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 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 ≥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.

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 hip1,2 and knee3,4 OA in a variety of populations, and longitudinal studies have
associated increased BMD with incident knee and hip OA. In addition, several studies have observed a stronger association between BMD and osteoarthrosis than that with joint space narrowing (JSN) (indicative of cartilage loss), 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 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 should affect both hip and spine BMD, the HBM index case defining HBM using DXA15, and most recently, a bone morphology measurement system measuring OxMorf v1.6, a bone morphology measurement system developed by the University of Oxford15,16. 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.

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. 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 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)19, 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).

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 ≥+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/osteoarthrosis/scoliosis, and a further 15.5% for other reasons including surgical/medical 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 ≥+3.2 plus total hip Z-score ≥+1.2 or b) total hip Z-score ≥+3.2 plus L1 Z-score ≥+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 DXA15, and most appropriately differentiated generalized HBM from artefact16. 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 images15,16. 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 ≥+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 reported16. Assessments in both HBM cases and controls included a structured interview and clinical examination. Supine AP pelvic radiographs were performed in participants aged ≥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 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.

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 HipMorf v1.6, a bone morphology measurement system developed by the University of Oxford15. 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”.
Radiographs were first given an overall OA grade using the Croft score (0–5) as originally defined 22, followed by semi-quantitative grading of individual radiographic features including osteophytes, JSN, cysts and sclerosis (Table I) using an established atlas 23. Categorical scores were converted to binary variables for analysis (Table I); a Croft grade of ≥3 (defined as two of osteophytosis, JSN, subchondral sclerosis or cyst formation 22) defined the presence of OA 24. Measurement of minimum JSW involved manual placement of two Bézier curves on the acetabular rim and femoral head by the operator—the OxMorf software then calculated the minimum distance between the two lines.

Image quality was rated by the operator at the time of assessment (good, poor, very poor); very poor films in terms of penetration/resolution/tilt/rotation were excluded. The presence of joint replacements was recorded and these hips excluded from the main analysis (a later sensitivity analysis included these films). At the end of the study, 5% of radiographs (n = 60 films, 119 hips [1 hip replacement]) were re-graded, blind, to establish intra-rater repeatability; kappa values were all >0.7 except for cysts (kappa 0.32, likely reflecting the very low prevalence of cysts overall) (Supplementary Table I). The intraclass correlation coefficient (ICC) for minimum measured JSW was 0.89.

Assessment of covariates

Values for age, gender and body mass index (BMI) were obtained from each pre-existing study dataset for use in the analysis. Age was the age in years at the time of X-ray. BMI was calculated as weight (kg)/height (metres²) using the closest available weight and height measurements to the time of the X-ray.

Statistical analysis

Demographic statistics for the different study populations were summarised as mean (SD) for continuous variables and counts (percentages) for categorical variables. In this case—control analysis, categorical variables were initially cross-tabulated and percentages calculated. The chi-squared (χ²) test was used to assess the association between binary variables, and the unpaired t-test to compare mean values for continuous JSW. Generalised estimating equations (GEE) using a logistic link function (logistic regression allowing for clustering) was used to compare minimum JSW (mm) in HBM cases and family controls, adjusting for confounders. Pre-planned sensitivity analyses included (1) exclusion of films rated as poor quality (2) a “person-level” analysis of the worst hip in each individual (3) adding radiographic hip replacements to the dataset, assuming these were performed for OA (4) excluding individuals with self-reported inflammatory arthritis and (5) re-defining hip OA using different Croft grade cut-offs. Interactions by age and gender were assessed by calculating OR according to categories of each variable, and generating a Wald test P-value for appropriate interaction terms. Data were analysed using Stata release 12 statistical software (StataCorp, College Station, TX, USA).

Results

Selection and characteristics of participants

Figure 1 summarises the selection of radiographs for inclusion in our study. 56 hip joints (n = 4 cases, 52 controls) were excluded from the outset due to unacceptable image quality. Hip replacements were also excluded (n = 16 cases, 35 controls). 2232 hips from 1135 individuals were included in the primary combined analysis comprising 530 HBM case hips, 272 family control hips, 1091 ChS control hips and 339 HCS control hips. 1097 individuals contributed two hips to the analysis and 38 individuals contributed only one hip. Demographics of the study population are shown in Table II. The combined control group was slightly older than the cases (mean age 64.8 years vs 63.0 years) with a higher proportion of females (84.4% vs 74.3%). As expected, cases had substantially higher values for standardised BMD at both hip and lumbar spine compared with controls. Cases also had a higher mean BMI (30.5 kg/m² vs 27.3 kg/m²), as previously reported 16.

Radiographic OA in HBM cases vs controls: unadjusted analyses

The unadjusted prevalence of each radiographic OA variable in cases was compared with that in each of the three control groups separately and then combined (Table III). The prevalence of radiographic hip OA (defined as Croft score ≥3) was 20.0% in HBM cases and 13.6% in the combined controls (P < 0.001). The prevalence of any osteophyte, moderate (≥grade 2) osteophytes, femoral osteophytes, subchondral sclerosis and chondrocalcinosis was also greater in cases compared with combined controls. No difference was observed between groups in the prevalence of JSN or cysts.

Radiographic OA in HBM cases vs controls: adjusted analyses

As additional adjustment for BMI gave very similar results to age and gender adjustment alone, all three covariates were included in our fully adjusted model. Radiographic hip OA remained more prevalent in HBM cases compared with combined controls after full adjustment (OR [95% CI] 1.52 [1.09, 2.11], P = 0.013, model 2, Table IV). In adjusted analyses of individual radiographic features of OA, HBM cases had an increased odds compared with controls of any osteophyte (2.12 [1.61, 2.79] P < 0.001), moderate osteophytes (2.39 [1.72, 3.33], P < 0.001) and femoral osteophytes (1.60 [1.18, 2.17], P = 0.003). Other radiographic features more prevalent in cases compared with controls included subchondral sclerosis (2.78 [1.49, 5.18], P = 0.001) and chondrocalcinosis (2.08 [1.07, 4.03], P = 0.030) although the prevalence of these features was much lower than that of osteophytes and overall OA. In contrast, the

Table I

| OA feature                  | Categorical grading | Binary variable (s) |
|----------------------------|---------------------|---------------------|
| Croft score (global hip OA)| 0–5                 | Croft score ≥3 (OA present) |
| Superior acetabular osteophyte | 0–3               | Any osteophyte (any OP grade ≥1), moderate osteophyte (any OP grade ≥2), femoral osteophyte (any femoral OP grade ≥1) |
| Lateral femoral osteophyte  | 0–3                 | Any osteophyte (any OP grade ≥1), moderate osteophyte (any OP grade ≥2), femoral osteophyte (any femoral OP grade ≥1) |
| JCN                        | 0–3                 | Any JSN (JSN grade ≥1), moderate JSN (JSN grade ≥2) |
| Subchondral sclerosis      | 0–1                 | Subchondral sclerosis (grade ≥1) |
| Cysts                      | 0–1                 | Cysts (grade ≥1) |
| Chondrocalcinosis          | 0–1                 | Chondrocalcinosis (grade ≥1) |
Fig. 1. (A) Selection of HBM case and family control X-rays (process of recruitment to study previously reported16). (B) Selection of Chingford study female control X-rays. (C) Selection of HCS EPOSA male and female control X-rays.

1Reason recorded for missing X-ray in HBM cases: unable to travel (n = 7), no X-rays at study centre (n = 23), unable to attend/wait/comply (n = 4), patient declined (n = 8), not done (reason unknown) (n = 9), reside abroad (n = 2), bilateral hip replacements (n = 6). 2Reason recorded for missing X-ray in family controls: did not continue in study (n = 1), unable to travel (n = 1), no X-rays at study centre (n = 9), unable to attend/wait/comply (n = 2), patient declined (n = 4), not done (reason unknown) (n = 3), bilateral hip replacements (n = 1). 3Sampling frame constructed from dates of year 2, 8 and 20 follow-up visits supplied by study team. 4Reason recorded for missing X-ray in HBM cases: bilateral hip replacements (n = 3), unknown (n = 7). 5Reason recorded for missing X-ray in HBM cases: bilateral hip replacements (n = 3), unknown (n = 7). 6One individual contributed only one hip. 7Excluded as missing lateral femoral osteophyte variable. 8Excluded as previous fracture with fixation device in situ precluding reliable assessment.
prevalence of JSN was similar in cases and controls (0.97 [0.72, 1.33], \(P = 0.869\)), and there was no strong evidence of a difference between groups in the prevalence of subchondral cysts (0.34 [0.08, 1.42], \(P = 0.193\)).

Separate analyses were performed comparing the prevalence of radiographic OA in HBM cases with that in (1) family controls (Supplementary Table 2) (2) ChS controls (females only, Supplementary Table 3) (3) HCS controls (Supplementary Table 4), and (4) between HBM male cases and all male controls (Supplementary Table 5). Findings were broadly consistent across these different subgroups, although confidence intervals were generally widened. The fully adjusted OR for hip OA was lower for HBM cases vs all pooled controls, however osteophytes remained strongly associated with HBM case status and the OR for subchondral sclerosis was similar to that seen overall. Minimum measured JSW did not differ between HBM cases vs family controls (1.32 [0.77, 2.27], \(P = 0.318\)) than for HBM cases vs all pooled controls, however osteophytes remained strongly associated with HBM case status and the OR for subchondral sclerosis was similar to that seen overall. Minimum measured JSW did not differ between HBM cases and family controls (Supplementary Table 2). Restricting analyses to those HBM individuals aged >65 years vs HCS controls (due to the older age range of the HCS population, Supplementary Table 4) resulted in small numbers; whilst the OR for hip OA was attenuated (1.14 [0.70, 1.86], \(P = 0.608\)), a strong association persisted for the osteophyte variables.

**Interaction with age and gender**

The suggestion that the association of radiographic OA with HBM is attenuated in older individuals was explored by examining age interactions in analyses comparing HBM cases with combined controls. Some evidence of a HBM-age interaction was found, with the odds of OA in cases vs controls greater in the younger age groups (Fig. 2; wald test \(P\) value for interaction term 0.04), suggesting that HBM cases may develop OA at an earlier age. Whilst the overall prevalence of hip OA was greater in males compared with females (27.5% and 12.4% respectively), there was no evidence of a gender interaction (\(P = 0.59\)).

**Sensitivity analyses**

31 case hips (5.7%) and 229 control hips (13.5%) were of poor quality in terms of resolution/penetration/artefact. Excluding these films resulted in point estimates that were essentially unchanged (OR for hip OA 1.57 [1.10, 2.23], \(P = 0.012\); any osteophyte 2.14 [1.59, 2.88], \(P < 0.001\); subchondral sclerosis 2.94 [1.52, 5.67], \(P = 0.001\)) (model 2). A person-level analysis of the worst hip per participant, also resulted in very similar point estimates (adjusted OR for hip OA 1.61 [1.14, 2.26, \(P = 0.007\); any osteophyte 2.79 [1.91, 4.06], \(P < 0.001\); subchondral sclerosis 2.40 [1.30, 4.43], \(P = 0.005\)). Although hip replacements were excluded from the main analysis, a sensitivity analysis was performed in which these hips were included, with total hip replacements (\(n = 50\)) assumed to have OA. This resulted in a small increase in the OR for hip OA in HBM (1.58 [1.15, 2.17], \(P = 0.005\), model 2, Supplementary Table 6). For HBM study cases and controls only, data on self-reported inflammatory arthritis were available. Excluding the hips of these individuals from the analysis (\(n = 35\) HBM cases, two family controls) resulted in only minor attenuation of the OR for hip OA overall (Supplementary Table 7), whilst a strong association with osteoarthritis persisted; numbers for this analysis were comparatively small.

The effect of applying different Croft grade cut-offs for radiographic hip OA is shown in Supplementary Table 8; if the Croft grade 3 definition was modified to require the presence of JSN (≥grade 1), there was little evidence of attenuation (OR 1.42 [1.02, 1.98], \(P = 0.038\)). Defining radiographic hip OA as Croft grade ≥4 (“severe radiographic OA”) strengthened the association with HBM (OR 1.99 [1.04, 3.81], \(P = 0.037\)), whereas a definition based on Croft grade ≥2 resulted in no association between HBM and hip OA (OR 1.04 [0.76, 1.41], \(P = 0.802\)).

**Discussion**

Our data are the first to support an increased prevalence of radiographic hip OA in a population of extreme HBM cases, compared with controls. Furthermore, features of OA reflecting excess bone formation (osteophytes and subchondral sclerosis) were more strongly associated with HBM case status than other OA features such as JSN and cysts, for which no clear association was seen. Taken with results from our recent pQCT study, these findings suggest that increased bone formation is a key feature of the HBM phenotype, which in turn leads to a greater risk of OA. HBM was suggested to represent an incidental finding based on more recent evidence that it is associated with significant co-morbidities. Our findings were generally consistent throughout the different control groups, other than HBM cases being more similar to family controls than to general population controls (a finding likely to be explained by shared genetic and environmental factors).
Associations between HBM and radiographic features of hip OA persisted following adjustment for the confounders age, gender and BMI.

The extent to which findings in this extreme HBM group can be generalised to populations with a more typical BMD distribution is uncertain. Our observation that OA in HBM appeared to be primarily characterised by osteophytes rather than JSN likely reflects relationships between OA and BMD in the wider population, as osteophytes were reportedly more strongly associated with increased BMD than JSN in previous population-based studies.\cite{1,2}

JSN is considered the best radiographic surrogate of cartilage loss\cite{26} and is arguably a prerequisite for the development of joint pain.\cite{27} JSN is generally associated, not all joints with osteophytes progress over time to develop the other structural changes of OA.\cite{3,4}. Osteophytes may even have a positive role in stabilising the OA joint against further deterioration,\cite{35} possibly explaining why “osteoarthritic” hip OA lacking osteophytes may progress more rapidly than hypertrophic forms of the disease.\cite{36,37} Against this hypothesis is our previous finding of increased joint replacement in HBM cases,\cite{11} supporting an increase in clinically significant OA in HBM, although it is worth noting that bony changes of OA may themselves be an important source of pain\cite{38,39} and furthermore that more severe radiographic appearances may affect the decision to offer joint replacement surgery.\cite{40}

Table IV
GEE regression analysis of radiographic hip OA variables in HBM cases vs all combined controls. Results show OR, with 95% confidence interval (95% CI). N (total no. of hip joints analysed) = 530 (HBM cases), 1702 (controls). Model 1—unadjusted, model 2—adjusted for age, gender and BMI. GEE = Generalised estimating equations with logistic link function

| Outcome                        | Model | OR (95% CI) in HBM cases vs controls | P      |
|--------------------------------|-------|--------------------------------------|--------|
| Croft score ≥3                 | 1     | 1.58 (1.17, 2.14)                    | 0.003  |
|                                | 2     | 1.52 (1.00, 2.11)                    | 0.013  |
| Osteophyte (any)               | 1     | 1.94 (1.51, 2.49)                    | <0.001 |
|                                | 2     | 2.12 (1.61, 2.79)                    | <0.001 |
| Moderate (≥grade 2) osteophyte | 1     | 2.35 (1.72, 3.21)                    | <0.001 |
|                                | 2     | 2.39 (1.72, 3.33)                    | <0.001 |
| Any femoral osteophyte         | 1     | 1.66 (1.23, 2.23)                    | 0.001  |
|                                | 2     | 1.60 (1.18, 2.17)                    | 0.003  |
| JSN (any)                      | 1     | 1.08 (0.81, 1.43)                    | 0.598  |
|                                | 2     | 0.97 (0.72, 1.33)                    | 0.869  |
| Moderate (≥grade 2) JSN        | 1     | 1.44 (0.82, 2.53)                    | 0.206  |
|                                | 2     | 1.48 (0.82, 2.69)                    | 0.196  |
| Cysts                          | 1     | 0.30 (0.07, 1.28)                    | 0.104  |
|                                | 2     | 0.34 (0.08, 1.42)                    | 0.139  |
| Sclerosis                      | 1     | 2.81 (1.54, 5.13)                    | 0.001  |
|                                | 2     | 2.78 (1.49, 5.18)                    | 0.001  |
| Chondrocalcinosis              | 1     | 1.62 (0.86, 3.05)                    | 0.135  |
|                                | 2     | 2.08 (1.07, 4.03)                    | 0.030  |
between HBM and OA. In contrast, a Croft grade cut-off of ≥2 (allowing OA to be defined by JSN alone) resulted in no association; this definition would include atrophic OA29,41, which might potentially have distinct risk factors. Indeed it was recently reported in a large population-based cohort that atrophic hip OA may actually be associated with lower BMD42. Defining hip OA as a Croft grade ≥3 but with JSN as one of the two required features, is closest to the definition of “composite OA” proposed by Javaid41, since the second feature in the vast majority of cases will be osteophytes. Definitions of hypertrophic OA have focussed on osteophytes, particularly femoral osteophytes29,41; however whereas some authors have defined hypertrophic OA as osteophytosis in the absence of JSN29,41, other definitions have required both osteophytes and JSN to be present41. In our study, defining hypertrophic OA as femoral osteophytosis without JSN strengthened the HBM-OA association (OR 1.69 [1.18, 2.43], P = 0.005). Therefore HBM appears to be associated with both composite and hypertrophic, but not atrophic, hip OA phenotypes.

As outlined in our introduction, extreme HBM is likely to be genetically determined with onset of elevated bone mass relatively early in life; the genetic basis of increased BMD in our HBM population is currently being investigated. Therefore, despite the cross-sectional nature of the analysis, we focus on the relationships we found reflect either a causal pathway between higher BMD and increased risk of OA, or genetic pleiotropy. However, it remains theoretically possible that local features of OA at the hip and/or lumbar spine, such as osteophytes, subchondral sclerosis and bursitis (in which osteophytes at the hip joint extend across the femoral neck), could have led to artefactual elevation of DXA BMD resulting in misclassification of case status. If this were the case, a spurious HBM-OA association could be induced. Every effort was made within the study design to avoid this; DXA scans were visually inspected for artefactual causes of raised BMD including significant OA, and the L1 vertebra was selected for the case definition as L1 Z-score was not associated with features of OA visible on lumbar DXA16,17. In fact, this approach may have led to some in-}

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**Competing interest statement**

The authors declare no competing interests relevant to this work.

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**Supplementary data**

Supplementary data related to this article can be found at [http://dx.doi.org/10.1016/j.joca.2014.06.007](http://dx.doi.org/10.1016/j.joca.2014.06.007).

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