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Prevalence of radiographic hip osteoarthritis is increased in high bone mass

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SUMMARY

Objective: Epidemiological studies have shown an association between increased bone mineral density (BMD) and osteoarthritis (OA), but whether this represents cause or effect remains unclear. In this study, we used a novel approach to investigate this question, determining whether individuals with High Bone Mass (HBM) have a higher prevalence of radiographic hip OA compared with controls.
Design: HBM cases came from the UK-based HBM study: HBM was defined by BMD Z-score. Unaffected relatives of index cases were recruited as family controls. Age-stratified random sampling was used to select further population controls from the Chingford and Hertfordshire cohort studies. Pelvic radiographs were pooled and assessed by a single observer blinded to case-control status. Analyses used logistic regression, adjusted for age, gender and body mass index (BMI).
Results: 530 HBM hips in 272 cases (mean age 62.9 years, 74% female) and 1702 control hips in 863 controls (mean age 64.8 years, 84% female) were analysed. The prevalence of radiographic OA, defined as Croft score $\geq$3, was higher in cases compared with controls (20.0% vs 13.6%), with adjusted odds ratio (OR) [95% CI] 1.52 [1.09, 2.11], $P = 0.013$. Osteophytes (OR 2.12 [1.61, 2.79], $P < 0.001$) and subchondral sclerosis (OR 2.78 [1.49, 5.18], $P = 0.001$) were more prevalent in cases. However, no difference in the prevalence of joint space narrowing (JSN) was seen (OR 0.97 [0.72, 1.33], $P = 0.869$).
Conclusions: An increased prevalence of radiographic hip OA and osteophytosis was observed in HBM cases compared with controls, in keeping with a positive association between HBM and OA and suggesting that OA in HBM has a hypertrophic phenotype.
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Introduction

Epidemiological studies have identified increased bone mineral density (BMD) as a potential risk factor for osteoarthritis (OA). For example, cross-sectional studies have demonstrated associations between increased BMD and both radiographic hip[1,2] and knee[3,4] OA in a variety of populations, and longitudinal studies have

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associated increased BMD with incident knee[5–8] and hip[9] OA. In addition, several studies have observed a stronger association between BMD and osteophytosis than that with joint space narrowing (JSN) (indicative of cartilage loss)[1,3,9], suggesting that increased BMD predisposes primarily to the bony features of OA. However, while the epidemiological association between increased BMD and radiographic OA is generally accepted, the topic remains controversial as it is possible that confounding[10] or reverse causality (in cross-sectional studies) may explain the relationships observed.

Studying a high bone mass (HBM) population represents a novel way to examine the OA-BMD relationship. As HBM is likely to be a lifelong genetically-determined trait, and OA is a disease of later life, this approach avoids uncertainty over the temporal sequence of events which complicates the interpretation of previous cross-sectional studies. Existing data on OA in association with extreme HBM phenotypes is limited to case reports and case series, and to our knowledge radiographic OA in a HBM population has never been systematically studied. We previously reported an increased prevalence of prior joint replacement, particularly hip replacement, in HBM cases within our UK-based HBM study compared with family controls[11]. While this suggests that OA risk may be elevated in HBM, joint replacement captures only end-stage disease, and provides limited information on OA phenotype. Recent pQCT analysis of this same HBM population revealed increases in total bone area in cases compared with controls suggestive of increased periosteal apposition[12], implying increased bone formation. This raises interesting parallels with OA, as alterations in the balance between bone formation and resorption are suggested to be a key component of the disease[13,14].

The aim of our study was to quantify and characterise radiographic hip OA in a population of individuals with extreme HBM. We wished to determine (1) whether the prevalence of radiographic hip OA is increased in HBM compared with both family-based and general population controls and (2) whether the OA observed in HBM has a characteristic phenotype based upon individual radiographic features of the disease. We hypothesized that the prevalence of radiographic OA would be increased in HBM cases, and that HBM may be associated with an excess of bone-forming features such as osteophytes and subchondral sclerosis.

Methods

The HBM population

The HBM study is a UK-based multi-centre observational study of adults with unexplained HBM. 335,115 DXA scans from 13 UK DXA databases were screened for T and/or Z-scores $\geq+4$. All DXA images were inspected by trained clinicians for artefactual causes of elevated DXA BMD; 49.4% of scans were excluded as their high T-/Z-scores reflected spinal degenerative disease/osteoarthritis/scoliosis, and a further 15.5% for other reasons including surgical/malignant/Pagetic artefacts etc. As generalized HBM should affect both hip and spine BMD, the HBM index case definition was refined to either a) L1 Z-score $\geq+3.2$ plus total hip Z-score $\geq+1.2$ or b) total hip Z-score $\geq+3.2$ plus L1 Z-score $\geq+1.2$. While standard definitions of HBM are lacking, a $+3.2$ threshold was similar to that used in a previous publication defining HBM using DXA[15], and most appropriately differentiated generalized HBM from artefact[16]. Misclassification of HBM case status due to lumbar OA was minimized by using L1 Z-score which, in contrast to lower lumbar levels, was not associated with OA assessed on DXA images[16,17].

Recruited index cases with unexplained HBM were asked to invite relatives and spouses to undergo DXA screening. In first-degree relatives of HBM index cases, given positive affection status within the family, HBM was defined as a summed L1 Z-score plus total hip Z-score $\geq+3.2$. 41% of relatives screened were affected and combined with HBM index cases; remaining unaffected first-degree relatives/spouses formed a family control group. Full details of this DXA database screening and recruitment were previously reported[16]. Assessments in both HBM cases and controls included a structured interview and clinical examination. Supine AP pelvic radiographs were performed in participants aged $\geq$40 years according to local protocols at each centre. Recruitment ran from July 2005–April 2010. Written informed consent was obtained from all participants in line with the Declaration of Helsinki[18] and the study was approved by the Bath multi-centre Research Ethics Committee (REC) and each NHS local REC. For this study, HBM cases were then categorised into 5-year age bands by gender, prior to selection of additional controls from two large population-based cohort studies, by age and gender-stratified random sampling.

Population-based controls

Chingford 1000 women study controls

The Chingford 1000 women study (ChS) started in 1989, initially recruiting 1003 women aged 45–64 from the age/sex register of a general practice in Chingford, North-East London[4]. 470 women (46.9%) remained under radiographic follow-up at 20 years. Supine pelvic radiographs were obtained in years 2, 8 and 20; radiographs from year 20 were digital and those from years 2 and 8 latterly digitised. Controls, according to age at the time of X-ray, were randomly sampled in a 2:1 ratio with HBM female cases for each age band apart from the lower (40–50 years) and upper (>80) bands (3:1). Where a control individual had more than one pelvic radiograph from different follow-up time-points, a single radiograph per participant was included; controls in the upper age bands were selected first to ensure sufficient numbers of available X-rays.

Hertfordshire cohort study (HCS) controls

The HCS[19] recruited approximately 3000 men and women born in Hertfordshire between 1931 and 1939 and still resident there in 1998–2003. Recently a subset of HCS participants were recruited into the European Project on Osteoarthritis (EPOSA)[20], as part of which 207 men and 203 women now aged between 71.5 years and 80.6 years had AP weight-bearing knee and/or supine pelvic X-rays performed during 2011. These individuals were randomly sampled 2:1 with HBM cases within each appropriate age band (70–75, 75–80 and >80).

Assessment of radiographs

All available case and control radiographs were pooled for assessment; reasons for unavailability of individual X-rays were ascertained and recorded. Radiographs were blinded and graded in a random order by a single observer (SH), following focussed radiological training. Radiographic assessment was performed using OxMorf v1.6,[1] a bone morphology measurement system developed by the University of Oxford[21]. The software was used to record gradings of the radiographic OA features, and to measure minimum joint space width (JSW) quantitatively. However, as differences in radiographic protocols between studies can result in varying degrees of magnification of the X-ray image, we could not reliably compare quantitative measures between studies; analysis of measured JSW was therefore limited to the HBM cases and family controls only.

[1] Previously known as “HipMorf”.

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