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High bone density and radiographic osteoarthritis: questions answered and unanswered

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Osteoarthritis (OA) has long been known to be associated with high bone mineral density (BMD). Epidemiological studies are consistent in finding that older women and men who have higher systemic BMD (i.e., BMD measured at appendicular and axial sites distal from joints) have an increased risk for the subsequent onset, or incidence, of knee radiographic OA (ROA)[1,2] and hip ROA[2]. A Mendelian randomization study also showed a strong association, consistent with a causal relationship between high femoral neck bone density and knee and hip OA[3].

Nearly all studies have found that the association of high BMD with the risk of knee and hip OA is particularly strong for OA defined by bony features such as osteophytes, either implicitly when using KL grade and Croft scores, which rely heavily on osteophytes to define OA, or explicitly when using individual radiographic features of osteophytes and joint space narrowing (JSN) to define subphenotypes of ROA[1,4,5]. The preponderance of evidence suggests that high systemic BMD is associated specifically with an osteophyte-predominant hypertrophic phenotype of ROA. Understanding this relationship may lead to a better grasp of the role of bone in the pathogenesis of OA and suggest novel targets for treatment or prevention of OA.

In contrast to knee ROA incidence, longitudinal studies of BMD and progression in knees with existing OA, defined by increases over time in JSN and/or osteophytes, have found either no association[1,2] or, paradoxically, a lower risk of OA progression in those with higher BMD[6]. The contrast with findings for incident disease suggests several possibilities. First, risk factors for the onset vs subsequent progression of existing ROA may differ.

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Conflicts of interest

The authors declare no conflicts of interest.

Second, the hypertrophic phenotype of OA associated with high BMD may have a more benign, clinical course than the OA phenotype in which JSN, a surrogate for cartilage loss, is present early in disease[4]. However, the most likely explanation for the failure to find an association of BMD with progression of OA is collider bias (also called index event bias[6,7]). Collider bias can be explained as follows: Risk factors for incidence can be detected because analyses compare the risk of disease in persons with vs those without risk factors. In a sample of persons with disease, everyone has risk factors for disease, and these are likely to be the same as risk factors for progression. Thus, studying risk factors for progression in a sample with disease is formidably challenging, since everyone has these risk factors. In OA, we have found, for example, that obesity is a risk factor for incidence but not progression[8], a difference almost certainly due to collider bias. The paper by Hartley et al.[9] finds associations of high BMD with worsening structural features only when they combine incidence and progression and don't find an association of high BMD with progression in joints with existing OA alone, consistent with collider bias.

The article in the present issue by Hartley and colleagues[9] is an important contribution to the many lingering questions about the role of high BMD in knee OA incidence and progression. For the past decade these authors have been investigating the occurrence of knee and hip ROA in the UK-based HBM study, a sample of middle-aged and older individuals and their first degree relatives who have unexplained extremely high hip and spine BMD, and a comparison group of family members with normal BMD and population controls[4]. A potential advantage of this study population is that the high BMD in these individuals is a longstanding characteristic that precedes the development of OA, consistent with a causal relationship, and a comparison of those with neither high nor low BMD drawn, in part, from the same families. The authors have previously reported from cross-sectional analyses that the high BMD group had an increased prevalence of an OA phenotype characterized by osteophytes and subchondral sclerosis, by bony spurs at pelvic tendon and ligament insertions (enthesophytes), but not by increases in JSN.

The findings reported in this issue are based on an 8-year follow-up of the high BMD subjects and their family members without high BMD, with a repeat knee radiograph to assess longitudinal changes in ROA, and an assessment of knee pain at the follow-up using the WOMAC questionnaire. Consistent with their previous findings they found strong and highly significant associations of high BMD with osteophyte development. While they found that JSN change (combining incidence and progression) was significantly more common in the high BMD group, this relationship was substantially weaker than that for osteophyte development. In addition, high BMD individuals had significantly higher WOMAC knee pain scores at the follow-up, which was largely explained by adjustment for the summed osteophyte score at the follow-up visit and not by the summed JSN score.

These findings are consistent with and extend previous longitudinal studies. In addition, the results confirm studies that have found that high BMD is also associated with an increased risk of incident knee JSN, albeit less so than with the risk of incident osteophytes[1]. When JSN is present in a knee with OA, there is a high risk of subsequent progressive cartilage loss and other structural damage. These findings and the current study's finding of increased knee pain in the high BMD subjects at the 8 year follow-up suggests that the

osteophyte-predominant phenotype of knee OA that occurs in individuals with high BMD is also characterized by cartilage loss and is likely a clinically significant form of the disease. In further support of this, a recent Mendelian randomization study found that high BMD had a causal association with total knee and total hip replacements[3]. In addition, Roemer et al.[10] using knee MRIs in the Framingham Knee OA study, found few knees with large osteophytes that did not have concomitant cartilage damage, and that the vast majority of hypertrophic knees with large osteophytes exhibited severe cartilage damage. Also, in the JOCO cohort, persons with intermediate and high hip BMD had an increased risk of incident symptomatic knee OA[11], suggesting that any structural effect also conferred an increased risk of pain. Therefore, we should seek opportunities to treat or prevent the profusion of osteophytes.

Several questions remain unanswered by these studies. First, does high bone density cause OA as a consequence of subchondral bone stiffness? In experiments in which bone stiffness was artificially increased, animals did not develop accelerated OA[12]; other animal experiments showed that in the initial stages of OA development, the subchondral bone envelope actually thins. It is only later that the cortical bone envelope thickens and becomes stiff.

If bone stiffness does not explain the association of high BMD and OA, what explanations are more likely? Increases in number and size of osteophytes and enthesophytes are tied to accelerated or abnormal endochondral ossification. The current report, like earlier ones, emphasizes that osteophyte growth is more striking in these families than JSN. Endochondral ossification also causes tidemark duplication (when the tidemark which separates calcified from non-calcified cartilage duplicates and moves toward the joint surface). This leads to JSN on X-ray and thinning of non-calcified cartilage and thin cartilage is more vulnerable to damage than thicker cartilage. However, if increased endochondral ossification were the process by which high BMD increased OA, why is the effect much greater for osteophyte growth than JSN when both should be affected by this process? Also, there is no evidence that high BMD is characterized by excess endochondral ossification outside the skeleton. So endochondral ossification is probably not the entire story.

A more likely explanation is that the process of osteophyte growth in these families may be triggered by cytokines or growth factors acting in a paracrine fashion. In animal models of OA, both BMP2 or transforming growth factor β−1 (TGF-β1) induce osteophyte growth without causing cartilage loss[13,14]. An alternative (or perhaps related) explanation is that some genes that promote high bone density have pleiotropic effects, stimulating the development of osteophytes. Indeed alleles in the Wnt/β - catenin signaling pathway are associated both with high bone density and OA risk[15]. This pathway influences development and regulation of both bone and cartilage and is likely to harbor candidates that would contribute both to high bone density and structural effects that might cause OA.

If a circulating growth factor or cytokine or a combination of them is implicated, this could suggest preventive interventions. However, it is unlikely that any intervention that negatively impacts skeletal health would be useful, given that persons affected by OA are

predominantly older women, a group at high risk of osteoporosis. In addition to identifying the causal factor, we would need to separate its effect on bone from that on osteophytes so as to avoid causing bone pathology. Even so, a better understanding of why and how high bone density increases risk of OA is needed. Insights may serve to identify a pathway to therapy.

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