

Thigh Muscle Cross-Sectional Areas and Strength in Advanced versus Early Painful Osteoarthritis – an Exploratory Between-Knee, Within-Person Comparison in Osteoarthritis Initiative Participants

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Full Length Article: 3800 words

Funding Source:

Image and clinical data acquisition was funded by the Osteoarthritis Initiative (OAI), which in turn is funded by the National Institute of Health, a branch of the Department of Health and Human Services, and conducted by the OAI Study Investigators. Private funding partners of the OAI include Merck Research Laboratories; Novartis Pharmaceuticals Corporation, GlaxoSmithKline; and Pfizer, Inc. Private sector funding for the OAI is managed by the Foundation for the National Institute of Health. The image analysis was supported by funds from Paracelsus Medical University Research Fund (PMU FFF).

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ABSTRACT

Objective: To compare side-differences and longitudinal change in thigh muscle anatomical cross-sectional areas (ACSAs) and (specific) strength between knees with painful early vs. advanced radiographic osteoarthritis, using a within-person, between-knee study design.

Methods: 44 of 2678 Osteoarthritis Initiative participants (31 women; 13 men) met the inclusion criteria of bilateral frequent knee pain, medial joint space narrowing (mJSN) in one knee, and no medial (or lateral) JSN in the contralateral knee. An axial T1-weighted spin-echo MRI sequence was used to determine thigh muscle ACSAs and MRI signal (mean and standard deviation) of the quadriceps (heads), hamstrings, and adductors at consistent locations. Isometric muscle strength was determined in extension/flexion (Goodstrength chair). Baseline quadriceps ACSA and strength were considered primary, and longitudinal changes of these secondary endpoints (paired t-tests).

Results: No significant side-differences in quadriceps (heads, or other thigh muscle) ACSAs or (specific) strength were observed between mJSN vs. no-JSN knees (and between JSN grade1 or JSN grade2/3 vs. no-JSN knees), neither in men nor in women. Two-year longitudinal changes in thigh muscle ACSAs and (specific) strength were small ($\leq 5.2\%$) and were not significantly different between mJSN and no-JSN knees. No consistent side-differences or longitudinal changes were observed in muscular MRI signal.

Conclusion: These exploratory cross-sectional findings do not support the concept that loss of (quadriceps) muscle mass, strength, or quality contribute to structural progression from early to advanced radiographic knee OA. The longitudinal findings indicate that structural progression of knee osteoarthritis is not necessarily associated with a concomitant loss of muscle function.

Key Words: Muscle – Knee osteoarthritis – Cross-sectional area – Strength – Magnetic Resonance Imaging

SIGNIFICANCE & INNOVATIONS

- This is the first study to compare thigh muscle anatomical cross-sectional areas (ACSAs) and strength cross-sectionally and longitudinally in knees with painful early vs. advanced radiographic OA (medial JSN).
- A between-knee, within-person study design was used to eliminate between-person confounding by differences in sex, age, weight, occupation/physical activity, and psychological factors between JSN and no-JSN knees.
- The exploratory cross-sectional findings do not support the concept that loss of (quadriceps) muscle mass, strength, or quality contribute to structural progression from early to advanced radiographic knee OA, and that muscle strengthening can potentially modify structural progression
- The longitudinal findings indicate that advanced radiographic status and structural progression in knee osteoarthritis are not necessarily associated with a concomitant loss of muscle function.

INTRODUCTION

Knee osteoarthritis (OA) is the leading cause for knee pain in people aged >55 years(1). Joint space narrowing (JSN) is a radiographic sign of advanced knee OA and has been shown to be associated with pain, when comparing knees with discordant radiographic OA status in the same person(2). Quadriceps weakness is a potentially modifiable risk factor for the onset or (structural) progression of knee OA(3). Quadriceps strengthening has been recommended by current guidelines for the clinical management of knee OA(4), but it is presently unclear, whether such therapeutic intervention can slow the structural progression of knee OA.

Recent studies found high quadriceps strength to be protective against the incidence of symptomatic knee OA, but failed to provide strong evidence for a role of muscle strength in the onset of radiographic knee OA(5-7). Because thigh muscles are important for providing stability of the knee during physical activity(7), and because joint instability is known to cause structural deterioration of OA joints (8), it is plausible to assume that adequate muscle strength may protect against structural progression of knee OA. Studies on the relationship between quadriceps strength and radiographic progression (once radiographic change is apparent), however, have produced inconsistent results (9-12). A recent study reported a relationship between muscle strength and worsening of the JSN grade in women, but not in men(13). A potential explanation for the inconsistency of the above findings is that experimental measurement of muscle strength is confounded by the willingness and ability of study participants to exert maximal voluntary muscle activation, and that these measures may therefore have limited reliability in patients with (painful) knee OA (14;15). A recent study investigated anatomical cross-sectional areas (ACSAs) and specific strength (strength/ACSA, as a measure of muscle quality) of thigh muscles using computer tomography in subjects with and without radiographic knee OA (16), but we are

not aware of previous studies that compared thigh muscle ACSAs or quality at different stages of radiographic knee OA. Further, we are not aware of previous work that has compared longitudinal changes in muscle ACSAs (or strength) in knees with early vs. advanced radiographic knee OA. Because participants with advanced (radiographic) knee OA may be expected to have greater functional limitations (17;18), limb disuse may secondarily cause muscle atrophy and fiber degeneration (19), hence leading to a vicious circle of structural (and functional) deterioration.

Because subjects with (different stages of) knee OA may display differences in body mass index (BMI) (16) and physical activity levels, which can both confound the analysis of muscle ACSAs and strength, we selected a between-knee, within-person design (2;20-22) for the current exploratory study. Magnetic resonance imaging (MRI) has been validated for measuring muscle ACSAs in vivo (23;24) and has recently been shown to be sensitive to short-term training effects(25) and between-limb muscle differences, using a between-knee, within-person study design(26). Further, we used MRI to extract muscle signal characteristics, as a potential measure of muscle quality (lipid content). Specifically, we tested the following hypotheses:

- 1) Thigh muscle (particularly quadriceps) ACSAs and strength are smaller and muscle MRI signal (T1-weighted) is greater in frequently painful knees with advanced radiographic OA (knees with JSN) than in frequently painful knees with early OA (knees without JSN).
- 2) Longitudinally, thigh muscle (particularly quadriceps) ACSAs and strength decrease, and muscle MRI signal increases, and this change is stronger in frequently painful knees with advanced radiographic OA than in frequently painful knees with early OA over a two year observation period.

Further, we explored whether results differ for knees with more severe JSN (grade 2/3) vs. no-JSN knees compared with knees with less severe JSN (grade 1) vs. no-JSN knees, and potential sex-differences in the above relationships.

PARTICIPANTS & METHODS

Participants

Participants for this study were drawn from the first half (2678 cases) of the Osteoarthritis Initiative (OAI) cohort (clinical data set 0.2.1) The OAI cohort consists of female and male participants aged 45-79 years ([http://www.oai-ucsf.edu/datarelease/.](http://www.oai-ucsf.edu/datarelease/)) The participants for this study were specifically selected to permit a between-knee, within-person comparison of painful knees with advanced radiographic knee OA (i.e. with JSN) vs. painful knees with early OA (i.e. without JSN) (20-22). At the baseline visit they had a BMI >25 kg/m²; frequent pain in both knees (pain, aching or stiffness in or around the knee for at least 1 month during the past 12 months); medial JSN (mJSN grade 1-3)(27) in one knee (with either no lateral JSN [lJSN], or less lJSN than mJSN), and neither mJSN nor lJSN in the contralateral knee. The primary selection was based on the radiographic baseline readings performed at the OAI clinical sites and was complemented by either central OAI readings (when available at the time point of participant selection) or by consensus evaluation of two experienced readers (A.G and D.H.) (20-22). Compared with our previous study, which included 73 no-JSN and 73 contralateral grade 1-3 mJSN knees (21), three participants with infrequent pain in the no-JSN knee were excluded.

Evaluation of thigh muscle ACSAs from MRI

Of the 70 participants selected, 44 had baseline axial MRI acquisitions of the thighs available (imaging data set 0.C.2), and 37 also had two-year-follow-up MRIs available (imaging data sets 3.C.2). These were acquired using a 3 Tesla Magnetom Trio scanner (Siemens Healthcare Erlangen, Germany), with participants positioned supine and the epiphyseal line of the femur being delineated via axial and coronal localizer images (Fig. 1a). The muscle acquisition of 15 axial non-fat-suppressed T1-weighted spin-echo MRIs (TR=500ms, TE=10ms) started 10cm proximal to the epiphyseal line (Fig. 1a) and extended 7.5 cm proximal (slice thickness 0.5cm, in-plane resolution 0.977mm, field of view 500mm, matrix 512x512). Details regarding the MRI techniques and protocols are available online (www.oai.ucsf.edu/datarelease/operationsmanuals.asp).

Given the fixed distance between the epiphyseal line and the most proximal slice, the muscle region of interest (ROI) delineated had an inconsistent location relative to the femur (and the thigh muscles), dependent on the individual femoral length. To adjust for this variation, we estimated the total femoral length from the body height, as described previously (26;28). A 33% location (from distal to proximal) was selected to analyze the quadriceps, hamstrings and adductors; this was the most proximal slice that could be consistently selected across the study participants (given their range of body heights), with proximal slices being more representative of total thigh muscle volumes than distal ones (29). ACSAs of single quadriceps heads (vastus medialis, lateralis, and intermedius, and rectus femoris) were assessed in the most distal slice that could be consistently measured in all participants (30% femoral length from distal), because these can be better separated distally than proximally. In some cases, it was noted that the image acquisition was not performed based on the 10cm distance measure from the epiphyseal line (Fig 1a), but from the knee joint space (n=4). In these cases, the 33% and 30% locations were selected as

closely as possible, adjusting for deviation from the original protocol. In cases in which the localizer images were lacking (n=10), the location of the axial images was visually compared to other cases, to confirm their position relative to the epiphyseal line or knee joint space.

Custom software was used to manually segment the quadriceps, hamstrings and adductors (33% slice), excluding inter-muscular adipose tissue (26) (Fig 1b). The same software was used to segment the four quadriceps heads and to determine the ACSAs and MRI signal (mean and standard deviation [SD]) of the segmented muscles, with T1-weighted high signal representing intramuscular lipid content (i.e. fatty atrophy). All segmentations were performed by a single trained reader (A.R.) who was blinded to the radiographic knee OA status and to the time point of the acquisitions (baseline, follow-up). Test-retest images were not available for OAI participants; however, the reproducibility for similar measurements amounted to 1.7% (coefficient of variation, four-fold repositioning of four participants in the same session) for the quadriceps, 3.4% for the hamstrings, and 9.9% for the adductors (30), with the greater precision error in the adductors potentially due to their oblique orientation relative to the axial images.

Evaluation of thigh muscle strength

Measurements of maximum isometric extensor and flexor strength were available from the OAI data base (clinical data set 0.2.2) for 42 of the above 44 participants; in two participants the strength data were not used, because values were considered obvious outliers (1 and 6 N for flexor strength, respectively). Of the 37 participants with longitudinal image data, 29 had strength measurements at baseline and 2 year follow-up (clinical data set 3.2.1). Muscle strength was measured using the “Good Strength Chair” (Metitur Oy, Jyvaskyla, Finland)

(26;31;32). The specific strength (N/cm^2) was calculated by dividing the extensor strength by the quadriceps ACSA, and the flexor strength by the hamstring ACSA (16;26).

Statistical analysis

Given its important role in knee biomechanics and the focus on the quadriceps in past literature(7), the comparison between baseline differences in quadriceps ACSAs in mJSN vs. contralateral no-JSN knees was considered the primary analysis, and comparison of (specific) extensor strength the co-primary analysis. Longitudinal (percent) change in quadriceps ACSAs in mJSN vs. contralateral no-JSN knees between baseline and two-year follow-up was considered the secondary analysis, and comparison of longitudinal change in (specific) extensor strength the co-secondary analysis. All other variables were considered exploratory. Two-sided paired t-tests were used to evaluate baseline differences in the Western Ontario McMaster Universities (WOMAC) pain scores(33) and of the measured variables. The correlation of quadriceps ACSAs with extensor strength and that of hamstring ACSAs with flexor strength was calculated in no-JSN and in mJSN knees, using linear regression (Pearson correlation coefficients). Given previous findings in cohorts with early and late-stage knee OA(7), sensitivity analyses were performed in strata of mJSN1 vs. no-JSN knees, and mJSN2/3 vs. no-JSN knees. Given previous findings on the relationship of muscle strength with radiographic progression in women vs. men (5;7), exploratory sensitivity analyses were also performed for both sexes.

Paired t-tests were used to descriptively evaluate whether longitudinal changes over time were significantly different from zero, and whether longitudinal percent changes were different between mJSN and no-JSN knees. Rates of change were further compared between mJSN1 vs. mJSN2/3 knees, between no-JSN knees of men vs. women, and between

mJSN knees of men vs. women (unpaired t-test). No adjustment for multiple comparisons was made, to not inadequately dilute the power of this exploratory study.

RESULTS

Demographics

44 participants (31 women; 13 men; age 47 to 78 years) fulfilled the specific inclusion criteria for the cross-sectional component of this within-person comparison. Ranges were 142-187 cm (mean±SD = 164±10 cm) for body height, 56.5-118.2 kg (mean±SD = 83.1±14.0 kg) for body weight, and 25.1-42.3 kg/m² (mean±SD = 30.8±4.3 kg/m²) for BMI. Of 27 mJSN1 knees, 17 were from women and 10 from men, and of 17 mJSN2/3 knees, 14 were from women and 3 from men. The WOMAC knee pain score (range 0-20, with 20 being the worst) was 5.9±4.5 (mean±SD) in the mJSN knees vs. 4.5±4.2 in the no-JSN knees (p=0.002). The score was 4.1±3.5 vs. 3.6±3.4 in mJSN1 vs. no-JSN knees (p=0.23), and 8.8±4.6 vs. 6.1±4.9 in mJSN2/3 vs. no-JSN knees (p=0.0009).

Cross-sectional comparisons

There were no significant differences between quadriceps ACSAs in mJSN vs. no-JSN knees (p=0.60; Table 1). Further, no significant differences were observed in absolute extensor strength and specific strength (p=0.91 and 0.33, respectively; Table 1). The correlation between quadriceps ACSA and extensor strength was r=0.43 in no-JSN knees (95% confidence interval [CI] 0.14-0.65) and r=0.54 in mJSN knees (95% CI 0.27-0.73); the correlation between hamstring ACSA and flexor strength was r=0.38 in no-JSN knees (95% CI 0.08-0.61) and r=0.60 in mJSN knees (95% CI 0.35-0.77). These correlations were significant different from zero (p<0.05), but were not significantly different between mJSN vs. non-JSN

knees ($p > 0.20$; Fischer Z-test). Further, no significant differences were found in other exploratory endpoints of quadriceps heads ACSAs, hamstring and adductor ACSAs, flexor (specific) strength ($p \geq 0.12$; Table 1), and in the mean and SD of the MRI signal of the segmented muscles ($p \geq 0.08$; Supplement Table 1).

Results were similar when stratifying the analysis for mJSN1 vs. no-JSN knees and for mJSN2/3 vs. no-JSN knees (Table 2); only the adductors in mJSN2/3 knees displayed significantly greater (but not smaller) ACSAs than contralateral no-JSN knees ($p = 0.0018$).

Although mJSN knees tended to have greater quadriceps ACSAs than no-JSN knees in men ($+3.0 \pm 14\%$), and lower ones in women ($-2.3 \pm 14\%$; Table 3), the opposite trend was observed for quadriceps strength ($-0.6 \pm 18\% / +3.2 \pm 24\%$). However, none of the differences reached statistical significance (Table 3). Further, no significant differences were observed in mJSN1 and mJSN2/3 strata vs. contralateral no-JSN knees in either men or women (Table 3); only adductor ACSAs in female mJSN2/3 knees were significantly greater (not smaller) than those in contralateral no-JSN knees ($p = 0.01$).

Longitudinal comparisons

The longitudinal (percent) changes were generally small ($\leq 1.9\%$ for the quadriceps and $< 10\%$ for other thigh muscle ACSAs; $\leq 5.2\%$ for extensor and $< 6.1\%$ for flexor strength); no significant changes were observed in quadriceps ACSAs or (specific) strength over two years (Table 4). Only the hamstring ACSAs of no-JSN knees (but none of the other measures) showed a significant reduction between baseline and follow-up ($-2.2 \pm 6\%$; $p = 0.03$; Table 4). No significant differences in longitudinal rates of change were observed between mJSN and contralateral no-JSN knees ($p \geq 0.16$; Table 4). Although longitudinal loss in muscle ACSAs

tended to be greater in mJSN2/3 than in mJSN1 knees, the opposite trend was observed for strength, but none of these trends reached statistical significance ($p \geq 0.20$; Table 4).

A trend towards greater loss of quadriceps ACSAs and extensor (specific) strength was observed in women compared to men (both in no-JSN and in mJSN knees), but none of the differences (between baseline and follow-up) was statistically significant; except for adductors ACSAs in mJSN vs. no-JSN knees in men ($p=0.04$; Table 5). Rates of change did not differ significantly between both sexes ($p \geq 0.17$; Table 5).

With regard to the MRI signal intensity, some significant changes were noted, and some differences in change between no-JSN and mJSN knees, but these only reached borderline significance, only applied to single muscles and strata at a time, and were not in a consistent direction (Supplement Tables 1 and 2).

DISCUSSION

The aim of this study was to test whether thigh muscle (particularly quadriceps) ACSAs and strength are smaller (and muscle MRI T1 high-signal areas greater) in knees with advanced radiographic OA than in knees with early OA, and whether muscle ACSAs and strength decrease, (and MRI T1 high-signal area increase) longitudinally, particularly in knees with advanced radiographic OA. However, our findings do not support the two above hypotheses, as we find only small (non-significant) differences in (quadriceps) ACSAs, strength and signal between mJSN and contralateral no-JSN knees, and only small changes over time.

Limitations of this study include the relatively small sample size, but its strength is the between-knee, within-person approach (2;20-22) that eliminates between-person confounding, such as differences in sex, age, weight, height, BMI, occupation/physical

activity levels, or willingness/ability to perform maximal voluntary muscle activation (14;15;34-38). A similar design was used in a previous study (26) that identified highly significant differences in quadriceps ACSAs and strength between knees with frequent pain and (contra-lateral) knees without pain (but the same KLG) in a similar number of participants (n=48). Given the mean, SD, and correlation of quadriceps ACSA between mJSN and no-JSN knees in the current study, a post-hoc analysis revealed that a side difference of $\geq 5.9\%$ could be detected with a power of at least 90% (non-central Student t-distribution).

The between-knee, within-person design is particularly beneficial for investigating parameters such as muscle ACSAs and strength that strongly depend on body height and weight (7), age (39), exercise levels (25), depression and other psychological factors(40), etc.. Brandt et al. (40) reported subjects with knee pain (but without radiographic knee OA) to have lower quadriceps and hamstring strength compared with patients with symptomatic (radiographic) knee OA, but these also had a lower BMI and more severe depression. Considerable systematic differences in body height and weight between knees with and without radiographic knee OA were also noted in another (cross-sectional) study on the role of muscle quality in OA (16). Another strength of our study is that, in contrast to other studies using OAI data (39;41), the anatomical location of the muscle measurements was adjusted to variation in body height (and femoral length). Further, potential remaining variations due to non-linear relationships between body height and femoral length did not affect the current comparison, because the same (anatomical) level was compared between both thighs. Although measures of muscle volumes are potentially more reliable than those of ACSAs, a recent study showed that both displayed high (and similar) correlations with in vivo joint moment magnitude (42).

Because a recent study found that pain had a significant effect on quadriceps (but not other thigh muscle) ACSAs and strength, even within defined radiographic strata of knee OA (26), we only included participants with frequent pain in both knees. Still, the WOMAC scores were slightly greater in the mJSN vs. no-JSN knees, and these differences may potentially cause overestimation of differences between knees with advanced radiographic vs. early OA. However, no differences were recorded, albeit our previous study showed that the methods used are highly sensitive, even in small numbers of participants when applied to a between-knee, within-person study design (26).

A further limitation of the current study is the relatively large number of parameters tested. To account for this, we focused on the quadriceps as primary (cross-sectional) and secondary (longitudinal) endpoint. Although the current study does not provide longitudinal data on muscle status in knees progressing from early to advanced radiographic knee OA, we attempt to infer the role of muscle by directly comparing knees with early and advanced OA in the same person. Yet, it needs to be kept in mind that our results may be specific to advanced radiographic vs. early painful knee OA, and cannot address questions pertaining to the onset of structural (radiographic) or symptomatic knee OA (5;7).

To our knowledge, this is the first study to systematically investigate (quadriceps) ACSAs in knees with different stages of (radiographic) knee OA, both cross-sectionally and longitudinally. Given the lack of differences in muscle status between mJSN and contralateral no-JSN knees, it is difficult to envisage how compromised muscles status should have led to structural progression from early to advanced radiographic knee OA in the participants studied. Further, the study of specific muscle strength and MRI signal characteristics (potentially associated with intra-muscular fat) did not suggest differences in muscle quality between mJSN and no JSN knees. Our study is in contrast to that of Petterson

et al (43) who found significantly lower muscle strength in patients with unilateral knee OA, but these authors compared knees with end-stage radiographic status (KLG4, prior to knee replacement) with contralateral knees that exhibited a pain score of <5 (of 10) on a verbal analogue scale and were yet unaffected by disease. The current results extend previous findings that did not observe a relationship between (quadriceps) muscle strength and structural (radiographic or MRI) progression of knee OA (9;10;12;44). Taken together with studies on a more evident relationship between pain and muscle status (26;40;44), our findings suggest that muscle loss (or weakness) are more likely directly caused by pain, but do not appear to cause structural progression of knee OA, once knee OA is present(2;44). However, our results do not exclude the possibility that there may be a threshold effect and that loss in muscle strength contributes to structural progression only if falling below a certain (although yet unknown) critical value, below which joint stability begins to be compromised. Further, our current results do not pertain to the onset (incidence) of symptomatic or radiographic knee OA in previously healthy knees (5;16;45), and disentangling this complex relationship warrants further prospective, longitudinal studies(16) , particularly because causality cannot be inferred from cross-sectional associations, or non-causality from lack of cross-sectional associations.

We do not find significant differences in longitudinal rates of change in (quadriceps) muscle ACSAs and specific strength between mJSN and no-JSN knees, indicating that early or advanced radiographic knee OA is not associated with a (measurable) decline in muscle status. The methodology used for measuring ACSAs, however, has previously been shown to be sensitive to change over time in short-term exercise intervention(25). In our current study, rates of change tended to be greater in women than in men, but the difference did not reach significance; confirmation of this observation is hence required in a larger cohort.

Our findings are in agreement with observations from Beattie et al. (39), who found similar rates of change in quadriceps muscle volume over two years in female OAI participants with radiographic OA compared to those without knee OA (39). Our results are particularly noteworthy, because we have shown previously that the mJSN knees studied here showed substantially greater longitudinal medial compartment cartilage loss in MRI over one year (about 1.8% per annum) than those without JSN (about 1%) (20). Hence, structural progression of knee OA does not appear to be necessarily associated with a concomitant loss of muscle mass, strength or quality.

In conclusion, these exploratory cross-sectional findings do not support the concept that loss of (quadriceps) muscle mass, strength, or quality contribute to structural progression from early to advanced radiographic knee OA. The longitudinal findings indicate that structural progression of knee osteoarthritis is not necessarily associated with a concomitant loss of muscle function.

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Acknowledgements

We would like to thank the OAI participants, OAI investigators and OAI Clinical Center's staff for generating this publicly available image data set. Further, we would like to thank Dr.

Wolfgang Hitzl (Paracelsus Medical University Research Office) for statistical advice. The image analysis was supported by funds from Paracelsus Medical University Research Fund.

Disclosure of interest

The images were acquired by the OAI, a public-private partnership comprised five contracts (N01-AR-2-2258; N01-AR-2-2259; N01-AR-2-2260; N01-AR-2-2261; N01-AR-2-2262) funded by the National Institute of Health, a branch of the Department of Health and Human Services, and conducted by the OAI Study Investigators. Private funding partners of the OAI include Merck Research Laboratories; Novartis Pharmaceuticals Corporation, GlaxoSmithKline; and Pfizer, Inc. Private sector funding for the OAI is managed by the Foundation for the National Institute of Health. This manuscript has received the approval of the OAI Publications Committee based on a review of its scientific content and data interpretation.

Felix Eckstein is CEO and is co-owner of Chondrometrics GmbH, a company providing MR image analysis services. He provides consulting services to MerckSerono, Novartis, Sanofi Aventis, and Abbot. Wolfgang Wirth is partially employed and is co-owner of Chondrometrics GmbH, and provides consulting services to MerckSerono. Torben Dannhauer and Martin Hudelmaier have part time appointments with Chondrometrics GmbH. Martina Sattler and Kent Kwoh have no competing interests. David Hunter is funded by an Australian Research Council Future Fellowship.

Author's Contribution

All authors have made substantial contributions to: (1) the conception and design of the study, or acquisition of data, or analysis and interpretation of data, (2) drafting the article or

revising it critically for important intellectual content, (3) final approval of the version to be submitted.

Figure legend:

Figure 1a. Coronal localizer image: *The acquisition of the 15 axial non-fat-suppressed spin-echo T1-weighted MRIs (0.5cm) started 10cm proximal to the distal femoral epiphyseal line and extended 7.5cm proximally. Body height was used to determine two slices located at 30% and 33% of femoral length from distal to proximal in each participant, to perform muscle segmentations at a consistent anatomical location.*

1b. Axial T1-weighted MR images of the thigh with segmented muscles: *The top image shows the segmented quadriceps (pink), hamstrings (dark blue), and adductors (turquoise) at 33% of femoral length (from distal to proximal); the bottom image shows the segmented quadriceps heads: Vastus medialis (brown), lateralis (yellow), and intermedius (turquoise), and rectus femoris (purple) at 30% of femoral length (from distal to proximal).*