2 **QUADRICEPS VOLUMES ARE REDUCED IN PEOPLE WITH PATELLOFEMORAL JOINT OSTEOARTHRITIS**

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2   **ABSTRACT**

Objectives

4   This study aimed to (i) compare the volumes of vastus medialis, vastus lateralis, vastus

intermedius and rectus femoris and the ratio of vastus medialis and vastus lateralis (VM/VL)

6   volumes between asymptomatic controls and patellofemoral joint osteoarthritis (PFJ OA)

participants; and (ii) assess the relationships between cross-sectional area (CSA) and volumes

8   of the vastus medialis and vastus lateralis in individuals with and without PFJ OA.

10   **Methods**

Twenty-two participants with PFJ OA and 11 controls aged $\geq$ 40 yrs were recruited from the

12   community and practitioner referrals. Muscle volumes of individual quadriceps components

were measured from thigh magnetic resonance (MR) images. The CSA of the vastus medialis

14   and lateralis were measured at 10 equally distributed levels (femoral condyles to lesser

femoral trochanter).

16

Results

18   PFJ OA individuals had smaller normalized vastus medialis (mean difference 0.90 cm^3.kg^{-1},

α=0.011), vastus lateralis (1.50 cm^3.kg^{-1}, α=0.012) and rectus femoris (0.71 cm^3.kg^{-1},

20   α=0.009) volumes than controls. No differences in the VM/VL ratio were observed. The CSA

at the 3rd level (controls) and 4th level (PFJ OA) above the femoral condyles best predicted

22   vastus medialis volume, whereas the vastus lateralis volume was best predicted by the CSA at

the 7th level (controls) and 6th level (PFJ OA) above the femoral condyles.

24

Conclusion

2   Reduced quadriceps muscle volume was a feature of PFJ OA. Muscle volume could be

     predicted from CSA measurements at specific levels in PFJ OA patients and controls.

4

Keywords

6   Vastus medialis, Vastus lateralis, Vasti, Knee, Patella, Arthritis, Muscle size

INTRODUCTION

The patellofemoral joint (PFJ) is the compartment most commonly affected in symptomatic

knee osteoarthritis (OA)[1] and is the dominant source of symptoms associated with knee

OA[2,3].Contemporary clinical guidelines recommend tailored OA management strategies to

optimize clinical outcomes, yet there is little known about modifiable impairments that could

guide effective management of PFJ OA. Quadriceps weakness plays an important role in the

pathogenesis of knee OA[4] and appears to be more important in the progression of PFJ disease

than tibiofemoral joint (TFJ) disease[5]. Dynamometry provides an indication of the force

produced by the entire quadriceps; however, the limitations of this technique include an

inability to evaluate contributions of the individual quadriceps subregions. This may be

important for PFJ OA, since imbalance of the medial (vastus medialis) and lateral (vastus

lateralis) quadriceps force may affect PFJ alignment[6] and hence PFJ contact pressure[7].

Considering that increased PFJ contact pressure is likely to be associated with the initiation

and progression of PFJ OA, an imbalance in the force generating capacity of the medial and

lateral vasti in people with PFJ OA may be a potentially modifiable factor associated with the

development or progression of PFJ OA.

Magnetic resonance (MR) imaging is one technique that is capable of evaluating the force

generating capacity of the individual vasti components. While measurement of muscle cross-

sectional area (CSA) from MR imaging is gaining popularity as a surrogate measure of

individual vasti muscle strength[8-10], more meaningful information may be obtained from

measures of muscle volume. A muscle's force generating capacity, sometimes also referred

to as peak isometric muscle strength or peak isometric force[11], is related to its volume and its

physiological cross sectional area (PCSA)[12]. However, prior studies[8-10] obtained anatomical

CSAs of muscles at various levels that may not be representative of the muscles' PCSAs. In a

pennate muscle, the anatomical CSA does not account for angle of muscle pennation or muscle fiber length and hence, may not be a true representative of muscle force. The CSA level of a muscle that has a strong correlation with the muscle's volume should provide an indication of the muscle's strength. The CSA at this level would provide a measurement that could be used to estimate peak isometric muscle force, and would negate the necessity to measure the entire muscle volume using MR, which can be expensive and time consuming.

The present study aimed to (i) compare the volumes of the individual quadriceps components (vastus medialis, vastus lateralis, vastus intermedius and rectus femoris) and the ratio of vastus medialis and vastus lateralis (VM/VL) volumes between controls and PFJ OA participants; and (ii) assess the relationships between CSA and volumes of the vastus medialis and vastus lateralis in individuals with and without PFJ OA.

MATERIALS AND METHODS

Participants

Twenty-two participants with PFJ OA (symptomatic and radiographic) and 11 controls (asymptomatic and no radiographic OA) ≥ 40 years of age were recruited for the study. The PFJ OA eligibility criteria were based on a previous study protocol[13]. Patients were included if they exhibited clinical symptoms arising from the PFJ (anterior or retropatellar knee pain severity ≥ 4 on an 11-point numerical pain scale during $\geq$ two PFJ loading activities: stair ambulation, squatting and rising from sitting; aggravating activities, symptoms present on most days during the past month) and radiographic criteria (Kellgren and Lawrence (KL) grading[14] applied to the lateral PFJ ≥ 2 from skyline views[3]. While the PFJ OA patients may have exhibited TFJ OA, PFJ OA patients were excluded if they exhibited a KL grading ≥ 2 from postero-anterior views in order to eliminate those with moderate-severe TFJ OA and

2   hence limit our cohort to those with predominant PFJ OA. The control participants had no

lower limb complaints, were physically active and had no radiographic OA (KL grade 0 in all

4   compartments). Exclusion criteria for all participants included major surgery (including

arthroplasty or osteotomy, but not arthroscopy); knee injections (within 3 months); current or

6   previous physiotherapy for knee pain (within 12 months); planned lower limb surgery

(following 6 months); history of hip or knee fractures; current conditions affecting the ability

8   to walk normally; concomitant pain from other knee structures, hips, ankles, feet or lumbar

spine; neurological or medical conditions; fibromyalgia; and contraindications for MR. Ethics

10   approval for the study was obtained from the University of Melbourne Human Research

Ethics Committee and the Department of Human Services Victoria Radiation Safety

12   committee. All participants provided written informed consent. Age, gender, height, body

weight and body mass index (BMI) were recorded for all subjects. The pain subscale of the

14   Knee Injury and Osteoarthritis Outcome Score (KOOS-pain) was used to score knee

osteoarthritis pain[15].

16

Measurement of quadriceps volume

18   MR imaging was performed in the supine position on the most symptomatic leg in the PFJ

OA group and the dominant leg in the control group. Both knees were fully extended to

20   ensure uniformity of positioning between subjects. The MR images were recorded on a

Siemens (Erlangen Germany) 3T Trio MR scanner using a T2-weighted fat-suppressed

22   (water excitation) MEDIC (multi-echo data image combination) gradient echo sequence (TE

= 12 ms, TR = 23 ms, NEX = 1, Flip angle 12 degrees, 155Hz/Px, Parallel imaging GRAPPA

24   2) with a slice thickness of 1 mm isotropic voxels. This sequence was chosen because it was

fast and gave reasonable delineation of muscle, cartilage and bone. The in-plane image

26   resolution was 397 x 916 pixels. The number of coronal images ranged from 300 to 400 for

2   each participant depending on their height. Acquisition time was approximately 25 minutes
per subject.

4

The CSAs of the vastus medialis, vastus lateralis, vastus intermedius and rectus femoris

6   muscles were measured on axial MR images from the origin of the muscle to the insertion by
manually digitizing muscle boundaries using commercially available software (Amira 5.2,

8   Visage Imaging, Berlin). For each muscle, the CSAs of each axial slice were summed and the
total sum of the muscle CSAs was then multiplied by the slice thickness to obtain the muscle

10   volume (Fig 1A). For each participant, the CSAs of the vastus medialis and vastus lateralis
were recorded at ten evenly spaced levels from the femoral condyles through to the lesser

12   trochanter (Fig 1B).

14

16

The intra-rater reliability of the muscle volume measurement technique was quantified in

18   nine randomly selected subjects (5 PFJ OA; 4 controls). The reliability coefficients obtained
for vastus lateralis (ICC=0.998; 95% CI: 0.991 to 1.00), vastus medialis (ICC=0.998; 95%

20   CI: 0.991 to 1.00), vastus intermedius (ICC=0.997; 95% CI: 0.987 to 0.999) and rectus
femoris (ICC=0.994; 95% CI: 0.975 to 0.999) indicate excellent repeatability of the

22   measures. Accordingly, the standard error of measurement (SEM) was acceptably low (vastus
lateralis 0.10 $cm^3.kg^{-1}$; vastus medialis 0.06 $cm^3.kg^{-1}$; vastus intermedius 0.14 $cm^3.kg^{-1}$; rectus

24   femoris 0.05 $cm^3.kg^{-1}$).

26   *Statistical analysis*

2   All data were analyzed with the Statistical Package for the Social Sciences (PASW Statistics 18, SPSS Inc., Chicago, IL) and $\alpha < 0.05$. Between-group differences in participant

4   characteristics were assessed using independent t-tests or chi square tests as appropriate. The ratio of vastus medialis to vastus lateralis (VM/VL) muscle volume was calculated for both

6   the control and PFJ OA groups. To control for the influence of body weight and gender, muscle volumes ($cm^3.kg^{-1}$) were normalized to body weight and all between-group

8   comparisons of muscle volumes were performed using an Analysis of Covariance (with and without gender as a covariate). Radiographic disease severity and knee pain are also potential

10   confounders, and the univariate association of radiographic disease severity of the PFJ (measured with the KL grading system[14]) and the KOOS-pain subscale with the individual

12   muscle volumes was determined using the Spearman's rho correlation coefficient. Regression analyses were performed on the ten equally-spaced CSAs (from the femoral condyles to

14   lesser trochanter of the femur) of vastus medialis and vastus lateralis to determine the CSA that best predicted the muscle volume in the control and PFJ OA groups. To evaluate whether

16   dominance influenced vasti muscle size, the CSA that best represented the medial and lateral vasti was also calculated for the non-dominant leg of the control group, and these were

18   compared to the dominant leg using a paired t-test.

20   **RESULTS**

Participant and disease characteristics

22   The control group (n = 11; age 53 ± 5 years, body weight 71 ± 14 kg, BMI 25 ± 3 $kg.m^{-2}$) and the PFJ OA group (n = 22; age 57 ± 11 years, weight 77 ± 13 kg, BMI 27 ± 4 $kg.m^{-2}$) were

24   matched for all participant characteristics (p > 0.05). There were more females than males in both groups (female: male ratios in the control and PFJ OA groups were 7:4 and 15:7,

26   respectively), with no difference in the frequencies (χ^2 = 0.546; p-value = 0.07). No

association was observed between muscle volumes and PFJ radiographic disease severity

(vastus medialis: r_s = -0.291; p = 0.189; vastus lateralis: r_s = -0.156; p = 0.487; VM/VL ratio:

r_s = -0.202; p = 0.367), or KOOS-pain (vastus medialis: r_s = -0.135; p = 0.550; vastus

lateralis: r_s = -0.119; p = 0.598; VM/VL ratio: r_s = 0.212; p = 0.344).

Between-group comparison of quadriceps volume

Individuals with PFJ OA had smaller normalized muscle volumes of vastus medialis (mean

difference 0.90 cm^3.kg^{-1}, 95% confidence interval [0.22 to 1.57]; α = 0.011), vastus lateralis

(1.50 cm^3.kg^{-1}, [0.35 to 2.64]; α = 0.012), and rectus femoris (0.71 cm^3.kg^{-1}, [0.19 to 1.22; α

= 0.009) than controls (Table 1). No differences were observed in vastus intermedius (0.56

cm^3.kg^{-1}, [-0.59 to 1.71]; α = 0.331). These results were reflected in peak isometric muscle

strength comparisons (see Supplementary Material). The ratio of VM/VL muscle volumes in

the PFJ OA group (0.66 ± 0.08) and the control group (0.64 ± 0.06) were not different (0.27,

[-0.50; 1.05]; α = 0.47).

Relationship between vastus medialis and lateralis volumes and cross-sectional areas

For the vastus medialis, regression modeling revealed that the CSA at the 3rd level (r^2 =

0.936; B = 17; α < 0.001) and 4th level above the femoral condyles (r^2 = 0.668; B = 18; α <

0.001) were the best predictors of muscle volume in the controls and PFJ OA participants,

respectively. For the vastus lateralis, muscle volume was predicted by the CSA at the 7th level

above the femoral condyles (r^2 = 0.916; B = 26; α < 0.001) in the controls, and at the 6th level

above the femoral condyles (r^2 = 0.705; B = 17; α < 0.001) in the PFJ OA participants. These

levels generally represented the largest CSA for each muscle.

Comparison of muscle size between dominant and non-dominant limbs

For the vastus medialis, the CSA at the 3rd level of the dominant leg (20 ± 6 cm^2) was not significantly different from the non-dominant leg (21 ± 7 cm^2); p = 0.161. Similarly, for the vastus lateralis there was no significant difference between the CSA at the 7th level for the dominant leg (28 ± 5 cm^2) and the non-dominant leg (27 ± 6 cm^2); p = 0.184.

DISCUSSION

The volumes of the vastus medialis and vastus lateralis, normalized to body weight, were significantly smaller in the PFJ OA group (approximately 20%) than the control group. However, we found no difference in the ratio of VM/VL volumes between those with and without PFJ OA. In both the PFJ OA and the control group, the ratio of VM/VL was approximately 0.67, indicating that the vastus medialis volume was approximately 2/3 that of the vastus lateralis in both groups. Based on the evidence from cadaveric and modeling studies, indicating that imbalance of the medial and lateral vasti contributes to heightened lateral PFJ stress[16,17], we considered that there may have been a lower ratio of VM/VL volumes in those with PFJ OA. Our finding of no difference in the VM/VL ratio implies that the force generating capacity of the vastus medialis is not affected to a greater extent than that of the vastus lateralis in our population with PFJ OA.

While we did not observe between-group differences in the relative muscle volume between the two heads of the vasti, it is possible that altered coordination and activation of the vastus medialis and lateralis may exist in those with PFJ OA. Indeed, modeling studies have identified that delayed activation of the medial quadriceps (relative to the lateral quadriceps) increases lateral patellar malalignment[18,19], leading to areas of heightened contact pressure across the lateral PFJ[16,17]. However, it is also possible that our findings may be more aligned with studies that did not observe differences in the onset timing of the medial and lateral vasti

between those with and without generalized knee OA[20-22]. While the current study cannot be compared to those studies that have investigated temporal aspects of the vasti activations in people with generalized knee OA, further investigation is required to establish whether the imbalances in activations of the vasti muscles, observed in younger people with patellofemoral pain[23,24], are also a feature of PFJ OA.

The finding of lower size in three of the four quadriceps in the PFJ OA group reflects previous reports of association between reduced quadriceps strength and PFJ OA[5,25]. Muscle weakness is influenced by muscle atrophy and the capacity to fully activate the muscle[4]. Hence, our findings suggest that vastus medialis, vastus lateralis and rectus femoris atrophy may be a feature of PFJ OA and likely contribute to torque deficits observed in these individuals. Smaller quadriceps muscles may have reduced capacity to absorb shock[26] or provide integrated sensorimotor function to the knee joint[27], thus rendering the joint more susceptible to damage[28]. Furthermore, results from a longitudinal cohort study[5] and an animal model[28] indicate that the PFJ is more susceptible to joint degeneration than the TFJ in the presence of lower quadriceps strength. Due to the cross-sectional nature of our research design it is not possible to determine whether the pain and structural changes associated with PFJ OA leads to muscle disuse and atrophy, or whether reduced muscle activity contributes to PFJ OA onset. However, our findings indicate that a program designed to improve strength in the vastus medialis and vastus lateralis, in addition to the rectus femoris, may benefit those with PFJ OA. However, such programs could also overload the PFJ[29], with potential to increase pain; thus, progression of load should be carefully managed. Further studies are required to confirm whether quadriceps strengthening could reduce symptoms or disease progression in people with PFJ OA.

2 We used MR imaging to quantify muscle size, which expanded on previous studies that

evaluated the strength of the quadriceps when represented as one whole muscle-tendon unit.

4 Since our study did not detect any imbalance in the relative contributions of the medial and

lateral vasti, it is not clear whether measurement of the sizes of the individual quadriceps

6 subregions provides greater value than overall quadriceps strength measures obtained from

dynamometry. Furthermore, MR imaging of the entire thigh is expensive and the segmenting

8 of muscle volumes is time-consuming. However, dynamometry is not readily available in the

clinical setting, and this instrumentation is expensive to purchase. Our results indicate that

10 CSAs of the VM and VL (at specified levels) may provide a valid indication of muscle size

for those clinicians and researchers without access to dynamometry.

12

Our study highlights that the VM CSA at approximately 8 cm (control) and 12 cm (PFJ OA)

14 above the femoral condyles were the best predictors of VM volume, while VL CSA at

approximately 24 cm (control) and 20 cm (PFJ OA) best predicted VL volume. The gross

16 anatomies of the two muscles are quite distinct, which was reflected in the disparate levels

that best represent the corresponding muscle volume. Indeed, these levels generally represent

18 the largest CSA for each individual vastus. However, previous studies have described vasti

CSA at a single level, with distances ranging from 3.8 cm[8,9] to 15 cm[10] superior to the

20 proximal patella pole, which may not represent the muscle volumes and force capacities of

these muscles. These studies ought to consider the specific CSA of the muscle that is most

22 representative of the muscle's volume, in addition to controlling for the effects of gender and

body weight.

24

In the current study, we investigated muscle size for the individual quadriceps components in

26 people with and without symptomatic radiographic PFJ OA. The quantification of muscle

2   volume used in the current study provides a better estimate of the force generating capacity of

the muscles than measuring anatomical CSAs, which may not be representative of the

4   muscle's PCSA. Our calculations of muscle volume, PCSA and peak isometric force values

in the control group (Table 1 and Supplementary Table) were in reasonable agreement with

6   those in the literature[30-32]. For example, our average muscle volume and PCSA of the controls

for vastus lateralis (505.1 cm^3 and 80.7 cm^2, respectively) were of similar magnitudes to

8   those of Friedrich and Brand (1990) (514.0 cm^3 and 64.4 cm^2, respectively)[31], while our

average muscle volume and PCSA of rectus femoris (206.7 cm^3 and 32.9 cm^2, respectively)

10   compare favorably to data reported by Klein Horsman et al. (2007) (226.3 cm^3 and 28.9 cm^2,

respectively)[30].

12

There are a number of limitations of our study that should be considered. The MR images

14   were performed under non-weight bearing conditions at full knee extension, which is

standard protocol for clinical imaging of the knee; however, it is not known whether the

16   results would have been the same if a weight-bearing activity (involving quadriceps

activation) was simulated. While these limitations may have influenced the calculations of

18   muscle volume, they are unlikely to have affected the between-group comparisons. The use

of the dominant leg to calculate muscle volume in the control group and the most

20   symptomatic leg in the PFJ OA may have resulted in bias. However, we performed some

preliminary analyses to confirm that the CSA for vastus medialis and vastus lateralis were not

22   different between legs in the control group. Therefore, it is unlikely that meaningful between-

leg differences in the control group would have affected our between-group comparisons. A

24   further limitation is the lack of detailed MR data, from which to score additional features of

osteoarthritis. For example, the radiographs cannot reveal features such as cartilage or bone

26   marrow lesions, synovitis or effusion. Therefore, we cannot rule out that some participants in

the control group may have had signs of OA that were not detectable on radiographs. However, currently radiographic definitions of OA remain the gold standard, and we can be confident that our control group was free of radiographically detected OA.

It is also acknowledged that neuromuscular factors contribute to a muscle's strength and that the strength and size of other antagonistic or synergistic muscles also influence the load on the PF joint, and therefore may be important for people with PFJ OA. Finally, the cross-sectional nature of the study design precludes any conclusions regarding the temporal relationship between muscle size and PFJ OA. Longitudinal studies are required to ascertain the role of quadriceps muscle size in the etiology and progression of PFJ OA.

CONCLUSION

There was no difference in the ratio of VM/VL volumes between those with and without PFJ OA. The volumes of the vastus medialis, vastus lateralis and rectus femoris, normalized to body weight, were approximately 20% smaller in the PFJ OA than the control group. Further studies are required to ascertain whether imbalance in the activations of the vastus medialis and lateralis is a feature of PFJ OA, and whether quadriceps strengthening can reduce symptoms or disease progression in people with PFJ OA.

Author Contributions

Harvi F Hart performed all analyses of quadriceps muscle volume and contributed to the writing of the paper

David C Ackland assisted with all data analyses, calculations of peak isometric force and contributed to the writing of the paper

Marcus G Pandy assisted with the calculations of peak isometric force and contributed to the writing of the paper

Kay M Crossley assisted with the data collection, statistical analyses and contributed to the writing of the paper

Conflict of interest

HFH, DCA, MGP and KMC do not have any conflicts of interest to declare

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FIGURE CAPTIONS

Fig 1: **(A)** Delineation of the vastus medialis (yellow), vastus lateralis (green), vastus intermedius (orange) and rectus femoris (purple) on axial MR images, where i) represents segmented and unsegmented proximal axial MR image, ii) represents segmented and unsegmented mid thigh axial MR image and iii) represents segmented and unsegmented distal axial MR image. **(B)** Cross-sectional areas of the vastus medialis and vastus lateralis were obtained at ten evenly spaced levels from the femoral condyles to the lesser trochanter of the femur (dashed lines). The solid black lines identify the levels that were the strongest predictors of muscle volume for the controls, whereas the solid gray lines identify the levels that were the strongest predictors of muscle volume for the PFJ OA participants.

FIGURES

Figure 1

(Separate file attachment)

TABLES

Table 1: Averaged muscle volumes of the quadriceps for the PFJ OA and control groups. Muscle volume and muscle volume normalized to subject mass are given, along with standard deviations (SD). Significant differences (p<0.05) in normalized muscle volume between the PFJOA subjects and control subjects are indicated.

Muscle		Muscle volume (SD) (cm^3)	Normalized muscle volume (SD) (cm^3/kg)
Vastus lateralis	PFJOA	453.1 (173.2)	5.8 (1.6)
	Control	505.1 (202.7)	p = 0.012 { 7.3 (1.4)
Vastus medialis	PFJOA	292.9 (100.9)	3.7 (0.9)
	Control	325.2 (129.3)	p = 0.011 { 4.6 (0.9)
Vastus intermedius	PFJOA	397.4 (173.7)	5.0 (1.6)
	Control	418.3 (191.4)	5.6 (1.3)
Rectus femoris	PFJOA	177.9 (71.3)	2.3 (0.7)
	Control	206.7 (81.1)	p = 0.009 { 3.0 (0.7)