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Research paper

# Physiological and architectural changes in the ageing muscle and their relation to strength and function in sarcopenia

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ABSTRACT

In the ageing muscle, many changes occur. Some are on an architectural level, like alterations in muscle composition, or modifications in the characteristics of the muscle fiber itself, where muscle fiber length, orientation and type change. Other changes are neuronal, which occur on all levels, from the central activation over the spinal properties down to the level of the motor unit and the neuromuscular junction. There are also hormonal factors that undergo agerelated concentration variations. All these alterations in the muscle have an effect on both strength and function. In this matter, they contribute to the process of sarcopenia. Although many different components are identified, it is still unclear to what degree these components contribute to the loss of muscle mass, strength and function. This review summarizes the occurring physiological and anatomical changes within the ageing muscle and links them to outcomes such as strength and function.



## 1. Introduction

As the largest organ of the body comprising about 40% of bodyweight, the skeletal muscle is essential for all activities of daily living (ADL). Indeed, in the elderly, those activities become progressively more at risk due to sarcopenia, which is the age-related loss of muscle mass, strength and functionality [1]. The prevalence, dependent upon the method used, ranges between 8.4% and 27.6% [2].

As for other physiological systems, muscle mass and strength decline with ageing. This decline in muscle mass averages 0.4–0.8 kg per decade after the second decade [3]. The loss of mass per year is higher in men (1%) than in women (0.5%) [4]. The reduction in both muscle fiber number and fiber size results in a smaller muscle cross sectional area (CSA) [5,6]. Muscle strength on the other hand peaks in the 30–39 year age group and has a steady decline thereafter, with a loss of about 1.5% each year starting at 50 years of age, accelerating to 3% per year after the age of 60 [7,8].

Sarcopenia is related to the aging process as muscle mass and muscle function decline. This decline is illustrated in cross-sectional and longitudinal studies. However, recent insights question the linear relation of these components. There are strong indicators that muscle mass is only one of multiple determinants of muscle strength, as immobility results in a more prominent change in strength then in mass. Reversibility of this phenomenon during resistance exercise is more distinct in strength then mass, due to an initial increase in neural drive [9–12]. This suggests that muscle architecture, contractile characteristics as well as hormonal and neuronal factors play their role [3,11]. Muscle composition has been correlated to maximal strength, independent of muscle size [13]. In a study by Clark et al. regarding muscle disuse atrophy, 50% of the loss of strength was due to neurological factors and 40% due to muscular ones [14,15].

Different approaches to defining and measuring muscle mass or strength make comparison between studies difficult. Muscle mass can be measured as a volume, by CSA or physiological CSA (PCSA). PCSA - requiring muscle volume, angle of fiber pennation as well as estimation of fiber length – is measured perpendicular to the line of pull of the fibers and could be a more valid index of the muscle's contractile capability [12]. Muscle mass is mostly measured in the passive state. Even during an isometric contraction there can be considerable changes in muscle morphology [16,17]. For example, there can be an increase in PSCA of up to 35% [18]. Thus, it is unclear which of these measures the most valid indicator is of muscular strength [19].

There is also a difference between strength, power, work, force and torque. Some studies suggest that power is more important than strength for ADL, regaining balance, rising from a chair or climbing steps [20,21]. Power is lost more rapidly than strength with ageing [22].

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In this article, the different determinants of muscle strength are described. Muscle mass, specific changes in muscle architecture, neuronal and hormonal changes are the four cornerstones of the complex relation between muscle mass and strength in the sarcopenic elderly.

## 2. Changes in muscle mass architecture

Muscle mass architecture is directed by specific changes in two factors: fiber characteristics and muscle composition [23].

### 2.1. Fiber characteristics

The function – development of strength – of the fiber is influenced by the following characteristics: type, orientation, length and atrophy.

#### 2.1.1. Fiber type

The myofibrillar protein represents up to 85% of muscle fiber [24]. There are two types of myofibers, based on the expression of myosin heavy chain isoforms [12,25]. Type 1 myofibers are slow-twitch/slow-oxidative. They are used for sustained, low-level activity and generate less force than type 2 fibers, which are fast-twitch/fast-glycolytic [26,27]. Type 2 myofibers are used for brief-duration intense activity or carrying heavy loads and are specialized for anaerobic metabolism [25–27]. Each muscle has a characteristic type 1 to type 2 myofiber ratio [26,28].

Between the myofibers, the sarcoplasm contains the inter-myofibrillar network, of which mitochondria and glycogen are important components. Mitochondria are more abundant present in muscles with type 1 fibers, glycogen in those with type 2 [29].

#### 2.1.2. Fiber orientation

The orientation of fibers in relation to connective tissue/tendon influences strength [12]. The direction of the fiber angle in relation to the force generation axis is called the pennation angle (PA). This PA determines the muscle torque and relates to maximum force development. A steeper angle affects the muscle performance negatively during contraction [30–32]. The angle can change according the conditions of muscle activation, to produce either maximal velocity under low loads or maximal force under high loads [33].

#### 2.1.3. Fiber atrophy

There are age-related modifications and denervation of type 2 fibers and a re-innervation of those fibers with axons from type 1 motor units [4,34–37]. Since re-innervated fibers adopt the metabolic and mechanical properties of the new motor unit, fiber CSA and muscle mass are reduced due to the loss of contractile proteins [4], maximal strength is reduced, contraction/relaxation times are extended and ATPase transport activity is reduced. Type 1 isoforms consume less ATP than type 2 at maximum contraction [26,38]. The underlying mechanisms of this fiber type shift are not entirely clear, but implicate the apoptotic loss of $\alpha$-motor neurons [38].

Advancing age is associated with a reduced expression of tropomyosin/troponin (associated with actin-myosin crossbridge formation), a higher expression of desmin (associated with force transmission) and an increased post-translational modification, all of which could impair protein function and thus diminishing force generation [38].

#### 2.1.4. Fiber length

Muscle fiber length is shorter in the elderly [39,40]. This alters the muscle-specific length-tension and force-velocity relationships. Melo et al. found knee extension torque to be 22–56% lower in older compared to younger adults, concluding that in more stretched positions, older subjects seem to lose the capacity to generate eccentric knee extension torque [40].

### 2.2. Muscle composition

Muscle composition, or quality, is paramount in the development of strength; one study defined muscle quality as force per muscle CSA [35]. The muscle quality worsens with advancing age, primarily due to increasing amounts of connective tissue and lipid accumulation within the muscle cell itself [41].

#### 2.2.1. Adipose tissue

In the ageing skeletal muscle, elevated adipose deposition is observed at both inter- and intramuscular sites [42]. The exact reason is unknown, but lipid accumulation in muscle correlates with a lower mitochondrial function [43]. This could explain why an increased ectopic muscle adiposity and total body adipose tissue negatively impacts strength, power and torque [44–46]. A higher muscle tissue fat content negatively affects performance [30]. Elevated ceramides, a class of neutral lipids, are not uncommon in older adults and are seen with increased intramyocellular lipid content [47]. This contributes to a reduction in function [48].

#### 2.2.2. Connective tissue

The relation between muscle fibers and their surrounding connective tissue or tendons is important for maintenance of the muscle integrity and function [49,50]. The arrangement of connective tissue in relation to individual fibers can influence force production [12]. The amount of intramuscular connective tissue increases dramatically in various pathological states – up to 50–700% during immobilization, tenotomy or denervation [50]. This leads to a separation of the individual muscle fibers, a reduced capillary density and a disruption of the normal three-dimensional orientation of the collagen fibers (the crimp structure). When the crimp angle of the collagen fibers decreases, the ability of the muscle to elongate is hindered [51].

The structure and composition of tendons are important for optimal force transfer and function. Tendon stiffness affects the time required to stretch the elastic component and will influence both the electromechanical delay and the rate of force development [52]. Tendons undergo age-related changes as collagen concentration decreases and extracellular matrix components (proteoglycans, glycosaminoglycans) increase [53]. In elderly, a training-induced increase in fiber length is compensated by an increase in tendon stiffness [54]. This enables the fibers to maintain their operational range within the optimal region of the length-tension and force-velocity relationships [35]. The exact relation of these changes in tendons are still unclear due to conflicting data [53].

Force transmission can be generated in two ways: longitudinal and lateral. The longitudinal force transfer from fiber to myotendineous junction creates a change in the force development rate and the power by changing the proteins-to-fiber ratio [55]. The lateral force transfer uses costameres - large membrane-cytoskeletal complexes – that couple the intracellular-extracellular matrix to transfer up to 80% of the force. As costameres are lost during aging also an important transfer mechanism fails [55]. Calcium reuptake is reduced with ageing, due to a loss of specific (ryanodine/dihydropyridine) receptors. This leads to a weaker excitation-contraction coupling and to a lessened motor coordination/task performance and a higher rate of muscle fatigue [38].