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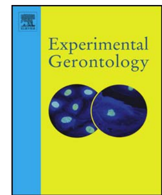

Human neuromuscular aging: Sex differences revealed at the myocellular level

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A B S T R A C T

Age-related muscle loss (sarcopenia) is a major clinical problem affecting both men and women – accompanied by muscle weakness, dysfunction, disability, and impaired quality of life. Current definitions of sarcopenia do not fully encompass the age-related changes in skeletal muscle. We therefore examined the influence of aging and sex on elements of skeletal muscle health using a thorough histopathological analysis of myocellular aging and assessments of neuromuscular performance. Two-hundred and twenty-one untrained males and females were separated into four age cohorts [mean age 25 y (n = 47), 37 y (n = 79), 61 y (n = 51), and 72 y (n = 44)]. Total (−12%), leg (−17%), and arm (−21%) lean mass were lower in both 61 y and 72 y than in 25 y or 37 y ($P < 0.05$). Knee extensor strength (−34%) and power (−43%) were lower ($P < 0.05$) in the older two groups, and explosive sit-to-stand power was lower by 37 y ($P < 0.05$). At the histological/myocellular level, type IIx atrophy was noted by 37 y and type IIa atrophy by 61 y ($P < 0.05$). These effects were driven by females, noted by substantial and progressive type IIa and IIx atrophy across age. Aged female muscle displayed greater within-type myofiber size heterogeneity and marked type I myofiber grouping (~5-fold greater) compared to males. These findings suggest the predominant mechanisms leading to whole muscle atrophy differ between aging males and females: myofiber atrophy in females vs. myofiber loss in males. Future studies will be important to better understand the mechanisms underlying sex differences in myocellular aging and optimize exercise prescriptions and adjunctive treatments to mitigate or reverse age-related changes.

1. Introduction

Sarcopenia affects tens of millions of adults worldwide, and reported prevalence ranges from ~10–50% in the aging population (Cruz-Jentoft et al., 2014; Janssen et al., 2000; Morley et al., 2014). Since the term was introduced in 1989 (Rosenberg, 1997), several attempts have been made to quantify and classify degrees of sarcopenia based on whole body lean mass (Janssen et al., 2004a; Janssen et al., 2002; Janssen et al., 2004b), limb muscle mass (Baumgartner et al., 1998), and whole body strength (Janssen et al., 2002; Scott et al., 2014). The health care burden attributable to sarcopenia is staggering – estimated at $18.5 billion in 2000 in the United States alone (Janssen et al., 2004b) – and presumably rising annually. Nonetheless, there remains no consensus on what operational definition to use when classifying sarcopenia (Beaudart et al., 2014).

Studies have demonstrated that lifetime muscle mass generally peaks at ~30–40 years of age and progressively declines thereafter (Forbes and Reina, 1970; Janssen et al., 2000), with accompanying

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functional deficits. These findings suggest that early detection and action is necessary, since exercise may curtail the rate of decline (Cartee et al., 2016; Mikkelsen et al., 2013; Wroblewski et al., 2011). However, studies that investigate the prevalence of sarcopenia throughout the lifespan often fail to examine the muscle at a cellular level. Understanding myocellular aging and potential influences of sex, activity, hormonal regulation, etc. could help direct treatment and prevention of age-related declines.

Age-related reductions in muscle mass are thought to result from a decline in total myofiber number and/or atrophy of the remaining type II myofibers (Kosek et al., 2006; Lexell et al., 1988; Merritt et al., 2013; Nilwik et al., 2013). Given the enormous power differences among type I (slow, oxidative), type IIa (fast, oxidative), and type IIx (fast, glycolytic) myofibers (Trappe et al., 2003), type II atrophy likely contributes to a weakened and less powerful phenotype at the whole muscle level in older adults. This is especially concerning given that strength and speed may be important in avoiding falls, which are a known contributor to dependence and reduced quality of life (Rubenstein, 2006).

Muscle health throughout aging may also be affected by the systemic environment, including alterations to the hormonal milieu. A number of circulating [e.g., insulin-like growth factor 1 (IGF-1) and testosterone] and locally expressed factors are thought to be important in the regulation of muscle mass based on their involvement in muscle protein synthesis (Yarasheski, 2003) and/or activation of the normally quiescent population of skeletal muscle satellite cells (Hawke and Garry, 2001). In addition, many of these factors are considered potential targets for intervention to counteract the slow progressive decline of muscle mass with aging (Neto et al., 2015).

Because of the multifaceted nature of the age-related muscle phenotype and its numerous potential contributors, the purpose of the present human investigation was to assess neuromuscular health across a wide range of ages, and to determine whether sex influences components of muscle aging. To this end, we quantified whole limb muscle mass, strength, power, histological phenotype including myofiber type distribution, type-specific myofiber size and type I grouping, and concentrations of circulating hormones thought to influence muscle mass regulation in a cohort of 221 individuals (119F, 102 M) across four age groups.

2. Methods

2.1. Subjects

Two hundred and twenty-one adults were recruited from the Birmingham, Alabama metropolitan area and divided into four cohorts defined by age range: 20–29 y, 30–50 y, 55–64 y, and 65–81 y. All potential subjects were screened via health history questionnaire including medication history and activity history; additionally, males ≥45 y and females ≥50 y were required to complete a physical examination and pass a maximal graded exercise stress test with 12-lead ECG. Individuals with a history of strength training within the previous five years were excluded. Individuals were also excluded for obesity (BMI ≥ 30), uncontrolled hypertension, diabetes, or other uncontrolled cardiometabolic disease, cognitive impairment, movement disorder, end-stage disease, or musculoskeletal or other disorder that could affect their ability to complete testing. Individuals receiving exogenous hormones were also excluded. The Institutional Review Boards of both the University of Alabama at Birmingham (UAB) and the Birmingham Veterans Affairs Medical Center approved the study. Each subject gave written informed consent prior to participation. Methods have been published previously (Bamman et al., 2004; Kelly et al., 2018; Kim et al., 2005a; Kim et al., 2005b; Kosek et al., 2006; Petrella et al., 2005) and are presented in brief.

2.2. Body composition

Total body lean mass and compartmentalized lean mass values, in addition to body fat percentage, were determined by dual energy X-ray absorptiometry (DXA) using a Lunar Prodigy (model #8743, GE Lunar Corporation, Madison, WI) and enCORE 2002 software (version 6.10.029) according to the manufacturer's instructions as described (Petrella et al., 2005). Compartmentalized DXA results were used to assess limb lean mass compartments including leg, arm, and thigh muscle mass, and skeletal muscle index (SMI) was calculated as described (Baumgartner et al., 1998; Merritt et al., 2013).

2.3. Neuromuscular testing

2.3.1. Knee extensor strength and power testing

Knee extensor power testing was conducted as detailed previously (Petrella et al., 2005). Subjects completed familiarization sessions to receive instruction on proper technique and to practice the testing protocols. To set the resistance load for the knee extensor power test, bilateral knee extension maximal voluntary isometric contraction (MVC) was first assessed as described (Petrella et al., 2005). Load-specific peak power was then determined during explosive, concentric, bilateral knee extension contractions using an external load equivalent to 40% of MVC (Petrella et al., 2005). Knee angular velocity was measured across a specific range of motion (from 0.873 rad (50°) to 0.349 (20°) of knee flexion) by 500 Hz electrogoniometry, and power in Watts was computed. Subjects were verbally encouraged to contract as fast as possible during each concentric repetition. Three repetitions were completed in succession and the repetition yielding peak power was used for analysis (Petrella et al., 2005).

2.3.2. Functional power, velocity, and motor unit activation

Sit-to-stand (STS) tests with surface electromyography (right quadriceps) and right knee electrogoniometry were performed as previously described (Petrella et al., 2007; Petrella et al., 2005). A 10-repetition test was performed at maximum speed to assess peak power and velocity. A separate 3-repetition test was performed at a standard cadence guided by an audiovisual metronome, and the quadriceps motor unit activation necessary to perform each phase (standing = concentric, sitting = eccentric) relative to maximum (recorded during unilateral knee extension MVC) was recorded as a measure of difficulty.

2.4. Muscle biopsy and tissue preparation procedures

All muscle biopsies were collected from the left *m. vastus lateralis* by percutaneous needle biopsy using a 5 mm Bergstrom biopsy needle under suction (Evans et al., 1982). At the bedside, visible connective and adipose tissues were removed with the aid of a dissecting microscope. A portion of the specimen (~50–70 mg) to be used for immunohistochemistry was mounted cross-sectionally on cork in Optimal Cutting Temperature (OCT, Tissue-Tek) mounting medium mixed with tragacanth gum, and frozen in liquid nitrogen-cooled isopentane. All samples were stored at −80 °C until analyses.

2.5. Myofiber size and type distribution

We have previously detailed our methods for myofiber typing and sizing based on myosin heavy chain (MHC) isoform immunoreactivity (Kim et al., 2005b). Briefly, the three primary myofiber types (I, IIa, IIx) and sarcolemmae were revealed on 6 μm formalin-fixed sections after a series of incubations with primary antibodies against MHCI (anti-MHCI mouse mAb NCL-MHCs, NovoCastra Laboratories, 1:100), laminin (anti-laminin mouse mAb VP-L551, NovoCastra Laboratories, 1:80), and MHCIIa (anti-MHCIIa mouse mAb, University of Iowa Hybridoma Bank, 1:80). MHC isoform specificities of these mAbs were confirmed

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