

## Original Article

# Patella bone density is lower in knee osteoarthritis patients experiencing moderate-to-severe pain at rest

W. Burnett<sup>1</sup>, S. Kontulainen<sup>2</sup>, C. McLennan<sup>3</sup>, D. Hazel<sup>3</sup>, C. Talmo<sup>3</sup>, D. Hunter<sup>4</sup>, D. Wilson<sup>5</sup>, J. Johnston<sup>6</sup>

<sup>1</sup>University of Saskatchewan, Division of Biomedical Engineering; <sup>2</sup>University of Saskatchewan, College of Kinesiology; <sup>3</sup>New England Baptist Hospital; <sup>4</sup>University of Sydney, Institute of Bone and Joint Research, Kolling Institute; Royal North Shore Hospital, Rheumatology Department; <sup>5</sup>University of British Columbia, Rheumatology Department; Vancouver Coastal Health Research Institute, Centre for Hip Health and Mobility; <sup>6</sup>University of Saskatchewan, College of Engineering; Department of Mechanical Engineering

## Abstract

**Objective:** To determine differences in patellar subchondral bone mineral density (BMD) between knee osteoarthritis (OA) patients with differing levels of pain at rest. **Methods:** The preoperative knee of 41 total knee replacement (TKR) patients was scanned using QCT and scored for pain using Western Ontario McMasters Osteoarthritis Index (WOMAC). ‘Pain at rest’ was defined as average pain while lying/sitting and nocturnal pain. Participants were divided into groups: ‘mild-to-no pain at rest’ and ‘moderate-to-severe pain at rest’. We used a depth-specific CT-based mapping technique to measure patellar subchondral BMD at depths of 0-2.5 mm, 2.5-5 mm, and 5-7.5 mm from the subchondral surface. Mean lateral and medial facet BMD were compared between groups using MANCOVA. **Results:** Mean adjusted BMD was lower in participants with ‘moderate-to-severe pain at rest’ over the total lateral facet at depths of 0-2.5 mm (10% lower,  $p=0.041$ ), 2.5-5 mm (20% lower,  $p=0.017$ ), and 5-7.5 mm (25% lower,  $p=0.004$ ), and over the total medial facet at 2.5-5 mm (22% lower,  $p=0.033$ ) and 5-7.5 mm (28% lower,  $p=0.016$ ). **Conclusions:** In OA patients with ‘moderate-to-severe pain at rest’, depth-specific density measures demonstrated up to 28% lower lateral and medial subchondral BMD. Patients with high levels of pain at rest may have reduced amounts of native bone prior to TKR.

**Keywords:** Osteoarthritis, Bone Mineral Density, Pain, Patella, Computed Tomography

## Introduction

Knee osteoarthritis (OA) is a debilitating and painful joint disease, and the leading cause of pain and disability in the elderly<sup>1</sup>. Pain is the dominant symptom of OA<sup>2</sup>, and is often the first indication of disease presence. Pain at rest, in particular, including nocturnal pain and pain while lying or sitting, is a common indication for total knee replacement (TKR)<sup>3-6</sup>. In fact, a recent study noted that various orthopaedic textbooks include a statement that patients *need* to have pain at rest to be a good candidate for joint replacement<sup>7</sup>. This is potentially troubling as a recent study by Haverkamp et al.<sup>7</sup> showed that the preoperative presence of noc-

turnal pain and pain while lying or sitting resulted in poorer patient outcomes, including poorer post-operative pain scores and physical impairment for both knee and hip replacements. In line with these findings, our previous research at the proximal tibia showed individuals with severe nocturnal pain to have a trend for lower medial tibial density<sup>8</sup>, which could compromise surgical outcomes and patient satisfaction, thereby explaining previous findings. We have not yet assessed whether individuals with pain at rest also have lower patellar density, which could affect the outcomes and prognosis following TKR.

Current imaging techniques used to assess patellofemoral (PF) OA severity and the pre-operative knee consist primarily of two-dimensional (2D) radiographic projection techniques. Although easy to interpret, these techniques may not provide a complete view of the patella as they may superimpose radiographic features of OA. Conversely, 3-dimensional (3D) imaging modalities, such as computed tomography (CT), allow the patella to be viewed from all angles. Recently, CT combined with custom image processing has been used to measure bone mineral density (BMD) in relation to depth from the subchondral surface at the patella<sup>9</sup>, proximal tibia<sup>8,10</sup>, proximal femur<sup>11</sup>, acetabulum<sup>12</sup>, and distal tibia<sup>13</sup>. Importantly, these depth-specific imaging techniques have

The authors have no conflict of interest.

Corresponding authors: 57 Campus Drive, Saskatoon, Saskatchewan, S7N 5A9, Canada

E-mail: dena.burnett@usask.ca (W. Burnett);  
jd.johnston@usask.ca (J. Johnston)

Edited by: F. Rauch

Accepted 22 December 2015

potential to make approximate distinctions between subchondral cortical BMD and less dense trabecular BMD layers<sup>14</sup>, which may help identify specific bony regions most affected by OA.

Using a depth-specific CT-based image processing tool, the objective of this study was to determine whether there are measurable differences in patellar subchondral BMD prior to TKR between OA patients experiencing moderate-to-severe pain at rest and those with mild-to-no pain at rest.

## Methods

### *Study participants*

We recruited 41 participants (17 male) diagnosed with OA prior to receiving TKR (mean age 64±10 years). Index knees were joints planned for replacement. Study exclusion criteria included pregnant women, patients having a revision knee replacement on the index joint (instead of primary TKR), and prior history of bone pathology at the knee. We also used the Self-Administered Comorbidity Questionnaire<sup>15</sup> to assess participants for any potential confounding comorbidities (e.g., diabetes, heart disease). Informed consent was obtained from all participants, and the New England Baptist Hospital institutional review board approved the study.

### *OA severity and symptomatic assessment*

Each participant was assessed for pain at the affected knee (index joint planned for TKR) using a 5-point Likert scale (0-none to 4-extreme) of the pain subsection of the Western Ontario McMasters Osteoarthritis Index (WOMAC)<sup>16</sup>. Participants were asked to assess the level of pain within the past 48-hours while walking on a flat surface, going up or down stairs, standing upright, in bed at night, and lying/sitting.

Participants were divided into two groups based on the average of non-weight-bearing WOMAC items associated with persistent pain at rest: pain while lying or sitting, and pain in bed at night<sup>17,18</sup>. Participants with an average score less than or equal to 1 were considered to have ‘mild-to-no pain at rest’ (n=19); participants with an average score greater than 1 were considered to have ‘moderate-to-severe pain at rest’ (n=22). We used this combined approach because it parallels the commonly reported ‘total’ pain score, which combines all 5 WOMAC pain scores, and because previous work has recommended separating WOMAC into weight-bearing (walking, stair climbing, standing) and non-weight-bearing activities<sup>17,19</sup>.

All patellar CT scans (including axial, sagittal, and coronal reconstructions) were retrospectively evaluated for patellofemoral (PF) OA severity using a standardized radiographic atlas<sup>20</sup> and a variation of the original Kellgren-Lawrence (KL) radiographic OA severity scoring system<sup>21</sup> using a 5-point Likert scale (0-none to 4-most severe). The modified KL system was primarily based upon radiographic evidence of osteophytes and sclerosis with minimal consideration for joint space narrowing. Measures of joint space width, which are unreliable from non-weight bearing CT images<sup>22</sup>, were not considered unless near bone-on-bone contact was observed. A single researcher (WB) performed all radiographic scorings. To test inter-observer reliability, all scans

were scored in random sequence on three independent occasions. Reliability for the single reader was good ( $\kappa=0.66$  to  $0.67$ ). If there was a disagreement between PF OA severity scores in any individual patient, the most frequent of the three scores was used in our analysis.

### *CT acquisition*

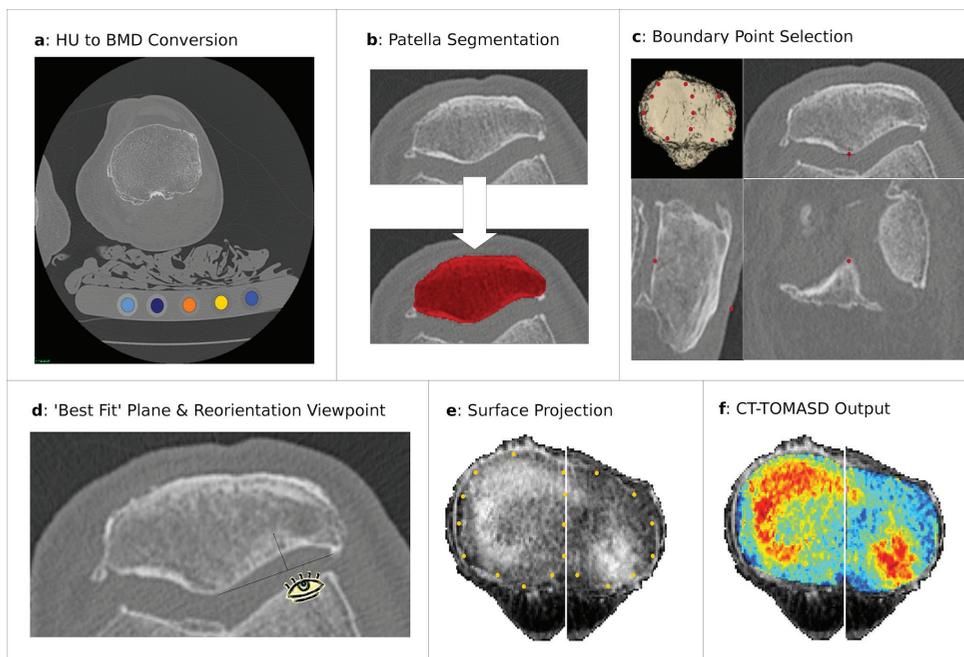
We used a single-energy CT scanner (Lightspeed 4-slice, General Electric, Milwaukee, WI, USA) for bone imaging. A solid quantitative CT (QCT) reference phantom of known bone mineral densities (Model 3T, Mindways Software Inc, Austin, TX, USA) was placed under the participants and included in all CT scans. The phantom was included to convert grayscale CT Hounsfield Units (HU) to equivalent apparent BMD ( $\text{mg}/\text{cm}^3 \text{K}_2\text{HPO}_4$ ). Participants were oriented supine within the CT gantry with both legs scanned simultaneously. Scans of both knees included the distal femur, the proximal tibia, the patella and the 66% site proximal to the distal tibial end-plate, which was used as an internal control<sup>23</sup>. Only the patella and the 66% tibia site were used in the current analysis.

CT scanning parameters included: 120 kVp tube voltage, 150 mAs tube current-time product, axial scanning plane, 0.625 mm isotropic voxel size (0.625 mm slice thickness, 0.625 x 0.625 mm in-plane pixel size), ~250 slices, ~60s scan time. A standard bone kernel (BONE) was used for CT image post-processing. Effective radiation dose was ~0.073 mSv per scan, estimated using shareware software (CT-DOSE, National Board of Health, Herley, Denmark). For comparison, the average effective radiation dose during a transatlantic flight from Europe to North America is about 0.05 mSv<sup>24</sup>.

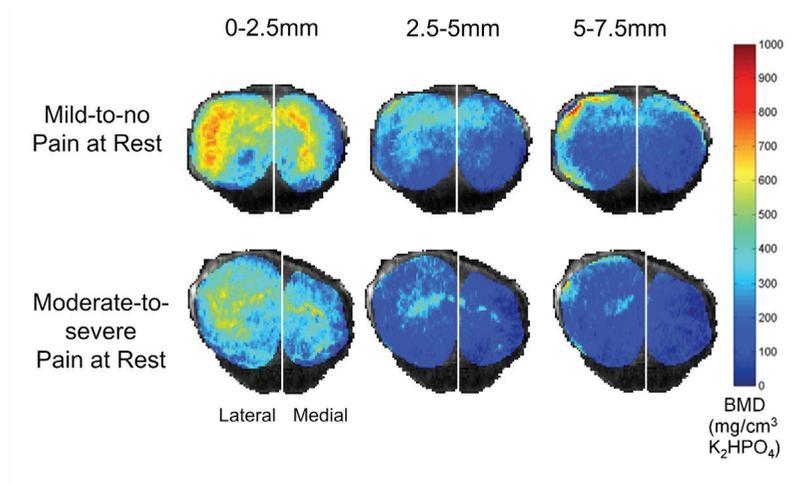
### *CT image analysis*

To determine subchondral volumetric BMD at the patella, we applied a depth-specific image processing method (computed tomography topographic mapping of subchondral density, CT-TOMASD)<sup>9</sup>. This method uses surface projection image processing to quantify subchondral BMD at pre-defined depths from the subchondral surface and is previously described in detail at the proximal tibia<sup>10,25</sup> and patella<sup>9</sup>. A single user (WB) performed all image processing and segmentations. Precision errors at evaluated regions (root mean square coefficients of variation, CV%) ranged from 0.7 to 2.4%<sup>9</sup>.

In summary, grayscale HU were converted to equivalent volumetric BMD ( $\text{mg}/\text{cm}^3 \text{K}_2\text{HPO}_4$ ) using linear regression equations developed from known reference phantom densities included in each individual serial image ( $r^2>0.99$ ) (Matlab 2010b; MathWorks, Natick, MA, USA) (Figure 1a). To define the subchondral surface, subject-specific segmenting thresholds were defined using the half maximum height method (HMH)<sup>26</sup>, which represents the density of a voxel with 50% cortical bone and 50% soft tissue and acts as a minimum value for voxels containing predominantly bone. Images were then semi-automatically segmented with commercial software (Analyze10.0; Mayo Foundation, Rochester, MN, USA) using region growing and manual correction with an interactive touch-screen tablet (Cintiq 21UX; Wacom, Krefeld, Germany) (Figure 1b).



**Figure 1.** Methodological sequence for CT-TOMASD analyses in the patella consists of converting CT grayscale intensity to BMD using a QCT reference phantom (a), followed by semi-automatic patellar segmentation in the transverse plane (b). Peripheral and interior boundary points are manually selected (c) to define medial and lateral facets; with the patella reoriented relative to ‘best fit’ planes passing through facet boundary points (d). A surface projection image-processing algorithm is performed to map 3D subchondral density in relation to depth (measured from the subchondral surface) directly at the patellar surface (e). CT-TOMASD analyses of the average BMD of each facet are performed (f).



**Figure 2.** Representative topographical color maps of average patellar BMD at depths of 0-2.5 mm, 2.5-5 mm and 5-7.5 mm in one participant reporting ‘mild-to-no pain at rest’ (top row) and one reporting ‘moderate-to-severe pain at rest’ (bottom row).

The lateral and medial facet surfaces were first outlined by manually selecting boundary points (Analyze 10.0) to define them (Figure 1c). The surface projection analysis requires the patellar subchondral surface to be oriented approximately parallel with each projected image. Therefore, for each facet, the segment image volume was realigned and reconstructed (reformatted) rel-

ative to the “best-fit” plane passing through the boundary points of each facet surface (defined using singular value decomposition) (Matlab 2010b) (Figure 1d).

Following realignment, average bone density, across three normalized layers (0-2.5 mm, 2.5-5 mm and 5-7.5 mm) was measured in relation to depth from the subchondral surface

	Mild-to-no pain at rest (n=19)	Moderate-to-severe pain at rest (n=22)
Sex Ratio	9M:10F	8M:14F
Age in years	67.5 ± 9.1	61.12 ± 10.3
BMI in kg/m <sup>2</sup>	28.2 ± 4.0	29.2 ± 3.3
Pain at Rest	0.66 ± 0.47	2.05 ± 0.41
Patellofemoral KL Grade 0/1/2/3/4	1/8/4/3/0	1/10/5/4/0

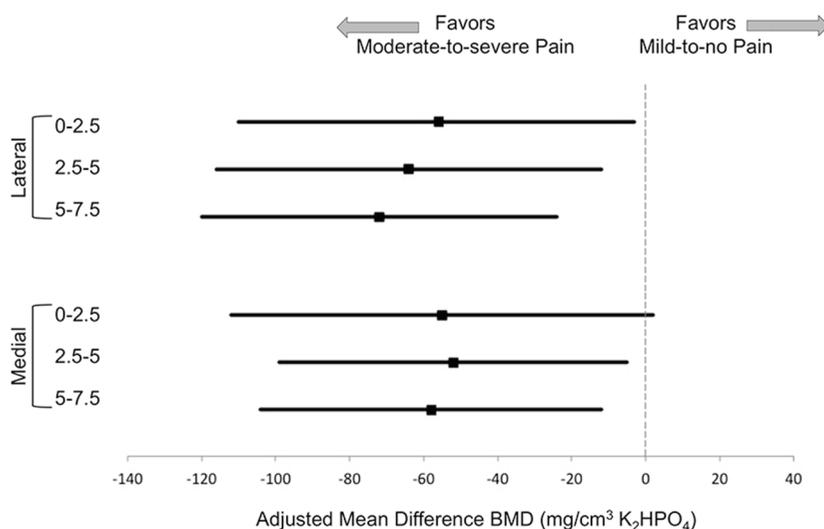
\*KL = Kellgren Lawrence

**Table 1.** Participant characteristics by pain group (mean ± SD).

Facet	Depth	BMD (mg/cm <sup>3</sup> K <sub>2</sub> HPO <sub>4</sub> )*		Adjusted mean difference**	% -Difference	p-value
		Mild-to-no pain at rest	Moderate-to-severe pain at rest			
Lateral	0-2.5 mm	566 ± 94	510 ± 70	-56 [-110, -3]	-10.4%	0.041 <sup>a</sup>
	2.5-5 mm	353 ± 83	289 ± 77	-64 [-116, -12]	-20.0%	0.017 <sup>a</sup>
	5-7.5 mm	325 ± 74	252 ± 74	-72 [-120, -24]	-25.1%	0.004 <sup>a</sup>
Medial	0-2.5 mm	447 ± 88	392 ± 75	-55 [-112, 2]	-13.0%	0.059
	2.5-5 mm	254 ± 68	202 ± 68	-52 [-99, -5]	-22.7%	0.033 <sup>a</sup>
	5-7.5 mm	234 ± 70	176 ± 67	-58 [-104, -12]	-28.1%	0.016 <sup>a</sup>

\*Results are mean ± SD  
 \*\*Multivariate model adjusted for age (64.10), sex (1.5952, 1=M 2=F), and OA severity (PF KL) (1.68); results are mean [95% CI].

**Table 2.** Patellar facet bone mineral density (BMD) by pain group ('mild-to-no pain at rest' and 'moderate-to-severe pain at rest'). Significant between-group differences are marked (<sup>a</sup>).



**Figure 3.** Adjusted mean difference and 95% confidence intervals in BMD between 'mild-to-no pain at rest' and 'moderate-to-severe pain at rest' groups at the medial and lateral facets at depths of 0-2.5 mm, 2.5-5 mm and 5-7.5 mm from the subchondral surface.

(Matlab 2010b) for each medial and lateral facet. To correct for potentially shallow measurements in large patellae and potentially excessively deep measurements in small patellae, subject-specific depth was normalized according to volume with subject-specific subchondral bone surface area and subject-specific patellar volume<sup>25</sup>.

The medial and lateral facet regions in the 2D projected images were then segmented using natural cubic splines fit to the previously selected boundary points (Figure 1e) (Matlab 2010b) while permitting manual adjustment of knot points. We performed analyses of the lateral and medial facets on each 2D projection image (0-2.5 mm, 2.5-5 mm and 5-7.5 mm layers) (Figure 1f, Figure 2). Depths between 0-2.5mm from the subchondral surface were classified as primarily subchondral mineralized tissue (subchondral cortical bone and calcified cartilage), based on a maximum subchondral mineralized zone thickness of 2.45 mm<sup>27</sup>. Depths below 2.5 mm (i.e., 2.5-5 mm and 5-7.5 mm) were classified as primarily subchondral trabecular bone.

#### Internal control

We compared cortical cross-sectional area and cortical BMD of the tibial shaft (66% of tibia length, proximal from distal tibia plateau)<sup>23</sup> to assess possible between-group differences in local (e.g., mechanical loading/unloading) and systemic factors (e.g., nutrition, medication)<sup>28</sup>.

#### Statistical analysis

We tested the equality of variances in subchondral BMD outcomes using Levene's test and between-group differences in potential confounding factors for BMD with  $\chi^2$  test (sex, PF KL grade) and t-tests (age, BMI).

We used multivariate analysis of covariance (MANCOVA) to compare patellar facet BMD between 'mild-to-no pain at rest', and 'moderate-to-severe pain at rest' groups. We selected sex, age, and PF OA severity as covariates<sup>28</sup>. We did not use BMI as a covariate because BMD values were normalized according to patient-specific patellar area and volume, taking patient size into account. For BMD measures with significant between-group differences, we report *F*-statistic, mean, standard deviation (SD), adjusted mean differences, and 95% confidence intervals. Similarly, we used MANCOVA to compare cross-sectional cortical area and mean cortical BMD at the tibial shaft between groups, also adjusting for age, sex, and PF OA severity. Statistical significance was set at  $p < 0.05$ .

## Results

There were no differences in sex distribution, age, KL grade, or BMI between the 'moderate-to-severe pain at rest' and 'mild-to-no pain at rest' groups (Table 1).

Across the total lateral facet, patients with 'moderate-to-severe pain at rest' had lower BMD at depths of 0-2.5 mm (10% lower,  $F_{1,36}=4.515, p=0.041$ ), 2.5-5 mm (20% lower,  $F_{1,36}=6.271, p=0.017$ ), and 5-7.5 mm (25% lower,  $F_{1,36}=9.377, p=0.004$ ) (Table 2, Figure 3). Across the total medial facet, patients with

'moderate-to-severe pain at rest' had lower BMD at depths of 2.5-5 mm (23% lower,  $F_{1,36}=4.933, p=0.033$ ), and 5-7.5 mm (28% lower,  $F_{1,36}=6.432, p=0.016$ ) (Table 2, Figure 3).

At the tibial shaft control site, there were no significant between-group differences in cross-sectional cortical area ( $F_{1,36}=1.338, p=0.255$ ) or mean cortical BMD ( $F_{1,36}=0.790, p=0.781$ ).

## Discussion

This depth-specific method identified lower patellar BMD in participants with 'moderate-to-severe pain at rest' than in participants with 'mild-to-no pain at rest'. Differences were observed in the lateral facet at all depths from the subchondral surface (0-2.5 mm, 2.5-5 mm and 5-7.5 mm) and in the medial facet at depths of 2.5-5 mm and 5-7.5 mm (which consist primarily of trabecular bone). These findings suggest that there may be previously unobserved alterations in patellar subchondral bone density in OA patients with high levels of pain at rest.

Our findings, which are limited to the patella, are consistent with prior research reporting associations between pain and low BMD<sup>8,29</sup>. Our previous study, with the same cohort, found a trend for lower medial proximal tibial BMD in OA patients with severe nocturnal pain<sup>8</sup>. Though, one study did find an association between pain and high tibial areal BMD (aBMD) measured using dual-energy x-ray absorptiometry (DXA)<sup>30</sup>. The reasons for these disagreements may be due to inherent limitations of DXA. For example, patient size and positioning sensitivities may affect aBMD measurements whereby larger and mis-positioned patients have more bone in the projection direction, resulting in an overestimation of aBMD<sup>31</sup>.

Although speculative, our results may provide insight into PF complications following TKR and why patients with high levels of pain at rest prior to TKR have less favorable pain outcomes at follow-up<sup>7</sup>. As well, our results may provide information for TKR PF preparation. In our previous work, subjects with radiographic PF OA had up to 30% lower BMD than healthy patellae<sup>9</sup>. In this study, OA patients with increased pain at rest tended to have even lower BMD (10-28% lower BMD than OA individuals with 'mild-to-no pain'). Importantly, the lower patella BMD seen in patients with high levels of pain at rest may result in poor patella bone stock in these individuals, potentially leading to inadequate implant fixation and higher rates of loosening<sup>32,33</sup>. As well, low BMD may lead to patella fracture, a devastating complication occurring after TKR. With PF OA, patellar resurfacing is a much debated treatment method, with a large study of 972 patients<sup>34</sup> and a meta-analysis<sup>35</sup> reporting that patellar resurfacing had little to no clinical effect on pain or function after TKR. Given these findings, combined with low patellar bone stock, surgeons may give greater consideration to proceeding with an unresurfaced patella in patients with moderate-to-severe pain at rest. Another approach suggested by Haverkamp et al<sup>7</sup>, and supported by study results, proposes that TKR should be performed either before the patient experiences pain at rest or in very early stages.

This study has specific strengths to consider. First, our study sample was comprised of a homogeneous group of OA patients

with similar OA status (all scheduled for TKR), which mitigated possible confounding factors affecting BMD and pain. Second, we used bone measures at the proximal tibia as an internal control to overrule possible between-group differences in systemic and local factors associated with cortical bone area and BMD. Third, we normalized all measurement depths and aligned all patellae in similar 3D orientations relative to landmark boundary points and best-fit planes. This minimized BMD differences due to dissimilar sizes and orientations, thereby permitting reliable comparisons between groups.

This study has certain limitations regarding pain assessment, sample size and patient selection. First, clinical pain assessment was based upon the entire knee, including the patella, proximal tibia, distal femur, tibiofemoral joint, and patellofemoral joint. For this reason, we are uncertain whether pain originated from the patella, other tissue, or a combination of tissues. Second, our study sample size was small (N=41). With a basic rule of 10 samples per predictor<sup>36</sup>, we were limited to the outcome (BMD) and three covariate factors (age, sex, OA severity) and could not add any additional predictors to our analysis (e.g., previous knee injury, smoking/alcohol history, activity level, occupation, specific medications). This limited our ability to explore potential reasons why individuals with elevated pain at rest had lower patellar BMD. Of note, we attempted to account for possible differences in physical activity (mechanical loading/unloading) through usage of internal control measures at the 66% tibial shaft site (cortical area, cortical BMD). Previous works have noted differences in tibial shaft cortical area<sup>37</sup> and BMD<sup>37,38</sup> between highly active individuals (e.g., sprinters, endurance runners, triple- and high-jumpers, hurdlers) and less active controls. However, in this study, we did not note any associations between pain and tibia shaft cortical area or BMD, potentially indicating, at least to some degree, similar levels of activity and mechanical loading amongst study participants. Third, we do not have surgical technique or follow-up data regarding patient pain levels post-surgery. As such, we are unsure if the patients with elevated pain at rest prior to TKR exhibited poorer patient outcomes post TKR, as seen previously<sup>7</sup>.

Patients experiencing 'moderate-to-severe pain at rest' had lower BMD in the lateral patellar facet at depths of 0-2.5 mm, 2.5-5 mm, and 5-7.5 mm from the subchondral surface, and lower BMD in the medial patellar facet at depths of 2.5-5 mm, and 5-7.5 mm, consisting primarily of subchondral trabecular bone. These findings are important as OA patients with high levels of pain at rest may have reduced amounts of native patellar bone stock prior to TKR, potentially leading to greater risk of complications and implant failure.

#### Acknowledgements

*This project was funded through support from the Canadian Arthritis Network (CAN) Pilot Grant Program for New Investigators and New England Baptist Hospital Research Funding Awards.*

## References

- Cooper C, McAlindon T, Coggon D, Egger P, Dieppe PA. Occupational activity and osteoarthritis of the knee. *Ann Rheum Dis* 1994;53:90-3.
- Hunter DJ, Felson DT. Osteoarthritis. *Br Med J* 2006; 332:639-42.
- Hudak P, Grassau P, Glazier R, et al. "Not everyone who needs one is going to get one": The influence of medical brokering on patient candidacy for total joint arthroplasty. *Med Decis Making* 2008;28:773.
- Mancuso CA, Ranawat CS, Esdaile JM, Johanson NA, E CM. Indications for total hip and total knee arthroplasties. *J Arthroplasty* 1996;11:34-46.
- Tierney W, Fitzgerald J, Heck D, et al. Tricompartmental knee replacement. A comparison of orthopaedic surgeons' self reported performance rates with surgical indications, contraindications, and expected outcomes. *Clin Orthop* 1994;305:209-17.
- Wright J, Coyte P, Hawker G, et al. Variation in orthopedic surgeons' perceptions of the indications for and outcomes of knee replacements. *Can Med Assoc J* 1995;152:687-97.
- Haverkamp D, Brokelman RBG, van Loon CJM, van Kampen A. Timing of arthroplasty, what is the influence of nocturnal pain and pain at rest on the outcome? *Knee Surg Sports Traumatol Arthrosc* 2013;21:2590-4.
- Burnett WD, Kontulainen S, McLennan C, et al. Knee osteoarthritis patients with severe nocturnal pain have altered subchondral tibial bone mineral density. *Osteoarthritis Cartilage* 2015.
- Burnett WD, Kontulainen SA, McLennan CE, Wilson DR, Hunter DJ, Johnston JD. Regional depth-specific subchondral bone density measures in osteoarthritic and normal patellae: In vivo precision and preliminary comparisons. *Osteoporos Int* 2014;25:1107-14.
- Johnston JD, McLennan CE, Hunter DJ, Wilson DR. In vivo precision of a depth-specific topographic mapping technique in the CT analysis of osteoarthritic and normal proximal tibial subchondral bone density. *Skeletal Radiol* 2010;40:1057-64.
- Wright DA, Meguid M, Lubovsky O, Whyne CM. Subchondral bone density distribution in the human femoral head. *Skeletal Radiol* 2011;41:677-83.
- Speirs AD, Beaulé PE, Rakhra KS, Schweitzer ME, Frei H. Increased acetabular subchondral bone density is associated with cam-type femoroacetabular impingement. *Osteoarthritis Cartilage* 2013;21:551-8.
- Intema F, Thomas TP, Anderson DD, et al. Subchondral bone remodeling is related to clinical improvement after joint distraction in the treatment of ankle osteoarthritis. *Osteoarthritis Cartilage* 2011;19:668-75.
- Milz S, Eckstein F, Putz R. The thickness of the subchondral plate and its correlation with the thickness of the uncalcified articular cartilage in the human patella. *Anat Embryol (Berl)* 1995;192:437-44.
- Sangha O, Stucki G, Liang MH, Fossel AH, Katz JN. The Self-Administered Comorbidity Questionnaire: A new method to assess comorbidity for clinical and health services research. *Arthritis Rheum* 2003;49:156-63.
- Bellamy N, Buchanan WW, Goldsmith CH, Campbell J, Stitt LW. Validation study of WOMAC: A health status in-

- strument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. *J Rheumatol* 1988;15:1833-40.
17. Stratford PW, Kennedy DM, Woodhouse LJ, Spadoni GF. Measurement properties of the WOMAC LK 3.1 pain scale. *Osteoarthritis Cartilage* 2007;15:266-72.
  18. Hensor EMA, Dube B, Kingsbury SR, Tennant A, Conaghan PG. Towards a clinical definition of early osteoarthritis: Onset of patient-reported knee pain begins on stairs. Data from the Osteoarthritis Initiative. *Arthritis Care Res* 2015;67:40-7.
  19. Lo GH, McAlindon TE, Niu J, et al. Bone marrow lesions and joint effusion are strongly and independently associated with weight-bearing pain in knee osteoarthritis: data from the osteoarthritis initiative. *Osteoarthritis Cartilage* 2009;17:1562-9.
  20. Altman RD, Hochberg M, Murphy WA, Jr., Wolfe F, Lequesne M. Atlas of individual radiographic features in osteoarthritis. *Osteoarthritis Cartilage* 1995;3(Suppl)A:3-70.
  21. Kellgren JH, Lawrence JS. Radiological assessment of osteoarthrosis. *Ann Rheum Dis* 1957;16:494-502.
  22. Chan WP, Lang P, Stevens MP, et al. Osteoarthritis of the knee: Comparison of radiography, CT, and MR imaging to assess extent and severity. *Am J Radiol* 1991;157:799-806.
  23. Kontulainen SA, Johnston JD, Liu D, et al. Strength indices from pQCT imaging predict up to 85% of variance in bone failure properties at tibial epiphysis and diaphysis. *J Musculoskelet Neuronal Interact* 2008;8:401-9.
  24. UNSCEAR 2000 Report to the General Assembly - Annex B: Exposures from natural radiation sources United Nations Scientific Committee on the Effects of Atomic Radiation.
  25. Johnston JD, Masri BA, Wilson DR. Computed tomography topographic mapping of subchondral density (CT-TO-MASD) in osteoarthritic and normal knees: methodological development and preliminary findings. *Osteoarthritis Cartilage* 2009;17:1319-26.
  26. Kontulainen S, Liu D, Manske S, Jamieson M, Sievänen H, McKay H. Analyzing Cortical Bone Cross-Sectional Geometry by Peripheral QCT: Comparison With Bone Histomorphometry. *J Clin Densitometry* 2007;10:86-92.
  27. Eckstein F, Milz S, Anetzberger H, Putz R. Thickness of the subchondral mineralised tissue zone (SMZ) in normal male and female and pathological human patellae. *J Anat* 1998;192:10.
  28. Frank AW, Labas MC, Johnston JD, Kontulainen SA. Site-specific variance in radius and tibia bone strength as determined by muscle size and body mass. *Physiother Can* 2012;64:292-301.
  29. Dore D, Ding C, Jones G. A pilot study of the reproducibility and validity of measuring knee subchondral bone density in the tibia. *Osteoarthritis Cartilage* 2008;16:1539-44.
  30. Akamatsu Y, Mitsugi N, Taki N, Ashi HK, Saito T. Medial versus lateral condyle bone mineral density ratios in a cross-sectional study: A potential marker for medial knee osteoarthritis severity. *Arthritis Care Res* 2012;64:1036-45.
  31. Watts NB. Fundamentals and pitfalls of bone densitometry using dual-energy X-ray absorptiometry (DXA). *Osteoporos Int* 2004;15:847-54.
  32. Levitz CL, Lotke PA, Karp JS. Long-term changes in bone mineral density following total knee replacement. *Clin Orthop* 1995;321:68-72.
  33. Sharkey PF, Hozack WJ, Rothman RH, Shastri S, Jacoby SM. Why are total knee arthroplasties failing today? *Clin Orthop* 2002;404:7-13.
  34. Lygre SHL, Espehaug B, Havelin LI, Vollset SE, Furnes O. Does patella resurfacing really matter? Pain and function in 972 patients after primary total knee arthroplasty. *Acta Orthop* 2010;81:99-107.
  35. Chen K, Li G, Yuan C, Zhang Q, Cai Z. Patellar resurfacing versus nonresurfacing in total knee arthroplasty: A meta-analysis of randomized controlled trials. *Int Orthop* 2013;37:1075-83.
  36. Peduzzi P, Concato J, Kemper E, Holford TR, Feinstein AR. A simulation study of the number of events per variable in logistic regression analysis. *J Clin Epidemiol* 1996;49:1373-9.
  37. Wilks DC, Winwood K, Gilliver SF, et al. Bone mass and geometry of the tibia and the radius of master sprinters, middle and long distance runners, race-walkers and sedentary control participants: a pQCT study. *Bone* 2009;45:91-7.
  38. Rantalainen T, Nikander R, Daly RM, Heinonen A, Sievänen H. Exercise loading and cortical bone distribution at the tibial shaft. *Bone* 2011;48:786-91.