

## Original Article

# Skeletal muscle strength in older adults. Angiotensin-converting enzyme (ACE) genotype affects: an UPDATE

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### Abstract

**Problem Statement :** Previous studies have associated angiotensin-converting enzyme (ACE) with variability in the skeletal muscle baseline strength, though conclusions have been inconsistent across investigations.

**Approach:** The purpose of this study was to review the most important studies that have been examined the possible association between ACE genotype and skeletal muscle baseline strength in elite male and female athletes involved in elderly populations. This research is needed because the possibility that the DD genotype may be associated with a greater proportion of fast twitch fibers could explain the influence of the ACE D allele upon strength/ power, particularly at high velocities, but this evidence remains equivocal in older people because more studies are necessary.

**Results:** Thus, according to scientific evidence, changes in muscle strength with exercise training in older individuals may be dependent on ACE I/D genotype. Of note, the results provide a novel insight that these genetic variations may interact to determine muscle mass in older women specially. The determination of this predisposition in this population, highlighting the interest of study, for the prophylactic attitude on the factors and causes of aging (sarcopenia, osteoporosis, risk of falls, reduction of functional physical) go through this analysis.

**Conclusions/Recommendations:** In this work, the state of the art related to the influence of the ACE genotype on skeletal muscle strength was presented and some important relations were reported.

**Keywords:** human genetics, resistance training, physical activity, elderly, muscle fibers.

### Introduction

Skeletal muscle is an important tissue that serves many functions in the body. Human movement depends on the conversion of Adenosine Triphosphate (ATP) into mechanical energy through the action of skeletal muscles. The main problem associated with aging is the loss of functional capacity [1] and independence [2]. Aging is associated with a number of physiologic and functional declines that can contribute to increased disability, frailty and falls. Contributing factors are the loss of muscle mass and strength as age increases, a phenomenon called sarcopenia, seen in both elderly men and women [3-5]. Sarcopenia is becoming recognized as a major cause of disability and morbidity in the elderly population and does not require a disease to occur, even though this loss of muscle mass and strength is accelerated by chronic diseases and sedentary behaviors. Indeed, neurological, metabolic, hormonal, nutritional, and physical-activity-related changes with age are likely to contribute to this fragility [6]. Thus, as with other diseases, prevention is better than cure [7]. Muscle strength commonly reaches its peak between the ages of 25-35 years, it can be maintained during the fifth decade, and then begins to decline at a pace of approximately 12-14% per decade starting at age 50 yr [8]. The maximum strength and power [65] are necessary to perform many everyday normal tasks like walking, climbing stairs or rising from a chair. Muscle power and rate of force development throughout physical training has been shown to be a key factor in maintaining functional performance and promoting a decreasing in falls and fractures, which with advancing age leads to decreased independence [9, 10]. The aging of the neuromuscular system also decreases the ability to generate force fast, thereby increasing the risk of falls, an aspect that has been considered with a growing interest [11]. Several studies have found that people with 75 years have, with respect to those aged 20 years, a decline of aerobic endurance (45%), handgrip strength (40%), legs strength (70%), joint mobility (50%) and neuromuscular coordination (90%) [11-14]. Additionally, the findings of Janssen et al. indicate that the loss of skeletal muscle mass with age is greater in the lower body, mainly in leg extensors, in both men and women [15]. Longitudinal studies also show a loss of approximately 1–2% per year in isokinetic

strength of the knee while the changes in the elbow flexors and extensors less dramatic and more significant in men than women [16]. Increased physical activity has been found to correlate with greater muscle strength and is associated with absence of self-reported mobility difficulties [62, 63]. Developing muscle strength with high velocity movements can improve one's ability to perform tasks and reduce the risk of injury, being this particularly important among elderly athletes [17]. Subsequently, that resistance training may contribute to better balance, coordination and agility, helping to prevent functional and postural dysfunctions [9, 10].

### **Mechanisms involved in skeletal muscle adaptations to exercise**

Exercise can be equated to a very complex stimulus causing different changes in cell function. Skeletal muscle is one of the tissues that respond well to exercise by undergoing a series of adjustments at the level of several of its components. Moreover, muscle cells will adapt differently to changes imposed by endurance or strength training, mainly because of the different adjustments that cause changes in the muscular system as well as the differences in other parameters such as fiber size and type composition [18]. Muscle hypertrophy is an adaptive response to overload that requires increasing gene transcription and synthesis of muscle-specific proteins, resulting in increased protein accumulation [19]. Protein synthesis and degradation are unequivocal conditions for the increase of muscles fibers size in response to training, being also correlated with an increased in RNA activity regulated by their phosphorylation state. The amino acid transport into exercising muscles is also improved by training, which enhances the availability for new muscles proteins synthesis. Muscle fiber hypertrophy depends on mRNA levels that increased gene transcription and the number of myonucleus. Human studies showed that in well trained subjects, the numbers of myonucleus are higher than sedentary, presenting a linear relationship with Cross-Sectional Area (CSA) of muscle that is reported both in young and elderly subjects [20]. Another study by Hikita et al. [21] shows that cross-sectional areas of the muscle fibers in untrained elderly men were much smaller than in untrained young men. These authors also observed that the hypertrophy of muscle fibers by 30% with training resulted in no change in the cytoplasm-to-myonucleus ratio, suggesting that the myonuclear population continues to adapt to growth stimuli induced by training with additional workload in the elderly muscles [21].

### **Effects of strength and power development in older adults**

Even with healthy elderly people, CSA comparisons imply a loss of strength at some 1.5% per year and of power at some 3.5% per year (averaged across the age range 65-84) [22]. With resistance training, these losses can be downsized, however, increased muscle strength is achieved mainly to improvements in neural activation patterns [23]. Indeed, recalling Hakkinen et al. [14] investigated the effects of 6 months of heavy-resistance training combined with explosive exercises on neural activation of the agonist and antagonist leg extensors. Muscle CSA of the quadriceps femoris, as well as maximal and explosive strength were examined in 10 middle-aged men, 11 middle-aged women, 11 elderly men and 10 elderly women [24]. This study concluded that the CSA of the quadriceps femoris increased in middle age men by 5%, in middle age women by 9%, in elderly women by 6%, respectively ( $p < 0.001$ ) and in elderly men by 2% (not significant). The enlargements in the muscle CSAs in both middle-aged and elderly subjects were much smaller in magnitude, demonstrating that neural adaptations seem to play a greater role in explaining strength and power gains during this strength-training protocol [14]. In elderly the proportion of fast and slow fibers seems to be associated with the increased muscle strength and CSA in response to strength training. Adults and elderly that show a higher proportion of fast twitch fibers have greater improvements in strength in comparison with other subjects of the same age [10]. Another study showed the effects of a 10-week progressive strength training program composed of a mixture of exercises for increasing muscle mass, maximal peak force, and explosive strength in 8 young and 10 old men [14]. Maximal isometric peak force increased from 25.6% ( $p < .05$ ) in young and from 16.5% ( $p < 0.01$ ) in old. No changes occurred in the muscle fiber distribution of type I during the training, whereas the proportion of subtype IIab and IIb increased in young and in older. The results suggest that both neural adaptations and the capacity of the skeletal muscle to undergo training-induced hypertrophy even in older people explain the gains observed in maximal force in older men. However, the improvements on maximal strength not only depended of the magnitude of hypertrophy observed during a few period training, because this increased can be explained by changes in nervous system and contractile proprieties of fiber type with training [13]. According to the previous statement, a short-term intervention of high-velocity power training and traditional slow-velocity progressive resistance training yielded similar increases of lower extremity power in the mobility-impaired elderly.

Nevertheless, neuromuscular adaptations to power training, rather than skeletal muscle hypertrophy, may facility the improvements in muscle quality [25]. Other factors, such as increased activation capacity of agonist muscles and reduced activation of antagonist muscles [14] might play a role in the strength gains observed with training in old age [26].

### **Fiber type and neuromuscular adaptations in older adults**

The impairment in muscle mechanical function is accompanied and partly caused by an age-related loss in neuromuscular function that comprise changes in maximal firing frequency, agonist muscle activation, antagonist muscle coactivation and spinal inhibitory circuitry [12]. Strength training appears to elicit effective countermeasures in elderly individuals even at a very old age (>80 years) by evoking muscle hypertrophy along with substantial changes in neuromuscular function. Notably, as we reported earlier, the training-induced changes in muscle mass and nervous system function leads to an increased ability to perform daily and functional activities [27]. A decrease in the number and size of type II fibers in particular accounts for the age-related decline in muscle mass and strength performance. Multiple denervation and re-innervation processes of muscle fibers seem to be responsible for the reduced number of muscle fibers. According to scientific data from recent studies [7, 23, 27], it has been suggested that it is not the decline in motoneurons that accounts for the loss in number of muscle fibers but the disturbed potential of fiber regeneration and re-innervation. Given these neuromuscular limitations in old age, it is important to apply adequate training interventions that delay or even reverse the onset of these constraints. Strength training has the potential to enhance maximal as well as rate of force development production capacity accomplished by neural factors [28].

### **Genetic influence in muscle adaptation**

Simple differences in mass or muscle function are also strongly genetically influenced [29, 30]. Analyses of the genetic determinants of strength in older people provide information about the contribution of both genes and environmental factors. Additionally, the interaction effects between genes and environment and the identification of genes or coding variants in relation to strength characteristics are also of interest [31]. At least 20% of the muscle training response is accounted by genetic factors independent of those exerting pre-training influence [32]. A study by Tiainen et al. [31] concluded that the heritability of muscle strength in older twins (68 years old) outweigh a genetic component of 14% in handgrip strength and of 31% in knee extensor strength. For lower extremity function (strength, power and walking speed) in older twins (60 years) the heritability coefficient has been estimated to be 34–52% [31, 33, 34]. High levels of heritability were also reported for elbow flexors strength by Thomis et al. [32], concluding that genetic factors are responsible for up to 77% of pre-training 1RM strength, 69% of isometric strength and 65-77% of eccentric strength. Comprehensive development of coordination is essential for other biological attributes such as speed, jumping ability, and agility and may enhance learning of movement technique, which is a prerequisite in all sports disciplines and daily activities [35]. These authors found for neuromuscular coordination as expressed by movement economy (assessed by the relative EMG activity of biceps long head) no genetic dependence for low velocities. Although, movement strategies and control of fast movements seem strongly genetically dependent. According to the gene map for performance and fitness phenotypes [36], very few studies have investigated the effect that specific candidate genes have over strength training response. The existing studies have identified few specific candidate genes that are only partially responsible for strength training adaptation [37-39]. Hence, further investigation remains necessary, mainly by the fact that strength is a complex phenotype very susceptible to environment effects.

### **Angiotensin Converting Enzyme (ACE) as a possible candidate gene**

One potential candidate gene is the Angiotensin Converting Enzyme (ACE) gene. ACE performs a key role in the regulation of the Renin-Angiotensin-Aldosterone System (RAS), being responsible for converting angiotensin I to angiotensin II: a potent vasoconstrictor [63]. ACE is also involved in breaking down bradykinin [40], a powerful vasodilator, into inactive fragments. This means that ACE is involved in simultaneously stimulating vasoconstriction and inhibiting vasodilatation, which results in increased vascular resistance and a rise in blood pressure [41, 42, 61]. While RAS is considered to be a critical component to central cardiovascular regulation, skeletal muscle, as other tissues has substantial ACE activity owing to local RAS activity [43]. In fact, angiotensin II-induced cardiac muscle cell proliferation contributes to cardiac myocyte hypertrophy via paracrine secretion of growth factor, which are a set of substances, most likely protein that along with the hormones and neurotransmitters. This plays an important role in communication intercellular, and also contributes to skeletal muscle hypertrophy of fibroblasts via the same method. The secretion of paracrine growth factor, causing the role of growth factors that is regulated by different mechanisms controlled by gene activation like the transcription and translation of the specific gene growth factor [44]. These research data suggest that RAS, and specifically ACE, may be involved with cell growth and muscle hypertrophy. This indicates a potential enzyme activity by ACE genotype in skeletal muscle mass and muscle strength. The ACE gene is located on chromosome 17. Within this gene, a 287-bp sequence insertion/deletion (I/D) polymorphism occurs in

intron 16 [45], resulting in three genotypes: II and DD, homozygote's, and ID, heterozygous. In Caucasians, the genotype frequency is approximately 25%, 50%, and 25% for II, ID, and DD genotypes respectively, however, there is some evidence of a different distribution in other racial groups [46]. As described below, ACE I/D polymorphism seems to be responsible for some of the genetic influence involved with strength training adaptation [39, 41, 47; 67; 68].

### ACE I/D polymorphism influence on muscle adaptation

Studies that focused on this issue show that the ACE D allele seems to be overrepresented among athletes who compete in power-oriented events [48; 64; 66; 69]. Likewise, an increased frequency of the ACE I allele has been identified in endurance athletes [49-52]. Indeed, the ACE I allele appears to be associated with a higher presence of type I fibers ( $p < 0.01$ ), which prove to be more efficient than type II fibers at speeds of slow contraction [53]. The positive association between sprint performance and D allele frequency gave forth to investigations into a potential connection between ACE genotype and strength training-related muscle phenotypes. However, further studies concerning the effect of ACE genotype on skeletal muscle strength and mass in response to strength training [32, 41, 54, 55] have yielded conflicting results. In fact, the three studies that investigated leg training protocols [54, 56, 57] also had inconsistency between their testing protocols. After dynamic training, Folland et al. [54] found a significant association between ACE D allele frequency and isometric strength gains. In turn, Williams et al. [40] study used isometric and isokinetic strength measurements, and reported no positive associations between ACE genotype and muscle strength adaptations. In the Charbonneau et al. [56] research, muscular adaptation of healthy older men and women was measured by one Repetition Maximum strength test (1RM), performed on both legs separately.

The results show that ACE genotype was significantly associated with muscle hypertrophy, however in Caucasian males only ( $p = 0.02$ ). Another research investigated the association between ACE genotype and power of skeletal muscle and found that II homozygote may have higher levels of nitric oxide concentrations, which would in turn raise mitochondrial efficiency and thus contractile function in skeletal muscle [57]. Furthermore, ACE I/D polymorphism, in another study showed no association with muscle function or muscularity phenotypes in older Caucasian men, although serum ACE activity appeared to have a small effect on muscle function [58]. The possibility that the DD genotype may be associated with a greater proportion of fast twitch fibers could explain any influence of the ACE D allele upon strength/ power, particularly at high velocities, but this evidence remains equivocal in older people because more studies are necessary. Only one study examine the influence of ACE genotype on the torque-velocity relationship and the time course of a twitch response, in an older population [58]. They found no evidence that ACE genotype is associated with muscle phenotypes of dynamic strength and power or contractile properties in 60-70-year-old men.

At baseline, it seems that ACE I/D genotype is not associated with measures of physical function in elderly [59]. However, following exercise training, individuals with the DD genotype showed greater gains in knee extensor strength compared to II individuals. Thus, according to this authors, changes in muscle strength with exercise training in older individuals may be dependent on ACE I/D genotype [59]. Additionally, among older individuals who exercised, those with the ACE DD or ID genotypes seem less likely to develop mobility limitation than those with the II genotype [60].

### Conclusion

Skeletal muscle is important in determining many performance and functional capabilities. Older individuals who lack muscle strength are far more likely to experience limited mobility, reduced independence and decreased quality of life. This lack of strength among the elderly tends to be correlated with the loss of muscle mass with age, known as sarcopenia, which can induce increases in falls and fractures.

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