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Letter to the Editor

Response to Letter to the Editor: 'Is subchondral bone mineral density associated with nocturnal pain in knee osteoarthritis patients?'

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Pan
Bone cyst
Malalignment

Author's reply:

We read with interest the letter by Chen and colleagues and welcome the opportunity to further explain the research outlined in the paper by Burnett *et al.*[1]. Before answering the authors' questions directly, it is important to note that our measures of subchondral bone cysts and knee alignment were acquired retrospective to bone mineral density (BMD) measures to provide potential explanations for unexpected BMD findings. Specifically, we anticipated that cyst and knee alignment measures would help explain the interesting trend noted of low medial BMD and high lateral BMD with increasing pain. This seemed irregular given that many of the participants were in varus alignment, which should result in high medial BMD and low lateral BMD[2–4]. Due to our small sample size and inherent links between BMD and preliminary cyst measures, these measures were not used as confounders in our statistical models. A superior approach would be to isolate measures of cyst presence from surrounding BMD, which is the aim of our ongoing work. However, because there appeared to be a link between pain, BMD, cyst presence and altered knee alignment, we found it prudent to address these secondary measures in the discussion as best we could with the data available to us. We appreciate the insightful comments by Chen and colleagues and hope that the additional information in this letter will provide perspective on these interesting topics to guide further research.

With regards to quantifying cyst presence, this was completed using a custom semi-quantitative approach combining methods from Kornaat *et al.*[5] and results from Chiba *et al.*[6]. A single researcher (JDJ) retrospectively evaluated all CT scans (mainly sagittal and coronal reconstructions) for cyst presence, size and number. Cysts were evident as voids primarily located in the subchondral cortical and subchondral trabecular bone regions (0–5 mm depth from surface). The central region of individual cysts (corresponding with largest area) was segmented using commercial software (Analyze 10.0; Mayo Foundation, Rochester, MN, USA) and an interactive touch-screen tablet. With the assumption that cysts are predominantly spherical in shape, segmented areas were converted to equivalent cyst diameters and volumes. Individual cyst sizes were classified as: *none*, 0–1.25 mm diameter, 0–1 mm^3 volume, as per Chiba *et al.*[6]; *mild*, 1.25–2.5 mm diameter, 1–8 mm^3 volume; *moderate*, 2.5–5 mm diameter, 8–65 mm^3 volume; *large*, >5 mm diameter, >65 mm^3 volume, as per Kornaat *et al.*[5]. In instances where there were multiple cysts, the volumes of individual cysts were summed and total cyst volume dictated the specific grouping. With regards to including cyst measures into our statistical analyses, we performed these analyses to address the request from Chen and colleagues. Our preliminary results suggest that both cyst presence and BMD are independently associated with pain. However, such results and statistical analyses are of questionable utility given that measures of BMD and cyst presence are inherently linked. Ideally, measures of cyst presence would be independent of surrounding BMD to facilitate assessment of the specific role that cysts may play in OA and related pain pathology. Our group is currently developing more sophisticated methods to isolate cysts from surrounding subchondral bone. In the future we hope to apply these new methods to address questions proposed by Chen and colleagues.

We appreciate Chen and colleagues letter highlighting the important potential role which cysts may have in OA-related pain. To our knowledge, however, there has been limited research evaluating links between subchondral bone cysts and pain. The paper referred by Chen and colleagues identifying cysts as a main factor contributing to pain in OA did not actually find an association between pain and cysts (the associations were between pain and joint effusion as well as osteophyte presence in the patellofemoral compartment)[5]. In recent years there appears to be more focus on evaluating the role of cysts in OA (see works by Chiba *et al.*[6,7] and McErlain *et al.*[8–10]), which is partly why we included a discussion of our preliminary observations regarding cysts in the paper. Our aim was to initiate discussion and offer potential direction to other researchers evaluating links between pain and structural abnormalities. As well, we wanted researchers to be cognisant that observed low BMD reported with OA[11,12] may be related to cyst presence as opposed to diminished bone architecture or mineralization.

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With regards to quantifying mechanical alignment, this was completed using a custom in-house approach evaluating relative joint space widths (JSW) between adjacent medial:lateral compartments. Using commercial software (Analyze 10.0) and an interactive touch-screen tablet, a single researcher (JDJ) retrospectively evaluated JSW of individual compartments from coronal and sagittal CT reconstructions, with medial and lateral JSWs evaluated equal distances from the tibial spine. Knowledge of the difference in JSW between the compartments, combined with the distance from the tibia spine, permitted estimation of mechanical alignment via Pythagorean's theorem. Our precision of this measure, assessed via root mean square coefficients of variation, is 0.6%. Using CT images of knees classified as having normal mechanical alignment (by an experienced orthopaedic surgeon who routinely assessed knee alignment), neural alignment was defined as 176–180°, which we assumed to be representative of neutral alignment defined via full-limb radiography (i.e., 178–182°)[13]. Of note, the 2° offset pertains to inherent differences in medial:lateral cartilage thickness, with lateral cartilage being thicker than medial cartilage[14]. For this study, malalignment of ±2° from the neutral position was defined as varus (−2°) and valgus (+2°)[13]. The authors recognize that this approach is limited as it has not been validated against full-limb radiographic measures and the measures are somewhat questionable given that CT images are non-weight bearing. However, as these individuals were late-stage OA scheduled for knee replacements, mechanical malalignment was evident (often with near bone-on-bone contact) with values ranging from −18° to +8° from the neutral position. We included mechanical alignment measures into our statistical analyses to address requests from Chen and colleagues. Inclusion of mechanical alignment did not affect study findings. With regards to the statement by Chen and colleagues that varus alignment would cause decreased medial BMD and increased lateral BMD, we believe the authors may have made a typographical error and we wish to correct this point. As noted by various groups[2–4], varus alignment was associated with high medial BMD and low lateral BMD; vice versa for valgus alignment[3].

With regards to patient selection, the inclusion and exclusion criteria was intentionally kept quite broad due to the small-scale, exploratory nature of the study as well as limited availability of study participants scheduled for knee replacements at the participating hospital. We did not collect information regarding previous knee injury or smoking/drinking status, nor did we collect information regarding exercise type and intensity or occupation, which are limitations of the study. We collected information regarding comorbidities (e.g., diabetes) using the Self-Administered Comorbidity Questionnaire[15]. In this study four individuals had diabetes (severe pain: $n = 1$; no pain: $n = 3$). Exclusion of these individuals from statistical analyses did not affect study findings. We thank Chen and colleagues for identifying these important potential contributors to pain and aim to address these issues in future work.

With regards to the treatment of knee pain, all participants were on some form of pain medication as these patients had late-stage OA and were scheduled for knee replacements. It is an interesting hypothesis that specific painkillers may have affected subchondral bone remodeling and nocturnal pain. We thank Chen and colleagues for their insight and hope to address this hypothesis in future work.

Lastly, with regards to the overall question that Chen and colleagues propose: “Is subchondral BMD associated with nocturnal pain in knee osteoarthritis patients?” the answer is yes, there is an *association*. However, as we have attempted to clarify in the paper (reiterated by Chen and colleagues), there also appears to be an association between BMD, cysts and knee alignment, and we are not sure which of these factors are actually *causing* pain (i.e., Is low BMD causing pain? Is cyst size and number causing pain?). We thank Chen and colleagues for the opportunity to expand upon our research methodology and identify additional study limitations. As well, we thank them for further discussion on the links between pain, BMD, cysts, knee alignment and various other aspects (e.g., injury, smoking/drinking, painkillers) which are all important factors to consider in future large-scale studies.

Conflict of interest

Nothing to declare. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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