Osteoarthritis and Cartilage 23 (2015) 1483–1490

Osteoarthritis and Cartilage

Knee osteoarthritis patients with severe nocturnal pain have altered proximal tibial subchondral bone mineral density

W.D. Burnett †, S.A. Kontulainen † ‡, C.E. McLennan §, D. Hazel §, C. Talmo §, D.J. Hunter ‖, D.R. Wilson ¶, J.D. Johnston † # *

† *Division of Biomedical Engineering, University of Saskatchewan, Saskatoon, SK, Canada*
‡ *College of Kinesiology, University of Saskatchewan, Saskatoon, SK, Canada*
§ *Division of Research, New England Baptist Hospital, Boston, MA, USA*
‖ *Institute of Bone and Joint Research, University of Sydney, Sydney, NSW, Australia*
¶ *Department of Orthopaedics and Centre for Hip Health and Mobility, University of British Columbia and Vancouver Costal Health Research Institute, Vancouver, BC, Canada*
# *Department of Mechanical Engineering, University of Saskatchewan, SK, Canada*

ARTICLE INFO

Article history:
Received 2 October 2014
Accepted 14 April 2015

Keywords:
Osteoarthritis
Knee
Pain
Subchondral bone
Proximal tibia
Computed tomography

SUMMARY

Objective: Our objective was to investigate relationships between proximal tibial subchondral bone mineral density (BMD) and nocturnal pain in patients with knee osteoarthritis (OA).
Methods: The preoperative knee of 42 patients booked for knee arthroplasty was scanned using quantitative computed tomography (QCT). Pain was measured using the Western Ontario and McMaster Universities Arthritis Index (WOMAC) and participants were categorized into three groups: 'no pain', 'moderate pain', and 'severe pain' while lying down at night. We used depth-specific image processing to assess tibial subchondral BMD at normalized depths of 0–2.5 mm, 2.5–5.0 mm and 5–10 mm relative to the subchondral surface. Regional analyses of each medial and lateral plateau included total BMD and maximum BMD within a 10 mm diameter core or 'focal spot'. The association between WOMAC pain scores and BMD measurements was assessed using Spearman's rank correlation. Regional BMD was compared pairwise between pain and no pain groups using multivariate analysis of covariance using age, sex, and BMI as covariates and Bonferroni adjustment for multiple comparisons.
Results: Lateral focal BMD at the 2.5–5 mm depth was related to nocturnal pain ($\rho = 0.388$, $P = 0.011$). The lateral focal BMD was 33% higher in participants with 'severe pain' than participants with 'no pain' at 2.5–5 mm depth ($P = 0.028$) and 32% higher at 5–10 mm depth ($P = 0.049$). There were no BMD differences at 0–2.5 mm from the subchondral surface.
Conclusion: This study suggests that local subchondral bone density may have a role in elucidating OA-related pain pathogenesis.

Introduction

Knee osteoarthritis (OA) is a leading cause of chronic pain and disability in the elderly[1]. Pain is the dominant symptom of OA[2] and is often the first indication that patients may be afflicted with OA. OA-related pain is complex[3,4], as it is a combination of social, psychological, and biological factors, with no simple unitary concept linking symptoms with structural damage[5]. Within the joint structure, pain could be due to the presence of various contributing factors (e.g., altered joint alignment, joint instability, osteophyte presence both peripherally and within the joint, inflammation, cyst presence, altered subchondral bone properties, bone marrow lesions (BMLs)). Importantly, underlying sources of pain may be masked by specific structural factors, such as altered joint alignment, osteophyte presence, and inflammation, which would likely present during dynamic weight-bearing activities such as climbing stairs or walking. To isolate potential underlying sources of pain, it is advantageous to study pain with non-weight bearing activities, such as lying in bed at night. Understanding

* Address correspondence and reprint requests to: J.D. Johnston, Department of Mechanical Engineering, University of Saskatchewan, 57 Campus Dr., Saskatoon, SK S7N 1G9, Canada. Tel: 1-306-966-1468.
E-mail address: james.johnston@usask.ca (J.D. Johnston).

http://dx.doi.org/10.1016/j.joca.2015.04.012

potential sources of pain during non-weight bearing activities, such as nocturnal pain, is also relevant as it is related to sleeplessness and other disruptions to quality of life in OA patients[6].

Knee OA is commonly characterized by subchondral bone changes, including altered subchondral bone thickness[7], bone volume fraction[8] and volumetric density[9,10], as well as the presence of BMLs as observed *via* magnetic resonance imaging (MRI)[11–13]. Little is known regarding associations between pain and altered subchondral bone morphology or density; however, BML presence and size have both shown strong associations with knee pain[4,13–17]. Of relevance to this study, BMLs have been shown to be associated with increased bone mineral density (BMD)[12] and have higher local BMD than surrounding bone tissue[11]. Importantly, altered BMD may disrupt local innervation[18] and/or the local mechanical behaviour of bone[19], and thus may be a factor in OA-related knee pain.

Our current understanding of the relationship between pain and altered BMD primarily relies on evidence from studies using two-dimensional (2D) dual-energy absorptiometry (DXA)[20,21]. However, these studies provide conflicting results, reporting that both higher areal BMD (aBMD)[20] and lower aBMD[21] are associated with OA-related pain. These conflicting results may be due to the inherent limitations of 2D projection techniques, such as patient size and positioning[22], unstandardized regions of interest (ROI)[12,21,23], and the inability to evaluate distinct regions or depths[22]. Three-dimensional (3D) computed tomography (CT) based depth-specific imaging techniques have the ability distinguish differences in subchondral volumetric BMD between normal and OA tibiae[10,24], and may have the ability to identify regional BMD differences in patients with and without pain. Depth-specific imaging techniques also have the potential to determine approximate contrasts between subchondral cortical BMD and less dense trabecular BMD layers[25], which may have different roles in OA-related pain.

Using a depth-specific CT-based image processing tool, the objective of this study was to determine whether there are associations between proximal tibial subchondral BMD and OA-related nocturnal pain.

Methods

Study participants

Fifty-two participants (23M: 29F; mean age 64, SD ± 9.4years) with OA were recruited prior to total knee replacement. Study exclusion criteria included: pregnant women, patients having a revision replacement instead of primary knee replacement, and patients with a prior history of bone pathology at the knee joint. CT images with excessive imaging artifacts, motion artifacts, or incomplete images were excluded, resulting in 42 study participants (17M: 25F; 64 ± 10 years). The Institutional Research Board of the New England Baptist Hospital approved the study. Informed consent was obtained from all study participants.

Knee assesment

OA severity was classified using Kellgren–Lawrence grading[26] and OA-related pain severity was measured at the affected knee joint using a 5-point Likert scale (0–4) of the pain subsection of the Western Ontario McMasters Osteoarthritis Index (WOMAC)[27]. Participants were asked to assess the level of pain in the affected knee joint within the past 24-h while walking on a flat surface, going up or down stairs, nocturnal pain at night in bed, sitting or lying down, and standing upright. This study was focused on non-weight bearing nocturnal pain at night in bed.

To help explain potentially high and low BMD findings, all CT scans (including axial, sagittal, and coronal reconstructions) were retrospectively evaluated for cyst presence, altered knee alignment, and joint laxity. Cyst size and number was semi-qualitatively scored using a simple combined scoring system (none, small, moderate, large) similar to the atlas system of Altman and Gold[28] (none, mild, moderate, severe). Knee alignment was characterized as varus, valgus, and neutral. Joint laxity was identified based upon evidence of medial or lateral shifting of the femur relative to the tibia. A single researcher (JDJ), trained by an experienced orthopaedic surgeon who routinely assessed cyst presence and knee alignment/laxity, performed all scorings.

CT acquisition

We used a single energy clinical 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 (mg/cm^3 K_2HPO_4) with both human and animal studies verifying that QCT density measures are accurate representations of true BMD[29,30]. Participants were oriented supine within the CT gantry and both legs were simultaneously scanned. Scans included the distal femur, patella, proximal tibia, and the 66% tibial shaft site proximal to the distal tibial endplate[31]. Only the proximal tibia and the 66% tibial shaft 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 slice thickness, 0.625 mm × 0.625 mm in-plane pixel size), ~250 slices, ~60 sec 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 trans-atlantic flight from Europe to North America is about 0.05 mSv[32].

CT image analysis

We used an earlier developed depth-specific image processing technique (computed tomography topographical mapping of subchondral density, CT-TOMASD)[24,33] to measure subchondral proximal tibial subchondral BMD. A single user (WDB) performed all image processing and segmentations. A precision study was performed on an independent sample using recommended techniques[34] and results were compared to previously published results from another user[33]. Precision errors (root mean square coefficients of variation, CV%)[34] ranged from 0.7% to 3.6%, and absolute percent differences in regional mean BMD between both users were all below 3%.

This method uses surface projection image processing to quantify volumetric subchondral bone density at user-defined depths from the subchondral bone surface. Briefly, equivalent volumetric BMD (mg/cm^3 K_2HPO_4) values were converted from grayscale HU using subject-specific linear regression equations developed from known densities within the QCT phantom included in each individual axial image ($r^2 > 0.99$) (Matlab 2010b; MathWorks, Natick, MA, USA)[24]. Subject-specific half maximum height thresholds[35] were then determined to define the proximal tibial subchondral surface. Serial images were individually segmented using semi-automatic region growing and manual correction techniques using commercial software (Analyze10.0; Mayo Foundation, Rochester, MN, USA) and an interactive touch-screen tablet