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Reduced rate of knee extensor torque development in older adults with knee osteoarthritis is associated with intrinsic muscle contractile deficits

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ABSTRACT

We examined the effect of knee osteoarthritis on the rate of torque development (RTD) of the knee extensors in older adults with advanced-stage knee osteoarthritis (OA; n = 15) and recreationally-active controls (n = 15) of similar age, sex and health status, as well as the relationship between RTD and the size and contractility of single muscle fibers. OA participants had lower RTD when expressed in absolute terms (Nm/ms). There were sex differences in peak RTD ($P < 0.05$), with greater RTD in men, but no group by sex interaction effects for any variables. The lower RTD in OA versus controls was not explained by variation between groups in the fiber type admixture of the muscle, and was mitigated when RTD was normalized to peak torque (PT). In knee OA volunteers, we found strong correlations between the RTD expressed relative to PT and the velocity of contraction of single myosin heavy chain (MHC) I and IIA/X muscle fibers ($r = 0.652$ and 0.862; both $P < 0.05$) and power output of MHC I fibers ($r = 0.642$; $P < 0.05$). In controls, RTD relative to PT was related to fiber cross-sectional area of MHC IIA/X fibers ($r = 0.707$; $P < 0.05$), but not measures of single fiber contractile performance. To our knowledge, these results represent the first demonstration that variation in whole muscle contractile kinetics in patients with advanced-stage knee osteoarthritis and healthy older adults is related, in part, to the size and function of single muscle fibers.

1. Introduction

Knee osteoarthritis (OA) is the leading cause of disability in older adults (Guccione et al., 1994) and its incidence is expected to increase several-fold in the coming decades with the expansion of the elderly population (Cram et al., 2012). As knee OA is the leading cause of functional disability in older adults (Centers for Disease Control and Prevention, 2009), knowledge of the determinants of physical function has important implications for alleviating the burden of disability on these patients.

Functional disability is fundamentally related to an impaired capacity for physical work, with lower extremity skeletal muscle function being of central importance (Guralnik et al., 1995; Reid and Fielding, 2012). In individuals with knee OA, knee extensor strength is markedly reduced secondary to muscle atrophy (Petterson et al., 2008), but also due to intrinsic deficits in the contractility of its constituent muscle fibers (Callahan et al., 2014b). Muscle force production, however, is likely not the only factor contributing to lower extremity dysfunction, as studies in mobility-limited older adults show that power output is more predictive of functionality than strength (Bean et al., 2003). Power output is the product of muscle force production and contractile velocity, suggesting that impairments in the velocity of muscle contraction may also contribute to disability (Pojednic et al., 2012; Reid and Fielding, 2012). Indeed, numerous daily functional tasks, including walking rapidly (Suetta et al., 2004), descending stairs (Nyland et al., 2007) and preventing falls (Pijnappels and Bobbert, 2005), require rapid force development. In older adults with knee OA, work from our laboratories (Winters et al., 2014) and others (Suetta et al., 2007) have found deficits in the rate of voluntary torque development (RTD) under isometric conditions in older adults with OA compared to controls that relate to functional impairments, such as reduced knee joint power output during walking (Winters et al., 2014). Moreover, RTD impairments in individuals with knee OA worsen acutely following total knee replacement (TKA; Winters et al., 2014) and are related to declines in functionality (Maffiuletti et al., 2010; Winters et al., 2014). Thus, reduced RTD likely contributes to functional disability in older adults with knee OA (Pojednic et al., 2012; Reid and Fielding, 2012).

Several factors regulate the rate of joint torque development, including neural activation (de Ruiter et al., 2004; Van Cutsem et al., 1998),

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fiber type admixture (Gür et al., 2003; Harridge et al., 1996; Korhonen et al., 2006), tendon/extracellular matrix stiffness (Bojsen-Møller et al., 2005; Reeves et al., 2003) and the contractile properties of individual muscle fibers (Harridge et al., 1996). Variation in neural activation is generally assumed to be the most important determinant of the rate of torque development (de Ruiter et al., 2004), and this could be particularly apparent in individuals with knee OA, who have deficits in neural activation (Berth et al., 2002; Petterson et al., 2008). However, variation in intrinsic muscle myofilament properties, such as fiber type admixture, atrophy of MHC II fibers (Nakamura et al., 1986; Reardon et al., 2001) and impaired single fiber contractile velocity (Callahan et al., 2014b) could also contribute. To our knowledge, however, no study has evaluated the relationship of these intrinsic muscle fiber size and myofilament properties to RTD in older adults with knee OA. Thus, our goal was to assess RTD during isometric contraction in older adults with knee OA and controls and evaluate potential relationships between RTD and muscle fiber type admixture and single muscle fiber size and contractility based on activity-dependent variation in these variables previously reported (Callahan et al., 2014b). Moreover, we investigated differences between men and women to determine whether sex-dependent variation in single muscle fiber contractile and structural characteristics described by our lab (Callahan et al., 2014a,b) and others (Krivickas et al., 2001, 2006) influence contractile properties at the whole muscle level.

2. Methods

2.1. Participants

Fifteen (7 men, 8 women) older adults with symptomatic knee OA were recruited from the Adult Reconstruction Clinic of the Department of Orthopedics at the University of Vermont Medical Center and the surrounding community. All participants self-reported receiving a clinical diagnosis of knee osteoarthritis, with seven individuals recruited in close proximity to total knee arthroplasty surgery (bilateral or staged-bilateral in 3 volunteers and unilateral in 4). We confirmed that volunteers had symptomatic (Bellamy et al., 1988) and radiographic (Kellgren and Lawrence grade 3 or 4; Kellgren and Lawrence, 1957) evidence for advanced knee OA. Volunteers were excluded if they had/have had: a history or clinical signs or symptoms of diabetes, heart failure, pulmonary disease, thyroid disease, peripheral arterial disease, neurological or neuromuscular disease or autoimmune disease; a history (within 10 yrs) of smoking; a history (within 10 yrs) of malignancy, excluding non-melanoma skin cancer; or prior knee replacement in either knee. All volunteers had normal blood counts/chemistry and renal, liver and thyroid function, based on standard blood tests. No participants were taking sex steroid replacement therapy (estrogen or estrogen/progestin therapy in women or androgen replacement in men), oral or inhaled corticosteroids or any other medication that might affect muscle function. Four OA volunteers (2 women, 2 men) were on stable regimens of HMG CoA reductase inhibitors (statins). Plasma creatine kinase levels were within the normative range in these volunteers and none had symptoms or signs of statin-induced myopathy. Of note, we have recently found that chronic, stable statin therapy does not affect skeletal muscle fiber size, mitochondrial morphology or contractile function in patients without myalgia or elevated creatine kinase levels (Rengo et al., unpublished observations), suggesting that inclusion of these individuals would not likely influence results. Additionally, 6 OA participants (4 men, 2 women) had hypertension and were on stable anti-hypertensive therapy, consisting of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (33%), diuretics (33%) and adrenergic blocking agents (33%). Eight (4 women, 4 men) of the individuals were on non-steroidal anti-inflammatory medications for their OA. None had received an intra-articular injection (hyaluronan or corticosteroid) for 6 months prior to testing and none had participated in any prescribed rehabilitation program for the 6 months prior to testing.

Active controls (8 men, 7 women) were selected to match OA participants for age and sex. Controls were healthy and free from disease or medications that could affect muscle size/function and were recruited using identical inclusion/exclusion criteria enumerated above for volunteers with knee OA, with notable exceptions. Controls did not have symptoms consistent with knee OA (Bellamy et al., 1988) or radiographic evidence of significant knee osteoarthritis (K&L grade > 2), and self-reported (via Stanford Brief Activity Survey) being recreationally-active, but were not actively training for athletic competition. Five individuals (3 men, 2 women) were on stable regimens of statins, although their plasma creatine kinase levels were within the normative range and none had symptoms or signs of statin-induced myopathy. Additionally, 6 controls (4 men, 2 women) had hypertension and were on stable anti-hypertensive therapy, consisting of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (67%), diuretics (33%) and adrenergic blocking agents (17%). Data on skeletal muscle size and contractile function at the cellular and molecular levels for individuals with OA and controls ($n = 31$) have recently been published (Callahan et al., 2014b, 2015). Physical characteristics are reproduced to provide the necessary descriptive information and muscle fiber size and functional data for the purposes of correlation analyses to assess determinants of RTD. Written informed consent was obtained from each volunteer prior to their participation. The protocol was approved by the Committees on Human Research at the University of Vermont and conformed to the *Declaration of Helsinki*.

2.2. Knee extensor muscle function and size

Isometric knee extensor torque and torque-time parameters were assessed at 55°, as described previously (Toth et al., 2010), using a multi-joint dynamometer (HUMAC NORM; CSMi, Stoughton, MA). Briefly, volunteers were seated in the dynamometer with hips and shoulders firmly secured by padded straps and were instructed to perform maximum knee extension "as hard and as fast as you can" for 4–5 s, to best capture both peak torque and RTD, as has been shown during similar rapid isometric contractions (Bemben et al., 1990). At least 2 min was provided to recover between subsequent attempts. Data recorded by the dynamometer corresponding to torque and position were analyzed after testing using custom-written MatLab software (MathWorks; Natick, MA). The highest torque value during each contraction was considered peak isometric torque for that trial. After smoothing the torque data by applying a 4th order Butterworth low-pass filter (10 Hz cutoff), the first derivative was taken to assess RTD. The peak RTD of the 5 trials was considered the peak RTD for that individual. The RTD was also calculated from the onset of torque development to 25% (RTD_{25}) and 50% (RTD_{50}) of peak isometric torque, as described (Winters et al., 2014) to facilitate comparison with previous studies and explore the potential that such measures may provide unique insights into muscle performance. The onset of torque development was defined as the point at which torque exceeded 2% of peak torque for a given contraction. Peak RTD was also normalized relative to peak torque of that contraction (RTD_{rel}) to control for variation between subjects in muscle size and strength (de Ruiter et al., 1999; Korhonen et al., 2006; Ranatunga, 1982), as we observed that peak RTD was related to overall peak torque and muscle size (see the Results section, Section 3.2).

Whole muscle size was assessed using computerized tomography (CT) and dual energy x-ray absorptiometry (DEXA; GE Lunar Prodigy; Madison, WI) as described (Callahan et al., 2015). Briefly, a cross-sectional area (CSA) of lean tissue (based on radiodensity) in the quadriceps muscle group were assessed by CT at mid-thigh. Muscle mass of the thigh region was assessed using DEXA. The thigh region was defined as the tissue between the femoral condyles (distal) a proximal cut-point marking 60% of the distance between the femoral condyles and the greater trochanter.