Quadriceps neuromuscular function and self-reported functional ability in knee osteoarthritis

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1Schulich School of Medicine and Dentistry, The University of Western Ontario; 2School of Kinesiology, Faculty of Health Sciences, The University of Western Ontario; 3Department of Medical Biophysics and Robarts Research Institute, The University of Western Ontario; 4Hand and Upper Limb Centre, St. Joseph’s Health Care, The University of Western Ontario; 5Department of Medical Imaging, The University of Western Ontario; and 6Departments of Clinical Neurological Sciences and Physical Medicine and Rehabilitation, The University of Western Ontario, London, Ontario, Canada

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Berger MJ, McKenzie CA, Chess DG, Goela A, Doherty TJ. Quadriceps neuromuscular function and self-reported functional ability in knee osteoarthritis. J Appl Physiol 113: 255–262, 2012. First published May 17, 2012; doi:10.1152/japplphysiol.00947.2011.—The purposes of this study were to determine 1) the relationships of self-reported function scores in patients with knee osteoarthritis (OA) to both maximal isometric torque and to isotonic power at a variety of loads, and 2) the degree to which muscle volume (MV) or voluntary activation (VA) are associated with torque and power measures in this population. Isometric maximal voluntary contraction (MVC) torque and isotonic power [performed at loads corresponding to 10, 20, 30, 40, and 50% MVC, and a minimal load (“Zero Load”)] were measured in 40 participants with knee OA. Functional ability was measured with the Western Ontario and McMaster Osteoarthritis Index (WOMAC) function subscale. MV was determined with magnetic resonance imaging, and VA was measured with the interpolated twitch technique. In general, power measured at lower loads (Zero Load and 10–30% MVC, \( r^2 = 0.21–0.28, P < 0.05 \)) predicted a greater proportion of the variance in function than MVC torque (\( r^2 = 0.18, P < 0.05 \)), with power measured at Zero Load showing the strongest association (\( r^2 = 0.28, P < 0.05 \)). MV was the strongest predictor of MVC torque and power measures in multiple regression models (\( r^2 = 0.42–0.72 \)). VA explained only 6% of the variance in MVC torque and was not significantly associated with power at any load (\( P > 0.05 \)). Quadriceps MVC torque and power are associated with self-reported function in knee OA, but muscle power at lower loads is more predictive of function than MVC torque. The variance in MVC torque and power between participants is due predominantly to differences in MV and has little to do with deficits in VA.

knee osteoarthritis; isometric torque; isotonic power; WOMAC; quadriceps muscle volume

QUADRICEPS MUSCLE WEAKNESS has been widely reported in patients with knee osteoarthritis (OA) (7). Weak quadriceps muscles are associated with mobility impairments (24, 30) and may be a risk factor for disease incidence and progression of OA (36, 40, 46). Despite its clinical relevance, the magnitude and mechanisms of quadriceps muscle weakness in knee OA have not been fully characterized.

In studies of quadriceps function, knee OA is usually defined dichotomously (i.e., present or absent) using radiographic scoring such as Kellgren-Lawrence grading (KLG), with KLG ≥ II representing presence of OA. The validity of using KLG is limited when considering the discrepancy that exists between clinical and radiographic features of knee OA (3). Furthermore, quadriceps strength is more strongly associated with measures of clinical severity than the severity of radiographic findings (30, 41). Consequently, the use of radiographic criteria to define knee OA and its severity may result in the introduction of substantial clinical heterogeneity between study groups and potential underestimation of muscle weakness may occur in those with clinically severe disease. For example, Palmieri-Smith et al. (31) reported that maximal isometric torque was similar between those with radiographically moderate and severe knee OA, suggesting a ceiling effect for radiographic stratification. Alternatively, it is possible that using a perceived disease severity measure (e.g., self-reported pain and disability), while often not considered as objective as radiographic classification, could allow for better estimation of the relationship between quadriceps strength and a patient-related measure of severity in knee OA.

Most activities of daily living do not require maximal contractions; however, quadriceps strength in knee OA studies is usually reported as maximal isometric torque (7). Quadriceps isometric power, the product of torque and velocity of movement, across a range of submaximal loads, has yet to be assessed in patients with knee OA. Muscle power declines more precipitously than torque in healthy older adults (27, 45), and there is evidence that deficits in muscle power are better targeted with velocity-specific training (for a review, see 7). Furthermore, evidence from the literature on aging suggests that power is a more robust predictor of functional outcomes than torque, presumably because most activities of daily living require a combination of adequate torque and velocity (2, 11, 13, 34, 39). It is important to determine whether power measures are more robust predictors of function than maximal isometric torque in patients with knee OA, to target the impairments that are contributing most substantially to disability.

While it is well established that muscle mass is the primary determinant of torque in studies of health, training, and aging (14), the mechanisms of muscle weakness have not been as well delineated in the OA literature. A number of studies report reductions in voluntary activation (VA), the ability to activate all motor neurons at their maximum firing frequencies during maximal voluntary contractions) in limbs affected by knee OA; however, a systematic review by Pietrosimone et al. (33) highlighted substantial variability in the degree of VA impairment between studies. Furthermore, studies of patients with mild knee OA report no difference in VA compared with a healthy control group (21, 47). However, Petterson et al. (32) reported that VA explained 40% of the variance in maximal

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isometric torque in patients with severe radiographic knee OA, while single-slice quadriceps cross-sectional area predicted only 27% of the variance, suggesting that the ability to maximally activate the quadriceps during maximal contractions is an important determinant of muscle weakness in those with more severe knee OA. The relationship between muscle size and VA with torque and power has not been established in a clinically heterogeneous sample.

Therefore, the purposes of this study were to 1) determine the relationships of self-reported function scores in patients with knee OA to both maximal isometric torque and to isotonic power at a variety of loads and 2) provide information concerning the factors contributing to potential torque and power deficits, by measuring the degree to which muscle volume (MV) or voluntary activation (VA) are associated with torque and power in this population.

MATERIALS AND METHODS

Study participants. Forty community-dwelling men (n = 21) and women (n = 19), recruited from local orthopedic outpatients clinics, volunteered to participate in the study (mean age = 60.7 ± 6.0 yr, mean height = 1.67 ± 0.09 m, mean body mass = 87.5 ± 17.0 kg, mean body mass index = 30.7 ± 5.3 kg/m²). Participants were included if they met the clinical criteria for knee OA outlined by the American College of Rheumatology (11) and had persistent knee pain that required referral to an orthopedic surgeon. All participants received a diagnosis of knee OA from the orthopedic surgeon based on symptoms, clinical assessment, and radiographs (16). Exclusion criteria included musculoskeletal, neurological, or rheumatological impairment of the lower limbs other than knee OA, prior high tibial osteotomy, unicompartmental or total knee arthroplasty, or cardiopulmonary impairment that precluded performing vigorous muscle contractions. If a patient had bilateral knee OA, the limb with the more severe symptoms (as reported by the patient) was selected as the test limb. Ethical approval for the study was obtained from the local research ethics board, and written consent was obtained from each participant prior to study commencement.

The Western Ontario and McMaster Osteoarthritis Index (WOMAC) is a cross-culturally validated and reliable instrument encompassing three domains of disease status (pain, stiffness, and function) (6). The WOMAC Likert version 3.0 was used to measure clinical severity in this study. The physical function subscale is commonly used as an outcome measure in intervention studies in the knee OA population, and its validity, reliability, and responsiveness have been previously established (6, 22, 25); therefore it was selected as the measure of self-reported function in the present study. The WOMAC physical function subscale has 17 items, and total score ranges from 0 to 68. Each item has five response options (none, mild, moderate, severe, extreme) corresponding to scores 0–4, with higher scores reflecting increasing severity.

Experimental setup and test protocol. Participants completed the entire test protocol in a single visit to the laboratory. For all participants, testing began with an introduction to muscle stimulation at rest (incremental increase in stimulus intensity of single, 100-μs pulses, until a plateau in twitch torque was observed) to familiarize participants to evoked contractions. This was followed by testing of maximum isometric torque to allow for normalization for isometric power testing. Other tests (isometric power and VA) were completed in a random order. All tests were separated by a minimum of 10 min rest to avoid fatigue, potentiation, and learning effects.

Participants were seated upright in a multijoint dynamometer (Biodex System 3, Shirley, NY), with knee and hip angles of 90° and 100°, respectively. The center of rotation of the knee was aligned with the axis of rotation of the dynamometer’s lever arm. The force transducer was positioned with its bottom edge two fingerbreadths proximal to the medial malleolus of the test leg and fixed with a Velcro strap. A seat-belt strap was positioned across the lap to avoid unwanted movement of synergist hip flexors during quadriceps contractions. Participants completed a warm-up of 3–5 submaximal isometric contractions (i.e., the instructions were to “perform a contraction at 50% of what you think your maximum is”). Participants then performed repeated, brief (~5 s) isometric maximal voluntary contractions (MVCs) of the quadriceps (3–5 repetitions), each separated by a minimum of 90 s of rest. The highest MVC torque was utilized as the value for maximal isometric torque (heretofore known as “MVC torque”) and to normalize submaximal torque during subsequent isotonic power testing.

To investigate load-velocity and load-power relationships, participants performed a series of isometric concentric quadriceps contractions through a 90° range of motion at a series of loads (defined by a percentage of MVC torque), at maximum velocity. Range of motion was tailored to each individual participant such that 90° from their full extension was used as the starting point for contraction. Loads set at 10, 20, 30, 40, and 50% of isometric MVC were programmed in a random order using the Biodex Isometric Mode. An additional torque level with a load of 1 N·m (the minimum load added to the resistance of the force transducer) was performed to determine power and velocity at the lowest possible load (i.e., “Zero Load”). For each contractile intensity, participants were instructed to move through the concentric phase as quickly as possible and allow for passive return to the initial position. Immediately thereafter a second contraction was performed at that same load. Peak velocity and the load programmed into the dynamometer at each intensity level were used to calculate isotonic power. A 1-min rest period separated each load. Load verbal encouragement and visual feedback using the real-time digital torque and velocity tracings were used during all contractions to help ensure maximal intensity and velocity.

Introduction to stimulation and measurement of voluntary activation. Aluminum foil electrodes, wrapped in paper towel and soaked in water and conducting gel, were cut into 6-cm-wide strips and placed over the belly of the quadriceps (9). Before application of the electrodes, participants were asked to perform submaximal isometric contractions, so that the bellies of the quadriceps could be visualized and palpated, to avoid erroneous electrode placement over antagonist muscle fibers. The cathode was placed with its proximal edge at a point just distal to the inguinal crease and the anode was placed three fingerbreadths proximal to the base of the patella.

The interpolated twitch technique was used to measure VA (5). The premise of the technique is that additional torque resulting from a supramaximal stimulus superimposed on a MVC is indicative of suboptimal central drive to the motor neurons innervating the muscle. Normalizing the superimposed twitch amplitude at the resting, potentiated control twitch amplitude provides an index of VA \( VA = [1 - \left(\text{superimposed twitch/potentiated resting twitch}\right)] \times 100\% \). A constant-current stimulator (Digitimer DS7AH, Digitimer, Hertfordshire, UK) delivered doublets (pulse width = 100 μs, interpulse interval = 10 μs, maximal voltage 400 V) to the intramuscular nerve fibers of the quadriceps. To ensure the activation of all muscle fibers, a series of incremental stimuli were delivered to the resting muscle until a plateau in twitch amplitude was obtained. The stimulus intensity was then increased by an additional 10% to achieve supramaximality. Patients were then instructed to perform a MVC in an identical fashion to the description above. When a plateau in the torque tracing was reached during MVC (~3 s into the contraction), the stimulator was triggered manually by the study examiner. A second stimulus was delivered ~3 s following the MVC to obtain the resting potentiated twitch (equal to ~38% of MVC torque, Fig. 1). This procedure was repeated three or four times for each subject with a minimum of 90 s rest between trials. VA was calculated as the median for all trials.

Magnetic resonance imaging of quadriceps muscle volume. MRI scans of the thigh were acquired using a 3.0-T MR system (GE Discovery MR750, GE Healthcare, Waukesha, WI) with an eight-coil torso phased array. The patient was positioned supine in the scanner.
Subsequently, a 3D threshold-growing tool was used to grow ROIs for the septal spaces. Any errors produced by the automatic tool were corrected manually. The software automatically calculated volume for water-only images by manually outlining the most proximal and distal slices with the brush tool to create regions of interest (ROI). This ensured that nonmuscle tissue (in particular fat) was not included in the analysis of the thigh images. Image analysis was performed on the water only images produced by the IDEAL reconstruction for assessment of MV.

A combination of manual and semiautomated techniques using open-source OsiriX image processing software (version 3.7, Geneva, Switzerland) was used to analyze images and calculate MV. Analysis began proximally from the first slice not containing the gluteal muscle to the last distal slice containing the rectus femoris, as this region is thought to represent maximal thigh muscle mass (48) and because it is difficult to differentiate between thigh muscles at the most proximal and distal slices (10). Quadriceps MV was calculated from the water-only images by manually outlining the most proximal and distal slices with the brush tool to create regions of interest (ROI). This process was repeated for every tenth slice in-between, and missing ROIs were generated automatically. Once the quadriceps had been roughly outlined, all pixel values outside the ROIs were set to zero. Subsequently, a 3D threshold-growing tool was used to grow ROIs for the quadriceps muscle tissue only from a defined seedpoint within the muscle. This was done to ensure exclusion of nonmuscular tissue in the septal spaces. Any errors produced by the automatic tool were corrected manually. The software automatically calculated volume for the series of ROIs. The reliability of this method defined by the intraclass correlation coefficients (ICC; 2,1) and 95% confidence intervals were high (intrarater: ICC = 0.997, 0.991–0.999; and interrater: ICC = 0.997, 0.988–0.999 based on 16 and 11 cases, respectively).

Data reduction and statistics. Torque and velocity of the dynamometer arm were sampled at 100 Hz, AD converted with a 12-bit converter (CED micro1401 mk II, Cambridge Electronic Design, Cambridge, UK), and displayed in real-time on a laboratory computer using commercially available software (Spike2 ver. 5, Cambridge Electronic Design). During offline analysis, power for each submaximal load was calculated as the product of the load (N·m) and peak velocity generated during the second contraction at each intensity level (rad/s). It is important to note that movements made in the isometric mode are not truly isometric as the dynamometer is not able to maintain a constant load throughout the range of motion (26). However, these movements are still velocity dependent and therefore serve the objectives of this study. For simplicity, they will still be referred to as isometric contractions. MVC torque and power were normalized to body mass to account for body size differences among participants. A further analysis was conducted by normalizing MVC torque and power to quadriceps muscle volume (i.e., specific torque and specific power) to determine the relationship between these parameters and self-reported function. Normality of the WOMAC function subscale score was confirmed visually and with Kolmogorov-Smirnoff test; therefore parametric statistics were used for subsequent analyses. The predictive value of MVC torque and power (as well as specific torque and power measures) measures to self-reported function was described with individual univariate linear regression models. Stepwise multiple regression models were used to determine the predictive utility of relevant variables to MVC torque and power. Relevant variables (sex, age, height, body mass, VA, and MV) were identified as those displaying a significant correlation with the dependent variable, using the Pearson correlation coefficient. It should be noted that when torque and power were used in the multiple regression analyses (i.e., as dependent variables), raw values were utilized. Level of significance was set at P < 0.05. All statistical tests were performed with SPSS Statistics Gradpack (Version 17.0, Chicago, IL).

RESULTS

Mean data for WOMAC scores (total and subscale), MVC torque, power, MV, and VA are presented in Table 1.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
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<tbody>
<tr>
<td>Total WOMAC score</td>
<td>40 ± 20 (5:80)</td>
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<tr>
<td>WOMAC pain score</td>
<td>8 ± 4 (1:15)</td>
</tr>
<tr>
<td>WOMAC stiffness score</td>
<td>4 ± 2 (0:8)</td>
</tr>
<tr>
<td>WOMAC function score</td>
<td>28 ± 15 (2:57)</td>
</tr>
<tr>
<td>Isometric torque, N·m/kg</td>
<td>1.81 ± 0.75 (0.72:3.64)</td>
</tr>
<tr>
<td>Power, N·m·rad·s⁻¹·kg⁻¹</td>
<td>0.07 ± 0.02 (0.04:0.10)</td>
</tr>
<tr>
<td>MVC 10%</td>
<td>1.09 ± 0.62 (0.28:2.54)</td>
</tr>
<tr>
<td>MVC 20%</td>
<td>1.94 ± 1.11 (0.33:4.83)</td>
</tr>
<tr>
<td>MVC 30%</td>
<td>2.44 ± 1.36 (0.48:6.51)</td>
</tr>
<tr>
<td>MVC 40%</td>
<td>2.74 ± 1.57 (0.51:7.70)</td>
</tr>
<tr>
<td>MVC 50%</td>
<td>2.44 ± 1.48 (0.40:7.82)</td>
</tr>
<tr>
<td>MV, cm³</td>
<td>853 ± 320 (455:1451)</td>
</tr>
<tr>
<td>VA, %</td>
<td>93.6 ± 5.9 (77:7:100)</td>
</tr>
</tbody>
</table>

Values are presented as means ± SD (minimum:maximum). BMI, body mass index; WOMAC, Western Ontario and McMaster Osteoarthritis Index; Zero Load, isotonic power measured at a load equivalent to the sum of the mass of the force transducer and 1 N·m; MVC, maximal voluntary contraction; MV, muscle volume; VA, voluntary activation.

Fig. 1. The interpolated twitch protocol for a representative subject. Arrows denote the onset of stimulation. Voluntary activation was calculated as 1 – (superimposed twitch/potentiated resting twitch) × 100%.
Table 2. Coefficients of determination for univariate regression models using WOMAC function subscale as the dependent variable

<table>
<thead>
<tr>
<th>Coefficient of Determination ($r^2$)</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isometric torque (N·m/kg)</td>
<td>0.18</td>
</tr>
<tr>
<td>Zero Load</td>
<td>0.28</td>
</tr>
<tr>
<td>10% MVC</td>
<td>0.20</td>
</tr>
<tr>
<td>20% MVC</td>
<td>0.22</td>
</tr>
<tr>
<td>30% MVC</td>
<td>0.21</td>
</tr>
<tr>
<td>40% MVC</td>
<td>0.15</td>
</tr>
<tr>
<td>50% MVC</td>
<td>0.14</td>
</tr>
</tbody>
</table>

**MV and voluntary activation.** Only a subset of participants were able to participate in this portion of the testing protocol due to either contraindication to MRI (3 male and 1 female participants) or intolerance to stimulation (3 male and 1 female participant). None of these participants were outside of two SDs of the mean for the entire sample with respect to demographic characteristics or MVC torque and power measures and were therefore included in all of the analyses described above.

Variables displaying a significant association with MVC torque and isotonic power at multiple loads are presented in Table 3. These variables were subsequently included into stepwise multiple linear regression models with MVC torque and power measures as the dependent factors (i.e., 7 individual models for each measure). The predictive power of each model (adjusted $r^2$) and $\beta$-coefficients for the variables included in each model are reported in Table 4. MV was uniformly the most robust predictor of MVC torque and power measures.

**DISCUSSION**

The results of this study suggest that quadriceps MVC torque and isotonic power are not uniform across a functional spectrum of knee OA participants. Participants reporting greater functional deficit tended to have lower MVC torque and power. Furthermore, the observations that isotonic power at lower loads and higher velocities were more predictive of self-reported function than MVC torque are novel and have potential implications for rehabilitation of quadriceps weakness in knee OA. Another important finding of this study is the observation that MV is an important predictor of MVC torque and power, while deficits in VA contribute very little to the variance in MVC torque and power measures.

There are currently no universally accepted criteria encompassing the clinical, radiological, and pathological features of knee OA to grade disease severity, and attempts to establish valid markers of disease that reflect the natural history of structural changes in knee OA are ongoing (15, 16). Classifying disease severity using radiographic criteria (e.g., Kellgren-Lawrence) in isolation or in concert with clinical markers has the potential to create clinically heterogeneous subgroups as there is considerable variability in symptom severity even in those with the most radiographically severe knee OA (3). For example, Palmieri-Smith et al. (31) reported that there was no difference in isometric torque between those with moderate (i.e., KLG II) vs. severe (KLG > II) radiographic knee OA, and this could be due to variability in symptom severity within each radiographic subgroup. As OA symptoms display a stronger association with quadriceps torque than radiographic severity (30, 41), we employed WOMAC as a continuous variable to determine whether isometric torque and isotonic power are predictive of functional ability in this population. While this method is not without limitations (see below), WOMAC has been shown to be a valid measure of clinical disease severity (38). Furthermore, absolute WOMAC scores have been used previously to provide objective markers for clinically relevant endpoints (16), and self-reported disease severity scores have been shown to be independent predictors of both objective functional performance (22, 29) and the decision to undergo total knee arthroplasty (16, 51). The results of our study suggest that MVC torque and power are reduced across a functional spectrum of knee OA, such that those with more severe functional deficit have lower torque than those with milder WOMAC scores (Fig. 2). The implication of this finding is that studies using dichotomous methods of stratification (i.e., OA vs. control group) have the potential to underestimate the magnitude of muscle weakness in those with severe OA and conversely overestimate it in those with mild OA. It should be noted that the strength of association between MVC torque and power vs. function was moderate (Table 2). It is unclear whether the relationship between MVC torque and disease severity would be stronger if another self-report scale were used. For example the Knee Injury and Osteoarthritis Outcome score (KOOS) contains elements of the WOMAC, but also has questions related to leisure and sports participation (37).

This is the first study to report a relationship between quadriceps' isotonic power at a range of loads and clinical disease severity. Isotonic rather than isokinetic contractions were used because they are more functionally relevant (26) and because severely impaired participants may not be able to achieve the velocities required during high-velocity isokinetic contractions (20). While the observation that power declines across a clinical spectrum of OA is novel, certain parallels can be drawn to similar observations in healthy older adults. Studies of healthy elders report that power deficits compared with young subjects occur more precipitously and are of greater magnitude than isometric deficits (27, 45). In our study, power measured at the lowest loads were stronger predictors of the variance in self-reported function than isotonic torque. In particular, power measured at Zero Load and at 20% MVC explained a larger proportion of the variance in function than isometric torque and power measured at higher loads. Similarly, there is evidence to suggest that power is a more robust predictor of function than torque in healthy elderly subjects. Bean et al. (2) reported that leg extensor peak power measured in older adults with mobility limitations explained a greater degree of variance in performance on the Short Physical Performance Battery than torque. It is interesting that power at Zero Load and not peak power was the strongest predictor of subjective function in the present study. This finding is consistent with the results of several studies reporting that power at lower loads better predicts function than power at higher loads or isometric torque (11, 49). Furthermore, it has been shown that velocity is the component of muscle power (as opposed to force) that better determines performance on a gait velocity test (23). Intuitively, reductions in power at the lowest contraction intensities should be more detrimental to function, since many activities of daily living are performed at higher contraction velocities with...
low-to-moderate loads (e.g., gait velocity, prevention of falling, etc.). Based on our results we can also make inferences about the mechanisms of quadriceps MVC torque and power deficits in knee OA. The traditional paradigm of weakness in knee OA is one of muscle fiber atrophy due to disuse induced by a painful knee joint; that is, predominantly disuse atrophy (18). Our results support this paradigm, as MV was the primary predictor MVC torque and power across a clinical spectrum of knee OA patients (Table 4).

Reductions in VA have also been postulated as a mechanism for reductions in muscle torque in patients with knee OA, with some studies reporting VA deficits as high as ~34% in an OA-affected limb (33). Our results do not support a major role for VA deficits as a mechanism of weakness in knee OA. First the mean VA achieved in our study was ~94%. This is similar to values of quadriceps VA we observed previously in a study of healthy young men (VA = ~96%, Ref. 9). Second, in the regression model with isometric torque as the independent variable, it was clear that muscle volume alone accounted for

Fig. 2. Scatterplots and lines of best fit for the relationships between WOMAC function subscale score on the x-axis vs. torque and power [measured at “Zero Load” and 10–50% maximal voluntary contraction (MVC)] on the y-axis. Zero load: isotonic power measured at a load equivalent to the sum of the mass of the force transducer and 1 N-m.
a large proportion of the variance (72%), while VA explained only an additional 6%. Furthermore, VA was not included in the regression models for power (Table 4). This finding is in contrast to Petterson et al. (32), who reported that VA was more predictive of variance in torque than quadriceps cross-sectional area in patients with severe radiographic knee OA. The methodology herein to measure MV and VA could explain the discrepancy between our results and previous studies. For MV, the use of water-only images may have improved the accuracy of our measures by eliminating the possibility of confusing bright water signal for fat. Furthermore, we segmented a large volume of the quadriceps as opposed to estimating MV using a single midthigh slice of the quadriceps, which has been shown to have error of 10% or greater depending on the slice used (28). The observation that MV is the greatest predictor of MVC torque in knee OA is also consistent with the aging literature (12). The observation that MV contributes so significantly to the variance in MVC torque and power measures has implications to the rehabilitation of quadriceps weakness in knee OA. It is unclear whether current rehabilitation paradigms appropriately target MV (i.e., induce hypertrophy or delay atrophy) or whether increased MV is accompanied by improvement in function.

Specific torque and power measures (derived from normalizing MVC torque and power to quadriceps muscle volume) provide an index of muscle quality in vivo (8). Interestingly, specific torque and specific power at Zero Load, 10%, 40%, and 50% MVC did not predict a significant proportion of the variance in self-reported function, while specific power at 20% and 30% explained a very small proportion of the variance in self-reported function (~12%). The observation that relationships between MVC torque and power with self-reported function disappeared (or were weakened at 20% and 30% MVC) when controlling for MV suggests that muscle volume mediates the relationship between MVC torque and power with self-reported function. It also suggests that muscle quality is not altered across a clinical severity spectrum of knee OA patients; however, this requires substantiation with in vitro studies to assess individual muscle fiber quality.

With respect to VA deficits, differences in methodology between studies could explain the variability observed to date (33). For example, in some studies, VA has been calculated by normalizing the superimposed twitch to an unpotentiated resting twitch (17, 19), which would cause an overestimation of VA deficit, since the superimposed twitch itself is potentiated by the MVC. We controlled for many methodological errors that may occur when using the interpolated twitch technique, including 1) the use of a superimposed doublet for improved sensitivity, 2) verification of supramaximality of the stimulus, and 3) normalization of the superimposed twitch to a potentiated control twitch (44). Furthermore, differences in the method for measuring activation levels could explain inter-study variation. For example, Petterson et al. (32) employed the burst superimposition technique and calculated activation using the central activation ratio, which differs from the interpolated twitch technique utilized in the present study to calculate VA. Direct comparison of the techniques has yielded intrasubject differences in VA (4).

There are several limitations to interpretation of these findings. First, the temporal association (i.e., does weakness precede disease severity or vice versa?) between muscle weakness and clinical severity cannot be determined. There is evidence from large population studies that muscle weakness precedes incident OA symptoms and radiographic changes (41, 46); however, this finding is not uniform in the literature (42, 43). Second, although justification has been provided herein for the use of WOMAC as a continuous variable to measure disease severity, it is in fact an ordinal measure. Consequently, the intervals between successive WOMAC values may not be equal (i.e., the difference between a score of 10 and 11 may be different from between 20 and 21), which could affect the strength of the relationship observed. Third, the measures of function in this study were self-reported. It is unknown if the relationships between MVC torque and power vs. function would persist or be more robust with objective functional outcome measures, such as timed “Up and Go” or a timed stair-climb test. Furthermore, we did not include other measures of quadriceps performance that could influence self-reported function. For

### Table 3. Correlation coefficients for parameters significantly associated with torque and power measures

<table>
<thead>
<tr>
<th>Isometric Torque</th>
<th>Zero Load</th>
<th>10% MVC</th>
<th>20% MVC</th>
<th>30% MVC</th>
<th>40% MVC</th>
<th>50% MVC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>0.65</td>
<td>0.64</td>
<td>0.69</td>
<td>0.68</td>
<td>0.69</td>
<td>0.78</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Height</td>
<td>0.59</td>
<td>0.38</td>
<td>0.59</td>
<td>0.60</td>
<td>0.69</td>
<td>0.53</td>
</tr>
<tr>
<td>Body mass</td>
<td>0.42</td>
<td>0.34</td>
<td>0.35</td>
<td>0.35</td>
<td>0.35</td>
<td>0.35</td>
</tr>
<tr>
<td>VA</td>
<td>0.49</td>
<td>0.70</td>
<td>0.82</td>
<td>0.83</td>
<td>0.81</td>
<td>0.78</td>
</tr>
<tr>
<td>MV</td>
<td>0.78</td>
<td>0.70</td>
<td>0.82</td>
<td>0.83</td>
<td>0.81</td>
<td>0.78</td>
</tr>
</tbody>
</table>

All correlations reported are significant ($P < 0.05$). Empty space indicates no significant correlation between study parameters.

### Table 4. Stepwise multiple linear regression models for torque and power measures

<table>
<thead>
<tr>
<th>Isometric torque</th>
<th>Factors Included</th>
<th>Adjusted $r^2$</th>
<th>$\beta$-Coefficient</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1</td>
<td>MV</td>
<td>0.72</td>
<td>0.85</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Model 2</td>
<td>MV, sex</td>
<td>0.76</td>
<td>0.70, 0.26</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Model 3</td>
<td>MV, sex, VA</td>
<td>0.82</td>
<td>0.62, 0.34, 0.26</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Power</th>
<th>Factors Included</th>
<th>Adjusted $r^2$</th>
<th>$\beta$-Coefficient</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zero Load</td>
<td>MV</td>
<td>0.42</td>
<td>0.66</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>10% MVC</td>
<td>MV</td>
<td>0.59</td>
<td>0.78</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>20% MVC</td>
<td>MV</td>
<td>0.62</td>
<td>0.80</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>30% MVC</td>
<td>MV</td>
<td>0.58</td>
<td>0.77</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>40% MVC</td>
<td>MV</td>
<td>0.55</td>
<td>0.75</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>50% MVC</td>
<td>MV</td>
<td>0.57</td>
<td>0.76</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Variables excluded: height, body mass; sex, height, age; height, body mass; sex, age, height, body mass; sex, age, height, body mass; sex, age, height, body mass; sex, age, height, body mass, VA; sex, age, height, body mass, VA.
example, it is possible that quadriceps endurance could be impaired in knee OA and quadriceps fatigue could have a strong association with function; however, this requires further study.

The results of this study have implications for future study design, rehabilitation, and further understanding of the mechanisms of neuromuscular dysfunction in knee OA. By defining disease severity using clinical criteria, we observed that quadriceps MVC torque and power are not uniform across a functional spectrum of knee OA. Furthermore in this first investigation of isometric muscle power in knee OA, power at high velocities displayed a stronger relationship with self-reported function than isometric torque, suggesting that these deficits should be addressed to attenuate disability in knee OA patients. Finally, MV is the factor that is most predictive of MVC torque and power in knee OA, while VA contributed very little to the variance in isometric torque and did not contribute to the variance in power at any load. This suggests that MV (i.e., attenuating muscle atrophy or inducing muscle hypertrophy) could be an objective benchmark for determining the efficacy of rehabilitation protocols in future research studies.

DISCLOSURES
No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS
Author contributions: M.J.B., C.A.M., D.G.C., A.G., and T.J.D. approved final version of manuscript. M.J.B., C.A.M., and T.J.D. edited and revised manuscript; M.J.B., C.A.M., performed experiments; M.J.B. prepared figures; M.J.B. and T.J.D. drafted manuscript; T.J.D. analyzed data; M.J.B., C.A.M., A.G., and T.J.D. interpreted results of research.

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REFERENCES


