on a population of progenitor cells called satellite cells. These cells are present between the sarcolema of the mature fiber and its basal lamina.

Aged skeletal muscles, particularly type II skeletal muscle fibers, are more susceptible than younger ones to contraction induced muscle damage and display an impaired regenerative capacity *(28)*. A number of factors have been proposed as contributing to the age related loss of skeletal muscle and its contractility, a state termed sarcopenia. Myogenic satellite cell nuclei comprise approximately 30% of the total muscle nuclei in the neonate, and this number decreases to approximately 5% by adulthood. This decrease appears to continue throughout the life span of the organism, with those who are elderly showing an even greater decrease from adulthood, although this result is not observed in all studies. It has been proposed that the decrease in the percentage of myogenic satellite cells with increasing age results from an increased number of myonuclei and a decrease in the number and proliferative capacity of myogenic satellite cells *(29)*. Recent findings suggest that the phenomenon is much more complex than merely myogenic satellite cell senescence. For example, the proliferation and fusion of myogenic satellite cells do not appear to be significantly altered with aging *(30)*. Changes in the aged cellular and extracellular milieu appear to reduce myogenic satellite cell activation *(31)* and possibly subsequent steps, such that new myofibers are thinner and more fragile helping to explain the increased susceptibility to contraction induced muscle damage. In support the critical role played by the host environment, Carlson and Faulkner found that the mass and the maximum force of old muscles grafted into young hosts were not significantly different from those of young muscles grafted into the same young hosts *(32)*. On the other hand, young muscles grafted into old hosts regenerated similarly to old muscle grafted into the same old hosts. On the basis of these findings, the authors proposed that the environment of a muscle is more important than the age of the muscle in determining regenerative capacity, and this hypothesis was recently supported using old-young mouse parabiotic pairings.

Skeletal muscle regenerative capacity has been shown to decline with age, and Carlson (1995) has suggested that a decrease in regeneration potential could contribute to a reduction in muscle mass in older individuals *(33)*. Satellite cells are quiescent in normal adult muscle, although they can be induced to proliferate under certain conditions to add myonuclei to existing fibers or to form new muscle fibers. Research in animals has indicated that the number or percentage of satellite cells is significantly diminished in older skeletal muscle, thus providing a potentional basis for the decline in muscle regeneration and adaptation potential in older animals *(34)*. Snow (1977) reported a 50% decrease in satellite cell number between the ages of 8 and 30 months in the soleus muscle of mice and rats, and also suggested that the satellite cells in older muscles were less metabolically active than those of young animals, based on morphological criteria *(35)*. Gibson and Schultz (1983) reported similar differences in satellite cell proportions in the extensor digitorum longus muscle between young and old rats but not between adult and old ones*(34)*. In addition, several morphological changes have been noted in satellite cells in adult compared to young animals, including decreased quantities of endoplasmatic reticu-

lum, golgi and ribosomes *(36)*. Possible changes in satellite cell characteristics in older human skeletal muscle are unclear and the studies that have been completed are associated with limitations in scope and methodology. Schmalbruch and Hellhammer (1976) reported a lover satellite cell proportion (0,6%) in a 73-year-old male compared to a satellite cell proportions (4%) in eight adults between 20 and 34 years of age*(37)*. However, no other older subjects were assessed in that investigation. Hikida et al (1998) reported similar proportions of satellite cells (2%) in young and older men *(38)*. Perhaps a more important issue than the number of satellite cells is the environment that regulates the activation, proliferation and terminal differentiation of satellite cells.

A number of therapies have been tested as means of preventing or reducing sarcopenia. In particular, resistance training has received significant attention. Resistance training in elderly individuals has many potential benefits including increased strength; increased bone mineral density; increase satellite cell number, particularly in older women; decreased myostatin levels and the potential to elevate bioavailable IGF-1 *(39)*. It should be noted, however, that although elderly subjects do respond well to resistance training, the adaptations in older people are not as pronounced as in younger subjects.

A therapy that is currently receiving significant attention is hormone replacement therapy. Aging is associated with changes in body composition, function, and metabolism, as well as a reduction in the activity of the growth hormone – IGF-1. These changes are similar to those in younger adults with pathological growth hormone deficiency. Since pathologically deficient patients display improvements in overall fitness and quality of life with supplementation of growth hormone, IGF-1, or both, similar clinical trials focusing on elderly subjects have been proposed. Results from rodent studies support this, as increases in local IGF-1 expression attenuated the loss of muscle mass and strength and increased myogenic satellite cell proliferation in older animals *(40)*. To date, there is no definite evidence that frail elderly human subjects benefit from restoration of growth hormone and IGF-1 levels to a young adult range. Furthermore, most studies addressing hormone supplementation have used elderly individuals in good health, partly because of the potential of these therapies to enhance the growth of hidden malignancies.

CONCLUSION

Although resistance training appears to be beneficial in reducing the effects of sarcopenia, some elderly subjects may be too frail or impaired in their current state for resistance training to be a viable therapy. In this case, hormone replacement therapy may provide a short time benefit to elderly patients who are preoperative and for whom increased muscle mass and strength would expedite recovery.

REFERENCES

1. NIKOLIĆ M, MALNAR-DRAGOJEVIĆ D, BOBINAC D, BAJEK S JERKOVIĆ R 2001 Age-related skeletal muscle atrophy in humans: an immunohistochemical and morphometric study. *Coll Antropol 25(2):* 545–553
2. NIKOLIC M, ŠOIĆ VRANIĆ T, ARBANAS J, CVIJANOVIĆ O, BAJEK S 2010 *Coll Antropol 34(2):* 105–108
3. HOLLOSZY J, CHEN M, CARTEE G, YOUNG J 1991 Skeletal muscle atrophy in old rats: differential changes in the three fiber types. *Mech Ageing Dev 60:* 199–213
4. LEXELL J, TAYLOR C, SJOSTROM M 1988 What is the cause of the ageing atrophy? Total number, size, and proportion of different fiber types studied in whole vastus lateralis muscle from 15 to 83 year old men. *J Neurol Sci 84:* 275–294
5. INOKUCHI S, ISHIKAWA H, IVANOTO S, KIMURA T 1975 Age related changes in the histochemical composition of rectus abdominis muscle of the adult human. *Hum Biol 47:* 231–349
6. ALNAQEEB M, GOLDSPINK G 1986 Changes in fibre type, number and diameter in developing and ageing skeletal muscle. *J Anat 153:* 31–45
7. BOOTH F, WEEDEN S, TSENG B 1994 Effect of aging on human skeletal muscle and motor function. *Med Sci Sports Exercise 26:* 556–560
8. GRIMBY G, DANNESKIOLD-SAMSOE B, HVID K, SALTIN B 1982 Morphology and enzymatic capaticy in arm and leg muscles in 78–81 year old men and women. *Acta Physiol Scand 115:* 125–134
9. COGGAN A, SPINA R, KING D, ROGERS M, BROWN M, NEMETH P, HOLLOSZY J 1992 Histochemical and enzymatic comparison of the gastrocnemius muscle of young and elderly men and women. *J Gerontol Sci 46:* B71–B76
10. ALNAQEEB M, GOLDSPINK G 1987 Changes in fibre type, number and diametar in developing and ageing skeletal muscle. *J Anatom 153:* 31–45
11. HENNEMAN E, MENDELL I 1981 Functional organization of motoneuron pool and its inputs. *In:* Handbook of Physiology. The Nervous System. Motor Control. Am Physiol Soc. sect I, vol 11, pt 1, chapter11. Bethesda, MD, p 423–507
12. GUTEMANN E, HANZLIKOVA V 1965 Age changes of motor endplates in muscle fibers of the rat. *Gerontologia 11:* 12–24
13. ROBBINS N, FAHIM M 1985 Progression of the age changes in mature mouse motor nerve terminals and its relation to locomotor activity. *J Neurocytol 14:* 1019–1036
14. CORDOSIS C, LAFONTAINE D 1987 Aging rat neuromuscular functions: A morphometric study of cholinesterase stained whole mounts and ultrastructure. *Muscle&Nerve 10:* 100–113
15. LUDATSCHER R, SILBERMANN M, GERSHON D, REZNICK A 1985 Evidence of Schwann cell degeneration in the aging mouse motor end plate region. *Exp Gerontol 20:* 80–91.
16. LIDDELL E, SHERRINGTON C 1925 Recruitment and some other features of reflex inhibition. *Proc R Soc 97:* 488–518
17. GUTMANN E, HANZLIKOVA V 1966 Motor units in old age. *Nature 209:* 921–922
18. EDSTROM L, LARSSON L 1987 Effects of age on contractile and enzyme –histochemical properties of fast and slow twitch single motor units in the rat. *J Physiol 392:* 129–145
19. HASHIZUME K, KANDA K, BURKE R 1988 Medial gastrocnemius motor nucleus in the rat: Age-related changes in the numbers and size of motoneurons. *J Comp Neurol 269:* 425–430
20. HASHIZUME K, KANDA K 1995 Differential effects of aging on motoneurons and peripheral nerves innervating the hindlimb and forelimb muscles of rats. *Neurosci Res 22:* 189–196
21. ISHIHARA A, NAITOH H, KATSUTA S 1987 Effects of ageing on the total number of muscle fibers and motoneurons of the tibialis anterior and soleus muscles in the rat. *Brain Res 435:* 355–358
22. TOMLINSON B, IRVING D 1977 The numbers of limb motor neurons in the human lumbosacral cord throughout life. *J Neurol Sci 34:* 213–219
23. LUFF A, EINSIEDEL L 1992 Motoneurone sprouting: A mechanism for recovery of muscle function. *Proc Aust Physiol Pharmacol Soc 23:* 40–50
24. FUJISAWA K 1974 Some observations on the skeletal musculature of aged rats. I. Histological aspects. *J Neurol Sci 22:* 353–366
25. LEXELL J, DOWNHAM D 1991 The occurrence of fibre-type grouping in healthy human muscle: a quantitative study of cross-

-sections of whole vastus lateralis from men between 15 and 83 years. *Acta Neuropath 81:* 377–381

26. BROWN W 1972 A method for estimating the number of motor units in thenar muscles and the changes in motor unit count with ageing. *J Neurol Neurosurg Psychiatry 35:* 845–852
27. TOMLINSON B, IRVING D 1977 The numbers of limb motor neurons in the human lumbosacral cord throughout life. *J Neurol Sci 34:* 213–219
28. SINGH M, DING W, MANFREDI J SOLARES G, ONEILL E, CLEMENTS K, RYAN N, KEHAYIAS J, FIELDING R, EVANS W 1999 Insulin like growth factor I in skeletal muscle after weight lifting exercise in frail elders. *Am J Physiol 277:* E135–143
29. KADI F, CHARIFI N, DENIS C, LEXELL J 2004 Satellite cells and myonuclei in young and elderly women and men. *Muscle& Nerve 29:* 120–127
30. GROUNDS M 1998 Age assosiated changes in the response of skeletal muscle cells to exercise and regeneration. *Ann NY Acad Sci 854:* 78–91
31. GOLDSPINK G, HERRIDGE S 2004 Growth factors and muscle aging. *Exp Geront 39:* 1433–1438
32. CARLSON B, FAULKNER J 1989 Muscle transformation between young and old rats: Age of hosts determines recovery. *Am J Physiol 256:* C1262–C1266
33. CARLSON B 1995 Factors influencing the repair and adaptation of muscles in aged individuals: satellite cells and innervation. *J Gerontol A Biol Sci Med Sci 50:* 96–100
34. GIBSON M, SCHULTS E 1983 Age-related differences in absolute numbers of skeletal muscle satellite cells. *Muscle&Nerve 6:* 574–580
35. SNOW M 1977 The effects of aging on satellite cells in skeletal muscles of mice and rats. *Cell Tissue Res 185:* 399–408
36. SCHULTS E 1976 Fine structure of satellite cells in growing skeletal muscle. *Am J Anat 147:* 49–70
37. SCHMALBRUCH H, HELLHAMMER U 1976 The number of satellite cells in normal human muscle. *Anat Rec 185:* 279–287
38. HIKIDA R, WALSH S, BARYLSKI N, CAMPOS G, HAGERMAN F, STARON R 1998 The effects of short-term resistance training on endocrine function in men and women. *Basic Apply Myology 8:* 419–431
39. ROTH S, MARTEL G, FERRELL R, METTEL E, HURLEY B, ROGERS M 2003 Myostatin gene expresion is reduced in humans with heavy resistance strength training: A brif communication. *Exp Biol Med 228:* 706–709
40. CHAKRAVARTHY M, DAVIS B, BOOTH F 2000 IGF-I restores satellite cell proliferative potential in immobilized old skeletal muscle. *J Appl Physiol 89:* 1365–1379